Effect of Nitroglycerin and Dipyridamole on Regional Coronary Resistance

By Wadie M. Fam, M.D., Ph.D., and Maurice McGregor, M.D.

ABSTRACT

We studied the changes caused by intravenous injection of nitroglycerin (0.3 to 0.6 mg) and dipyridamole (5 to 10 mg) on the resistance of large and small coronary arteries of dogs. The direction of change in resistance of large conductive vessels (Re) was estimated by dividing the pressure drop from aorta to a superficial branch by the flow in that vessel. The total resistance (Rt) in the same vessel was estimated by relating aortic pressure to the same flow. The effects of both drugs on aortic pressure were comparable 3 to 7 minutes after injection. Nitroglycerin during this period caused a reduction in Re, whereas dipyridamole caused a significant reduction in Rt for 12 minutes but no consistent changes in Re. In the same preparation, small intracoronary doses of the drugs, which hardly affected the aortic pressure, caused comparable changes in resistance. This was also evident in a preparation in which the flow in the coronary vessel was held constant. These two drugs therefore differ in their site of action on the coronary vascular bed, a difference which may explain their contrasting therapeutic effects in chronic coronary disease in man.

ADDITIONAL KEY WORDS angina pectoris coronary resistance large coronary arteries coronary arterioles coronary flow dog

The contrast between the clinical and pharmacological effects of two coronary vasodilator drugs, nitroglycerin and dipyridamole, offers an interesting paradox. Nitroglycerin, which is therapeutically effective in angina pectoris (1, 2), causes only a very transient increase in coronary flow (3-6), but dipyridamole, which does not relieve angina pectoris, causes a sustained increase in coronary flow (6, 7). In a previous study in the dog (8) we found that nitroglycerin increased the collateral flow available to the myocardium distal to a chronically occluded vessel even though it did not produce any sustained increase in total coronary flow. Dipyridamole, on the other hand, did not increase collateral flow, in spite of its capacity to increase total coronary flow from aorta to coronary sinus. It was suggested that this could be explained if these two vasodilator drugs differed not only in the degree and duration of vasodilation but also in the site at which they produced their effects.

We have previously suggested (8, 9) that the coronary arterial tree can be divided functionally into the larger conductive vessels and the smaller precapillary resistive arterioles, the latter being the presumed site of autoregulation. The present study was designed to test the hypothesis that these two types of vessels react differently to the therapeutic agents in question; nitroglycerin producing dilation principally of the large conductive vessels while the vasodilator effect of dipyridamole is principally on the small arteriolar resistance vessels.

Methods

Nine mongrel dogs weighing 23 to 30 kg were anesthetized with an initial intravenous dose of chloralose (40 mg/kg) and urethane (4 mg/kg), which was repeated as required. All dogs received an initial dose of 75 mg heparin and subsequent doses of 25 mg hourly. Ventilation was maintained with a Harvard pump respirator via
The experimental preparation. Pressure transducers (P.T.) are connected to measure the aortic pressure and the pressure difference between aortic pressure and the pressure in a large superficial coronary artery (Press. Diff.). An electromagnetic flowmeter measures the blood flow through the same vessel.

an endotracheal tube. Sufficient oxygen was added to the inspired gas to keep the arterial oxygen tension above 100 mm Hg (range in the 9 dogs, 100 to 360 mm Hg). The chest was opened by left thoracotomy, and the edges of the pericardium were sewed to the chest wall so that the heart was supported in a pericardial cradle.

After exposure of the anterior descending or left circumflex coronary branch near its origin, in five animals a noncannulating electromagnetic flow transducer (2 or 2.5 mm i.d.) was placed on the vessel for the measurement of flow (Qcor) (Fig. 1). Flow was measured by a sine-wave electromagnetic flowmeter (Biotronics model BL-410-1) and a Sanborn direct-writing polygraph (model 150). Each flow transducer was calibrated with blood, and its proper gate setting was determined prior to each experiment. Zero flow was repeatedly determined by occluding the vessel distal to the transducer with a fine cuffed hemostat.

A smaller distal branch of the same artery was cannulated with a polyethylene cannula (1 mm o.d.), and the pressure at the tip of this cannula, referred to as the distal coronary pressure (Pd), was measured with a pressure transducer (Sanborn 267 A). The pressure in the ascending aorta (Pao) was simultaneously measured using a side-hole catheter introduced through the femoral artery and advanced to the root of the aorta. Thus the pressure difference from the aorta near the origin of the left coronary artery to the tip of

| Control Values and the Changes from Control Following Intracoronary Injection of Nitroglycerin in Five Dogs |
|------------------|--------|------------------|--------|
|                   |       | Average change from control after injection |
|                   |       | 1 min            | 3 min  | 6 min |
| No. of experiments | 11    | 8               |       |
| Pao (mm Hg)       | 100±6.0 | -16±5.2*        |       |
| Heart rate (beats/min) | 150±3.6 | +1.5±1.4        |       |
| Pao flow (ml/min)  | 3.0±0.9 | +1.0±0.7        |       |
| Flow (ml/min)     | 4.60±0.90 | +1.8±0.70*    |       |
| DC (mm Hg/ml per min) | 0.24±0.06 | -0.12±0.03*    |       |

Values are ± se. *P<0.01; **P<0.005.

FIGURE 1

| TABLE 1 |

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the cannula lying in the superficial coronary branch could be measured. In some experiments this difference was measured by connecting both pressure sources to the two sides of a differential transducer (Sanborn 267 B). The response time of the electrical "mean" pressure signals in both recording systems was indistinguishable (90% response = 1.9 sec).

The coronary arterial system, from its origin at the aortic root down to all points of pressure equivalent to that at the tip of the distal cannula, consists of larger conductive vessels. The resistance of this system (Re) can be computed as

\[ \text{Re} = \frac{\text{PAo} - \text{PD}}{Q_{\text{cor}}} \]

The pressure difference between aortic root and right atrium divided by flow in the same branch gave a ratio referred to as the total resistance (RT). For this purpose, right atrial pressure was considered as zero: \( \text{RT} = \text{PAo} / Q_{\text{cor}} \).

In the preparation described in Figure 1 (5 animals) the flow could vary. In this variable flow preparation we tested first the effect of intravenous administration of both drugs. The dose, approximately once to twice the equivalent of therapeutic levels, ranged from 0.3 to 0.6 mg nitroglycerin and 5 to 10 mg dipyridamole. Each drug was dissolved in 10 ml of saline and injected over a period of 1 minute. Each animal received at least two doses of nitroglycerin and one dose of dipyridamole. Approximately 15 minutes was allowed to elapse after nitroglycerin injections and 25 minutes after dipyridamole injections before subsequent doses were injected. Results were uninfluenced by the sequence in which the drugs were given.

In the same preparation (variable flow) two other animals received intracoronary doses of the drugs dissolved in 0.5 ml of normal saline and injected through a fine teflon catheter (0.87 mm o.d.) inserted into the coronary artery just proximal to the flowmeter. Nitroglycerin was given in doses varying from 0.1 to 0.005 mg (6 experiments) and dipyridamole in single doses of 0.5 and 1 mg (2 experiments). In this way fluctuation of blood pressure following each injection was minimized.

In two additional dogs the effects of nitroglycerin and dipyridamole were tested under conditions of constant coronary flow. The circumflex branch was ligated and cannulated near its origin using a large stainless steel cannula (4 mm i.d.) constructed with a side-arm at a right
angle 7 mm from its distal orifice. Perfusion pressure measured at this site was 0 to 1.7 mm Hg above pressure at the distal orifice of the cannula, depending on the flow rate, and an appropriate correction was made in all readings. The cannula was connected to the infusion line of a Harvard infusion-withdrawal pump which was continuously supplied with arterial blood by a catheter inserted into the femoral artery. Resistance was calculated as described above, except that perfusion pressure replaced aortic root pressure and flow was pre-set by the infusion rate. The rate of flow selected was usually that which would give a mean perfusion pressure equal to that at the aortic root. Drugs were dissolved in 1 ml saline and injected into the infusion line. Nitroglycerin was given in doses of 0.01 to 0.03 mg (3 experiments), and dipyridamole in doses of 0.5 to 1 mg (2 experiments).

Results

NITROGLYCERIN

The effects of intravenous nitroglycerin (0.3 mg) in a representative variable flow experiment are shown in Figure 2 and average values from the first five experiments in Table 1 and Figure 8. During, and for 1 to 2 minutes after, administration there was invariably some lowering of blood pressure, and coronary flow was either transiently increased, unchanged, or transiently reduced as in Figure 2. The effect apparently varied with the degree of systemic hypotension at this time. Immediately following the injection, both total coronary vascular resistance ($R_T$) and the resistance of the large superficial conductive vessels ($R_c$) were reduced. After this period of instability, values gradually returned to control levels. From 3 minutes onwards, aortic pressure, heart rate, coronary flow, and total coronary vascular resistance were insignificantly different from control values. In spite of this, however, both the difference between the aortic root pressure and the distal coronary pressure and the calculated value for $R_c$ were reduced for at least 6 minutes following each intravenous injection.

The effects of an intracoronary injection of 0.005 mg nitroglycerin in the same variable flow preparation are illustrated in Figure 3. The smaller intracoronary injection was given more rapidly, and systemic pressure effects were less. After a transient increase in flow and fall in $R_T$, these variables returned to control levels within 20 sec. $R_c$, however, remained depressed for approximately 3 minutes. Larger intracoronary doses (0.1 to 0.01

An experiment illustrating changes in the circumflex artery following intracoronary injection of 0.005 mg nitroglycerin. Change in aortic pressure is minimal and there is only a brief increase in coronary flow. $R_c$, however, remains depressed for 3 minutes.

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An experiment illustrating the changes following intracoronary injection of 0.03 mg nitroglycerin when the circumflex branch was perfused by arterial blood. In spite of a fixed coronary flow (67.5 ml/min) there was a reduction in $R_c$ for 4 minutes.

Changes following intravenous injection of 5 mg dipyridamole. There is a sustained increase in flow and reduction of $R_r$.

mg) of the drug caused greater lowering of blood pressure (5 to 12 mm Hg), which lasted 2 to 3 minutes. In spite of this, $R_c$ was always depressed for 3 to 5 minutes and $R_r$ was not altered for more than 60 sec.

In the constant flow preparation, intracoro-
TABLE 2
Control Values and the Changes from Control Following Intravenous Injection of Dipyridamole in Five Dogs

<table>
<thead>
<tr>
<th></th>
<th>Mean control value</th>
<th>Average change from control after injection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 min</td>
<td>5 min</td>
</tr>
<tr>
<td>No. of experiments</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>PAO (mm Hg)</td>
<td>93.0 ± 7.3</td>
<td>-10.4 ± 2.8*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>154.0 ± 4.0</td>
<td>-9.5 ± 5.7</td>
</tr>
<tr>
<td>PAO - Po (mm Hg)</td>
<td>5.2 ± 1.3</td>
<td>+4.0 ± 1.1*</td>
</tr>
<tr>
<td>Cor. flow (ml/min)</td>
<td>25.9 ± 4.0</td>
<td>+15.5 ± 2.6‡</td>
</tr>
<tr>
<td>RT (mm Hg/ml per min)</td>
<td>4.10 ± 1.00</td>
<td>-1.90 ± 0.52*</td>
</tr>
<tr>
<td>Rc (mm Hg/ml per min)</td>
<td>0.21 ± 0.05</td>
<td>+0.02 ± 0.01</td>
</tr>
</tbody>
</table>

Values are ± SE. *P < 0.025; †P < 0.05; ‡P < 0.01. Other symbols are same as those in Table 1.

Changes following intracoronary injection of 1 mg dipyridamole. There is a sustained increase in flow and reduction of Rr.

DIPYRIDAMOLE

The effects of dipyridamole were very different. A typical intravenous injection in the variable flow preparation is shown in Figure 5, and average values for five such injections in Table 2 and Figure 8. In contrast to nitroglycerin, dipyridamole caused a sustained increase in coronary flow that lasted approximately 15 minutes from the end of the drug injection in spite of a decrease in blood pressure which was comparable to, though more sustained than, that observed after nitroglycerin. The increase in coronary flow was always accompanied by a proportional increase in the pressure drop across the super-
Changes following intracoronary injection of 0.5 mg dipyridamole. With flow held constant (67.5 ml/min), there is no change in $R_c$ but a sustained fall in $R_t$.

Discussion

Several defects of design must be considered before interpretation of these experiments is attempted. In the variable-flow studies, pressure was measured at the aortic root rather than at the origin of the coronary artery. Because the orientation of the pressure-sensing catheter to the stream was not defined, the pressures recorded were neither true "end pressures" nor true "side pressures." Furthermore, as the distal cannula completely occluded the branch into which it was tied, the distal pressure must be considered to be an imperfect index of the "side pressure" existing at the first proximal bifurcation where the angle of bifurcation was neither 90° nor constant. These defects were, however, common to all observations and are unlikely to explain the differences between the effects of the two drugs.

The word resistance has been used throughout to indicate the ratio of mean pressure drop to mean flow, mean values being obtained from signals of instantaneous pressure and flow by electrical integrating devices. Even under conditions of constant flow and pressure, it is unlikely that the relationship of pressure to flow in the coronary vessels would be linear. Thus a change in the ratio of one to the other need not necessarily imply a change in vasomotor tone. Furthermore, the coronary vessels have elastic properties, are innervated, and must be compressed to a variable degree depending on the force of myocardial contraction. Their resistance is influenced by the metabolic state of the heart.
Thus, before deducing that a drug exerts a direct effect on the vessel wall, the possibility that changes in calculated resistance might be an indirect result of the drugs must be considered. When given intravenously both drugs caused a fall in blood pressure, which was more rapid in onset following nitroglycerin (Fig. 8). In the first 2 minutes after drug administration, nitroglycerin caused tachycardia and dipyridamole caused bradycardia. Thus, it is not possible to be certain of the cause of the changes in resistance during this unsteady state. However, from 3 minutes onwards, following administration of either drug, the changes in blood pressure and heart rate were less marked and were comparable in direction. At this time there was, following dipyridamole, a sustained increase in coronary flow, a finding consistent with previous evidence (4, 10). In contrast, nitroglycerin caused no sustained increase in coronary flow, but after the initial 3 minutes, there was a reduction in the pressure drop down the large superficial vessels and a corresponding reduction in calculated resistance of these vessels. As these vessels lay on the epicardial surface, the change in resistance is unlikely to have been the consequence of altered myocardial contraction and suggests rather a vasodilation of the vessel under study. Comparable reductions in resistance of the large vessels were observed when systemic effects were reduced by giving a smaller dose by the intracoronary route when flow was held constant. Dipyridamole, in contrast, caused no consistent change in this resistance, while it invariably lowered total resistance under conditions of variable or constant flow. These findings are consistent with the radiological evidence in man and in

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**FIGURE 8**

Comparison of average changes from control values following intravenous injections of nitroglycerin and dipyridamole (see Tables 1 and 2). Vertical bars indicate standard error of the mean at 5½ to 6 minutes.

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**FIGURE 9**

Theoretical model of the coronary supply to an area of myocardium (B) distal to an occluded coronary branch (see text). 

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animals that nitroglycerin increases the diameter of the coronary vessels (11-13) for several minutes, but dipyridamole does not (13).

Although the magnitude of the changes in resistance of large vessels following nitroglycerin was small, only a very short length of the artery could be examined. We suggest however, that the direction of change observed in this small section of vessel reflects the changes throughout the conductive coronary arteries. The actual value of the resistance offered by all the conductive vessels, either in the normal heart or in the presence of coronary disease, is unknown.

These observations are consistent with the initial suggestion that these two drugs might have substantially different sites of action and with the observations in chronic ischemic preparations that nitroglycerin, unlike dipyridamole, promotes retrograde flow without any sustained effect on total flow (8). As previously suggested, these differences might also account for the different therapeutic effectiveness of these two drugs in the presence of coronary vascular disease.

The model pictured in Figure 9 shows two adjacent areas of myocardium, A distal to a healthy coronary branch and B distal to an obstructed coronary branch. Flow to the latter is via collateral channels. Increased flow or the presence of disease in the surviving patent vessel increases resistance above values found in the normal heart. The present study indicates that, apart from a brief initial period, nitroglycerin dilates the conductive channels, and dipyridamole appears to have its principal and sustained effects on the small resistive vessels. It seems likely that under conditions of stress, when ischemia at B causes maximum dilation of the resistive vessels supplying this area, administration of nitroglycerin may increase flow to B by increasing the bore of the conductive arteries and possibly of the collateral channels as well. Dipyridamole, however, under these conditions may be expected to cause dilation only of the resistive vessels in the nonischemic area, A. In this way, flow through adequately perfused muscle, A, would increase, but supply to the ischemic area, B, would be unaffected or could even be reduced.

An experiment in a variable-flow preparation illustrating the effect of intravenous injection of 0.6 mg nitroglycerin when the resistance of the superficial vessel (Rc) was abnormally high. Nitroglycerin reduced Rc without affecting Rr (see text).

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If the above hypothesis were correct it would suggest that nitroglycerin could relieve angina pectoris in this way only after the establishment of collateral blood supply. Under some circumstances, however, the nitrite drugs may well relieve angina pectoris through other mechanisms. The possibility that it may act by causing a reduction of myocardial oxygen consumption has been considered elsewhere (14). An alternative possibility depends on the possible role of coronary spasm in causing anginal attacks. Zones of narrowing of coronary vessels have been observed during angiocardiology and these can be eliminated by administration of nitrates. It is of interest that in some of our preparations, with the passage of time there was a marked elevation of resistance in the segment of conductive vessel under study. Such an experiment is illustrated in Figure 10, in which the pressure drop down the superficial segment of vessel has risen from an average value of 5 mm Hg to 13 mm Hg in the absence of any increase in flow. This presumably represents large-vessel spasm which, as shown in the figure, could be relieved for several minutes by administration of nitroglycerin.

It may be argued that in the above example the relief of large-vessel spasm caused no increase in flow and that without this no therapeutic action can be deduced. This is, of course, because the large-vessel resistance measured in these experiments is too small a fraction of the total coronary resistance to influence flow. In the same preparation, however, with further passage of time, the large-vessel resistance increased even further (Fig. 11). At a comparable aortic pressure, coronary flow was now less and the gradient increased further. Administration of nitroglycerin again caused a reduction of large-vessel resistance. There was now, however, an increase in coronary flow that lasted for 5 minutes. Thus, when large-vessel resistance reaches critical levels, as it may in chronic coronary
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...disease, nitroglycerin can cause a sustained increase in flow. Whether or not spasm plays any part in clinical angina pectoris, the evidence presented in these studies suggests that the beneficial action of nitrates may depend largely on their ability to reduce large-vessel resistance with only a transient fall in small vessel resistance.

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