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Treatment of Inoperable Coronary Disease and Refractory Angina: Spinal Stimulators, Epidurals, Gene Therapy, Transmyocardial Laser, and Counterpulsation

Nelson Svorkdal, BSP, MD, FRCPC

Intractable angina from refractory coronary disease is a severe form of myocardial ischemia for which revascularization provides no prognostic benefit. Inoperable coronary disease is also accompanied by a “vicious cycle” of myocardial dystrophy from a chronic alteration of the cardiac sympathetic tone and sensitization of damaged cardiac tissues. Several adjunctive treatments have demonstrated efficacy when revascularization is either unsuccessful or contraindicated. Spinal cord stimulation modifies the neurologic input and output of the heart by delivering a very low dose of electrical current to the dorsal columns of the high thoracic spinal cord. Neural fibers then release CRP and other endogenous peptides to the coronary circulation reducing myocardial oxygen demand and enhancing vasodilation of collaterals to improve the myocardial blood flow of the most diseased regions of the heart. Randomized study has shown the survival data at five years is comparable to bypass for high-risk patients. Transmyocardial laser revascularization creates small channels into ischemic myocardium in an effort to enhance flow though studies have shown no improvement in prognosis over medical therapy alone. Enhanced external counterpulsation uses noninvasive pneumatic compression of the legs to improve diastolic filling of the coronary vessels and promote development of collateral flow. The compressor regimen requires thirty-five hours of therapy over a seven-week treatment period. Therapeutic angiogenesis requires injection of cytokines to promote neovascularization and improve myocardial perfusion into the regions affected by chronic ischemia. Phase 3 trials are pending. High thoracic epidural blockade produces a rapid and potent sympatholysis, coronary vasodilation and reduced myocardial oxygen demand in refractory coronary disease. This technique can be used as an adjunct to bypass surgery or medical therapy in chronic or acute unstable angina. Epidurals are easy to perform and often available for outpatient or inpatient use. The rapid anti-ischemic effect may complement therapeutic angiogenesis or other interventions with delayed onset to clinical benefit. A new era for interventional and implant cardiology is beginning to emerge as more clinicians, including cardiologists, gradually learn new procedures to safely provide more therapeutic options for patients suffering refractory angina.

Refractory angina is caused by severe coronary disease that is not amenable to revascularization and is unresponsive to maximal medical therapy. Some authors estimate that 2.4 million patients in the United States have refractory ischemia, and the number is increasing by more than 100,000 patients every year. A recent study reported that as many as 12% of patients presenting for angiograms have a coronary anatomy that is inoperable and associated with a poor prognosis. A follow-up study of this cohort was completed to evaluate the 1-year outcome of maximal medical management. The analyses showed a high annual rate of myocardial infarction (25.5%), rehospitalization (128%), and mortality (16.9%). Many of the patients remained incapacitated by persistent angina and limited function.

The American College of Cardiology/American Heart Association Guidelines (ACC/AHA) have also identified several other clinical subgroups of patients as having little or no prognostic benefit from coronary artery bypass graft (CABG) surgery (Table 1). Surgical risks may also be prohibitive for reoperation or complex coronary lesions in the presence of advanced age or significant comorbid disease, or both. Likewise, the reports of widespread cognitive decline (42% of CABG patients 5 years after discharge) and neurologic sequelae from cardiopulmonary bypass have given new impetus for clinicians and their patients to consider the available alternatives such as spinal cord stimulation, gene therapy, and transmyocardial laser revascularization, among others. This article reviews the dynamic pathophysiology of refractory angina and summarizes some recent objective data for several emerging treatment options.

Spinal cord stimulation, enhanced external counterpulsation, transmyocardial laser revascularization, and therapeutic angiogenesis are low-risk modalities that are anti-ischemic and have been the subject of randomized, controlled trials. Although all the mechanisms of action are not completely understood, they have demonstrated...
safety and efficacy as adjunctive therapies for optimizing the myocardial oxygen supply-to-demand ratio in a debilitated patient population that has a challenging cardiac pathology. The ACC/AHA has formally recognized the value of these techniques and has included them in the 2002 Consensus Guidelines for the management of chronic, stable angina pectoris.

Neurophysiology of Angina Pectoris

Coronary artery disease reduces the oxygen supply to the myocardium, causing ischemic injury and the release of several chemical mediators. Bradykinin is one of several substances responsible for the “pain” of angina. A whole cascade of cytokines activates and sensitizes chemoreceptors of afferent autonomic fibers along the epicardial surface of the myocardium. Adenosine, for example, produces a direct algesic effect on the A2 receptor. Serotonin amplifies the afferent activation through hyperalgesic action on 5HT1 receptors, potentiating primary somatic C fibers via 5HT2 receptors and excitatory sympathetic nociception via 5HT3 receptors. Cardiac tissue injury releases other compounds that are involved in the process of sensitization, including potassium, lactate, substance P, and prostaglandin E2.

Sympathetic fibers are the predominant afferents of the cardiac plexus and they originate on the epicardial surface of the myocardium. They carry most of the nociceptive impulses to the central nervous system. Vagal afferents primarily transmit impulses from the endocardium as well as some information from the inferoposterior aspect of the epicardium.

### Table 1. Patient Groups with Ischemic Heart Disease but No Prognostic Benefit from Coronary Artery Bypass Graft

| Mild disease | a. Mild angina with one or two vessel disease not involving proximal LAD*  
|             | b. Stenoses <60% other than left main coronary with no inducible ischemia |
| Unstable angina or Non-Q wave MI* with | a. one or two vessel disease not involving proximal LAD* and/or  
| Q-wave MI* with | a. progressive LV* failure with coronary stenosis compromising myocardium outside the infarcted area  
| Complex lesions | a. multi-vessel lesions that lack collaterals and cannot be revascularized  
| Previous CABG* | a. still patent IMA* to LAD* and with ischemia outside that distribution |

MI = myocardial infarction; LV = left ventricle; LAD = left anterior descending artery. ACC/AHA Guidelines for Coronary Artery Bypass Graft Surgery. JACC 34(4)1262-1347, 1999.

Sympathetic Fibers Magnify the Nociceptive Impulse

Ischemic tissue damage creates nociceptive impulses that are then dispersed cephalad and caudal through the network of the thoracic sympathetic ganglia and Lissauer’s tract (see Figure 1). A painful stimulus conducted from the T3 dermatome, for example, may spread along these pathways before simultaneously entering the dorsal horn at several levels of the spinal cord. The signal thus becomes magnified and is perceived by the patient to be radiating to the corresponding somatic receptive fields (ie, C5—shoulder; or T4—lower sternum). Jaw pain often results from stimulation of the vagus, which bypasses the tho-
A Vicious Cycle of Refractory Angina

Figure 1. Myocardial dystrophy.10,16

The sympathetic afferent terminations have a large rostral–caudal distribution, but a much lower density than the somatic system in the dorsal horn of the spinal cord. These factors account for the diffuse nature of visceral pain such as angina, thus making it more difficult for patients to localize the painful origin than a stimulus of superficial pain that originates from a skin or muscular injury of the thoracic cage.
Central Sensitization and Magnification

Afferent input from a visceral injury will activate second order neurons in laminae I, II, and V of the dorsal horn. The receptors in these regions are primarily nociceptive and have hyperalgesic potential. Central sensitization can be induced with activation of immediate early genes such as cFOS corresponding to the release of N-methyl-D-aspartate (NMDA) and other excitatory amino acids. This sensitization facilitates greater transmission of information along the axons of dorsal columns and the contralateral spinothalamic tract as well as causing some neurons to expand their reception of somatic inputs. The net result is to intensify and extend the duration of pain experienced from cardiac injury as well as recruit the convergent somatic fibers to become hyperalgesic. The nociceptive traffic to the thalamus and higher cortical structures increases significantly.

The clinical correlate of this phenomenon is that axial chest-wall pain will often accompany myocardial ischemia. Angina may also arise or persist in the absence of a significant change in the electrocardiogram or corresponding enzyme rise.

Sensation Associated with “Silent Ischemia”

Silent ischemia is relatively common, and although not associated with a discrete sensation of chest pain, is often accompanied by other visceral disturbances. One possible explanation is that some ascending pathways do not integrate with the spinothalamic tracts or dorsal columns, but will rather transmit information via anterolateral or intermediolateral tracts directly to the ventromedial nucleus of the thalamus. This region is responsible for the “affective–emotional” components of pain and an autonomic response, but may not quantify or discriminate the location or intensity of pain. Thus, nausea, diaphoresis, or a “feeling of doom” may be the primary complaint on presentation with silent myocardial ischemia. These lesions are typically subendocardial rather than epicardial or transmural.

Thalamic and Cortical Centers

Positron emission tomographic (PET) scans and functional magnetic resonance imaging have recently provided some insight into the involvement of higher centers in visceral injuries. Angina pectoris produces noxious stimuli that are transmitted by the dorsal columns and spinothalamic tracts to the nuclei in the lateral thalamus. These cells project into the somatosensory cortex, which encodes the intensity and spatial location of pain.

The spinothalamic tracts and dorsal columns also transmit some impulses from angina to the nuclei of the medial thalamus. This region projects to the frontal cortex, anterior cingulated gyrus, and other perlimbic regions that generate the affective and cognitive responses to pain. “Fear” lives here. The medial thalamus is also responsible for activating a sympathosympathetic efferent reflex to the nociceptive afferent stimulus.

Sympathetic Efferent Reflex

The sympathetic response to myocardial ischemia is pronounced and sustained. McCance et al measured the noradrenaline spill-over into the coronary sinus after acute coronary syndromes and myocardial infarction. The threefold increase in cardiac noradrenaline persisted even during pain-free periods for up to 3 months after an acute event, even when treated with β-blockers.

The sequelae of this reflex efferent sympatheexcitation are a significant exacerbation of the imbalance between myocardial oxygen supply and demand. Higher sympathetic tone contributes to arrhythmogenicity, constriction of subendocardial resistance vessels, higher rate–pressure product and wall tension, and platelet aggregation, followed by degranulation and endothelial proliferation. If uncontrolled, this adds an element of gain to the “vicious circle,” which may then spiral into a myocardial sympathetic dystrophy and hypersensitive cardiac sensory network.

New Strategies for Refractory Coronary Disease

New low-risk, anti-ischemic strategies for refractory coronary disease include spinal cord stimulation (SCS), therapeutic angiogenesis, transmyocardial laser, enhanced external counterpulsation, and high thoracic epidural.

Spinal Cord Stimulation

Electrical stimulation of the spinal cord has been used to treat various tissue injuries for approxi-
approximately 40 years. In 1987, Murphy and Giles published the first case report in which SCS was used for the treatment of myocardial ischemia. Since then, many centers around the world have used animal studies and human trials of patients with the most refractory coronary disease to investigate the anti-ischemic mechanisms of this technique. Long-term clinical outcomes have also been the focus of recently published prospective, randomized trials.

**Therapeutic Application**

“Primum non nocere.” At the Health Sciences Center, Winnipeg, many patients with refractory coronary disease are initially treated with a non-invasive neuromodulation technique using precordial transcutaneous electrical nerve stimulation (TENS). Its use in chronic refractory angina was first reported in 1982 by Mannheimer et al. It has subsequently been used effectively in acute unstable angina and as a bridge therapy to provide several weeks of clinical stabilization prior to insertion of the permanent stimulator device. No formal studies have calculated the predictive value of TENS for the likelihood of long-term success from SCS. Some of the Center’s ambulatory outpatients use TENS as successful antianginal therapy for consecutive months while they are awaiting implantation of a spinal cord stimulator.

The implantation of a permanent spinal cord stimulator is a simple procedure performed under local anesthetic by an anesthesiologist or neurosurgeon in an alert patient in the prone position. The loss-of-resistance technique is used to access the epidural space approximately 16 cm caudal to the C7 spinous process. This usually corresponds to the T5–T6 interspace. A Pisces Quad Plus quadripolar lead (Medtronic, Minneapolis, Minn) is advanced under fluoroscopic guidance through the epidural space along the anatomic midline. The tip is positioned at the approximate level of C7–T1 interspace. A temporary screening pulse generator is attached to the lead and an intraoperative stimulation test is performed. The lead tip is repositioned until the patient experiences a gentle bilateral paresthesia over the area of the chest most often affected by angina. Satisfactory coverage is essential for a good clinical outcome. The permanent Irel 3 impulse generator (Medtronic, Minneapolis, Minn) is secured within a shallow subcutaneous pouch developed over the iliac fossa or hip pocket region. A tunneled extension wire connects it to the quadripolar lead.

The entire implant procedure requires approximately 90 minutes of operative time and full patient cooperation. Postoperatively, the patient can easily make adjustments to the intensity and frequency of stimulation with a hand-held portable programmer. Most individuals are discharged on their first postoperative day since the incisions are small, the physiologic trespass is minimal, and the rate of severe complications is very low.

**Anti-Ischemic Effects**

Many of the standard measures of myocardial ischemia in patients with severe coronary artery disease are significantly improved by treatment with SCS. Treadmill times, ST segment depression with right atrial pacing, and the total ischemic burden on ambulatory Holter monitoring were all improved with the use of SCS compared with control. Myocardial oxygen consumption at maximal pacing is significantly reduced by the application of SCS. Blood sampled from the coronary sinus actually demonstrates a shift in the ischemic threshold as lactate metabolism is converted from production to extraction.

Echocardiographic studies have also demonstrated improved left ventricular function in patients with severe angina pectoris who were treated with SCS.

Many of the improvements in ischemic measures are as a result of improved myocardial blood flow in response to SCS, which has been shown to increase the mean value of regional myocardial perfusion by 11% as measured by PET. It is significant that the flow is increased by 24% to regions of low basal myocardial blood flow (<0.6 mL/min/g) and reduced by 7% to regions of high basal myocardial blood flow (>1.0 mL/min/g). This redistribution indicates that SCS produces a “Robin Hood” effect by redistributing flow from nonischemic areas to ischemic areas. This may occur through beds of collateral vessels recruited by calcitonin gene related peptide (CGRP) and other endogenous vasodilators released directly to the coronary circulation in response to SCS. Fortunately, neurostimulation does not conceal pain associated with ischemia or infarction, so that patients retain a valuable early warning signal.

**Treating the “Vicious Cycle”**

Sympathetic tone may increase dramatically in response to myocardial ischemia and remain elevated for a sustained time period.
acute coronary event, the elevated noradrenaline spillover into the coronary sinus can persist during pain-free periods for up to 3 months, despite adequate dosing of β-blockers. This reflex increase in sympathetic tone may exacerbate the myocardial oxygen imbalance via vasoconstriction of subendocardial resistance vessels and higher metabolic demands of the heart. If left unchecked, these factors perpetuate a “vicious cycle” that produces more ischemic tissue injury and myocardial dystrophy (see Figure 1). One study has shown that SCS stops this reflex pathway and reduces noradrenaline spillover during pacing-induced ischemia from 47% to 18% (P = .02).

SCS can also have a significant effect on other neural modifiers of regional cardiac function and myocardial blood flow. The intrinsic cardiac neurons produce impulses at a much greater frequency in the presence of ischemia. In an animal model, electrical stimulation of the spinal cord at T1–T2 can significantly reduce this hyperactive response: 511 ± 197 impulses per minute decreased to 169 ± 99 with SCS (P < .01).

**Contraindications, Limitations, and Complications**

A permanent spinal cord stimulator should not be implanted in patients with an implantable cardiac defibrillator. SCS can produce some baseline electrical artifact on the electrocardiogram, and clinical and experimental data are insufficient to know if this will be adequately filtered by the defibrillator’s software. Our experience with pacemaker patients is that no inhibition or inadvertent reprogramming occurs with the concurrent use of SCS. The absolute contraindications for stimulator implantation include irreversible bleeding diathesis, malignancy of the neuraxis, and severe cognitive impairment because the placement and management of the stimulator require full patient cooperation.

TENS has shown efficacy in treatment of acute coronary syndromes. However, because SCS has only been studied in patients with chronic refractory angina pectoris, stimulators should not be implanted as part of the acute management of myocardial infarction or coronary syndromes.

The complication rate is very low when SCS is used to treat ischemic heart disease. The combined rate of minor complications is 6.8% and includes lead migration, subcutaneous infections, electrode fracture, or early battery demise. The advent of multichannel, programmable devices with effective anchoring systems has effectively reduced the revision rate of electrodes that are placed percutaneously. The perioperative rate of major complications is 0%, and no cases have been reported of procedurally related myocardial infarctions, stroke, death, paralysis, or sepsis when stimulators are implanted for this clinical indication.

**Clinical Outcomes**

Reported in 1998 were the initial results of the randomized, controlled Electrical Stimulation versus Bypass surgery (ESBY) trial in which 104 patients with coronary artery disease were randomized to either SCS or CABG. All of the patients had refractory angina and were categorized as high-risk surgical candidates without prognostic benefit from revascularization.

The mortality rate at 6 months was significantly better in the SCS group compared with CABG (1.9% vs 13.7%, P = .02). Some of the patients who died were either awaiting surgery or had perioperative events. After 5 years of follow-up, there was no difference in survival between the SCS and CABG groups (75.5% vs 68.6%, P = NS). Mortality from cardiac causes accounted for 66% of deaths and was equal between groups. Procedural morbidity was low in the SCS group. The stimulating electrodes were removed because of infection in 1 patient (1.9%) and surgically repositioned in 3 of 53 patients (5.7%).

A significantly greater number of patients discontinued β-blockers (P < .01), long-acting nitrates (P < .0001), and calcium channel blockers (P < .05) in the CABG group. Separate survival data was not calculated in the subgroups that discontinued medication after surgery.

**Cost-Benefit**

Even though the CABG patients took fewer medications after surgery than the stimulator group, SCS was significantly less expensive (P < .01). The pulse generators for SCS needed replacement after an average life span of 3.3 years. Total hospitalizations did not differ between the groups in 2 years of follow-up after the primary intervention (4.2 days vs 3.7 days, P = NS). The average length of hospital stay after CABG was 11 days, including at least 1 day of intensive care, while the SCS group required 5 days (P < .0001) and no intensive care. Ekre et al report that the hospitalization for SCS has decreased to 2.5 days since the completion of the ESBY trial.
tients who receive a spinal cord stimulator for refractory angina are admitted on the morning of their surgery and discharged on the first postoperative day.44

Observational studies on the cost-benefit of this technique have shown that SCS was responsible for reducing the number of hospitalizations (0.27 patients per year after SCS vs 0.97 after revascularization; \( P = .02 \))\(^45\) and their duration (2.5 days vs 8.3 days, \( P = 0.04 \)) for patients with severe coronary artery disease.

Patients with intractable angina who are being treated with SCS require fewer invasive tests, which results in a 30% annual saving in medical costs.\(^46\) The Danish study calculates a combined yearly saving of $8,430 (US) per patient for each angina patient treated with SCS. Merry et al\(^47\) estimate that the complete cost of implating a stimulator for refractory angina can be recovered within 15 months. This compares very favorably to the high cumulative costs of either CABG surgery\(^48\) or percutaneous coronary stenting which are greater than $50,000 (US) at 5 years.\(^49\)

**Therapeutic Angiogenesis**

Neovascularization is the gradual development of a collateral blood supply in response to vessel stenoses at the interface of normal and ischemic regions.\(^50\) This vasculogenesis is naturally occurring and may provide nutrient perfusion sufficient to maintain the function and integrity of tissues such as the myocardium. The role of angiogenic growth factors in this process, as well their potential to therapeutically augment vessel growth, has been known for many years.\(^51\) They have recently been used clinically as a complementary treatment for vascular insufficiency. The two cytokines that have been used in most clinical trials for refractory angina are fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF).\(^52\)

**Therapeutic Application**

The angiogenic cytokines are delivered by gene transfer or as recombinant protein directly to the ischemic region of the myocardium. Proteins may be given by injection directly into the myocardium or as an intracoronary infusion.\(^52\) Gene transfer with naked DNA\(^53\) or an adenoviral vector\(^54\) can be injected through either the epicardial or endocardial surface into the myocardium. The transendocardial approach is a minimally invasive, catheter-based injection technique which is directed by electromechanical mapping of the left ventricle.\(^55\) VEGF or FGF may also be injected into the myocardium as an adjunct at the time of CABG surgery\(^56\) or through a thoracotomy incision. Intraoperative transeosophageal echocardiography can be a useful tool to guide the placement of the needle tip to ensure growth factors are injected into the myocardium and not the left ventricular cavity.\(^57\)

**Anti-Ischemic Effects**

Several clinical trials have been completed or are ongoing to quantify the objective anti-ischemic benefits VEGF or FGF. A randomized, double-blind, placebo-controlled trial of naked plasmid DNA used a catheter-based technique to inject escalating doses of VEGF2 directly into the myocardium of patients with chronic, refractory angina.\(^55\) Treadmill times improved significantly at 12-week follow-up in the treatment group (479 ± 51.5 vs 607.3 ± 52.4 seconds, \( P = .02 \)). Single photon emission computed tomography (SPECT) myocardial imaging was evaluated in some of the patients who were receiving gene therapy, and a 23% improvement (\( P = .074 \)) was noted in their perfusion scores at 4 weeks. The segments that had been underperfused at baseline experienced the greatest improvement in perfusion scores in a dose-related response to gene therapy (baseline 1.65 ± 0.44 vs 4 weeks 1.07 ± 0.50, \( P = .016 \)).\(^53\) Treadmill times and myocardial perfusion scores did not improve in the placebo group.

The VEGF in Ischemia for Vascular Angiogenesis (VIVA) trial\(^58\) was also a double-blind, placebo-controlled design that used variable doses of intracoronary and intravenous injections of rhVEGF, a recombinant protein. Treadmill times improved in the high-dose group by 30 seconds from baseline at 60 days and by 48 seconds at 120 days (\( P = .01 \)); however, myocardial perfusion and function were unchanged at rest or under stress in all dose categories.

**Contraindications and Limitations**

Most studies of therapeutic angiogenesis have reported low rates of procedurally related morbidity and mortality. Hypotension, proteinuria, and angioma formation have not occurred in clinical trials.\(^8\) One postoperative death occurred after gene transfer in a study of 30 patients with chronic, refractory angina.\(^59\)
The theoretical risks of promoting angiogenesis include deterioration of diabetic retinopathy, progression of atherosclerosis, and potentiation of malignancies that are influenced by growth factors. Research that has been published to date has not reported a significant incidence of these complications; however, larger clinical studies with long-term follow-up need to be completed to address these questions.

FGF and VEGF have not been studied in the acute management of myocardial infarction, unstable angina, or in those patients with severely compromised left ventricular function (ejection fraction < 20%). Early studies of injections of autologous stem cells and other pluripotent substrates into the ischemic myocardium have shown promising results in the promotion of angiogenesis and myocardial regeneration. Therapeutic angiogenesis is limited to the management of chronic coronary disease and has no role in acute unstable angina. It is available in very few tertiary referral centers. Approval by the US Food and Drug Administration (FDA) awaits the results of pending phase III trials.

**Clinical Outcomes**

No randomized studies on the use of therapeutic angiogenesis have reported 5-year outcomes. The combined 1-year mortality of four VEGF studies was 3 of 85 patients (3.5%). These studies did not have a comparable group of control patients; however, these results appear more favorable than the 1-year mortality of 16.8% in a parallel study of patients with inoperable coronary disease who were treated with medical therapy.

**Transmyocardial Laser Revascularization**

Transmyocardial laser revascularization (TMR) and percutaneous laser revascularization (PTMR) techniques use the thermal energy of laser beams to create multiple channels through ischemic regions of myocardium that are not amenable to interventions of the responsible epicardial coronary artery. These perforations are intended to recreate a sinusoidal network of vessels to deliver nutrient flow. Some research has indicated sympathetic denervation of the left ventricle, the promotion of angiogenesis, or both. The first trials began in 1982, and since then, the FDA approved CO₂ and Holmium:YAG lasers for use in TMR in refractory angina.

**Therapeutic Application**

TMR is performed thoracoscopically or through a small left thoracotomy incision. The pericardium is dissected, and the laser probe is placed directly on the affected area on the free wall of the left ventricle. Up to 40 high-energy beams are delivered from the epicardial surface. TMR has been used at the time of CABG surgery when complete revascularization is not possible. Transesophageal echocardiography provides an intraoperative monitor to confirm that channels are transmural.

PTMR transmits an Holmium:YAG laser beam through an optical fiber to create a smaller number of intramural channels from the endocardial surface. The small gauge catheter is inserted into the femoral artery and directed to the affected wall of the left ventricle by using either fluoroscopy or an electromechanical mapping device. The procedural morbidity is less than TMR and many patients are discharged from hospital the same day.

**Anti-Ischemic Effects**

In several randomized clinical trials of patients with end-stage coronary disease, TMR demonstrated no improvement in myocardial perfusion compared with medical therapy. One trial of 275 patients documented a significant improvement in exercise tolerance (5.0 vs 3.9 METS, \( P = .05 \)) but no change in dipyridamole-thallium imaging at 3, 6, and 12 months. Contradictory results were reported in a study of 192 patients in whom myocardial perfusion was measured with 201Tl:SPECT scanning. At 1 year, the perfusion improved by 20% in the TMR group and decreased by 27% in the control group (\( P < .002 \)); however, the 1-year mortality in the TMR group was 15% and not significantly better than medical management.

No differences in exercise tolerance or myocardial perfusion were found in three recent blinded trials of PMR compared to placebo. In the Direct Myocardial Revascularization in Regeneration of Endomyocardial Channels (DIRECT) trial, randomized patients were placed into one of three treatment limbs to compare placebo with either low-dose or high-dose laser treatment. At 30 days, 8.2% of patients in the low-dose group had suffered a major adverse coronary event, compared with 4.1% in the high-dose group. The incidence in the placebo group was 0%. At 12 months, the high-dose group had the greatest incidence of a major adverse coronary event (21.4%), including significantly more
non-Q wave myocardial infarctions, and yet more than 40% of all patients improved by two or more functional classes, including the placebo group. Quantitative assessment of ischemia demonstrated no difference in stress-induced ST change or SPECT imaging.

**Contraindications and Limitations**
Mortality rates in early studies of TMR approached 20%, although this has decreased in subsequent investigations with more stringent selection criteria. Those with a higher risk of adverse outcome from TMR include patients with a left ventricular ejection fraction of less than 20%, congestive heart failure, recent myocardial infarction, severe arrhythmias, left ventricular mural thrombus, ischemic region beyond the left ventricular free wall, and concurrent major illnesses such as severe chronic obstructive pulmonary disease.

Recent studies have also indicated that diabetic patients have a significantly lower likelihood of symptomatic benefit from TMR (odds ratio = 0.43), and patients with a body mass index that is less than 25 are at three times greater risk of mortality within 1 year of the procedure (odds ratio = 2.97). Catheter-based techniques require retrograde cannulation of the aortic valve and therefore cannot be performed in patients with valvular stenosis or prosthesis.

PMR is used in Europe though not in the United States, because it has not been granted FDA approval.

**Clinical Outcomes**
A recent review of multiple randomized trials indicates there is no difference in long-term prognosis between medical therapy and transmyocardial laser. The 12-month mortality rate in the largest of these studies is approximately 15%. These findings reinforce the importance of accounting for a placebo effect of any interventional treatment of patients with end-stage coronary disease.

Despite the lack of convincing evidence of prognostic benefit, the FDA has approved TMR for use in symptomatic relief of angina. Similarly, the ACC/AHA give this intervention a class IIa indication in the 2002 Guidelines for Treating Chronic, Stable Angina.

**Enhanced External Counterpulsation**
Enhanced external counterpulsation (EECP) is a noninvasive technique to enhance diastolic coronary filling and reduce cardiac afterload, similar to intra-aortic balloon counterpulsation. The improvement in the diastolic coronary flow and in the recruitment of collateral circulation has been known since 1963. A stationary compressor system is controlled by an electrocardiographic gating mechanism that allows the rapid, sequential inflation of large pneumatic cuffs that are applied to the lower legs and upper thighs. The cuffs are inflated to 300 mm Hg with diastole and deflated with systole. Cardiac output is improved by the Starling mechanism as venous return is increased upon inflation and the ventricle is unloaded with the sudden drop in diastolic pressure on deflation. These effects restore an equitable balance between the determinants of myocardial oxygen supply and demand.

Other mechanisms may also explain the improvements in collateral bed development. The resulting shear forces of increased diastolic flow from EECP cause an increase in VEGF and other angiogenic factors that enhance the growth of new collateral vessels. Vasodilation is enhanced by significant and sustained increases in plasma nitric oxide levels and corresponding reductions in endothelin, a potent vasoconstrictor.

**Therapeutic Application**
Chronic stable angina pectoris has been successfully treated on an outpatient basis with EECP. The standard treatment regimen extends over a period of 5 to 7 weeks and consists of 35 sessions of 1-hour duration. This routine has been used in China since 1976 when serial stress tests indicated a steady increase in treadmill times after 12 and 24 hours of EECP, though the improvements achieved a plateau at 36 hours of therapy. The duration of benefit is also difficult to predict, as 39% of patients required additional treatment with EECP and thereby increased the mean time of treatment to 55.7 hours. The optimal hemodynamic effects of EECP correlated with cuff pressures of 300 mm Hg and produced a diastolic/systolic unloading ratio of 1.5 to 2.0.

Approximately 100 centers around the world are currently involved in the International EECP Patient Registry. More than 5000 patients have been enrolled in the United States, Europe, and Asia since 1998, and long-term data is collected on an ongoing basis to document safety, efficacy, and patterns of use.

**Anti-Ischemic Effects**
One randomized, sham–control study of 139 patients with “unremediable angina” demonstrated...
an increase from baseline ($P \leq .01$) in time to exercise-induced ST depression ($\geq 1$ mm) for the active counterpulsation (CP) group compared to the inactive CP. Changes in exercise duration also occurred in both groups, but without a significant difference between active and inactive CP, indicating a possible placebo effect.86

Quantifiable reductions in exercise-induced reversible perfusion defects from 35% to 22% were seen after EECP ($P < .01$) in a small study of 12 patients.87 This may suggest the development of collateral circulation. Lawson et al reported similar results in a case series of 18 patients with reversible perfusion defects on thallium stress tests.88 The complete resolution of defects occurred in 11 of 18 patients at the completion of their treatment regimen. At 3-year follow-up, 8 of the 18 patients still had no perfusion abnormalities.

Contraindications and Limitations

Some morbidity and patient discomfort is associated with CP therapy. The active CP group experienced significantly more pain in the back and legs ($P = .01$) as well as superficial skin lesions ($P = .005$).87 Nearly 10% (7 of 71 patients) withdrew from the active CP group in the Multicenter Study of Enhanced External Counterpulsation (MUST-EECP) because of adverse events.86 From a logistic standpoint, the 35 hours of treatment is inconvenient and the EECP compressor is cumbersome, because portable units are not widely available.

The clinical application of EECP is contraindicated in decompensated heart failure, severe aortic insufficiency, pacemakers and implantable cardiac defibrillators, atrial fibrillation or frequent ectopy, severe peripheral vascular disease, acute myocardial infarction or unstable angina, severe hypertension of 180/110 mm Hg or more, bleeding diathesis, and pregnancy.80,85 Several independent predictors of reduced effectiveness are diabetes, three-vessel disease, prior CABG, and a history of congestive heart failure. All were associated with an unfavorable odds ratio (<1.0) of significant improvement.85 Though EECP has been approved by the FDA, limits on reimbursement currently pose a problem for the broader application of this technique.

Clinical Outcomes

Very little long-term outcome data is available for patients with refractory stable angina who have been treated with EECP. At 5-year follow-up, 64% of treated patients remained free of major adverse coronary events; however, in those with demonstrable improvement in scintigraphy, the survival was 77% without a major adverse coronary event.89 In a subset of 597 patients enrolled in the International EECP Patient Registry,83 the mortality at 24 months was 7%, which compares favorably with historical controls of a similar cohort.

High Thoracic Epidural Anesthesia

High thoracic epidural anesthesia (HTEA) is a minimally invasive technique that has been used effectively in the acute and chronic treatment of refractory angina and myocardial injury.37,90,91 Many of the benefits provided by thoracic epidurals in the surgical model of tissue injury can be extrapolated to ischemic injury of cardiac tissue.92 Sympathetic blockade, vasodilation, decreased determinants of oxygen demand, reduced arrhythmias and neuroendocrine response, selective regional analgesia, and reduced platelet adhesiveness are epidural effects that can have a significant role in the treatment of myocardial injury.92 The high thoracic epidural is also a very simple, versatile procedure that can even be performed in outpatient clinics as long as there is a sterile field and monitoring.

Therapeutic Application

A flexible, narrow-gauge catheter is introduced through a standard 17-gauge Tuohy needle into the epidural space between the second and third thoracic vertebrae (T2–T3) by using a percutaneous loss-of-resistance technique. Approximately 5 cm of catheter is inserted into the epidural space and then injected with local anesthetic (bupivacaine, 0.25%–0.5%) in incremental doses of 2 mL to achieve sensory and sympathetic inhibition between dermatomes T1 and T5. This analgesia may be maintained with a continuous infusion or repeated intermittent boluses as a perioperative adjunct to CABG surgery. In this circumstance, it has been shown to reduce time to extubation, postoperative pain,93 myocardial injury, arrhythmias, and provide greater hemodynamic stability.94-96 Despite theoretical concerns of adverse neurologic outcomes, no symptomatic epidural hematomas have been reported as a result of a TEA inserted before full heparinization of CABG surgery has occurred.

One study of nine patients with acute ischemia showed a significant reduction in pulmonary capillary wedge pressure (11.6 ± 1.7 mm
Hg pre-TEA vs 6.7 ± 1.3 mm Hg post-TEA, P < .05), although the mean arterial pressure, coronary perfusion pressure, and cardiac index did not change. Stroke volume increased, which indicated that TEA had created a beneficial shift in the ventricular function curve. In keeping with these central hemodynamic effects, HTEA has been effectively used to wean some refractory patients from intra-aortic balloon pump support98 and as a stabilizing bridge treatment for patients who are clinically deteriorating while awaiting surgery. Several case series have been published that used a tunneled epidural catheter to treat chronic, refractory angina,99 though no randomized controlled trials have been reported. Patients are taught to self-administer local anesthetic with a sterile syringe technique or portable patient-controlled epidural analgesia device.91 Of particular interest in this group is the significant reductions in the daily injections that are required over time (2.00 ± 0.47 vs 0.25 ± 0.10 injections per day at 1 and 6 months, respectively; P < .01).100 Serial sympathetic blocks, as with the treatment of reflex sympathetic dystrophy, appear to slow the "vicious cycle" and thereby improve some fundamental components of cardiac physiology.37,44 More than 50% of percutaneous epidural catheters, however, become occluded or dislodged,99 so once the patients at our institution have been stabilized with epidural infusions, they receive long-term treatment with spinal cord stimulator implants.101 When the clinical response to epidural blockade is significant but a stimulator is contraindicated (ie, implantable cardiac defibrillator), the intrathecal Algomed pump (Medtronic Inc, Minneapolis, Minn) is implanted.102 This subcutaneous device is patient controlled and has a reservoir that may be refilled. The intrathecal catheter injects local anesthetic at T3 and has a low rate of occlusion.

Anti-Ischemic Effects
Several experimental trials have quantified the anti-ischemic effects of HTEA. In laboratory studies that involved the ligation of the left anterior descending coronary artery, the infarct size was reduced by 46% in animals treated with HTEA compared with controls,103 thereby indicating a significant cardioprotective effect from HTEA. One study evaluated ischemic changes in 10 patients with severe coronary disease during control stress and then with HTEA. The global ejection fraction was moderately improved (46% to 53.2%, P < .05), and the regional wall-motion score was significantly improved (8.8 vs 11.8, P < .01), as were ST-segment changes (–1.03 mV vs –1.84 mV, P < .01) comparing HTEA with control.104 Blomberg et al investigated the vasomotor effects of a dense T1–T6 epidural blockade (bupivacaine, 5 mg/mL) on the stenoses in 27 patients with severely diseased coronary vasculature. The diameter of the stenotic coronary segments significantly increased (1.34 ± 0.11 to 1.56 ± 0.13 mm, P < .002), but no change occurred in the diameter of the normal epicardial arteries (3.07 ± 0.13 to 2.99 ± 0.13 mm, NS).105 Two of the 27 patients actually had angina during the study, along with ST changes and lactate production at rest. HTEA blockade abolished the angina within 10 minutes, and coronary sinus samples showed a significant reduction in myocardial lactate production (P < .01). The epidural block also reduced determinants of myocardial oxygen demand, such as rate–pressure product and wall tension.

Olausson et al10 randomized 36 patients with severe acute, unstable angina who were receiving treatment with β-blockers, calcium antagonists, aspirin, heparin, and nitroglycerin infusion. All had failed at least one attempt to wean the nitroglycerin infusion and were then assigned to either epidural (HTEA T1–T5 blockade) infusion treatment and discontinuation of heparin and nitrates, or to a control group of continued maximal medical therapy. Myocardial ischemia was assessed by 48-hour Holter monitoring, and all measures were significantly lower in the HTEA group. The incidence of ischemic episodes (22% vs 61% min; P < .05), the number per patient (1.0 ± 0.6 vs 3.6 ± 0.9; P < .05), the duration (4.1 ± 2.5 min vs 19.7 ± 6.2 min; P < .05), and ischemic burden (mean area-under-ST-time curve, 6.8 ± 4.3 vs 32.2 ± 14.3 mm·min; P < .05) were all improved by HTEA, indicating a significant anti-ischemic activity.

Contraindications and Limitations
HTEA is widely used with few absolute contraindications. It is not advised, however, in patients with elevated intracranial pressure, irreversible bleeding diathesis, or those with a true allergy to amide local anesthetics. Significant cognitive impairment would be a relative contraindication for this technique, because much information is required from the patient on an ongoing basis to adjust therapy. Patients with very severe aortic stenosis may not tolerate the hemodynamic changes of even a limited sympathetic block and should also be excluded from HTEA.

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For patients with externalized catheters, vigilant follow-up is necessary for dressing changes and to evaluate the system’s integrity; the occlusion and extrusion rate is more than 50%. Immunological systems require a long-term schedule of frequent refills.

Clinical Outcomes
Patients in these case series were followed for variable time periods (7 days to 3.2 years) with variable dosing regimens as symptoms required. A dose–response curve of the anti-ischemic potency of neuraxial local anesthetic has not been documented. Randomized, controlled trials of HTEA which record survival free of a major adverse coronary event at 1 year and 5 years have not appeared in the literature, even though dramatic clinical improvements have been widely reported in critically ill patients with advanced ischemic heart disease.

Blomberg and others have articulated the anti-ischemic mechanisms; however, widespread application in this patient population is unlikely until longitudinal studies are conducted with treadmill and perfusion measures and a comparable control group.

The Anesthesiologists’ Role in Treating Refractory Angina
Anesthesiologists can provide technical and advisory assistance regarding spinal cord stimulators and other emerging therapeutic options for treating patients who suffer from refractory angina. The clinical problem of end-stage cardiac disease is expanding as the number of patients increase by more than 100,000 per year in the United States.

One fundamental responsibility of the anesthesiologist is to provide treatment options that minimize patient risk and optimize cardiac function. As more patients survive primary and subsequent coronary events, the severe pathologic changes of the coronary arteries and myocardium are often compounded by comorbid disease and a “vicious circle” of cardiac decompensation. These patients are increasingly vulnerable to higher morbidity and mortality from conventional treatments such as revascularization procedures or standard medical therapy.

Spinal cord stimulation, enhanced external counterpulsation, and therapeutic angiogenesis are low-risk procedures that have demonstrated safety and efficacy in this patient subgroup, along with acceptable outcomes in long-term follow-up.

Because anesthesiologists are very familiar with some of these emerging techniques, they can have a very active role in selecting patients for minimally invasive adjuncts during both the acute and chronic phases of refractory angina. Cardiothoracic anesthesiologists, for example, often use the anti-ischemic benefits of HTEA to optimize these high-risk patients preoperatively when surgery is deemed feasible and the calculated risk is acceptable. The postoperative use of epidurals may also enhance analgesia, tissue function, and decrease complications. The anesthesiologist may use transesophageal echocardiography as an intraoperative tool to guide surgeons for complementary strategies such as the injection of VEGF or TMR at the time of bypass.

Interventional pain management specialists can also provide consultation and technical expertise to cardiologists and cardiac surgeons by providing bridge treatment and definitive care for patients who are not candidates for revascularization. Tunneled epidural catheters or TENS, for example, can be initiated to stabilize refractory angina patients already in the hospital during the acute phase of treatment. This can be continued and monitored through the anesthesiology outpatient pain clinics while they begin the screening process to determine candidacy for a permanent implant of spinal cord stimulation.

Researchers will also design trials that use multimodal therapy. This approach is born of the recognition that no single technique, including revascularization, is effective for every patient. Combining the use of two or more minimally invasive techniques allows the advantages of one procedure to supplement the deficiencies of another. This therapeutic approach is similar to pharmacotherapy that combines the complementary anti-ischemic effects of different drugs, such as β-blockers and nitrates, to maximize patient benefit with little additional risk.

Some examples of multimodal therapy include:
1. Expediting the onset of the antianginal effects of VEGF, TMR, or EECP with concurrent use of SCS or HTEA.
2. Improving left ventricular function with EECP or SCS for patients who are receiving an intramyocardial injection of VEGF or pluripotent stem cells.
3. Reducing perioperative complications, such as arrhythmias, from TMR by using a sustained infusion of HTEA well into the postoperative period.
In conclusion, therapeutic angiogenesis, spinal cord stimulation, enhanced external counterpulsation, transmyocardial laser revascularization, and high thoracic epidural anesthesia will provide important options in the evolving management of refractory angina. Anesthesiologists can have a pivotal role in their clinical application.

References


