REVIEW

CME CREDIT

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# New options for untreatable coronary artery disease: Angiogenesis and laser revascularization

## ABSTRACT

Some patients with severe symptomatic coronary artery disease despite maximal medical therapy are not eligible for bypass surgery or percutaneous coronary intervention, but may be eligible for two newer therapies: therapeutic angiogenesis with growth factors and transmyocardial laser revascularization.

## KEY POINTS

All patients with symptomatic coronary artery disease should receive maximal medical therapy, which includes aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, nitrates, and lipid-lowering agents.

Patient selection for the newer treatments is based on symptoms, comorbid states, ischemia documented by an imaging test, and left ventricular function.

The newer treatments are effective in improving symptoms and decreasing hospitalization rates but have not shown survival benefit.

TWO NEW TREATMENTS for coronary artery disease may help the growing group of patients who have run out of other options:

- Therapeutic angiogenesis—giving drugs that stimulate growth of collateral vessels, either by injection directly into the myocardium or by intracoronary or intravenous infusion.
- Transmyocardial revascularization—using a laser to create multiple tiny holes in the myocardium, either as a catheter-based procedure or during open surgery.

At present, these therapies are available only in major referral centers, but they are moving out of the realm of experimental protocols. In fact, community cardiologists with patients with refractory angina despite maximal medical therapy should consider referring them to a center that does these procedures. TABLES 1 and 2 outline the eligibility requirements for these procedures.

## THE PROBLEM: REFRACTORY, UNTREATABLE CORONARY DISEASE

The established treatments for obstructive coronary artery disease are medical therapy, bypass surgery, and percutaneous coronary interventions. But a growing number of patients continue to have significant angina despite maximal medical therapy and are not candidates for bypass surgery or percutaneous interventions. These patients fall into two general groups: those with severe diffuse disease in native coronary vessels and those with recurrent narrowing or occlusion of bypass grafts.

According to a recent study,[1] approxi-

**TABLE 1**

## Inclusion and exclusion criteria for therapeutic angiogenesis and transmyocardial revascularization

**Inclusion criteria**

Stable angina in Canadian Cardiovascular Society class III or IV
Angina refractory to maximal medical therapy
Area of ischemic myocardium on an imaging stress study
Severe coronary artery disease not amenable to coronary artery bypass grafting or percutaneous intervention

**Exclusion criteria**

Concurrent severe illness with markedly reduced life-expectancy
Unstable angina
Severe left ventricular systolic dysfunction with an ejection fraction of less than 20%

**For growth factor therapy:**

Cancer
Funduscopic signs of diabetic retinopathy

**For transmyocardial revascularization:**

Left ventricular thrombus

**TABLE 2**

## The Canadian Cardiovascular Society classification system for angina

**Class I**

No angina with ordinary physical activity such as walking or climbing stairs
Angina with strenuous or rapid or prolonged exertion at work or recreation

**Class II**

Slight limitation of ordinary physical activity
Angina with walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, in wind, or when under emotional stress, or only during the few hours after awakening
Angina with walking more than two blocks on the level and climbing more than one flight of stairs at a normal pace in normal conditions

**Class III**

Marked limitation of ordinary physical activity
Angina with walking one or two blocks on the level and climbing more than one flight in normal conditions

**Class IV**

Inability to carry on any physical activity without discomfort
Angina may be present even at rest

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mately 5% of patients undergoing coronary angiography may be candidates for newer treatments. Considering that 1,713,000 cardiac catheterizations were performed in 1996 in the United States,[2] approximately 100,000 patients per year may be eligible.

## TRY MAXIMAL MEDICAL THERAPY FIRST

We cannot overemphasize the importance of maximal medical therapy. Before considering a new type of therapy, we recommend a trial of medical therapy in optimum doses (FIGURE 1). All patients with symptomatic coronary artery disease should receive the following drugs, if they have no contraindications to them:

- Aspirin to prevent platelet aggregation (81 to 325 mg per day)
- A beta-blocker to reduce ischemia and angina, ideally a long-acting formulation that can be given once a day (eg, atenelol 50 to 100 mg per day, or metoprolol XL 50 to 100 mg per day); some patients may tolerate higher doses and achieve more benefit.
- An angiotensin-converting enzyme (ACE) inhibitor: ACE inhibitors not only have a salutary effect on left ventricular function but are also anti-ischemic and may stimulate growth of collateral blood vessels. Examples: captopril 50 mg three times a day, enalapril 20 mg twice a day, or preferably lisinopril 20 to 40 mg once a day
- A nitrate to increase exercise capacity
- Lipid-lowering agents to achieve an LDL level less than 100 mg/dL.

In addition, as appropriate, some patients need:

- Advice or referral on stopping all forms of tobacco use
- Optimum control of hyperglycemia
- A calcium channel blocker as a substitute for a beta-blocker if the patient has a contraindication to beta-blockers or if a beta-blocker produces unacceptable side effects, or in combination with a beta-blocker if initial therapy with a beta-blocker is not successful in reducing angina.[3]

## THERAPEUTIC ANGIOGENESIS

Therapeutic angiogenesis involves giving growth factors capable of generating new blood

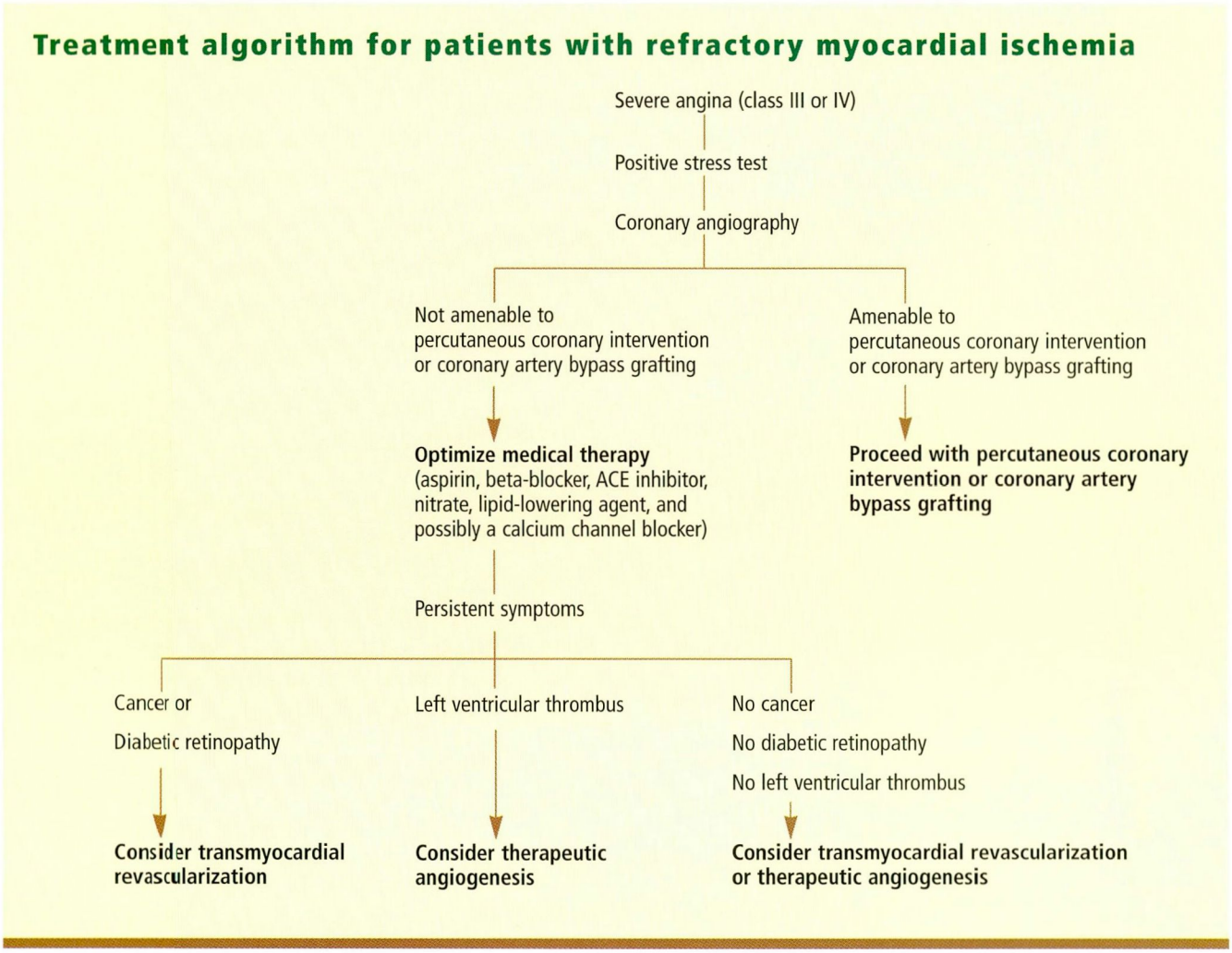


**FIGURE 1.** Algorithm for considering therapeutic angiogenesis and transmyocardial revascularization.

vessels in ischemic myocardium (FIGURE 2). The primary growth factors studied include vascular endothelial growth factor (VEGF) in both the protein and DNA form and fibroblast growth factors 1 and 2, which are proteins.

## Studies of therapeutic angiogenesis

Several clinical trials have been published[4–9] about the use of growth factors for therapeutic angiogenesis in patients with ischemic heart disease.

**Inclusion criteria.** Patients were eligible if they had all of the following:

- Stable angina in class III or IV of the Canadian Cardiovascular Society system (TABLE 2)
- Angina refractory to maximal medical therapy
- Ischemic myocardium on an imaging stress study
- Severe coronary artery disease not amenable to bypass surgery or percutaneous interventions.

**Exclusion criteria.** Patients were excluded if they had any of the following:

- Evidence of cancer
- Funduscopic signs of diabetic retinopathy
- Severe left ventricular systolic dysfunction with an ejection fraction of less than 20%.

**Results** were generally favorable, and better in studies that used injections of the growth factors into the myocardium than in studies that used intracoronary or intravenous infusions.

Schumacher et al[4] gave intramyocardial injections of fibroblast growth factor-1 to 20

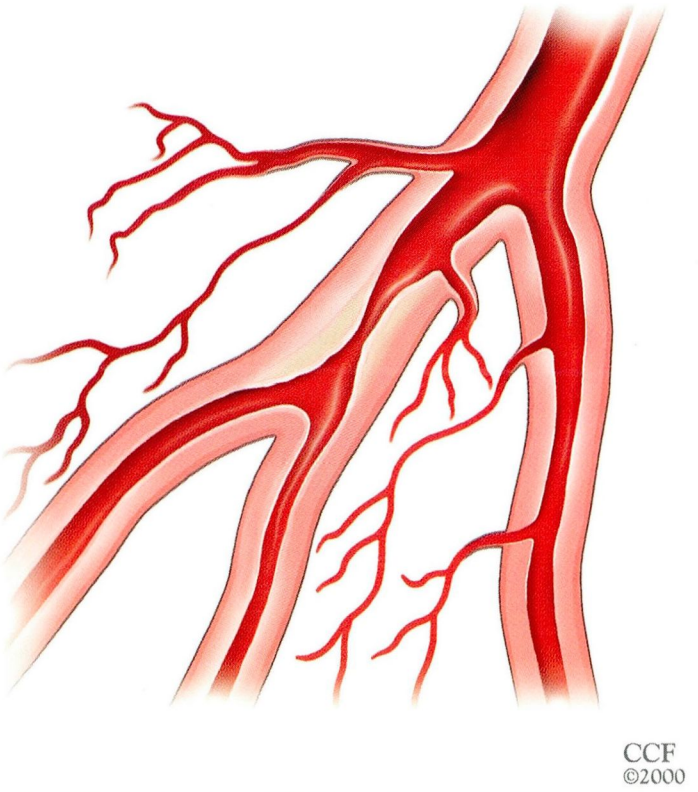


**FIGURE 2.** Artist's representation of growth of collateral blood vessels after growth factor therapy in an area of severe obstructive coronary artery disease.

patients undergoing coronary artery bypass grafting, near the insertion of the internal mammary artery graft. Compared with 20 patients who received placebo injections, the treated patients had evidence of increased collateral growth at follow-up angiography.

Sellke et al[5] gave intramyocardial injections of fibroblast growth factor 2 in slow-release beads to eight patients undergoing coronary artery bypass grafting, in an area of the myocardium not amenable to revascularization. Three patients demonstrated improved perfusion in the nonrevascularized region on follow-up nuclear perfusion scans.

Henry et al[6] gave intracoronary infusions of VEGF in various doses to 15 patients undergoing coronary angiography who had ischemia and were not suitable candidates for traditional revascularization. At 30 and 60 days, myocardial perfusion improved in 7 of the 15 patients. In addition, collateral density increased in 5 of 7 patients who underwent a second angiogram at 60 days.

Losordo et al[7] gave intramyocardial injections of VEGF DNA to five patients via minimally invasive thoracotomy. All five showed improvement in angina and on nuclear perfusion scans at 30 and 60 days, and on angiography at 60 days.

In another trial using VEGF DNA, Losordo et al[8] gave intramyocardial injections to 16 patients with severe angina. All patients had a decrease in anginal episodes: the mean number of episodes decreased from 50 per week at baseline to 3 per week at 90 days ($P < .0001$). Nitroglycerin use also decreased, from a mean of 61 tablets per week at baseline to 3 per week at 90 days ($P < .0001$), and perfusion improved significantly.

On the other hand, a randomized trial of therapeutic angiogenesis with one intracoronary and three intravenous injections of VEGF failed to show any benefit.[9] The negative results of this study can be possibly attributed to intravenous as opposed to intracoronary or intramyocardial administration of the growth factor and to use of the protein rather than the DNA.

The FGF Initiating Revascularization Support Trial (FIRST), a multicenter, placebo-controlled, double-blind study of 337 patients ineligible for angioplasty or bypass surgery, demonstrated that intracoronary injection of fibroblast growth factor resulted in improved quality of life and decreased angina (presented at the American College of Cardiology 49th Annual Scientific Session, Anaheim, Calif, March 12–15, 2000).

## Risks of growth factor-mediated angiogenesis

The main concern about growth factor-mediated angiogenesis is pathological angiogenesis, which is thought to play a role in several diseases, including cancer, diabetic proliferative retinopathy, and accelerated atherosclerosis.[10] So far, however, these potential complications have not materialized.

**Tumor growth.** Growth factors may contribute to the growth of malignant tumors. For this reason, patients with a history of cancer have been excluded from the trials. No increase in new malignancies was seen in the clinical trials to date, however.

**Diabetic proliferative retinopathy.** Patients in most of the clinical trials underwent formal ophthalmologic examinations, and at present there are no reports of neovascularization in the retina. Initially, patients with diabetes were excluded, but several later trials included diabetic patients without retinopathy.

**Progression of atherosclerosis.** In the clinical trials so far there has been no increase in acute ischemic syndromes or progression of atherosclerosis observed on serial angiography.

**Other effects.** Both VEGF and fibroblast growth factor may cause transient hypotension at high doses or with rapid infusion. Slowing the infusion rate may help in these cases. There have been rare reports of proteinuria and thrombocytopenia with fibroblast growth factor, and spider angiomas and peripheral edema with VEGF.

Treatment was well tolerated in the clinical trials.

### Future applications

Trials to date have only enrolled patients with severe symptomatic coronary artery disease or peripheral vascular disease. This therapy may also benefit patients with ischemic cardiomyopathy without angina but a large amount of hibernating myocardium, atherosclerosis after heart transplantation, severe restenosis, and microvascular disease.

## TRANSMYOCARDIAL REVASCULARIZATION

Transmyocardial revascularization consists of creating multiple (10–50) small channels in the myocardium with a laser (FIGURE 3).

### Mechanism unclear

The mechanism by which this treatment should improve angina is not known. At first, the theory was that the new channels would perfuse the myocardium directly, but in fact they probably close up relatively quickly. Another theory is that the laser destroys nerve endings and therefore the treatment merely blocks angina pain. A third theory, which we favor, is that the treatment may induce angiogenesis. In fact, combining transmyocardial revascularization with therapeutic angiogenesis, injecting growth factors into a laser-created channel, may have a synergistic effect.[11]

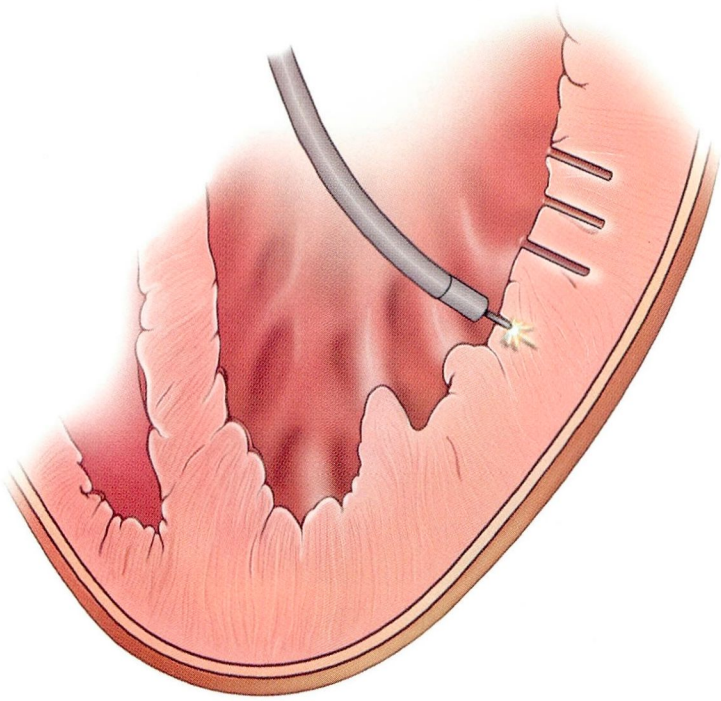


**FIGURE 3.** Transmyocardial revascularization via a catheter-based approach in the left ventricle.

### Performed surgically or percutaneously

Transmyocardial revascularization can be performed surgically with thoracotomy, with channels created from the epicardium to the endocardium. It can also be performed percutaneously with a catheter-based technique, with channels created from the endocardium to the epicardium.

The advantage of a catheter-based technique is that it makes the entire left ventricle accessible, whereas with surgery only the free wall of the left ventricle is accessible. Thus, a patient with septal ischemia cannot be treated with surgical transmyocardial revascularization.

The advantage of a surgical approach is that one can visualize the heart better and

**Electromechanical mapping guides percutaneous therapy**

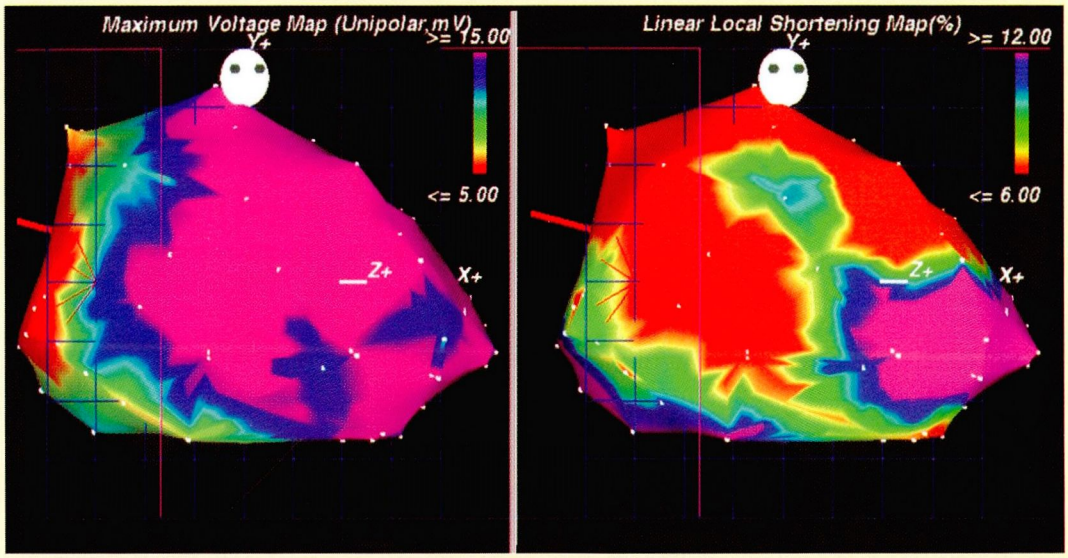


**FIGURE 4.** Electromechanical mapping of the heart. **Left,** the voltage map depicts the electrical activity of the left ventricle, with violet indicating areas of strongest voltage value and red indicating the weakest value. **Right,** the linear local shortening map depicts the mechanical function of the ventricle. In this right anterior oblique view, the septal and anterior portions display low mechanical values while the voltage map displays high values; the mismatch suggests hibernating or stunned muscle, which may benefit from percutaneous transmyocardial revascularization.

COURTESY OF BIOSENSE WEBSTER

**At 1 year patients had less angina, less hospitalization, and fewer cardiac events**

thus place the channels where they are truly needed, ie, in the ischemic area.

New technology may help in guiding the percutaneous procedure more precisely. A location system, called Biosense (FIGURE 4), uses three external magnetic sources and a left ventricular catheter with sensors in its tip. A computer workstation triangulates the position of the catheter and displays a three-dimensional reconstruction of the electrical and mechanical function of the left ventricle.[12]

### Trials of transmyocardial revascularization

Three multicenter, randomized, controlled trials of transmyocardial revascularization have been performed to date,[13–15] and in all three the frequency and severity of angina decreased after the procedure in follow-up of up to 1 year. There was no difference in mortality in any of these trials, but the studies were not powered to detect a difference in mortality.

Schofield et al[13] randomly assigned 188 patients to undergo either transmyocardial revascularization (via a small thoracotomy) plus medical therapy or medical therapy alone. At 3, 6, and 12 months, patients treated with transmyocardial revascularization had significantly decreased angina, increased functional capacity, less need for antianginal medications, and fewer hospital admissions. There was, however, no significant difference in the primary endpoint, which was the 12-minute walking distance at 12 months.

Frazier et al[14] recently reported results of transmyocardial revascularization in 192 patients with end-stage coronary artery disease. At 12 months, those assigned to transmyocardial revascularization had a significant improvement in angina symptoms and a marked reduction in hospitalization rates.

Allen et al[15] reported results of 275 patients with refractory angina randomized to transmyocardial revascularization or con-

tinued medical therapy. At 1 year, patients in the transmyocardial revascularization group demonstrated significant improvement in angina, survival free of cardiac events, and freedom from cardiac-related hospitalization.

## Risks of transmyocardial revascularization

Transmyocardial revascularization is not risk-free. In the initial observational studies, the perioperative mortality rate was 10% to 20%,[16,17] and even higher among patients with severely depressed left ventricular function and recent myocardial infarction. In the more recent trials the perioperative mortality rate was around 5%.[14,15]

Perioperative morbidity remains considerable. Approximately 30% of patients have at least one complication (nonfatal myocardial infarction, congestive heart failure, arrhythmia, or wound or respiratory infection).[13–15] However, keep in mind that patients undergoing transmyocardial revascularization are at extremely high risk to begin with, and similar patients treated medically have a dismal prognosis.

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