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Functional Evaluation of Internal Mammary Artery Bypass Grafts in the Early and Late Postoperative Periods

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Objectives. **We sought to determine whether internal mammary artery grafts adapt to an increase in myocardial flow demand and whether they restore maximal flow reserve.**

Background. **Although mammary grafts are now considered the graft of choice for coronary artery bypass surgery, there is still controversy about whether they can provide adequate flow at periods of peak myocardial demand.**

Methods. **Of 28 patients with a mammary graft anastomosed to the left anterior descending coronary artery, 15 were studied early (mean [±SD] 8 ± 2 days) and 13 late (19 ± 15 months) after operation by quantitative angiography and selective intravascular Doppler analysis at baseline, during pacing and after injection of papaverine and isosorbide dinitrate into the graft. Eleven patients with a normal left anterior descending artery served as control subjects.**

Results. **At baseline, mean graft diameter (2.39 ± 0.41 vs. 2.42 ± 0.45 mm) and bypass flow (38 ± 22 vs. 30 ± 12 ml/min) were similar in the early and late postoperative periods. Significant and similar vasodilation was observed in mammary grafts after administration of papaverine (+6 ± 5% vs. +9 ± 6%) and nitrates (+14 ± 7% vs. +16 ± 9%) both early and late after bypass surgery. Graft diameter increased during pacing late (+6 ± 3%, $p < 0.05$) but not early after operation. Bypass flow increased similarly during pacing in both groups, but maximal flow reserve induced by papaverine was significantly lower in mammary grafts studied early (2.70 ± 0.62) than those studied late (3.66 ± 0.81, $p < 0.01$) and in normal coronary arteries (4.05 ± 0.96, $p < 0.001$).**

Conclusions. **An increase in myocardial blood flow induced by pacing resulted in vasodilation of mammary grafts in the late but not in the early postoperative period. Significant vasodilation of mammary grafts after papaverine and isosorbide dinitrate administration was observed both early and late after operation. However, bypass flow reserve after papaverine injection was significantly lower in the early postoperative period but normalized over time. This finding seems unrelated to the conduit; rather, it appears to be related to the periphery and could be the result of injury to the microvasculature during operation.**

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Coronary artery bypass surgery is a widely used therapeutic measure for symptomatic coronary artery disease. The internal mammary artery is now considered the graft of choice because of its high long-term patency rate (1–3). Use of at least one mammary artery anastomosed to the left anterior descending coronary artery has resulted in a reduction in risk of late cardiac events and an improvement in survival (2–4).

However, there is still a controversy over whether mammary grafts can provide adequate flow supply at periods of peak myocardial demand (5–8). Mammary grafts are narrower and longer than saphenous vein grafts and might have greater resistance to coronary blood flow. Several methods have been used to evaluate the flow capacity of mammary grafts, including intraoperative graft flow measurements (9–14), implantable Doppler miniprobes (15), dye-densitometric techniques (16), digital substraction angiographic techniques (17) and myocardial scintigraphy (18–21), but the results remain controversial (22), mainly because of underestimation of bypass flow reserve by the technique used. In addition, clinical conditions suggesting inadequate perfusion by mammary grafts, mostly in the perioperative period, have been reported (6,23,24).

The development of quantitative angiography (25,26) and intravascular Doppler velocity analysis (27–31) has enabled accurate, repeated measurements of bypass flow. The first studies were limited by the size of the Doppler catheter (3F), which could impair the flow in the conduit (27). More recently a Doppler-tipped 0.018-in. (0.037-cm) diameter guide wire has been validated for accurate measurement of intravascular flow velocity (28–31).

In the present study we sought to determine whether mammary grafts can adapt to an increase in flow demand and thus restore the normal flow reserve capacity of bypassed vessels. Furthermore, we compared the adaptation of mam-

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Table 1. Clinical Characteristics of Study Patients

	LAD (n = 11)	Mammary Artery Graft	
		Early Postop (n = 15)	Late Postop (n = 13)
Demographic data*			
Age (yr)	59 ± 10	60 ± 10	59 ± 10
Gender (M/F)	5/6	15/0	8/5
Postop delay	—	8 ± 2 d	19 ± 15 mo
Risk factors			
Hypertension (%)	30	40	27
Diabetes mellitus (%)	0	13	18
History of smoking (%)	40	57	45
Cholesterol level (mg/dl)	280 ± 25	263 ± 55	259 ± 43
Hemoglobinemia (mg/dl)	13.8 ± 0.4	10.6 ± 0.6	14.8 ± 1.7*
Baseline heart rate (beats/min)	71 ± 11	81 ± 12	80 ± 10
Baseline blood pressure (mm Hg)	101 ± 8	82 ± 16	107 ± 13*
Angiographic data*			
% stenosis of LAD	—	77 ± 19	93 ± 11
Normal regional function	11/11	12/15	10/13
Extent of runoff (1–3)	3.0 ± 0.0	2.4 ± 0.7	2.6 ± 0.6
Vessel diameter (mm)	2.92 ± 0.54	2.39 ± 0.41	2.42 ± 0.45
IMA/LAD diameter	—	1.20 ± 0.12	1.34 ± 0.24
Baseline flow data			
Average peak velocity (cm/s)	28 ± 7	26 ± 10	22 ± 4
Diastolic/systolic velocity ratio	2.03 ± 0.72	1.43 ± 0.67	0.70 ± 0.20*
Flow (ml/min)	57 ± 22	38 ± 22	30 ± 12

*$p < 0.01$ versus internal mammary artery (IMA) graft at early postoperative (Early Postop) period. Data presented are mean value ± SD. F = female; LAD = left anterior descending coronary artery; Late Postop = Late postoperative period; M = male.

mary grafts in the early postoperative period with that of long-term grafts studied late after coronary artery bypass surgery. The grafts were investigated during a moderate increase in blood flow induced by pacing and after papaverine administration, which is known to induce a maximal increase in blood flow (32–34).

Methods

Patients. Twenty-eight patients with an internal mammary artery anastomosed to the left anterior descending coronary artery were studied during cardiac catheterization. Their clinical characteristics are shown in Table 1. The patients were investigated in the context of a postoperative angiographic follow-up study, and all were asymptomatic. Criteria for inclusion were an angiographically normal graft with good runoff and the absence of severe wall motion abnormalities in the revascularized areas. The extent of the revascularized area (runoff) was qualitatively graded from 1 (small runoff) to 3 (large runoff), depending on the number of diagonal branches arising from the left anterior descending artery and the length of these arteries. Fifteen patients were studied in the early postoperative period, just before hospital discharge, and 13 others in the late postoperative period, at least 11 months after operation. There was no difference in risk factors, regional function and quality of runoff between patients studied early versus late after operation (Table 1). Eleven patients with a normal left anterior descending artery who were investigated for atypical chest pain and underwent the same protocol served as the control group. All patients gave informed consent to the study, which was approved by the ethics committee of our institution. All vasoactive drugs were discontinued 1 to 2 days before the study.

Study protocol. Coronary angiography was performed by standard femoral approach. Selective injection of the native coronary arteries and grafts was performed by diagnostic 6F catheters. A projection for optimal visualization of the graft near the center of the 7-in. (17.8-cm) image-intensifier field was chosen, and all subsequent injections were performed according to standard quantitative angiography: calibration using the empty diagnostic catheter, unchanged single projection throughout the study and nonionic contrast medium (iohexol, 350 mg of iodine/100 ml). All angiography was performed with manual injection. After injection of a single bolus of 5,000 IU of heparin, a 0.018-in. (0.037-cm) Doppler guide wire (Flowire, Cardiometrics) was advanced through a 6F catheter into the initial portion of the graft and was adjusted until a good blood flow velocity signal was obtained. A 5F unipolar pacing wire was placed into the right atrium. Blood flow velocity, arterial blood pressure obtained through the coronary catheter and the electrocardiogram (ECG) were recorded throughout the study.

The time course of the study protocol was as follows: Measurements of coronary blood flow velocity at rest, as well

as a baseline angiogram, were first obtained at least 3 min after the last contrast injection. Two minutes later, heart rate was increased by atrial pacing to 130 beats/min. At the end of a 2-min period of pacing, blood flow velocity was recorded, and a second angiogram was obtained. Two minutes later, 12 mg of papaverine (2 mg/ml, 0.9% saline solution) was injected directly into the graft, and the resultant increase in blood flow velocity was recorded. At maximal hyperemia, a third angiogram was obtained. Important but asymptomatic ST segment changes were commonly observed after papaverine administration, and one patient experienced nonsustained polymorphic ventricular tachycardia (resembling torsades de pointe), as has been reported with papaverine (33,34). Three minutes after angiography with papaverine, when blood flow velocity had returned to baseline, 2 mg of isosorbide Dinitrate was injected directly into the graft. The resultant increased in blood flow velocity was recorded, and the last angiogram was obtained 1 min later. Heart rate and arterial pressure were measured immediately before each angiogram.

Quantitative angiographic analysis. Quantitative analysis of grafts was performed with an automated coronary analysis program with edge contour detection that was implemented at a Cardiac Work Station (Philips, Eindhoven, The Netherlands) connected to a Digital Cardiac Imaging System (DCI, Philips) at our catheterization laboratory. The first well opacified end-diastolic frame detected by simultaneous ECG recording was selected for analysis. The lumen diameter of the same vessel segment, identified by anatomic reference points at the level of the blood velocity recording, was measured by automated contour detection algorithms. Absolute dimensions were calculated by reference to the known size of the shaft of the empty catheter, measured 2 to 3 cm from the tip positioned within the ostium of the graft. The cross-sectional area of the graft was computed, assuming a circular cross section. The ratio between the graft diameter measured 2 to 3 cm proximal to the anastomosis to the left anterior descending coronary artery and the diameter of the left anterior descending artery at the level of the mammary anastomosis was also calculated in grafts early and late after bypass. Measurements of vessel dimensions were previously evaluated for precision and short-term variability in our laboratory in 22 patients by means of two angiograms obtained 3 min apart. The mean difference in lumen diameter measured from the two angiograms was 0.06 mm (2%), and the measurement variability (standard deviation of the mean difference) was also 0.06 mm.

Flow velocity measurements. All bypass flow velocity measurements with the Doppler guide wire (Flowire, Cardiometrics) were performed as previously described (31,35). In brief, the 0.018-in. (0.037-cm) guide wire has a 12-MHz piezoelectric ultrasound transducer at its distal tip and permits recording of flow velocity from the frequency shift between the transmitted and returning signals. Time-averaged and instantaneous peak velocity values are processed by a computer using fast Fourier transformation techniques that display a gray-scale depiction of all velocities recorded in the sample volume at one point in time. Bypass blood flow was estimated as previously validated by Doucette et al. (31) as the product of average velocity and cross-sectional area. Average peak velocity was calculated on-line by the system, and average velocity was derived as the average peak velocity/2, assuming a time-averaged parabolic velocity profile across the vessel (31). The diastolic/systolic peak velocity ratio was computed from the digitized spectral velocities from the average of three cardiac cycles. In the 11 control patients, we assessed the stability and reproductibility of velocity and flow measurements for 20 min during a similar protocol. Flow measurement variability between two measurements of blood flow at 20-min intervals was 4%, mainly as a result of variability in measurements of vessel dimensions, because velocity remained almost unchanged. Maximal bypass flow reserve was calculated as the ratio of peak blood flow after papaverine administration to blood flow at rest.

Statistical analysis. Results are expressed as mean value ± SD in text and Table 1; in the figures they are expressed as mean value ± SEM. Vessel diameters expressed in absolute values were compared for changes during pacing after administration of isosorbide dinitrate and papaverine using one-way analysis of variance for repeated measurements. Changes in grafts in the early and in late postoperative periods, as well as in normal control coronary arteries, were compared using a nonparametric Mann-Whitney-Wilcoxon test.

Results

Baseline characteristics. Mean heart rate was similar (81 ± 12 vs. 80 ± 10 beats/min), but mean blood pressure was lower by 25 mm Hg, early than late after bypass surgery ($p < 0.01$) (Table 1). Hemoglobinemia was also slightly lower in the early postoperative period (11 ± 1 vs. 15 ± 2 g/dl, $p < 0.01$). No significant change in mean heart rate or mean arterial blood pressure was observed after injection of nitrates or papaverine. Both groups of patients achieved a similar increase in mean heart rate during pacing, with no significant change in mean blood pressure. No difference in regional function or quality of runoff was observed between the two groups of patients.

Graft dimensions and average peak velocity were similar between the early and late postoperative periods. Diastolic/systolic velocity ratio was higher early after operation than later (1.43 ± 0.67 vs. 0.70 ± 0.20, $p < 0.001$) (Fig. 1). Bypass flow was slightly but not significantly higher early after bypass surgery than later (38 ± 22 vs. 30 ± 12 ml/min) (Fig. 2). Normal left anterior descending coronary arteries were slightly larger (2.92 ± 0.54 mm) than mammary grafts in the early (2.39 ± 0.41 mm) and late (2.42 ± 0.45 mm) postoperative periods, whereas average peak velocity was similar to that in mammary grafts. Accordingly, baseline flow, measured proximally in left anterior descending coronary arteries, was also higher (57 ± 22 ml/min) than that in mammary arteries, which were grafted more distally.

Quantitative angiographic data. Significant vasodilation during pacing was observed in mammary grafts (+6 ± 3%, $p < 0.001$ vs. baseline) (Fig. 3 and 4) in the late postoperative

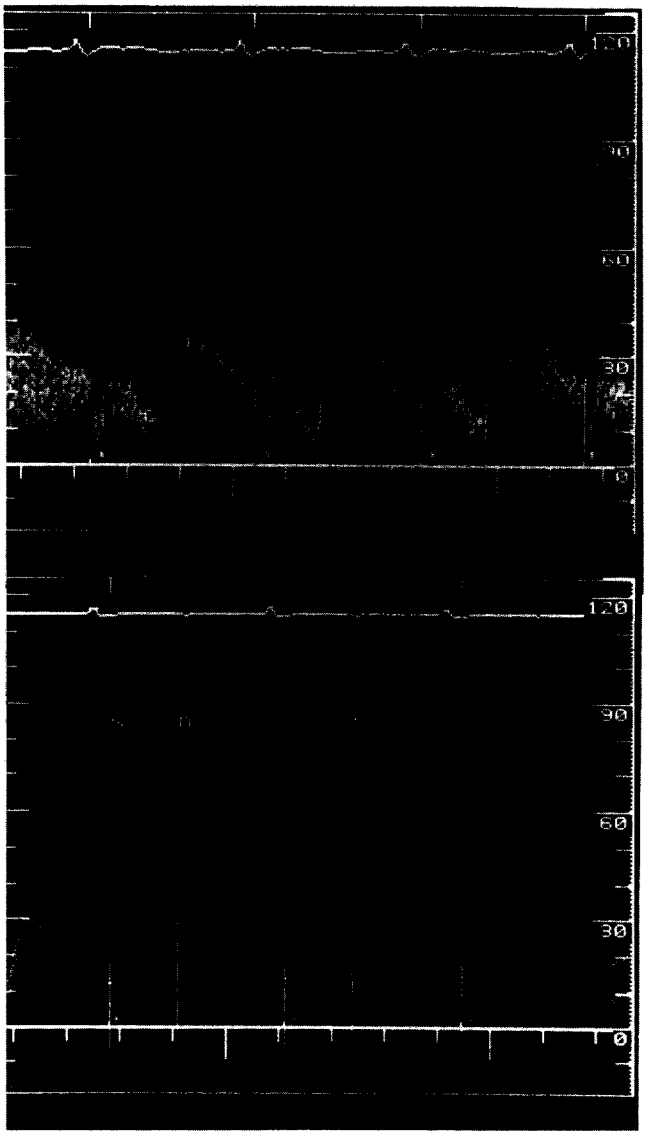

Figure 1. Typical recording of blood flow velocity in the proximal segment of mammary artery grafts in the early (**top**) and late (**bottom**) postoperative periods. Early after operation, flow was predominantly diastolic (D) but become predominantly systolic (S) late after operation.

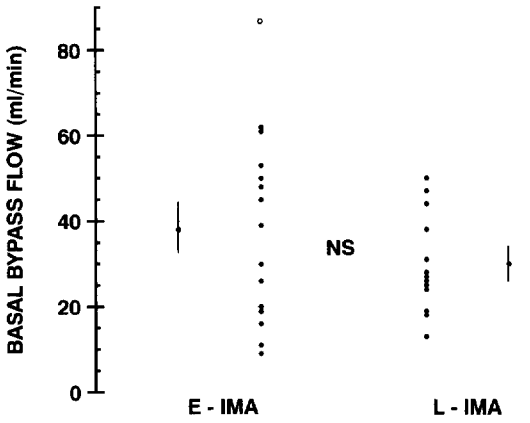

Figure 2. Comparison between baseline bypass flow in internal mammary artery (IMA) grafts in the early (E) and late (L) postoperative periods. Baseline flow was similar in the two groups. Early after bypass surgery, one patient (**open circle**) had unexplained very high baseline flow. His bypass flow reserve was also severely reduced. Except for this patient, no relation was observed between bypass flow and flow reserve.

period only. In normal coronary arteries, vasodilation was of borderline significance due to three patients with paradoxal vasoconstriction during pacing (Fig. 4). After papaverine, mammary graft diameters increased by 0.14 ± 0.10 mm early after surgery (+6 ± 5%, $p < 0.001$ vs. baseline) and by 0.21 ± 0.11 mm late after surgery (+9 ± 6%, $p < 0.001$ vs. baseline; p = NS for early vs. late vasodilation after papaverine) (Fig. 3). With isosorbide dinitrate, there was a similar increase in mammary graft diameters of 0.33 ± 0.14 mm (+14 ± 7%, $p < 0.001$ vs. baseline) and 0.36 ± 0.14 mm (+16 ± 9%, $p < 0.001$ vs. baseline) early and late after bypass surgery, respectively (Fig. 3). Vasodilation with papaverine and nitrates was slightly but not significantly higher in normal coronary arteries than in mammary grafts (+17 ± 15% and +25 ± 20%, respectively, both $p < 0.001$ vs. baseline).

Bypass flow data. After dye injection, flow velocity increased significantly less in mammary grafts in the early (+65 ± 25%) versus late (+105 ± 31%, $p < 0.001$) postoperative period. During pacing, flow velocity increased similarly early and late after bypass surgery (+24 ± 14% vs. +21 ± 8%, p = NS) (Fig. 5). Because vessel dimensions increased significantly in the late postoperative period only (Fig. 3), the increase in flow in mammary grafts during pacing was slightly higher late than early after operation (+36 ± 13% vs. +29 ± 16%, p = NS) (Fig. 5). However, the increase in flow during pacing was lower in mammary grafts early after operation than in normal coronary arteries (+44 ± 19%, $p < 0.05$) but was similar in mammary grafts late after operation and in left anterior descending coronary arteries. Flow velocity increased markedly but briefly with isosorbide dinitrate. In mammary grafts, maximal increase in velocity was also lower in the early than in late postoperative period (+182 ± 54% vs. 146 ± 33%, respectively, $p < 0.01$). However, at 1 min, velocity had nearly returned to baseline, and, essentially because of the net vasodilation observed (Fig. 3), bypass flow increased in mammary grafts by 38% and 51% early and late after operation, respectively ($p < 0.01$ vs. baseline; p = NS, early vs. late postoperative period). With papaverine, velocity in mammary grafts increased by 138 ± 48% in the early postoperative period, less than in the late postoperative period (+208 ± 49%, $p < 0.01$ vs. early after operation) and in normal coronary arteries (+196 ± 31%, $p < 0.025$ vs. early after operation and p = NS vs. late after operation) (Fig. 6). Accordingly, maximal bypass flow reserve was also very significantly decreased in mammary grafts at early versus late study (2.70 ± 0.62 vs. 3.66 ± 0.81, $p < 0.01$) and versus normal coronary arteries (4.05 ± 0.96, $p < 0.001$).

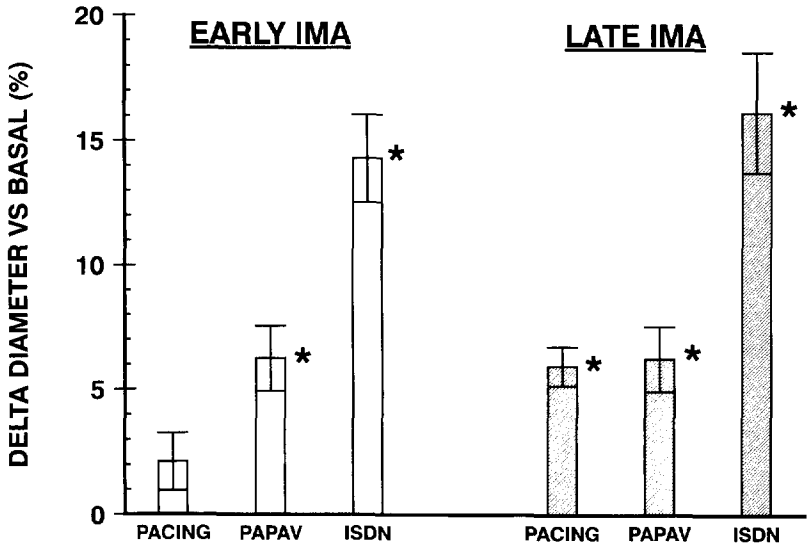

Figure 3. Comparison of change in diameter (DELTA DIAMETER) observed with pacing and administration of papaverine (PAPAV) and isosorbide dinitrate (ISDN) in internal mammary grafts (IMA) early and late after operation. *p < 0.01 versus baseline.

Discussion

Our data show that coronary artery bypass grafting with the internal mammary artery restores nearly normal flow reserve in the late but not early postoperative period (Fig. 6). Quantitative angiography, combined with intravascular Doppler imaging, allows assessment of whether grafts adapt to increased flow demand. During pacing, we observed that long-term, not short-term, mammary grafts also have the capacity to adapt their size dynamically to flow demand (Fig. 3 and 4).

Restoration of flow reserve by mammary grafts. Although mammary grafts are now used widely and increasingly, the problem of restoring normal hemodynamic performance in coronary artery bypass grafts is still unresolved (5–8). In the perioperative period, clinical conditions suggesting inadequate perfusion by mammary grafts have been reported (6,7,24,25) and are attributed to a disproportionate relation between flow and myocardial demand. Furthermore, Tedoriya et al. (8) used an animal model to show that mammary grafts could be less physiologically advantageous than grafts originating from the ascending aorta in their ability to supply blood to the predominantly diastolic coronary circulation. Diastolic flow was significantly lower in a pedicled mammary graft than in a graft emerging from the ascending aorta. Our results are in accordance with their finding because the diastolic/systolic velocity ratio measured proximally in our long-term mammary grafts was 0.70 ± 0.20 (i.e., predominantly systolic flow). Bach et al. (35) used long-term mammary grafts to show a similar, predominantly systolic pattern in the proximal part of the mammary graft but not distally, where they found a predominantly diastolic pattern. Surprisingly, in short-term mammary grafts, we found predominantly diastolic flow measured in the proximal part of the graft. The transition from a predominantly

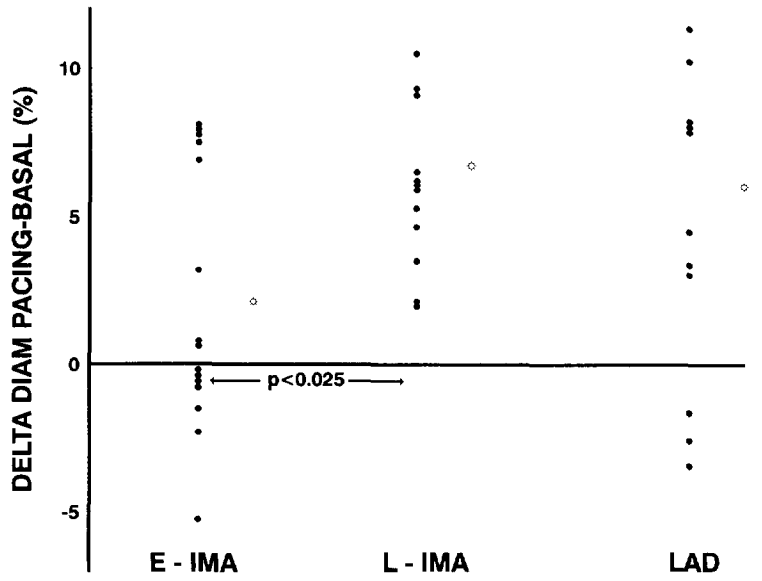

Figure 4. Individual data for increase in diameter (DELTA DIAM) of internal mammary artery (IMA) grafts with pacing early (E) and late (L) after bypass surgery and in normal left anterior descending coronary arteries (LAD).

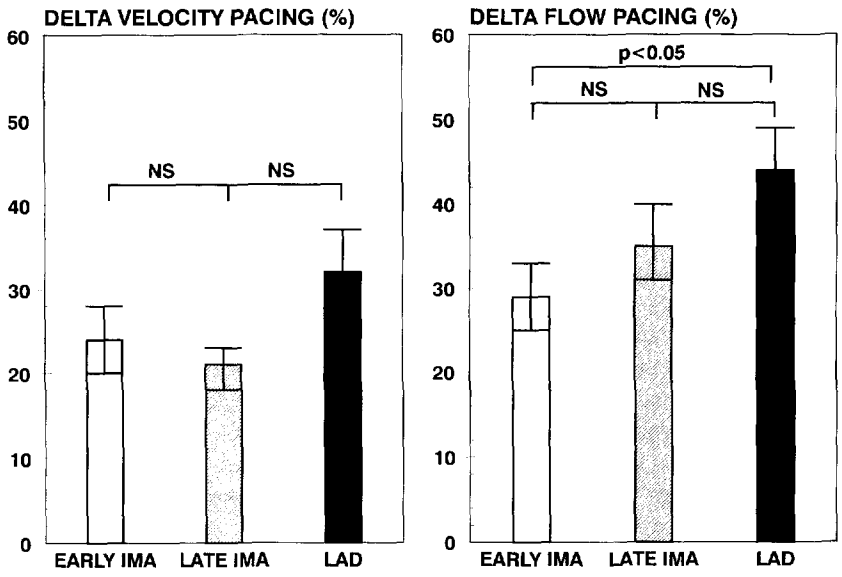

Figure 5. Comparison of change (DELTA) in velocity and flow (as percent of baseline velocity or flow) during pacing in internal mammary artery (IMA) grafts early and late after bypass surgery and in normal left anterior descending coronary arteries (LAD).

diastolic pattern in short-term grafts to a predominantly systolic pattern in long-term grafts might be related to differences in the intrinsic properties of the mammary artery wall (36) and in the elasticity of the walls of short- and long-term mammary grafts. However, to our knowledge, no experimental data are available to support this hypothesis.

Several perioperative studies (9–16) have shown that blood flow in newly anastomosed mammary grafts is lower than in vein grafts at rest or after ischemic reactive and pharmacologically induced coronary hyperemia. In contrast, other studies (17–21) performed later after bypass surgery have suggested that these alterations in blood flow are transient. They reported equal flow supply at rest and after stimulation in mammary grafts and in venous grafts or normal coronary arteries. However, studies of flow reserve late after mammary graft surgery have been hampered by methodologic problems, such as underestimation of bypass flow reserve, due either to the technique used to measure bypass flow or to the stimulus used to test flow reserve (22). Nevertheless, in a study by Kawasuji et al. (6) using radionuclide ventriculography monitoring during exercise, a higher proportion of patients had a decrease in regional left ventricular ejection fraction during exercise, suggesting inadequate flow for maximal demand in patients with a mammary versus a venous graft anastomosed to the left anterior descending coronary artery. However, these patients were studied 1 month after bypass surgery (in contrast to our patients who were studied at least 11 months after revascularization), and no data are available on the quality of the revascularization and runoff of the grafts. Dion et al. (4) reported a 7.4% incidence of abnormal findings on maximal stress thallium scintigraphy in 400 patients with bilateral mammary grafts and late angiographic controls, but many of

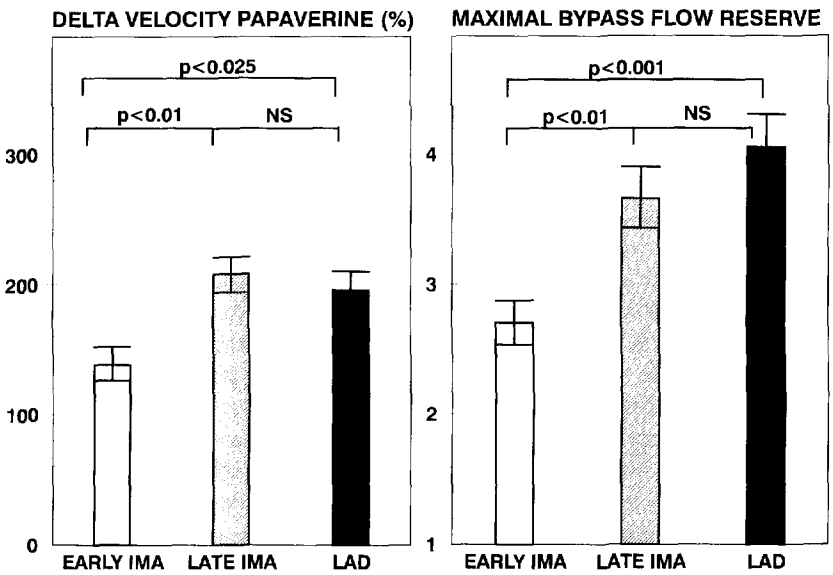

Figure 6. Comparison of change (DELTA) in velocity (as percent of baseline velocity) and maximal bypass flow reserve after papaverine injection (maximal flow after papaverine/baseline flow ratio). Abbreviations as in Figure 5.

the patients with abnormal stress thallium scintigraphic results either had an occluded graft or progression of native coronary artery disease.

In our study, flow was measured by quantitative angiography combined with intravascular Doppler imaging (31). This technique is accurate for measuring blood flow even over the range that can occur in normal coronary vessels and thus should not underestimate the increase in flow in our protocol. Maximal flow reserve was studied by selective injection of papaverine directly into the graft at a dosage sufficient to induce maximal vasodilation (32,33). Our results show that flow reserve was reduced in mammary grafts in the early versus late postoperative period and in normal coronary arteries (Fig. 6). Flow reserve, the ratio of maximal hyperemic flow to rest flow, depends on several factors (22,37) that must be considered in any attempt to clarify the mechanisms involved in the reduced flow reserve observed early after operation.

First, coronary blood flow at rest should be a true baseline flow and should be comparable among the different patients. In our patients, baseline flow was similar between the early and late postoperative periods (Fig. 2). Despite the finding that patients studied early were slightly anemic, which could increase blood flow (38), their blood pressure was lower than that in patients studied later, which could counteract this effect. Heart rate, another important determinant of myocardial blood flow, and one that can interfere with the reproducibility and variability of coronary flow reserve measurements (37), was not different between early and late mammary grafts.

Second, the characteristics of the bypass conduit have to be evaluated. However, in our patients there was no difference between short- and long-term grafts with regard to graft size, graft/coronary size ratio and vasodilatory response to papaverine (Fig. 3). Thus, it is unlikely that graft dimensions played a role in the difference in bypass flow reserve observed.

Third, the epicardial coronary arteries and myocardium revascularized by the graft must be comparable. Wilson et al. (22) demonstrated in saphenous venous grafts that restoration of normal maximal flow reserve only occurred in grafts perfusing a nonstenotic coronary vessel and normal myocardium. In their study, moderate diffuse coronary atherosclerosis did not significantly impair flow reserve. In the normal coronary circulation, blood flow is regulated more by the arteriolar bed, and epicardial coronary vessels provide little resistance to flow. In our patients, epicardial coronary arteries were free of significant stenosis distal to the anastomosis at both early and late study. All patients had severe narrowing or complete obstruction of the grafted left anterior descending coronary artery proximal to the anastomosis, thereby minimizing the risk of flow competition. In the early postoperative period, it is also difficult to exclude some degree of stunning still present after bypass surgery. The finding that bypass flow during pacing increased less in mammary grafts early after operation than in normal coronary arteries could favor this hypothesis of stunning, at least in some patients. However, there was no significant difference in regional function between grafts early and after operation. Thus, this cannot account for the profound difference in maximal flow reserve observed between mammary grafts early and late after bypass.

Fourth, many abnormalities of the microvasculature (30,39) may diminish maximal flow capacity independently of the hemodynamic performance of the bypass conduit and epicardial coronary artery (40–46) (e.g., previous myocardial infarction (40), ventricular hypertrophy (41,42) or prolonged hypertension (43). Hypertension and previous myocardial infarction were equally distributed between our two groups of patients, and no ventricular hypertrophy was present. The reduced flow reserve observed during revascularization could be a direct result of the effect of cardioplegia on the microvasculature, insufficient myocardial protection during cardiopulmonary bypass (47), embolization of thrombi or humoral agents elaborated from embolized thrombi, as has previously been shown in unstable angina (48,49), and possibly abnormal vasodilation of microvessels already at rest. In our study, baseline flow, graft conduit dimensions, epicardial coronary arteries and myocardium were apparently similar between the early and late postoperative periods. Our results therefore favor a reduced maximal flow reserve early after operation due to peripheral factors probably related to an impairment of the microcirculation rather than the capacity of the conduit itself.

Flow-induced vasodilation during pacing. Another important finding of our study is that mammary grafts can increase their diameter during pacing in the late postoperative period, in accordance with similar data obtained by Hanet et al. (50), By contrast, in the early postoperative period, mammary grafts do not show the ability to dynamically adapt their cross-sectional area to an abrupt increase in blood flow demand. Vasodilation during pacing allows the graft to increase its flow at lower velocities (Fig. 5). This could minimize the increase in shear stress and turbulent flow that promotes endothelial injury and atherosclerosis progression. Animal studies (51–53) have shown that increasing blood flow through normal arteries induced vasodilation mediated by the release of endothelium-deriving relaxing factor. This flow-induced vasodilation has been shown in different models in humans (50,54), including the coronary arteries of heart transplant recipients (55) and in free epigastric artery bypass grafts (56). The absence of innervation of the latter conduits favors local regulation, probably related by the endothelium. Although our data do not provide direct evidence that the release of relaxing substance by the endothelium is responsible for the vasodilation observed during pacing, this response is most likely the angiographic manifestation of flow-induced endothelium-dependent vasodilation, confirming a preserved endothelium function in long-term mammary grafts, as suggested by other studies (57–59). The lack of significant vasodilation during pacing in mammary grafts in the early postoperative period despite normal vasodilation with nitrates (not endothelium-dependent vasodilation) could represent endothelial dysfunction (54) that may have been temporarily caused by the harvesting of the conduit or by the mechanisms underlying the early adaptation of the conduit to its new function. Recovery of endothelial function could be an important factor contributing to the function and

patency of mammary grafts, to their protection against proliferation of atherosclerotic changes and to their ability to adapt dynamically to the requirements of the coronary circulation (60–62).

The lack of significant vasodilation in the coronary arteries of our control group during pacing shows that signs of abnormal endothelium function can be found even in angiographically normal coronary arteries (Fig. 4). Our control group comprised patients with high risk factors for atherosclerosis and with atypical chest pain who were referred for cardiac catheterization. Several studies (63,64) using quantitative angiography and acetylcholine infusion or cold pressor testing have reported a significant relation between risk factors, particularly cholesterol levels, and endothelium dysfunction. Despite similar increased risk factors, and in contrast to coronary arteries, long-term mammary grafts maintain normal endothelial function, as observed by Werner et al. (57) with acetylcholine. This could represent an important factor for the protection of the graft against atherosclerosis.

Study limitations. The limitations of quantitative angiography and intracoronary Doppler flow velocity measurements have been previously described (25,26,31,37). Use of the 6F catheter could result in some degree of obstruction of flow in the internal mammary artery. However, the same techniques were used in both short- and long-term grafts, allowing comparison of flow reserve between the two groups. Furthermore, flow reserve in long-term grafts was normal compared with that in normal coronary arteries with a catheter placed in the left main coronary ostium, another finding in support of the hypothesis of no or minimal obstruction. Other limitations of our study include the relatively small number of patients studied and the fact that the patients studied late after operation are not the same as those studied early. Nevertheless, flow reserve was markedly reduced early after operation compared with that in normal coronary arteries, and, by contrast, flow reserve in long-term grafts was found to be in the range of normal values. Another limitation is the existence of native anterograde flow in some patients, making it difficult to determine whether the increase in flow was through the graft or through the native coronary artery. However, all grafts were anastomosed to severely narrowed coronary arteries, half of which were totally occluded.

Conclusions and clinical implications. Quantitative angiography combined with intravascular Doppler velocity analysis appears to be a reliable technique for studying the hemodynamic performance of bypass conduits. From a functional point of view, our study confirms the excellent results with mammary artery grafts in coronary bypass surgery. These grafts are able to adapt their dimensions to flow demand, probably through a preserved endothelial function, at least in the late postoperative period. This enables them to adapt to blood flow requirements. The favorable vasomotor properties of mammary grafts are probably an important contributing factor to the excellent long-term clinical functional results observed in coronary artery bypass surgery. Furthermore, long-term mammary grafts can restore flow reserve to near normal levels. The reduced flow reserve observed in the early postoperative period seems to be related more to peripheral factors, such as an impairment of the microcirculation early after cardiopulmonary bypass than to the conduit itself. Clinically, the implantation of mammary grafts of adequate size (i.e., correct match of graft to coronary artery size) can be recommended, even in coronary arteries supplying a large territory, without unfavorable consequences.

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