

Treatment Options for Angina Pectoris and the Future Role of Enhanced External Counterpulsation

DAVID R. HOLMES, JR., M.D., FACC

Division of Cardiovascular Disease, Mayo Clinic Foundation, St. Mary's Hospital, Rochester, Minnesota, USA

Summary: Patients with coronary artery disease have a variety of treatment options available to them. These include medications to control anginal episodes and, when appropriate, revascularization interventions in the form of coronary artery bypass graft and angioplasty. Despite advances in the treatment of angina, a substantial number of patients continue to have symptoms that can significantly impair their quality of life. These patients may benefit from enhanced external counterpulsation (EECP). With recent results of the latest clinical trial of EECP just published, the role of EECP, including its position in the hierarchy of treatment options, needs to be seriously considered.

Key words: angina pectoris, angioplasty, coronary artery bypass graft, coronary artery disease, enhanced external counterpulsation

Introduction

Patients referred to enhanced external counterpulsation (EECP) often have a typical presentation and prior history before undergoing treatment. One typical case would be a 70-year-old man with hypertension, hyperlipidemia, diabetes, and a prior history of smoking. The patient has experienced typical angina since the 1970s, undergoing coronary artery bypass grafting in 1979. Despite medical treatment, his angina

accelerated throughout the years, requiring angiography in 1997. At the time of this procedure, he had left main and triple-vessel disease, but his vein grafts were occluded and his distal vessels were small and diffusely diseased. His left internal mammary artery (LIMA) implant to the left anterior descending artery (LAD) was patent. Angiography was complicated by an embolic right posterior cerebral stroke.

Two months after his angiography, the patient underwent an adenosine sestamibi stress test. This disclosed a medium-sized region of septal and inferolateral ischemia, a small inferior infarct, and moderate cardiac enlargement. Medical treatment was continued. He was seen again in 1999, complaining of more angina. An echocardiogram documented decreased left ventricular function with an ejection fraction of 30 to 35%.

At this point in his life, the patient had progressive daily and nocturnal angina despite maximized medications. It was relieved with rest or with one to two doses of sublingual nitroglycerin. He had experienced weight gain because of inactivity. The patient was very hesitant to undergo repeat angiography, given the embolic stroke he had experienced in the past. He was then referred for evaluation of EECP.

It is important for cardiologists to realize that patient goals can be very different from those of their physicians. Patients would like to live forever and prevent infarction and stroke, while at the same time avoid making any changes in lifestyle. They also want to avoid taking medications and surgery. Therefore, the cardiologist needs to see how EECP can help the patient achieve these goals.

The Revascularization Option

Cardiologists have found that revascularization is often the best option for suitable patients. When considering coronary artery bypass graft or percutaneous catheter intervention (PCI), some definite benefits can be summarized, among them improved quality of life and decreased angina in most patients (Table I).

As different revascularization options are considered, several algorithms are used. In addition to the patient's symptoms, the physician also looks at any comorbid conditions, such as diabetes mellitus and chronic renal insufficiency. Left

Address for reprints:

David R. Holmes, Jr., M.D., FACC
Professor of Medicine
Cardiovascular Disease Division
Mayo Clinic and Foundation
St. Mary's Hospital
200 First Street, S.W.
Rochester, MN 55905, USA
e-mail: dholmes@mayo.edu

TABLE I Benefits of revascularization

- Improved functional class, exercise capacity — most patients
- Improved survival — some subsets
- Improved quality of life — most patients
- Decreases angina — most patients
- Decreases need for some medications — most patients
- No change in subsequent MI — most patients

Abbreviation: MI = myocardial infarction.

ventricular function is also analyzed. Coronary artery status is very important in terms of the ability to revascularize as well as the extent, severity, and location of disease. Prior interventions are also taken into consideration, as many patients already have a history of an earlier intervention. Finally, the physician must evaluate and put into perspective the patient's and family's expectations.

Today, there are a host of other options that are currently accepted (Table II). Medical therapy and risk factor modification form the backbone irrespective of what other therapy is selected. In addition, there are some exciting evolving treatment options, including gene therapy, spinal cord stimulation, and EECP.

For each of these evolving strategies, there are advantages and disadvantages. Enhanced external counterpulsation has some specific advantages, particularly in patients who are not candidates for additional revascularization procedure.

In the U.S. alone, there are 2.4 million patients with coronary artery disease not amenable to bypass or angioplasty. These numbers are expected to increase with failures of previously placed vein grafts. In patients who have already undergone revascularization, there are a number of reasons why they may not be able to undergo the procedure again. One reason may be the extent and severity of their disease. Another may be left ventricular dysfunction. Some patients may not have limited ischemia but significant symptoms. In these cases, the patients may not be able to exercise long enough to measure ischemia or there may be a gradient in ischemia between the different vascular territories. Other reasons may be comorbid conditions as well as prior interventions. The risk/benefit ratio may also not be favorable for some patients to undergo a repeat revascularization procedure.

TABLE II Current and evolving treatment options for symptomatic coronary artery disease

Currently Accepted	Evolving
• Calcium-channel blockers	• Transmyocardial revascularization
• Beta blockers	• Spinal cord stimulation
• Nitrates	• Enhanced external counterpulsation
• Percutaneous interventions	
• Coronary artery bypass graft	

Managing the Unrevascularizable Patient

Such difficult cases require entertaining other options. These patients may require a second opinion to see what can be done. For example, have they been on optimal doses of medications? Is standard revascularization possible at all? Other options include EECP, transmyocardial revascularization (TMR), percutaneous myocardial revascularization (PMR), and growth factors.

As options are considered for these patients, the physician needs to keep in mind the science behind the disease and identify trial endpoints to be used in the decision-making process. A good case in point is exercise tolerance testing. There is high variability from day to day. Survival is another difficult endpoint. Patients with severe left ventricular function who are truly unable to undergo revascularization will have relatively limited survival. Another endpoint to consider is health-related quality of life. Although it is very important, quality of life is relatively a soft endpoint because of the placebo effect.

The Future of Enhanced External Counterpulsation

Enhanced external counterpulsation continues to be the focus of multiple investigations. Most recently, results of a multicenter international trial of 175 patients have been published.¹ Participants had chronic stable angina and a positive radionuclide perfusion test at baseline. This was repeated within 6 months after EECP. The majority of subjects had undergone prior revascularization by PCI (75%) and/or bypass graft (41%). More than half (51%) had a history of myocardial infarction; less than a quarter (21%) had a history of diabetes mellitus.

The frequency of severe angina was substantially less after treatment with EECP (Fig. 1). Improvement in angina, defined by one or more changes in angina class, occurred in 85% of patients. Exercise tolerance and time to angina was analyzed at 12 weeks and then again after 12 months. Patients were significantly better in terms of how long they were able

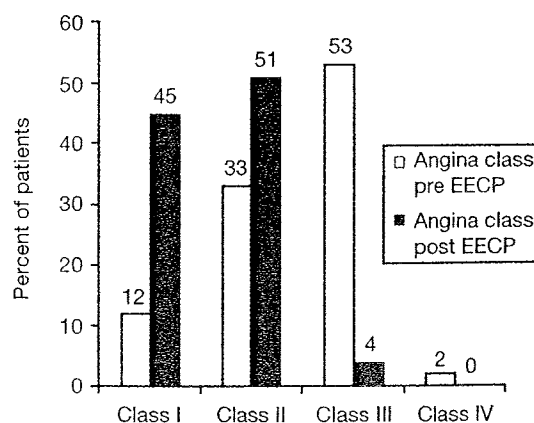


FIG. 1 Improvement in angina class after enhanced external counterpulsation (EECP). Adapted from Ref. No. 1 with permission.

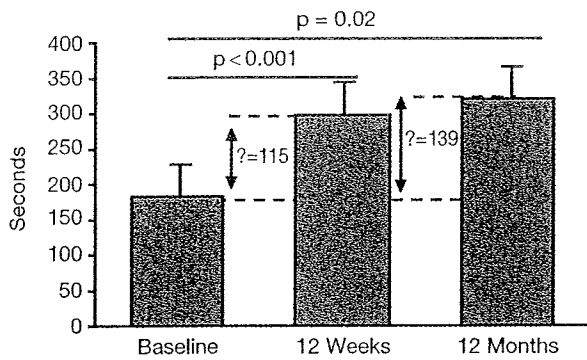


FIG. 2 Improvement in exercise tolerance time to angina before and after EECP. Adapted from Ref. No. 1 with permission.

to last on the treadmill before experiencing angina (Fig. 2). In the group with the same level of exercise pre and post EECP, 83% had significant improvement during radionuclide perfusion treadmill stress tests. While 17% experienced no change, none of the patients got worse. In those patients who underwent maximal exercise testing, 54% improved during the test, 42% had no change, and 8% got worse. There was no change in double product.

Conclusion

The patient cited at the beginning of this paper began his first EECP treatment in March 1999. At the time, his angina required oxygen and door-to-door wheelchair transport. Anginal episodes began to decline after several weeks of treatment, from five recorded during Week 1 to one episode by Week 5. At this time, the patient was able to resume bowling three games without angina; previously, one game required the patient to use up to six nitroglycerins. By Week 7, the patient

was walking his dog and back to full activity without any anginal episodes recorded. At the end of 6 months, the patient was back to full activity without major limitation, with stable symptoms, and with no clinical events.

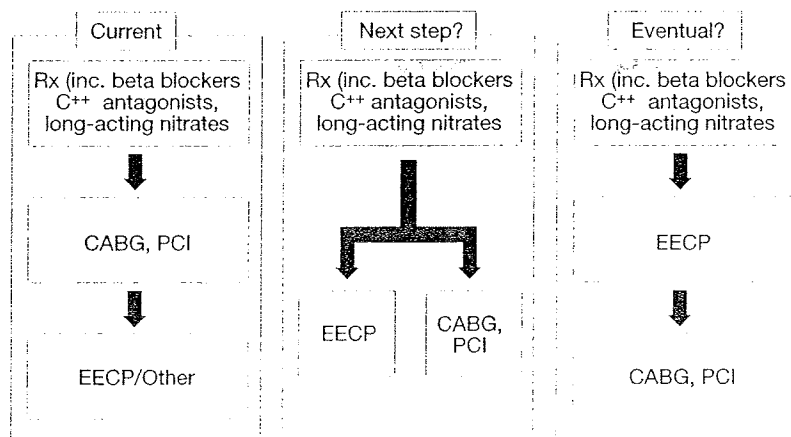
This patient's success illustrates the evolution taking place in the treatment of symptomatic coronary artery disease. Today, perhaps a different approach to this treatment should replace the current, existing algorithm (Table III). After medications have been tried, EECP might be considered as an adjunctive to conventional revascularization instead of being used after these procedures are performed or have failed. Eventually, it is possible that EECP may be an option to be entertained before revascularization. Although the clinical community does not know much about the mechanism behind EECP, patients do not care. What they do care about is the fact that they are much better, doing the things that they want to do.

Discussion

Participant: I have treated 30 patients with EECP. One patient, who was operated on the day before yesterday, was previously inoperable, after two bypasses and two angioplasties. We put him on the machine last February. He developed unstable angina 6 months back. I opened up the proximals circumflex and he was symptom free. He again came back with very serious unstable angina, and was admitted to the hospital. This time, an angiogram showed that he has two very well developed diagonal branches and a PVA, which was getting some collaterals through. He then underwent surgery. So, there is something happening here. Some of the vessels, which were considered to be inoperable are now increasing in size.

Conti: Well, let me just comment on that too because we would like to believe that it improves coronary collateral blood flow and there are data with intraaortic balloon counterpulsation that document that collateral blood flow is improved, particularly in the dog which is a different kind of animal and

TABLE III Treatment algorithm evolution for symptomatic coronary artery disease and the role of enhanced external counterpulsation (EECP)



Abbreviations: C = calcium, CABG = coronary artery bypass graft, PCI = percutaneous catheter intervention.

there are robust collaterals all over the place. But it has got to be something like that that is related to either decreased endothelin or increased nitric oxide, something has got to happen to blood flow. And the most logical thing I think is collateral blood flow improving. There are no serial data that I know of people looking at collaterals with angiography unless Bill knows of some. I am not aware of any.

Beller: Is it possible Dr. DeMaria, since you are an expert in this, that by using some of the new quantitative approaches to contrast echocardiography with sort of the arrival time, sort of destroying microbubbles and sort of quantitating the contrast, this could be used as a tool to look at sort of serial perfusion in a more frequent manner, have you looked at that?

DeMaria: We are in the process of doing that very thing right now. You know, they are long studies because patients are out 7 weeks and we have got some data but not enough to make any comment.

Reference

1. Stys TP, Lawson WE, Hui JC, Fleishman B, Manzo K, Strobeck JE, Tartaglia J, Ramasamy S, Suwita R, Zheng ZS, Liang H, Werner D: Effects of enhanced external counterpulsation on stress radionuclide coronary perfusion and exercise capacity in chronic stable angina pectoris. *Am J Cardiol* 2002;89:822-824