Does coronary artery bypass surgery restore normal maximal coronary flow reserve?

The effect of diffuse atherosclerosis and focal obstructive lesions

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ABSTRACT Aortocoronary vein bypass surgery might not restore normal maximal coronary flow reserve to bypassed coronary vessels because residual diffuse coronary atherosclerosis might limit maximal hyperemia. To investigate the effect of diffuse atherosclerosis and a focal stenosis at the graft-coronary anastomosis, we measured coronary flow reserve with an extensively validated sub-selective Doppler catheter in 24 patients with 35 bypass grafts perfusing angiographically normal coronary vessels. The Doppler catheter was positioned in the midportion of the graft, and coronary flow reserve was measured as the peak/resting velocity ratio after selective graft injection of a maximally vasodilating dose of papaverine. Luminal dimensions of the bypass graft, graft-coronary insertion, and bypassed coronary vessel were measured by quantitative coronary angiography (Brown/Dodge method). Measurements of coronary flow reserve and coronary dimensions of vein bypass grafts were compared with similar measurements obtained from 13 patients with normal coronary vessels and normal myocardium. Seventeen of the 35 bypass grafts perfused unobstructed coronary–vein graft anastomoses (<50% area stenosis) and normal myocardium. The coronary flow reserve of these 17 bypass grafts was normal (5.0 ± 0.4, mean ± SEM) and not significantly different from that measured in normal arteries (5.1 ± 0.6), even though the cross-sectional area of the native coronary artery just distal to the bypass insertion was 40% smaller than in matched normal vessels. Bypass grafts perfusing hypertrophied (n = 2) or infarcted (n = 6) myocardium had significantly reduced coronary flow reserve compared with normal vessels (2.7 ± 0.3; p < .01), even when the infarcted wall had only minimal hypokinesis. In grafts perfusing normal myocardium, coronary flow reserve was significantly correlated with a minimum cross-sectional area of the graft at the point of coronary insertion (r = .77) and the percent area stenosis of the graft-coronary insertion (r = .77). All bypass grafts having lesions at the graft-coronary insertion producing less than 50% area stenosis or with greater than 2.0 mm² minimum cross-sectional area had normal coronary flow reserve. These results demonstrate that myocardial revascularization with an aortocoronary vein bypass graft restores a normal maximal flow reserve capacity to the perfusion field of the graft, provided that the graft perfuses a nonstenotic coronary vessel and normal myocardium. These findings suggest that moderate, diffuse coronary atherosclerosis does not significantly impair maximal coronary flow reserve. Moreover, quantitative angiographic measurements may be useful in predicting the functional significance of lesions at the graft-coronary anastomosis.


AORTOCoronary vein bypass surgery for obstructive coronary artery disease is an effective means of reducing or eliminating symptoms of myocardial ischemia.1,2 Additionally, many noninvasive mea-

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Measurements of cardiac function and provokable myocardial ischemia return to normal (e.g., exercise electrocardiography,1,3,4 thallium-201 scintigraphy,5 and exercise isotope ventriculography6). Several previous studies have suggested, however, that although successful bypass surgery improved coronary flow reserve in the perfusion field of the bypass graft, it does not restore it to normal levels.7–14 Many investigators have concluded that diffuse coronary atherosclerosis in the bypassed artery persistently impairs maximal flow reserve.

The magnitude of the contribution of diffuse atherosclerosis to coronary resistance is important. A prior study in patients with widespread coronary artery dis-
ease demonstrated that the reserve capacity of coronary vessels could not be accurately predicted by angiographic assessments of focal stenoses that compare the dimension of the stenosis to an adjacent "normal" portion of the coronary artery (i.e., percent area or diameter stenosis). This lack of correlation between percent arterial stenosis and the capacity of the artery to conduct hyperemic blood flow could result from the direct effects of diffuse coronary luminal narrowing (increased resistance to hyperemic flow) or from a masking of the severity of focal stenoses. If the former is true, then quantitative angiographic techniques for predicting the impact of individual coronary lesions on flow reserve must also account for the resistance produced by diffuse atherosclerosis. Conversely, if diffuse atherosclerosis merely masks focal lesions without itself increasing the resistance to hyperemic blood flow, then absolute measurements of coronary stenosis geometry might be useful in determining the physiologic importance of individual stenoses in patients with advanced coronary artery disease.

Many prior studies of coronary flow reserve in bypassed arteries may have been hampered by methodologic problems. The first measurements of flow reserve in vessels perfused by vein bypass grafts were obtained in the operating room soon after anastomosis of the graft and discontinuance of cardiopulmonary bypass. The effects of recent cardiopulmonary bypass with prolonged anesthesia, methodologic problems associated with measurement of graft blood flow, and nonstandard techniques of producing distal arteriolar vasodilation, however, probably resulted in a significant underestimation of the postoperative flow reserve capacity of the perfusion field supplied by the bypass graft.

The late postoperative flow reserve capacity of vein bypass grafts has been measured in the cardiac catheterization laboratory with xenon-133 scintigraphy and digital subtraction angiographic measurements of myocardial blood flow. Some investigators using these methods suggest that bypassed coronary vessels have a diminished flow reserve capacity, while others have found that flow reserve returns to normal after surgery. Unfortunately, methodologic problems in the measurement of coronary flow reserve, submaximal techniques for producing coronary vasodilation, or inclusion of patients with abnormalities in the myocardium that, independent of atherosclerosis, reduce flow reserve (e.g., infarction, hypertrophy), have hampered each of these studies. As a result, a reduction in coronary bypass graft flow reserve observed in such patients might have resulted entirely from underestimation of maximal hyperemic blood flow or an abnormal distal arteriolar bed rather than from diffuse atherosclerosis.

The recent development and validation of a small coronary Doppler catheter along with characterization of the dose-response kinetics of intracoronary papaverine in conscious humans have enabled accurate repeated measurements of maximal coronary flow reserve in conscious humans undergoing cardiac catheterization. The purpose of this study was to determine whether aortocoronary vein bypass grafts restore normal maximal coronary flow reserve and whether quantitative angiographic measurements of arterial dimensions could be used to predict the flow reserve capacity of bypassed vessels.

Methods

Patient selection

Patients with aortocoronary vein bypass grafts. Twenty-four patients who had previously undergone aortocoronary vein bypass surgery and subsequently underwent diagnostic coronary angiography for the evaluation of a chest pain syndrome were selected for study. In these 24 patients, 35 vein grafts were studied. Each vein bypass graft supplied a single, angiographically normal-appearing coronary vessel (<50% area stenosis at any point, excluding the vein graft–coronary insertion). In every patient, the native coronary vessel was occluded proximal to the graft insertion site and did not receive or provide angiographically visible collateral blood flow. Consequently, the vein bypass graft was the dominant source of perfusion to the bypassed coronary vessel. All patients were studied 2 or more months after bypass surgery (mean 3.9 ± 0.8 years, range 2 months to 10 years). Most patients had severe multivessel coronary artery disease and multiple vein grafts.

The vein bypass grafts were divided into two groups. One group consisted of 17 vein bypass grafts in 13 patients, which perfused an angiographically normal distal coronary artery (less than 50% area stenosis at any point, including the vein graft–coronary insertion) and normal myocardium. Additionally, there were no identifiable abnormalities that might have reduced arteriolar vasodilator capacity. The ventricular wall perfused by the bypass graft was shown to have normal motion by either contrast or equilibrium radionuclide ventriculography. Left ventricular hypertrophy was excluded by M mode and cross-sectional echocardiography (left ventricular wall thickness less than or equal to 1.1 cm) or by rapid acquisition computed axial tomography (left ventricular mass <130 g/mm²). Finally, there was no historical or electrocardiographic evidence of infarction in the myocardium supplied by the bypass graft. Myocardial infarction was defined by (1) a clinical history of infarction with an elevation of total serum creatine kinase to threefold the upper limit of normal with increased creatine kinase MB fraction, (2) classic evolutionary electrocardiographic changes (with or without development of Q waves), (3) an electrocardiogram showing pathologic Q waves of greater than 0.4 sec duration, or (4) a focal wall motion abnormality demonstrated by contrast or equilibrium radionuclide ventriculography.

The second group comprised 18 vein bypass grafts in 14 patients, which perfused previously infarcted (n = 6) or hypertrophied myocardium (n = 1), or with a stenosis at the graft insertion site (greater than 50% area stenosis by quantitative
angiography; n = 9). Two additional grafts that had a coronary insertion stenosis also perfused infarcted (n = 1) or hypertrophied (n = 1) myocardium. Left ventricular hypertrophy and myocardial infarction were defined by the criteria described above.

Patients with normal coronary vessels. Measurements of flow reserve and arterial lumen caliber obtained from patients with vein bypass grafts were compared with similar measurements obtained by identical techniques from 13 patients with normal coronary vessels perfusing normal myocardium, who were undergoing coronary angiography for the diagnosis of a chest pain syndrome. In these normal patients, hypertrophy and infarction were excluded as described above. Data obtained from 10 of these patients have been previously reported.25

Informed consent was obtained from each patient for the flow reserve studies. All studies were approved by the Institutional Review Board of the University of Iowa or the University of Minnesota.

Catheterization protocol

Patients with aortocoronary vein bypass grafts. Patients were brought to the catheterization laboratory in a fasting state. Although a variety of premedications were given, no patient received atropine. After administration of nitroglycerin and completion of diagnostic coronary angiography, angiograms of each vein bypass graft and distal native coronary vessel studied were obtained in orthogonal projections. A low dose intravenous infusion of nitroglycerin was initiated (8 µg/min). Each graft was cannulated with a No. 8F femoral coronary guiding catheter (USCI, Bard, Inc.). A No. 3F 20 MHz coronary Doppler catheter (Cardiovascular Bioengineering, University of Iowa) was advanced through the guiding catheter into the midpoint of the graft. Validation studies of this coronary Doppler catheter performed over a wide range of coronary blood flows (0.1 to 5.7 × resting flow) have been previously published.28 The catheter position was adjusted to obtain an acceptable signal of phasic graft blood flow velocity. The 20 MHz pulsed Doppler meter (Bioengineering Department, University of Iowa Hospitals and Clinics, University of Iowa) was range gated to obtain maximal intragraft blood flow velocity. Mean and phasic signals of graft blood flow velocity (kHz shift), arterial blood pressure obtained via the guiding catheter, heart rate, and the electrocardiogram were continuously recorded on a multichannel Gould recorder. The arterial pressure waveform obtained from the guiding catheter was damped by the presence of the coronary Doppler catheter; consequently only mean arterial blood pressure could be accurately monitored.

After measurements of resting graft blood flow velocity, 4 to 8 mg of papaverine HCl (2 mg/ml 0.9% saline) was injected into the graft and the resultant increase in graft blood flow velocity recorded. To confirm that any dose of papaverine produced maximal hyperemia, an additional dose (2 to 4 mg larger than the prior dose) was administered and the resultant hyperemic response recorded. In 31 of 35 vein grafts studied (and in all vein grafts with peak/resting velocity ratio < 3.5), the guiding catheter was withdrawn from the coronary ostium at maximal hyperemic flow to exclude the possibility that the guiding catheter obstructed blood flow into the vein graft.

Patients with normal coronary vessels. After completion of diagnostic coronary angiography (including orthogonal angiograms of the left and right coronary arteries), low dose infusion of intravenous nitroglycerin (8 µg/min) was initiated. The coronary Doppler catheter was advanced through a No. 8F guiding catheter into the proximal portion of the right (n = 5), left anterior descending (n = 4), or circumflex (n = 4) coronary artery, and the position and signal were adjusted in a manner similar to that described above. Measurements of resting coronary blood flow velocity were obtained, and maximal coronary flow reserve was measured by means of incremental doses of intracoronary papaverine in a manner similar to that previously described.25

Coronary flow reserve analysis. Coronary flow reserve was calculated as the quotient of peak blood flow velocity (maximal mean kHz shift after administration of papaverine) and mean resting blood flow velocity. To characterize the change in coronary vascular resistance at maximal hyperemia, a minimal coronary vascular resistance index was calculated as the quotient of the mean aortic blood pressure at peak flow velocity (mm Hg)/peak blood flow velocity (kHz shift) and mean aortic blood pressure at resting flow velocity/resting blood flow velocity.

Quantitative angiographic analysis. In patients with vein bypass grafts, quantitative angiographic measurements (Brown/Dodge method) of graft dimensions were made (1) at the location of the Doppler catheter within the graft, (2) at the site of graft insertion into the coronary vessel, and (3) in the native coronary vessel immediately distal to the bypass graft insertion site. This technique has been described in detail elsewhere.28 Orthogonal angiograms were not available for three grafts, and consequently quantitative dimensions could not be calculated.

To compare the dimensions of bypassed coronary vessels and normal vessels, we also used quantitative coronary angiography to analyze the lumen caliber of the mid left anterior descending (immediately proximal to the second diagonal branch origin) and distal right coronary arteries (immediately proximal to the origin of the posterior descending artery) in six patients with normal coronary vessels having a dominant right coronary artery. We chose these two sites because they were common sites of vein bypass—coronary anastomosis. The lateral circumflex branches were also commonly bypassed, but the size of circumflex lateral branches was highly variable among patients, making a comparison between normal and bypassed vessel dimensions difficult. Each normal patient had received nitroglycerin before angiography.

Analysis of lumen caliber. We estimated the extent of diffuse luminal narrowing present in bypassed native coronary vessels by comparing the cross-sectional area of the bypassed vessel just beyond the point of vein graft insertion with matched segments of coronary vessels analyzed from angiograms obtained from the normal patients. The mid left anterior descending area in bypassed vessels (n = 11) was compared with that of normal vessels (midway between the first and second diagonal branches, n = 6). The bypassed distal right coronary area (n = 6) was compared with that of normal dominant right coronary vessels (n = 6) (immediately proximal to the origin of the posterior descending artery).

Statistical analysis. All data are presented as mean ± SEM. Differences in group means were tested by analysis of variance (Bonferroni's method). Regression coefficients were obtained by the quadratic regression method (Clinfo). A p value of less than .05 was considered statistically significant.

Results

Hemodynamics. Table 1 displays the mean aortic blood pressure and heart rate of each group. These important determinants of resting myocardial blood flow and coronary reserve were not significantly different between groups.

Coronary flow reserve in normal vein grafts perfusing normal myocardium. Coronary flow reserve measured in normal grafts perfusing nonstenotic vein graft–coronary insertions, angiographically normal distal coronary arteries, and normal myocardium (5.0 ± 0.4) was
nearly identical to that measured in normal coronary arteries (5.1 ± 0.6; table 1, figure 1). Likewise, the coronary vascular resistance index at maximal hyperemia was similar between the two groups (0.20 ± 0.01 and 0.20 ± 0.02, respectively).

The time from onset of papaverine injection until 90% of the eventual peak hyperemia was achieved varied widely but was significantly longer in bypassed vessels (20 ± 1 sec, mean ± SEM; range 14 to 29) than in normal coronary vessels (15 ± 1 sec, range 7 to 23 sec; p < .01 vs vein bypass grafts).

Flow reserve in normal vein grafts perfusing abnormal myocardium. Flow reserve was significantly reduced in normal bypass grafts perfusing hypertrophied or infarcted myocardium. The flow reserve averaged 2.7 ± 0.3 × resting flow in unobstructed vein grafts perfusing infarcted myocardium and was significantly less than the flow reserve measured both in grafts perfusing normal myocardium (p < .01) and in normal unby-passed coronary vessels (p < .01). Importantly, two patients who had previously suffered infarction, with only mild residual hypokinesis of the affected ventricular wall, had reduced flow reserve in the vein graft perfusing the infarcted myocardium (2.4 and 3.2 peak/resting velocity ratio). The flow reserve in the two grafts perfusing hypertrophied myocardium was also diminished (2.5 and 2.7 peak/resting velocity ratio).

Quantitative angiographic analysis of vein graft–coronary insertion cross-sectional area and coronary lumen caliper: effect on flow reserve

Relationship between coronary lumen caliper and flow reserve. The average cross-sectional area of the angiographically normal-appearing segment of bypassed native coronary vessels (just distal to the site of bypass insertion) was significantly smaller than the cross-sectional area of matched segments of coronary vessels studied in normal patients (figure 2, table 2). On average, the cross-sectional area of bypassed vessels was 40% (range 31% to 77%) less than that of matched segments in normal vessels. The cross-sectional area of bypassed coronary arteries (at the site of bypass insertion) perfusing normal myocardium, however, did not predict the flow reserve capacity of the vessel (r = .46, p = .26).

Effect of focal stenosis at the coronary insertion of coronary flow reserve

Minimum luminal area. In bypass grafts perfusing normal myocardium, the minimum cross-sectional area at the point of coronary insertion was correlated with the flow reserve capacity of the bypass graft (r = .77, figure 3). Importantly, all vein bypass grafts with a minimum cross-sectional area over 2.0 mm² perfusing normal myocardium (n = 15) had normal flow reserve (> 3.5 peak/resting velocity), but seven of eight grafts with a minimum cross-sectional area under 2.0 mm² at the coronary insertion had a diminished flow reserve (mean 2.4 ± 0.3, p < .01 vs grafts with >2.0 mm² minimum cross-sectional area, figure 4).

Percent area stenosis. Measurements of the percent

![Figure 1](http://circ.ahajournals.org/Downloadedfrom)
area stenosis of the bypass graft at the point of coronary insertion were also correlated with flow reserve (r = .77, figures 4 and 5). Each of 17 bypass grafts with less than 50% area stenosis (including the insertion point) perfusing normal myocardium had normal coronary flow reserve. The minimum cross-sectional area (at the vein graft–coronary insertion) of these bypassed vessels with less than 50% stenosis ranged from 2.1 to 5.2 mm².

Seven of nine grafts with more than 50% area stenosis had diminished flow reserve. The minimum arterial areas at the vein graft–coronary insertion in the two patients with more than 50% area stenosis and normal flow reserve were 1.2 and 2.7 mm². The remaining grafts with more than 50% stenosis and abnormally low flow reserve had a minimum cross-sectional area of less than 1.5 mm².

Discussion

In this study, we have shown that myocardial revascularization with an aortocoronary vein bypass graft restores normal maximal flow reserve to the perfusion field of the graft, provided that it perfuses an angiographically normal-appearing coronary vessel and normal myocardium. If the myocardium supplied by the graft is hypertrophied or infarcted, or if a significant localized obstruction is present in the vascular system (graft, recipient vessel, or anastomotic site), then flow reserve may be diminished. Importantly, grafts with a stenosis at the coronary insertion had normal flow reserve if the minimum area of the insertion stenosis was over 2.0 mm² or if there was less than 50% area stenosis (compared with the adjacent coronary cross-sectional area).

Comparison with prior studies. Our results are in conflict with those of other investigators who found that flow reserve was diminished in perfusion fields supplied by aortocoronary vein bypass grafts. Several factors might account for the disparity in results. Previous studies in which measurements of coronary flow reserve were obtained immediately after cessation of cardiopulmonary bypass suffer from many methodologic problems. Hiratzka et al. have shown that cardiopulmonary bypass, in itself, markedly alters coronary hemodynamics and, in dogs, reduced coronary flow reserve from 4.4 ± 0.2 (peak/resting velocity ratio, mean ± SEM) measured preoperatively to 3.0 ± 0.3 15 to 20 minutes after cessation of cardiopulmonary bypass. Moreover, intraoperative measurements of graft flow reserve were usually obtained with an electromagnetic flowmeter placed intraoperatively. Problems with contact between the vessel studied and the flowmeter may result in artifactual changes in measured coronary flow. Consequently, studies performed immediately after bypass may yield inaccurate results that tend to underestimate flow reserve after recovery from surgery.

Other investigators have also reported that coronary flow reserve measured in patients undergoing cardiac catheterization months or years after bypass surgery remains depressed. These studies, however, may have been fraught with problems in patient selection and methodologic limitations in measurement of coronary flow reserve. Patients were often not rigorously screened for evidence of prior myocardial infarction or ventricular hypertrophy. Prior studies have demonstrated that infarction reduces coronary flow

| TABLE 2 |
| Quantitative angiographic dimensions of normal coronary arteries, unobstructed bypassed coronary arteries, and vein bypass grafts |

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<tr>
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<th>Cross-sectional area (mm²)</th>
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<td>Mid LAD</td>
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<td>Normal coronary</td>
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<td>Bypassed coronary</td>
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<td>Bypassed coronary</td>
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<td>Vein graft</td>
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LAD = left anterior descending coronary artery; RCA = right coronary artery.

*p < .05 vs normal coronary and vein bypass graft.
It is our experience that coronary flow reserve in a vessel perfusing previously infarcted myocardium may be impaired even when the infarction resulted in only a minimal regional wall motion abnormality. Many other factors can also reduce the vasodilator capacity of the arteriolar bed and, independent of the vascular supply, reduce flow reserve (e.g., chronic hypertension or cardiomyopathy). Prior inclusion of patients with these abnormalities that commonly coexist with atherosclerosis could have reduced the average flow reserve measured in vein bypass grafts.

Problems in measuring maximal flow reserve might also have hampered prior investigators’ studies of flow reserve late after aortocoronary bypass surgery. Scintigraphy has well-known limitations in measuring maximal hyperemic flow rates greater than 200 ml/min/100 g and thus tends to underestimate the magnitude of flow reserve. Coronary flow reserve measured in normal coronary vessels by digital subtraction angiographic techniques with iodinated contrast material as the vasodilator (2.59 ± 0.11, mean ± SEM) is significantly less than that measured in animals by an electromagnetic flowmeter (3.9 ± 0.9) or in humans by an intracoronary Doppler catheter (mean 3.5). Consequently, these methods might not presently allow investigators to accurately measure maximal coronary flow reserve.

Accurate assessment of maximal flow reserve requires the use of an agent capable of producing maximal coronary vasodilation. Prior studies often employed a submaximal vasodilatory stimulus (e.g., iodinated contrast material, isoproterenol). We used a dose of intracoronary papaverine, which we previously have shown to produce maximal coronary vasodilation. Moreover, an additional larger dose of papaverine was administered to be certain that maximal vasodilation had been achieved. Finally, we found that the time from vasodilator injection until peak hyperemia was longer in bypassed coronary vessels than in native coronary arteries. The probable explanation for this finding is that bypass grafts are generally longer and have a greater cross-sectional area than coronary vessels. Consequently, the transit time of the vasodilator from the vessel orifice to the microvasculature might be greater in bypassed coronary circulations. If measurements of hyperemic blood flow in vein grafts and native coronary vessels were obtained at the same time after vasodilator injection, hyperemic blood flow in bypass grafts may have been measured as flow was still rising, resulting in an underestimation of peak blood flow.

Potential methodologic limitations. There are several potential problems inherent in measuring coronary flow reserve in vein bypass grafts with a small Doppler catheter. First, the coronary Doppler catheter measures blood flow velocity in only a small portion of the stream. If the portion of the graft where flow was measured did not change linearly with respect to total

FIGURE 3. Relationship between the minimal lumen cross-sectional area at the point of coronary insertion and coronary flow reserve.

FIGURE 4. Left, Minimal cross-sectional area at the coronary insertion site in bypass grafts perfusing normal myocardium with normal (> 3.5 peak/resting velocity ratio) or abnormal (< 3.5) flow reserve. Right, Percent area stenosis at the coronary insertion site in grafts perfusing normal or abnormal coronary flow reserve.

FIGURE 5. Relationship between percent area stenosis of the graft-coronary insertion and coronary flow reserve in vein grafts perfusing normal myocardium.
blood flow within the graft, then the normally linear relationship between blood flow and blood flow velocity would not exist. In this study, however, we were careful to measure flow in the midportion of the graft. Preliminary studies by Freed et al.\textsuperscript{33} have shown that the flow velocity profile in the midportion of the vein bypass grafts is parabolic, resembling that in native coronary vessels. Additionally, we were able to adjust the sample window of blood flow velocity over a relatively wide range (about 1 to 2 mm) without significantly changing mean blood flow velocity measurements, suggesting that blood flow velocity was similar throughout the diameter of the graft.

A second potential problem in measuring flow reserve in grafts is that the guiding catheter used to position the Doppler catheter could have obstructed maximal hyperemic flow into the graft. To determine whether guiding catheter obstruction was present, we carefully withdrew the guiding catheter from the graft ostium in 31 of 35 vein grafts (and all grafts with less than 3.7 peak/resting velocity ratio) to ensure that it did not obstruct maximal hyperemic flow. In nine of these 35 vein grafts, a significant increase in hyperemic flow velocity was observed after withdrawal of the guiding catheter. Importantly, obstruction to maximal hyperemic flow velocity by the guiding catheter was not always associated with damping in arterial pressure measured from the guiding catheter lumen.

Implications. There are two important implications of this study. First, moderate diffuse coronary artery disease, known to be present in most patients with widespread coronary atherosclerosis and quantitated in the present study, did not significantly reduce maximal coronary flow reserve. Prior histologic studies have shown that patients with widespread coronary artery disease have diffuse thickening of the coronary arterial wall and obstruction of 30% to 60% of the normal luminal area in portions of the vessel that appear, angiographically, to be normal.\textsuperscript{34} Studies by McPherson et al.\textsuperscript{35} with high-frequency echocardiography have directly demonstrated diffuse thickening of the coronary arterial wall of angiographically normal vessels in patients studied intraoperatively during aorto-coronary vein bypass surgery. In our study, the average cross-sectional area of the mid left anterior descending artery of patients with obstructive coronary disease was only 54% of that measured in normal vessels by an identical technique. Even though 69% of the patients studied had severe three-vessel coronary artery disease and despite the diffuse luminal narrowing distal to the insertion of the vein graft, the flow reserve capacity of bypassed coronary arteries perfusing normal myocardium was identical to that of normal native coronary vessels. Hence, although diffuse coronary artery disease of the magnitude we observed may cause underestimation of the severity of a focal area of stenosis, it did not reduce maximal hyperemic flow. The lack of hemodynamic significance of the angiographically inapparent diffuse disease may be related to the location and total extent of luminal narrowing present in our patients. Although these patients were not preselected, coronary flow reserve might be impaired by more severe and more widespread diffuse narrowing than was present in these patients. The extent of diffuse luminal narrowing required to produce a physiologically significant diminution of flow reserve remains to be defined.

The second implication of this study is that focal obstructive lesions at the insertion of vein grafts into native coronary vessels must produce a moderate-to-severe reduction in lumen caliber (minimum vascular cross-sectional area <2.0 mm\textsuperscript{2}, >50% area stenosis) to reduce the flow reserve capacity of the bypassed vessel. Since the “normal” dimensions of bypassed coronary vessels vary widely, the minimum area of a very small branch could be less than 2.0 mm\textsuperscript{2} and yet the flow reserve would be normal if less than 50% of the vascular lumen area was obstructed. Conversely, an aneurysmally dilated vessel might have more than 50% area stenosis, but a cross-sectional area of more than 2.0 mm\textsuperscript{2} would suggest that the reserve capacity of the vessel would be normal. In patients with more severe diffuse coronary narrowing, however, percent stenosis measurements might be a less accurate predictor of the functional impairment in maximal coronary blood flow because the severity of a focal lesion might be minimized by the adjacent diffuse narrowing.

In two previous studies from our laboratory, measurements of coronary flow reserve have also been shown to correlate with the minimum coronary cross-sectional area.\textsuperscript{36, 37} In intraoperative studies, left anterior descending arteries with proximal stenoses of more than 3.5 mm\textsuperscript{2} minimal cross-sectional area were always found to have normal flow reserve. Studies performed during coronary angiography demonstrated that coronary vessels with lesions with more than 2.5 mm\textsuperscript{2} minimal area (located more than 1.5 cm from the coronary ostium) had normal flow reserve.\textsuperscript{37} Our finding in this study of normal flow reserve in more distal coronary vessels (e.g., mid left anterior descending) with minimal areas of over 2.0 mm\textsuperscript{2} at the point of bypass insertion is consonant with those prior studies. This is because the normal caliber of coronary vessels at the point of bypass insertion is significantly less than
that of the proximal left anterior descending coronary artery.

Finally, it should not be assumed that all lesions at the coronary insertion that produce either less than 50% area stenosis or with over 2.0 mm² cross-sectional area never result in myocardial ischemia. These studies were performed after coronary vasodilation with nitroglycerin. Coronary lesions are known to be dynamic. Lesions that do not result in functional obstruction when vasodilated might restrict increases in coronary blood flow if smooth muscle tone is augmented. However, in such patients, treatment with vasodilating agents might be more appropriate than anatomic correction of the coronary stenosis (e.g., coronary angioplasty or repeat coronary bypass surgery). Additionally, the normal dimensions of coronary arteries at the insertion of a bypass graft may be influenced by a variety of factors (e.g., sex, body size, coronary dominance, left ventricular mass) and the extent of diffuse luminal narrowing may vary widely between patients. Total reliance on absolute measurements of coronary dimensions should be tempered by these factors.

In summary, these studies show that aortocoronary vein bypass surgery restores maximal coronary flow reserve and suggests that mild-to-moderate diffuse coronary atherosclerosis does not impair coronary reserve. Moreover, these studies emphasize the utility of quantitative angiographic measurements in the interpretation of the coronary angiogram.

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