Myocardial perfusion after aortocoronary bypass surgery: measurements at rest and after administration of isoproterenol

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ABSTRACT This study examined quantitative regional myocardial perfusion (RMP) measured by the washout of $^{133}$Xe at rest and after an isoproterenol challenge in 50 patients (group I) studied 8 to 14 days after they underwent saphenous vein bypass grafting to the left coronary artery, and compared this with RMP measured in the native left coronary artery in 14 patients (group II) with significant coronary artery disease and in 12 normal subjects (group III). The double product of the heart rate and aortic systolic pressure was used as an indicator of demand. The statistical significance of group comparisons was analyzed with Dunn's multiple comparisons among means test. Analysis of the data showed no significant difference among the groups with respect to aortic systolic pressure. In subjects at rest, heart rate was lower in groups II and III than in group I, and double product was lower in group II than in group I. After isoproterenol, both heart rate and double product were lower in group II compared with groups I and III, but there was no significant difference between groups I and III with respect to heart rate or double product. Mean resting RMP in group II was lower than in group I; however, results of other group comparisons were insignificant for resting parameters. After isoproterenol, mean flow (ml/100 g/min) in group I was similar to flow in group III (130 ± 24 vs 139 ± 26). In contrast, the average flow response after isoproterenol was significantly less in group II when compared with that in group I (105 ± 20 vs 130 ± 24) and with that in group III (105 ± 20 vs 139 ± 26). Because of differences in levels of demand with isoproterenol, the change in flow was normalized to the percent increase in double product. These data showed results similar to those above, i.e., normalized RMP in patients with coronary artery disease was significantly lower than that in normal subjects (82 ± 41 vs 119 ± 57) and in revascularized patients (82 ± 41 vs 105 ± 54). However, there was no significant difference between normal subjects and patients who had undergone surgery. To further evaluate the relationship of flow response to demand parameters, we plotted RMP/double product vs resistance. The data revealed a significant correlation between these variables in all groups both in subjects at rest and after isoproterenol. For group III the slope of this plot, which represents the intensity of flow response to a unit change in resistance, was −0.81 in subjects at rest and −1.13 after isoproterenol. In group II this response was blunted (−0.59 at rest and −0.52 with isoproterenol). After myocardial revascularization (group I), the response returned toward normal (−0.81 at rest and −0.92 with isoproterenol). The data show that RMP improves in patients after revascularization when compared with that in patients with coronary artery disease and is similar to flow in normal control subjects both at rest and after an increased oxygen demand resulting from isoproterenol-induced stress. Normalizing the flow response to the degree of change in demand, as well as comparing the flow response to a unit change in resistance, elicited similar findings.


THE PURPOSE of coronary artery bypass grafting (CABG) is to restore myocardial blood flow to within normal physiologic limits. However, the vast literature evaluating CABG has dealt mainly with secondary results, such as relief of angina, improvement in left ventricular function, and increased longevity.1–6 Several recent studies have evaluated the degree of improvement in myocardial perfusion after CABG with noninvasive or indirect measurement techniques.7–9 Those in which $^{201}$TI imaging has been used have attempted to qualitatively demonstrate improved perfusion and/or to predict graft patency.10–12 More recently, attempts to analyze thallium scintigrams on a semi

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quantitative basis have been made with studies of subjects at rest, during exercise, or after a pharmacologic intervention.\textsuperscript{13-15}

Left ventricular function, as an indirect measure of perfusion assessed by resting and exercise radionuclide angiography, has shown an abnormal functional response to exercise in the patient with coronary artery disease and a return toward normal after successful revascularization.\textsuperscript{16-18}

Quantitative approaches to the measurement of coronary blood flow include clearance methods that use nitrous oxide,\textsuperscript{19, 20} hydrogen/helium,\textsuperscript{21} \textsuperscript{85}Rb,\textsuperscript{22} \textsuperscript{85}Kr,\textsuperscript{23} argon,\textsuperscript{24, 25} and \textsuperscript{133}Xe.\textsuperscript{26-29} Additional quantitative methods include coronary sinus thermodilution\textsuperscript{30} and videodensitometry.\textsuperscript{31, 32}

In patients with significant coronary artery disease, abnormal flow responses to the increased demand induced by atrial pacing\textsuperscript{33} and isoproterenol challenge\textsuperscript{34, 35} have been observed. In patients who have undergone surgery, resting flows have been measured by several techniques.\textsuperscript{36-39} The majority of studies, however, did not examine the ability of grafts to provide a normal flow response to increased demand. They also have not compared this response to that measured in the normal and diseased native artery. To our knowledge, only one study examined myocardial blood flow by the xenon technique; in this study of 20 postoperative patients flows were measured in only six during low-level exercise.\textsuperscript{40} Also, flows were measured in left anterior descending (LAD) and right coronary artery grafts, but not in the circumflex distribution of the left ventricle. In a previous study from our laboratory flow responses in saphenous vein and internal mammary artery grafts were compared after isoproterenol challenge and both of these were compared with flow in the normal circulation.\textsuperscript{41} However, in the previous study regional flow responses were not assessed (i.e., LAD and circumflex distributions) and graft flows were not compared with flows in patients with coronary artery disease.

The purpose of this study was to examine the ability of the saphenous vein bypass graft to increase myocardial blood flow to the anteroseptal and posterolateral walls of the left ventricle under the stress of an isoproterenol infusion and to compare this response with that in patients with significant coronary artery disease and that in patients with normal coronary arteries. A comparison between the patients with coronary artery disease and normal subjects was also made.

Methods

Subjects. For this study, 76 patients were evaluated in the Catheterization Laboratory at Mount Sinai Medical Center in Milwaukee, Wl. Fifty patients (group I) were studied 8 to 14 days after undergoing myocardial revascularization as a routine procedure to evaluate graft patency. Regional myocardial perfusion (RMP) was measured in 28 vein grafts placed to the LAD and in 22 vein grafts to a marginal branch of the circumflex artery. Another 14 patients were studied and found to have coronary artery disease. Flows were measured in eight patients who had disease of the LAD and circumflex arteries, in five patients with disease in the LAD only, and in one patient with circumflex disease only. Thus, a total of 22 regional flow measurements were made in these patients with coronary artery disease (group II). Twelve patients, studied for clinical indications, were found to have normal coronary arteries and normal left ventricular function (group III).

Procedures. Procedures for cardiac catheterization and measurement of RMP were explained to all patients and informed consent was obtained. \textbeta\text-superscript{-}Blocks were stopped 12 to 24 hr before catheterization. Patients in whom \textbeta\text-superscript{-}blockers could not be discontinued because of unstable angina were not included in the study. Patients who were off of \textbeta\text-superscript{-}blockers were also excluded if their heart rate responses to isoproterenol were inadequate, i.e., if they increased less than 20\% over baseline. Other medications such as nitroglycerin, vasodilators, digoxin, and tranquilizers were withheld for 6 hr before the study.

Each patient was brought to the catheterization laboratory while in a postabsorptive state and premedicated with 0.6 mg of atropine, 50 mg of pentobarbital, and 25 mg of promethazine. Coronary arteriography was performed with a modified Judkins technique.\textsuperscript{32}

After diagnostic arteriographic examination of the patients, flows were measured at rest and again after the infusion of intravenous isoproterenol at a rate of 4 to 8 \textmu g/min to produce an approximately 50\% increase in heart rate. Regional flow rates in the left ventricular myocardium were measured after the selective injection of 10 to 12 mCi of \textsuperscript{133}Xe into the native left coronary artery or saphenous vein graft according to the method previously described.\textsuperscript{37, 43, 44}

Briefly, the disappearance of radioactivity from multiple areas of the myocardium was recorded on a multicrystal scintillation camera (System Seventy-Seven, Baird Corporation, Bedford, MA) positioned over the chest with the patient in the left anterior oblique position. Counts of time data at each pixel were processed on-line with a DCC 116 minicomputer (Digital Computer Controls, Inc., Hudson, MA) interfaced with the System Seventy-Seven gamma camera. Using the method of least squares, the computer performed a monoeponential regression analysis on the data for the first 39 sec after peak count to obtain a slope (\kappa) of the washout curve for each pixel.\textsuperscript{45}

Figure 1 illustrates a semilogarithmic plot of log count vs time for the first 39 sec of washout obtained from one crystal. Myocardial blood flow (F) in ml/100 g/min was computed for each pixel according to the Kety-Schmidt formula as

\[ F = (\kappa) \times \frac{\lambda}{\rho} \times 100 \]

where \kappa represents the slope of the washout curve, \lambda equals the partition coefficient of xenon (0.72), and \rho is the specific gravity of the myocardium (1.05).

Data analysis. Selection of pixels for inclusion in the flow calculations was based on the four following criteria: (1) The pixels were within the marker borders. (2) The pixel with the highest peak count was noted (all other pixels had a peak count that was no less than 20\% of this maximum count). (3) The peak count for each pixel occurred less than 12 sec after the earliest peak time. (4) The standard deviation (calculated from regression analysis) was within 15\% of the flow in that pixel. These criteria rigidly defined acceptable computer-generated flows.
We also analyzed the interrelationships of flow, demand, and resistance. We examined flow/double product to make comparisons among patients who may be stressed to different levels of demand. We defined resistance as aortic diastolic pressure divided by flow per beat to normalize patient-to-patient variation in heart rate. Subsequently, RMP/double product was plotted against coronary resistance for both the resting and isoproterenol studies. Regression analysis was used to assess the relationship between these variables in the three groups of patients and we evaluated the slope obtained from regression analysis to assess the intensity of flow response to a unit drop in resistance.

**Statistical analysis.** We compared hemodynamic measurements, measurements of RMP, and those of RMP normalized to demand, in subjects at rest and during isoproterenol challenge, among the three groups with Dunn’s multiple comparisons among means test.\(^{57}\) Standard regression techniques were used for the analysis of flow per demand vs resistance.\(^{48}\)

**Criteria for a valid study.** Criteria for inclusion in the study were as follows: (1) coronary arteriogram, graft visualization, and ventriculography of diagnostic quality, (2) in patients in group II, a lesion of greater than 50% by visual interpretation of two observers, (3) in patients in group I, no significant stenosis in the graft anastomosis or the vessel distal to the graft, (4) a 20% increase in heart rate and double product and either an increase or no change in aortic systolic pressure after the isoproterenol infusion, and (5) valid computer-generated flows, as previously defined.

**Critique of methods.** Several advantages and limitations of measuring RMP with the \(^{133}\)Xe washout technique have been previously discussed at length.\(^{29,49}\) To our knowledge, \(^{133}\)Xe has been the most widely used indicator in clinical measurements of myocardial blood flow. Advantages of its use include the following: the procedure is performed easily during catheterization, xenon has a rapid washout from the heart so that the patient dose remains small, interventional studies can be performed with minimal background correction, and the calculation time is approximately 1 min, with further data processing requiring an additional 15 to 20 min per study.

Limitations in the measurement of blood flow with \(^{133}\)Xe include the questionable accuracy of the blood-myocardium partition coefficient in the Kety-Schmidt formula\(^{50}\) because this varies according to the amount of fat present in the heart. Also, the specific gravity of the heart varies according to the degree of ischemia or scarring in the myocardium. However, in this study both the resting and isoproterenol challenge measurements of RMP were obtained in each subject so that any relative flow differences caused by the above would be factored out. A recent study in our laboratory in 19 patients confirmed the reproducibility of the technique with a standard deviation of 6 ml/100 g/min for the left coronary artery.\(^{51}\)

Several problems of geometry exist, one being the representation of a three-dimensional structure by a two-dimensional image. Also, flows occurring in overlapping walls cannot be distinguished because each crystal detects the radiation originating from both walls beneath it. By placing the patient in a left anterior oblique position, a greater separation of the LAD and circumflex distributions is obtained; however, unquantifiable overlap may occur.

Another consideration involves the selection of the specific region to be used in the comparisons. Because xenon is highly diffusible, sufficient counts for flow measurement will generally be delivered to all areas perfused by a coronary artery or graft. Flow can, therefore, be measured in severely ischemic zones and the calculated values will not reflect the most highly perfused zones only. Two reported studies in animals in which microspheres and \(^{133}\)Xe were used to measure flow support this statement. In one study, flows at rest and after isoproterenol

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**FIGURE 1.** The washout of \(^{133}\)Xe from the myocardium. *Top.* The number of counts per second recorded by one crystal of the multicrystal gamma camera. *Bottom.* The plot of the natural logarithm of the counts as calculated by the computer. The slope is determined by linear regression from the first 39 sec of the washout and the flow is then computed with the Kety formula as described in the Methods.

On-line interfacing of the computer and the graphics system of the System Seventy-Seven allowed immediate production and inspection of functional flow images. After a native left coronary injection, the LAD and circumflex regional flows were determined by averaging the individual pixel flows in the area of the distribution of each vessel. Regional flows were used to provide more accurate comparisons with flows obtained in the aorta-to-LAD and aorta-to-circumflex graft distributions.

The double product of heart rate and peak aortic systolic pressure was used as an indicator of demand. Patients who had less than a 20% increase in heart rate or double product, or who had a drop in aortic systolic pressure with isoproterenol stress, as sometimes occurs in the volume-depleted patient, were excluded from the study.

Because individual patients were "stressed" to different levels of demand, we normalized flow (RMP\(_d\)) to demand. We divided the change in flow from rest to isoproterenol challenge (\(\Delta\)RMP) by the percent change in double product (\(\%\Delta DP\)) as follows:

\[
\text{RMP}_d = \frac{\Delta \text{RMP}}{\% \Delta \text{DP}}
\]

We chose to normalize flow by looking at the absolute change in flow from rest to a challenged state because use of a percent change in flow can have the effect of "penalizing" a good resting value and "rewarding" a poor resting flow. For example, a normal resting flow of 80 ml that increases, again normally, to 120 with isoproterenol, represents a 50% increase, whereas an abnormal resting value of 30 that increases to a still abnormal value of 60 with isoproterenol represents a 100% increase in flow. We did choose, however, to compare this absolute flow change to a percent change in demand because we were interested in how flow responds to a relative degree of increased demand in a particular individual.
challenge showed a close correlation (r = .74), although xenon-measured flows tended to be lower.\textsuperscript{52} When a coronary artery was ligated in dogs, flows in marginal and infarcted areas also correlated well (r = .73). In the second study, left ventricular and RMP rates obtained under conditions of varying heterogeneity of flow induced by partial coronary constriction and infusion of isoproterenol were studied.\textsuperscript{53} Perfusion distal to the constriction of the LAD was reduced up to 54%. In these animals, flow per unit mass as determined by \textsuperscript{133}Xe and by a radioactive microsphere technique correlated highly (r = .95, slope not different from unity). Regional flow rates were also highly correlated; however, \textsuperscript{133}Xe overestimated microsphere flow in ischemic areas distal to the coronary lesion by 10% to 15%. Collectively, the data support the utility of the \textsuperscript{133}Xe washout measurement technique for studies of patients with coronary artery disease.

**Results**

Table 1 is a summary of the mean hemodynamic and perfusion data, both in subjects at rest and after isoproterenol challenge, for the three groups. We have also listed mean data for the subgroups of LAD and circumflex distributions of subjects with normal (group III) and diseased (group II) native arteries for comparison with data on patients with LAD and circumflex grafts (group I).

Analysis of the data showed no significant difference between groups with respect to aortic systolic pressure. At rest, heart rate was lower in patients with coronary artery disease (group II) than in those with grafts (group I). Resting heart rate was also lower in normal subjects (group III) than in those with grafts for the major group comparison, but there was no significant difference for the subgroup comparisons. Resting double product was lower in group II than group I for the major group comparison and the LAD subgroup. There were no other significant group differences for the resting double product. After isoproterenol, heart rate and double product were lower in group II than in groups I and III for the major groups. For the subgroups the findings were similar, with the exception that mean double product in the patients with diseased circumflex arteries was not significantly different from that in patients with aorta-to-circumflex artery grafts.

Resting RMP in group I was the same as in group III. Resting RMP in group II was lower than that in group I, except in the circumflex subgroup. There was no difference in resting RMPs in groups II and III. The flow response after isoproterenol was not significantly different when comparing that in patients with grafts with that in normal control subjects. RMP after isoproterenol was significantly lower in patients with coronary artery disease than in normal control subjects and was also significantly lower in patients with coronary artery disease than in those with vein grafts, except in the circumflex subgroup. In this subgroup RMP was lower in the diseased artery than in the circumflex graft, but this difference did not reach statistical significance.

Results of a typical study in a patient with normal coronary arteries are shown in figure 2. There was a 108% increase in global left coronary flow. A typical study in a patient with two-vessel disease of the left coronary artery (figure 3) showed a lower increase in flow with isoproterenol. In contrast, a typical graft patient (figure 4) responded in a manner similar to the normal response.

Figure 5 illustrates the individual flow responses for the three major groups and the subgroups, and shows that flows in all patient groups increased after isoproterenol. The mean responses are also illustrated.

Table 2 summarizes the mean data for the change in RMP normalized to the percent change in demand.

| TABLE 1 |
| Mean hemodynamic and myocardial perfusion data |

<table>
<thead>
<tr>
<th>Group</th>
<th>Psys rest</th>
<th>Psys ISO</th>
<th>HR rest</th>
<th>HR ISO</th>
<th>DP rest</th>
<th>DP ISO</th>
<th>RMP rest</th>
<th>RMP ISO</th>
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<tr>
<td>I</td>
<td>50</td>
<td>134±29</td>
<td>139±28</td>
<td>85±12</td>
<td>118±11</td>
<td>11,297±2,956</td>
<td>16359±3,326</td>
<td>85±22</td>
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<tr>
<td>II</td>
<td>22</td>
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<td>73±9</td>
<td>100±8</td>
<td>9,463±2,169</td>
<td>14018±2,781</td>
<td>68±15</td>
</tr>
<tr>
<td>III</td>
<td>12</td>
<td>135±23</td>
<td>143±27</td>
<td>77±13</td>
<td>115±16</td>
<td>10,314±1,751</td>
<td>16211±2,766</td>
<td>76±15</td>
</tr>
</tbody>
</table>

LAD = left anterior descending coronary artery; Cx = circumflex artery; HR = heart rate (bpm); Psys = systolic aortic pressure (mm Hg); DP = double product (HR × Psys); RMP = regional myocardial perfusion (ml/100 g/min); ISO = isoproterenol.

\textsuperscript{4}Statistically significant within 95% confidence interval by Dunn's multiple comparisons among means test.

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There was a significant difference between flow response in normal subjects and that in patients with coronary artery disease. There was also a significant difference between patients who had undergone revascularization and those with coronary artery disease for the major group comparisons, but the difference was not significant in the subgroup comparisons. A comparison between group III and group I, however, showed no significant difference at all. We have also listed the percent change in double product, which

<table>
<thead>
<tr>
<th>TABLE 2</th>
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<tr>
<td><strong>Mean data for the correlation of flow to demand parameters</strong></td>
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<table>
<thead>
<tr>
<th>n</th>
<th>RMP</th>
<th>RMP/DP vs resistance</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Group I</td>
<td>50</td>
<td>105 ± 54</td>
</tr>
<tr>
<td>Group II</td>
<td>22</td>
<td>82 ± 41</td>
</tr>
<tr>
<td>Group III</td>
<td>12</td>
<td>119 ± 57</td>
</tr>
</tbody>
</table>

LAD subgroup

| Group I | 28 | 114 ± 52 | | 48 ± 22 | | 79 ± 22 | 66 ± 15 | .88 | .78 | -0.80 | -0.91 |
| Group II | 13 | 89 ± 49 | | 48 ± 12 | | 90 ± 29 | 69 ± 19 | .90 | .70 | -0.60 | -0.54 |
| Group III | 12 | 129 ± 64 | | 58 ± 19 | | 86 ± 19 | 62 ± 23 | .89 | .89 | -0.79 | -1.07 |

Cx subgroup

| Group I | 22 | 93 ± 55 | | 47 ± 18 | | 83 ± 27 | 68 ± 15 | .94 | .84 | -0.84 | -0.93 |
| Group II | 9 | 71 ± 25 | | 51 ± 13 | | 80 ± 28 | 69 ± 16 | .89 | .53 | -0.57 | -0.47 |
| Group III | 12 | 106 ± 48 | | 58 ± 18 | | 86 ± 18 | 66 ± 20 | .89 | .92 | -0.81 | -1.13 |

RMP = change in flow normalized to a percent change in double product (%ΔRMP); RMP/DP = regional myocardial perfusion (ml/100 g/min) per double product; other abbreviations are as in table 1.

*Statistically significant within 95% confidence interval by Dunn’s multiple comparisons among means test.

FIGURE 2. Data from a patient with a normal left coronary artery. There was a 108% increase in global RMP with isoproterenol (from 75 ml/100 g/min at rest to 156 ml/100 g/min after isoproterenol), with similar increases in subregional flows. LAD = left anterior descending coronary artery; Cx = circumflex artery; HR = heart rate; BP = blood pressure; DP = double product.

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shows that this change was significantly higher in group III compared with that in groups II and I. The subgroup comparisons yielded similar results, with the exception that there was no significant difference between the percent change in demand in group III and that in group II in the circumflex subgroup.

The plots of RMP/double product vs resistance for the three subject groups are illustrated in figure 6. We have also summarized the correlation data for these plots in table 2. There was no significant difference between groups with respect to coronary vascular resistance. We noted that there was a good correlation among the RMP/double product vs resistance values in all three groups, both in subjects at rest and after isoproterenol, with r values ranging between .64 and .91. The slope values, which represent the intensity of flow response to a unit drop in resistance, were interesting. In the normal patients (group III), slopes were -0.81 at rest and -1.13 with isoproterenol. In contrast, the slopes in patients in group II were blunted, i.e., -0.59 at rest and -0.52 with isoproterenol. After myocardial revascularization, group I patients showed slopes closer to normal values, i.e., -0.81 at rest and -0.92 with isoproterenol.

**Discussion**

This study confirms earlier reports of coronary blood flow measurements at rest and after demand is increased in normal subjects. In the patient with coronary artery disease, it confirms earlier work that demonstrated diminished coronary flow in the area distal to a 50% or greater stenosis with increased demand in these patients compared with that in normal subjects. Furthermore, the data indicate that after aortocoronary vein bypass surgery, the flow response allowed because of the vein graft is markedly improved compared with that in patients with coronary artery disease and is similar to that seen in normal subjects.

**Myocardial perfusion and coronary artery disease.** The major consequence of occlusive coronary atherosclerosis is myocardial ischemia, which results in angina pectoris and regional and/or global mechanical dysfunction that may progress to myocardial infarction and ultimately death. The objective of CABG is to restore adequate blood supply to ischemic areas of myocardium and thus relieve the effects of inadequate coronary blood flow. Studies in which indirect approaches were used have suggested that this occurs,

![Graph showing data for coronary artery disease](image-url)
but quantitative data from all regions of the myocardium are difficult to obtain. Radioactive inert gas wash-out techniques employed at the time of catheterization lend themselves to quantitative regional evaluation. The direct measurement of quantitative flow in the bed supplied by a vein bypass graft in patients at rest and after demand is increased should provide evidence that the physiologic response to increased demand after CABG approaches that seen in normal subjects.

Using the $^{133}$Xe method, Cannon et al. demonstrated in 1972 that resting myocardial blood flow was significantly lower in patients with two-vessel disease than in normal individuals. However, in only 50% of patients with single-vessel disease could a region of diminished perfusion be localized. In a later report this group evaluated a large patient population and reported that mean resting left ventricular perfusion was not significantly depressed in those with single LAD lesions or two-vessel lesions producing less than 50% occlusion, but that blood flow was reduced in patients with significant two-vessel disease. In the same laboratory, Schmidt et al. paced patients to a heart rate of approximately 150 beats/min and compared responses of those with normal coronary arteries or with lesions producing less than 50% occlusion with responses of those with lesions producing greater than 50% occlusion. It was found that although resting flow was the same in the two groups, flow with a pacing-increased heart rate was significantly less distal to a 50% or greater occlusion than in a normal artery. However, perfusion in the remainder of the left ventricle was no different than normal. After isoproterenol challenge Horwitz et al. also observed abnormal flow responses that were not identified at rest in patients with significant coronary artery disease.

Because of the results of these and other studies, we believed that resting flow would not be adequate to characterize the ability of the saphenous vein bypass graft to provide nutrient flow to the myocardium distal to a stenosis. We also chose to use isoproterenol stress because we found that it produced a greater flow response than pacing to the same heart rate, presumably because of the increased contractility caused by an isoproterenol infusion. The mean flow value obtained

**FIGURE 4.** Data from a patient with a graft to the left anterior descending coronary artery. The resting flow was 79 ml/100 g/min and increased to 133 ml/100 g/min with isoproterenol, a 68% increase. HR = heart rate; BP = blood pressure; DP = double product.
with atrial pacing in patients with insignificant disease has been reported to be 73 ml/100 g/min,\textsuperscript{33} whereas mean flow obtained in this study in normal subjects with the use of isoproterenol was 139 ml/100 g/min.

The \(\beta\)-adrenergic stimulation induced by isoproterenol results in positive inotropic and chronotropic responses. In normal muscle, it greatly increases contractile element velocity and length, with the macroscopic effect of increasing \(dP/dt\) and stroke volume.\textsuperscript{56} The increased contractility and heart rate serve to increase myocardial oxygen demand, which causes coronary vasodilation and an increase in coronary blood flow proportional to the contractile changes.\textsuperscript{34, 56} A study of experimentally induced ischemia in which radioactive microspheres were used to measure RMP showed a significantly decreased response in borderline and moderately ischemic areas compared with that in normal areas, while in severely ischemic or infarcted zones there was no increase in flow.\textsuperscript{53} This study and the previously cited study by Horwitz et al.\textsuperscript{34} demonstrate that regional myocardial perfusion measurements obtained with the use of isoproterenol in the catheterization laboratory may distinguish an adequately vascularized bed from a potentially ischemic bed that cannot meet increased flow requirements because of a flow-limiting coronary obstruction.

To date, however, we have not been able to show a correlation between flow and varying degrees of percent stenosis in individual patients. A subsequent

FIGURE 5. Individual flow responses in the three patient groups and subgroups at rest (R) and with isoproterenol (ISO). Top. Data from the patients who underwent myocardial revascularization (group I); middle, data from the patients with coronary artery disease (CAD) (group II); bottom, data from the normal subjects (group III). The left-hand column illustrates the major groups, the middle column the left anterior descending (LAD) subgroups, and the right-hand column the circumflex (Cx) groups.
study by Horwitz et al. reported a differentiation in flow based on different degrees of coronary artery stenoses ranging from 0 to 100%. On the basis of a recent study by White et al., in which they measured the reactive hyperemic response of coronary flow velocity intraoperatively with a Doppler flow transducer and found no correlation with the degree of coronary artery percent stenosis (as assessed by a caliper measurement of the coronary arteriogram), we would question these results.

In this study, the data showed that mean resting flows were lower in patients with coronary artery disease than in the patients who underwent revascularization. As expected, the flow response to isoproterenol was also lower in the patient with diseased arteries than in the CABG patient or in the normal control subject. The fact that there was no difference between the CABG patients and normal controls suggests that the surgery restores myocardial perfusion to nearly normal levels. When normalizing flow to demand, i.e., analyzing the change in coronary flow vs the percent change in double product, we found similar results. There was no significant difference between normal subjects and patients who underwent revascularization; however, there were significant differences between normal subjects and patients with coronary artery disease as well as between CABG patients and patients with coronary artery disease. The normalized flow value was somewhat lower in postoperative patients when compared with normal, although this difference was statistically nonsignificant. This suggests that the probable diffuse nature of coronary artery disease does not lend itself to complete revascularization.

The goal of assessing the significance of a lesion in the individual patient remains elusive. Although isoproterenol increases myocardial oxygen demand and

FIGURE 6. The data for all groups. Regional myocardial perfusion per double product (RMP/DP) is plotted on the vertical (y) axis vs resistance and diastolic pressure divided by flow per beat [Pdias/ (RMP/HR)] is on the horizontal (x) axis. Also listed are the linear regression equations for each plot for the resting and the isoproterenol (ISO) data. Top, data from group I; middle, the data from group II; bottom, data from group III. The left-hand column illustrates the resting data, and the right-hand column the ISO data.
increases perfusion more than does atrial pacing, it clearly does not cause maximal coronary dilatation. Its usefulness in the assessment of coronary reserve in disease states, such as coronary obstruction, is therefore suboptimal. Also, it enhances flow primarily by increasing contractility — a parameter we cannot measure with the use of double product as an index of demand. Maximum flows reported in humans are in the range of 200 to 400 ml/100 g/min. To assess the physiologic significance of a lesion, we need an agent for use in the catheterization laboratory that will produce a maximal flow response as well as a technique that will rapidly and reproducibly measure flows in the 200 to 400 ml/100 g/min range.

**The concept of flow/demand vs resistance.** Traditionally, coronary reserve is defined as the ratio of peak flow to control flow. It is theorized that the normal response of flow to increased demand should be linear. This is an accepted concept that has been corroborated by both canine and human studies. An ischemic response, on the other hand, has been conceptualized to be nonlinear, signifying that after a certain critical challenge flow will plateau and will not meet continued increasing demand. In general, this concept has also been supported by various other investigations and by our present study. However, some critical questions remain. (1) Will the coronary blood flow response in normal subjects remain linear if the demand is mediated by various means, e.g., exercise, pharmacologic intervention, or pacing? Some previous studies and this study show that this is not the case. (2) What is the value of the critical challenge? In other words, at what point would the flow plateau with increasing demand? It seems quite plausible that the value of the critical challenge should be an intrinsic one that would vary from one “normal” left ventricle to another.

With this in mind, we evaluated the correlation between regional myocardial perfusion and the demand parameters of peak systolic aortic pressure, heart rate, and double product. In studying all subject groups it was found that there was a poor correlation of flow with all three parameters in subjects at rest and after they received isoproterenol. However, it was of interest that the flow vs double product response followed two distinctly different lines in the resting and postisoproterenol states. This suggested to us that the flow response to different interventions may not be linear. Furthermore, coronary physiology suggests a complex relationship among flow, demand, and resistance. Autoregulation is defined as the ability to maintain constant coronary blood flow over a wide range of perfusion pressures. This is accomplished by varying resistance at the arteriolar level. It is not difficult to understand then that this phenomenon, i.e., varying resistance, is the same mechanism that regulates flow during increased or decreased metabolic activity or demand. This operates up to a point at which a flow-limiting stenosis, i.e., that greater than 50%, in a conductance vessel restricts flow.

Therefore, to study this relationship, we plotted flow per demand against resistance per beat as previously defined. As described earlier, the data revealed a significant correlation between these variables in all groups, at rest and after isoproterenol, with r values between .64 and .91. In plotting the resting data in the normal group, the linear function was defined as 

\[ y = -0.81 x + 144.85, \] 

which showed that flow per demand increased with decreasing values for resistance normalized per heart rate. This is acceptable physiologically. The slope, \( m = -0.81 \), was the measure of flow increase per unit drop in resistance, and thus defined the intensity of the flow response to the drop in resistance. The slope for the isoproterenol equation was \(-1.13\), which indicated that the intensity of the flow response was more vigorous when demand was mediated pharmacologically. The slope for patients with coronary artery disease, however, was blunted \((-0.59\) at rest and \(-0.52\) with isoproterenol), suggesting that flow in this patient group had leveled off despite increasing demand as a result of a flow-limiting stenosis in a conductance vessel. After revascularization these values improve toward normal \((m = -0.81\) at rest and \(m = -0.92\) with isoproterenol).

The values in patients after surgery (in which the fixed resistance had been bypassed) were not as high as the normal values, particularly with an isoproterenol challenge, which is consistent with pathologic data that suggest that coronary artery disease is a diffuse process that cannot be totally circumvented by placement of a saphenous vein graft.

In conclusion, our overall results indicate that RMP distal to aortic coronary bypass grafts to the anteroseptal and posterolateral walls of the left ventricle approaches that in normal arteries when an increased demand is produced by an isoproterenol infusion. Although the range of responses was wide, the group means revealed higher flow rates in the revascularized patients when compared with a similar group of patients with coronary artery disease. Similar findings were noted when flow was normalized to a change in demand and when the flow response was compared with unit change in resistance. The wide range of individual flow responses in both surgical and coronary artery disease patients was expected in light of the clinical
spectrum of patients that ranged from those with isolated lesions and normal ventricles to those with diffuse and/or multivessel coronary artery disease, previous infarction, and marked left ventricular dysfunction. This study shows that within the limits of the demand placed on the myocardium by an isoproterenol infusion to heart rates of approximately 35% over those at rest, the myocardial perfusion response distal to vein bypass grafts is not significantly different from that in normal subjects. Thus, in light of this and previous studies in patients with coronary artery disease, it appears that myocardial revascularization restores the response of myocardial blood flow to isoproterenol challenge to near normal levels.

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