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 dispersion appearance 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. Cineventriculography 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 technique 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 µCi of 133Xe, 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 ¼ inch aperture. The probes were 99% efficient for 133Xe. The two probes were calibrated with a 133Xe 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 ml/100 g/min and \( k \), the clearance constant, is 0.6931/(half-time in minutes), \( \lambda \) is the myocardium-to-blood partition coefficient for \(^{133}\)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:

\[
\text{Total peripheral resistance (dyn-sec/cm}^4) = \frac{\text{mean aortic pressure (mm Hg)}}{\text{cardiac output (ml/min)}} \times 80 \times 10^4
\]

Coronary resistance/100 g of myocardium was calculated as:

\[
\text{Coronary resistance/100 g (dyn-sec/cm}^4\text{-100 g)} = \frac{\text{mean aortic pressure (mm Hg)}}{\text{coronary blood flow/(ml/min-100 g)}} \times 80 \times 10^4
\]

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 \( \mu \)g/min, was begun. If no heart rate response occurred the rate of the infusion was increased to 3 \( \mu \)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 1 |

Resting Hemodynamics and Changes Due to Isoproterenol

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<tr>
<th>Patient</th>
<th>LVEDP</th>
<th>EF</th>
<th>CO</th>
<th>HR</th>
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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 = aoritic pressure systolic/diastolic (mm Hg); TPR = total peripheral resistance (dyne/sec/cm\(^2\)); CBF = coronary blood flow (ml/100 g/min); CR = coronary resistance/100 g (\( \times 10^4 \) dyne-sec/cm\(^4\)/100 g); sd = standard deviation.

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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.\textsuperscript{7, 8} Although its accuracy in the case of primary myocardial disease...
Results have been shown that the myocardial oxygen consumption is directly related to the rate-pressure product. This relationship can be expressed as:

\[ \text{Myocardial oxygen consumption} = k \times \text{Heart rate} \times \text{Systolic blood pressure} \]

where \( k \) is a constant. The heart rate-pressure product is a measure of the myocardial oxygen demand, and it is calculated by multiplying the heart rate by the systolic blood pressure.

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 vasodilation 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 vasodilation, 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 un-
changed.
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 func-
tion, an alternate explanation is that during symp-
pathetic 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. 6
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 im-
paired 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 cor-
ony resistance can occur. If so, during basal condi-
tions, a relatively high percentage of the cardiac
output would be distributed to the coronary circula-
tion in some patients with primary myocardial disease,
and little or no redistribution to this region could oc-
cur 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 evi-
dence that the increased diffusion distance from capillary
lumina to the center of hypertrophied cardiac muscle
fibers may result in hypoxia. 10 If hypoxia is present at
rest, local vasodilatation might occur. If so, when oxy-
gen needs increase, there would be a limitation in the
capacity to deliver additional oxygen to the myocar-
dium.

The term primary myocardial disease may encom-
pass a variety of disorders. In a recent study Henry et
al. 11 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 obser-
vations, 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 con-
considered.

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References

1. Sones FM, Shirey EK: Cine coronary arteriography. Mod
Core Cardiovasc Dis 31: 735, 1962
2. Kasner IS, Kennedy JW: Measurement of left ventricular
volumes in men by single-plane cineangiography. Invest
Radiol 4: 83, 1969
3. Ross RS, Udina K, Lichtlen PR, Rees JR: Measurement of
myocardial blood flow in animals and man by selective injec-
tion of radioactive inert gas into the coronary arteries. Circ
Res 15: 28, 1964
4. Bonte FJ, Parkey RW, Stokely EM, Lewis SE, Horwitz LD,
Curby GC: Radionuclide determination of myocardial blood
5. Horwitz LD, Curby GC, Parkey RW, Bonte FJ: Differen-
tiation of physiologically significant coronary artery
lesions by coronary blood flow measurements during
6. Keyt SS, Schmidt CF: The nitrous oxide method for the
quantitative determination of cerebral blood flow in man:
Theory, procedure and normal values. J Clin Invest 27: 476,
1948
7. Katz LN, Feinberg H: The relation of cardiac effort to
myocardial oxygen consumption and coronary flow. Circ Res
6: 656. 1958
8. Robinson BF: Relation of heart rate and systolic blood pressure
to the onset of pain in angina pectoris. Circulation 35: 1073,
1967
9. Klocke FJ, Kasner GA, Ross J, Braunwald E: Mechanism of
increase of myocardial oxygen uptake produced by
10. Bishop SP, Aultschald RA: Evidence for increased glycolytic
metabolism in cardiac hypertrophy and congestive heart
failure. In Cardiac Hypertrophy, edited by Alpert NR. New
state and reduced myocardial oxygen consumption in the
human heart. Am J Cardiol 31: 300, 1973

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