BRIEF REVIEW

Emerging Treatments for Refractory Angina

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How to manage patients with angina refractory to multiple revascularization procedures or aggressive medical therapy is a real problem in the United States today. In a sense, it is a tribute to the success of cardiologists and cardiovascular surgeons in keeping otherwise seriously ill patients alive. Nonetheless, of the hundreds of thousands of patients in the United States who have undergone percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) each year for the past decade, many remain symptomatic or become symptomatic again within months or years. There is a limit to how many repeat revascularization attempts can be made because of the patient's coronary anatomy, conduit availability, left ventricular function, age, comorbidity, etc. For those patients in whom repeat (or initial) PTCA or CABG is not appropriate—and in whom aggressive medical therapy still fails to maintain a quality of life that patients are comfortable with—several emergent therapies have been proposed as follows: (1) techniques to reduce anginal pain by neural stimulation or blockade and (2) procedures that enhance (or may enhance) coronary myocardial perfusion.

Neural Techniques To Reduce Anginal Pain

There are several methods available to block pain associated with cardiac ischemia. These include sympathectomy, autotransplantation and, more recently, transcutaneous electrical nerve stimulation (1) and thoracic epidural anesthesia (2). The most encouraging approach appears to be spinal cord stimulation. This technique has been used since 1985, and studies have shown not only a decrease in angina but an improvement in exercise test parameters. Perhaps most impressively, when compared with CABG in a recent randomized study of 104 patients performed in Sweden (3), equivalent symptom relief was demonstrated after insertion of a pulse generator in the epidural space. The main drawback to this procedure is that it is invasive. At present, the major research in this technique is taking place at centers in Europe.

Procedures To Enhance Myocardial Perfusion

There are three types of procedures currently used to increase myocardial perfusion; two are invasive and one is noninvasive. The invasive procedures include long-term intermittent intravenous therapy with urokinase (4) and transmyocardial laser revascularization (5), an operation which utilizes the myocardial sinusoids to create new channels to deliver blood to the myocardium. Results in early case-control studies showed promise with this technique, and this has been confirmed in a multicenter, prospective but nonrandomized trial of 200 patients not amenable to PTCA or CABG. Anginal symptoms decreased, as did exercise radionuclide perfusion defects. A randomized study is currently underway. An additional invasive procedure is still investigational but has received intensive media attention within the past year—angiogenic therapy of the human heart, that is, injection of the angiogenic protein FGF-1 close to the left anterior descending artery during CABG. Postoperative myocardial revascularization was significantly greater than in control patients receiving inactivated protein (6).

The only truly noninvasive procedure reporting an increase in myocardial perfusion is enhanced external counterpulsation (EECP), a technique originally introduced over 20 years ago. At that time, its initial clinical results were limited, but it has been modified sufficiently in recent years to warrant reevaluation by clinicians, especially those who treat patients with refractory angina. This reevaluation is prompted by: (1) the data accumulated at Stony Brook, the first United States institution to use EECP and (2) results of a recently completed multicenter trial. The remainder of this review will describe the current status of this technique.

Enhanced External Counterpulsation

EECP involves the inflation of a series of compressive balloons, with compressions timed to the patient's electrocardiogram. The device increases myocardial oxygen supply by increasing diastolic perfusion pressure and reduces cardiac workload by decreasing left ventricular workload. In the early 1980s, Chinese investigators reported on their extensive experience in treating angina patients with an enhanced version of the original device using three cuffs, rather than the original two, and using sequential calf-to-thigh counterpulsation and a pneumatic, rather than hydraulic, compressing medium. The diastolic pressure was augmented much more than with the previous system. Investigators at Stony Brook then assessed the efficacy of EECP in producing sustained benefits in selected patients with chronic angina refractory to conventional therapy. Exercise-thallium imaging was used to document improvement in exercise tolerance and the degree of exertional myocardial ischemia before and after EECP treatment. The change in functional status after EECP was assessed by anginal diaries and symptom-limited stress testing.

In the initial Stony Brook experience (studies conducted between 1989 and 1991), 18 patients (17 men and one woman) were treated with EECP in an outpatient setting for 1 hour daily for a total of 36 hours (7). The 18 patients

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chosen for study had chronic stable angina despite medical and surgical therapy. Other patients were excluded because of clinical congestive heart failure, aortic insufficiency, myocardial infarction within the previous 3 months, significant ventricular ectopic activity or atrial fibrillation, nonischemic cardiomyopathy, severe occlusive peripheral vascular disease, recurrent deep vein thrombophlebitis, systemic hypertension (> 180/110 mm Hg) or a bleeding diathesis. All patients were monitored hemodynamically and clinically during treatment. Diastolic augmentation pressures were progressively increased by increasing the external compression. The highest external pressure used to maximize the diastolic/systolic pressure ratio (diastolic augmentation) was 280 mm Hg. Blood pressure waveforms were continuously monitored by finger plethysmography.

Adjustments in anginal medications and other risk factor modification changes were determined by patients and their physicians during the course of the study. No other therapeutic interventions were performed during the study.

After completing the course of EECP therapy, patients underwent a thallium-201 stress test, with their usual medications continued, although exercise duration was the same as that during baseline testing so as to provide a valid comparison of imaging test results. A maximal symptom-lined stress test was also performed within 1 week of cessation of EECP treatment to assess exercise tolerance.

All 18 patients experienced substantial improvements in anginal symptoms after EECP; 16 were completely free of angina during the usual activities of daily living. Thallium-201 stress testing showed a complete resolution of ischemic defects in 12 patients (67%), a decrease in the area of ischemia in two patients (11%) and no change in four patients (22%). Thus, 14 patients had a reduction in myocardial ischemia after EECP as assessed by thallium-201 imaging ($p < 0.01$).

Comparison of maximal stress test results before and after EECP showed that EECP produced a 19% increase in exercise duration. Subgroup analysis of the 14 patients who showed improvement in their thallium-201 scans after EECP revealed increases in both exercise duration (from 8.58 + 0.66 to 10.44 + 0.59 minutes, $p < 0.001$) and double product (from 21,827 + 2,044 to 24,842 + 1,707 mm Hg × bpm, $p < 0.01$) during maximal stress testing after EECP.

At a mean follow-up of 3 years, we successfully contacted 17 of the 18 patients who underwent EECP therapy in this initial study. Thirteen patients (72%) reported the continued absence of limiting angina; also, no myocardial infarctions or other ischemic events had occurred in these patients. Furthermore, repeat thallium-201 stress testing, performed in 10 of the 14 originally improved patients, again showed improvement from the pre-EECP test in eight patients and worsening in only two patients (8).

Certain angiographic features seemed to predict the best clinical result. Fifty patients formed this study group—almost evenly divided into subgroups with 1-, 2- or 3-vessel residual disease, a definition somewhat different from the traditional meaning of the term. Patients with at least one open conduit (i.e., the 1- and 2-vessel residual disease subgroup) fared best. Thus, although perfusion defects improved in 95% of patients (18 of 19) with residual 1-vessel coronary artery disease and in 90% of patients (17 of 19) with residual 2-vessel coronary artery disease, in those with stenotic grafts and 3-vessel disease, improvement was seen in only 42% (five of 12).

Although the investigators found these results extremely encouraging in the extremely symptomatic population studied, the Stony Brook series lacked a suitable control group. Accordingly, a multicenter trial (9) was begun in 1995 with the goal of enrolling at least 120 patients to measure the effect of EECP vs. placebo on symptoms and various exercise parameters measured before and after treatment. Seven teaching hospitals enrolled patients, with Stony Brook serving as the core laboratory and data collection center. For entry into the study, all patients had to have documented coronary artery disease and positive exercise tests, as well as chronic angina, and be free of the exclusion criteria mentioned earlier. The protocol called for either active treatment (full pulsation) or inactive treatment (weak pulsation). Enrollment was completed in 1997, with 139 patients enrolled. The results demonstrated increased exercise duration, increased time to ST segment depression and reduced anginal episodes in the EECP treated patients. The latter two findings were significantly different from that reported with inactively treated patients. Symptomatic improvement seemed to persist during a 1-year follow-up period. No differences in benefits were noted between patients with and without prior revascularization procedures (10). There were few serious adverse side effects in the trial. Despite the difficulty in performing this sham-controlled study, the positive results suggest that EECP can be a potentially useful procedure for many patients, although the exact mechanisms of its long-range benefits remain to be elucidated.

Summary

In summary, cardiologists and cardiothoracic surgeons have an increasing array of invasive and noninvasive techniques to treat the patient with angina refractory to conventional therapy. It is encouraging to note that several of these techniques (e.g., spinal stimulation, transmyocardial laser revascularization, angiogenic therapy, EECP) have been, or are, being tested with randomized placebo-controlled trials. This is as it should be, because without such trials, cardiologists, cardiothoracic surgeons and patients will be left with the kind of nonscientifically based claims that have characterized chelation therapy.

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