Local Perivascular Delivery of Basic Fibroblast Growth Factor in Patients Undergoing Coronary Bypass Surgery
Results of a Phase I Randomized, Double-Blind, Placebo-Controlled Trial

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Background—Angiogenesis is a promising treatment strategy for patients who are not candidates for standard revascularization, because it promotes the growth of new blood vessels in ischemic myocardium.

Methods and Results—We conducted a randomized, double-blind, placebo-controlled study of basic fibroblast growth factor (bFGF; 10 or 100 μg versus placebo) delivered via sustained-release heparin-alginate microcapsules implanted in ischemic and viable but ungraftable myocardial territories in patients undergoing CABG. Twenty-four patients were randomized to 10 μg of bFGF (n = 8), 100 μg of bFGF (n = 8), or placebo (n = 8), in addition to undergoing CABG. There were 2 operative deaths and 3 Q-wave myocardial infarctions. There were no treatment-related adverse events, and there was no rise in serum bFGF levels. Clinical follow-up was available for all patients (16.0 ± 6.8 months). Three control patients had recurrent angina, 2 of whom required repeat revascularization. One patient in the 10-μg bFGF group had angina, whereas all patients in the 100-μg bFGF group remained angina-free. Stress nuclear perfusion imaging at baseline and 3 months after CABG showed a trend toward worsening of the defect size in the placebo group (20.7 ± 3.7% to 23.8 ± 5.7%, P = 0.06), no significant change in the 10-μg bFGF group, and significant improvement in the 100-μg bFGF group (19.2 ± 5.0% to 9.1 ± 5.9%, P = 0.01). Magnetic resonance assessment of the target ischemic zone in a subset of patients showed a trend toward a reduction in the target ischemic area in the 100-μg bFGF group (10.7 ± 3.9% to 3.7 ± 6.3%, P = 0.06).

Conclusions—This study of bFGF in patients undergoing CABG demonstrates the safety and feasibility of this mode of therapy in patients with viable myocardium that cannot be adequately revascularized. (Circulation. 1999;100:1865-1871.)

Key Words: heart diseases ■ angiogenesis ■ growth substances ■ myocardium

Ischemic coronary disease remains the leading cause of morbidity and mortality in the Western world. Current therapeutic approaches aim to relieve symptoms and cardiac events by reducing myocardial oxygen demand with medical therapy, to prevent further disease progression by modifying risk factors, or to restore flow to a localized segment of the arterial tree by coronary angioplasty (PTCA) or bypass surgery (CABG). When CABG is selected as the treatment option, its success may be limited by the inability to provide complete revascularization in those patients in whom the artery that supplies a viable but underperfused myocardial territory is not graftable because of diffuse disease, calcifications, or small size. Complete revascularization cannot be achieved in up to 37% of patients undergoing CABG.1 This number is probably much lower today. However, patients who undergo complete revascularization have improved 5-year survival and angina-free survival compared with patients who have incomplete revascularization.1 Therefore, an adjunctive treatment strategy is warranted in patients undergoing CABG if complete revascularization is not possible. Percutaneous catheter-based revascularization is often precluded secondary to the same attributes that made the myocardial territory ungraftable: diffuse disease and small or calcified vessels.

The availability of various angiogenic growth factors, particularly basic fibroblast growth factor (bFGF) and vascular endothelial growth factor, and their implication in developmental, ischemia-induced, and tumor angiogenesis have
led to studies that have demonstrated their therapeutic benefit in animal models of myocardial ischemia.\textsuperscript{2–9} We previously demonstrated that epicardially implanted heparin-alginate pellets containing either 10 or 100 \( \mu \)g of bFGF resulted in functionally significant angiogenesis in a porcine model of chronic myocardial ischemia, with very low plasma bFGF levels, no acute hemodynamic effects, and no significant toxicity.\textsuperscript{5,8} Based on these preclinical results, we designed and implemented a phase I randomized, double-blind, placebo-controlled study to evaluate the safety and preliminary efficacy of local periadventitial bFGF as an adjunct to CABG surgery. In this trial, patients with a viable and ischemic myocardial area that could not be revascularized were randomized to receive heparin-alginate pellets containing 10 or 100 \( \mu \)g of bFGF or placebo that were placed on the epicardial surface during CABG.

**Methods**

**Patient Selection**

The study population consisted of patients undergoing CABG at Beth Israel Deaconess Medical Center and Albert Einstein College of Medicine in Boston, Mass. The inclusion criteria included an area of myocardium supplied by a major coronary artery with advanced disease not amenable to bypass grafting or percutaneous intervention, inducible ischemia, and the ability to understand and sign the informed consent and to comply with planned follow-up. Patients with the following criteria were excluded from consideration for the study: absence of inducible ischemia or myocardial viability of the target area, hypertrophic or restrictive cardiomyopathy, left ventricular ejection fraction <20\%, significant valvular heart disease, renal dysfunction (serum creatinine >2.5 mg/dL), history of malignancy within the previous 5 years, or unexplained hematological or chemical abnormalities before CABG.

The design and performance of the study were approved by the Food and Drug Administration under an investigator-sponsored investigational new drug (BB-IND 5725). The study was approved by the Committee for Clinical Investigation at both institutions. The first patient was enrolled in September 1996 and the last patient in May 1998.

**Preparation of bFGF-Containing Heparin-Alginate Pellets**

Calcium alginate pellets provide a stable platform for bFGF because of enhanced retention of activity and storage time and thus were used as devices for controlled bFGF release in vivo.\textsuperscript{5,8,10} Heparin-sepharose beads (Pharmacia LKB) were sterilized under ultraviolet light for 30 minutes and then mixed with filter-sterilized sodium alginate.\textsuperscript{8,10} The mixed slurry was dropped through a needle into a sepharose beads (Pharmacia LKB) were sterilized under ultraviolet (for 10-100 mg dose) or 125 \( \mu \)g of bFGF resulted in 80\% of bFGF in solution is absorbed into heparin-alginate pellets.\textsuperscript{5,10,11} The end product was sterilized under ultraviolet light for 30 minutes. With each preparation, several beads were cultured to ensure sterility. Blank or bFGF-loaded pellets were identical in appearance, which ensured that the surgeons and investigators were blinded with regard to which pellet was being used.

**bFGF Heparin-Alginate Delivery**

After completion of coronary bypasses to all areas of the heart that could be revascularized and failure to graft the target vessel (which on occasions involved probing of the target vessel), multiple linear incisions were made in the epicardial fat surrounding the target vessel. Heparin-alginate pellets (containing bFGF or placebo) were inserted into the epicardial fat overlying the artery and secured in place by a 6.0 prolene suture to close the subepicardial incision. A total of 10 pellets were used in each patient (2 to 3 pellets were placed in each incision; Figure 1).\textsuperscript{5,8} The left internal mammary artery (LIMA) was placed on the left anterior descending artery (LAD), and proximal vein-to-aorta anastomoses were constructed. Ventilation was reestablished, and cardiopulmonary bypass was terminated. Routine closure was then performed.

**In-Hospital Follow-Up**

The postoperative course was evaluated, including hemodynamic parameters, duration of ventilatory support, postoperative ECGs, postoperative cardiac isoenzymes, duration of hospitalization, and any evidence of infection. Serum bFGF levels were measured (ELISA, R&D Systems) before implantation and on the first, third, and fifth postoperative days. Complete blood count, coagulation parameters, serum chemistries, and urinalysis were performed before treatment and at days 3 and 5 after treatment. In the first 10 patients, stress nuclear perfusion imaging and MRI (at the Beth Israel Deaconess Medical Center) were performed before CABG; however, owing to the confounding effect of CABG (realized after an interim analysis of the first 10 patients by the Data Safety and Monitoring Committee), the remaining patients underwent stress nuclear perfusion scans (rest-thallium/dipyridamole sestamibi) and MRI after CABG (before discharge). The surgeon, other investigators, and patients were blinded to treatment assignment.

**Long-Term Follow-Up**

All patients were contacted by the investigators at 6 weeks; 2, 3, 4, and 6 months; 1 year; and then yearly thereafter to assess clinical events (death, myocardial infarction, recurrent angina, or any repeat revascularization). Complete blood count, coagulation parameters, serum chemistries, urinalysis, and serum bFGF level measurements were repeated at 3 months. Patients underwent stress nuclear scans at 3 months (dual-isotope studies with rest thallium and stress [pharmacological stress with dipyridamole sestamibi]). In addition, patients at the Beth Israel Deaconess Medical Center underwent repeat MRI 3 months after CABG. Clinical follow-up of \( \geq 6 \) months was available for all patients, with a mean follow-up of 16.0±6.8 months.

**Imaging Studies**

Rest thallium/dipyridamole sestamibi studies were performed according to the ADAC protocol. We compared baseline and 90-day

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**Figure 1.** A, Schematic showing severe 3-vessel disease in a patient undergoing CABG. Although LAD and left circumflex artery (LCX) are graftable, RCA is not. Ten heparin-alginate microcapsules containing bFGF or placebo are implanted in the subepicardial fat along the distribution of the posterior descending artery. B, Study enrollment: 46 eligible patients (Pts) were screened for the study; of these, 22 underwent complete revascularization (revasc) and 24 had an ungraftable territory and were randomized to receive bFGF (10 or 100 \( \mu \)g) or placebo.
nuclear scans using the size of the stress perfusion defect, as determined by pixel analysis. MRI was performed in the body coil of a 1.5-T whole-body Siemens Vision system as previously described and validated.7 Baseline anatomic images were obtained by a turboFLASH (turbo Fast Low-Angle SHot) technique to identify coordinates for apical 4-chamber, 2-chamber, and short-axis views. Functional imaging was performed during breathhold by use of shared-center turboFLASH in each of the 3 mutually perpendicular standard views, producing 24 sequential image frames each, collected over 12 heartbeats to measure regional wall motion. MR perfusion imaging was performed as follows: a series of 4 inversion recovery images (1 every second heartbeat) was obtained to minimize the signal intensity from myocardium in the fourth frame. With the best TI determined by these scout images, a series of concurrent parallel images were acquired in diastole during breathhold, 1 every other heartbeat, at baseline and again with contrast injection (0.05 mmol/kg gadodiamide).7 In addition, complete blood count, coagulation parameters, serum chemistries, urinalysis, and serum bFGF level measurements were repeated at 3 months.

Statistical Methods
Data are expressed as mean±SD. Continuous variables were compared by paired Student’s t test (baseline and follow-up). Nuclear perfusion scans were also compared by ANOVA. All reported probability values were 2-tailed, and a P value ≤0.05 was considered statistically significant.

Results

Patient Population and Enrollment Procedure
Seventy-eight patients scheduled for CABG were screened for enrollment into the study on the basis of an angiogram that showed a major epicardial coronary artery (posterior descending artery, significant diagonal, obtuse marginal, or ramus intermedius branch, or significant posterolateral branch) that was considered by an interventional cardiologist and a cardiothoracic surgeon not involved in the study unlikely to be graftable on the basis of its angiographic appearance (diffusely diseased or heavily calcified). Patients were approached for enrollment in the study, and screening tests were performed to ensure that all eligibility criteria were met, including demonstrable ischemia in the target myocardial area.

Forty-six patients who met all eligibility criteria and agreed to participate in the study underwent CABG, during which a noninvasive cardiac surgeon determined whether the target area was indeed ungraftable. Bypass surgery of the target vessel was performed in 22 cases, and those patients were excluded from additional study. The remaining 24 patients (19 patients at Beth Israel Deaconess Medical Center and 5 at Montefiore Medical Center, Bronx, NY) who had a coronary artery that could not receive a graft at the time of surgery were randomized to receive 10 heparin-algin late pellets containing placebo or 1 of 2 doses of bFGF (10 or 100 μg). Baseline clinical characteristics of these patients are summarized in Table 1. There was no significant difference between the study groups in any of the clinical parameters, including the extent of coronary disease or presence of any risk factor, except that patients in both 10- and 100-μg bFGF treatment groups were somewhat older than controls, and there were more women in the 10-μg bFGF group. The baseline resting ejection fraction was 50.3±13.8%, and 5 of the 24 patients had an ejection fraction <30%.

Short-Term Results
The extent of CABG surgery was the same in all treatment groups; there were no significant differences with regard to the number of grafts, duration of surgery (average 3.0±0.9 hours), or cross-clamp time (average 56±13 minutes) (Table 2). The target vessel was the right coronary artery (RCA) in 15 patients, left circumflex artery in 7, and diagonal branch of the LAD in 2.

One patient in the control group died 24 hours after surgery secondary to an autopsy-documented occlusion of 1 of the saphenous vein grafts, with a large myocardial infarction in that territory. A second death occurred in a patient in the 100-μg bFGF group who could not be weaned off cardiopulmonary bypass (preoperative ejection fraction of 20%); an autopsy revealed patent grafts with extensive myocardial scarring and a thin rim of epicardial viable myocardium. Two other patients (both in the control group) required intra-aortic balloon pump support after surgery (1 patient, the intra-aortic balloon pump was inserted before surgery). Two patients (1 in the control group and 1 in the 10-μg bFGF group) had a Q-wave myocardial infarction in the target myocardial distribution, and 1 patient in the 10-μg bFGF

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EF indicates ejection fraction.

*Serum cholesterol >200 mg/dL.
group had a Q-wave myocardial infarction in a nontarget myocardial distribution. Placement of bFGF-containing heparin-alginate microspheres had no significant short-term effects on blood pressure (Table 2) or heart rate; the mean arterial pressure was 84.8 ± 10.6 mm Hg before bypass, 89 ± 12 mm Hg on day 1, 93 ± 7 mm Hg on day 3, and 83.4 ± 11.1 mm Hg on day 5 and was not different among the treatment groups. Pharmacokinetic evaluation did not reveal any significant increase in serum bFGF levels above baseline in any of the groups (average bFGF levels in 15 patients: 17.4 ± 3.3, 15.90 ± 1.4, 15.9 ± 1.8, and 16 ± 1.8 pg/mL at baseline and postoperative days 1, 3, and 5, respectively), and there were no significant differences in bFGF levels between the different treatment groups. The average postoperative hospital stay was 5.30 ± 1.3 days (range 4 to 8 days). There were no acute effects on serum chemistries, hematologic and coagulation profiles, liver function tests, or urinalysis. Two patients developed superficial wound infections along the chest incision that necessitated surgical debridement, and another patient with diabetes mellitus had delayed healing of the saphenous vein graft harvest site. Microbiological evaluation of the beads showed no aerobic or anaerobic growth in samples from 28 of the 46 preparations.

Clinical Follow-Up
Clinical follow-up was available in the 22 surviving patients (7 from the placebo group, 8 from the 10-μg-bFGF group, and 7 from the 100-μg-bFGF group) and averaged 16.0 ± 6.8 months. At last follow-up, all patients were angina-free except for 3 patients in the placebo group (Canadian Cardiovascular Society [CCS] class II in 1 and class III in 2 patients) and 1 patient in the 10-μg bFGF group (CCS class II). Two of the 3 placebo patients with angina underwent successful percutaneous revascularization (1 involved the target vessel and the second involved a vein graft stenosis). After hospital discharge, none of the patients died or sustained a myocardial infarction. There were no delayed wound infections, no clinical evidence of pericarditis, and no other adverse events. Laboratory evaluation at 90 days (available in 21 patients) did not show any adverse effect on complete blood count, coagulation parameters, serum chemistries, or urinalysis.

Myocardial Perfusion Studies

Nuclear Perfusion Imaging
Twenty of the surviving 22 patients underwent stress nuclear perfusion imaging 90 days after CABG. In the first 10 patients, baseline studies were performed before CABG. It became clear as the study progressed, however, that this was not a true baseline because of the confounding effect of CABG. Therefore, in the remaining 12 patients, rest-thallium/dipyridamole sestamibi nuclear testing was performed after CABG and before hospital discharge. The baseline stress target area defect size was 20.6 ± 5.2% of the left ventricle and was similar in all 3 treatment groups (22.3 ± 5.4% in controls, 19.2 ± 5.0% for the 10-μg bFGF group, and 20.4 ± 5.7% for the 100-μg bFGF group, ANOVA P = 0.56). At the time of follow-up nuclear scans, when paired t tests were used, there was a trend toward worsening (increase in the defect size) in the placebo group (Figure 2; 20.7 ± 3.7% at baseline to 23.8 ± 5.7% at follow-up, P = 0.06). Studies in the 10-μg bFGF group showed no change in defect size (19.2 ± 5.0% to 16.9 ± 8.1%, P = 0.39), whereas defect size in the 100-μg bFGF group was significantly improved compared with baseline (19.2 ± 5.0% to 9.1 ± 5.9%, P = 0.01). The change in defect size was significantly different among the 3

![Figure 2. Target nuclear perfusion defect in all 3 treatment groups at baseline and 3 months after CABG showing a significant decrease in size of nuclear perfusion defect in 100-μg bFGF group. LV indicates left ventricle.](image-url)
groups (ANOVA $P=0.005$). Semiquantitative analysis of stress images demonstrated worsening of the defect in 3 of 6 patients and no change in 3 of 6 patients in the control group. Of 8 patients in the 10-μg bFGF group, the target nuclear defect size worsened in 2 patients, remained unchanged in 2, and improved in 4. Finally, of the 6 patients in the 100-μg bFGF group who underwent follow-up nuclear testing, there was improvement in 5 patients and no change in 1 patient (Figure 3).

**Magnetic Resonance Imaging**

Functional and perfusion MRI were performed in 8 patients at the Beth Israel Deaconess Medical Center at baseline and at 90-day follow-up (4 controls and 4 bFGF-treated patients [1 patient in the 10-μg bFGF group and 3 in the 100-μg bFGF group]). Baseline resting target wall motion (radial wall motion) was 21.7±6.7% in the placebo group and 27.3±17.0% in patients treated with 100 μg of bFGF (compared with 35.7±10.9% for normal revascularized wall). No changes in resting target wall motion were seen at follow-up (23.7±9.3% in placebo and 32.3±12.4% in 100-μg bFGF–treated subjects). The extent of the resting delayed contrast arrival zone, which reflects underperfused myocardium,2,7,13 for placebo and bFGF-treated patients was 10.7±3.9% and 15.7±2.3% at baseline and decreased to 7.8±6.9% ($P=0.37$) and 3.7±6.3% ($P=0.06$) at follow-up, respectively, with a trend toward improvement in the 100-μg bFGF group.

**Discussion**

Recent advances in growth factor therapy for the treatment of ischemic disease of the heart and peripheral vasculature offer hope of a novel treatment strategy that is based on generation of new blood supply in the diseased heart. Members of the fibroblast growth factor family, vascular endothelial growth factor family, and several other molecules have all been shown to result in functionally significant angiogenesis in animal models of acute and chronic myocardial and peripheral limb ischemia.2–5,8,9,14,15 The promising preclinical data have propelled the use of these angiogenic growth factors in clinical studies of ischemic heart and peripheral vascular disease.2,12,14,16 These growth factors are presumed to induce neovascularization by stimulating endothelial and smooth muscle cell proliferation and migration, dissolving the extracellular matrix, attracting pericytes and macrophages, and finally forming and “sealing” new vascular structures with deposition of new matrix.2,17

Approximately 500 000 PTCA and 375 000 CABS procedures are performed annually in the United States. A signif-
ificant number of patients are suboptimal candidates for CABG or PTCA or do not receive complete revascularization with these procedures. These patients would likely benefit from additional measures to achieve complete revascularization, and therapeutic angiogenesis may serve this role. Although several phase I open-label angiogenesis studies have been completed to date, the interpretation of data is confounded by the lack of placebo control and blinding.

Because of the protracted course of new collateral development, the potential for hemodynamic disturbances associated with bolus intravascular delivery, and the possibility for toxicity from elevated circulating levels of angiogenic growth factors, we used a local sustained bFGF delivery strategy using heparin-alginate microcapsules. This delivery system allows prolonged (4 to 6 weeks) sustained release (first-order kinetics). In animal studies, there was a dose-dependent effect of bFGF that was not associated with detectable serum levels, hemodynamic effects, or local or systemic toxicity.

Of the 46 patients judged to have a major coronary artery that could not be grafted on the basis of angiographic appearance, 22 patients were actually successfully grafted at the time of CABG. Thus, preoperative assessment of arterial suitability for bypass proved to be inaccurate in almost 50% of cases. In accordance with prior observations, the major epicardial artery most likely to be unsuitable for grafting was the RCA. In no case was the LAD considered ungraftable. This paucity of LAD cases is probably a reflection of the reluctance to refer those patients in whom the LAD may not be bypassed for surgical intervention.

The combination CABG/bFGF therapy was not associated with an excess rate of complications. Two operative deaths in this study most likely reflect the higher operative risk in patients with advanced coronary disease and left ventricular dysfunction who have incomplete revascularization. The absence of hemodynamic abnormalities associated with heparin-alginate bFGF delivery is consistent with the undetectable serum levels of bFGF at any time after growth factor administration. In addition, the lack of short- or intermediate-term adverse effects on serum chemistries, hematologic profile, liver function tests, or urinalysis also suggests that this mode of delivery is not associated with systemic toxicity. These observations therefore emphasize the safety of heparin-alginate bFGF delivery at the time of CABG.

Despite the small numbers of patients in the study, several observations point to a potential therapeutic effect of this mode of bFGF therapy in the selected group of patients. The frequency of recurrent angina 90 days after CABG in 4 (18%) of 22 patients is probably related to incomplete revascularization. More importantly, the lack of angina in all patients treated with 100 µg of bFGF and the presence of angina in 3 of 7 (repeat revascularization in 2 of 7) patients who received placebo are provocative and suggest a treatment-related beneficial effect. This surmise is substantiated by the analysis of imaging end points. (It should be noted that the imaging protocol was altered midway through the study.) Quantitative analysis of perfusion images showed a significant improvement in the size of the target perfusion defect in 5 of 6 patients in the 100-µg bFGF group. At the same time, the defect size remained unchanged in 3 of 6 and worsened in the remaining 3 placebo patients, with the 10-µg bFGF group showing no significant changes. This trend toward improved perfusion in the 100-µg bFGF group is supported by the MR perfusion scans, which showed a trend toward reduction in the size of the ischemic zone.

Schumacher and colleagues reported the use of wild-type acidic fibroblast growth factor injections close to the LIMA touchdown site on the LAD in 20 patients undergoing CABG. Twelve weeks after injection, digital subtraction angiography showed a pronounced accumulation of contrast medium extending peripherally distal to the LIMA touchdown site. In this nonrandomized study, however, the authors did not report on clinical or functional measures of angiogenesis. In contrast, in our randomized, double-blind, placebo-controlled investigation, there was a suggestion of clinical benefit and myocardial perfusion enhancement in bFGF-treated patients (particularly in the 100-µg group).

In conclusion, this randomized, double-blind, placebo-controlled study of bFGF in patients undergoing CABG demonstrates the safety and feasibility of this mode of therapy in patients with viable and ischemic but unrevascularizable myocardium. These results warrant a larger multicenter trial to assess the clinical benefit of this combination approach to myocardial revascularization, which is currently under way.

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