Effect of Isoproterenol on Coronary Blood Flow in Primary Myocardial Disease

By Lawrence D. Horwitz, M.D., George C. Curry, M.D., Robert W. Parkey, M.D., and Frederick J. Bonte, M.D.

SUMMARY

At cardiac catheterization, the effect of isoproterenol on coronary blood flow was compared in six patients with primary myocardial disease and six patients who appeared to have no cardiac disease. Coronary blood flow was measured by selective coronary artery injection of xenon-133 and external monitoring of disappearance curves with a dual probe, digital scintillation counter. In the presence of similar changes in cardiac output and heart rate-systolic pressure product, changes in coronary blood flow and coronary resistance in response to isoproterenol were significantly less ($P < 0.05$) in the subjects with primary myocardial disease than in the normal subjects.

**Additional Indexing Words:** Cardiomyopathy, Cardiac output, Coronary resistance, Cardiac hypertrophy

THE PATHOPHYSIOLOGY of primary myocardial disease is an enigma. Since the coronary arteries appear to be anatomically normal in this disorder, it is generally assumed that myocardial perfusion is normal. However, measurements of coronary flow dynamics in primary myocardial disease have been lacking. Accordingly, we investigated the ability of patients with primary myocardial disease to increase their coronary blood flow in response to an appropriate stimulus. This was accomplished by comparing the effect of an infusion of isoproterenol in a group of subjects with this disorder and a group of normal subjects.

Methods

A diagnosis of primary myocardial disease was made in six subjects. All had a well-documented clinical history of congestive heart failure, diminished ejection fraction, normal coronary angiograms, and no evidence of valvular or congenital heart disease. None had a history of high blood pressure or alcoholism. There was no obvious infectious origin in any of these cases.

Six additional subjects were considered normal controls. They included five patients studied because of chest pain of a type atypical for coronary artery disease, and one patient with mild prolapse of the posterior mitral valve leaflet.

Patients were premedicated with meperidine, 50 mg, and promethazine, 50 mg, intramuscularly. Right and left heart catheterizations were performed. Pressures were measured with Statham P23Db transducers. Cardiac outputs were measured with the dye-dilution technique, utilizing indocyanine green as the indicator. Cineangiography was performed with the patient in the right anterior oblique position, and a power injection of 40 to 50 ml of meglumine diatrizoate was administered into the left ventricle through an 8F NIH catheter. Multiple projection coronary cineangiograms were obtained by the Sones technic in all subjects. A General Electric 9-6 inch image intensifier system and 35 mm film exposed at 60 frames/sec were used for angiography. Left ventricular ejection fractions were obtained by planimetry of tracings made from end-diastolic and end-systolic frames.

After completion of angiography a 15 min rest period was allowed. Coronary blood flow was then measured by injection of 150-300 $\mu$Ci of $^{133}Xe$, dissolved in 0.5 ml of saline, into the right or left coronary orifice. The catheter was withdrawn from the orifice immediately after the injection.

Myocardial disappearance curves were measured with two Picker low-energy probes containing thallium-activated sodium iodide crystals 1.5 inches in diameter and ¼ inch thick. Each had a cylindrical lead collimator with a 1/4 inch aperture. The probes were 99% efficient for $^{133}Xe$. The two probes were calibrated with a $^{133}Xe$ source so that each gave identical counting rates. One probe was positioned vertically over the fluoroscopically-determined center of the left ventricle. The other probe was placed over the right chest and angled outward at 20 degrees from the vertical position to record only over the right lung. The curves were processed with a digital unit consisting of a Picker 628-145 dual-rate computer, which includes two fast 5-decade scalers with buffer storage units and a high-speed, parallel entry printer. A two-channel pulse-height analyzer with base set at 100, a window of 200, and a range set at 0.5 Mv was used. Counts were recorded every 1.8 sec until the counting rate had subsided to approximately 5% of the peak.
counting rate level. During the counting period, heart rate, aortic pressure, and cardiac output were measured.

To calculate coronary flow, the counts from the probe over the right lung were subtracted from simultaneous counts over the left ventricle and the difference plotted against time on semilogarithmic paper. Coronary flow was calculated by the equation, \( F = (k \cdot \lambda \cdot w)/p \), in which \( F \) is coronary flow in \( \text{ml}/100 \text{ g/min} \) and \( k \), the clearance constant, is 0.6931/(half-time in minutes), \( \lambda \) is the myocardium-to-blood partition coefficient for \(^{133}\text{Xe} \) (0.7), \( w \) is 100, since the mass of myocardium perfused is unknown and by convention flow is expressed in terms of 100 g of tissue, and \( p \) is 1.05, the specific gravity of myocardium. The partition coefficient was extrapolated from measurements obtained in normal dogs, since none have been made in primary myocardial disease. Any error in this value would reflect itself in absolute values of coronary flow, but since this should be a constant factor, estimates of relative change in coronary flow between resting and isoproterenol states are likely to be correct. Total peripheral resistance was calculated as:

\[
\text{Total peripheral resistance (dyne-sec/cm}^2\) = \frac{\text{mean aortic pressure (mm Hg)}}{\text{cardiac output (ml/min)}} \times 80 \times 10^9
\]

Coronary resistance/100 g of myocardium was calculated as:

\[
\text{Coronary resistance/100 g (dyne-sec/cm}^2\text{-100 g)} = \frac{\text{mean aortic pressure (mm Hg)}}{\text{coronary blood flow/(ml/min-100 g)}} \times 80 \times 10^9
\]

This measurement will be directly proportional to the total coronary resistance if it is assumed that the flow/100 g is applicable to the entire heart.

After control measurements were established, an intravenous infusion of isoproterenol, 2 \( \mu \text{g/min} \), was begun. If no heart rate response occurred the rate of the infusion was increased to 3 \( \mu \text{g/min} \). After five minutes or more, when a stable heart rate had been attained, the coronary flow, cardiac output, heart rate, and pressure measurements were repeated. Statistical analyses were performed by comparing the two groups with the unpaired Student’s \( t \)-test.

**Results**

Hemodynamic measurements for all subjects at rest and during isoproterenol infusion are shown in table 1. All subjects had resting cardiac outputs in the normal range for our laboratory. The resting left ventricular end-diastolic pressure was elevated in two patients with primary myocardial disease (PE and WY). All six of the subjects with primary myocardial disease had abnormal resting ejection fractions (below 55%).

### Resting Coronary Flow

The xenon-133 myocardial disappearance curves were well described by mono-exponential functions in all subjects (fig. 1). Although resting coronary flow

<table>
<thead>
<tr>
<th>Table 1</th>
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**Resting Hemodynamics and Changes Due to Isoproterenol**

<table>
<thead>
<tr>
<th>Patient</th>
<th>LVEDP</th>
<th>EF</th>
<th>CO</th>
<th>HR</th>
<th>AP S/D</th>
<th>TPR</th>
<th>CBF</th>
<th>CR</th>
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<tr>
<td><strong>Six Subjects with Normal Coronary Arteries</strong></td>
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<tr>
<td>RH</td>
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<td>6.4</td>
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<td>125/55</td>
<td>960</td>
<td>53</td>
<td>12</td>
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<td>125/55</td>
<td>640</td>
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<td>76</td>
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<td>88</td>
<td>140/80</td>
<td>1040</td>
<td>78</td>
<td>10</td>
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<td>55</td>
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<td>120/70</td>
<td>960</td>
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<td>14</td>
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<td>61</td>
<td>12</td>
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<td>1037</td>
<td>154</td>
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<td></td>
</tr>
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<td>12.7</td>
<td>19/10</td>
<td>760</td>
<td>25</td>
<td>3</td>
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<td>12.9</td>
<td>17/8</td>
<td>530</td>
<td>53</td>
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<td></td>
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</tbody>
</table>

| **Six Subjects with Primary Myocardial Disease** | | | | | | | | | | | | | | | |
| AT | 5 | 33 | 6.2 | 81 | 140/80 | 1360 | 59 | 18 | 8.0 | 102 | 150/75 | 1040 | 132 | 8 |
| NT | 10 | 50 | 2.8 | 120 | 171/90 | 3520 | 95 | 15 | 3.8 | 144 | 151/82 | 2000 | 134 | 7 |
| WH | 3 | 38 | 6.4 | 70 | 140/60 | 1120 | 73 | 12 | 11.0 | 84 | 166/66 | 720 | 108 | 9 |
| PE | 28 | 37 | 5.6 | 110 | 120/70 | 1280 | 55 | 16 | 10.0 | 125 | 120/60 | 720 | 99 | 9 |
| WY | 17 | 29 | 4.6 | 70 | 95/45 | 1120 | 70 | 9 | 7.2 | 107 | 110/72 | 800 | 102 | 7 |
| CC | 6 | 28 | 5.6 | 90 | 120/80 | 1280 | 83 | 11 | 7.2 | 108 | 100/70 | 800 | 90 | 9 |
| Mean | 5.2 | 90 | 131/71 | 1613 | 73 | 13 | 7.8 | 114 | 133/71 | 1013 | 111 | 8 |
| sd | 1.3 | 21 | 26/16 | 938 | 15 | 3 | 2.5 | 19 | 26/8 | 497 | 18 | 1 |

Abbreviations: LVEDP = left ventricular end-diastolic pressure (mm Hg); EF = ejection fraction (%); CO = cardiac output (L/min); HR = heart rate (beats/min); AP S/D = aortic pressure systolic/diastolic (mm Hg); TPR = total peripheral resistance (dyne-sec/cm²); CBF = coronary blood flow (ml/100 g/min); CR = coronary resistance/100 g (× 10⁹ dyne-sec/cm²/100 g); sd = standard deviation.

*Circulation, Volume 50, September 1974*
Myocardial disappearance curves in a subject with primary myocardial disease. Semilogarithmic plots of the initial resting and isoproterenol curves are plotted with each dot representing the counts over a 1.8 sec interval. Counts are plotted to approximately 15% of the initial value and expressed as counts/min (CPM).

Values tended to be slightly higher in the subjects with primary myocardial disease than in the normal controls, there was no statistical difference. The mean for the control group was $61 \pm 25$ (sd) ml/100 g/min and the mean for the primary myocardial disease group was $73 \pm 15$ ml/100 g/min. Cardiac outputs were similar in the two groups, $5.5 \pm 1.0$ L/min for the control group vs $5.2 \pm 1.3$ L/min for the study group, and not different statistically. Mean coronary resistance was slightly higher in the normal patients, but the difference was not different statistically. Peripheral resistance was $1467 \pm 760$ dyne-sec in the normal subjects and $1613 \pm 938$ in the primary myocardial disease group.

Effect of Isoproterenol

Isoproterenol resulted in similar elevations in cardiac output in both groups; the mean value during the infusion was 7.8 L/min for each, representing increases of 53% and 42% for control and primary myocardial disease groups respectively. However, coronary flow increased 93 ml/100 g/min (152%) in the controls vs 38 ml/100 g/min (52%) in the study group. The difference was statistically significant, $P < 0.05$ for both mean change and percentage change in coronary blood flow.

Mean coronary resistance fell $7.2 \times 10^4$ dyne-sec/cm$^2$/100 g in the control group vs $4.8 \times 10^4$ dyne-sec/cm$^2$/100 g for the study group. This difference was not significant for mean change but was for percentage change ($P < 0.05$). Changes in peripheral resistance were similar in both groups.

Figure 2 depicts the relationship between percent-

age change in cardiac output and percentage change in coronary blood flow in the two groups. A line of identity is shown which represents all potential values for which the increment in coronary blood flow is equal to the increment in cardiac output. The patients with primary myocardial disease tended to cluster around this line. In contrast, in all six of the patients with normal coronary arteries, the percentage increase in coronary blood flow was substantially greater than the change in cardiac output.

Figure 3 is a similar figure showing the relationship between percentage change in coronary resistance/100 g and percentage change in total peripheral resistance. Whereas in all the normal subjects the isoproterenol-induced fall in coronary resistance markedly exceeded the fall in coronary resistance, in the subjects with primary myocardial disease, the fall in coronary resistance was usually either the same or less than the fall in peripheral resistance.

Relationship of Coronary Flow to an Index of Myocardial Oxygen Consumption

The product of the heart rate and systolic blood pressure has been reported to be a reliable index to myocardial oxygen consumption in humans. Although its accuracy in the case of primary myocardial disease is unknown, it was thought worthwhile to check the relationship between coronary blood flow and this product in the two groups.

In the control group, the correlation coefficient between the log of oxygen consumption and coronary flow was 0.79; in the primary myocardial disease group it was 0.81. The relationships are shown in Figure 3, where the normal lines are shown for comparison.

Figure 3 shows a line of identity which demarcates those points where the percentage increase in coronary blood flow is equal to the percentage increase in cardiac output. This line is shown for the normal group, where it appears to demarcate the majority of points. In the primary myocardial disease group, the majority of points are above this line, indicating an increased proportion of total coronary flow due to an increased oxygen consumption in these patients.

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Coronary flow in PMD

Dial disease has not been specifically documented, its general applicability to both normal and diseased hearts has led us to assume that it does reflect changes in myocardial energy demand in our subjects. To calculate this value we multiplied the heart rate by the peak systolic brachial artery pressure and divided the product by 100 to reduce it to convenient units. The heart rate-pressure product is plotted vs coronary blood flow for all values in all subjects in figure 4. The mean heart rate-pressure products were 89 ± 26 vs 121 ± 47 at rest and 151 ± 33 vs 148 ± 38 during isoproterenol infusion for the normal and primary myocardial disease groups, respectively; there were no significant differences between the two groups of subjects.

To analyze whether the coronary flow was appropriate for the level of myocardial oxygen consumption, each coronary flow value was divided by the simultaneous heart rate-pressure product and the two groups of subjects compared statistically. The mean value in the normal subjects was 1.41 ± 0.27 (SD) and in the primary myocardial disease subjects was 0.66 ± 0.24; the difference was statistically significant (P < 0.01). Mean values for the normal group were higher both at rest and with isoproterenol; this difference was significant at rest but not with isoproterenol, where there was a large scatter in the normal group.

Discussion

In normal subjects isoproterenol augments and redistributes the cardiac output. The redistribution occurs through vasodilatation in certain regions of the systemic circulation, including the coronary arteries. In our normal subjects, the percentage decrease in coronary resistance was approximately twice the percentage decrease in total peripheral resistance; this resulted in a much greater percentage increase in coronary flow than in cardiac output.

In the patients with primary myocardial disease, cardiac output increased by amounts comparable to results found in the normal subjects, but the redistribution of flow was absent. The fall in coronary resistance did not exceed the fall in peripheral resistance, and as a result, the percentage increase in coronary flow did not exceed the percentage increase in cardiac output. Therefore, a normal response to isoproterenol, coronary vasodilatation, was not demonstrable in our patients with primary myocardial disease.

It appears to be unlikely that this result could be explained on the basis of lack of responsiveness to isoproterenol. Normally, isoproterenol induces vasodilatation through two mechanisms: direct beta-adrenergic receptor stimulation, and indirectly, through an increase in metabolic needs. The comparable increases in heart rate and cardiac output in the two groups are suggestive evidence of substantial direct beta-adrenergic receptor stimulation. The comparable heart rate-blood pressure products are evidence that similar increases in myocardial oxygen consumption occurred in both groups and that the indirect metabolic stimulus was present. It is noteworthy that the expected fall in total peripheral resistance did occur in the primary myocardial disease.
patients, although the coronary resistance was unaltered.

Caution should be exercised in interpreting these data in terms of adequacy of myocardial perfusion. On the one hand it could be suggested that the relatively low coronary flows for a given heart rate-blood pressure product imply improved cardiac efficiency. However, in view of the disturbed cardiac pump function, an alternate explanation is that during sympathetic stimulation coronary flow was at less than desirable levels for optimum cardiac function. If this latter explanation is correct, it is of interest to speculate on possible mechanisms by which this could occur.

In coronary artery disease infiltration of vessels by atherosclerosis reduces the capacity of the coronary vasculature to vasodilate in response to isoproterenol. A similar mechanism could be present in primary myocardial disease. Fibrosis has frequently been noted in this disorder, and it is conceivable that in some cases there is sufficient involvement of small arteries or arterioles to interfere with their function. Alternatively, a biochemical abnormality could reduce responsiveness of the vascular smooth muscle.

In view of the observation of relatively low coronary resistances at rest in some of the patients with primary myocardial disease, another explanation for the impaired response in this condition can be considered. The coronary vessels may be so widely dilated at rest in such individuals that little additional fall in coronary resistance can occur. If so, during basal conditions, a relatively high percentage of the cardiac output would be distributed to the coronary circulation in some patients with primary myocardial disease, and little or no redistribution to this region could occur with beta-adrenergic receptor stimulation. This would explain the prominence of the coronary vasculature on resting angiograms in many patients with primary myocardial disease. There is evidence that the increased diffusion distance from capillary lumina to the center of hypertrophied cardiac muscle fibers may result in hypoxia. If hypoxia is present at rest, local vasodilatation might occur. If so, when oxygen needs increase, there would be a limitation in the capacity to deliver additional oxygen to the myocardium.

The term primary myocardial disease may encompass a variety of disorders. In a recent study Henry et al. reported that resting coronary flows and oxygen consumptions were low in a group of patients with left ventricular dysfunction, including three subjects who would have met our definition of primary myocardial disease. Our six subjects did not have such findings and this may reflect etiological differences within this category of patient. However, in view of our observations, the possibility that alterations in the relationship between coronary flow and myocardial nutritional requirements may occur in some patients with primary myocardial disease should be considered.

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References


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