

Refractory Angina: Current Options

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The term refractory angina needs to be defined precisely if one is to learn anything from different management strategies. The dictionary definition of refractory is 1) hard to manage; 2) stubborn; 3) obstinate; 4) not yielding readily to treatment.

Refractory angina patients can be of two kinds: acute and chronic.

Acute Refractory Angina

In my opinion, in the acutely symptomatic patient, refractory angina should be considered only when there is ongoing chest discomfort or angina-equivalent symptoms associated with ongoing changes on the electrocardiogram, such as transient ST-segment depression occurring while the patient is receiving maximum aggressive anti-ischemic, antithrombotic and general medical therapy. This includes hypertension control and heart rate control, whether it be fast or slow. Maximum anti-ischemic and anticoagulation therapy also need to be defined. Maximum therapy generally consists of:

1. Oral beta-blockers up to a maximum tolerated dose resulting in a decrease in heart rate to around 60 bpm and a slight lowering of blood pressure. Beta-blockers, oral or intravenous, still remain the mainstay of therapy for recurrent myocardial ischemia.
2. Oral calcium channel blockers if chest discomfort persists despite beta blockade to a maximum tolerated or prescribable dose. It has been my practice not to use calcium antagonists as first-line therapy in these patients, although I admit that they are effective. My own practice is to use them in a situation in which the patient has received nitrates and beta-blockers prior to presentation and continues to have ischemic chest pain. All types of calcium antagonists can be used as long as they do not increase heart rate. Thus, the dihydropyridines are acceptable in the patient who is already receiving a beta-blocker. Verapamil and diltiazem on the other hand might not be appropriate in a patient whose heart rate is in the 50s and blood pressure in the low 100s.
3. Nitrates to maximum tolerable dose, i.e., a dose that does not decrease blood pressure excessively. In the acute situation in which the patient is having recurrent refractory angina, my own preference is to use an

- intravenous nitrate since the intravenous preparation is easy to adjust if hypotension or bradycardia occurs.
4. Anti-platelet therapy with aspirin.
5. In the acutely symptomatic patient, anticoagulant therapy with intravenous unfractionated heparin to raise the APTT 1.5 to 2 times normal or subcutaneous low molecular weight heparin given in the appropriate dose depending on the product used.
6. One of the statins should also be used in these patients since there is accumulating evidence that these agents work rapidly to diminish the inflammatory response in the unstable plaque and improve endothelial function generally.

In clinical practice, these listed strategies generally stabilize the acute clinical situation, i.e., decrease the episodes of chest discomfort to zero, and theoretically stabilize the underlying pathology, i.e., plaque disruption.

In more recent times, patients with recurrent symptoms due to myocardial ischemia despite aggressive medical therapy have been treated with glycoprotein 2B3A receptor blockers. Often, these are patients who undergo percutaneous revascularization procedures.

The Clopidigrel in Unstable Angina to Prevent Recurrent Events (CURE) trial suggests that clopidigrel should be considered in these patients, but the hazards of excess bleeding make me cautious at this point in time. Moreover, neither drug has been tested in patients with refractory angina.

Characteristics of the Acute Refractory Angina Patient

There is no generic refractory angina patient. Patients may have different electrocardiographic changes during angina involving multiple leads or a few leads, CKMb may be positive or negative, troponin I may be positive or negative, CRP may be positive or negative, left ventricular function may be normal or abnormal and coronary pathology varies tremendously in the extent, location, severity, morphology, etc. Patients who are refractory more than likely have multivessel coronary artery disease and possibly some LV dysfunction. I am always suspicious of left main coronary artery stenosis in these patients, and certainly patients with a previous angioplasty who might now have restenosis or a coronary bypass graft surgery patient who might have graft failure are high on my list in patients who have refractory symptoms.

One can be suspicious that a patient may be potentially refractory and have a poor prognosis if biochemical markers such as troponin T or I are elevated and also if C-reactive protein levels are elevated.

Risk Assessment

Antman and colleagues published a TIMI risk score that I find quite useful in patients admitted to hospital with acute recurrent angina. They used data from TIMI IIB and the Essence trials and found that seven variables were predictive of the combined end point of death, MI or recurrent

Table 1. Acute Refractory Angina

- Maximum medical therapy*
 - Beta-blockers
 - Nitrates
 - Antiplatelet therapy (aspirin)
 - Anticoagulant therapy
 - Statin therapy
 - Calcium antagonist if ischemia persists
 - Glycoprotein 2b3a receptor blocker if ischemia persists
 - Clopidigrel can be considered if ischemia persists

* See text for details.

ischemia at 14 days. These included age 65 or greater, three risk factors for coronary artery disease, prior 50% coronary stenosis, ST-segment change on admission, angina occurring twice in 24 hours, aspirin use within 7 days and increased serum cardiac markers. There was a striking difference in cardiac events in those who had zero or one risk factor (4.7%) compared to those who had six or seven risk factors (40.9%). There was a clear-cut graded increase in end points as the number of risk factors increased. Thus, one can add the high TIMI risk score to the other factors that might alert the physician to a potentially refractory state and poor prognosis.

Pathogenesis

The pathogenesis of acute refractory angina may in many instances be related to non-occlusive thrombus at the site of a disrupted plaque. Thus it makes good sense to anticoagulate the patient. How long a patient should be anticoagulated is not clear, but most recommend anticoagulation in

refractory patients until a revascularization procedure is accomplished. It has not been my practice to use low molecular weight heparin routinely in the usual patient with recurrent angina, but I certainly accept the fact that current clinical trials suggest that the use of low molecular weight heparins may be better in refractory patients, particularly those who have biochemical markers such as troponin I or troponin T. In addition, patients whose C-reactive protein is elevated might also benefit most from long-term therapy with low molecular weight heparin. However, one must not forget that refractoriness may be related to extra-cardiac factors such as hypertension, tachycardia, anemia, hypoxia due to chronic lung disease, hyperthyroidism, infection with resultant fever and other systemic illnesses that may contribute to increasing myocardial oxygen demands in the setting of coronary artery disease. These causes of refractory angina can be corrected relatively simply and oftentimes will stabilize the patient who has been refractory.

Use of Statins and ACE Inhibitors

Use of lipid lowering agents (i.e., the statins) in the acute phase of any patient's illness needs to be considered since there is evidence that statins alter vascular reactivity quite early. Their use in patients is justified as an attempt to stabilize the disruptive plaque if that is the etiology of the patient's condition. Although the HOPE trial was not performed in patients specifically with refractory symptoms of angina, the data are so persuasive that unless there is a contraindication to their use, Ramapril should be used in

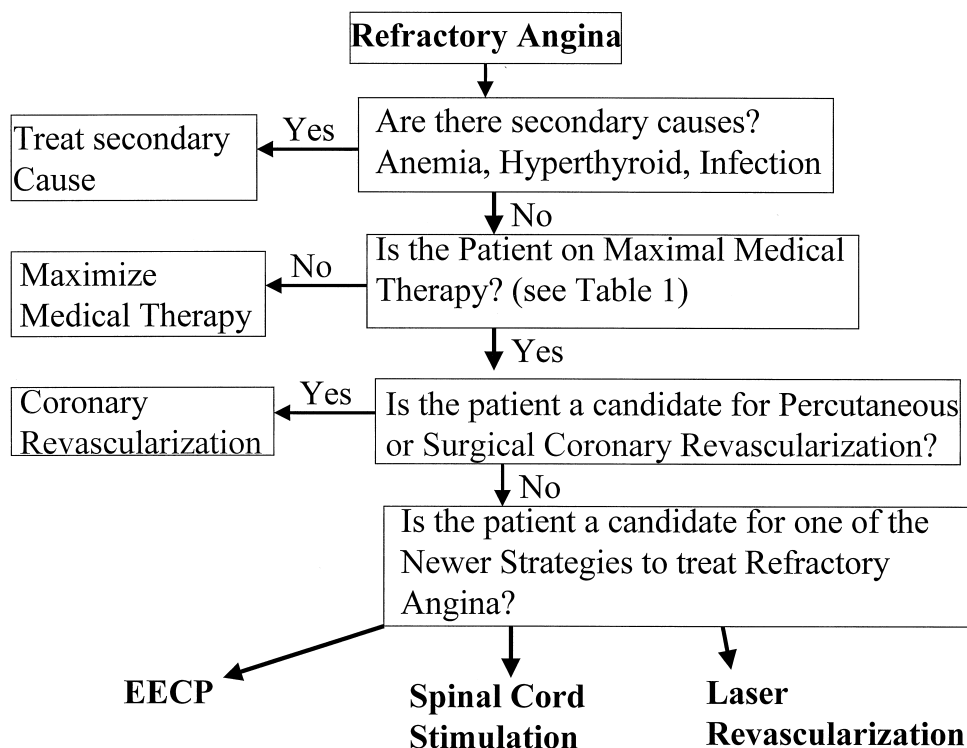


Figure 1. Algorithm to assess and treat refractory angina.

the management strategy of these patients with refractory symptoms.

Clinical Trials and Refractory Angina

Clinical trials such as the unstable angina study performed by the National Cooperative Study Group, TIMI 3B, VAN-QWISH, FRISC II, AVERT, MIRACL, TACTICS and CURE are important clinical trials in the area of unstable coronary artery disease, but they do not specifically address the question of what to do with patients who have refractory symptoms related to myocardial ischemia.

Obviously, if patients continue to be symptomatic despite aggressive medical therapy, then revascularization must be considered. These are the patients who for the most part undergo coronary angiography, and once coronary angiography is performed, decision-making will be related to angiographic findings (e.g., percent stenosis, presence or absence of serial stenoses in the same vessel, proximal vs. mid vs. distal stenoses, chronic vs. acute stenoses [plaque morphology may define this situation], long stenoses vs. short stenoses, TIMI grade coronary blood flow and the presence or absence of collaterals).

It has been said that patients with single-vessel disease do quite well with aggressive medical therapy, but all single-vessel disease is not the same. It is highly unlikely that a patient with a high-grade proximal LAD stenosis was randomized in any clinical trial. Most cardiologists assume that this is a potentially lethal lesion and move quickly to angioplasty or in some instances beating heart single blood vessel bypass. Several other points need to be made about past clinical trials. The first point is that medical therapy was not protocol driven in past trials, thus "optimum medical therapy" may not have always been optimum by 2001 standards. In addition, in angioplasty trials of the past, stents were not a part of therapy comparing medical to angioplasty therapy. Thus, the current practice of aggressive protocol-driven medical therapy plus aggressive modern-day angioplasty/stents needs testing. The ongoing Clinical Outcome Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial may provide us information in this regard.

Summary (Acute Refractory Angina)

As always is the case in clinical cardiology, judgment must be used to make clinical decisions about management strategies. Not every patient needs emergent coronary angiography. Conservative and invasive management should not be considered as competing strategies but rather as complementary approaches to management. Treatment strategy should be based on:

1. Severity of symptoms
2. Extent of provoked myocardial ischemia
3. Extent of coronary artery pathology
4. Status of LV function
5. Presence or absence of comorbid disease
6. Pathogenesis

Chronic Refractory Angina

One can arbitrarily define the patients with chronic refractory angina as those in whom medical therapy has failed to completely eradicate the angina, but the symptoms are relatively stable and the patients have some limitation of daily living activities. If revascularization is possible, then it should be done. However, there are many patients in whom the coronary pathology is not suitable for revascularization. In these patients, three therapies are currently being used to manage patients with persistent chronic stable angina.

Transmyocardial Laser Revascularization

The first and most highly visible is transmyocardial laser revascularization (TMR). Data were recently discussed on Accel. Dr. Larry Bonchek interviewed Dr. Keith Horvath of Northwestern University. They discussed the topic of sustained angina relief 5 years after TMR with a CO₂ laser. Results in 80 patients indicate that 90% have at least one class sustained improvement in Canadian Cardiovascular Society Angina class at 5 years, and 20% of the 80 patients were angina free. Dr. Horvath believes that the laser technique will be used in combination with traditional coronary artery revascularization to provide a more complete revascularization and perhaps eliminate angina in the majority of patients.

Recently, percutaneous catheter-based laser revascularization (PMR) using a Holmium-Yag laser in the placebo-controlled trial Direct Myocardial Revascularization in Regeneration of Endomyocardial Channels (DIRECT) failed to show benefit in 300 randomized patients. Most experts have given up on PMR, but some believe that more work needs to be done in order to better understand the fundamental processes occurring in the myocardium.

Enhanced External Counterpulsation

The second approach is enhanced external counterpulsation (EECP). In a randomized trial, it was found that EECP reduced angina and extended time to exercise-induced ischemia in patients with symptomatic coronary artery disease who were receiving aggressive medical therapy and were not candidates for revascularization. The basic principle is one of diastolic augmentation. It is a non-invasive procedure involving inflation and deflation of compressive cuffs wrapped around the patients calves, lower thighs and upper thighs timed to the cardiac cycle. Thirty-five 1-hour treatments are currently recommended. Theoretically, this should result in a decreased myocardial oxygen demand and an increase in coronary blood flow. Long-term benefit may be the result of opening dormant coronary collateral circulation, but this is theory and not proven. This therapy is contraindicated in patients with deep vein thrombosis, phlebitis and patients with fast irregular heart rhythms. In patients with severe peripheral vascular disease, it may be difficult to augment diastolic pressure, and these patients may not be suitable candidates for this procedure.

Spinal Cord Stimulation

The third approach is spinal cord stimulation. Like EECF, this procedure should be reserved for patients who have persistent symptoms despite aggressive medical therapy and who are not candidates for a revascularization procedure. A patient with severe peripheral vascular disease is a poor candidate for EECF but might be an excellent candidate for spinal cord stimulation. Many are skeptical of this procedure and are concerned that it masks myocardial ischemia while relieving pain. However, several investigators have reported that after spinal cord stimulation, there is a reduction of angina, increased exercise capacity and a reduced degree of ST-segment depression during a comparable workload when the patient is not receiving spinal cord stimulation. At maximum workload, ST-segment depression and angina were noted in patients with spinal cord stimulation similar to that in a control situation. This argues that myocardial ischemia was not masked during spinal cord stimulation. Contraindications to this therapy include, unstable angina, unfavorable physical condition, cardiac pacemaker or ICD, lack of patient compliance, obvious infection, allergic or immune response to implanted materials and anticoagulation that might increase bleeding at the implantation site.

Summary

There are two types of refractory angina, acute and chronic. In both groups of patients, one must be aware that extracardiac factors such as hypertension, tachycardia, hypoxia, systemic illness, infection, etc. can be the cause of angina despite aggressive medical therapy. These issues must be attended to in every patient.

In the acute refractory angina patient, risk assessment is mandatory, since these patients are at increased risk for myocardial infarctions and sudden cardiac death. Risk assessment should be accomplished as quickly as possible, and aggressive anti-ischemic therapy should be instituted along with antithrombotic and antiplatelet therapy. In the majority of these cases, symptoms will markedly diminish or abate. If they don't, revascularization must be considered on an urgent basis.

In the chronic refractory angina patients, traditional coronary revascularization still needs to be considered. Although there is a risk of myocardial infarction and sudden cardiac death, it is far less than those who present acutely. For the most part, these are the patients whose activities of daily living are limited, and patients are generally not satisfied with their overall quality of life. At the present time, three options are available that have been studied. These include transmyocardial laser revascularization, spinal cord stimulation and enhanced external counterpulsation. With these three procedures, clearly there may be a placebo effect, but all three therapies warrant consideration in patients who are unhappy with their functional status and are

continuing to have symptoms that limit activities of daily living.

Questions for ACC Current Journal Review

1. What should a physician look for in patients whose angina is refractory to standard medical therapy?

Answer: Secondary causes of angina including anemia, hypertension, tachycardia, hyperthyroidism, hypoxia of any cause and infection should be checked for. Obviously, progression of disease, restenosis of a graft or coronary artery after angioplasty, bypass graft failure, etc. can account for refractoriness of angina, but they require noninvasive and sometimes invasive testing to determine what is going on.

2. In patients with chronic refractory angina, despite previous revascularization and aggressive medical therapy, enhanced external counterpulsation provides an alternative to standard therapy. How many treatments are required to show benefit?

Answer: In the experience of many who have used this procedure, patients begin to notice a difference in their ability to exercise more and have fewer episodes of angina at about 15 treatments. The current recommendation is that these patients receive 35 1-hour treatments.

3. In patients with chronic stable angina, does transmyocardial revascularization provide sustained angina relief?

Answer: Some recent data discussed on ACCEL have indicated that 90% of patients sustained improvement of at least one Canadian Cardiovascular Society Class at 5 years, and 20% of the 80 patients were angina free.

4. Percutaneous catheter-based laser revascularization (PMR) has been used to treat people with stable angina. What is the evidence that it is effective therapy?


Answer: In a recent placebo-controlled trial called DIRECT, PMR failed to show benefit in the 300 patients that were randomized. Most feel that PMR is not worth trying routinely in patients with the current methodology, but further investigation is warranted.

5. Spinal Cord Stimulation does relieve angina pectoris, but does it relieve or does it mask myocardial ischemia?

Answer: Several investigators have shown that in addition to the reduction of the angina, there is increased exercise capacity and reduced ST-segment depression during a comparable workload when the patient is not receiving spinal cord stimulation.

Suggested Reading

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