Dopamine-Induced Alterations in Coronary Hemodynamics in Dogs

By Harold L. Brooks, M.D., Paul D. Stein, M.D., James L. Matson, M.D., and John W. Hyland, M.D.

ABSTRACT

The effect of intravenous infusions of dopamine on left circumflex coronary blood flow and myocardial oxygen consumption in doses ranging from 5 to 100 μg/kg/min was studied in 17 open-chest dogs anesthetized with chloralose. Flow was measured with an electromagnetic flowmeter. Dopamine caused a progressive and linear increase of coronary flow that was proportional to increases in myocardial oxygen consumption up to a dose of 80 μg/kg/min; at this dose, the increase over control was 365% (28 to 129 ml/min). These changes accompanied marked increases in stroke volume, left ventricular dP/dt, and mean systolic ejection rate. Mean aortic pressure and heart rate changed little at doses below 10 μg/kg/min, but increased steadily with doses over the range of 15 to 40 μg/kg/min.

Dopamine is a potent stimulator of coronary blood flow and myocardial contractility. The fact that the increased coronary flow was proportional to increases in myocardial oxygen consumption indicates that the induced coronary vasodilation is secondary to increased myocardial oxygen demands, rather than the result of primary coronary vasodilation.

ADDITIONAL KEY WORDS catecholamines coronary vasodilation myocardial oxygen consumption beta-receptor stimulation inotropism 3-hydroxytyramine electromagnetic blood flowmeter coronary blood flow

Dopamine causes a uniform dose-related increase in cardiac output, stroke volume, systolic blood pressure, and myocardial contractility in dogs and in man (1-3). The unique combination of cardiac stimulation, peripheral vasoconstriction, and renal vasodilation has suggested that it may be useful in the treatment of selected patients in cardiogenic shock (4). This study was undertaken to determine the effects of dopamine on coronary artery blood flow and myocardial oxygen consumption.

Materials and Methods

Experiments were performed on healthy mongrel dogs of either sex, ranging in weight from 15 to 23 kg. The animals were anesthetized with a warmed solution of 1.6% chloralose, 80 mg/kg iv, after induction of anesthesia with an injection of thiopental, 7 mg/kg iv. Additional supplementary doses of 5 to 10 ml of warmed chloralose solution were given during the study to maintain a relatively uniform state of anesthesia as judged by absence of corneal reflexes. However, no anesthetic agent was given after control measurements were made. Respiration was maintained at a steady rate by a Harvard respiratory pump connected to a cuffed endotracheal tube, with steady supplemental oxygen administered to maintain arterial blood oxygen saturation above 98% throughout the experiment.

A left thoracotomy was performed at the fifth intercostal space; the pericardium was opened, reflected backward, and sutured to adjacent tissue to form a pericardial cradle. A short segment of the left circumflex artery near its origin was dissected free of adjacent tissue. A flow transducer of appropriate size to ensure a snug fit was applied to the vessel. Simultaneously
recorded mean and pulsatile left circumflex coronary artery blood flow were measured with a gated sine-wave electromagnetic flowmeter (5).1 Zero reference was obtained by mechanical occlusion of the artery with either a pneumatic occlusive cuff or a silk snare around a segment of the artery, 3 to 5 mm distal to the flow transducer. Flow transducers were calibrated by placing them upon a segment of excised artery of appropriate size, stripped of adventitia, and suspended between plastic cannulas in a saline bath. Saline was then infused through the system at known rates controlled by an adjustable stopcock distal to the flow transducer, volume flow being determined by timed collection. Cardiac output was determined by injecting indocyanine green2 into the right atrium and sampling blood from the brachial artery. Left ventricular pressure was measured through a 4-cm 14 T-gauge semirigid Teflon needle3 inserted directly into the left ventricular apical dimple and connected directly to a Statham P23D pressure transducer without intervening tubing. The first derivative of left ventricular pressure was continuously determined by means of a resistance-capacitance differentiating circuit with a time constant of 0.5 msec and a frequency response linear up to 75 cps. Pulsatile and mean arterial blood pressures were measured at the arch of the aorta through a 13-gauge steel arterial needle inserted into the right carotid artery and passed in retrograde fashion. All recordings were made on an Electronics-for-Medicine 12-channel photographic recorder. Lead II of the electrocardiogram was continuously monitored.

In nine of the experiments, arterial and coronary sinus blood samples were collected simultaneously, and O2 content was determined in duplicate by the method of Van Slyke and Neill (6). Coronary sinus blood was withdrawn continuously determined by means of a resistance-capacitance differentiating circuit with a time constant of 0.5 msec and a frequency response linear up to 75 cps. Pulsatile and mean arterial blood pressures were measured at the arch of the aorta through a 13-gauge steel arterial needle inserted into the right carotid artery and passed in retrograde fashion. All recordings were made on an Electronics-for-Medicine 12-channel photographic recorder. Lead II of the electrocardiogram was continuously monitored.

In nine of the experiments, arterial and coronary sinus blood samples were collected simultaneously, and O2 content was determined in duplicate by the method of Van Slyke and Neill (6). Coronary sinus blood was withdrawn through a specially prepared indwelling polyethylene catheter inserted directly into the distal end of the coronary sinus and secured with a purse-string suture. The calculation of myocardial oxygen consumption was made by multiplying coronary arteriovenous oxygen difference by 2.5 times the left circumflex blood flow. This factor is coronary arteriovenous oxygen difference by 2.5 times the left circumflex blood flow. This factor is based upon the studies of Gregg and associates (7), Olson et al. (8), and Rayford et al. (9).

Left circumflex coronary artery resistance was calculated as the ratio of mean aortic blood pressure (mm Hg) to left circumflex blood flow (ml/min) (10). Myocardial oxygen extraction was calculated as the ratio (in volumes percent) of coronary arteriovenous oxygen difference to arterial oxygen content. Mechanical efficiency was calculated as the ratio of left ventricular work (kg-m/min) to 2.06 times myocardial oxygen consumption (ml/min). (The conversion factor of 2.06 is used to convert ml of oxygen to kg-m mechanical work at a respiratory quotient of 0.8 (11).)

Dopamine4 was freshly prepared for each experiment, being diluted with isotonic saline into a stock solution of 200 μg/ml. The drug was infused at a constant rate through a polyethylene catheter inserted into the brachial vein as follows: Control responses were recorded. A given infusion rate was begun, 5 minutes was allowed for peak responses to develop, and recordings were then made of these responses over the following 3 to 5 minutes. The infusion rate was then increased to a higher dose level. The infusion was discontinued at various intervals throughout the experiment to allow reassessment of controls. Doses ranged from 5 to 100 μg/kg/min. Propranolol,5 0.6 mg/kg, was given intravenously to three different dogs during dopamine infusion; measurements were made 15 minutes after injection.

Since the principal changes in systemic hemodynamics occurred in the range of 5 to 40 μg/kg/min, statistical analyses on these data were not carried out beyond this dose. Linear regression curves of the absolute change from control were fitted by the method of least squares (12).

Results

Figure 1 shows the progressive dose-related increase in left circumflex blood flow in all experiments. This relationship was linear (F = 58) up to the 80 μg/kg/min dose. Figure 2 presents the measured variables on equal coordinates in terms of percent change from control. The increase in coronary flow was accompanied by increases in left ventricular dP/dt, cardiac output and, to a lesser degree, heart rate. Mean aortic pressure was essentially unchanged until the infusion of 15 μg/kg/min when a dose-related increase in pressure began. Above the 40 μg/kg/min dose, no further increases in pressures occurred consistently. The regression analysis data for these and other hemodynamic variables ex-

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1 Biotronics Laboratories.
2 Cardio-Green, Hynson, Westcott and Dunning, Inc.
3 Becton, Dickinson & Co.
4 Obtained from Calif. Corp. for Biochemical Research as 3,4-dihydroxyphenylethylamine • hydrochloride.
5 Inderal, Ayerst Laboratories, New York, N. Y.
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**Figure 1**
Least-squares regression slope showing linear relationship of left circumflex blood flow (LCBF) in percent change from control to increasing doses of dopamine in all experiments.

**Table 1**
Regression Analysis Data of Six Variables Showing Linear Response to Dopamine Infusion up to 40 μg/kg/min

<table>
<thead>
<tr>
<th>Variable</th>
<th>Source of variation</th>
<th>Degrees of freedom</th>
<th>Mean squares</th>
<th>P value</th>
<th>Significance</th>
<th>Slope</th>
</tr>
</thead>
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<tr>
<td>Left circumflex blood flow</td>
<td>Linear regression</td>
<td>1</td>
<td>14,641</td>
<td>15</td>
<td>&lt; 0.001</td>
<td>y = -0.70 + 1.40x</td>
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<tr>
<td></td>
<td>Lack of fit</td>
<td>15</td>
<td>41</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Experimental error</td>
<td>53</td>
<td>95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac output</td>
<td>Linear regression</td>
<td>1</td>
<td>2.73</td>
<td>15</td>
<td>&lt; 0.001</td>
<td>y = 0.36 + 0.02x</td>
</tr>
<tr>
<td></td>
<td>Lack of fit</td>
<td>15</td>
<td>.27</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Experimental error</td>
<td>51</td>
<td>.18</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Stroke volume</td>
<td>Linear regression</td>
<td>1</td>
<td>135</td>
<td>14</td>
<td>&lt; 0.001</td>
<td>y = 0.83 + 0.14x</td>
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<td></td>
<td>Lack of fit</td>
<td>15</td>
<td>5.4</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Experimental error</td>
<td>51</td>
<td>9.5</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Left ventricular work</td>
<td>Linear regression</td>
<td>1</td>
<td>40.8</td>
<td>34</td>
<td>&lt; 0.001</td>
<td>y = 0.32 + 0.07x</td>
</tr>
<tr>
<td>(kg-m/min)</td>
<td>Lack of fit</td>
<td>16</td>
<td>1.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Experimental error</td>
<td>50</td>
<td>1.2</td>
<td></td>
<td></td>
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<tr>
<td>Mean systolic ejection rate</td>
<td>Linear regression</td>
<td>1</td>
<td>10,880</td>
<td>16</td>
<td>&lt; 0.001</td>
<td>y = 19.59 + 1.31x</td>
</tr>
<tr>
<td>(ml/sec)</td>
<td>Lack of fit</td>
<td>14</td>
<td>610</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Experimental error</td>
<td>45</td>
<td>649</td>
<td></td>
<td></td>
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<td>Left ventricular dP/dt</td>
<td>Linear regression</td>
<td>1</td>
<td>37,802,109</td>
<td>4.7</td>
<td>&lt; 0.01</td>
<td>y = 3010 + 89.26x</td>
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<tr>
<td>(mm Hg/sec)</td>
<td>Lack of fit</td>
<td>12</td>
<td>9,412,243</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Experimental error</td>
<td>35</td>
<td>8,022,011</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Composite graph showing dose-related effects of dopamine infusion upon left circumflex blood flow (LCBF), left ventricular $\frac{dP}{dt}$, cardiac output (CO), coronary artery resistance (CAR), heart rate (HR), and mean aortic blood pressure (BP), plotted as percent change from control. Note that coronary flow and LV $\frac{dP}{dt}$ rise out of proportion to blood pressure and heart rate.

pressed in terms of absolute change from control appear in Table 1.

The effects of dopamine upon coronary flow and systemic hemodynamics always became evident within 15 to 30 seconds after beginning infusions, peak effects appeared to be reached within 2 to 3 minutes. No ventricular arrhythmias occurred at doses less than 30 µg/kg/min; they occurred sporadically at higher doses.

Figure 3 shows graphically an analysis of the results of those experiments in which myocardial arteriovenous oxygen differences were measured, in terms of the ratio of myocardial oxygen consumption to left circumflex blood flow with a line expressing a one-to-one relationship also shown. It is evident that equal numbers of experiments fall both above and below this line, indicating no definite

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For a table giving the results of these experiments, order document NAPS-00352 from ASIS National Auxiliary Publications Service, c/o CCM Information Sciences, Inc., 22 West 34th Street, New York, New York 10001; remitting $1.00 for microfiche or $3.00 for photocopies.

Circulation Research, Vol. XXIV, May 1969
DOPAMINE AND CORONARY HEMODYNAMICS

Effects of beta-receptor blockade on dopamine-induced increases in coronary blood flow in three dogs and at different dose levels (15, 50, and 90 μg/kg/min).

Discussion

The results of this study show that dopamine increases coronary blood flow over a very wide dose range proportionally more than it increases coronary perfusion pressure, indicating an overall effect of coronary vasodilation. In this respect dopamine is similar to the other two naturally occurring catecholamines, epinephrine and norepinephrine (13, 14).

The dopamine-induced increases in coronary flow appeared to be proportional to increases in myocardial oxygen consumption, indicating that the increments in coronary flow were secondary to the increased myocardial oxygen demands, barring any significant degree of intramyocardial arteriovenous shunting. This observation was further substantiated by the fact that myocardial oxygen extraction in eight of the nine dogs showed small and variable changes.

The present study indicated that over a wide dose range dopamine caused increases in coronary flow just sufficient to meet the induced energy demands on the myocardium, this being therefore a secondary vasodilation of the coronary bed. This was further supported by the fact that the dopamine-induced changes in both coronary and systemic hemodynamics were abolished by beta-receptor blockade. Whether catecholamines...
have a direct action on alpha or on beta receptors in the large or small coronary vessels is still controversial—both primary coronary arteriolar vasoconstriction (15, 16) and vasodilation (17) have been reported. Our data do not permit any further specific conclusions regarding this complex question.

Dopamine's effect of increased myocardial contractility with proportionally similar increases in coronary blood flow and myocardial oxygen consumption justify further studies of coronary hemodynamics in man with particular reference to those with coronary artery disease.

Acknowledgments

The authors wish to express their appreciation to Mr. Guy Prater and Mr. Phillip Dee for their very capable technical assistance and to Mr. Stan Shannon and Mrs. Betty Capen of the Goddard Computer Science Institute of Dallas, Texas, for their valuable assistance in computer programming and statistical analysis.

References

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Circ Res. 1969;24:699-704
doi: 10.1161/01.RES.24.5.699

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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