Effect of Coronary Vasodilator Drugs on Retrograde Flow in Areas of Chronic Myocardial Ischemia

By Wadie M. Fam, B.Ch., D.M.Sc., M.D., and Maurice McGregor, B.Ch., M.D., M.R.C.P.

Until recently it was widely believed that the therapeutic value of nitroglycerin in angina pectoris depended on the capacity of this drug to increase coronary flow by vasodilatation. While brief increase of coronary flow may follow on the administration of nitrates in the dog, this effect is very short-lived1-3 and in man with ischemic heart disease, there is no evidence that therapeutic doses of nitrates produce any increase in coronary flow4 or increase in coronary sinus oxygen content4,5 during the time interval when they are known to be therapeutically effective. It is likewise remarkable that the drug dipyridamole, which is capable of increasing coronary flow and coronary sinus oxygen content to a marked degree for 10 to 20 minutes,6,7 is much less effective therapeutically than nitroglycerin.

In the studies quoted, however, the total coronary flow, or a representative portion of the total, was measured. It must be supposed that if the relief of angina pectoris by the nitrate drugs is to be attributed to changes in coronary flow, they must cause an increase in the flow to the ischemic area of muscle. It is conceivable that they could have this effect without significantly altering total coronary flow. Likewise in the presence of occlusive coronary disease, a drug might well increase total coronary flow by dilatation of healthy coronary arteries without increasing in any way the flow to an ischemic zone supplied by a diseased vessel.

The amount of blood available to an ischemic area can be estimated by the backflow technique,10 which measures the amount of blood reaching the arterial bed of an obstructed coronary artery through the interarterial coronary collateral channels. This paper reports a study in which the effects of nitroglycerin and dipyridamole on retrograde coronary flow are contrasted. Such studies have been well documented in normal dogs.

Experimental preparation. R. Cor. = right coronary artery. L. Cor. = left coronary artery. Circ. = the circumflex branch of the left coronary artery. A.D. = the anterior descending branch of the left coronary artery. C.C. = the collecting cannula placed in the distal end of the circumflex branch of the left coronary artery. F.A. = femoral artery. P.T. = pressure transducer.
and only four normal animals have been included for purposes of comparison. In the remaining animals an attempt was made to simulate the coronary circulation of the patient with angina pectoris. Slow occlusion of a branch or branches of the coronary system resulted, in surviving animals, in a great increase in collateral anastomosis between the ischemic area and surrounding healthy vessels. The contrasting effects of nitroglycerin and dipyridamole in such animals are the subject of this report.

Methods

Seventeen mongrel dogs weighing 45 to 65 pounds were used in this study. Twelve animals ("chronic ischemic" dogs) had been operated upon five to six months previous to the retrograde flow study for the placement of ameroid constrictors on the anterior descending and circumflex branches of the left coronary artery. By this means slow occlusion of the vessels is achieved over a period of approximately three weeks. In each of these animals postmortem injection with radiopaque mass into the right coronary artery demonstrated the development of rich collateral anastomosis. The lumens of the constricted arteries were found to be occluded or to be reduced by 90% of their diameter in all cases. In six dogs the internal mammary artery was implanted in the myocardium during the same operation; all had received 50 mg dipyridamole three times daily since the time of surgery in an attempt to increase the survival rate. The drug was stopped at least 24 hours before the retrograde flow study. For purposes of comparison studies also were carried out on five normal dogs.

All animals were anesthetized with an initial dose of pentobarbital sodium, Nembutal, (30 mg/kg) intravenously. Ventilation with air was maintained with a Bird or Harvard pump respirator via an endotracheal tube.
Coronary Vasodilator Drugs

Retrograde flow was determined using a modification of the method originally described by Anrep and Häusler in 1928. The chest was opened by left thoracotomy, the pericardium incised, and the circumflex branch of the left coronary artery isolated. This branch was then ligated approximately 1 cm from its origin or immediately distal to the ameroid constrictor. Distal to the ligature the artery was cannulated and connected through a system of tubing and stopcocks to a cannula in the femoral artery. In this way perfusion of the cannulated circumflex artery with femoral arterial blood could be maintained throughout the experiment except during measurements of retrograde flow or pressure from the cannulated circumflex (fig. 1). Measurements of retrograde flow were made by collecting, for 30-second periods, the blood which emerged from the circumflex cannula held at the level of the anterior surface of the heart. These measurements were repeated every one to one and one-half minutes.

Systemic arterial pressure (femoral artery or ascending aorta) and "peripheral coronary" pressure (measured at 0 flow in the cannulated circumflex artery) were measured repeatedly and mean pressure was obtained by electrical integration. In two normal dogs and two with chronic ischemia, a catheter was placed under fluoroscopic control in the coronary sinus, and blood samples from this site and from the systemic arterial and retrograde circumflex cannulas were analyzed for oxygen content using a spectrophotometric technique (Nahas).

When three successive determinations of retrograde flow were within 0.5 ml/min they were averaged and, with corresponding values for blood pressure, heart rate, and peripheral coronary pressure, were recorded as the "control" values for any given dog. Nitroglycerin (0.6 or 0.9 mg) or dipyridamole (5 to 10 mg) was then given intravenously and data were recorded every minute for approximately 30 minutes or until the values had become stable again. When this occurred the second drug was administered. In five instances nitroglycerin (0.6 mg) was administered, as a crushed tablet rubbed into the base of the tongue. The effects appeared identical to those following intravenous injection but were approximately one minute later in onset. In most instances nitroglycerin was administered first, followed by dipyridamole. In five instances a second nitroglycerin study was repeated following the dipyridamole study.

Results

There were no differences in the results observed in dogs with or without prior implantation of the internal mammary artery.

Comparisons were made between the effects of nitroglycerin and dipyridamole in 12 ischemic dogs. An example of the data recorded during an experiment in which systemic pressure was allowed to change is shown in figure 2. Both drugs caused a fall in systemic pressure, an effect which was invariably more rapid following intravenous nitroglycerin than following dipyridamole. For purposes of statistical analyses, values were compared at the following times after the administration of the test drug: Period 1, the

*Pressure transducer 267B with 296T or 150 polygraphs. Sanborn Company, Waltham, Massachusetts.

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**Average change from control (C) in Periods 1, 2, and 3 in ten chronic "ischemic" dogs and four "normal" dogs following each drug.
### Average Control Values and Changes Following Nitroglycerin and Dipyridamole in Ten Ischemic Dogs

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Nitroglycerin</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>± SD</td>
</tr>
<tr>
<td>Heart rate</td>
<td>(10)</td>
<td>140</td>
<td>±0.2</td>
</tr>
<tr>
<td>B.P. systolic mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>(10)</td>
<td>110.6</td>
<td>±41.9</td>
</tr>
<tr>
<td>B.P. diastolic mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>(10)</td>
<td>22.03</td>
<td>6.7</td>
</tr>
<tr>
<td>B.P. mean mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>(10)</td>
<td>86.7</td>
<td>±32.5</td>
</tr>
<tr>
<td>Retrograde flow mll/30 sec</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>(10)</td>
<td>25.0</td>
<td>±3.65</td>
</tr>
<tr>
<td>B.P. mean × 100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>(9)</td>
<td>28.5</td>
<td>±10.9</td>
</tr>
<tr>
<td>Per. cor. press. mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>(8)</td>
<td>66.2</td>
<td>±17.8</td>
</tr>
<tr>
<td>B.P. mean × 100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>(8)</td>
<td>74.98</td>
<td>±7.99</td>
</tr>
</tbody>
</table>

* Significant change. In first eight columns this reflects change of mean values from mean control value (t-test). In the last four columns this reflects the significance of differences between controls and the changes produced by each drug as assessed by paired t-tests.

Time of maximum fall in systemic pressure. This ranged from one-half to one minute after intravenous nitroglycerin, one to two minutes after sublingual nitroglycerin, and seven to nine minutes after intravenous dipyridamole. Period 2, five minutes after Period 1. Period 3, the time of recovery or stabilization of blood pressure. Complete return to control values was not always obtained but maximum recovery was observed from ten to seventeen minutes after administration of nitroglycerin, and thirty to forty minutes after dipyridamole. The average control value and the average change in each period derived from one comparison in each animal are shown in figure 3 and table 1, which also reflect the difference between the changes produced by nitroglycerin and dipyridamole respectively. The results in the ten experiments in which blood pressure varied may be summarized as follows:

While nitroglycerin caused no change in heart rate, dipyridamole caused bradycardia which was greatest during Period 1. Both drugs caused reduction in systemic blood pressure and at the time of maximal fall, Period 1, the effect of nitroglycerin was greater than dipyridamole (table 1).
At the time of maximal fall of blood pressure, Period 1, following dipyridamole, there was a reduction in retrograde flow in each experiment. The average of the percentage changes was -30%. By contrast, after nitroglycerin there was little change. In seven animals there was a small reduction and in three animals a small increase in retrograde flow in spite of the lowered aortic pressure. The average change of -12% was statistically insignificant. Due to the effect of systemic pressure on retrograde flow, comparison was made between values for retrograde flow per 100 mm Hg systemic mean pressure. While dipyridamole produced no significant change in this value in any period, nitroglycerin caused an increase averaging +41.7% in Period 1 and +20.2% in Period 2, both of which were statistically significant ($P < 0.02$ and $P < 0.05$ respectively).

Together with the fall in systemic blood pressure there was a fall in peripheral coronary pressure following both drugs (Figs. 2 and 3). Following nitroglycerin this was less marked and less sustained and peripheral coronary pressure was not significantly below control values in Periods 2 and 3 in spite of continued depression of systemic pressure. By contrast, following dipyridamole the peripheral coronary mean pressure fell more than the systemic mean pressure and did not recover rapidly. To illustrate the change in relationship between pressures at these two sites, peripheral coronary mean pressure was
computed as a percentage of systemic mean pressure. While dipyridamole caused a reduction in this value in Periods 1, 2, and 3 nitroglycerin caused an increase in this value in each period (table 1 and fig. 3). The difference between the two drugs was significant in Period 1 ($P < 0.02$) and in Period 2 ($P < 0.01$).

The same changes were observed in both studies in which blood pressure was maintained at near constant levels by an arterial reservoir. Initially, when systemic pressure was reduced by lowering the reservoir there was a concomitant reduction in the retrograde flow and peripheral coronary pressure. When the systemic pressure was restored and held constant, nitroglycerin caused a marked increase in retrograde coronary flow and peripheral coronary pressure, with no change in the oxygen saturation of coronary sinus blood. By contrast, following the use of dipyridamole it was difficult to maintain the systemic pressure constant in spite of large transfusion from the reservoir. In the first nine minutes following dipyridamole administration, however, during which time it was possible to maintain the systemic pressure at near control levels, no change in retrograde flow or pressure was observed in spite of a marked increase in the coronary sinus oxygen saturation. One of these experiments is illustrated in figure 4.

**NORMAL DOGS**

The average and range of control values and the average changes following nitroglycerin and dipyridamole in the four normal dogs in which the pressure was not kept constant are reflected in table 1b. These values are not treated statistically. Control retrograde flow and mean coronary pressure in this group were lower than in the ischemic dogs. Following both drugs there was a comparable drop in the mean systemic pressure and a parallel drop in retrograde flow and peripheral coronary pressure. The changes in the retrograde flow and peripheral coronary pressure per 100 mm Hg mean systemic pressure were insignificant and there was no difference between the two drugs in these respects. Like-

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**TABLE 1B**

<table>
<thead>
<tr>
<th>Heart rate</th>
<th>B.P. (mean)</th>
<th>Retro. Flow</th>
<th>Mean. press. X 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.09 min</td>
<td>60.8</td>
<td>73.3</td>
</tr>
<tr>
<td>Period 1</td>
<td>+8.5</td>
<td>-1.6</td>
<td>-2.2</td>
</tr>
<tr>
<td>Period 2</td>
<td>-7.0</td>
<td>-1.6</td>
<td>-2.3</td>
</tr>
<tr>
<td>Period 3</td>
<td>-6.3</td>
<td>-1.6</td>
<td>-2.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nitro. mm Hg</th>
<th>B.P. (mean)</th>
<th>Retro. Flow</th>
<th>Mean. press. X 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.09 min</td>
<td>60.8</td>
<td>73.3</td>
</tr>
<tr>
<td>Period 1</td>
<td>-10.3</td>
<td>-1.6</td>
<td>-2.2</td>
</tr>
<tr>
<td>Period 2</td>
<td>-10.5</td>
<td>-1.6</td>
<td>-2.3</td>
</tr>
<tr>
<td>Period 3</td>
<td>-10.3</td>
<td>-1.6</td>
<td>-2.3</td>
</tr>
</tbody>
</table>

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wise in the one normal dog in which aortic pressure was maintained at control levels, nitroglycerin did not influence retrograde flow.

**CORONARY ARTERIOVENOUS OXYGEN DIFFERENCE**

In seven dogs, samples from the aorta, the coronary sinus, and the cannulated coronary artery were analysed for oxygen. Data from four experiments in which blood pressure was not held constant are shown in table 2. Nitroglycerin caused no change in the coronary arteriovenous difference in the normal dogs or in the ischemic dogs. By contrast, dipyridamole caused a marked increase in the coronary sinus oxygen content in both the normal and ischemic dogs. This difference persisted

\[\text{HEART RATE} \quad \text{bpm} / \min\]
\[\text{BLOOD PRESSURE} \quad \text{mm Hg}\]
\[\text{CORONARY SINUS} \quad \text{O}_2 \%\]
\[\text{RETROGRADE FLOW} \quad \text{cc} / 30 \min\]

**FIGURE 4**

Effect of nitroglycerin and dipyridamole in "ischemic" dog when arterial pressure was held constant. Continuous line represents mean aortic pressure. Broken line represents mean peripheral coronary pressure with the corresponding systolic and diastolic values (vertical bars).

**TABLE 2**

Arterial and Coronary Sinus Oxygen Percentage During Control Period and Periods 1, 2, and 3 in Two "Normal" and Two "Ischemic" Dogs

<table>
<thead>
<tr>
<th>Dog</th>
<th>Nitroglycerin</th>
<th>Dipyridamole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Period 1</td>
</tr>
<tr>
<td>Ischemic</td>
<td>89.0</td>
<td>18.8</td>
</tr>
<tr>
<td>Ischemic</td>
<td>95.0</td>
<td>20.2</td>
</tr>
<tr>
<td>Normal</td>
<td>90.8</td>
<td>20.2</td>
</tr>
<tr>
<td>Normal</td>
<td>92.5</td>
<td>32.4</td>
</tr>
</tbody>
</table>
after the maximum drop in blood pressure and diminished slowly during recovery up to a period of approximately 30 minutes. In three experiments in which blood pressure was held constant, the effects of the two drugs were in no way different from the above.

**Discussion**

Before attempting to interpret these results it is necessary to consider the possible significance of retrograde flow measured in this manner. The blood emerging from the distal end of the occluded artery has the same saturation as arterial blood, receiving no contribution from venous channels. We have confirmed this observation in another study and in seven of the experiments reported above. It is known that retrograde flow may vary independent of total coronary flow but varies with aortic pressure in an almost linear fashion.

In normal dogs the flow measured in this way is small. It is not augmented significantly by nitroglycerin, by dipyridamole, or by other vasodilator drugs and may fall if such drugs produce a fall in systemic pressure. The response of retrograde flow to nitroglycerin and dipyridamole in the five normal dogs in the present study was in accordance with our previous findings and with the results of others.

By contrast, in the 12 chronic ischemic dogs in which postmortem injection studies showed well developed collateral circulation, control values were much greater. In these animals there was a marked difference between the action of nitroglycerin and dipyridamole on the retrograde flow. At the time of the maximum effect of each drug on blood pressure, Period 1, nitroglycerin administration caused a greater drop in systemic pressure than dipyridamole and was associated with a higher heart rate, but in spite of this, the retrograde flow diminished much less following nitroglycerin than after dipyridamole.

The influence of systemic pressure on retrograde flow suggests that ideally in a study such as this coronary perfusion pressure should be maintained constant. Initially, however, this was not done and the computed index of retrograde flow per 100 mm Hg systemic pressure was an attempt to determine the relative changes in retrograde flow with the influence of changing perfusion pressure eliminated. The validity of this index rests on the almost linear relationship between aortic pressure and retrograde flow which has been demonstrated by Gregg et al. and confirmed in our studies (e.g., fig. 4).

While dipyridamole caused no significant change in this index the administration of nitroglycerin caused an average 41% increase. This suggested that if the marked fall in perfusion pressure attending experiments such as these could be avoided, administration of nitroglycerin would cause an increase in retrograde flow while dipyridamole would not. The results observed when aortic pressure was artificially maintained confirmed this and indicated that increased flow was available to the ischemic area together with an increase in the pressure available to drive it through the capillary bed as a result of nitroglycerin administration.

It is further relevant to observe that the therapeutic use of nitroglycerin in man does not cause hypotension. By contrast with its effects in the resting subject we have found that administration of 0.6 mg nitroglycerin sublingually to ten upright, normal subjects and nine anginal patients performing light exercise, resulted in no significant change in systemic pressure at the time of its therapeutic effect, nine minutes after administration.

Finally, it is of interest to contrast the other known effects of these two drugs on the coronary circulation. Both drugs may be said to be coronary artery vasodilators insofar as their administration causes enlargement of radiologically identifiable coronary arteries in dogs and man. Dipyridamole has been shown to cause an increase in coronary flow lasting 10 to 20 minutes in the dog with a concomitant increase in coronary sinus oxygen content in dogs and man. We have not, however, been able to show that...
CORONARY VASODILATOR DRUGS

its acute administration influences the pain or electrocardiographic changes induced by effort in anginal subjects\(^9\) by contrast with nitroglycerin, which is extremely effective in delaying the onset of pain and electrocardiographic abnormalities when such subjects are exercised\(^9\). Although this therapeutic action lasts for at least 10 minutes the increase in coronary flow which follows the administration of nitrates to dogs is transitory, lasting 30 to 60 seconds.\(^1\) In man, during the period when nitrate preparations are known to be therapeutically effective, no increase in coronary flow\(^4\) or increase in coronary sinus oxygen content can be demonstrated.\(^9\) These facts and the results of this study suggest that dipyridamole, while producing an increase in total coronary flow, fails to increase collateral flow to the ischemic areas of myocardium and for this reason is ineffective therapeutically. Nitroglycerin, on the other hand, produces no therapeutically important increase in total coronary flow but probably causes augmentation of collateral flow to under-perfused areas.

This implies that these two drugs must have different sites of action in the coronary tree. Of several possibilities one appears most consistent with the known facts. Let us assume as a model (fig. 5) two adjacent areas of myocardium, MA and MB, in the areas of a healthy coronary artery, A, and an occluded coronary artery, B, respectively. Flow in the muscle area MB is maintained by a collateral vessel, C, branching from the patent coronary artery, A. Increased flow to the ischemic area MB could result from vasodilatation of artery A or of collateral channel C or both together, so long as there was no substantial fall of resistance in the muscle area MA. Nitroglycerin probably acts in this way. Dipyridamole may well cause so great a fall in resistance in the small myocardial arteries and arterioles at MA and MB as to lower the pressure available to perfuse the collateral channel C. There is thus no significant increase in flow to the ischemic area MB.

Summary

The effects of two coronary vasodilator drugs, nitroglycerin and dipyridamole, on the coronary collateral flow were studied in twelve dogs with chronic myocardial ischemia and in five normal dogs, by means of the retrograde flow technique.

In the ischemic dogs with well developed collateral circulation, both drugs caused a reduction in systemic blood pressure. Dipyridamole caused a significant reduction in both the retrograde flow and peripheral coronary pressure as well. Nitroglycerin, by contrast, did not cause a significant reduction in either retrograde flow or peripheral coronary pressure in spite of a greater fall in mean arterial pressure. When arterial pressure was held constant artificially, nitroglycerin caused a large increase of retrograde flow in chronic “ischemic” dogs while dipyridamole did not.

In normal dogs these differences between the two drugs were not observed. Both drugs caused a reduction of retrograde flow and
peripheral coronary pressure which paralleled the reduction in systemic pressure.

In both ischemic and normal dogs, dipyridamole caused a reduction in the coronary arteriovenous oxygen difference. Nitroglycerin did not change this value.

Reported differences between these two drugs, together with these observations, suggest that nitroglycerin may have an action which is to be seen only in the presence of well developed collateral circulation; this is to increase flow through collateral channels without significantly altering total coronary artery flow. Dipyridamole does not seem to alter collateral flow but does increase total coronary flow. The site of action of these two drugs in the coronary vascular tree must thus be different.

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References


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