REVIEW

Current and Future Treatment Strategies for Refractory Angina

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Patients with refractory angina are not candidates for revascularization and have both class III or IV angina and objective evidence of ischemia despite optimal medical therapy. An estimated 300,000 to 900,000 patients in the United States have refractory angina, and 25,000 to 75,000 new cases are diagnosed each year. This review focuses on treatment strategies for refractory angina and includes the mechanism of action and clinical trial data for each strategy. The pharmacological agents that have been used are ranolazine, ivabradine, nicorandil, L-arginine, testosterone, and estrogen; currently, only L-arginine, testosterone, and estrogen are approved by the Food and Drug Administration. Results with the noninvasive treatments of enhanced external counterpulsation and transcutaneous electrical nerve stimulation are provided. Invasive treatment strategies including spinal cord stimulation, transmyocardial revascularization, percutaneous myocardial revascularization, and gene therapy are also reviewed.

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EECP = enhanced external counterpulsation; FGF = fibroblast growth factor; PMR = percutaneous myocardial revascularization; SCS = spinal cord stimulation; TENS = transcutaneous electrical nerve stimulation; TMR = transmyocardial revascularization; VEGF = vascular endothelial growth factor

Cardiovascular medicine has seen many advances in the treatment of coronary artery disease during the past 3 decades. A consequence of this success is the increasing number of patients with severe coronary artery disease who now survive. This could perhaps be thought of as a reversal of Darwinian principles: "unnatural selection and survival of the sickest." From an epidemiological and clinical perspective, an increasing number of patients with severe chronic coronary artery disease present with congestive heart failure, arrhythmias, and refractory angina.

Refractory angina is a term used to describe patients who despite optimal medical therapy have both angina and objective evidence of ischemia and are not considered candidates for revascularization. Mannheimer et al[1] reported that approximately 5% to 15% of patients with angina meet the criteria for refractory angina. When these data are combined with results from the Third National Health and Nutrition Examination Survey, an estimated 300,000 to 900,000 patients in the United States have refractory angina, and 25,000 to 75,000 new cases will be diagnosed each year.[2] Therefore, refractory angina is a clinical problem of considerable magnitude. This review focuses on current and future therapeutic options for the management of refractory angina. Treatments can be organized into 3 groups: pharmacological therapies, noninvasive nonpharmacological therapies, and invasive therapies (Table 1). The mechanism of action and clinical trial data for each treatment option are provided.

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PHARMACOLOGICAL THERAPIES

Optimal Standard Therapy

Angina is the result of myocardial ischemia that occurs when the supply of oxygen is unable to meet the demand. Treatment strategies focus on decreasing oxygen demand and/or increasing the supply. The standard treatment for symptomatic relief in patients with chronic stable angina should include β-blockers and/or non–dihydropyridine calcium channel blockers titrated to the lowest heart rate and blood pressure level tolerated. In addition, a long-acting nitrate should be given with use of an interrupted dose schedule to prevent nitrate tolerance. Aggressive risk factor modification with smoking cessation, cholesterol-modifying agents, and exercise training should be offered. Patients who have ongoing anginal symptoms despite receiving optimal standard therapy should be considered for the alternative treatment strategies described subsequently.

Ranolazine

Ranolazine is a partial inhibitor of fatty acid oxidation that has been shown to have antianginal effects.[3] The actual mechanism by which it reduces anginal symptoms is not entirely known but is thought to be related to its metabolic effects that reduce oxygen demand.

The Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) trial investigated the anti-ischemic effects of ranolazine and long-term survival of 191 patients with chronic severe angina.[4] Treatment with ranolazine resulted in a 24- to 56-second improvement in exercise tolerance ($P<.001$) in patients who took 500 to 1500 mg of ranolazine twice daily. The Combination Assessment of Ranolazine In Stable Angina (CARISA) trial investigated the effects of ranolazine in combination with other anti-

TABLE 1. **Summary of Treatment Strategies for Refractory Angina***

Treatment	Improvement in time to onset of ST-segment depression	Improvement in total exercise time	Reduction in anginal class	Improvement in myocardial perfusion	FDA approved (AHA class indication)
Pharmacological					
Ranolazine	No	Yes	Yes	NA	No
Ivabradine	Yes	Yes	Yes	NA	No
Nicorandil	Yes	Yes	Yes	Yes	No
L-arginine	Yes	Yes	NA	NA	Yes
Testosterone	Yes	No	NA	NA	Yes
Estrogen	Yes	Yes	Yes	NA	Yes
Noninvasive					
EECP	Yes	Yes	Yes	Yes	Yes (IIb)
TENS	Yes	Yes	Yes	NA	Yes
Invasive					
SCS	Yes	Yes	Yes	Yes	Yes (IIb)
TMR	No	Yes	Yes	No	Yes (IIa)
PMR	No	No	No	No	No
Gene therapy	Yes	Yes	Yes	Yes	No

*AHA = American Heart Association; EECP = enhanced external counterpulsation; FDA = Food and Drug Administration; NA = not available; PMR = percutaneous myocardial revascularization; SCS = spinal cord stimulation; TENS = transcutaneous electrical nerve stimulation; TMR = transmyocardial revascularization.

anginal agents.[5] In this phase 3 double-blind, placebo-controlled clinical trial, 823 patients with refractory angina who were receiving standard therapy with atenolol, diltiazem, or amlodipine were randomized to placebo, ranolazine at 750 mg twice daily, or ranolazine at 1000 mg twice daily. After 12 weeks, patients in both ranolazine arms had a 26% increase in total exercise time (P=.03) and a decrease in the number of anginal episodes per week. The time to onset of 1 mm of ST-segment depression during exercise testing did not change. The most common adverse reactions to ranolazine were constipation, dizziness, nausea, and asthenia, which occurred in 8% of patients. Patients in the treatment arms also had an increase in the QT interval, the clinical importance of which is unknown. Ranolazine is currently not approved by the Food and Drug Administration (FDA) because of issues regarding prolongation of the QT interval.

IVABRADINE

Ivabradine is a selective and specific inhibitor of the I_f ion channel, which is responsible for the primary sinoatrial node pacemaker current.[6] Because of its ability to decrease heart rate and myocardial oxygen demand with no negative inotropic effects, ivabradine is a potential therapy for chronic stable angina.

Borer et al[7] conducted a randomized, double-blind, placebo-controlled trial investigating the use of ivabradine in patients with stable angina. Patients underwent a washout period during which β-blockers and calcium channel blockers were discontinued. Patients were then randomized to placebo or ivabradine (2.5, 5.0, or 10.0 mg twice daily) for 2 weeks, followed by a 3-month open-label extension phase with 10 mg of ivabradine twice a day. At the end of the blinded phase, patients who received 10 mg of ivabradine twice a day had a 12% increase in the time to onset of 1-mm ST-segment depression (P<.005) and a 9.5% increase in exercise tolerance compared with patients who received placebo (P<.02). Also, patients who received ivabradine had a reduction in heart rate of 20 beats/min at rest and with peak exercise at the end of the study. During the open-label phase of the study, ivabradine use resulted in a 77% decrease in the frequency of anginal events (P<.001). Visual disturbances occurred in 14.8% of the patients who received 10 mg of ivabradine twice a day.

Tardif[8] compared ivabradine with atenolol in 932 patients with stable angina. Total exercise duration increased by 86.8±129.0 seconds with ivabradine at 7.5 mg twice daily and by 91.7±118.8 seconds with ivabradine at 10 mg twice daily compared with an increase of 78.8±133.4 seconds with atenolol at 100 mg daily. Like ranolazine, ivabradine has not yet been approved by the FDA.

NICORANDIL

Nicorandil is a nicotinamide ester that has both nitrate-like and adenosine triphosphate–potassium channel activating properties.[9] Its pharmacological effects include the ability to reduce both preload and afterload by vasodilation of the arterial and venous systems. In addition, nicorandil's adenosine triphosphate–potassium channel activation may offer cardioprotection via a "preconditioning" effect on the myocardium.

Several small randomized trials have shown that nicorandil given at doses of 10 or 20 mg twice a day prolongs the time to onset of ST-segment depression and exercise

duration during stress testing in patients with stable angina.[10-13] Nicorandil has also been shown to improve myocardial perfusion at rest and with exercise.[14] The preconditioning and possible cardioprotective effects of nicorandil were investigated in the Impact Of Nicorandil in Angina (IONA) trial that randomized 5126 patients with stable angina to either placebo or nicorandil at 20 mg twice a day.[15] After 3 years, patients treated with nicorandil had a 17% relative risk reduction (P=.014) in the composite primary end point of deaths due to coronary heart disease, nonfatal myocardial infarction, and admission for cardiac chest pain. Compared with the placebo group, the nicorandil group had no significant change in systemic blood pressure. The main adverse reactions to treatment were headaches and gastrointestinal discomfort. Nicorandil is available for clinical use in Europe and Japan but is not currently approved by the FDA for use in the United States.

L-ARGININE

Several other pharmacological therapies for chronic angina have been investigated in small clinical trials. L-arginine has been proposed as a potential therapy that would increase coronary blood flow by improving endothelium-dependent vasodilation.[16] A single-center, double-blind, placebo-controlled trial involving 22 patients with stable angina showed that treatment with oral L-arginine resulted in an increase in exercise duration and maximum workload during stress testing as well as a decrease in the time to onset of ST-segment depression.[17]

TESTOSTERONE AND ESTROGEN

Testosterone has been shown to result in coronary artery dilatation and increased blood flow in humans. The mechanism appears to be endothelium independent and may involve the ion channels in vascular smooth muscle cells.[18,19] A randomized, double-blind, placebo-controlled trial involving 46 male patients with stable angina receiving medical therapy showed that treatment with transdermal testosterone improved the time to onset of ST-segment depression during exercise testing and improved quality of life.[20] Although none of the patients experienced adverse prostatic or hematologic effects, concern exists regarding long-term therapy with testosterone.

Estrogen has been investigated as an antianginal agent and has been shown to dilate coronary arteries and improve endothelial function.[21,22] A randomized, double-blind, placebo-controlled trial involving 74 female patients with stable angina showed that estradiol and norethindrone therapy improved exercise duration and the time to onset of ST-segment depression.[23] The number of ischemic events decreased in the treatment group. However, these benefits must be weighed against the initial increase in cardiac events caused by estrogen therapy for females with coronary artery disease.[24]

NONINVASIVE THERAPIES

ENHANCED EXTERNAL COUNTERPULSATION

Enhanced external counterpulsation (EECP) is based on the concept of counterpulsation and consists of 3 pairs of pneumatic cuffs placed around the lower extremities at the calves, lower thighs, and upper thighs (Figure 1). An electrocardiographic trigger is used to sequentially inflate the cuffs, starting at the calves, during onset of diastole and simultaneously deflate all cuffs before onset of systole. A standard course of EECP therapy consists of 35 one-hour sessions during a 7-week period. The mechanism by which EECP improves anginal symptoms is poorly understood but may involve nonspecific placebo effects and various hemodynamic factors. Hemodynamically, EECP acts like intra-aortic balloon counterpulsation by augmenting diastolic blood flow in multiple vascular beds, including the coronary arteries, and by reducing cardiac afterload.[25] Endothelial function has been shown to improve after a course of EECP therapy.[26] In addition, EECP therapy has been associated with the release of growth factors, such as vascular endothelial growth factor (VEGF), that promote the formation of collaterals in the coronary circulation.[27] Finally, EECP therapy may result in a "training effect" by decreasing peripheral vascular resistance in the same manner as physical exercise.[28]

Several controlled and uncontrolled trials have investigated the use of EECP therapy for patients with refractory angina, and results are summarized in Table 2.[28-39] The Multicenter Study of Enhanced External Counterpulsation (MUST-EECP) trial conducted by Arora et al[33] is a double-blind, sham-controlled study in which 139 patients with chronic stable angina were randomized to either active EECP therapy or sham treatment with subtherapeutic cuff inflations. After 35 sessions, patients in the active treatment arm had a 15% increase in the time to onset of 1-mm ST-segment depression (P=.01) and 25% fewer anginal symptoms per week (P<.035). These effects were not seen in the patients in the sham-controlled arm. An international registry of patients who underwent EECP therapy showed an improvement in anginal symptoms and quality of life.[38]

Although one trial involving a sham-controlled arm supports the use of EECP therapy, further larger-scale sham-controlled studies regarding the effectiveness of EECP therapy and its mechanisms of action need to be conducted. Currently, EECP therapy is one of the most widely used and promising treatments of refractory angina. Enhanced external counterpulsation therapy is FDA approved and is recommended by the American Heart Association as a

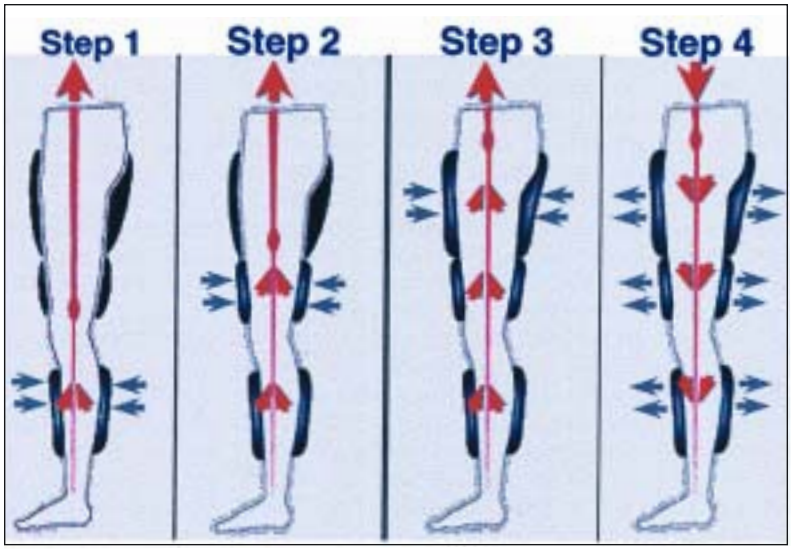

FIGURE 1. Enhanced external counterpulsation. Step 1, Inflation initiates retrograde pulse wave. Step 2, Inflation of cuffs on lower thigh, 50 milliseconds later. Step 3, Inflation of cuffs on upper thigh, 50 milliseconds later. Step 4, Simultaneous deflation of all 3 cuffs.

potential therapy for refractory angina. It has a class IIb indication (usefulness/efficacy is less well established).[40]

Transcutaneous Electrical Nerve Stimulation

The concept of neurostimulation to regulate pain dates to the ancient use of acupuncture, and its use in modern medicine began in the 1970s. Currently, the 2 main methods of neurostimulation are transcutaneous electrical nerve stimulation (TENS) and spinal cord stimulation (SCS). TENS consists of a neurostimulator unit and 2 electrodes. One electrode is placed in the dermatome, the site of the highest intensity of pain, and the other is placed in the contralateral dermatome. Stimulation of the larger non–pain-conducting nerves is believed to inhibit transmission through the smaller pain-conducting nerve fibers.

Several small clinical trials have investigated the efficacy of TENS in the treatment of refractory angina.[41-45] Mannheimer et al[45] randomized 21 patients with class III or IV chronic angina to placebo or TENS therapy for 5 weeks. Patients in the active arm received 15 to 50 mA pulses at a frequency of 70 Hz for 1 hour 3 times a day with an additional 1 to 10 minutes of therapy as needed for breakthrough pain. After 5 weeks, patients treated with TENS had a 15% increase in exercise tolerance during stress testing (P=.01)

TABLE 2. **Published Controlled and Uncontrolled Trials of Enhanced External Counterpulsation in Patients With Stable Angina***

Reference	No. of patients	Angina (% with ≥1 CCS class change)	Nitrate use	Exercise tolerance (%)	Time to ST-segment depression	Cardiac perfusion (%)
Zheng et al[29]	200	Decrease (97)	NA	NA	NA	NA
Lawson et al[30]	18	Decrease (100)	Decrease	Increase (67)	NA	Increase (78)
Lawson et al[28]	27	NA	NA	Increase (81)	NA	Increase (78)
Lawson et al[31]	50	Decrease (100)	Decrease	NA	NA	Increase (80)
Lawson et al[32]	60	Decrease	NA	Increase	NA	Increase (75)
Arora et al[33]	139	Decrease	Decrease	Increase	Increase	NA
Lawson et al[34]	33	Decrease (100)	Decrease	NA	NA	Increase (79)
Urano et al[35]	12	NA	NA	Increase	Increase	Increase
Masuda et al[36]	11	NA	NA	Increase	Increase	Increase
Stys et al[37]	395	Decrease (88)	NA	NA	NA	NA
Barsness et al[38]	978	Decrease (81)	Decrease	NA	NA	NA
Stys et al[39]	175	Decrease (85)	NA	Increase	NA	Increase (83)

*CCS = Canadian Cardiovascular Society; NA = not available.
Adapted from *J Am Coll Cardiol*. 2003;41:1918-1925, with permission from the American College of Cardiology Foundation.

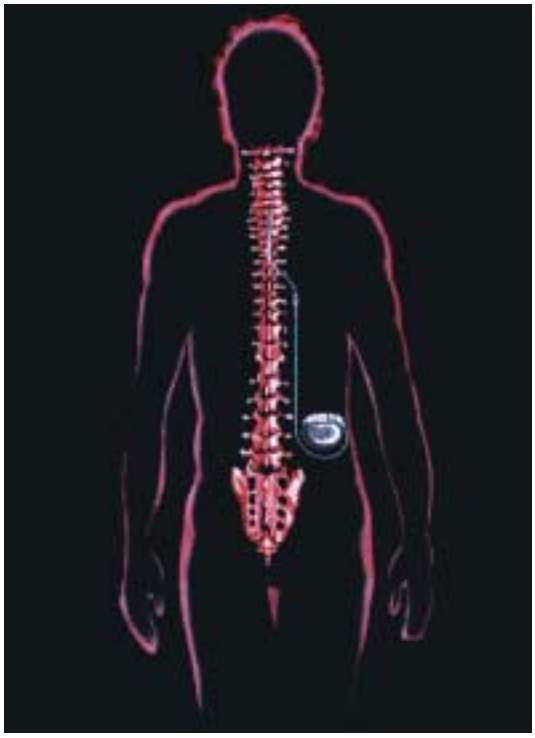

FIGURE 2. The spinal cord stimulator consists of an epidural lead, an extension wire, and a pulse generator. The lead is placed in the epidural space at the level of C7 through T1.

and a 17% decrease in anginal symptoms per week (P=.05). However, these modest improvements could have been due to a placebo effect since a sham-controlled arm was not included. During therapy, patients experienced skin irritation, breakdown at the electrode sites, and paresthesias.

INVASIVE THERAPIES

Spinal Cord Stimulation

Spinal cord stimulation (SCS) is similar to TENS in concept and consists of 3 components: an epidural lead, an extension wire, and a pulse generator (Figure 2). The epidural lead is placed in the epidural space at the level of C7 through T1, and the pacemaker-sized generator is surgically implanted in the left lower abdominal area. Patients receive 3 one-hour stimulations a day and can activate the device with a handheld magnet to treat episodes of breakthrough pain. It is believed that SCS blocks pain by stimulating the dorsal columns, which inhibits transmission through the pain-conducting spinothalamic tract.[46-50] However, pain due to an acute coronary syndrome has not been shown to be blocked in clinical trials and will continue to cause typical symptoms despite stimulation.[51] Also, SCS has been shown to decrease sympathetic tone and improve myocardial blood flow.[52-54]

Several clinical trials have investigated the use of SCS for refractory angina.[55-58] Hautvast et al[56] showed that 6 weeks of therapy with SCS in 25 patients with class III and IV chronic angina resulted in a 39% increase in the time to onset of ST-segment depression (P<.05) and a 19% increase in exercise capacity (P<.05) during treadmill testing. Also, SCS reduced the number of anginal attacks and use of nitroglycerin by 41% and 48% (P<.05), respectively.

In the Electrical Stimulation Versus Coronary Artery Bypass Surgery in Severe Angina Pectoris (ESBY) trial, 104 patients with chronic angina who were considered to have only symptomatic benefit from coronary artery bypass surgery were randomized to SCS or coronary artery bypass surgery.[58] Spinal cord stimulation was as effective as bypass surgery for improving anginal symptoms (4 vs 5 episodes per week, respectively) and was associated with less procedure-related mortality (2% vs 14%; P<.05) and stroke (4% vs 16%; P<.05).

Di Pede et al[59] recently published the results of a registry of patients who had undergone SCS. Treatment with SCS resulted in an improvement in the Canadian Cardiovascular Society angina class of 1 class or higher in 80% of patients and 2 classes or higher in 42% of patients. The main adverse reactions to SCS are the risk of epidural hematoma and infection, occurring in about 1% of patients. In addition, SCS may interfere with the function of pacemakers and implantable defibrillators.

Although results of the initial trials appear promising, these trials had a small number of patients, and none had a sham-controlled arm to prevent a placebo effect. The American Heart Association currently considers SCS a possible treatment of refractory angina. It has a class IIb indication (usefulness/efficacy is less well established).[40]

Transmyocardial Revascularization

The concept of myocardial revascularization began in 1956 when Goldman et al[60] proposed that the formation of artificial conduits in the subendocardium would improve oxygen delivery to myocytes. Initially, needles were used. In 1986, Okada et al[61] became the first to use laser technology to generate myocardial channels. Currently, 2 types of lasers are used—carbon dioxide and holmium:YAG. The carbon dioxide system transmits the laser through a series of mirrors and lenses, whereas the holmium:YAG system uses an optical fiber. In transmyocardial revascularization (TMR), a left thoracotomy is performed, and the laser is transmitted directly into the myocardium. If a carbon dioxide laser is used, a single pulse is delivered to generate a channel. If a holmium:YAG system is used, several pulses are needed to form a single channel. With either system, a total of 25 to 40 conduits are formed.

TABLE 3. **Summary of Trials of TMR in Patients With Refractory Angina***

Reference	No. of patients	Laser	Percentage with decrease ≥2 CCS angina classes			Improvement in exercise time (s)			Survival, TMR vs control	Improvement in perfusion
			TMR	Control	*P* value	TMR	Control	*P* value		
Allen et al[62]	275	Holmium:YAG	76	32	<.001	+5	+3.9 MET	<.05	NS	No
Frazier et al[63]	192	Carbon dioxide	72	13	<.001	NA	NA		NS	Yes
Schofield et al[64]	188	Carbon dioxide	25	4	<.001	NA	NA		NS	No
Burkhoff et al[65]	182	Holmium:YAG	48	14	<.001	+65	–64	<.001	NS	No
Aaberge et al[66]	100	Carbon dioxide	39	0	<.01	NS	NS		NS	NA
Jones et al[67]	86	Holmium:YAG	NA	NA		+119	–85	<.001	NA	No

*CCS = Canadian Cardiovascular Society; MET = metabolic equivalent; NA = not available; NS = not statistically significant; TMR = transmyocardial revascularization.

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Several studies have investigated the use of TMR for refractory angina. In the largest trial, Allen et al[62] randomized 275 patients with class IV refractory angina to TMR with a holmium:YAG laser plus continued medical therapy or medical therapy alone. At 12 months, the TMR group had a greater percentage of patients with a decrease of 2 or more angina classes (76% vs 32%; *P*<.001) and a greater amount of exertional tolerance on stress testing (5.0 vs 3.9 metabolic equivalents; *P*<.05). There was no improvement in mortality or perfusion. The second largest trial was conducted by Frazier et al[63] who randomized 192 patients with class III or IV refractory angina to TMR with a carbon dioxide laser plus medical therapy or medical therapy alone. At 12 months, the TMR group had a greater percentage of patients with a decrease of 2 or more angina classes (72% vs 13%; *P*<.001). Unlike patients in the study by Allen et al,[62] TMR-treated patients did not have an improvement in exertional tolerance despite an improvement in perfusion. These 2 trials along with 4 other investigations of TMR are summarized in Table 3.[62-67] In general, TMR has been shown to improve anginal symptoms and exertional tolerance but does not seem to improve mortality or myocardial perfusion.

Registry data from the Society of Thoracic Surgeons involving 3717 patients who underwent TMR showed an increase in the number of annual TMR procedures performed between 1998 and 2001 (59 in the first half of 1998 and 572 in the last half of 2001).[68] Interestingly, 67% of these procedures were for TMR plus bypass surgery, an off-label use for TMR. The perioperative mortality rate in the registry was 6.4%; this is higher than the rate from clinical studies of TMR, which ranges from 1.1% to 5.3%. The mortality rate was higher in older patients, diabetic patients, and patients with a recent acute coronary syndrome. Despite the trends reported in this registry, the use of TMR has decreased in recent years because of the availability of other treatments such as EECP.

The actual mechanism by which TMR improves anginal symptoms is unknown. It was originally believed to be due to improved myocardial perfusion through open channels.[69] However, subsequent studies have shown that the channels fill with necrotic debris and close shortly after the procedure.[70-73] Other proposed mechanisms have included angiogenesis through the release of growth factors and denervation of pain fibers by the laser.[74,75] A placebo effect is certainly possible and is perhaps the most plausible theory given the lack of randomized trials with a sham-controlled arm. Although use of TMR for chronic angina has decreased, the American Heart Association considers it a class IIa indication (weight of evidence favors efficacy) for the treatment of chronic angina.[40]

Percutaneous Myocardial Revascularization

Percutaneous myocardial revascularization (PMR) is based on the same concept as TMR except that it is performed percutaneously. A guiding catheter is placed into the left ventricle via a femoral approach, and a holmium:YAG laser fiber is advanced through the catheter into the endocardium. Several pulses are then delivered to generate a channel. Clinical trials of PMR are summarized in Table 4.[76-79] Unlike studies of TMR, several of these investigations used sham-controlled arms. In the Direct Myocardial Revascularization In Regeneration of Endomyocardial Channels Trial (DIRECT), Leon[76] randomized 298 patients with refractory angina to PMR or a sham procedure. He found no significant difference in anginal symptoms or exertional tolerance at follow-up. Stone et al[78] found similar results in their study of 141 patients with refractory angina who were randomized to PMR or a sham procedure. The only sham-controlled trial to show clinical benefit was the one by Salem et al[79] involving 82 patients. At follow-up, more patients in the PMR group had a decrease of 2 or more anginal classes than did the sham-controlled group (41% vs 13%; *P*=.006). Therefore, based on the results of the sham-controlled trials, PMR is not an effective therapy

TABLE 4. **Summary of Trials of PMR for Refractory Angina***

Reference	No. of patients	Percentage with decrease ≥2 CCS angina classes			Improvement in exercise time (s)		
		PMR	Control	*P* value	PMR	Control	*P* value
Leon[76]†	298	NS	NS		NS	NS	
Oesterle et al[77]	221	30	12	.002	+89	+13	.008
Stone et al[78]†	141	NS	NS		NS	NS	
Salem et al[79]†	82	35	14	.04	NA	NA	

*CCS = Canadian Cardiovascular Society; NA = not available; NS = not statistically significant; PMR = percutaneous myocardial revascularization.
†Sham-controlled trial.
Adapted from *J Am Coll Cardiol*. 2003;41:173-178, with permission from the American College of Cardiology Foundation.

for chronic angina. It is unknown why TMR is effective and PMR is not, but the placebo effect in the surgical TMR trials may be the reason. Percutaneous myocardial revascularization has not been approved by the FDA for the treatment of chronic refractory angina.

Gene Therapy

The use of gene therapy to induce the formation of collaterals via angiogenesis was first pioneered by Isner et al.[80] The concept of gene therapy centers around 3 factors: the gene target to be delivered, the vector used to package the gene target, and the mode of delivery to the site of action. The 2 main gene factors currently being investigated are VEGF and basic fibroblast growth factor (FGF). These gene targets have been packaged in either a plasmid or an adenovirus for delivery to the target organ by surgical or percutaneous methods.

Several phase 1 clinical trials of gene therapy have been conducted in patients with refractory angina and have shown improvement in exercise tolerance, anginal symptoms, and myocardial perfusion.[81-86] Two trials have had a placebo-controlled arm. The Angiogenic Gene Therapy (AGENT) trial involved 79 patients with class II or III angina who were randomized to direct injection of adenovirus containing basic FGF or placebo.[87] After 12 weeks, patients in the active treatment arm had a 30% increase in exercise duration on treadmill testing. Although 2 patients in the active treatment arm experienced transient elevations in liver enzyme levels, no major adverse reactions occurred. In the follow-up placebo-controlled, double-blind trial, AGENT-2, 52 patients with refractory angina were randomized to an intracoronary injection of 10^{10} adenoviral particles containing a gene encoding FGF (Ad5FGF-4) or placebo.[88] At 8 weeks, the Ad5FGF-4 injection resulted in a significant reduction in the ischemic defect size, determined by adenosine single-photon emission computed tomography (4.2% absolute reduction; $P<.001$), and placebo-treated patients had no improvement ($P=.32$). However, the change in reversible perfusion defect size between Ad5FGF-4 and placebo was not significant (4.2% vs 1.6%; $P=.14$). The Vascular Endothelial Growth Factor in Ischemia for Vascular Angiogenesis (VIVA) trial randomized 178 patients with refractory angina to placebo, low-dose VEGF, or high-dose VEGF.[89] After 120 days, patients receiving high-dose VEGF had a significant improvement in angina class and a trend toward improvement in exercise duration and frequency of anginal symptoms.

At this time, gene therapy appears to be a promising therapy for refractory angina, but it is still considered experimental. Limitations include vector-associated toxicities and immune response to vectors. Larger randomized trials are needed to determine long-term efficacy and safety. Direct injection of progenitor cells is a possible strategy to induce angiogenesis, and phase 1 and 2 clinical trials are currently under way.

CONCLUSION

Refractory angina is a difficult clinical condition that is growing in prevalence. Current treatment options for refractory angina can be classified into 3 groups: pharmacological, nonpharmacological noninvasive, and invasive. Although none of these therapies have been shown to improve mortality, some improve symptoms and quality of life. At this time, L-arginine, testosterone, estrogen, EECP, TENS, SCS, and TMR are the only treatments that are FDA approved. Currently, EECP is the most widely used therapy and is the only FDA-approved treatment for refractory angina that has been supported by sham-controlled data. Trials with SCS are currently in progress and will hopefully result in an increase in clinical use for refractory angina. Use of TMR has decreased because of its invasiveness, and results may be due to a placebo effect. The pharmacological agents ranolazine, ivabradine, and nicorandil appear effective, but additional phase 3 trials need to be conducted before they can receive FDA approval. Finally, gene therapy appears promising but is currently considered experimental.

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