Differentiation of Physiologically Significant Coronary Artery Lesions by Coronary Blood Flow Measurements During Isoproterenol Infusion

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 normal coronary arteries and normal left ventricular function, and eight patients with angiographically defined coronary lesions. 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. Resting values did not differ in the two groups. In the normal group isoproterenol increased mean coronary blood flow 93 ml/100 g/min (152%) and cardiac output 2.3 liters/min (42%); coronary resistance/100 g decreased 60 ± 4% (SEM), while total peripheral resistance decreased 29 ± 4%. In the coronary disease group coronary blood flow increased 20 ml/100 g/min (33%) and cardiac output increased 2.8 liters/min (62%); coronary resistance decreased 26 ± 9% and total peripheral resistance decreased 37 ± 4%. In all normal patients the percent increase in coronary blood flow markedly exceeded the percent increase in cardiac output and the percent fall in coronary resistance markedly exceeded the percent fall in total peripheral resistance. In six of the eight patients with coronary lesions the percent increase in coronary blood flow was less than the percent increase in cardiac output and the fall in coronary resistance was less than the fall in total peripheral resistance. Thus measurement of coronary blood flow, cardiac output, and aortic pressure before and during isoproterenol infusion may permit differentiation of those subjects with physiologically significant coronary obstructions.

Additional Indexing Words: Coronary artery disease Cardiac output Coronary resistance

Measurements of coronary blood flow at rest have usually shown no significant differences between normal subjects and patients with coronary artery disease. It has been suggested that technical limitations of available methods for quantitation of coronary flow may preclude detection of myocardial perfusion abnormalities due to coronary lesions. There have been few studies of the extent to which flow in diseased coronary arteries can increase in response to stress, and these have varied in their conclusions.

Isoproterenol is a potent coronary vasodilator which increases coronary blood flow, cardiac output, and myocardial oxygen consumption. The purpose of this investigation was to compare the effect of intravenous isoproterenol upon coronary blood flow in a group of patients with normal coronary arteries and a group with angiographically demonstrable obstructive coronary artery lesions. Coronary blood flow was measured by selective coronary artery injections of xenon-133 and external monitoring of myocardial disappearance curves.
with a highly-sensitive, dual-probe, digital scintillation counter system.

Methods

Fourteen patients were studied during diagnostic cardiac catheterizations. Each was in the fasting state and had been premedicated with meperidine 50 mg and promethazine 50 mg intramuscularly. A short polyethylene cannula was placed in the left brachial artery via a percutaneous needle puncture and catheters were inserted into the right brachial artery and vein through a cutdown. After measurement of right and left heart pressures, cardiac outputs were obtained with the dye-dilution technique, utilizing indocyanine green as the indicator. With the patient in the right anterior oblique position, cineventriculography was performed by power injection of 40 to 50 ml of meglumine diatrizoate into the left ventricle through a #8 NIH catheter. Selective coronary cineangiography by the Sones technique\textsuperscript{14} was performed in all subjects. A General Electric 9"-6" image intensifier system and 35-mm film exposed at 60 frames per second were employed for the cineangiograms. Multiple projections of each coronary artery were obtained. The films were reviewed by several observers who agreed they were of adequate quality for accurate morphologic diagnosis. Ventriculograms were analyzed for localized wall motion abnormalities\textsuperscript{15} and ejection fractions were obtained by planimetry of tracings made from end-diastolic and end-systolic frames.\textsuperscript{16}

After completion of the angiograms a 15-minute rest period was allowed. Previous studies indicate that this is an adequate period for recovery of effects of the angiographic contrast material.\textsuperscript{17} 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 with the patient lying flat. Immediately after the injection, the catheter was flushed with 4 ml of saline and withdrawn from the coronary orifice.

Disappearance curves of that portion of the injected \(^{133}\)Xe taken up by the myocardium were measured with 2 Picker 628-015 low-energy probes containing thallium-activated sodium iodide crystals 1.5 inches in diameter and 1/4 inch thick. These probes are 99% efficient for \(^{133}\)Xe and each has a cylindrical lead collimator with a 1-1/8 inch aperture.

The two probes were calibrated with a \(^{133}\)Xe source so that each gave identical counting rates at all counting rate levels applicable to this study. One probe was positioned vertically, directly over the fluoroscopically-determined center of the left ventricle. The other probe was placed over the right chest and angled outward at 20° from the vertical 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 2-channel pulse height analyzer with base set at 100, a window of 200, and a range set at 0.5 MeV 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 was measured from the electrocardiogram, aortic pressure was measured with a Statham P23Db transducer, and cardiac output was measured by the dye-dilution technique.

To obtain coronary flow the counts from the probe over the right lung were subtracted from the simultaneous counts over the left ventricle and the difference plotted against time on semilogarithmic paper. \( F = (k \cdot \lambda \cdot w)/\rho \) in which the clearance constant \( k = 0.6931/(\text{half-time in minutes}) \), \( \lambda \) = the myocardium-to-blood partition coefficient for \(^{133}\)Xe (0.7), \( w = 100 \), since the mass of myocardium perfused is unknown and by convention flow is expressed in terms of 100 grams of tissue, and \( \rho \) = 1.05, the specific gravity of myocardium.\textsuperscript{2,18}

Total peripheral resistance was calculated as:

\[ \text{Total peripheral resistance (dyne-sec/cm}^3\text{)} = \frac{\text{mean aortic pressure (mm Hg)}}{\text{cardiac output (ml/min)}} \times 80 \times 10^3 \]

Coronary resistance per 100 grams of myocardium was calculated as:

\[ \text{Coronary resistance/100 g (dyne-sec/cm}^3\text{–100 g)} = \frac{\text{mean aortic pressure (mm Hg)}}{\text{coronary blood flow/(ml/min–100 g)}} \times 80 \times 10^3 \]

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 obtained, an intravenous infusion of isoproterenol, 2 \( \mu \)g per minute, was begun. If no heart rate response occurred, the rate of the infusion was increased to 3 \( \mu \)g per minute. After 5 min or more, when a stable heart rate had been attained, the coronary flow, cardiac output, heart rate, and pressure measurements were repeated. In one patient with coronary artery disease (IE), a mild episode of angina occurred during the isoproterenol infusion just at the termination of the coronary flow measurement. No other untoward effects due to the experimental protocol were encountered.

On the basis of the coronary angiograms the patients were divided into two groups. A group of six patients, three men and three women aged 35–61 years, had no significant obstructive coronary lesions. They included four patients catheterized because of atypical chest pain in whom no cardiac abnormalities were detected, one patient (LL) with a prolapsed posterior mitral valve leaflet, and one patient (RT) with atypical chest pain who had an isolated distal stenosis of the first diagonal branch of the left anterior descending artery. All patients in this group had no wall motion abnormalities and an ejection fraction of at least 55%. In one patient in this group flows were obtained in both coronary arteries and the results averaged for statistical comparisons.

The remaining eight patients had either complete occlusions or stenoses of at least 70% of the cross-sectional area in one or more of the main left, left anterior descending, left circumflex, or right coronary arteries. They included four men and four women aged 39 to 64 years. Four had involvement of three major
vessels, two had involvement of two major vessels, and two had involvement of only one major vessel. The findings on the coronary angiograms and left ventriculograms in the eight patients with coronary artery disease are shown in table 1. Statistical comparisons were performed by comparing the two groups with the unpaired Student's t test.

Critique of Methods

There are several potential problems in the measurement of myocardial desaturation with a bolus of diffusible radioactive indicator. A suitable radionuclide and a sensitive radiation detecting system are necessary prerequisites. Detectors placed over the chest wall will measure changes in both the heart and the lung. It has been suggested that the indicator may not reach those myocardial regions with below average perfusion. Analysis of myocardial disappearance curves as a single exponential decline has been criticized. Cardiac adipose tissue may influence measurements with lipid-soluble tracers.

Xenon-133 is a lipidophilic, gamma emitter which is physiologically inert and freely diffusable. A major advantage is its rapid rate of excretion; 95% is removed from the blood in a single circulation through the lungs. However, counts are present in the lungs throughout the time of inscription of the myocardial disappearance curve, since the excreted Xenon is not instantaneously removed from the airways. Accordingly, since an external detector over the precordium cannot distinguish between myocardial and lung counts, it will overestimate the myocardial counts. As shown in figure 1, the lung counts are low the first 6-8 sec but then rise to a peak which subsequently subsides slowly. Thus, in the latter portions of the curve lung contamination can alter the shape of the washout curve. Therefore, we have subtracted the lung counts, obtained with a second sensor, from the precordial counts to more closely approximate a purely cardiac disappearance curve.

Most detector systems used previously for coronary flow measurements by the bolus disappearance method have included probes with a relatively low sensitivity for the radionuclide, have used analog recorders which make accurate plots on semilog paper more difficult, and have not used a pulse height analyzer to filter out scattered and background contamination. The high sensitivity of the digital system used in this study offered increased accuracy and accounts for the very low scatter of the data shown in figures 1-3.

It has previously been demonstrated that disappearance curves of 133Xe injected intramyocardially in regions with localized damage are approximated more accurately by multiple exponential curves than a single exponential curve. However, such regions, which may be supplied by both direct and collateral coronary flow, may well have much more disparate blood transit times than is typical for most myocardial tissue. In this study, a single exponential accurately described the curves to 15% of the initial count level. Below 15% it is difficult to evaluate the curves, since at this time much of the isotope is

Table 1

Findings on Angiography in Eight Patients With Coronary Artery Disease

<table>
<thead>
<tr>
<th>Patient</th>
<th>Coronary Lesions</th>
<th>Ventriculogram</th>
</tr>
</thead>
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<tr>
<td>GC</td>
<td>80% stenosis main LCA; total occlusion proximal RCA</td>
<td>Anterolateral and inferior hypokinesis; EF = 56%</td>
</tr>
<tr>
<td>LR</td>
<td>90% stenosis middle portion RCA; 50% stenosis proximal LAD</td>
<td>Normal wall motion; EF = 69%</td>
</tr>
<tr>
<td>RC</td>
<td>70% stenosis proximal LAD; total occlusion proximal RCA; 50% stenosis LCF marginal branch</td>
<td>Normal wall motion; EF = 70%</td>
</tr>
<tr>
<td>HR</td>
<td>Total occlusion proximal RCA</td>
<td>Apical akinesis; inferior hypokinesis; EF = 54%</td>
</tr>
<tr>
<td>DR</td>
<td>90% stenosis middle portion LAD; total occlusion middle portion RCA; 80% occlusion LCF marginal branch</td>
<td>Normal wall motion; EF = 74%</td>
</tr>
<tr>
<td>AL</td>
<td>Total occlusion proximal LAD; total occlusion proximal RCA; 70% stenosis distal LCF</td>
<td>Diffuse hypokinesis with apical paradox; EF = 18%</td>
</tr>
<tr>
<td>JH</td>
<td>90% stenosis proximal LAD</td>
<td>Anterior hypokinesis; EF = 59%</td>
</tr>
<tr>
<td>IE</td>
<td>80% stenosis proximal LAD; 90% stenosis proximal LCF; 80% stenosis proximal RCA</td>
<td>Hypokinesis distal anterolateral wall; EF = 63%</td>
</tr>
</tbody>
</table>

Abbreviations: LCA = main left coronary artery; LAD = left anterior descending coronary artery; LCF = left circumflex coronary artery; RCA = right coronary artery; EF = ejection fraction.
lodged in epicardial fat rather than in myocardium. Although it is likely that a slow myocardial component is present, it is apparently a small fraction of the total flow and difficult to detect by the bolus disappearance technique. Reports of substantial slow flow components with intracoronary injection may be influenced by failure to allow for lung counts as noted above.

It has been postulated that $^{133}$Xe injected into a coronary artery will preferentially enter normal regions and fail to enter diseased regions. If so, flow measurements would wholly or predominantly reflect flow only in relatively normal regions. However, using a multiple-crystal scintillation camera technique for estimation of regional flow, Cannon et al. have recently established that $^{133}$Xe does diffuse into diseased regions. Therefore, the disappearance curves measured in this study should reflect an average flow in both diseased and nondiseased regions of the left ventricular myocardium. Although subtle redistribution of flow could have been missed, the study was undertaken on the postulate that relatively large alterations in average left ventricular coronary flow would ensue and that significant differences between normal subjects and those with coronary disease could be expected.

**Results**

Figure 1 is a semilogarithmic plot of a disappearance curve in a patient with normal coronary arteries. Counts from each of the two probes are plotted separately and the estimated myocardial counts derived by subtracting the counts obtained with the probe over the lung from the simultaneous counts obtained with the precordial probe are also shown. Figures 2 and 3 are semilogarithmic plots of the myocardial disappearance curves at rest and during isoproterenol infusion in a subject with normal coronary arteries and a patient with coronary artery disease, respectively. In every
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subject, the myocardial disappearance curves in both states were closely approximated by a straight line on semilogarithmic plots, which indicates that the decrement in counts was well described by a single exponential term.

The upper portion of table 2 shows the individual and mean values in the six patients with angiographically normal coronary arteries. Coronary blood flow, cardiac output, heart rate, and aortic pulse pressure increased in all six patients during the isoproterenol infusion. The mean increase in coronary blood flow was 93 ml/100 g/min (152%) and the mean increase in cardiac output was 2.3 liters/min (42%). Total peripheral resistance and coronary resistance/100 grams both fell in response to isoproterenol. Total peripheral resistance decreased by 29% and coronary resistance by 60%.

The lower portion of table 2 shows the individual and mean values in the eight subjects with obstructive coronary lesions. During both control and isoproterenol states the mean cardiac output, heart rate, pulse pressure, and total peripheral resistance were similar to and not statistically different from the measurements in the group with normal coronary arteries. The coronary blood flow and coronary resistance/100 grams during the resting control periods were also not significantly different from the resting control values in the group with normal vessels. However, the increment in coronary blood flow with isoproterenol infusion was reduced and the mean coronary blood flow during isoproterenol infusion was significantly diminished (P < 0.01) in the subjects with coronary disease. In the coronary disease group the mean increase in coronary flow was 20 ml/100 g/min (33%) and the mean increase in cardiac output was 2.8 liters/min (62%). Total peripheral resistance fell by 37% and coronary resistance fell by 26%. The coronary resistance after isoproterenol was significantly less in the coronary disease group (P < 0.01).

Figure 4 illustrates the relationship between the percentage change in coronary blood flow and the percentage change in cardiac output in both groups. The line of identity represents those values at which the increment in coronary blood flow is equal to the increment in cardiac output. In all six of the patients with normal coronary arteries the

Table 2

Changes Due to Isoproterenol

<table>
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<tr>
<th>Patient</th>
<th>Coronary</th>
<th>CO</th>
<th>HR</th>
<th>APS/D</th>
<th>TPR</th>
<th>CBF</th>
<th>CR</th>
<th>CO</th>
<th>HR</th>
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<th>TPR</th>
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<td>125/55</td>
<td>960</td>
<td>53</td>
<td>12.0</td>
<td>10.1</td>
<td>118</td>
<td>125/55</td>
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<td>88</td>
<td>140/80</td>
<td>1040</td>
<td>78</td>
<td>10.4</td>
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<td>150/75</td>
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<tr>
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<td>110</td>
<td>125/66</td>
<td>640</td>
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<td>L</td>
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<td>73</td>
<td>120/65</td>
<td>1467</td>
<td>61</td>
<td>12.1</td>
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<td>720</td>
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<td>5.6</td>
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<tr>
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<td>2000</td>
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<tr>
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<td>1600</td>
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<td>8.8</td>
<td>9.5</td>
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<tr>
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<td>73</td>
<td>120/64</td>
<td>1530</td>
<td>61</td>
<td>11.3</td>
<td>7.3</td>
<td>102</td>
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<td>470</td>
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<td></td>
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</table>

Abbreviations: CO = cardiac output (liters/min); HR = heart rate (beats/minute); APS/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 grams (X 10³ dyne·sec/cm²/100 g); R = right coronary artery; L = left coronary artery; SD = standard deviation; P = p value for unpaired group comparison of control versus isoproterenol means; NS = P > 0.05.

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percentage increase in coronary blood flow markedly exceeded the percentage increase in cardiac output. In contrast, measurements in six of the eight patients with coronary artery disease exhibited a smaller percentage increase in coronary flow than the percentage increase in cardiac output.

Figure 5 illustrates the relationship between the percentage change in coronary resistance/100 grams and the percentage change in total peripheral resistance in both groups. The line of identity represents those values at which the decrement in coronary resistance is equal to the decrement in total peripheral resistance. In the six patients with normal coronary arteries the percentage decrease in coronary resistance markedly exceeded the percentage decrease in total peripheral resistance. In six patients with coronary disease the decrement in coronary resistance was less than the decrement in total peripheral resistance. These were the same six patients in whom coronary flow increased by a smaller percentage than cardiac output.

Discussion

In this study, as in previous reports, resting coronary flow measurements did not distinguish between patients with atherosclerotic coronary obstructions and those with normal coronary arteries. This apparent anomaly, whereby a condition caused by inadequate perfusion could not be detected by perfusion measurements, may reflect the low sensitivity of resting average coronary flow measurements to nonhomogeneous flow abnormalities, but could also reflect the ability of even severely diseased coronary arteries to maintain adequate flow for tissue needs at rest.

Nonuniform, localized regions with diminished flow in hearts involved by coronary artery disease have been demonstrated in anesthetized patients by direct intramyocardial injections of radioactive tracer, and confirmed in resting, conscious pa-

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**Figure 4**

Relationship between change in coronary blood flow and change in cardiac output. The percentage change in coronary blood flow due to isoproterenol is plotted as a function of the percentage change in cardiac output in six subjects with angiographically normal coronary arteries and eight subjects with angiographic lesions of a major coronary artery. An identity line which demarcates those points where the percentage increase in coronary blood flow is equal to the percentage increase in cardiac output is shown.

**Figure 5**

Relationship between change in coronary resistance and change in total peripheral resistance. The percentage change in coronary resistance per 100 grams of myocardium due to isoproterenol is plotted as a function of the percentage change in total peripheral resistance in the same subjects shown in figure 4. An identity line which demonstrates those points where the percentage decrease in coronary resistance is equal to the percentage decrease in total peripheral resistance is shown.
tients with a multiple crystal scintillation camera and intracoronary injection of tracer. However, the extent to which such heterogeneity of flow is abnormal has not been clarified, since considerable variation in local flow rates has also been noted in the hearts of normal subjects. The presence of regional variation in local myocardial perfusion rates may be a factor in the failure of most studies of resting measurements of total myocardial flow, or flow in major coronary arteries, to accurately differentiate patients with physiologically significant coronary artery obstructive lesions. It is also conceivable that relatively low flow rates sufficient to meet tissue needs at rest can be met by diseased vessels, although the ability to dilate in response to appropriate stimuli is limited.

Isoproterenol, by stimulating beta-adrenergic receptors and increasing myocardial oxygen consumption, induces vasodilatation of the coronary arteries. By increasing both heart rate and stroke volume, isoproterenol augments cardiac output consistently.

As illustrated in figure 4, in normal subjects isoproterenol resulted in increases in coronary flow which substantially exceeded the increases in cardiac output. The increment in coronary flow in this group is probably due partially to a redistribution of flow whereby a greater proportion of the total cardiac output enters the coronary system. However, in six of the eight patients with angiographic evidence of coronary obstruction the percentage increase in coronary flow was less than the increase in cardiac output. In these individuals there may have been an unfavorable redistribution of flow which resulted in a reduced proportion of the total cardiac output entering the coronary system during isoproterenol infusion.

This variation in flow patterns may indicate differences in capacity of the coronary resistance vessels to dilate in response to isoproterenol. As shown in figure 5, normal subjects exhibit greater percentage decreases in coronary resistance than in total peripheral resistance, probably because of selective vasodilatation induced by beta-adrenergic stimulation. In contrast, in six patients with coronary artery disease the calculated decrease in coronary resistance was slight or absent and less than the decrease in total peripheral resistance. A possible explanation is that, in these individuals, selective vasodilatation occurred in skeletal muscle and other organs but the coronary resistance vessels could not dilate as completely as occurred in the normal individuals. If so, the distinguishing feature of those patients with physiologically significant lesions could be the failure of the coronary resistance to decrease more than the total peripheral resistance with beta-adrenergic stimulation, reflecting impairment of coronary vasodilatative capacity by atherosclerosis.

However, caution is advisable in interpreting results in the patients with coronary artery disease. With imposition of the isoproterenol stress, changes in regional perfusion could have altered the mass of myocardium to which the tracer was distributed. If so, this would have influenced the estimates of coronary blood flow and resistance.

In two subjects with angiographic coronary lesions (RC and DF), the changes in coronary flow and resistance resembled those of the normal patients. Perhaps, despite the anatomic lesions, substantial portions of the diseased artery retained a normal functional capacity or development of vasoactive collateral channels permitted sufficient vasodilatation to lower coronary resistance to normal, or nearly normal, levels with isoproterenol infusion. Normal ejection fractions and hemodynamics were present in these two patients, an observation which suggests the perfusion defect may have been less severe than in others in this group. Alternatively, alterations in distribution of tracer could have influenced the measurements in these patients to a greater extent than in others.

It can be concluded that measurement of average coronary flow by the bolus radioactive disappearance technique, a simple, relatively inexpensive method which can be performed in a standard cardiac catheterization laboratory, before and during isoproterenol infusion, can provide information concerning the physiological significance of angiographic abnormalities of the coronary arteries. Such an assessment should include simultaneous measurements of coronary flow, cardiac output, and aortic pressure. Sensitivity to isoproterenol varies and a relatively small change in coronary resistance could be normal if total peripheral resistance changes were small. However, provided clear-cut evidence of a cardiac response to isoproterenol is present, i.e., increases in heart rate and cardiac output, a percentage decrement in coronary resistance which exceeds the percentage decrement in total peripheral resistance presumably indicates a normal coronary blood flow reserve capacity.

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