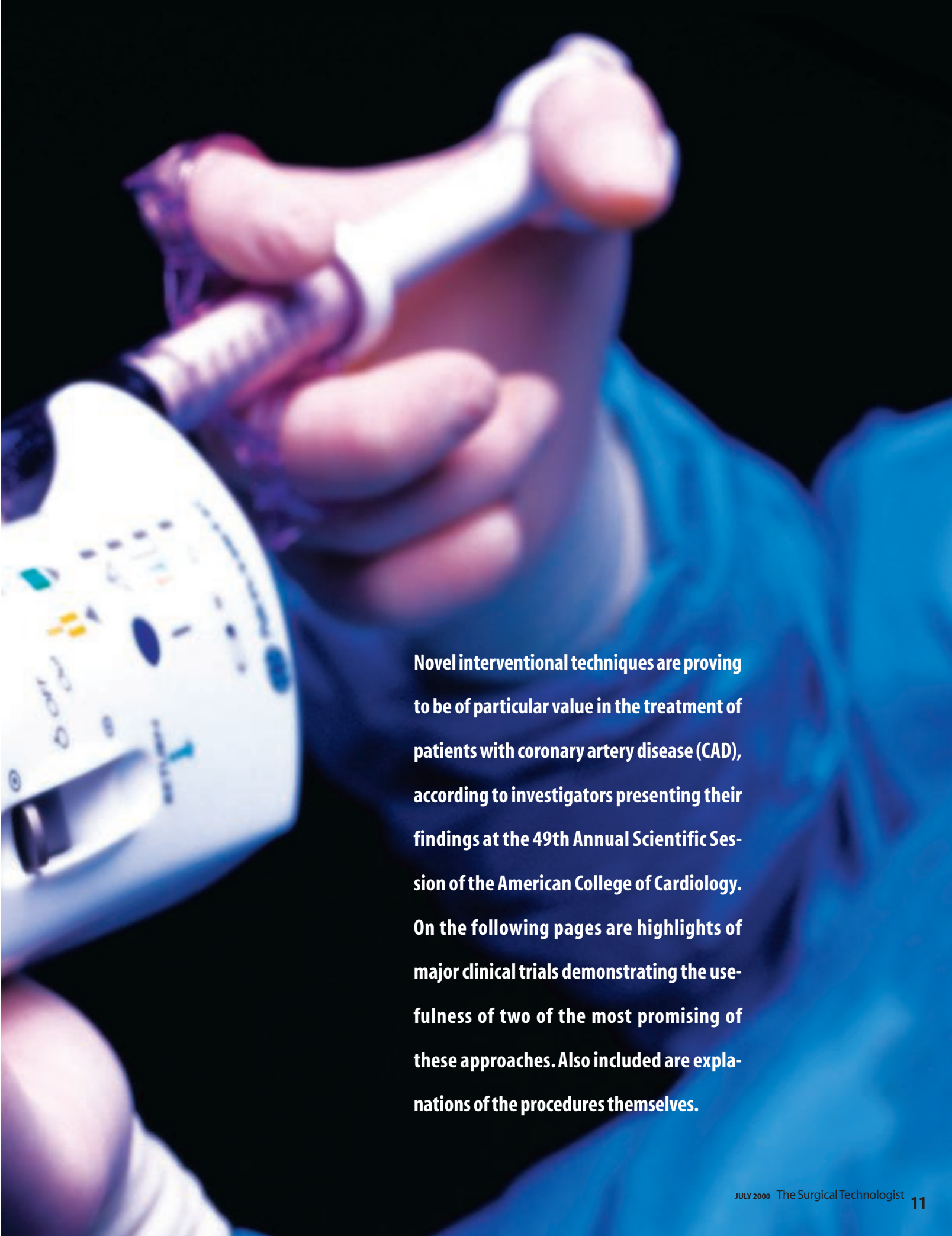


by Lawrence M Prescott, PhD

NEW INTERVENTIONAL TECHNOLOGIES EXPAND TREATMENT OPTIONS FOR CARDIOVASCULAR DISEASE





Novel interventional techniques are proving to be of particular value in the treatment of patients with coronary artery disease (CAD), according to investigators presenting their findings at the 49th Annual Scientific Session of the American College of Cardiology. On the following pages are highlights of major clinical trials demonstrating the usefulness of two of the most promising of these approaches. Also included are explanations of the procedures themselves.

The significance of coronary artery disease

With its effects upon the brain, heart, kidneys, other vital organs, and extremities, coronary artery disease (CAD) is a leading cause of morbidity and mortality in the United States and in most Western countries with almost 25 million people worldwide suffering from the disease. Despite progress in prevention and treatment that has reduced the death rate from CAD by more than one-quarter, angina pectoris, myocardial infarction (MI) and sudden death are still major problems. In the United States alone, acute MI causes 35 percent of deaths in middle-aged men.

Since CAD is still untreatable, the traditional treatment approaches involve stopping or slowing the disease and reducing the possibilities of myocardial infarction and sudden death. These approaches include smoking cessation, diet, drug therapy for atherosclerosis, hypertension, and relief of CAD symptoms, and non-invasive, minimally invasive, and invasive interventional and surgical procedures.

Beta radiation vascular brachytherapy

Background

Percutaneous transluminal coronary angioplasty (PTCA), generally known as balloon angioplasty, is the most commonly used interventional procedure for opening narrowed coronary arteries (Figure 1). The major limitation of this approach is the frequency of coronary artery re-narrowing, resulting in the need for repeat procedures or bypass surgery or both in nearly half of the patients within six months of the PTCA. Numerous studies have shown, however, that stenting with a metal scaffolding device is superior to balloon angioplasty alone in terms of need for repeat revascularization, significantly reducing the rate of recurrence of arterial narrowing (Figure 2).

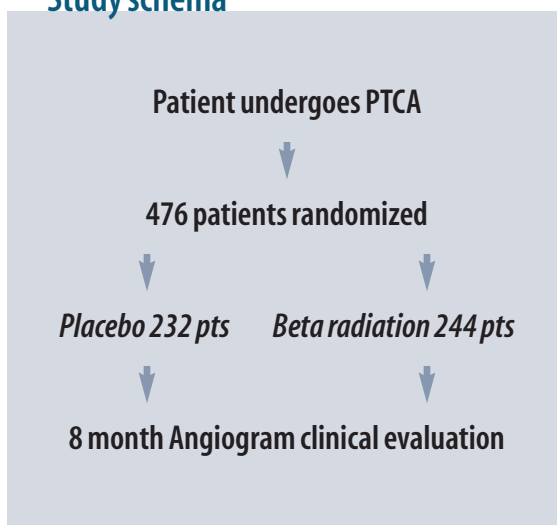
More than 75 percent of all patients who undergo balloon angioplasty for CAD—about 700,000 people per year in the United States—receive stents in an effort to prolong the benefits of the procedure. Unfortunately, approximately 25 percent of these patients will later suffer from

in-stent restenosis, a condition where the stent becomes narrowed with new tissue growth. The treatment of in-stent restenosis poses a very difficult challenge to cardiologists because the chance of recurrent restenosis in previously stented patients is in the 40 percent to 80 percent range. Currently there are no definitive therapies that effectively treat in-stent restenosis other than bypass surgery, an expensive and highly invasive procedure that requires a long recuperation period.

Intracoronary brachytherapy technology

Recently, cardiologists have been testing a form of radiotherapy, which involves the temporary

Study schema



insertion of radioactive metal pellets or wires into the widened artery, to see whether it can prevent the tissue regrowth within the stent. Metal inserts that emit gamma radiation, called intracoronary brachytherapy, have already proved useful for preventing in-stent restenosis in several clinical trials of this treatment. Less studied is beta radiation, which is much less penetrating than gamma radiation, and is easier to use.

In this regard, the Beta-Cath™ System, developed by Novoste Corporation, can be used in conjunction with a typical balloon angioplasty procedure or with angioplasty that includes a new stent placement to temporarily deliver beta radiation to the angioplasty or stent site. The sys-

tem contains Strontium-90 seeds that deliver beta radiation through a closed-end lumen catheter temporarily placed inside the patient's artery. Beta radiation is a highly localized, less penetrating form of radiation than gamma radiation, so it requires little or no incremental shielding and exposes medical staff to significantly less radiation than even the X-ray imaging associated with angioplasty procedure. The whole body radiation to the patient in the procedure is less than 1.0 percent of that which is received during the X-ray portion of the angioplasty procedure, and the beta radiation is placed in the body for less than five minutes, only treating the angioplasty site and not traveling any-

where else in the body. The physician, therefore, is able to remain along side the patient throughout the treatment.

Clinical study

Findings from a landmark clinical study, known as the Strontium-90 Treatment of Angiographic Restenosis Trial (START), show that beta radiation, using the Beta-Cath™ system, reduced the risk of repeat in-stent restenosis or the need for additional treatment in patients with in-stent restenosis, compared to those on placebo. The results were presented by Jeffrey J Popma, MD, director of interventional cardiology, Brigham and Women's Hospital, Boston, Massachusetts.

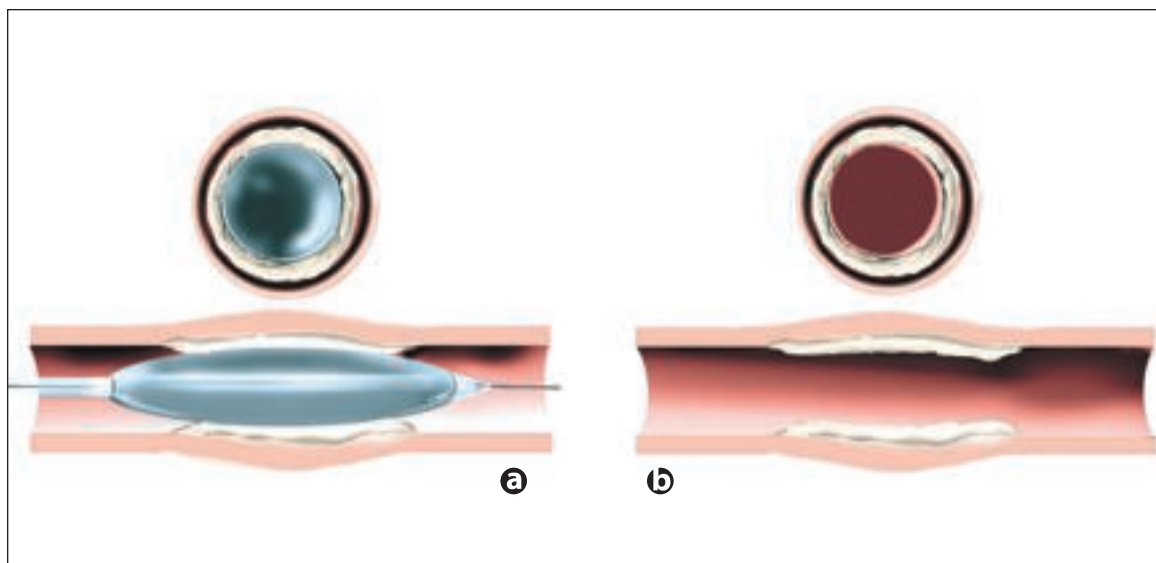


FIGURE 1

Balloon angioplasty

- Ⓐ Balloon angioplasty is often used to widen the vessel opening of a partially blocked artery.
- Ⓑ Restenosis may occur, even after a successful balloon angioplasty.

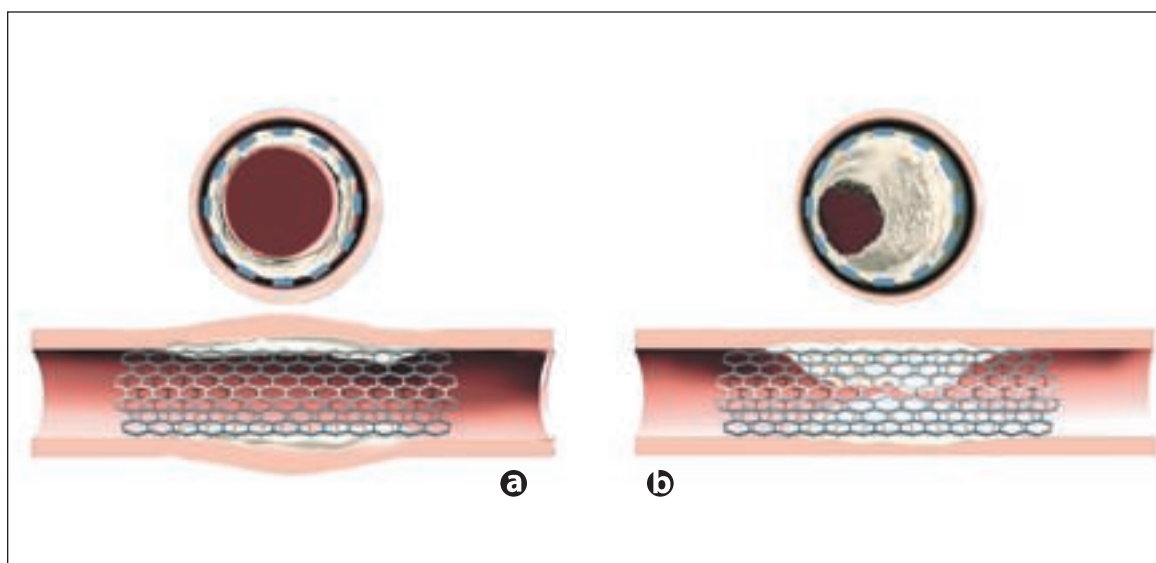


FIGURE 2

Stent

- Ⓐ A stent may be placed after balloon angioplasty to help maintain the integrity of the vessel.
- Ⓑ However, restenosis within the stent can occur.

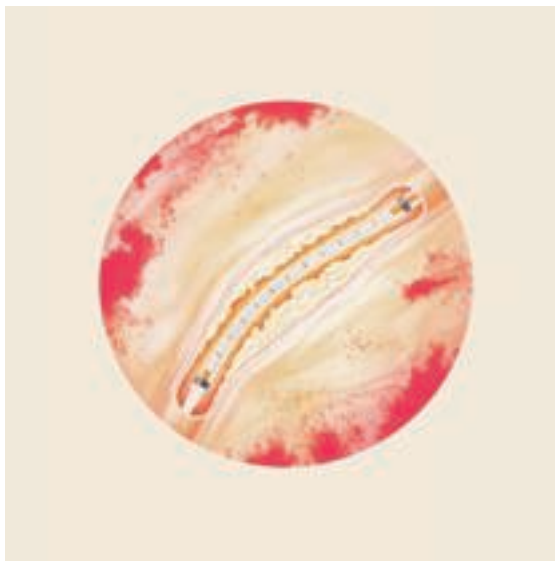
FIGURE 3

Radiation Source Train is delivered hydraulically by the transfer device (right) through the delivery catheter to the injury site.



FIGURE 4

The use of intravascular radiation has proven successful in reducing the incidence of restenosis.



To assess the safety and efficacy of intracoronary beta radiation following successful coronary intervention in patients with in-stent restenosis, a total of 476 patients were enrolled into this prospective, multicenter (50 sites in North America and Europe), randomized, placebo-controlled, triple-masked clinical trial. The patients presented with single-lesion, single-vessel disease, all with in-stent restenosis greater than 50 percent and lesion length treatable with a 20 mm balloon.

Immediately following the procedure to open their blocked stents, patients were randomly assigned to either a placebo or an active radiation source train, all of which were 30 mm in length, and both delivered through the Beta-Cath™ system (Figure 3). Depending on the artery diameter, a dose of either 16 or 20 gray was administered. A total of 21.7 percent of patients in the beta radiation group and 20.7 percent of patients receiving placebo received a new stent in conjunction with their treatment.

The primary endpoint was eight-month target vessel revascularization (TVR). This was the percentage of patients who required an additional procedure such as bypass surgery within eight months to re-open the originally treated artery at any location within the vessel (Figure 4). The secondary efficacy endpoints were eight-month angiographic restenosis and late loss. Angiographic restenosis was measured on angiogram by the percentage of patients who had greater than 50 percent stenosis in the treated artery within eight months of the intracoronary brachytherapy procedure. Late loss was measured by later clinical thrombosis observed long-term (eight months) in the treated group. The safety endpoint was eight-month major adverse cardiac events (MACE), a composite endpoint including TVR, MI, and death.

Overall, the Beta-Cath™ System performed reliably, with short treatment times of three to five minutes achieved with Strontium-90 radiation. Most importantly, a significant treatment effect was demonstrated for all clinical and angiographic outcome parameters.

The stent segment restenosis rate went from 41 percent in the placebo group to 14 percent

with beta radiation treatment, for a 66 percent reduction in patients who received beta radiation compared to those on placebo. The total analyzed segment restenosis rate (stent segment, injured segment, radiated segment) was 45 percent in the placebo group versus 29 percent in the beta radiation-treated patients, for a reduction of 63 percent. Evaluation of the primary endpoint of TVR showed an increase of TVR in 16 percent of actively-treated patients compared to 34 percent of those on placebo, for a reduction of 34 percent, a significant difference in favor of beta radiation. With regard to MACE at eight months, there was a 34.4 percent reduction in favor of beta radiation brachytherapy (25.9 percent or placebo versus 18 percent on beta radiation) and a 240-day, event-free survival in respect to the Strontium-90 treatment.

Finally, Popma addressed some concern about late thrombosis in patients receiving new stents together with radiation, according to recent clinical findings. In 31 to 270 days following treatment, late clinical thrombosis was not noted in any of the 21 percent of patients in the START study with new coronary stent lacements who underwent intracoronary brachytherapy.

Percutaneous transmyocardial revascularization

Background

Some patients with advanced heart disease have had so many unsuccessful treatments (angioplasties, coronary artery bypass graft surgery, maximal medical therapy) that they have run out of effective alternatives. These individuals often are called “no option” patients. They have significant chest pain that impairs their day-to-day function but are not considered candidates for any further bypass surgery or angioplasty.

PTMR technology

A new form of revascularization—transmyocardial laser revascularization—had been proven to provide a surgical treatment alternative for patients with severe angina pectoris refractory to traditional therapies. Now, a non-surgical form, known as percutaneous transmyocardial revas-

FIGURE 5

Percutaneous transmyocardial revascularization is now possible through a non-surgical procedure where a catheter is threaded into the patient's leg and through the artery to the heart.

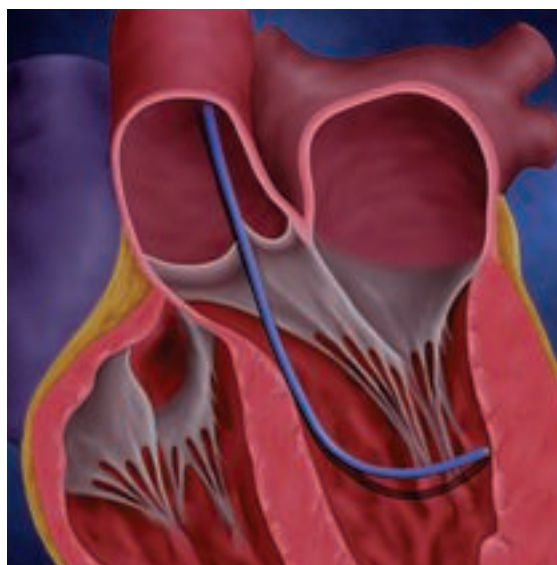
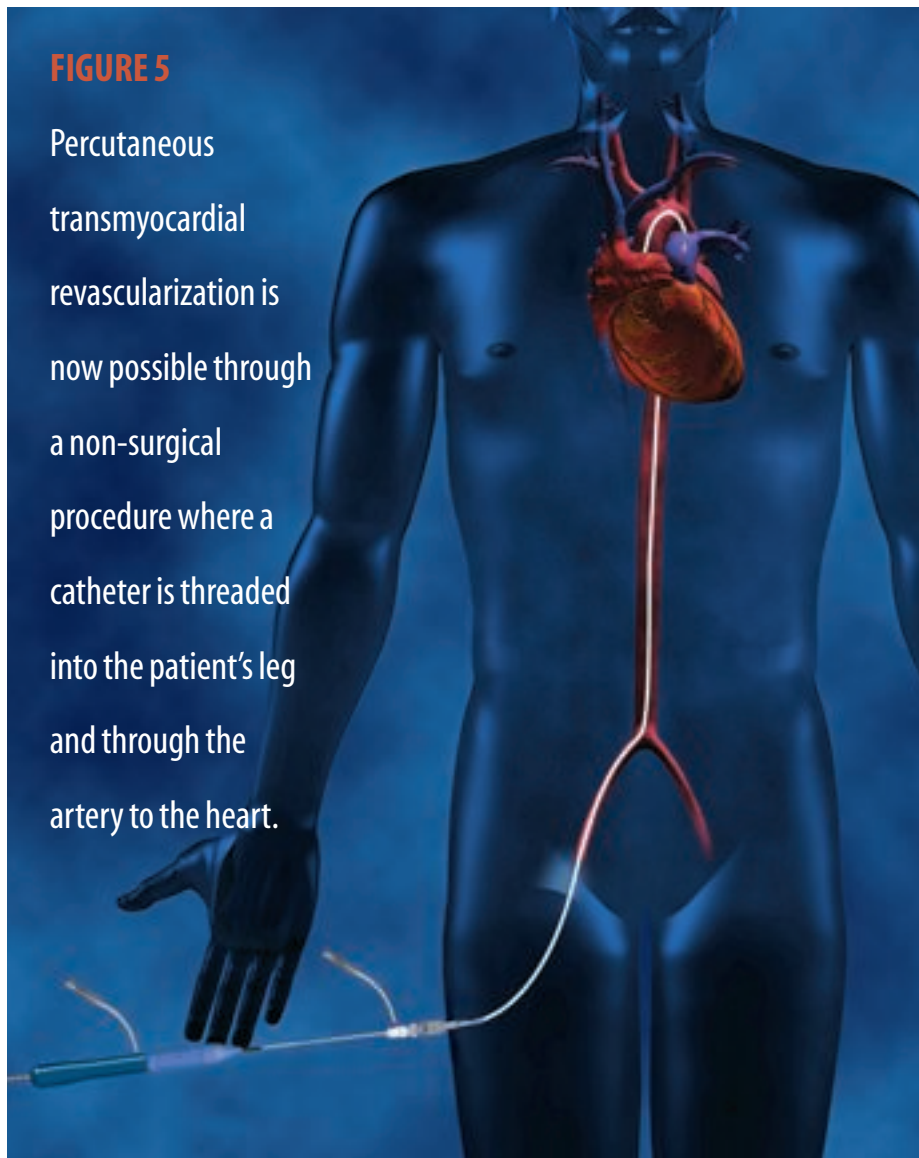


FIGURE 6

The PTMR catheter is positioned within the left ventricle against the endocardial surface.

FIGURE 7

A laser delivery system creates multiple PTMR channels within the endocardial wall.

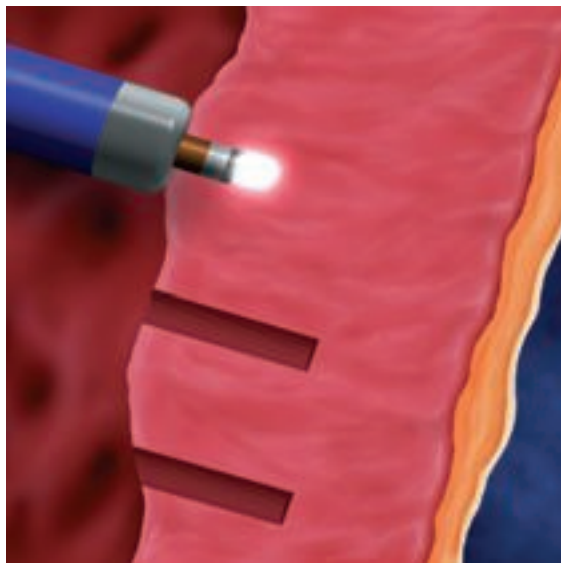


FIGURE 8

PTMR channels promote redistribution of intramyocardial blood flow.

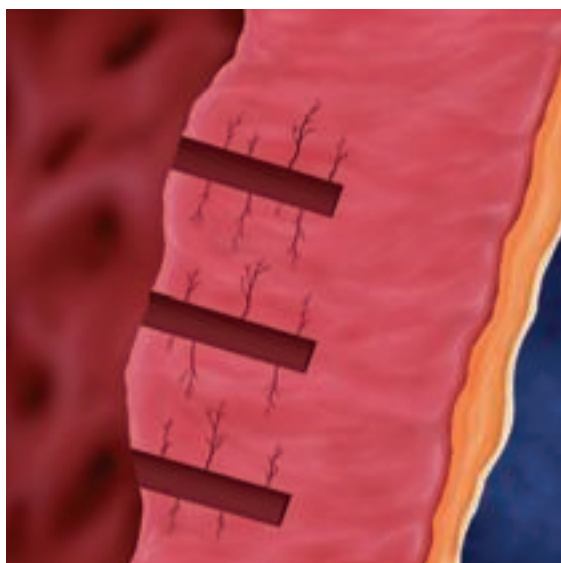
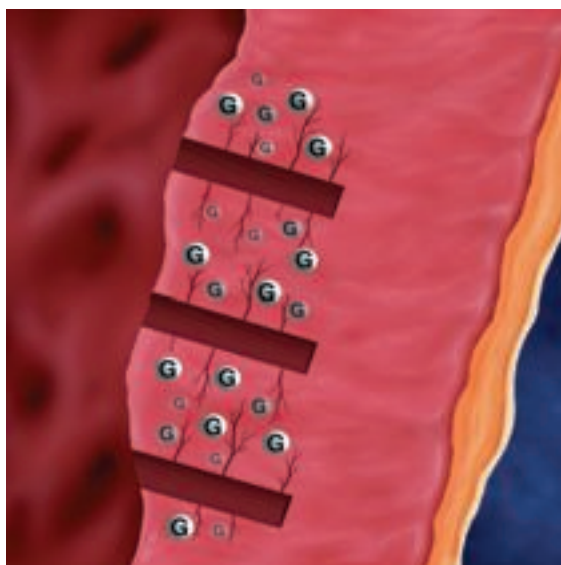


FIGURE 9

Cellular growth factors are released at the treatment site, promoting angiogenesis.



cularization (PTMR), has been developed (Eclipse® TMR 2000 Laser System, Eclipse Surgical Technologies).

PTMR is performed under local anesthesia in the cardiac catheterization laboratory. A small incision is made in the patient's leg and a catheter is threaded through the artery to the heart (Figure 5). The steerable PTMR catheter is positioned within the left ventricle against the endocardial surface (Figure 6). A fiberoptic helium/YAG laser delivery system is inserted in the catheter and advanced while laser energy is being delivered to create a PTMR channel. The catheter is repositioned approximately 12 to 26 times and fired each time to create multiple channels (Figure 7). The entire procedure takes about one hour, with the laser portion lasting up to 30 minutes. Patients are hospitalized for about one day.

There are two proposed mechanisms of action. First, the channels may allow blood flow to oxygen-starved areas of the myocardium, thus relieving angina (Figure 8). Secondly, it is believed that, as these channels heal, cellular growth factors are released at the treatment site, promoting angiogenesis, which results in the development of new blood vessels (Figure 9). As the PTMR channels recede, the increased perfusion can, thus, be maintained long term (Figures 10 and 11).

Clinical study

Late-breaking results from a large, multicenter clinical trial pointed out that PTMR is a relatively safe technique with significant long-term benefits for patients who continue to have severe, debilitating angina pectoris despite receiving maximal medical therapy. Results were reported by Emerson C Perin, MD, Texas Heart Institute at St Luke's Episcopal Hospital, Baylor College of Medicine, Houston, Texas.

"There have been many reports of results from the surgical approach, but this is one of the first presentations of one-year follow-up data on PTMR," Perin said. "Not having to open the chest, with all the complications that can ensue makes PTMR potentially a more benign proce-

cedure. Furthermore, PTMR significantly improves angina and exercise time at six months and one year.”

To reach these conclusions, 325 patients were enrolled into a major, randomized, 20-center trial to test whether PTMR might provide long-term relief for these individuals with severe, refractory angina pectoris. Patients were considered eligible if they had class III or IV refractory angina in place of conventional revascularization techniques, such as angioplasty, bypass surgery, or maximal medical therapy. These individuals were randomly assigned to either PTMR (163 pts) or continued maximal medical therapy (162 pts). At baseline, 72 percent of the total patient population were Class III, 25 percent were Class IV, and 3 percent were Class II. Follow-up was carried out at six months and 12 months. During the study, because of their condition, a total of 7 percent of patients on medical management were crossed over to PTMR.

Findings from this study demonstrated that, at six months and 12 months, PTMR-treated individuals had significantly greater improvements in anginal class and exercise tolerance compared to those on maximal medical therapy. At 12 months follow-up, there were more PTMR-treated patients in class II, class I, and without angina than were seen in the persons on continuing medical therapy. In this regard, 55 percent of those in the PTMR group were angina Class II or less versus 31 percent of patients in the maximal medical therapy group. Furthermore, PTMR-treated individuals were able to exercise longer than those on the continuing medical therapy. Patients who received PTMR were able to exercise 101 seconds longer than they could at baseline before treatment, while those in the maximal therapy group had a 16-second decrease in exercise time compared to baseline one year previously.

According to Patrick L Whitlow, MD, director of interventional cardiology, Cleveland Clinic Foundation, Cleveland, Ohio, another of the study’s principal investigators, “We are very encouraged by these results. For these very sick patients with few, if any, treatment alternatives,

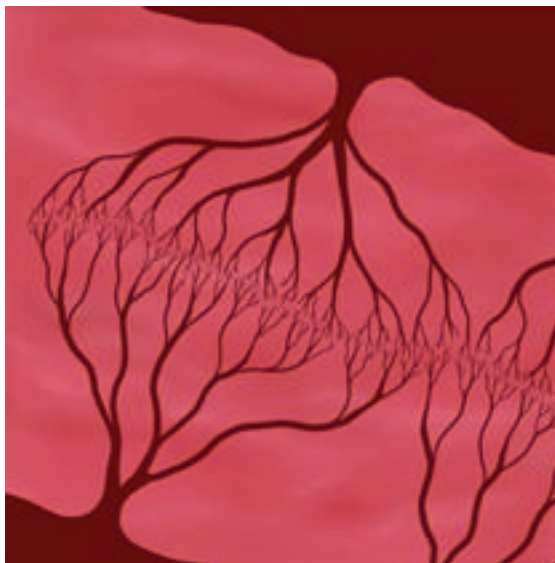


FIGURE 10
Intramyocardial blood flow increases through newly created vessels.

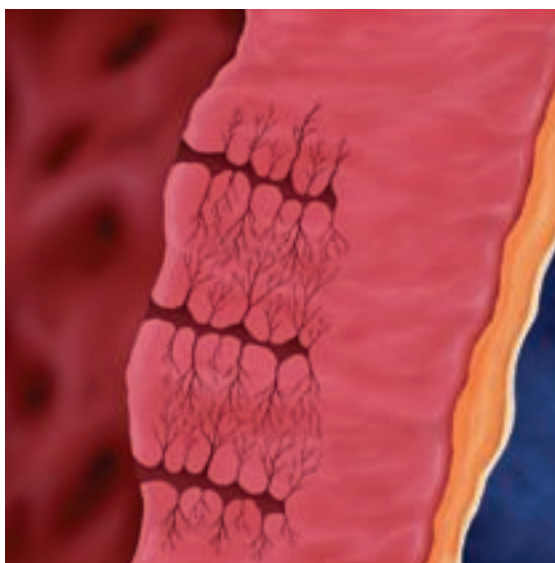


FIGURE 11
Although channels recede, increased perfusion is maintained long term.

PTMR is a relatively low-risk procedure that can dramatically impact their quality of life.”

About the author

Lawrence M Prescott, PhD, is a freelance medical, health, and science writer previously employed as an infectious disease specialist and clinical pathologist by the World Health Organization.

Reference

Popma JJ, Perin EC, presenters. “The Late Breaking Treatments in Interventional Cardiology”: Scientific Session, American College of Cardiology; March 12-15, 2000; Anaheim, Calif.

Illustrations courtesy of Novoste Corporation and Eclipse Surgical Technologies.