The New England
Journal of Medicine

Volume 316 MARCH 19, 1987 Number 12

INTRAVASCULAR STENTS TO PREVENT OCCLUSION AND RESTENOSIS AFTER TRANSLUMINAL ANGIOPLASTY

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Abstract Occlusion and restenosis are the most common reasons that transluminal balloon angioplasty may fail to provide long-term benefit. An intravascular mechanical support was therefore developed with the aim of preventing restenosis and sudden closure of diseased arteries after angioplasty. The endoprosthesis consists of a self-expandable stainless-steel mesh that can be implanted nonsurgically in the coronary or peripheral arteries. Experiments in animals showed complete intimal coverage within weeks and no late thrombosis during a follow-up period of up to one year.

We performed 10 implantations in 6 patients for iliac or femoral arterial disease; 24 coronary-artery stents were implanted in 19 patients who presented with coronary-artery restenoses (n = 17) or abrupt closure (n = 4) after transluminal angioplasty or deterioration of coronary-bypass grafts (n = 3). We observed three complications in the group with coronary disease. One thrombotic occlusion of a stent resulted in asymptomatic closure, a second acute thrombosis was managed successfully with thrombolysis, and one patient died after bypass surgery for a suspected but unfound occlusion. Follow-up in the patients has continued for nine months without evidence of any further restenoses within the stented segments.

Our preliminary experience suggests that this vascular endoprosthesis may offer a useful way to prevent occlusion and restenosis after transluminal angioplasty. Long-term follow-up will be required to validate the early success of this procedure. (N Engl J Med 1987; 316:701-6.)

ALTHOUGH most stenoses of coronary and peripheral arteries can now be traversed and dilated by balloon angioplasty, the unpredictable problems of abrupt closure and late restenosis of the dilated segment continue to compromise the overall results of this promising procedure. In addition to the pharmacologic,[1] mechanical,[2,3] and thermal techniques[4-6] under investigation to deal with these problems, intravascular stents may provide a useful approach to preventing both acute occlusion and late restenosis.[7-13]

None of the current designs of intravascular stents are ideal, however, especially with respect to homogeneous distribution of force, ease of placement, conformability, and stability. A new system has been developed, consisting of a stainless-steel multifilament, self-expanding, macroporous stent and an innovative instrument for placing it (Medinvent SA, Lausanne, Switzerland). We report our preliminary experience with the placement of stents in peripheral and coronary arteries after transluminal balloon angioplasty of a diseased arterial segment.

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Supported in part by a grant (3,835,083) from the Swiss National Fund.

METHODS

Description of the Stent

The stent is woven from a surgical-grade stainless-steel alloy formulated according to the specifications of the International Standards Organization. The prosthesis (Fig. 1) is geometrically stable, pliable, and self-expanding. Its elastic and pliable properties are such that its diameter can be substantially reduced by moderate elongation. It can be constrained on a small-diameter delivery catheter, and as the constraining membrane is progressively removed, the elastic device will return to its original (unconstrained) larger diameter (Fig. 1). When the prosthesis is implanted in a vessel whose caliber is less than that of its unconstrained diameter, the residual elastic radial force in the prosthesis will tend to dilate the artery. Dilation will continue until an equilibrium is attained between the circumferential elastic resistance of the arterial wall and the dilating force of the prosthesis. The constrained wire-mesh prosthesis is held at the distal end of the delivery catheter (Fig. 1A) by a doubled-over membrane, the outer layer of which can be progressively withdrawn. Two radiopaque metal markers on the delivery catheter facilitate identification of the end of the prosthesis at the time of its deployment. The outer diameter of the loaded catheter system is 1.57 mm, and prostheses up to 6.5 mm in expanded diameter can be mounted on this delivery device. Prostheses larger in diameter for use in peripheral arteries have correspondingly larger delivery systems.

Experiments in Animals

Prostheses up to 6.5 mm in diameter were mounted on the delivery catheter and were passed with conventional guiding catheters into the femoral, popliteal, and coronary arteries.

Peripheral Arterial Implants

In three mongrel dogs weighing 25 to 35 kg that were given heparin, eight transluminal implants were placed in branches of the femoral arteries at the level of the knee through the common femoral artery. The diameters of the prostheses ranged from 2 to 6.5 mm, and the lengths ranged from 20 to 70 mm. No anticoagulants were given after placement. All the dogs were evaluated weekly by Doppler-flow monitoring for four weeks and at three-month intervals by angiography.

Coronary Arterial Implants

In seven dogs, seven coronary prostheses were implanted through the femoral artery with use of 8 French coronary guiding catheters. Under fluoroscopy, one stent was placed in the right coronary artery, one was placed in the first marginal branch of the right coronary artery, and five were placed in the proximal left anterior descending coronary artery. One of the five last-mentioned prostheses extended into the left main coronary artery. The stents ranged from 2.5 to 3.5 mm in diameter and 15 to 20 mm in length. Again, no anticoagulants were given after implantation, but an intraoperative heparinized perfusion was given.

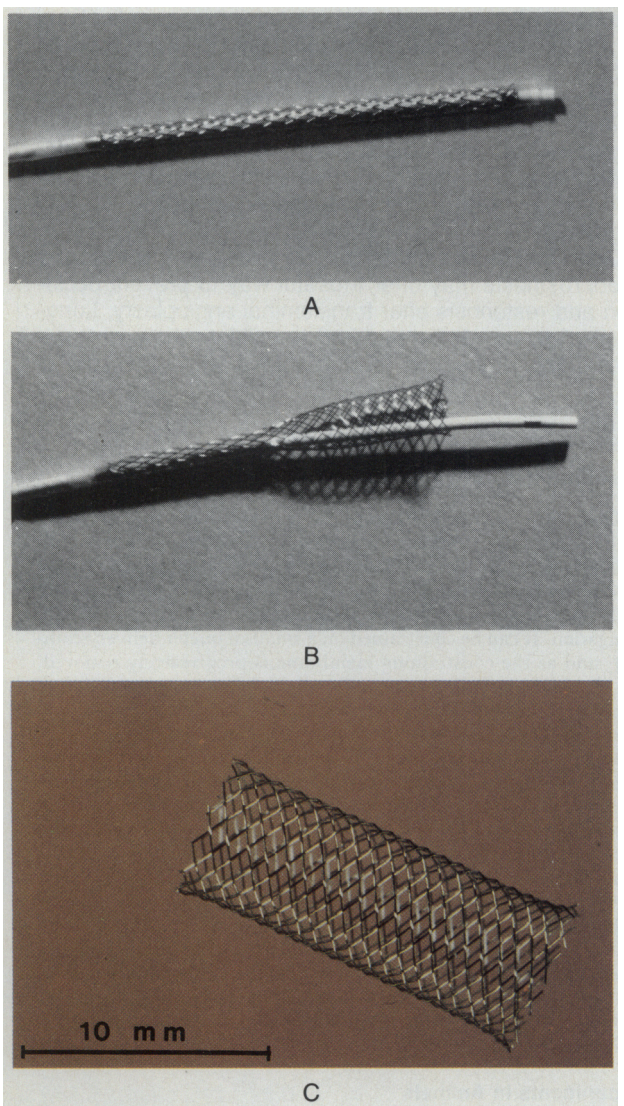

Figure 1. The Self-Expanding, Elastic, Macroporous Tubular Prosthesis, Which Is Woven from Stainless Steel, Is Shown (Panel A) Constrained on the Delivery Catheter, (B) Half Open during Deployment, and (C) Unconstrained and Fully Expanded.

Implants in Humans

After the trials in animals, a protocol for implants in humans was approved by the hospital ethics committee, and informed consent according to the Helsinki Declaration was obtained from each patient before the intervention.

Peripheral Arterial Implants

For peripheral arterial implantation, highly symptomatic patients were selected who had (1) iliac or femoral arteries with long and complex stenoses in which balloon angioplasty had either failed or offered a poor prognosis, or (2) iliac or femoral restenosis after previous angioplasty.

Ten stents were implanted during seven procedures in six patients (four femoral and three iliac arteries). Stent diameters ranged from 6 to 12 mm, and lengths from 30 to 80 mm. Prostheses up to 6.5 mm in expanded diameter were delivered through an 8 French coronary guiding catheter; larger stents were deployed with use of an 8 French delivery system introduced directly through an ordinary 9 French arterial introducing sheath. Drug therapy consisted of acetylsalicylic acid (500 mg) the day before the intervention and a bolus injection of 10,000 IU of heparin during the implantation, followed by intravenous heparin (partial thromboplastin time at least twice the control value) until oral acenocoumarol had prolonged the prothrombin time to a therapeutic level (2½ times control). A fixed combination of aspirin (330 mg) plus dipyridamole (75 mg) once daily in addition to oral acenocoumarol was also given from the first postoperative day during the first three months of follow-up.

In two patients, totally occluded arteries were recanalized and stents were placed. One patient had a left superficial femoral-artery occlusion 30 cm in length, which failed to remain patent despite adequate balloon angioplasty followed by local infusion of urokinase. Two consecutive prostheses 6 mm in diameter and 8 cm in length were implanted. A longstanding 8-cm occlusion of the left external iliac artery was mechanically recanalized and dilated, and since no adequate flow was attained, a stent 8 cm in length and 12 mm in diameter was placed (Fig. 2). All the other prostheses were placed in stenotic arteries that had not responded satisfactorily to balloon angioplasty.

Coronary Arterial Implants

Three conditions were considered indications for the insertion of endoluminal stents in coronary vessels or coronary-bypass grafts: (1) restenosis of a major coronary artery after previous balloon angioplasty; (2) stenosis of aortocoronary-bypass grafts (in these patients the stents were placed in the bypass grafts themselves); and (3) acute coronary occlusion secondary to intimal dissection following balloon angioplasty (the placements of stents in these patients were categorized as emergency implantations).

Twenty-four coronary stents were implanted after transluminal balloon angioplasty in 19 patients during 20 operative procedures. In one patient the deployment of the stent in the left anterior descending coronary artery failed because of mechanical problems with the delivery catheter; since no reserve device was available, implantation was abandoned, without further complications.

After successful angioplasty, the balloon catheter was exchanged for the stent delivery system over a 0.014-inch (0.036-cm) exchange guide wire. The diameter of the stent was chosen to be about 15 percent larger than that of the native artery. Stents 15 or 20 mm in length, depending on the lesion, were placed to cover the entire diseased segment. Finally, the inner surface was smoothed by brief balloon dilatation.

The pharmacologic treatment involved inhibitors of platelet aggregation (1 g of aspirin the day before the procedure) and intraoperative heparin (15,000 units intravenously). During stent implantation, 50,000 to 100,000 units of urokinase were slowly in-

fused through the coronary guiding catheter. Intravenous heparin was continued postoperatively until the oral anticoagulation with acenocoumarol became effective. All patients received calcium-channel–blocking agents, 330 mg of aspirin, and 75 mg of dipyridamole (Persantine) per day, starting four to eight hours after the operation.

Eleven stents were placed in the left anterior descending coronary arteries, eight stents in the right coronary arteries, two in the circumflex arteries, and three in venous coronary-artery bypass grafts. Two patients received a second stent at a later date, in each case for a new lesion, not adjacent to the original stent. There were four emergency implantations for acute occlusion following transluminal coronary angioplasty.

Results

Experiments in Animals

Peripheral Arterial Implants

Two dogs were chosen to be killed after six months and one after nine months. Six stents were fully patent, one demonstrated a mural thrombus with a 50 percent reduction in luminal diameter, and one, which was perfused in a retrograde manner in an artery that had been ligated proximally, showed complete recanalization. The prostheses remained free from intimal hyperplasia; moreover, all the side branches leaving the stented segments of the main vessel remained patent (Fig. 3). Figure 4 shows an example of a prosthesis firmly embedded in the arterial wall. This specimen was recovered from a branch of the femoral artery at the level of the left knee nine months after implantation. Scanning electron microscopy showed the neointima smoothly filling the pores between the stent filaments. The neointimal layer was about 450 μm thick, and no signs of necrosis due to the continuous mural pressure of the metal filaments were seen. The endothelial surface was very similar to the original arterial endothelium.

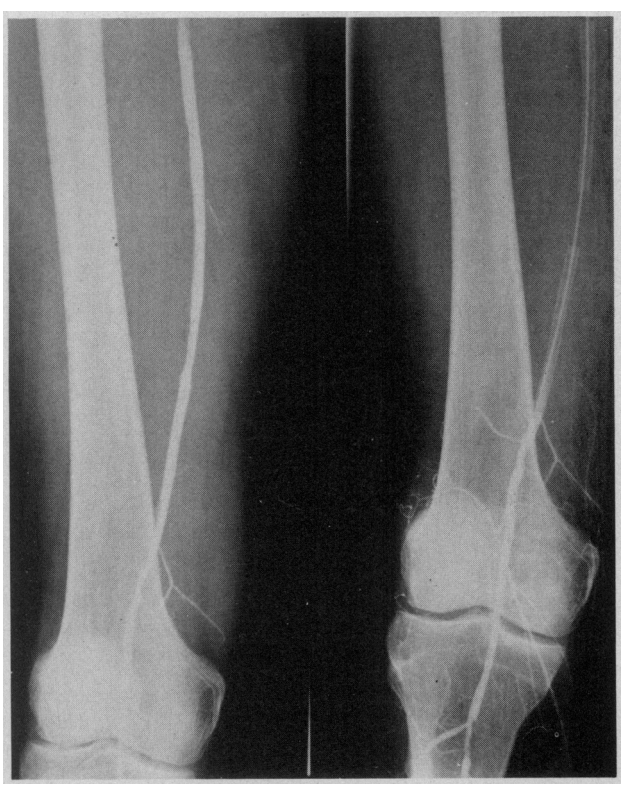

Figure 2. Superficial Femoral Artery after Mechanical Recanalization of a Total Occlusion 30 cm Long, Followed by Implantation of Two Endoprostheses.

For better visualization of the stents, the right-hand panel shows contrast medium injected at a point distal to the two prostheses through a 4.5 French angiography catheter. Note the nonstented lesion 4 cm below the knee. Three more prostheses were implanted three months later to treat severe lesions within nonstented segments.

Coronary Arterial Implants

Angiography performed three and six months after implantation showed no signs of obstruction, either from thrombus or hyperplasia. However, after the dogs were killed at nine months, one unobstructive mural thrombus that was considerably larger than the coronary artery was seen in a stent (there had been a mismatching of diameters). In the single case in which the stent extended into the left main coronary artery, there was no interference with blood flow in the circumflex artery.

Clinical Experience

Peripheral Arterial Implants in Patients

There were no instances of restenosis as judged from a reappearance of symptoms, a decrease of peripheral blood flow by Doppler measurements, or digital subtraction angiography. No important side effects were reported, although one patient continued for two weeks to report an occasional sensation of a foreign body in the iliac area. Mean follow-up in this series is more than six months at this writing. Adequate blood flow and the disappearance of severe claudication were observed in each case. One patient's symptoms reappeared after three months because of high-grade stenoses of the nonstented femoral arterial segments proximal to and between the stents (Fig. 2). These stenoses were therefore dilated and reinforced with three additional stents — one overlapping the first two prostheses and two upstream of the first implants. Again, there was clinical improvement, reduction of the pressure gradient, and an increase in peripheral flow as demonstrated by Doppler evaluation. Although hemodynamically unimportant endothelial thickening within the stents was noted during follow-up angiography, the patient remained clinically well after nine months of follow-up.

Coronary Implants in Patients

Occlusion of the stent occurred twice when the myocardium perfused by the vessel was already hypokinetic from an old nontransmural infarction; however, the prosthesis was successfully recanalized in one patient after local infusion of 100,000 units of urokinase. Thrombolytic therapy was refused by the second

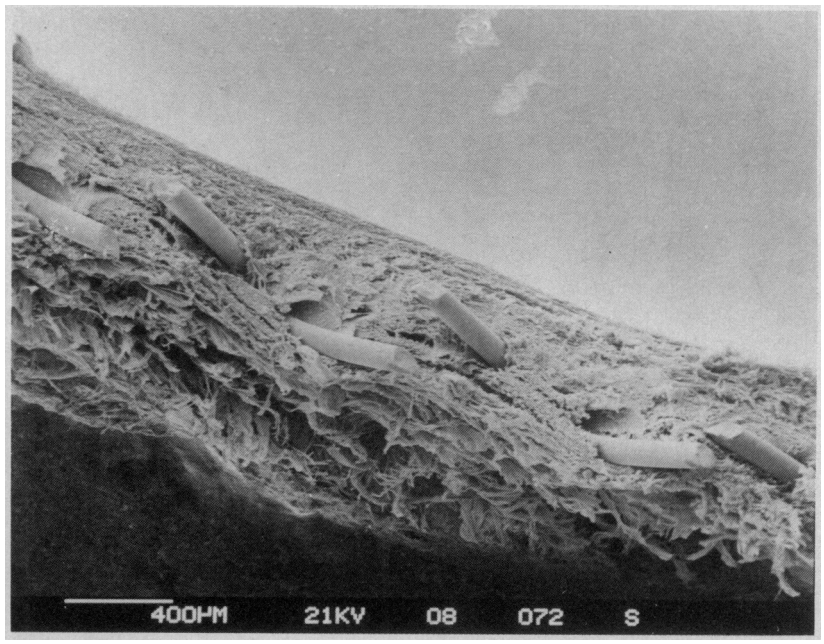

Figure 4. Scanning Electron Micrograph of a Prosthesis Firmly Embedded in the Femoral Artery of a Dog at the Level of the Left Knee Nine Months after Implantation.

patient, who now has mild angina with exertion, seven months after the procedure.

One patient presented a special problem. He was a 56-year-old man who had a 90 percent proximal stenosis of the left anterior descending coronary artery causing residual angina one week after an anteroapical infarction. After angioplasty, symptomatic restenosis occurred within two months. The lesion was redilated and a stent was placed. Two days later the patient underwent maximal stress testing with no evidence of ischemia. Fifteen minutes afterwards, electrocardiographic signs of anterolateral ischemia developed. In the absence of immediately available angiographic facilities, the patient was transferred for bypass surgery (internal mammary implant), at which time the signs of ischemia had disappeared and the prosthesis was found to be patent. The postoperative period was complicated by problems with hemostasis and signs of cardiac tamponade. The following day the patient had hypoxia and subsequently died. Postmortem examination revealed a patent bypass graft and some traces of a recent thrombus in the prosthesis, which was correctly situated without extension into the left-main bifurcation. No clear link could be established between death and the prosthesis, although the stent may have contributed to coronary spasm soon after stress testing.

Emergency Implantation

In all four patients in whom a stent was implanted to relieve an acute coronary occlusion after balloon angioplasty, adequate coronary flow was immediately restored. Simultaneously, the electrocardiogram became normal and symptoms of angina pectoris disappeared. Myocardial enzyme measurements showed no signs of myocardial damage. Figure 5 shows a left anterior descending coronary artery before and six months after emergency implantation of a prosthesis 3.5 mm in expanded diameter and 20 mm in length. A stent was later placed in the right coronary artery of the same patient because of restenosis.

Follow-up

The patient whose vessels are shown in Figure 5 had symptomatic restenosis of the nonstented right coronary artery, which had also been dilated at the time of the first procedure; this stenosis was dilated a second time and a stent was placed that has remained patent. A new stenosis proximal to the stent developed in one patient four

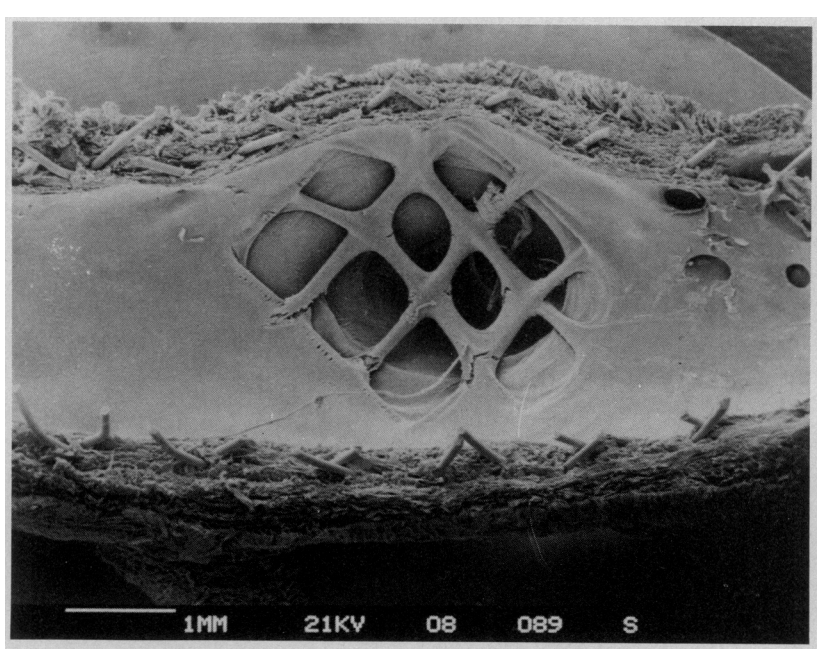

Figure 3. Scanning Electron Micrograph of a Stent Covering the Orifice of a Side Branch of a Canine Femoral Artery.

Nine months after implantation, the metal wires are completely coated with a smooth neointimal lining, which does not compromise blood flow to the branch artery.

months after the first procedure; this lesion was also dilated and reinforced with a separate stent.

All the other patients recovered normally and left the hospital within four days of the procedure. Follow-up consisted of weekly and then monthly clinical examinations, stress tests at two-month intervals, and — up to now in 12 patients — coronary angiography within three to six months after the intervention. There were no clinical signs of restenosis (except in the patients in whom a second prosthesis was implanted because of new lesions) as judged by the clinical history and exercise testing. Coronary angiography showed the endoluminal stent smoothly embedded with no traces of serious luminal narrowing or suggestion of intimal hyperplasia within the stent.

Discussion

Restenosis and acute occlusion following transluminal angioplasty of coronary and peripheral arteries restrict the usefulness of this procedure. With restenosis rates as high as 33 percent after coronary angioplasty and even higher (68 percent) in multivessel angioplasty, the overall value of balloon angioplasty is diminished even when one considers the low morbidity of this procedure, which is frequently repeated several times. The socioeconomic implications of repeated angioplasties for restenosis are important and compromise the comparatively low cost of the intervention.

The rates of early and late repeated occlusion after peripheral and coronary angioplasty are independent of the operator's skill and the quality of the equipment. Longer inflation times, high doses of calcium-channel blockers, steroids, and other drug regimens have so far failed to solve these problems. An alternative approach is to provide a suitable endoluminal support for the diseased vessel wall.

Several designs have been proposed, including elastically self-expanding spirals, memory-metal types (thermally expandable and relatively inelastic), and balloon deformable (quasi-rigid) models. Endothelialization with uniform and consistent intimal thickening and patency of side branches, such as we have described, has also been reported by others,[9] but with some minor differences. It appears that the length of time it takes to cover the stent surface depends on the thickness of the metal element. Thus, Wright et al.[9] reported only 30 percent covering after one month for wire 0.46 mm thick, whereas we found complete covering of 0.09-mm filaments within three weeks. As compared with inelastic devices, we think that the self-expanding stent, by virtue of its inherent pliability, provides a smooth transition between the stented segment and adjacent native artery; this has been corroborated by histologic studies of the junction between the stent and the nonstented artery. A longitudinal flexible stent, which is also flexible even when mounted on its delivery catheter, will permit easier access through tortuous vessels to the target site.

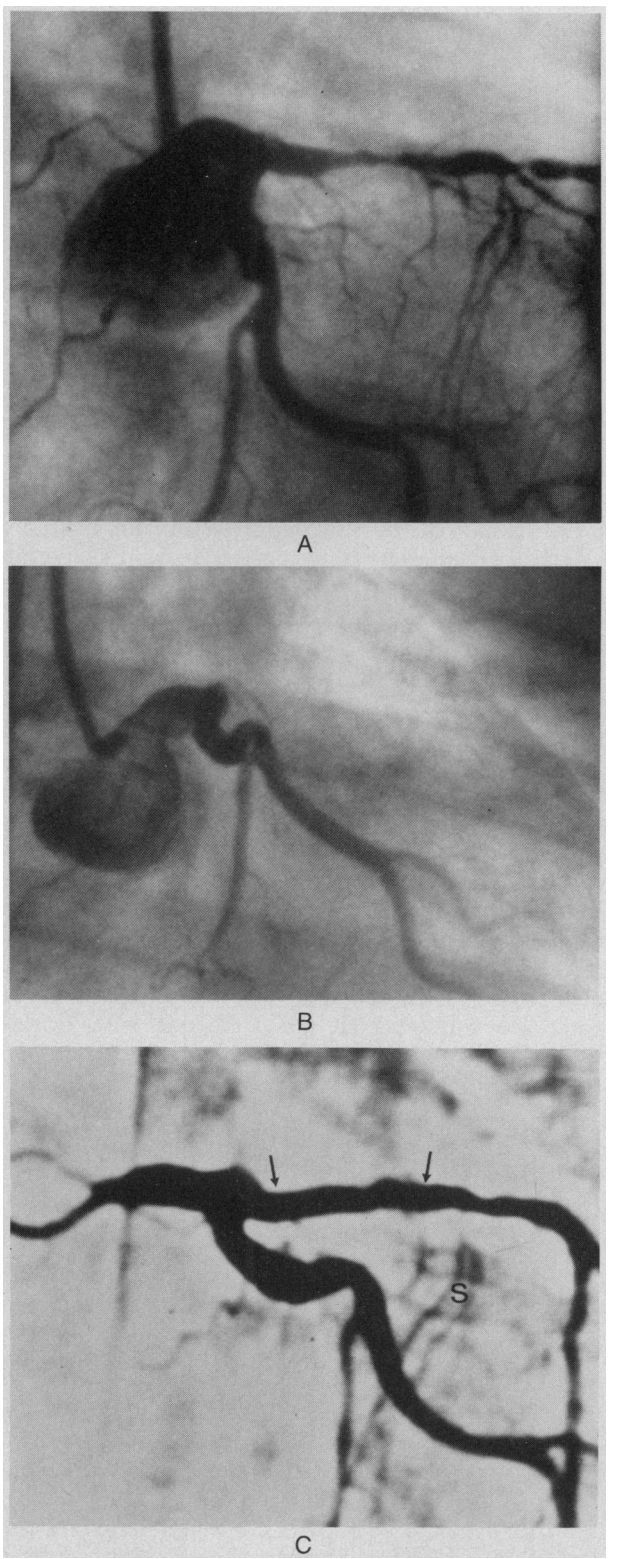

Figure 5. Left Coronary Artery (Panel A) before Angioplasty, (B) after the Development of Complete Occlusion after Angioplasty, and (C) Six Months after Emergency Recanalization of, and Stent Implantation in, the Left Anterior Descending Coronary Artery.

The stent is invisible (Panel C) because of the high density of the contrast material; its position is shown by the arrows (upper vessel), the distal end being just proximal to the septal branch (S).

Our experiments in healthy animals have shown that the endoprosthesis is well tolerated for up to one year. Our preliminary results in patients who received a total of 10 peripheral and 24 coronary implants revealed no cases of restenosis within the stented segment after follow-up ranging from nine weeks to nine months, whereas the statistical likelihood of such an event is approximately 30 percent or more. We also found it possible to reopen arteries that became occluded after a previous angioplasty, with favorable medium-term results. It is possible, of course, that many of the arteries that we studied might have remained patent after angioplasty even without the placement of a stent; randomized trials will be necessary to ascertain the long-term benefit.

As for the potential risks of this method, little is known about the possible longer-term complications. We have no long-term information (beyond 12 months in canine arteries) on the outcome of the patency of side branches, and although the prostheses are completely endothelialized, infection could conceivably be a future pitfall. We have specifically avoided traversing major branch vessels, not only because of uncertainty about long-term patency, but also because to do so would prevent later angioplasty should it be required. We have also specifically avoided placing stents in segments having sudden changes in vessel caliber, since we believe that these might pose a higher risk of thrombogenesis. Similarly, poor distal runoff or lesions leading to competitive flow might increase the risk of thrombosis and could have been responsible for the occlusion of the stent in two of our patients. It is also possible that stents may induce coronary spasm, since any foreign body (e.g., a guide wire) within the arterial lumen can enhance vasomotor tone; this could explain the ischemic reaction 15 minutes after maximal stress testing in the patient in whom no signs of thrombus were seen at surgery.

Further studies will determine with greater precision the benefits and risks of this new approach. On the basis of our preliminary experience, we suggest that intravascular stents may represent a valuable adjunct to transluminal angioplasty.

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