Refractory Chronic Stable Angina – Now What?

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What Is Refractory Chronic Angina?

The term refractory angina needs to be defined precisely if one is to learn anything from different management strategies. A dictionary definition of refractory is 1. hard to manage, 2. stubborn, 3. obstinate, 4. not yielding readily to treatment. Chronic refractory angina patients are those in whom medical therapy has failed to eradicate the angina completely, and whose symptoms are relatively stable with some limitations of daily living activities.

The following comments focus on the patient with chronic refractory stable angina who is not amenable to revascularization, and on modern maximum medical therapy.

An algorithm to answer the question, “Now what?” is as follows: Are there secondary causes of the condition—for example, anemia, hyperthyroidism, infection, and so forth? If the answer is yes, then the secondary cause should be treated. If the answer is no, the next step is to insure that the patient is on maximum medical therapy. If so, then the next step is to determine whether the patient is a candidate for a revascularization procedure, either percutaneous coronary intervention or coronary artery bypass graft surgery. If the patient is a candidate, obviously revascularization is warranted. If the patient cannot or will not be revascularized, then the patient becomes a candidate for one of the newer strategies to treat refractory chronic angina pectoris. These include enhanced external counterpulsation (EECP), spinal cord stimulation (SCS), transmyocardial laser revascularization (TMR), and perhaps metabolic therapy using a partial fatty acid oxidation (pFOX) inhibitor.

Transmyocardial Laser Revascularization

Transmyocardial laser revascularization is the most highly visible of the treatment strategies, and some data have been presented on ACCEL. In an interview conducted by Dr. Lawrence Borchek, he and Dr. Keith Horvath of Northwestern University discussed the topic of sustained angina relief five years after TMR with a CO₂ laser.¹ Results in 80 patients indicate that 90% have at least a one-class sustained improvement in Canadian Cardiovascular Society angina class at five years and 20% of the 80 patients were angina free. Dr. Horvath believes that the laser technique will be used in combination with revascularization to provide a more complete revascularization and perhaps eliminate angina in the majority of patients. Unfortunately, despite this obvious enthusiastic support for TMR, it doesn’t seem to be a popular way to manage chronic refractory angina.

Enhanced External Counterpulsation

Another approach is EECP. A randomized trial showed that EECP reduced angina and extended time to exercise-induced ischemia in patients with symptomatic coronary disease who were receiving aggressive medical therapy and were not candidates for revascularization.² Since the basic principle is one of diastolic augmentation, EECP makes good physiologic sense, and, theoretically, should result in decreased myocardial oxygen demand and an increase in coronary blood flow. However, in the majority of patients, measurements using radionuclide perfusion imaging fail to show any increased perfusion in the short term versus control studies. It is still possible that long-term benefit may be the result of enhanced coronary collateral circulation, but this is theory and not proven. The most recent hypothesis of why this treatment works is that it perhaps acts in a fashion simulating exercise training, since the muscles of the calves, thigh, and buttocks are systematically compressed and relaxed for 1-hour periods over a 35-day treatment schedule. This also is theory and needs clinical testing. As with all therapies, there clearly is some placebo effect, but I don’t believe that symptom relief is due only to placebo effect.

The limitations of this procedure are that it is contraindicated in patients with deep vein thrombosis; phlebitis; fast, irregular rhythms; severe hypertension; and peripheral vascular disease. In the latter two conditions, it may be difficult to augment diastolic pressure. Severe aortic insufficiency is probably also a contraindication, as it is with intra-aortic balloon counterpulsation.

Spinal Cord Stimulation

Another approach is spinal cord stimulation (SCS). Like EECP, SCS should be reserved for patients who have persistent symptoms despite aggressive medical therapy and who are not candidates for revascularization procedures. Many seem to be skeptical of this procedure and are concerned that it masks myocardial ischemia while relieving pain. However, several investigators have reported that after SCS, they note in their patients a reduction of angina, increased exercise capaci-
ty, and a reduced degree of ST-segment depression during a comparable workload when the patient is not receiving SCS. However, at maximum workloads, ST-segment depression and angina similar to that in a control situation were noted in patients with SCS. This supports the argument that when angina is relieved, myocardial ischemia is not masked during spinal cord stimulation.

Partial Fatty Acid Oxidation (pFOX) Inhibition

The pFOX inhibitor ranolazine is being considered by the Food and Drug administration (FDA) for clinical use in the United States. Two clinical trials, MARISA, (Monotherapy Assessment of Ranolazine in Stable Angina) and CARISA, (Combined Assessment of Ranolazine in Stable Angina) were performed using the pFOX inhibitor ranolazine in patients with chronic stable angina. Both trials showed that versus placebo, low-dose atenolol, low-dose diltiazem, or low-dose amlodipine, exercise duration was increased, as was time to angina and time to ST-segment depression.4

Summary

Two of these therapies, EECP and TMR, are available on a clinical basis, whereas SCS is being investigated in the United States in a randomized trial called STARTSTIM (Stimulation Therapy for Angina Refractory to Standard Treatment Intervention or Medication). Multiple studies have been done in Europe showing the efficacy of SCS, and this forms the background information for the STARTSTIM investigation. The pFOX inhibitors have not yet been approved by the FDA, although there is a pFOX inhibitor that is being used in Europe, apparently successfully. If and when the pFOX inhibitors are approved by the FDA, perhaps they will provide us an alternative therapy for our patients with refractory chronic stable angina. Refractory chronic stable angina is not going to go away and will no doubt become an increasing problem, particularly in older patients. All four therapies warrant consideration in patients who are not happy with their lifestyles and who continue to have symptoms that limit activities of daily living. At the present time, the four therapies outlined above should not be considered a substitute for modern maximum aggressive medical therapy and revascularization therapy in patients with chronic stable angina. They should be used in addition to these therapies in the patient whose angina persists and interferes with activities of daily living, resulting in an unhappy lifestyle.

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References

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