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Robert Forman, … , James M. Downey, Edmund H. Sonnenblick

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Research Article

The effects of both intracoronary and intravenous administration of nitroglycerin on transmural distribution of blood flow in the left ventricle after partial coronary artery occlusion was investigated using two independent methods. In 16 open chest, anesthetized dogs, tubing supplying the cannulated left coronary artery was partially occluded. Strain gauges sutured paralled to superficial and deep fibers of the myocardium separately recorded the contractile force of each layer. With occlusion set so that depression of the deep contractile force was imminent. 12 μg intracoronary nitroglycerin in seven dogs depressed only the deep contractile force without changing systemic hemodynamics. Intravenous administration of 180 μg nitroglycerin in nine dogs resulted in a decrease of deep contractile force and aortic pressure often associated with an increase in superficial contractile force. Distribution of myocardial blood flow during peak coronary flow after intracoronary administration of nitroglycerin or during a decrease in aortic pressure after intravenous nitroglycerin administration was determined by the tissue uptake of an intracoronary bolus of rubidium-^{80}. This was compared with the uptake of potassium-^{42} injected before nitroglycerin. Intravenous or intracoronary administration of nitroglycerin caused a significant reduction in subendocardial blood flow with a decrease in the subendocardial/subepicardial ratio of isotope.

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Nitroglycerin and Heterogeneity of Myocardial Blood Flow

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ROBERT FORMAN, EDWARD S. KIRK, JAMES M. DOWNEY, and EDMUND H. SONNENBLICK

From Peter Bent Brigham Hospital and Harvard Medical School, Boston, Massachusetts 02115

ABSTRACT The effects of both intracoronary and intravenous administration of nitroglycerin on transmural distribution of blood flow in the left ventricle after partial coronary artery occlusion was investigated using two independent methods. In 16 open chest, anesthetized dogs, tubing supplying the cannulated left coronary artery was partially occluded. Strain gauges sutured parallel to superficial and deep fibers of the myocardium separately recorded the contractile force of each layer. With occlusion set so that depression of the deep contractile force was imminent, 12 μg intracoronary nitroglycerin in seven dogs depressed only the deep contractile force without changing systemic hemodynamics. Intravenous administration of 180 μg nitroglycerin in nine dogs resulted in a decrease of deep contractile force and aortic pressure often associated with an increase in superficial contractile force. Distribution of myocardial blood flow during peak coronary flow after intracoronary administration of nitroglycerin or during a decrease in aortic pressure after intravenous nitroglycerin administration was determined by the tissue uptake of an intracoronary bolus of rubidium-^{86}. This was compared with the uptake of potassium-^{42} injected before nitroglycerin. Intravenous or intracoronary administration of nitroglycerin caused a significant reduction in subendocardial blood flow with a decrease in the subendocardial/subepicardial ratio of isotope.

These experiments suggest that under conditions of acute partial coronary occlusion, the autoregulatory response results in more fully dilated subendocardial vessels causing them to be less responsive to nitroglycerin. Nitroglycerin may then reduce the vascular resistance in the subepicardial more than the subendocardial vessels, resulting in a "steal" of blood flow from deep to superficial myocardium.

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Dr. Forman is an awardee of the Lilly International Fellowship Program. His current address is the Cardiac Laboratory, Groote Schuur Hospital, Cape Town, South Africa.

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INTRODUCTION

The mechanism whereby nitroglycerin relieves the pain of angina pectoris in obstructive coronary artery disease is unknown. In the past it was generally believed that nitroglycerin produced this therapeutic effect by increasing myocardial blood flow through dilation of the coronary vessels (1). However, in the presence of critical obstruction of coronary arteries, the resistance vessels are probably dilated already and thus have lost their responsiveness to vasodilating drugs (2, 3). Alternatively it has been postulated that nitroglycerin acts by lowering the oxygen requirements of the heart through the reduction of arterial pressure by decreasing peripheral resistance (4) and reduction of heart size by decreasing venous return (5). Others have suggested that nitroglycerin may have its action by increasing flow through collateral channels, leading to a chronically ischemic area of myocardium without significantly altering total flow (6). To date there is insufficient evidence to confirm any of the above hypotheses.

Most recently evidence has been presented that nitroglycerin alters the transmural distribution of the coronary blood flow promoting flow selectively to the suben-

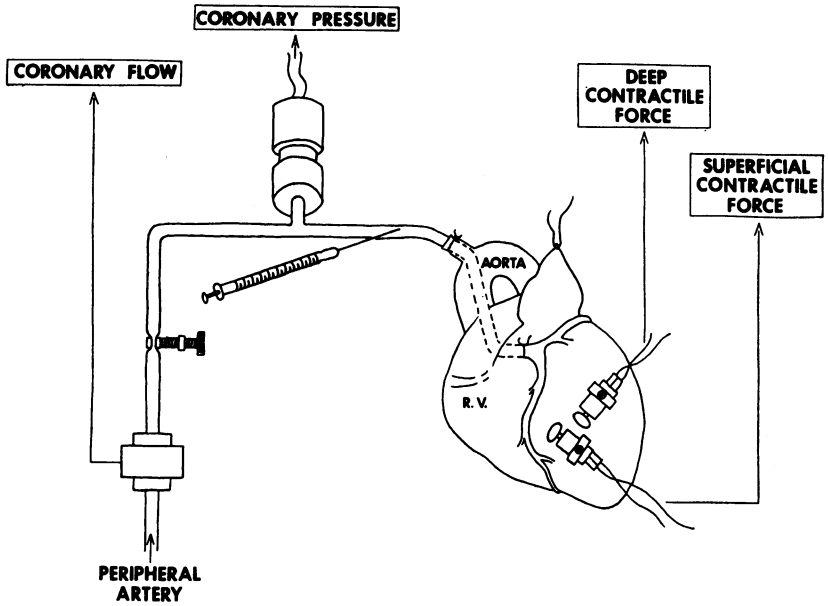

FIGURE 1 A diagram of the preparation used for all experiments. The common left coronary artery was cannulated and perfused with blood from a peripheral artery. The system, made of plastic tubing, included an extracorporeal electromagnetic flowmeter, a screw clamp which constricted the tubing, and a side arm attached to a pressure transducer. Intracoronary nitroglycerin was administered by injection through the tubing as shown. The force gauge recording superficial contractile force was orientated parallel to the epicardial fibers and attached with shallow sutures while the other was attached with deep sutures and orientated perpendicular to the epicardial fibers.

docardium (7, 8). These investigators have suggested that nitroglycerin causes a preferential dilation of the deep coronary arteries and thus increases blood flow to the ischemic subendocardium of the angina patient.

To test this hypothesis we have evaluated the effect of nitroglycerin on blood flow and/or function in the subendocardium after it was placed on the verge of ischemia by partial occlusion of the left coronary artery. By administering nitroglycerin selectively into the coronary system, the direct effects of the drug on the coronary vessels have been studied in the absence of systemic hypotension. Experiments have also been performed with systemic administration of nitroglycerin. To measure changes in transmural coronary blood flow, contractile forces have been recorded simultaneously from both superficial and deep layers of the left ventricle using a technique employing strain-gauge arches (9, 10). Additionally, the distribution of the myocardial blood flow across the heart wall has been measured by the tissue uptake of ^{86}Rb or ^{42}K (11).

METHODS

Preparation of dogs. The experiments were performed on 16 mongrel dogs weighing between 18 and 32 kg. The animals were anesthetized with intravenous sodium pentobarbital (12.5 mg/lb) and ventilated with 100% oxygen by endotracheal tube using a positive pressure respirator. After thoracotomy in the fifth left intercostal space, the left main coronary artery was isolated. The model employed is shown diagrammatically in Fig. 1. A Gregg cannula was inserted through the left subclavian artery into the left main coronary artery and firmly ligated in this position. The left coronary artery received its blood supply from a peripheral artery via plastic tubing. Coronary flow was measured with an electromagnetic flow meter using an extracorporeal flow transducer[1] in series with the cannula. Partial occlusion of the tubing was obtained with a screw clamp.

Separation of the contractile forces of the superficial from deep fibers was obtained by taking advantage of the fiber orientation of the anterior wall of the left ventricle which rotates 120° from the most superficial to the deepest layers (12). Two isometric strain-gauge arches[2] were sutured to the anterior wall of the left ventricle in each experiment. One was oriented parallel to the subepicardial fibers and attached with shallow sutures and the other was attached to the inner fibers with deep sutures and oriented perpendicular to the epicardial fibers. The gauges were tested to verify their responsiveness. If the gauges were functioning properly only the gauge attached to the superficial fibers responded to local cooling of the epicardial fibers caused by topical cold saline whereas both gauges responded to systemically administered inotropic stimulus (e.g., isoproterenol infusion) (9, 10).

[1] Biotronex Laboratory, Inc., Silver Spring, Md.

[2] Walton-Brodie types, from John Warren, Department of Pharmacology, University of South Carolina, Charlestown, S. C.

Procedure. As the perfusion tubing was gradually occluded, contractile force in the "deep" gauge declined before that in the "superficial" gauge. In all experiments the perfusion tubing was narrowed to a point just before that where depression of contractile force of the "deep" gauge occurred. In seven dogs a bolus of 5 μCi of ^{42}K in saline was then injected into the perfusion tubing. Within 2 min, 12 μg of nitroglycerin in 20 μl saline was administered into the perfusion tubing followed by 5 μCi of ^{86}Rb at approximately the time of peak increase in coronary flow. In a second group of nine dogs, 180 μg nitroglycerin was injected intravenously within 2 min of an intracoronary injection of ^{42}K. An intracoronary bolus of ^{86}Rb was subsequently injected during the resultant maximum fall in systemic pressure. The two isotopes were interchanged in alternate experiments.

1 min after the last injection of isotope the hearts were excised, frozen, and four separate full thickness segments of the left ventricle removed. Each segment was sliced into four approximately equal layers, from outer to inner wall, weighed to the nearest milligram, and dissolved in 3 ml nitric acid. The samples were placed in a well counter and counts corresponding to two different ranges of gamma ray energies were recorded. The radioactivity of each isotope was calculated, taking into account the decay of ^{42}K during the counting procedure.

In six dogs who received intravenous nitroglycerin, a segment of myocardium under the "deep" gauge was removed and analyzed similarly.

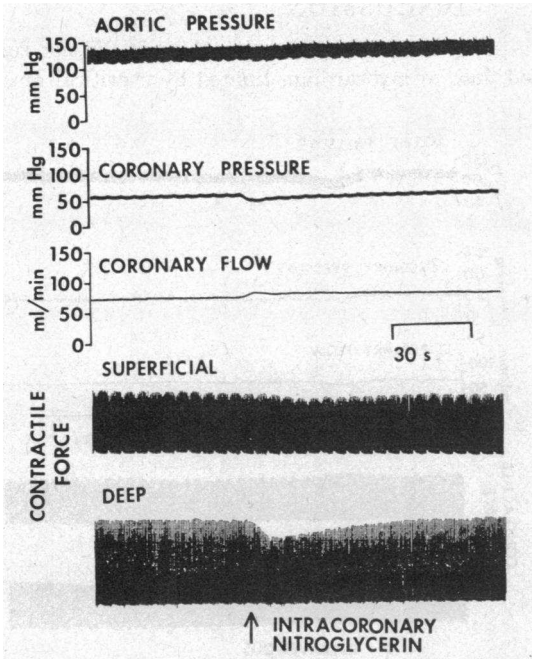

FIGURE 2 Representative recording of the decrease in deep contractile force caused by intracoronary nitroglycerin. Partial occlusion of the coronary artery before this record has reduced coronary pressure from a mean of 112 to 58 mm Hg. Nitroglycerin caused a small increase in coronary flow (8 ml/min) which increased the pressure drop across the occlusion resulting in a drop in coronary pressure to 47 mm Hg. Systemic blood pressure was unaffected.

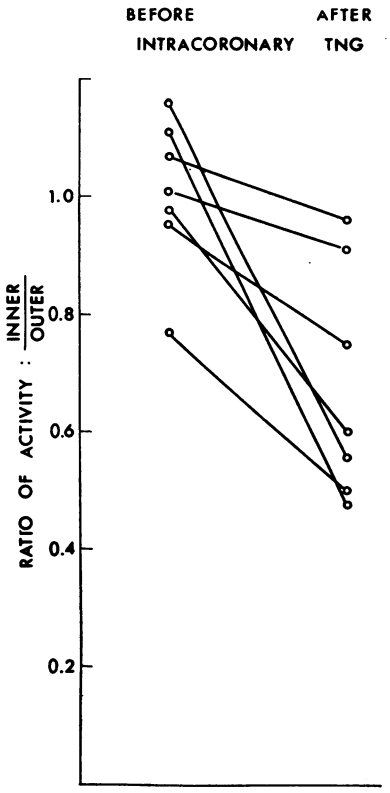

FIGURE 3 The inner half to outer half ratio of ^{86}Rb or ^{42}K uptake in the ventricular wall before and after intracoronary nitroglycerin. A line joins the two ratios from each experiment. In every experiment nitroglycerin caused the ratio to fall indicating that myocardial blood flow was redistributed away from the subendocardium.

RESULTS

Partial occlusion of the left main coronary artery to a level where a fall in contractile force of the "deep" gauge was imminent, reduced mean coronary perfusion pressure from a control average of 105 mm Hg (range, 87–125 mm Hg) to an average of 70 mm Hg (range, 57–83 mm Hg).

This amounted to a 33% (range, 19–49%) reduction in perfusion relative to the control state while the mean coronary flow was decreased by only 10% (range, 6–35%) indicating autoregulation of the coronary blood flow was occurring.

Intracoronary nitroglycerin. After administration of intracoronary nitroglycerin at this level of partial occlusion, the contractile force of the "deep" gauge diminished in every case which averaged a 21% decrease while only small and inconsistent changes in "superficial" contractility occurred. "Deep" force was restored to normal levels when the coronary flow returned to its preinjection level (Fig. 2). After the administration of intracoronary nitroglycerin, the mean coronary flow

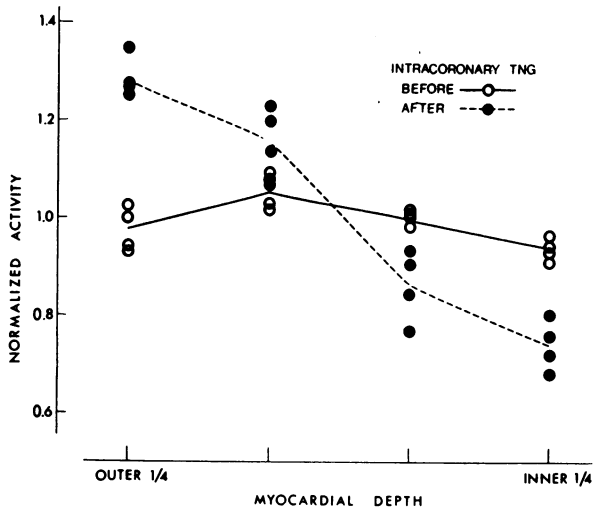

FIGURE 4 Normalized uptake of ^{86}Rb and ^{42}K at four levels of myocardial depth from a single representative experiment in which intracoronary nitroglycerin was administered. 16 samples were analyzed for each isotope, four at each level. The uptake of the isotope was uniform across the wall in the presence of the occlusion but before nitroglycerin. Nitroglycerin caused a gradient across the wall which indicated that myocardial blood flow steadily decreased from epicardium to endocardium.

increased by 5% (range, 3–7%), and coronary perfusion pressure decreased by a mean of 10 mm Hg (range, 7–16 mm Hg). Systemic pressure was unaffected by the administration of these levels of intracoronary nitroglycerin.

The results of isotope analysis have been expressed as an inner to outer ratio before and after nitroglycerin administration (Fig. 3). The ratios represent the activity of the inner half of the myocardial segment (in counts/gram for each isotope) divided by the activity of the outer half. The mean of the four separate inner/outer ratios of each segment from individual dogs was obtained by meaning the logarithm of their ratios. Before nitroglycerin, the inner/outer ratio of activity averaged 1.07±0.15 (SE). After intracoronary injection of nitroglycerin, this ratio decreased in all of the seven dogs ($P < 0.01$) to an average of 0.68±0.18 (SE). This significance of differences was obtained using analysis of variance of the logarithm of mean differences in each heart (13).

A more detailed analysis of the four slices from four different segments of one heart obtained from a representative single experiment is shown in Fig. 4. The activity of each slice has been divided by the activity of the full thickness segments. A uniform activity is demonstrated across the heart wall before administration of nitroglycerin, whereas after nitroglycerin the activity decreased progressively from outer to inner slices for each segment.

Intravenous nitroglycerin. A representative example of the results obtained after intravenous nitroglycerin on the contractile force in the presence of critical coronary obstruction is shown in Fig. 5. The force recorded from the "deep" gauge fell an average of 32% with the fall in aortic pressure. In contrast, contractile force of the superficial gauge commonly increased. Coronary flow increased briefly and then fell as systemic hypotension occurred. In the absence of any restriction to coronary flow systemic administration of nitroglycerin did not lead to any reduction in either deep or superficial contractile force.

The inner/outer ratios of isotope in the presence of critical coronary obstruction before and after intravenous administration of nitroglycerin are shown in Fig. 6. After nitroglycerin the inner/outer ratio was reduced in seven dogs and unaltered in one dog. Statistical analysis as described above show that the reduction in the mean inner/outer ratio from 0.82±0.07 (SE) to 0.62±0.09 (SE) after intravenous injection was significant ($P < 0.01$). In six hearts segments of ventricle excised from under the "deep" gauge all showed a decrease ($P < 0.01$) in the inner/outer ratio after intravenous nitroglycerin administration (Fig. 7).

DISCUSSION

This study has shown that nitroglycerin did not restore blood flow to myocardium limited by a critical obstruc-

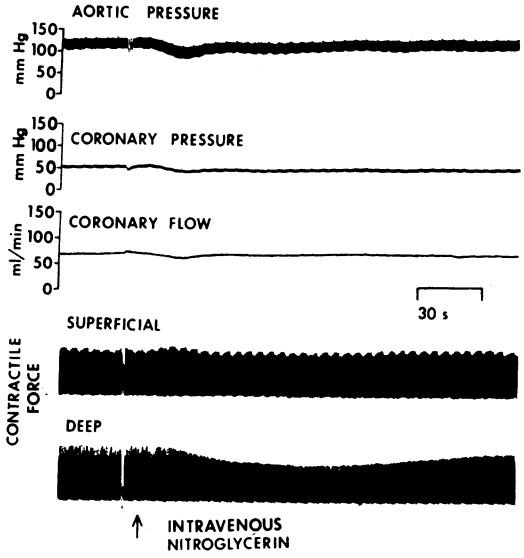

FIGURE 5 Representative recording of the decrease in deep contractile force caused by intravenous nitroglycerin. This record was obtained from the same animal as Fig. 2 with the same degree of partial occlusion of the coronary artery. Nitroglycerin caused a decrease in systemic pressure which is reflected in a 11 mm Hg decrease in coronary pressure. Coronary flow fell concomitantly.

tion of a coronary artery. On the contrary, the direct effect of nitroglycerin was a redistribution of coronary blood flow away from the subendocardium, as evidenced by both the myocardial redistribution of the radioisotope as well as a diminution of the contractile force of deep layers in the ventricular wall. Even when the drug was administered systemically, the net effect was a redistribution of blood flow away from the subendocardium.

Several methods are available for determining the distribution of blood flow within the myocardium. Because of their relatively rapid washout, freely diffusable tracers, such as labeled antipyrine (14), do not allow enough time for multiple measurements as were done in this experiment. Whereas labeled microspheres may overcome the problems associated with rapid washout of diffusable tracers, the intramyocardial distribution of microspheres appears to be dependent upon the particle size as well as the distribution of blood flow (15). For these reasons the potassium uptake technique (11) was considered the most suitable for this study. The major disadvantage of this technique is that the tissue clearance

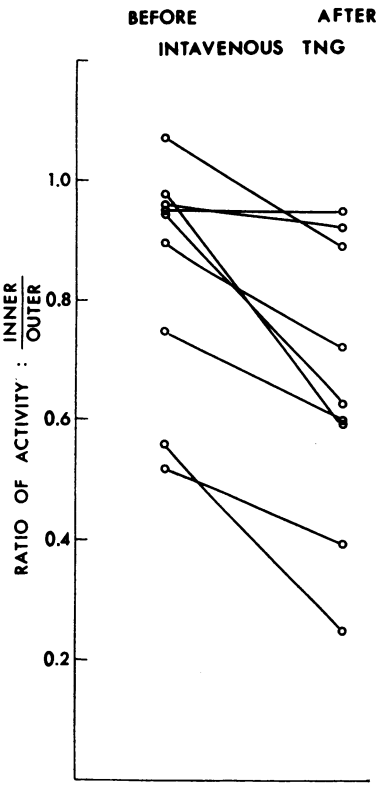

FIGURE 6 The inner half to outer half ratios of ^{86}Rb and ^{42}K uptake in the ventricular wall before and after intravenous nitroglycerin. A line joins the two ratios from each experiment. After nitroglycerin the ratio fell in all but one experiment indicating that myocardial blood flow was redistributed away from the subendocardium.

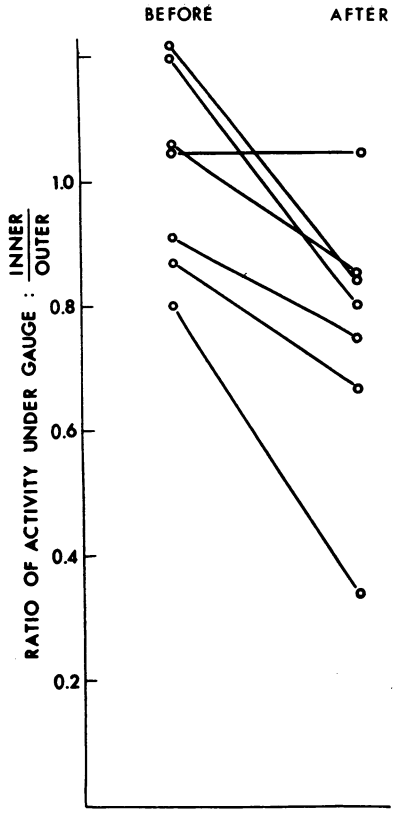

FIGURE 7 The inner half to outer half ratio of ^{86}Rb and ^{42}K uptake in the tissue directly beneath the "deep" force gauge before and after intravenous nitroglycerin. The similarity between the results under the gauge and that of the remaining ventricle (Fig. 6) indicates that the tissue under the gauge was representative of the ventricle.

is limited by diffusion as well as blood flow rate (16). However, any error introduced by diffusion limitations would only result in an under estimation of differences in blood flow. The reduced uptake of isotope in the subendocardium may to a small extent also reflect the net potassium efflux from ischemic myocardium.

The present results have been explained as follows. With narrowing of the coronary arterial perfusion system, pressure distal to the restriction fell. Mean coronary flow, however, was only slightly reduced due to an autoregulatory dilation of the distal coronary bed. Several studies have shown that a progressive reduction in coronary arterial pressure will eventually result in a preferential reduction of blood flow in deep layers of the heart wall relative to the superficial layers (14, 17, 18). Under conditions of the present experiment, this point was being approached but, before nitroglycerin administration, had not been reached. Thus, in the control period, the ratio of deep to superficial activity remained normal and "deep" force gauges were minimally altered. However, maximal dilation of the deep

vasculature was being approached as attested to by the fact that any further restriction to coronary flow lead to reduced contractile forces recorded by "deep" gauges.

It is postulated that administration of intracoronary nitroglycerin resulted in a further dilation of the superficial vessels which still had tone, while little or no response was possible in the deeper vessels which were already dilated. The reduction in total coronary resistance caused by the dilation of the superficial vessels resulted in a further fall in the perfusion pressure distal to the occlusion. These changes produced a "steal" phenomenon, reducing flow to the passive deep vessels while flow was increased to the superficial vessels. The reduction of flow to the subendocardial tissue was indicated by the decrease in the inner to outer ratio of isotope uptake in response to nitroglycerin as well as a fall in contractile force of the "deep" gauge.

When nitroglycerin was given intravenously, under similar conditions of critical obstruction of the coronary artery, coronary flow fell as systemic hypotension occurred. The effect of dilation of vessels which still had tone was offset by a decrease in perfusion pressure. Thus, in addition to the direct effect of nitroglycerin shown by the intracoronary injections, the decreased perfusion pressure contributed to a preferential reduction of blood flow in the deep layers (14, 17, 18). These effects apparently obscure the effects of hypotension to cause a reduction in intramyocardial pressure, which would favor subendocardial flow. The observation that intravenous nitroglycerin caused no reduction in the deep layer contractile force in the absence of coronary occlusion shows that changes in the pre- or afterload of the heart do not cause the decrease in deep layer contractile force. The deterioration of deep layer function when nitroglycerin was given intravenously under conditions of critical obstruction of the coronary artery appears to be the direct result of reduced flow to the subendocardial tissue.

It is possible that the tissue under the gauges may not be representative of the rest of the myocardium. Not only do the fibers beneath the gauge experience a preload which is different from that of the remaining heart but the sutures which anchor the device may compromise the local circulation. However, the close correlation between the blood flow measurements in the tissue under the gauge and that of the rest of the ventricle indicates that the above was not the case.

Recently Mathes and Rival (19) also using the uptake of ^{86}Rb as an indicator of coronary blood flow, have reported that nitroglycerin effected the removal of a transmural flow differential caused by partial coronary occlusion. Although this conclusion stands in direct conflict with the present results, the model of myocardial ischemia used was significantly different from the present one. The level of coronary occlusion which was employed depressed the mechanical function of the heart so severely that peak systolic pressure fell to less than 80 mm Hg. In the present experiment, coronary occlusion was adjusted so that ischemic depression was not overt but was imminent. Their model is further complicated by the simultaneous infusion of norepinephrine which by itself has been shown to alter the transmural distribution of coronary blood flow (20). Finally, since nitroglycerin was administered intravenously, their results represent the net effect of systemic hypotension, inotropic stimulation, and severe myocardial ischemia as well as a coronary arterial response to nitroglycerin. The response of the coronary vessels alone in their experiment is therefore unclear.

The results of the present study may be viewed relative to other studies where nitroglycerin was said to alter the transmural distribution of coronary blood flow. Winbury, Howe, and Weiss (8) interpret increases in polarographically recorded oxygen tensions in the subendocardium after administration of nitroglycerin as evidence for a redistribution of myocardial blood flow towards the subendocardium. Although most of their observations were made in the presence of a normal coronary circulation, similar results are shown with intravenous injection of nitroglycerin during partial occlusion of the left anterior descending coronary artery. However, the undefined degree of partial occlusion along with the potential for collateral flow from adjacent branches of the left coronary artery make comparisons with the present experiment difficult. It is tempting to associate the results of the present study with the initial decline in subendocardial oxygen tension observed by Winbury et al. (8). The measurements of regional flow in the present study were made during peak alteration in total coronary flow. It was presumed that the regional flow returned to its status before nitroglycerin *pari passu* with the pressure and total coronary flow measurements. Moreover, in the present study where the partial occlusion was sufficient to cause some depression of deep layer contractility, nitroglycerin did not cause any increase in contractility corresponding to the late increase in subendocardial oxygen tension seen by Winbury et al. (8). However, they employ a model to explain their data which requires assumptions that (*a*) the subendocardium is normally ischemic, a concept not supported by studies of the uptake of various isotopes (14, 20) and (*b*) nitroglycerin dilates resistance vessels which do not participate in autoregulation, which is not consistent with our own (unpublished) observations and that of others (2) that myocardial ischemia abolishes the fall in vascular resistance following nitroglycerin administration.

Becker, Fortuin, and Pitt (7) using radioactive microspheres, chose to examine the distribution of flow within a region made ischemic by total occlusion of its vascular supply. Their preparation in which the ischemic region received all of its blood flow via collateral channels clearly differs from that used in the present experiment.

Though it should be recognized that the present canine model is acute by definition and does not have a developed collateral circulation, we believe that these experiments represent an experimental model which is most analogous to the clinical conditions of diffuse myocardial ischemia resulting from lesions in the main stem coronary arteries. The level of occlusion was chosen so that, like in the patient with angina pectoris, the myocardium is on the verge of ischemia. Under these conditions the direct myocardial effect of nitroglycerin on the canine heart was to actually divert flow away from the vulnerable subendocardium. This observation may help to explain the paradoxical clinical observation that electrocardiographic evidence of subendocardial ischemia may occasionally be induced by the administration of nitroglycerin (21). We conclude that it is unlikely that the action of nitroglycerin to avert or relieve the pain of angina pectoris is through selective dilation of the deep coronary vessels.

ACKNOWLEDGMENTS

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REFERENCES

1. Goodman, L., and A. Gilman. 1941. The Pharmacological Basis of Therapeutics. The MacMillan Company, New York. 1st edition.
2. Cronin, R. F. P. 1966. Influence of arterial oxygen tension on the coronary vasodilator action of nitroglycerin. *Circulation.* **34**(Suppl. 3): 81.
3. Gorlin, R., N. Brachfeld, C. MacLeod, and P. Bopp. 1959. Effect of nitroglycerin on the coronary circulation in patients with coronary artery disease or increased left ventricular work. *Circulation.* **19**: 705.
4. Brunton, T. L. 1867. On the use of nitrite of amyl in angina pectoris. *Lancet.* **2**: 97.
5. Williams, J. F., Jr., G. Glick, and E. Braunwald. 1965. Studies on cardiac dimensions in intact unanesthetized man. V. Effects of nitroglycerin. *Circulation.* **32**: 767.
6. Fam, W. M., and M. McGregor. 1964. The effect of coronary vasodilator drugs on retrograde flow in areas of chronic myocardial ischemia. *Circ. Res.* **15**: 355.
7. Becker, L. C., N. J. Fortuin, and B. Pitt. 1971. Effect of ischemia and anti anginal drugs on the distribution of radioactive microspheres in the canine left ventricle. *Circ. Res.* **28**: 263.
8. Winbury, M. W., B. B. Howe, and H. R. Weiss. 1971. Effect of nitroglycerin and dipyridamole on epicardial and endocardial oxygen tension—further evidence for redistribution of myocardial blood flow. *J. Pharmacol. Exp. Ther.* **176**: 184.
9. Kirk, E. S., M. E. Turbow, C. W. Urschel, and E. H. Sonnenblick. 1970. Non-uniform contractility across the heart wall caused by redistribution of coronary flow. *J. Clin. Invest.* **49**: 51a. (Abstr.)
10. Kirk, E. S., M. E. Turbow, H. Brooks, and E. H. Sonnenblick. 1971. Myocardial performance relative to altered coronary blood flow. Proceedings of the International Symposium on Myocardial Blood Flow in Man. Pisa. In press.
11. Sapirstein, L. A. 1958. Regional blood flow by fractional distribution of indicators. *Am. J. Physiol.* **193**: 161.
12. Streeter, D. D., Jr., H. M. Spotnitz, D. P. Patel, J. Ross, Jr., and E. H. Sonnenblick. 1969. Fiber orientation in the canine left ventricle during diastole and systole. *Circ. Res.* **24**: 339.
13. Snedecor, G. W., and W. G. Cochran. 1967. Statistical Methods. Iowa State University Press, Ames, Iowa. 6th edition. 329.
14. Griggs, D. M., Jr., and Y. Nakamura. 1968. Effect of coronary constriction on myocardial distribution of iodo-antipyrine-^{131}I. *Am. J. Physiol.* **129**: 370.
15. Domenech, R. J., J. I. E. Hoffman, M. I. Noble, K. B. Saunders, J. R. Henson, and S. Subijanto. 1969. Total and regional coronary blood flow measured by radioactive microspheres in conscious and anesthetized dogs. *Circ. Res.* **25**: 581.
16. Love, W. D., and G. E. Burch. 1959. Influence of the rate of coronary plasma on the extraction of Rb^{86} from coronary blood. *Circ. Res.* **7**: 24.
17. Salisbury, P. F., C. E. Cross, and P. A. Rieben. 1963. Acute ischemia of the inner layers of the ventricular wall. *Am. Heart J.* **66**: 650.
18. Moir, T. W., and D. W. DeBra. 1967. Effect of left ventricular hypertension, ischemia and vasoactive drugs on the myocardial distribution of coronary flow. *Circ. Res.* **21**: 65.
19. Mathes, P., and J. Rival. 1971. Effect of nitroglycerin on total and regional coronary blood flow in the normal and ischemic canine myocardium. *Cardiovasc. Res.* **5**: 54.
20. Love, W. D., and G. E. Burch. 1957. Differences in the rate of Rb^{86} uptake by several regions of the myocardium of control dogs and dogs receiving L-norepinephrine or Pitressin. *J. Clin. Invest.* **36**: 479.
21. Russek, H. I., K. F. Urbach, and B. L. Zohman. 1955. Paradoxical action of glyceryl trinitrate (nitroglycerin) in coronary patients. *J. Am. Med. Assoc.* **158**: 1017.