JACC Vol. 18, No. 6
November 15, 1991:1517–23

REPORTS ON THERAPY

Recanalization of Chronically Occluded Aortocoronary Saphenous Vein Bypass Grafts by Extended Infusion of Urokinase: Initial Results And Short-Term Clinical Follow-Up

JOSEPH R. HARTMANN, MD, FACC, LOUIS S. McKEEVER, MD, FACC, NICHOLAS J. STAMATO, MD, FACC, VINCENT J. BUFALINO, MD, FACC, JOSEPH C. MAREK, MD, FACC, ALAN S. BROWN, MD, FACC, MARK J. GOODWIN, MD, FACC, JOHN M. CAHILL, MD, FACC, ELAINE L. ENGER, MS

Downers Grove and Lombard, Illinois

Chronic occlusion of saphenous vein aortocoronary bypass grafts is a common problem. Although percutaneous transluminal angioplasty of a saphenous vein with a stenotic lesion is feasible, angioplasty alone of a totally occluded vein graft yields uniformly poor results. Patients with such occlusion are often subjected to repeat aortocoronary bypass surgery. Experience with a new technique that allows angioplasty to be performed in a totally occluded saphenous vein bypass graft is reported. This technique utilizes infusion of prolonged low dose urokinase directly into the proximal portion of the occluded graft.

Forty-six consecutive patients with 47 totally occluded grafts were studied. Patients had undergone end to side saphenous vein bypass grafting 1 to 13 (mean 7) years previously. All patients presented with new or worsening angina pectoris with ST-T changes or non-Q wave acute myocardial infarction and all had a totally occluded saphenous vein bypass graft. The new technique entailed the positioning of an angiographic catheter into the stub of the occluded graft and the advancement of an infusion wire into the graft. Patients were returned to the coronary care unit, where urokinase was delivered at a dose of 100,000 to 250,000 U/h. The total dose of urokinase ranged from 0.7 to 9.8 million U over 7.5 to 77 h (mean 31). After therapy, recanalization was seen in 37 (79%) of the 47 grafts.

In 20 successfully treated patients, angiography was performed 1 to 24 (mean 11) months after treatment; 13 (65%) of these grafts were patent. It is concluded that direct, extended, low dose infusion of urokinase in a totally occluded saphenous vein bypass graft offers a promising alternative to repeat bypass surgery.

(J Am Coll Cardiol 1991;18:1517–23)

Saphenous vein graft occlusion is the predominant cause of recurrent ischemia in patients who have undergone coronary bypass surgery (1). Each year, >14,000 repeat aortocoronary bypass procedures are performed in the United States (2,3). Vein graft occlusion is prevalent during the 1st year after initial surgery. By 1 month after operation, up to 18% of vein grafts are occluded (4). At the end of the 1st postoperative year, the incidence of closure escalates to between 16% and 30% (1,5,6). Closure rates >50% have been reported by 11 years after bypass surgery (7).

Thrombosis due to disruption of endothelial tissue and platelet activation during surgical manipulation appears to play a major role in early vein graft occlusion (4). The pathogenesis of late occlusion appears to be more complex. As a result of chronic injury, a hyperplastic proliferative response occurs, combined with a tendency toward thrombosis. Thus, a late graft occlusion is thought to result from an atherosclerotic-like lesion with or without associated thrombus. Although patients who receive antiplatelet therapy at the time of coronary artery bypass grafting and on a long-term basis thereafter have a reduced rate of thrombotic occlusion, their risk still ranges between 9% and 20% by the end of the 1st year (5,8).

Recurrent angina after aortocoronary bypass grafting may require repeat surgery. However, reoperation is associated with up to twice the mortality rate of the initial procedure and is less effective at controlling angina (9,10). Balloon angioplasty often fails to recanalize a totally occluded vein graft and exposes the patient to the risk of distal embolization (11). In addition, reocclusion of a graft opened by balloon angioplasty has been reported (12) to occur in approximately 33% of patients whose procedure is performed within 3 years of graft placement and in 66% of those who undergo angioplasty >3 years after coronary artery bypass grafting (12).

In 1988, we reported (13) a new technique for dissolving thrombus in a chronically occluded aortocoronary saphenous vein bypass graft; previous studies (14–16) had been limited to short-term infusion (<2 h) of thrombolytic agents

From the Midwest Cardiovascular Institute, Downers Grove, and Midwest Heart Research Foundation, Lombard, Illinois.

Manuscript received October 30, 1990; revised manuscript received May 10, 1991, accepted May 30, 1991.

Address for reprints: Joseph R. Hartmann, MD, Midwest Heart Research Foundation, 2340 Highland Avenue, Suite 200, Lombard, Illinois 60148.

0735-1097/91/$3.50

in acutely occluded grafts. We treated 12 patients whose graft had been totally occluded for 2 to 8 weeks with extended infusion of low dose urokinase. Graft patency was demonstrated in 11 of 12 of these patients after treatment.

In this report, we describe the treatment outcome in 46 consecutive patients (including the original 12 patients) who had one or more completely occluded saphenous vein grafts who received extended urokinase infusion between January 1987 and July 1990. We also report angiographic follow-up findings in 20 successfully treated patients.

Methods

Study patients. Between January 1987 and July 1990, 46 consecutive patients underwent attempted recanalization of a chronically occluded aortocoronary saphenous vein bypass graft using this procedure. One patient had two occluded grafts treated. Forty patients were male (87%) and six were female (13%); their age ranged from 48 to 83 years (mean 60). Patients had undergone coronary bypass surgery between 1 and 13 (mean 7) years previously. All patients presented with signs and symptoms of ischemia; 5 (11%) with exertional angina and 41 (89%) with accelerating angina at rest. All patients developed ST segment and T wave abnormalities associated with chest pain or during exercise. Although the duration of potential graft occlusion was difficult to determine by history alone, it was estimated to range from 0.2 to 28 weeks. Patients with an acute Q wave myocardial infarction were excluded. However, the procedure was attempted in eight patients who presented with a non-Q wave myocardial infarction. Twenty-eight patients (61%) had a history of myocardial infarction before treatment and 20 (43%) demonstrated myocardial infarction in the zone of the treated graft. All patients gave written informed consent.

The sites of the 47 occluded grafts were: left anterior descending artery, 16 cases (34%); right coronary artery, 14 cases (30%); obtuse marginal artery, 10 cases (21%); left circumflex artery, 4 cases (9%); and diagonal artery, 3 cases (6%). The native coronary vessel to the zone of the graft was occluded in 41 cases (87%). In 10 cases, angioplasty of vessels other than the target native vessel or graft was performed during the same hospitalization.

Procedure. A 7F angiographic catheter was passed into the orifice of the occluded saphenous vein bypass graft using the Judkins technique. A 0.014-Hi-torque floppy guide wire was inserted into a 0.038- (145-cm) straight end-hole SOS infusion wire after the stylet was removed. The SOS guide wire assembly was advanced through a Toughy-Borst adaptor to the end of the angiographic catheter. The guide wire was then cautiously advanced as far as possible into the occluded graft. A steering handle attached to the guide wire facilitated manipulation of its preformed tip. In the event that the Hi-torque floppy guide wire could not be advanced, an intermediate or standard guide wire was substituted. Only minimal force was applied when passing the guide wire to reduce the risk of perforation. Once the guide wire was positioned, the SOS wire was passed over the guide wire to a position several centimeters into the graft and the guide wire was then removed. The Toughy-Borst adaptor was tightened to secure the SOS wire position and an infusion adaptor was attached.

A urokinase (Abbokinase, Abbott Laboratories) infusion was initiated both proximally through the angiographic catheter and distally through the SOS wire at a rate of 50,000 U/h (total 100,000 U/h) (Fig. 1). The sheath and angiographic catheter were sutured to the skin and covered with a sterile dressing. The patient was brought to the critical care unit for continued coaxial urokinase infusion (Fig. 2).

Heparin was administered intravenously throughout the procedure and the dose adjusted to maintain a partial thromboplastin time of 70 to 150 s. Prophylactic antibiotic therapy was instituted in patients requiring frequent catheter manipulation or a longer duration of infusion. Fibrinogen, hemoglobin and cardiac enzyme levels were monitored frequently. Angiographic visualization was performed one to two times daily to determine the degree of thrombus dissolution. Provided there was no contraindication, the urokinase dose was increased to a total dose of 250,000 U/h if thrombolysis was unsatisfactory at the time of revisualization. In addition, the SOS infusion wire was advanced over a guide wire to the most distal point of occlusion. The urokinase infusion was typically discontinued when the graft appeared patent or when no progress in thrombolysis was evident after a minimum of 24 h. When flow was noted in the distal native coronary artery and a lesion was visualized, the graft was dilated by balloon angioplasty. In the event of residual thrombus after angioplasty, the urokinase infusion was continued for 4 to 24 h.

Successfully treated patients were discharged on therapy with warfarin and aspirin unless these agents were contraindicated. Medical therapy with nitrates, a calcium channel antagonist or a beta-adrenergic blocking agent was prescribed as necessary.

Efficacy. Initial therapy was judged to be successful when the target vein graft demonstrated patency, defined as Thrombolysis in Myocardial Infarction (TIMI) grade II or III flow after thrombolytic infusion and balloon angioplasty. Therapy was judged a failure when the graft remained occluded defined as TIMI grade 0 or I flow after therapy (17).

Complications. A prospective compilation of cerebrovascular accidents, transient ischemic attacks, myocardial infarction, femoral artery occlusion or hematoma, systemic or local infections and the need for blood transfusion was performed during the hospital stay in which the procedure was conducted.

Clinical and angiographic follow-up. All successfully treated patients were followed up for the development of recurrent angina, myocardial infarction, repeat coronary artery bypass surgery and death. The follow-up period ranged from 6 to 48 months (mean 27.2). Twenty patients

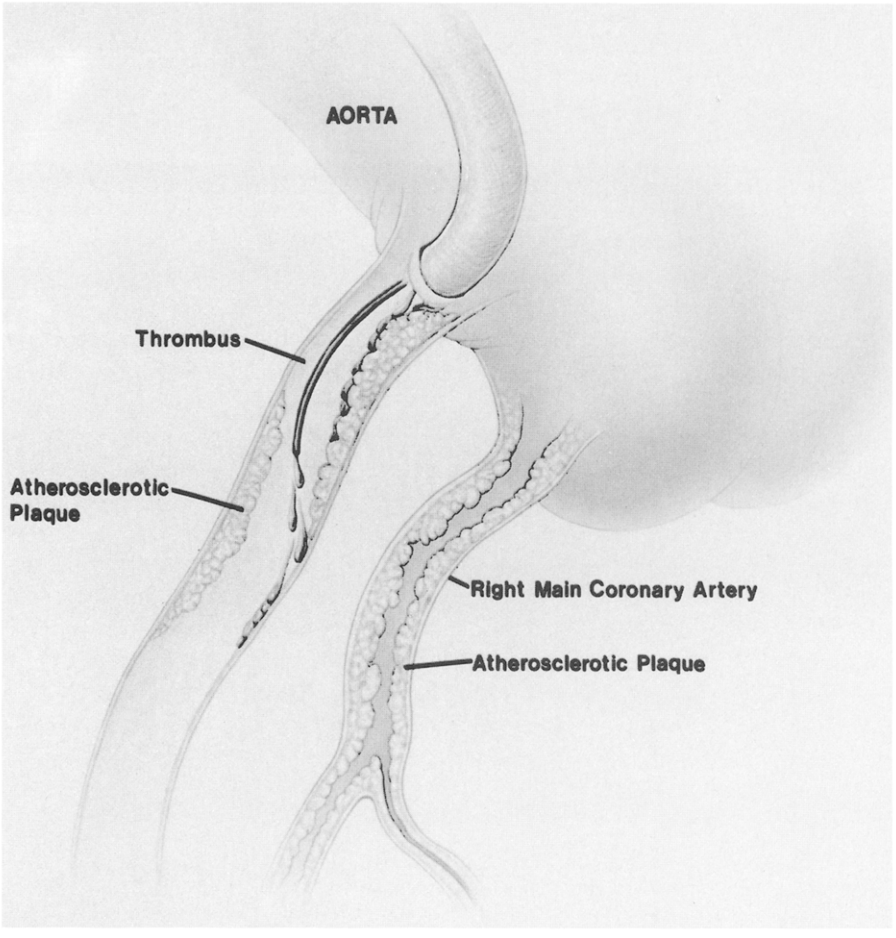

Figure 1. An SOS wire positioned several centimeters into the occluded graft. Coaxial urokinase infusion was given through the angiographic catheter (proximal) and SOS wire (distal).

underwent follow-up angiography; 14 because of recurrent symptoms and 6 electively while free of symptoms.

Results

Initial therapy. Successful recanalization was achieved in 37 (79%) of 47 occluded saphenous vein bypass grafts. Adjunctive balloon angioplasty of a residual lesion was performed in 35 (95%) of these 37 cases; 7 patients also had angioplasty of other vessels performed after successful urokinase therapy. In 10 cases (21%), graft patency was not achieved; clinical details of the treatment failures appear in Table 1. Difficulty in positioning the angiographic catheter or SOS wire, or both, was experienced in five of these unsuccessful cases. In two patients, the procedure was terminated prematurely as a consequence of discomfort associated with confinement of movement despite evidence of lysis in the proximal portion of the target graft. The procedure was discontinued in two patients by the investigator; in one because of a history of upper gastrointestinal bleeding and in the other because of a procedure-related femoral hematoma.

At final angiography, the TIMI flow grades were as follows: grade III, 29 cases (62%); grade II, 8 cases (17%); grade I, 3 cases (6%); and grade 0, 7 cases (15%). The duration of urokinase infusion ranged from 7.5 to 77 h (mean 31). Total urokinase dose ranged from 0.72 to 9.79 million U. The duration of previous graft occlusion determined by history was 0.2 to 18 weeks (mean 2.4) in successfully treated patients and 0.2 to 28 weeks (mean 7.4) in those in whom the procedure failed to open the graft.

Complications. A complication related to the procedure developed in 15 patients. Six patients (13%) developed chest pain and ST segment elevation suggestive of infarction during urokinase infusion. In the first patient, the urokinase infusion was discontinued and Q wave infarction developed. In the subsequent five patients, anterograde flow to the native coronary artery through the graft with significant residual thrombus was evident. Therefore, the urokinase dose was increased to a total of 200,000 to 250,000 U/h. In four of these five patients, chest pain subsided and ST segment elevation resolved without evidence of Q wave infarction. However, the fifth patient experienced local bleeding and hypotension requiring premature termination of therapy and later completed a Q wave infarction.

Ten patients (22%) developed a significant hematoma. One patient (2%) experienced a decrease in hemoglobin to 9.8 g/dl that necessitated a single unit blood transfusion and premature discontinuation of thrombolytic therapy. Four additional patients (9%) demonstrated a decrease in hemoglobin of approximately 2 g/dl for which transfusion was not

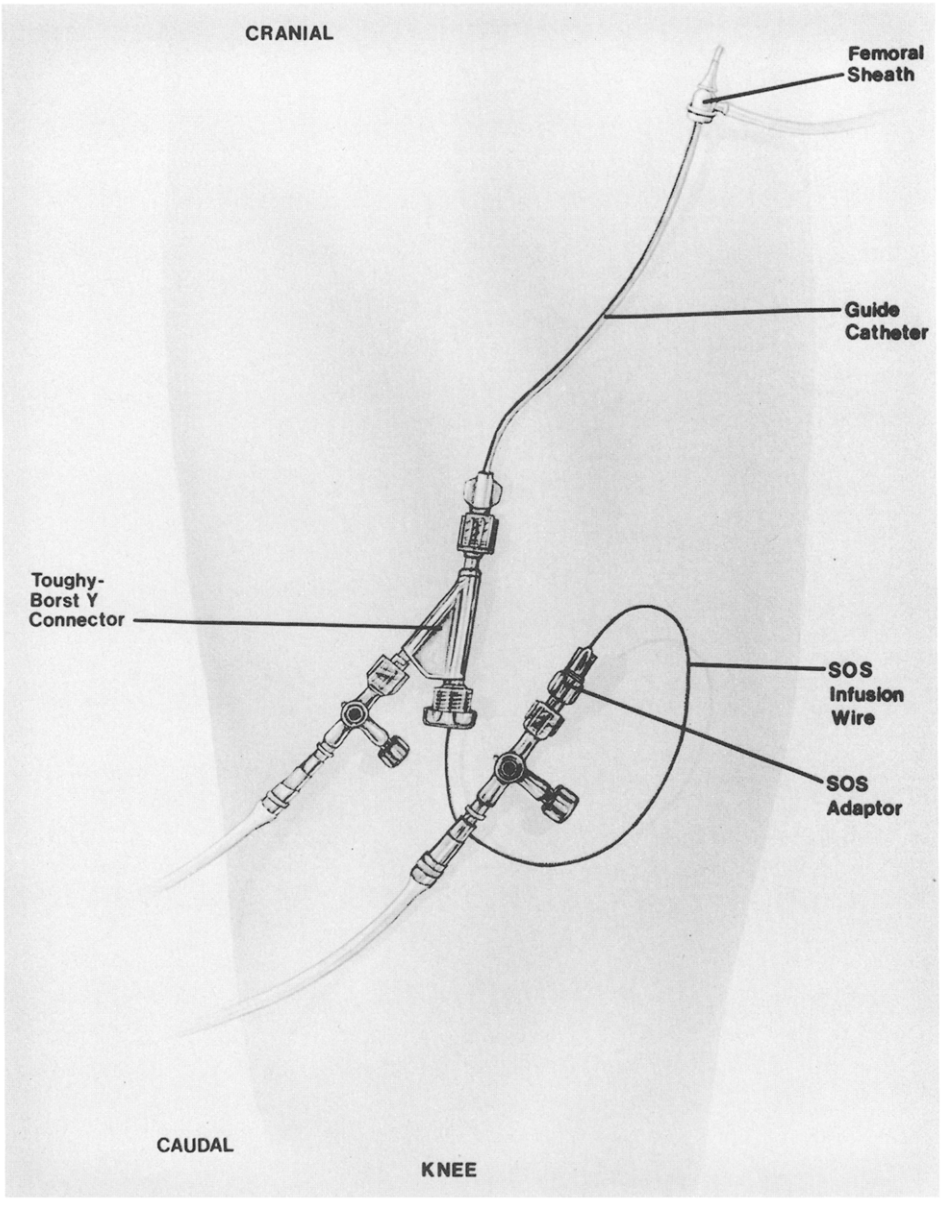

Figure 2. Illustration of limb demonstrating the procedural set-up.

deemed necessary. Fibrinogen levels were measured in all patients during therapy. In one patient, the nadir fibrinogen level was <100 mg/dl; in seven patients, a level <200 mg/dl was demonstrated. No patient exhibited transient or permanent neurologic symptoms or findings.

Clinical follow-up. All successfully treated patients were followed up clinically for symptoms of angina pectoris, myocardial infarction, abnormal exercise electrocardiographic findings and the need for further intervention. The mean follow-up interval was 27.2 months (range 6 to 48). During the follow-up period, 14 patients experienced angina pectoris, 2 developed congestive heart failure and 4 underwent repeat aortocoronary bypass surgery. There were four deaths during the follow-up period (two sudden, one due to congestive heart failure and one in which circumstances are unknown). Twenty-two patients (61%) remained free of symptoms during the follow-up period.

Angiographic follow-up. Twenty successfully treated patients underwent repeat angiography during the 27-month follow-up period. Fourteen patients returned with angina pectoris; six remained asymptomatic and underwent elective angiography. The clinical characteristics of these 20 patients are presented in Table 2. The grafts in 13 patients (65%) were patent (Fig. 3, A to E), but 2 of the 13 required angioplasty for recurrent graft stenosis. Ten of these patients had been maintained on warfarin therapy after their recanalization procedure. The grafts in seven patients (35%) were occluded; six of these patients had been treated with long-term warfarin therapy. Of the seven patients with an occluded bypass graft, four underwent repeat

Table 1. Clinical Characteristics of 10 Patients Experiencing a Urokinase Treatment Failure

Pt No.	Age (yr)/ Gender	Graft Site	Urokinase		Comments
			Duration of Infusion (h)	Total Dose (U)	
1	62/M	OM	72	2,700,000	No reflow phenomenon
2	62/F	LAD	21	1,260,000	Difficulty positioning catheter; discontinued by patient
3	62/F	RCA	18	1,800,000	Discontinued by patient
4	52/M	Diag	17.5	1,300,000	Difficulty positioning catheter
5	61/M	LAD	17	850,000	Difficulty positioning catheter
6	83/F	Diag	42	4,200,000	No reflow phenomenon
7	52/M	OM	15.5	1,500,000	Difficulty positioning catheter
8	62/M	OM	22.75	2,275,000	Difficulty positioning catheter
9	56/F	OM	27.5	4,500,000	Discontinued by investigator because of a history of bleeding
10	53/M	RCA	33.75	4,570,000	Discontinued by investigator because of an adverse event (see text)

Diag = diagonal branch; F = female; LAD = left anterior descending coronary artery; M = male; OM = obtuse marginal branch; Pt = patient; RCA = right coronary artery.

bypass surgery, two were successfully treated with repeat extended urokinase infusion and one patient was treated medically.

Discussion

Initial therapy. The technique of prolonged urokinase infusion into a saphenous vein bypass graft was first attempted with use of a protocol similar to that used for chronic peripheral arterial thrombosis (13). Our present experience yielded a 79% success rate and we have identified several factors that appear to predict success. 1) Recently occluded bypass grafts apparently respond to urokinase therapy more frequently than do grafts known or thought to be occluded for a longer time. Thus, although the precise interval of graft occlusion is difficult to determine by history alone, the duration of graft occlusion ranged from 0.2 to 18 weeks (mean 2.4) in the patients with successful recanalization compared with 0.2 to 28 weeks (mean 7.4) in those in whom the procedure failed. 2) To be amenable to this

Table 2. Long-Term Follow-Up of 20 Patients After Successful Extended Urokinase Infusion

Pt No.	Age (yr)/ Gender	Initial Site of Occlusion	Years After CABG* to Urokinase Infusion	Total Urokinase Dose (U)	Follow-Up After Urokinase		Graft Status*
					Duration (mo)	Reason	
1	48/M	LAD	4	4,000,000	6	Elective	Patent
2	63/M	RCA	8	2,400,000	3	Symptoms	Patent
3	54/M	LCx	8	4,649,000	24	Symptoms	Occluded
4	67/M	OM	10	3,725,000	23	Symptoms	Patent
5	65/M	RCA	1	4,400,000	3	Symptoms	Patent
6	56/M	LAD	11	1,600,000	22	Symptoms	Occluded
7	69/M	OM	5	2,400,000	5	Symptoms	Occluded
8	64/M	OM	10	3,900,000	5	Elective	Patent
9	66/M	RCA	4	6,950,000	22	Symptoms	Occluded
10	69/M	OM	8	1,600,000	24	Elective	Patent
11	55/M	RCA	12	870,000	5	Symptoms	Patent
12	73/M	LAD	5	825,000	2	Symptoms	Patent
13	61/M	LCx	4	4,750,000	3	Symptoms	Occluded
14	63/M	LAD	6	9,690,000	1	Symptoms	Patent
15	67/M	RCA	3	5,925,000	8	Elective	Patent
16	65/M	OM	7	1,670,000	12	Symptoms	Patent
17	62/M	RCA	9	7,560,000	9	Symptoms	Occluded
18	65/M	RCA	3	2,600,000	9	Elective	Occluded
19	49/M	RCA	4	4,875,000	7	Elective	Patent
20	57/M	Diag	9	720,000	13	Symptoms	Patent

*Patients 3, 6, 7 and 17 underwent repeat coronary artery bypass grafting. Patient 18 was medically managed. Patients 9 and 13 underwent repeat urokinase infusion followed by successful angioplasty. CABG = coronary artery bypass grafting; LCx = left circumflex coronary artery; other abbreviations as in Table 1.

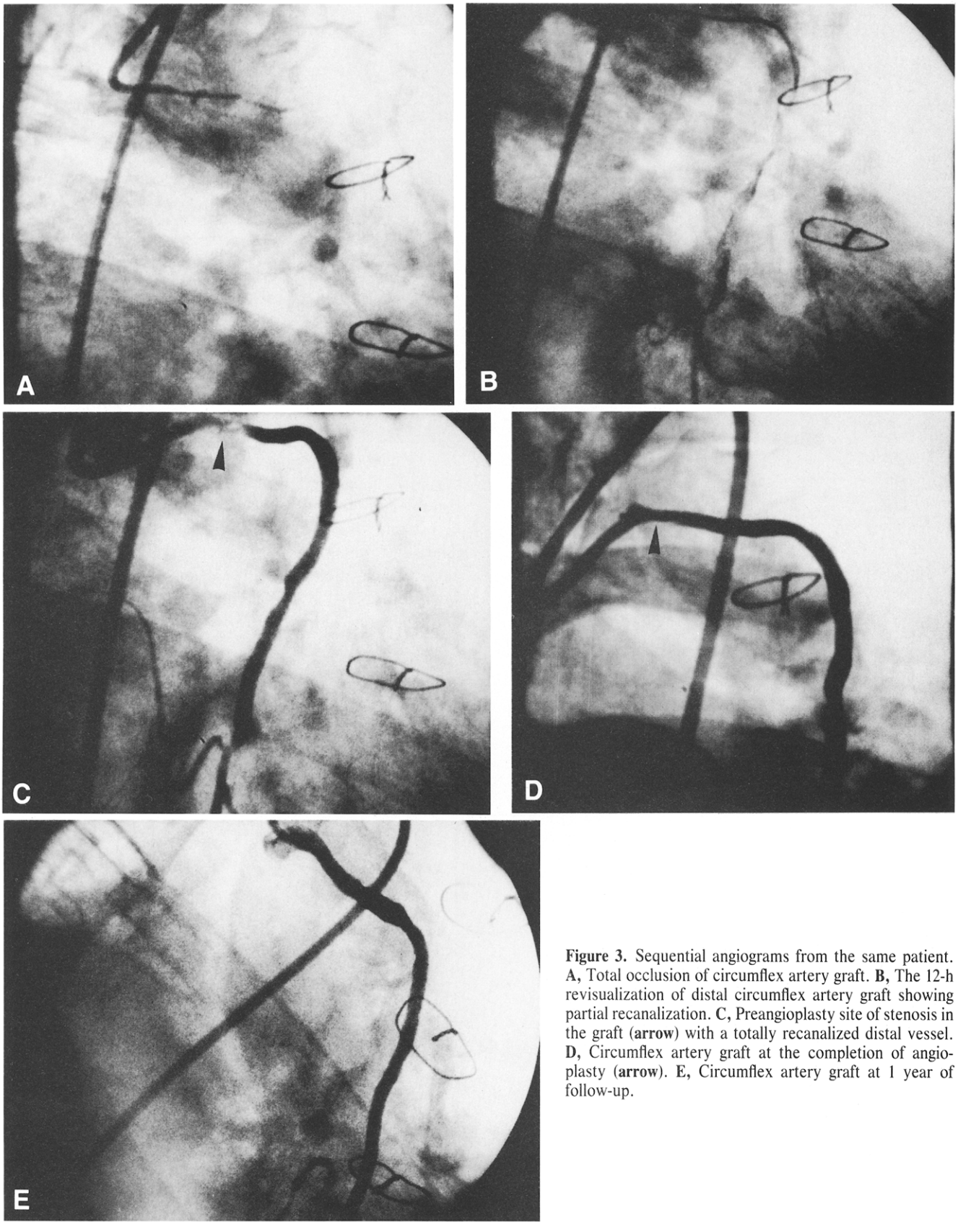

Figure 3. Sequential angiograms from the same patient. **A,** Total occlusion of circumflex artery graft. **B,** The 12-h revisualization of distal circumflex artery graft showing partial recanalization. **C,** Preangioplasty site of stenosis in the graft (**arrow**) with a totally recanalized distal vessel. **D,** Circumflex artery graft at the completion of angioplasty (**arrow**). **E,** Circumflex artery graft at 1 year of follow-up.

procedure, the saphenous vein graft must have a stub that facilitates reliable positioning of both the catheter and the infusion wire. 3) Although difficult to quantify, the presence of significant viable myocardium in the distribution of the vein graft appears to allow for greater success. 4) Patient acceptance of the prolonged time (up to 77 h) required for successful lysis is necessary. Because patient discomfort secondary to restricted body movement may be significant, adequate analgesia and sedation are mandatory.

The relative lack of acute complications during the procedure is of significance. No central nervous system events or symptoms were noted in any patient. Although all patients were receiving optimal maintenance anticoagulant therapy with heparin during the thrombolytic period, bleeding complications were minimal. Only one patient (2%) required blood transfusion.

The problem of embolic myocardial infarction and myocardial ischemia requires special attention. We previously reported (18) on three patients with this condition and have now observed it in a total of six patients (13%). In four of these patients, increasing the dose of urokinase resulted in the resolution of the signs of ischemia and little or no evidence of myocardial necrosis. Of the six patients, three presented with prior evidence of an infarct in the zone of the graft. Given the small number of patients exhibiting this phenomenon, further investigation is required to identify potential predisposing factors.

Clinical and angiographic follow-up. Although the clinical follow-up period is limited to a mean of 27 months and the angiographic follow-up to 20 patients, the results are encouraging. The 65% confirmed patency rate and the 61% freedom from recurrent angina are exceptional given the significant symptoms in this group at baseline. In addition, two patients with reocclusion were successfully retreated with urokinase infusion. Although no clear trend toward improvement in long-term graft patency among patients maintained on warfarin therapy was demonstrated, we currently place all patients with a successfully recanalized graft on both warfarin and aspirin therapy before hospital discharge.

Conclusions. Although broader, more widespread experience needs to be gathered to define the risk of myocardial infarction, cerebrovascular accident and other complications, our initial results and follow-up data suggest that extended infusion of urokinase in occluded saphenous vein bypass grafts offers an excellent treatment option for selected patients with resistant symptoms due to vein graft occlusion. In carefully selected patients, it is a safe and effective alternative to repeat aortocoronary bypass surgery.

We express our appreciation to Julie Gurgone, Mary Kobus and Beatrice Wolf for their efforts in data collection. We also thank the staff and nurses of the cardiac catheterization laboratory and coronary care unit at Elmhurst Memorial and Good Sarmaritan Hospitals.

References

1. Stein B, Fuster V, Halperin JL, Chesebro JH. Antithrombotic therapy in cardiac disease: an emerging approach based on pathogenesis and risk. Circulation 1989;80:1501–13.
2. Cosgrove DM, Loop FD, Lytle BW, et al. Predictors of reoperation after myocardial revascularization. J Thorac Cardiovasc Surg 1986;92:811–21.
3. Cameron A, Kemp H, Green G. Reoperation of coronary artery disease: ten years of clinical follow up. Circulation 1988;78(suppl I):I-158–62.
4. Fuster V, Chesebro JH. Role of platelets and platelet inhibitors in aortocoronary artery vein-graft disease. Circulation 1986;73:227–32.
5. Chesebro JH, Fuster V, Elveback LR, et al. Effect of dipyridamole and aspirin on later vein-graft patency after coronary bypass operations. N Engl J Med 1984;310:209–14.
6. Bourassa MG, Fisher LD, Campeau L, Gillespie MJ, McConney M, Lespérance J. Long-term fate of bypass grafts: the Coronary Artery Surgery Study (CASS) and Montreal Heart Institute experiences. Circulation 1985;72(suppl V):V-71–8.
7. Bourassa MG, Enjalbert M, Campeau L, Lespérance J. Progression of coronary artery disease between 10 and 12 years after coronary artery bypass graft surgery. In: Roskamm H, ed. Progression of Coronary Arteriosclerosis. Berlin: Springer-Verlag, 1983:150.
8. Goldman S, Copeland J, Moritz T, et al. Saphenous vein graft patency 1 year after coronary artery bypass surgery and effects of antiplatelet therapy: results of a Veterans Administration Cooperative Study. Circulation 1989;80:1190–7.
9. Reul GJ, Cooley DA, Ott DA, Coelho A, Chapa L, Eterovic I. Reoperation for recurrent coronary artery disease: causes, indications, and results in 169 patients. Arch Surg 1979;114:1269–75.
10. Grondin CM, Campeau L, Thornton JC, Engle JC, Cross FS, Schreiber H. Coronary artery bypass grafting with saphenous vein. Circulation 1989;79(suppl I):I-24–9.
11. de Feyter PJ, Serruys P, van den Brand M, Meester H, Beatt K, Suryapranata H. Percutaneous transluminal angioplasty of a totally occluded venous bypass graft: a challenge that should be resisted. Am J Cardiol 1989;64:88–90.
12. Platko WP, Hollman J, Whitlow PL, Franco I. Percutaneous transluminal angioplasty of saphenous vein graft stenosis: long-term follow-up. J Am Coll Cardiol 1989;14:1645–50.
13. Hartmann J, McKeever L, Teran J, et al. Prolonged infusion of urokinase for recanalization of chronically occluded aortocoronary bypass grafts. Am J Cardiol 1988;61:189–91.
14. Frumin H, Goldberg MJ, Rubenfire J, Levine FH. Late thrombolysis of an occluded aortocoronary saphenous vein graft. Am Heart J 1983;106: 401–3.
15. Smuckler AL, Rufty AJ, Headley RN, Welbourne R. Thrombolysis in an aortocoronary saphenous vein graft. Cathet Cardiovasc Diagn 1982;8: 507–12.
16. Rentrop P, Blanke H, Karsch KR, Kostering H, Oster H, Leitz H. Recanalization of an acutely occluded aortocoronary bypass by intragraft fibrinolysis. Circulation 1980;62:1123–6.
17. TIMI Study Group. Special report. The Thrombolysis in Myocardial Infarction (TIMI) trial: phase I findings. N Engl J Med 1985;312:932–6.
18. McKeever LS, Hartmann JR, Bufalino VJ, et al. Acute myocardial infarction complicating recanalization of aortocoronary bypass grafts with urokinase therapy. Am J Cardiol 1989;64:683–5.