Some Patients Can’t Be Revascularized with PCI or CABG

Despite the advances that have occurred in coronary revascularization, there is a growing population of patients who are not candidates for either coronary artery bypass grafting (CABG) or conventional percutaneous coronary intervention (PCI). This population is heterogeneous and includes patients with diffuse coronary disease, comorbid conditions or multiple previous bypass operations resulting in no remaining suitable conduits.

The majority of such patients present with anginal symptoms that are unresponsive to both conventional medical therapy and revascularization techniques. A number of such patients have continued to increase as life expectancy is increasing, even for very sick patients, many of whom have already undergone multiple PCIs or previous surgical revascularization, and thus are not candidates for additional procedures. Such patients are said to have refractory angina pectoris, and an understanding of the therapeutic options for these patients is becoming more vital for physicians treating patients with coronary disease today. It has been estimated that > 100,000 patients each year may be diagnosed as having this condition.

A patient with refractory angina pectoris must meet 2 criteria before he or she is labeled. These criteria include objective ischemia producing severe anginal symptoms, and all known conventional therapies (PCI or CABGs) are not feasible. Patients with refractory angina have either marked limitation of ordinary physical activity or are unable to perform any ordinary physical activity without discomfort (Canadian Cardiovascular Society [CCS] functional class III or IV) despite optimal medical therapy. There must be some objective evidence of ischemia, as demonstrated by exercise treadmill testing, stress imaging studies or coronary physiologic studies. Symptoms must continue despite maximally tolerated medical therapy and with a consensus that revascularization by either PCI or CABG is not feasible.

There are a number of therapeutic options available for such patients. Small, uncontrolled studies have shown a potential benefit for additional antiplatelet and antithrombotic therapy. In randomized trial, neurostimulation has been shown to be effective in reducing angina symptoms. Enhanced external counterpulsation is a viable treatment option for some patients. In many randomized trials, laser revascularization has been shown to diminish angina symptoms, although no placebo-controlled studies exist to date except for the DIRECT trial. However, the results of this trial led by Marty Leon have tempered the initial enthusiasm surrounding myocardial laser revascularization. This randomized, placebo-controlled, prospective trial enrolled 298 patients into three treatment arms: placebo procedure, low-dose or high-dose laser channels. The unique aspect of the trial was that none of the patients enrolled knew which arm of the study they were in. After six months of follow-up, the trial was stopped prematurely after all three groups noted a similar increase in exercise duration, exercise time to symptoms and exercise time to 1-mm ST-segment depression. Furthermore, there was a similar increase in the percentage of patients who reported at least a two-class improvement in anginal symptoms after six months. There were no differences in major adverse cardiac events after six months of follow-up.

Gene therapy is a promising area of research in this field. Percutaneous in situ coronary venous arterialization is in its infancy, but may be able to treat many patients if proved successful. No data support the role of chelation therapy.

Howard Cohen: The intractable angina patient subset is obviously very difficult to treat. Our institution participated in the DIRECT trial and thought the patients were benefiting, but the results proved otherwise. However, low-tech EECP therapy has proved helpful for our patients with refractory angina. Our institution has used EECP therapy extensively, though I am not entirely certain how it works. EECP doesn’t necessarily show immediate benefit, but after several weeks of therapy, there is remarkable improvement in the patients’ angina. Perhaps Kirk Garratt could tell us about Mayo Clinic’s experience with EECP. I have had to tell some of my patients who have asked to undergo intervention that it would not provide lasting effectiveness. Instead, I have performed EECP on these patients who, though previously non-functional, returned to a much more normal lifestyle after treatment. Their angina did not entirely disappear, but their symptoms became much more controllable. Furthermore, I believe there is a misconception within the medical community that patients who have angina and suffer from anemia require only a hemoglobin of 10 and a hematocrit of 30 to protect them. Our practice has seen a fairly large number of patients who have mild to moderate renal insufficiency, creatinines in the 2 to 3 range, hematocrits of 30, and who suffer from angina. It is amazing how much these patients improve when given 25% more oxygen-carrying capacity, either with Procrit or with frequent transfusions to maintain a hematocrit level in the 40 range. These patients have diffuse disease but can be managed with this low-tech therapy. I see approximately two patients a month who are candidates for this therapy.

As for gene therapy, I don’t know where it’s headed, but it certainly merits further investigation.

Fayaz Shawl: Would you say that the DIRECT trial has brought closure to this?

Howard Cohen: It has for us. We are not doing any of that.

Gary Roubin: Our institution is definitely finished with that as well. The problem lies in the fact that there is nothing more to be done in terms of angioplasty or stenting for those
patients whose anatomy is stable — which constitutes the bulk of our patients. Their total occlusions are well collateralized; their vein grafts are gone; perhaps their LIMA is available, perhaps a RIMA. We interventional cardiologists are called as a last resort to treat these types of patients; we’re more or less the “end of the line.” Intractable angina is difficult to study because it oftentimes becomes tractable after two or three weeks. Angina in these patients continually improves and worsens. I frequently receive calls from physicians — invariably at 5:00 pm on a Friday — regarding patients who are on ten drips and who have a 1.5 mm diagonal hanging off their left main artery. I am obviously the last resort for these patients!

Also, we often see patients who experience severe pain at the beginning of their coronary disease, then undergo multiple surgeries and interventions, and eventually exhaust all treatment options. At our institution, we launched a bone marrow stem cell extraction program in which we inject stem cells into the myocardium. The animal work showed exciting results, but it has proven rather cumbersome in practice. On average, we perform one of these cases per month. Our institution has a Fellow dedicated to this program who works with Marty. With only one case a month, however, we have concluded that this therapy is unlikely to become the solution to the problem. Nicholas Kipshidze has presented some impressive data on epicardial angiogenesis in animal models. Kipshidze and colleagues performed a variation of the Vineburg procedure, then, they injected a variety of angiogenic agents through an arterial conduit sutured to the epicardium without any anastomosis. The images of the new vessel growth through the myocardium are extraordinary. We are a long way from solving this problem, but angiogenesis therapy will likely be the answer to the problem of intractable angina.

Philip Walker: I will be facetious and say that when patients are at this stage, we peripheral vascular surgeons are often called to revascularize their leg or do something with their aorta. The data from the transmyocardial laser revascularization trial underscores the importance of conducting prospective randomized trials to establish efficacy of therapeutic interventions. There are parallels in the peripheral vascular disease patient group, where we know that some patients with minor degrees of superficial tissue loss or ulceration, or rest pain and limiting claudication, will improve over time without revascularization, sometimes healing their ulcers, even though their peripheral perfusion pressures remain very low. We have a very limited understanding of what is going on with these patients. The peripheral vascular group at our institution is exploring what is happening at the microcirculatory level in peripheral arterial disease patients. We are studying what is happening at the mitochondrial level when there is a change to a more anaerobic metabolism which occurs when the oxygen supply is reduced. It may be that these local adaptations allow clinical improvement despite any measurable change in the perfusion pressure. There may be some pharmacologic methods of manipulating these local changes. I suspect that similar parallels exist in the heart as well.

Gary Roubin: Two angiogenesis trials currently under way in the periphery show that there may also be some options for the myocardium. It is so much easier to identify the location of occlusions in the periphery and to inject various angiogenic agents to try to create better bridging collaterals. Nicholas Kipshidze and colleagues have thus far recruited four patients with non-healing ulcers and intractable claudication for a single-blind, randomized trial. These patients have been injected with a simple fibrin compound obtained from Baxter. The sham injection is saline alone; the active injection is a thick fibrin compound. The healing of the ulcers and the improvement in the claudication in those patients who received the active fibrin has been remarkable, albeit anecdotal, given the small number of patients. Interest in this therapy has grown within our group over the last six months. We began slowly and are now increasing patient recruitment. Obviously, we are motivated to continue the study since the initial clinical perception shows patients are benefiting. If this therapy is effective in the periphery, we will then have to determine how to get the material into the myocardium. I am confident that some clever method will be found to do this intravascularly and perhaps extravascularly as well. There are indeed some interesting therapies coming down the pike.

Howard Cohen: Injecting the collateral vessels with these growth factors may be sufficient to heal ulcers, but will it be effective in eliminating ischemia in patients with angina? To heal an ulcer at rest where there is enough blood flow is one thing, but it is another thing to achieve a more marked blood flow so that angina and ischemia are eliminated. Of course, there is vast microcirculation in the heart, but if there is not enough of a conduit or epicardial flow, these growth factors may not be helpful.

Raoul Bonan: Perhaps a new imaging technology is needed that will enable us to promote angiogenesis in the myocardium. The quality of the magnetic resonance images we are beginning to see, for example, allows us to determine the patient’s perfusion, anatomy, and blood flow dynamics. Magnetic resonance imaging may also guide the intracardiac delivery of such a growth factor substance which could even be observed passing through the wall. An excellent imaging technology would reduce the need for so many double-blind studies.

Howard Cohen: Kirk, would you tell us about the imaging technology you are utilizing at the Mayo Clinic?

Kirk Garratt: Magnetic resonance imaging is the primary new imaging technology utilized at the Mayo Clinic laboratory. We are currently in the process of acquiring and installing an MRI unit (probably a 1.5) as well as a Magnet open-architecture device that will allow vascular procedures to be performed alongside the patient. These new systems, equipped with intrarterial antennae, offer phenomenal imaging quality. I agree with Raoul that MRI technology probably offers the greatest hope for patients with intractable angina, but I’m not yet certain how it will best be applied.
I would like to comment on EECP which Howard mentioned. In my experience, EECP is one of the easiest, most reliable, safe, effective, and inexpensive tools available today. In fact, it can actually generate profits. Frankly, I don’t understand why EECP isn’t more widely used. We have a fairly robust EECP program at Mayo Clinic and have been very fortunate to steal some phenomenally talented people from Jim Zidar’s institution and my alma mater, Duke University. This talented group includes Arnie Weisler, Steve Hamill, and Doug Packer. Our most recent “acquisition” was Greg Barsman, who has been running our EECP laboratory for the last three years. The results Mayo Clinic has seen in approximately 150 patients who have undergone EECP over the last two years closely resemble those from the international EECP registry. Overall, approximately 75% of the patients showed improvement. Roughly 1% of these patients experienced a deterioration in their function, and these were almost exclusively those who started out with Class I angina. The patients who experienced the greatest improvement were all Class III and IV patients. The anginal status was reliably improved by at least one grade in 80–90% of patients. I have no idea how EECP works exactly. There are some data suggesting that collateral flow is improved. Tim Henry and others have been interested in measuring VGEF levels which seem to rise in these patients. Perhaps it is a stimulus for neovascularization.

Fayaz Shawl: A blinded trial for EECP is probably necessary as well.

Kirk Garratt: Yes, probably so. The EECP trials that have been performed used two means of blinding. One method was to use sham pressures that were too low to really effect any change in peripheral or central perfusion. It is possible that the patients were savvy enough to know when they were being squeezed firmly as opposed to softly. One particular trial suggested an improvement with effective therapy that was not observed in the placebo control group. Gregg showed me some data from Germany on perfusion imaging with stress testing in which improvements were observed in the effective therapy group and none in the sham group. Of course, there are some data showing very rich collateral development in animals who underwent EECP.

Fayaz Shawl: I want to return to what Raoul said about magnetic resonance imaging. A study by Donald Bain’s group published in last month’s Circulation involved approximately 20 patients with refractory symptoms who were not candidates for surgery or angioplasty. The patients received a baseline MRI followed by Biosense-guided laser revascularization. The investigators found improvement in the patients’ perfusion and function. I believe a randomized trial is planned on that basis. The MRI findings in this study were very impressive.

Jeff Werner: Though I have always avoided asking this question, I will do so anyway. Gary mentioned receiving calls when patients present with a single diagonal or a hanging single obtuse marginal, and is about the only vessel that has a lesion. We currently have a patient who has undergone multiple surgeries and has a non-grafted, nontreated distal calcified obtuse marginal that has been imaged several times. This patient clearly has reversible ischemia. Several operators (though not myself) have attempted to cross this lesion with only partial success. What about so-called controlled infarction angioplasty? Is there a role for this technique in patients with intractable angina and a way to determine which patients could tolerate this procedure?

Fayaz Shawl: I have not performed any controlled infarction angioplasty procedures, but let’s ask the panel members.

Gary Roubin: Increasingly aggressive methods tend to be employed in these cases. It is feasible to run a Rotablator wire down the vessel and ablate these lesions. The artery can be opened or perforated and then coil embolized. That, in fact, is what results in one or two of these cases each year: the vessel is destroyed when the operator tries to cross it aggressively; it occludes or perforates, and is then embolized with a coil. We haven’t really addressed the unpleasant issue of perforations in this discussion. With Jiri Vitek’s guidance at our lab, we have become fairly adept at using coils. The magnetic resonance imaging issue is extremely important and merits in-depth discussion. Our institution plans to install an MRI unit adjacent to the cath lab so that peripheral procedures can be performed. It is difficult to imagine that online MRI reconstruction of the myocardium will be feasible, even with the best software. It would require the one-to-one feedback now available in the periphery. The algorithms required to take into account the cardiac wall movement present overwhelming software challenges. I do think that MRI will be utilized in the future to access parts of the myocardium for the injection of angiogenic agents.

Raoul Bonan: A program is currently in place at the National Institutes of Health where hypertrophic cardiomyopathy is targeted with a needle with the guidance of an antenna. Animal experiments on this technique are already under way.

Gary Roubin: The most experienced operators have been able to bring the online reconstruction time down to about three to five minutes.

Fayaz Shawl: Does anyone have any comments or suggestions? Thank you all for your participation.