Current Nonpharmacologic Management of Coronary Artery Disease: Focus on External Counterpulsation

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Opinion statement

The basic principle of enhanced external counterpulsation (EECP) is diastolic augmentation of arterial pressure, lowering of systolic arterial pressure along with increasing venous return. EECP is a noninvasive procedure involving sequential inflation and rapid deflation of compressive cuffs wrapped around the patient's calves, thighs, and lower abdomen, timed to the cardiac cycle using the electrocardiogram. Theoretically, this should result in decreased myocardial oxygen demand and an increased coronary blood flow. Long-term benefits may be the result of the opening of dormant coronary collateral circulation, but this is theory and not proven. Extracardiac factors, such as peripheral arterial stiffness, endothelial dysfunction, and elevated myocardial oxygen demand, are also the therapeutic targets for EECP. There is some evidence that long-term benefits may be the result of a training effect due to 35 1-hour diastolic inflations at 300 mm Hg and systolic deflations of the compressive cuffs. To date, the extracardiac effects of EECP have received little attention and peripheral vascular adaptations to EECP have not been investigated. EECP, by promoting lower-extremity arterial "run-off" and intermittent reactive hyperemia in the legs with each inflation/deflation cycle of the compressive cuffs, may improve peripheral vascular function, thus inducing changes in peripheral vascular biology that will reduce ventricular work and myocardial oxygen demand in patients with coronary artery disease similar to that of exercise. At the University of Florida, this therapy is used for patients with chronic stable angina who are refractory to medical therapy and are not candidates for a revascularization procedure. The treatment does take time (35 once-a-day 1-hour treatments), and not all patients are candidates for the procedure. For example, patients with severe peripheral vascular disease, severe hypertension, thrombophlebitis, markedly irregular heart rhythm, and severe aorta insufficiency are excluded. Approximately 75% of patients report improvement (*ie*, a decrease in symptoms and an increase in exercise duration). Our results are such that this management strategy does deserve consideration in patients with persistent chronic stable angina on maximum medical therapy who are not candidates for revascularization and are unhappy with their lifestyle.

Introduction

No one knows the precise number, but it has been estimated that in the population over 30 years of age, the number of patients with angina pectoris is approximately 213 per 100,000 persons [1]. An additional 350,000 persons per year (as assessed by the Framingham Heart Study guidelines) develop chronic stable angina [2].

The American Heart Association estimates that there are over 6 million Americans with complaints of chest discomfort [3], and if one extrapolates from the number of myocardial infarctions in the United States, the estimated number of patients with chronic stable angina pectoris totals approximately 16,500,000 [4]. Thus, this is a huge patient population and because of modern aggressive medical and revascularization strategies, many patients are living into older age who are no longer candidates for revascularization strategy. Perhaps it is best to define this group of patients as those having refractory angina that has become difficult to manage and not yielding readily to the treatment plan for the patient. This is the patient population that is currently being treated with enhanced external counterpulsation (EECP).

Treatment

Modern medical therapy of chronic stable angina

- Modern medical management of chronic stable angina can be summarized briefly using the ABCs of management: (A)—aspirin, anti-angina therapy, angiotensin-converting enzyme inhibitors (angiotensin receptor blockers), angioplasty or stent; (B)—β blockers, blood pressure control; (C)—cholesterol lowering, cigarette smoking cessation, clopidogrel (after percutaneous coronary intervention [PCI] or stent), coronary artery bypass graft (CABG) surgery; (D)—diet to maintain weight control, diabetes control; and (E)—education, exercise, EECP.

Managing the patient with 'refractory' angina

- It is useful to think of the following scheme when confronted with a patient whose angina is not under control. Several questions need to be addressed. 1) Are there secondary causes, such as anemia, infection, hyperthyroidism, hypertension, tachycardia, hypoxia, and so forth? If any of these are present, the secondary causes need to be treated. 2) If secondary causes of angina are absent, the next step is to ask "Is the patient on maximized medical therapy as outlined above?" If the answer is no, aggressive medical therapy must be initiated. 3) If the answer is yes and the patient is receiving maximized medical therapy, the next step is to ask "Is the patient a candidate for percutaneous or surgical myocardial revascularization?" If the answer is yes, that should be done. 4) If the patient is not a revascularization candidate, one can offer several strategies. These include partial fatty acid oxidation inhibition [5••], laser revascularization [6], spinal cord stimulation [7], and EECP [8••,9,10•,11]. In this article, the use of EECP is discussed.

What is EECP?

- Enhanced external counterpulsation is nonpharmacologic outpatient therapy involving sequential inflation and deflation of compressive cuffs around patients' calves, thighs, and lower abdomen. The events are timed to the cardiac cycle using the electrocardiogram. Cuffs inflate sequentially during diastole from the calves proximally, and then the cuffs rapidly deflate at the onset of systole.

Contraindications to EECP

- Absolute contraindications to EECP include the following: 1) thrombophlebitis or deep vein thrombosis of calves or thighs (in this situation, high pressure compression of the deep veins will be painful and may result in a pulmonary embolus); 2) grossly irregular rhythm, especially during

tachycardia. The EECP device will have difficulty following the electrocardiogram and inflating and deflating the cuffs at the appropriate time in diastole and systole; 3) severe aortic regurgitation (increasing diastolic aortic pressure will increase the amount of aortic insufficiency); and 4) severe aortic stenosis. Rapidly deflating the compressive cuff prior to systole may markedly decrease aortic systolic pressure because cardiac output may not be increased due to fixed aortic valve obstruction.

- Relative contraindications to EECP include the following: 1) severe peripheral arterial disease (*eg*, ankle-brachial indices of less than 0.3). A trial of EECP may result in diastolic augmentation in this group of patients but it is less likely than in patients whose ankle-brachial indices are normal or near normal; and 2) severe hypertension (*eg*, systolic blood pressure > 180 mm Hg). If aortic diastolic pressure is too high, diastolic augmentation may not be possible.

Case presentation

- One of our typical patients is as follows: A 62-year-old white male had chest discomfort on minimal exertion, such as walking to the mailbox. He is a diabetic requiring insulin, glucophage, and Avandia (GlaxoSmithKline, Research Triangle Park, NC). He takes Lipitor (Pfizer, New York, NY), an angiotensin-converting enzyme inhibitor, a β blocker, aspirin, clopidogrel, isosorbide mononitrate, and sublingual glycerol trinitrate. Physical examination revealed mild hypertension and mild obesity. An adenosine thallium stress test revealed anterior ischemia. The patient was turned down for CABG surgery. The patient did have proximal coronary artery stenoses, but his target vessels were quite poor. Ventricular function at left ventriculography was normal, indicating viable myocardium. The patient underwent 35 1-hour EECP treatments. Following treatment, exercise tolerance increased. He was a Canadian Cardiovascular Society (CCVS) class 3 before EECP, and after 35 treatments he became CCVS class 1, which persisted for 6 months. At 1 year, he reports that his health was "good," his quality of life was "very good," and he is quite satisfied with the results of EECP. This case example is fairly typical of the clinical response to EECP reported by patients with chronic stable angina. Of course, one doesn't get this good a response in every patient. Approximately 75% to 80% of patients report marked improvement manifested as a decrease in angina, decrease in requirements for sublingual nitroglycerin, and increase in exercise capacity. Approximately 20% report no angina.

Mechanical effects of EECP

- During EECP, cuffs inflate sequentially in diastole and aortic diastolic pressure increases.
- Prior to the onset of systole, cuffs rapidly deflate and there is a rapid fall in aortic pressure, which promotes lower-extremity "runoff" and leads to a decrease in systolic pressure, which unloads the left ventricle and decreases the work of the ventricle, thus decreasing myocardial oxygen demand.
- The combined desired physiologic effects of EECP are increased coronary blood flow and decreased myocardial oxygen demand. No single drug has this effect on cardiac hemodynamics.

- Unlike intra-aortic balloon counterpulsation, EECP also enhances venous return, possibly promoting a further increase in cardiac output by the Starling mechanism.

Physiologic studies in the cardiac catheterization laboratory

- Studies in the catheterization laboratory using EECP to assess hemodynamic responses have revealed the following [12]: 1) A gradual increase in aortic diastolic pressure as compression pressures increase: this is as one would expect. It is also possible to show a dose response of EECP as measured by intracoronary pressure. Prior to EECP, at baseline, the usual systolic pressure contour and dicrotic notch is seen. As external compression during diastole is increased gradually from 100 to 300 mm Hg, a gradual increase in the aortic diastolic pressure to maximum occurs. 2) A gradual fall in systolic pressure during EECP as compression pressures increase: this is also an expected result similar to what happens with intra-aortic balloon counterpulsation. 3) In patients undergoing EECP in the cardiac catheterization laboratory, intracoronary diastolic pressure rises and intracoronary peak diastolic flow velocity also increases secondary to diastolic compression of the calves, thighs, and lower abdomen.
- Theoretically, these hemodynamic changes increase coronary blood flow by increasing coronary artery diastolic perfusion pressure and decrease myocardial oxygen demand by decreasing aortic systolic pressure.

Clinical studies

Registry data

- There are registry data in over 5000 patients in whom at baseline prior to EECP therapy 4% were class 1, 15% class 2, 58% class 3, and 23% class 4. Thus, the majority of patients were in the 3 and 4 CCVS class for angina pectoris. Following 35 treatments with EECP, these classes shifted as follows: 21% no angina, 26% class 1, 36% class 2, 14% class 3, and 3% class 4.
- Follow-up data in patients at 6, 12, 24, and 36 months reveal essentially the same angina class over that period of time. Of course, these data are not clinical trial data, they are reports by the patient of their clinical status to the physician.

Long-term observational study

- Lawson *et al.* [8••] performed a long-term follow-up study of patients with chronic stable angina undergoing EECP. Thirty-five patients were followed for 5 years. Seventy-three percent had multivessel disease, 45% prior myocardial infarction, and 61% prior revascularization. After 5 years of follow-up, 21 of 33, or 64%, were alive without any major adverse cardiac event.

Randomized clinical trial

- The only randomized trial of EECP was performed by Arora *et al.* [9]. This was a multicenter trial of EECP. The purpose of the study was to assess the safety and efficacy of EECP in 139 patients with angina, documented coronary artery disease, and a positive exercise treadmill test. These patients were treated with 35 hours of active counterpulsation (300 mm Hg external compression) or inactive (sham) counterpulsation (70 mm Hg external

compression) over a 4- to 7-week period. Results indicate that active EECP reduced angina and extended time to exercise-induced ischemia in patients with symptomatic coronary artery disease more than sham EECP.

EECP as primary revascularization therapy

- More recently, Fitzgerald *et al.* [10•] reported the effectiveness of EECP in a cohort of patients from the international EECP patient registry. They compared patients with prior PCI or CABG surgery (454) to a group of patients who were candidates for PCI or CABG but chose EECP as their initial revascularization treatment. This latter group of patients responded to treatment with EECP with decreased anginal episodes and nitroglycerin requirements and with improvement in their CCVS functional class similarly to previously revascularized patients. This treatment resulted in sustained and often progressive reduction in angina over the succeeding 6 months. These investigators hypothesized that using EECP as the primary revascularization intervention *(ie,* before angioplasty or CABG) after medical therapy proves unsatisfactory should at least be considered in patients who did not want to be revascularized.

EECP potential mechanism of sustained benefit

- Enhanced external counterpulsation may facilitate the development of coronary collaterals, as has been reported with intra-aortic balloon counterpulsation. Unfortunately, there are no data to prove this point because no one has performed sequential systematic coronary angiography in these patients over a long period of time (*eg,* 6 months). Some have shown that EECP stimulates endothelial cell production of nitric oxide and also decreases production of the vasoconstrictor endothelin [13•,14].

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Elveback LR, Connolly DC, Melton LJ 3rd: **Coronary heart disease in residents of Rochester, Minnesota. VII. Incidence, 1950 through 1982.** *Mayo Clin Proc* 1986, **61:**896–900.
2. Kannel W, Feinleib M: **Natural history of angina pectoris in the Framingham study. Prognosis and survival.** *Am J Cardiol* 1972, **29:**154–163.
3. American Heart Association: *2002 Heart and Stroke Statistical Update.* Dallas, TX: American Heart Association; 2001.
4. Rouleau JL, Talajic M, Sussex B, *et al.*: **Myocardial infarction patients in the 1990s—their risk factors, stratification and survival in Canada: the Canadian Assessment of Myocardial Infarction (CAMI) Study.** *J Am Coll Cardiol* 1996, **27:**1119–1127.
5. •• Chaitman BR, Pepine CJ, Parker JO, *et al.*: **Effects of ranolazine with atenolol, amlodipine, or diltiazem on exercise tolerance and angina frequency in patients with severe chronic angina: a randomized controlled trial.** *JAMA* 2004, **291:**365–367.

Ranolazine is not yet available clinically but should prove to be an additional anti-angina agent whose mechanism of action is different from any of the currently used drugs.

6. Allen KB, Dowling RD, Fudge TL, *et al.*: **Comparison of transmyocardial revascularization with medical therapy in patients with refractory angina.** *N Engl J Med* 1999, **341:**1029–1036.
7. Mannheimer C, Eliasson T, Augustinsson LE, *et al.*: **Electrical stimulation versus coronary artery bypass surgery in severe angina pectoris. The ESBY Study.** *Circulation* 1998, **97:**1157–1163.

8.•• Lawson WE, Hui John CK, Cohn PF: **Long-term prognosis of patients with angina treated with enhanced external counterpulsation: five-year follow-up study.** *Clin Cardiol* 2000, **23:**254–258.

This paper documents the long-term effectiveness of EECP but does not indicate the mechanism.

9. Arora RR, Chou TM, Jain D, *et al.*: **Multicenter study of enhanced external counterpulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes.** *J Am Coll Cardiol* 1999, **33:**1833–1840.

10.• Fitzgerald CP, Lawson WE, Hui JCK, *et al.*: **Enhanced external counterpulsation as initial revascularization treatment for angina refractory to medical therapy.** *Cardiology* 2003, **100:**129–135.

At the moment, EECP is not being used as first-line therapy or instead of revascularization. However, that may change in the future, especially if the patient refuses revascularization.

11. Conti CR: **EECP-enhanced external counterpulsation.** *J Am Coll Cardiol* 1999, **33:**1841–1842.

12. Michaels AD, Accad M, Ports TA, Grossman W: **Left ventricular systolic unloading and augmentation of intracoronary pressure and doppler flow during enhanced external counterpulsation.** *Circulation* 2002, **106:**1237–1242.

13.• Masuda D, Nohara R, Hirai T, *et al.*: **Enhanced external counterpulsation improved myocardial perfusion and coronary flow reserve in patients with chronic stable angina: evaluation by(13)N-ammonia positron emission tomography.** *Eur Heart J* 2001, **22:**1451–1458.

This is an interesting study, but it may not be the mechanism of long-term benefit of EECP. However, in some instances there may be improvement in collateral coronary artery blood flow combined with other effects, such as improvement in peripheral muscle performance.

14. Wu GF, Qiang SZ, Zheng ZS, *et al.*: **A neurohormonal mechanism for the effectiveness of enhanced external counterpulsation.** *Circulation* 1999, **100:**I–832.