Flow-Mediated Vasodilation During Pacing of the Free Epigastric Artery Bypass Graft Early and Late Postoperatively

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Objectives. **The free epigastric artery bypass graft is proposed as an alternative conduit to the saphenous vein graft, known for its high rate of attrition. The aim of our study was to assess its endothelial function in vivo.**

Background. **The endothelium of arterial bypass grafts plays a role in both the performance and the patency of such grafts.**

Methods. **We studied 73 epigastric grafts early (mean ± SD 10 ± 3 days) and 36 late (12 ± 5 months) after coronary bypass surgery with quantitative angiography at rest, after 2 min of atrial pacing (130 beats/min) and after injection of isosorbide dinitrate (1 to 2 mg) into the graft.**

Results. **At rest, mean epigastric graft diameter was lower in the late than in the early postoperative period (2.26 ± 0.39 vs. 2.61 ± 0.49 mm, $p < 0.001$). Early after operation, epigastric grafts with a small or an intermediate runoff, but not those with a large runoff, were capable of vasodilation with nitrates (+0.09 ± 0.10 mm). Late after operation, vasodilation after administration of isosorbide dinitrate was similar in epigastric grafts with a large runoff and in those with a small or intermediate runoff (+0.23 ± 0.09 vs. +0.23 ± 0.18 mm). Significant vasodilation during pacing was observed late (+4 ± 9%, $p < 0.01$) but not early postoperatively, except in a subset of patients with grafts capable of vasodilation after nitrates. A correlation between the response to nitrates and the response during pacing was observed early ($r = 0.579$, $p < 0.001$) and late postoperatively ($r = 0.530$, $p = 0.02$).**

Conclusions. **Flow-mediated vasodilation during pacing was observed in most epigastric grafts late, but not early, after operation. This endothelium-dependent dilation was correlated with the importance of the vasodilation observed with nitrates (endothelium-independent), which was related to the importance of the runoff only in the early postoperative period. The ability of epigastric grafts late postoperatively to dynamically adapt their dimensions to an acute increase in demand could contribute to the good functional results of this new alternative arterial graft.**

(J Am Coll Cardiol 1996;27:415–20)

An increase of blood flow through normal arteries results in vasodilation, induced by release of endothelium-derived relaxing factor, as shown in animal (1–4) and human (5–9) studies. This ability to adapt vasomotor tone to changes of myocardial flow demand is lost in the presence of atherosclerosis (5,6). Recently, Hanet et al. (7) showed that an increase in myocardial blood flow demand induced by pacing results in vasodilation of internal mammary artery grafts but not of saphenous vein grafts, late after coronary bypass surgery, confirming other data (10–13) showing a better endothelium function in mammary artery grafts than in vein grafts. Preservation of the integrity of the endothelium might be of importance with respect to both favorable functional results of the graft and late patency rate (14–16).

The inferior epigastric artery was recently introduced as an alternative conduit for coronary bypass surgery (17–19), especially in conditions of unavailability or unsuitability of the saphenous veins or in addition to mammary arteries in an attempt to achieve total arterial revascularization. Data recently obtained in vivo (20) showed that the inferior epigastric artery has a high endothelial capacity to release endothelium-derived relaxing factor. The present study was designed to evaluate in vivo the endothelium-dependent ability of free epigastric grafts to adapt their vasomotor tone to an increase in myocardial blood flow demand induced by rapid atrial pacing in the early and late postoperative periods.

Methods

Patients. Eighty-six patients (82 men, 4 women, mean age ± SD 59 ± 9 years) were studied during cardiac catheterization, performed in the context of an ongoing angiographic follow-up study (18,19). Angiographic exclusion criteria for the present protocol were diffuse or focal narrowing of the graft or poor runoff flow to the target vessel. All patients gave oral

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Manuscript received May 1, 1995; revised manuscript received August 24, 1995, accepted August 31, 1995.

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0735-1097/96/$15.00
0735-1097(95)00453-X

informed consent for this angiographic study, and the Committee on Human Research of our institution approved the study protocol.

The inferior epigastric artery, used as a free aortocoronary bypass graft as previously described (18), was anastomosed to the right coronary artery in 86% of cases (distal right coronary artery [n = 60], posterior descending artery [n = 12] and posterior left ventricular branch [n = 2]) or to a marginal branch of the left circumflex coronary artery in 12% of cases (n = 10). In two cases, the epigastric artery was anastomosed to a diagonal branch of the left anterior descending coronary artery.

Angiography was performed at two occasions: 1) in 73 patients, in the early postoperative period just before hospital discharge (mean 10 ± 3 days postoperatively), and 2) in 36 patients, in the late postoperative period, 1 year (mean 12 ± 5 months) postoperatively. Twenty-three of these 36 patients had both evaluations, early and late postoperatively.

Study protocol. Diagnostic coronary angiography was performed by standard femoral approach. All vasoactive medications were discontinued 1 to 2 days before the study. Selective injections of the native coronary arteries and of the grafts were obtained by diagnostic 6F catheters. The size of the areas revascularized by the epigastric graft (runoff) was qualitatively graded by an independent observer from 1 to 3 (small, intermediate or large), depending on the number of branches revascularized and their length (19).

After the diagnostic angiography, a 5F unipolar pacing wire was placed in the right atrium and a diagnostic 6F catheter was selectively positioned in the ostium of the epigastric graft. A projection for optimal visualization of the epigastric graft near the center of the image intensifier field (7 in. [17.8 cm]) was chosen, and all subsequent graft injections were performed according to the standards of quantitative angiography (21): calibration by using the empty diagnostic catheter, unchanged single projection throughout the study and nonionic contrast medium (iohexol, 350 mg iodine/100 ml). All angiograms were obtained by manual injection. At follow-up, the same projection used early postoperatively was used in the 23 patients who underwent both evaluations.

After an interval of ≥10 min after the diagnostic coronary angiograms, a baseline angiogram was obtained during sinus rhythm. One minute later, heart rate was increased by atrial pacing up to 130 beats/min for 2 min and a second angiogram was obtained as described by Hanet et al. (7,8). Pacing was stopped immediately after this angiogram. In nine patients, it was impossible to achieve a heart rate of 130 beats/min. In these patients, pacing rate was maintained just below the Wenckebach point (≥120 beats/min). Two minutes after the end of pacing, 1 to 2 mg of isosorbide dinitrate was injected into the epigastric graft and a third angiogram was obtained 1 min later. Measurements of heart rate and blood pressure were obtained just before contrast injections.

The quantitative analysis of the epigastric graft was performed with the help of a computer-based coronary angiographic analysis system (CAAS, Pie Data Medical, Maastricht, The Netherlands) (21). Since January 1992, the quantitative analysis has been performed with a similar system, directly implemented in the Digital Cardiac Imaging System (DCI, Philips, Eindhoven) of our catheterization laboratory. The first well opacified end-diastolic frame, detected by simultaneous electrocardiographic recording was selected for analysis. Lumen diameter of the same vessel segment, selected in the proximal part of the graft and identified with the help of anatomic reference points (side branches, clips placed during operation), was measured by using automated contour detection algorithms. The precision and variability of such measurements have been reported previously (22). The precision and short-term variability of measured vessel dimensions have also been evaluated in our laboratory, with similar results. Short-term variability of two angiograms obtained 3 min apart was studied in 23 patients. The mean difference in lumen diameter measured from the repeated angiograms was −0.03 ± 0.08 mm. The intraclass correlation coefficient was 0.994.

Statistical analysis. Data are expressed as mean value ± SD unless otherwise specified. Modifications of vessel diameters were studied by two-way analysis of variance for repeated measures (early or late evaluation; basal state, pacing or nitrate injection). Significant main or interaction effects were clarified by Student t tests with pooled error terms, using DATASIM statistical software (Desktop Press). Other comparisons were performed by t test or Wilcoxon rank sum test for continuous and ordinal variables, respectively. Because data are partially matched, all comparisons between early and late evaluations were made 1) with the use of paired tests in the subgroup of 23 subjects having both early and late measurements, and 2) with the use of unpaired tests in the subgroup of 50 subjects with only early and 13 patients with only late evaluations. Both sets of p values were then combined by the Fisher procedure (23), as performed in meta-analyses (24,25).

Because correlations between changes in vessel diameter after pacing and after nitrate injection are biased by the common basal measures (effect of regression to the mean), responses to both stimuli were studied by Pearson partial correlations, which are correlations between absolute values of diameters after pacing and nitrate injection, corrected by basal measurements. Spearman rank coefficient was used to assess the correlation between differential diameters and quality of runoff. All tests were two-tailed.

Results

Baseline characteristics. The characteristics of the patients in the early and in late postoperative periods are listed in Table 1. Mean blood pressure was higher in the late than in the early period by 16 mm Hg ($p < 0.001$), but heart rate was slightly slower (77 ± 11 vs. 85 ± 12 beats/min, $p = 0.013$). Regional function and quality of runoff were similar in the groups studied early and late after bypass surgery.

Systemic effects. A similar heart rate was achieved during pacing early and late postoperatively, without significant change in mean arterial pressure. There was also no significant

Table 1. Patient Characteristics

	Postoperative Study		p
	Early (n = 73)	Late (n = 36)	Value
Age (yr)	59 ± 9	60 ± 8	NS
Gender (M/F)	69/4	35/1	NS
Interval after operation	10 ± 3 days	12 ± 5 mo	—
Heart rate (beats/min)	85 ± 12	77 ± 12	0.013
Blood pressure (mm Hg)	81 ± 11	97 ± 13	<0.001
Quality of runoff (%)			NS
Small	8%	3%	
Intermediate	40%	28%	
Large	51%	69%	
Regional function (%)			NS
Normal	62%	72%	
Hypokinesia/kinesia	38%	28%	
LVEF (%)	62 ± 12%	61 ± 11%	NS

Unless otherwise indicated, values are presented as mean value ± SD. F = female; LVEF = left ventricular ejection fraction; M = male.

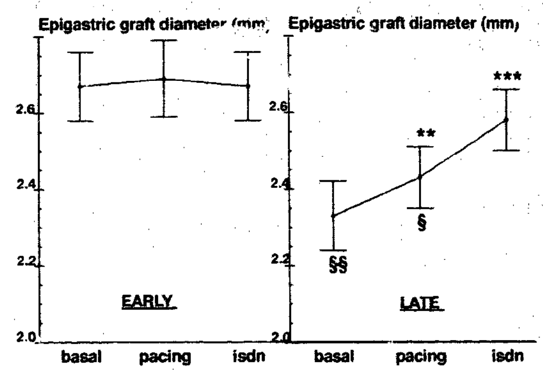


Figure 2. Changes in mean epigastric graft diameter observed during pacing and after isosorbide dinitrate (isdn) injection, in the early and late postoperative periods, in the 23 patients who underwent both evaluations (**p = 0.002 vs. basal; ***p < 0.001 vs. basal; §p = 0.023 vs. early evaluation; §§p = 0.004 vs. early evaluation).

difference in heart rate or arterial blood pressure after injection of nitrates into the graft.

Quantitative angiographic data. At rest, mean epigastric graft diameter was lower in the late than in the early postoperative period (2.26 ± 0.39 vs. 2.61 ± 0.49 mm, $p < 0.001$, Fig. 1). However, mean epigastric graft diameter achieved after isosorbide dinitrate was not statistically different between the early and late periods (2.65 ± 0.47 vs. 2.50 ± 0.37 mm, p = NS). Significant vasodilation with nitrates (+11 ± 7%) was observed only late (from 2.26 ± 0.39 to 2.50 ± 0.37 mm, $p < 0.001$, Fig. 1) but not early postoperatively. Similarly, no vasodilation during pacing was observed, at least for the total group, early postoperatively, contrasting with a significant vasodilation (+4 ± 9%) observed in long-term epigastric grafts (from 2.26 ± 0.39 to 2.33 ± 0.41 mm, $p < 0.01$, Fig. 1). The same evolution with pacing and nitrates was observed in the selected subgroup of 23 patients who underwent both early and late pacing as in the total group (Fig. 2). Baseline characteristics of these 23 patients were not different from those of the total group.

A significant correlation between the response to nitrates and the response during pacing (Fig. 3 and 4) was observed early ($r = 0.579$, $p < 0.001$) and late ($r = 0.530$, $p = 0.001$) postoperatively. Early postoperatively, epigastric grafts capable of vasodilation with nitrates also appeared to be capable of vasodilation during pacing. Late postoperatively, most of the epigastric grafts increased their dimensions during pacing. Hemodynamic factors and left ventricular function did not differ between patients with epigastric grafts with or without nitrate-induced vasodilation early and later postoperatively. In contrast, a significant correlation ($r = -0.411$, $p < 0.001$) was

Figure 1. Changes in mean epigastric graft diameter observed during pacing and after isosorbide dinitrate (isdn) injection in the early (n = 73) and late (n = 36) postoperative periods (**p = 0.009 vs. basal; ***p < 0.001 vs. basal; §§p < 0.001 vs. early evaluation; §p = 0.003 vs. early evaluation).

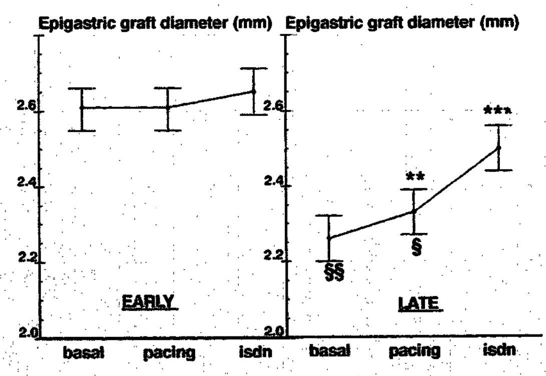
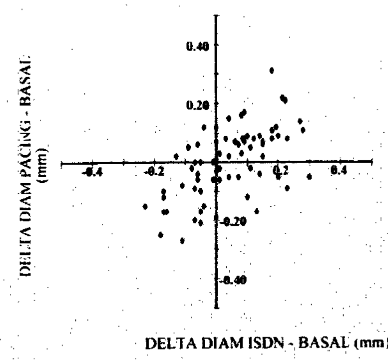


Figure 3. Changes (DELTA) in lumen diameter (DIAM) of epigastric grafts in response to pacing plotted against change in lumen diameter observed after isosorbide dinitrate (ISDN) injection into the graft in the early postoperative period. A correlation ($r = 0.579$, $p < 0.001$) was observed between the response recorded during pacing and that seen after isosorbide dinitrate.



JACC Vol. 27, No. 2
February 1996:415–20

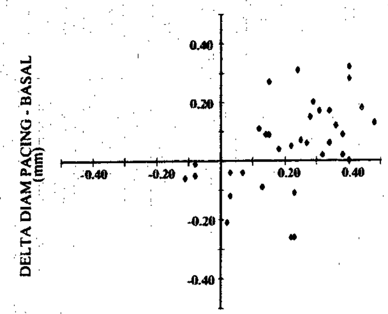


Figure 4. Changes in lumen diameter of epigastric grafts in response to pacing, plotted against changes in lumen diameter observed after isosorbide dinitrate injection into the graft, in the late postoperative period. A correlation (r = 0.530, p = 0.002) was observed between the response during pacing and the response seen after isosorbide dinitrate. Abbreviations as in Figure 3.

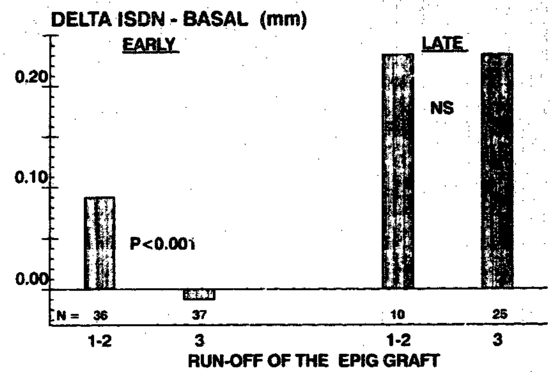


Figure 5. Comparison of the vasodilation observed after isosorbide dinitrate administration in the epigastric graft (EPIG) early (**left**) and late (**right**) after bypass surgery, according to the importance of the runoff of the graft (1–2 = small or intermediate runoff, 3 = large runoff). Only epigastric grafts with a small or intermediate runoff were capable of vasodilation with isosorbide dinitrate early postoperatively, contrasting with a more enhanced vasodilation observed late postoperatively in both groups. Other abbreviations as in Figure 3.

seen between the vasodilation observed with nitrates and the quality of the runoff of the graft in the early postoperative period. Epigastric grafts with a small or intermediate runoff, but not those with a large runoff, were capable of vasodilation with isosorbide dinitrate (+0.09 ± 0.10 mm vs. −0.01 ± 0.12 mm, Fig. 5). This correlation was not seen in the late postoperative period, where a similar vasodilation with nitrates was observed in patients with a small or intermediate runoff and patients with a large runoff (0.23 ± 0.09 vs. 0.23 ± 0.18 mm).

Discussion

Recently, attempts to improve late results of coronary artery bypass surgery have focused on the extended use of arterial conduits, based on the superiority of internal mammary artery grafts in term of late patency rate and clinical results (26–28). The function and patency of coronary bypass grafts are influenced by several factors, including the biologic properties of the conduit used. In this setting, the endothelium not only plays a crucial role in the regulation of vasomotor tone (29–31), but also contributes to the maintenance of a nonthrombogenic surface (32) and to the control of vascular smooth muscle cell proliferation (33). The inferior epigastric artery is histologically quite similar to the internal mammary artery. Inferior epigastric arteries have no or few fenestrations in the internal elastic lamina, which could be an important factor in preventing the migration of smooth muscle cells from the media to the intima, but epigastric grafts, similar to coronary arteries (16,17,34), are slightly more muscular than the internal mammary artery. Mügge et al. (20) recently compared the vascular reactivity of internal mammary and inferior epigastric arteries. They showed that both vessels had a similar endothelium-independent relaxation in response to nitrates but that epigastric arteries had a greater endothelium-dependent relaxation in response to acetylcholine, substance P and bradykinin and, thus, a higher endothelial capacity to release endothelium-derived relaxing factor.

Our data demonstrate in vivo that free epigastric grafts have the ability to adapt their dimensions during an acute increase in myocardial demand at least in the late postoperative period. Pacing-induced tachycardia, by increasing myocardial flow, represents a physiologic stimulus for release of endothelium-derived relaxing factor, as a result of the increase in shear stress, as shown in animal models (1–4) and in different human arteries (5–9) including coronary arteries of the transplanted heart (8) or internal mammary grafts (7). This property not only is indirect evidence of a preserved endothelial function, contributing probably to the function and the patency of these grafts, but also could enable the graft to increase its flow at a lower increase in velocity, thereby minimizing the increase in shear stress and turbulent flow that promote endothelial injury and progression of atherosclerosis (29,35,36).

Early postoperative period. Organic nitrates, like isosorbide dinitrate, are potent dilators of smooth muscle, not depending on the presence of the endothelium. Early postoperatively, vasodilation with isosorbide dinitrate was observed only in <50% of the epigastric grafts, mainly in relation to the importance of the runoff of the graft, as previously described in a larger group (19). In the early postoperative period, epigastric grafts with a small or intermediate runoff were capable of vasodilation with nitrates (Fig. 5). That these grafts were also capable of vasodilation during pacing, as suggested in Figure 1, is an argument for a preserved endothelial function, already seen a few days after bypass surgery in these epigastric grafts. In contrast, those grafts with a large runoff were not capable of vasodilation after nitrate injection. The basal diameter of the latter grafts was larger than that of epigastric grafts capable of vasodilation with nitrates, but the two types of grafts had same dimensions after nitrate administration, suggesting an already maximal dilation at rest to meet the myocardial requirement. Impairment of endothelial function and of the smooth muscle layer due to the surgical harvesting technique is less likely to explain the absence of response to nitrates and to pacing in these grafts, in view of this relation between the importance of runoff and the vasodilation observed with nitrates. Nevertheless, given this absence of vasodilator reserve of these epigastric grafts in control conditions, the lack of vasodilation response to atrial pacing provides no evidence for or against preserved endothelium function. Further studies, using local acetylcholine infusion, for example, might clarify the problem of this subgroup of epigastric grafts.

Late postoperative period. In contrast, late postoperatively, even epigastric grafts with a large runoff were capable of vasodilation after nitrates in a manner similar to that of grafts with a smaller runoff (Fig. 4), suggesting restoration of a higher basal vasomotor tone. In the same way, basal diameter was smaller in late epigastric grafts than in early grafts, but dimensions of the conduits after nitrates were similar (Fig. 1) in late and early grafts. Thus, epigastric grafts adapt to the coronary circulation during months after operation. Due to a higher basal vasomotor tone and a preserved endothelial function, chronic epigastric grafts are able—like mammary grafts, but in contrast to venous grafts (7,13)—to dynamically increase their dimensions in response to an acute increase in flow demand, which could be a factor contributing to good functional results for the new arterial grafts. As this flow-mediated vasodilation is demonstrated for the first time in a free arterial aortocoronary bypass graft, this observation is also consistent with the hypothesis of the preponderance of the local regulation mediated by the endothelium and unrelated to innervation. Because the contribution of the graft conduit to the total vascular resistance is small, the physiologic importance of this flow-mediated vasodilation is probably limited in terms of ability of the graft to provide adequate blood flow supply at periods of peak myocardial demand, as during exercise. Flow-mediated vasodilation may allow arteries to accommodate increased blood flow without an excessive increase in flow velocity and in shear stress, which is inversely proportional to the third power of the radius of the vessel (29). Impairment of this dilation could result in abnormally high levels of wall shear stress at times of increased blood flow. In preliminary data from our group (37), intravascular Doppler velocity measurements recently suggested that during pacing, saphenous vein grafts increase their blood flow supply entirely by an increase in flow velocity. In contrast, arterial grafts (internal mammary grafts and epigastric grafts) provide an increase in flow similar to that of vein grafts, but this increased blood flow is accommodated by a dilation of the graft conduit with a relatively lower increase in flow velocity or shear stress. This decrease in shear stress could result in less development of turbulent flow, a condition that results in damage to vascular endothelium. This vicious circle explains possibly, at least partially, why atherosclerosis (35,36), once present, tends to be a progressive disease. However, more long-term clinical and angiographic follow-up studies are required 1) to determine whether these attributes of the epigastric graft will be associated with a higher patency rate than that of vein grafts, and 2) to define the true efficacy of this new material.

We thank the staff of the cardiac catheterization laboratory for their continued support during this study and Lawrence Collin for typing the manuscript.

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