Enhanced External Counterpulsation

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Since the advent of bypass surgery in 1966 and coronary angioplasty in 1977, there has been an explosion in the area of coronary revascularization for atherosclerotic disease. In every cardiology clinic, however, there is an increasingly large population of patients who have persistent anginal symptoms, who have exhausted the standard revascularization armamentarium, and who remain severely restricted. Following bypass surgery, only 75% of patients are symptom free from ischemic events for 5 years or more, and only 50% remain so after 10 years or more.[1] Even the successes of reoperation and catheter-based revascularization techniques have not kept in check the population of patients with intractable angina and no conventional revascularization options.

Following bypass surgery, only 75% of patients are symptom free from ischemic events for 5 years or more, and only 50% remain so after 10 years or more.

Enhanced external counterpulsation (EECP) has been used as a treatment for angina in China for 2 decades but has only recently sparked interest in the United States. Refinements in the technology utilized in this old concept have led to increasing promise for this treatment. The noninvasive technique provides augmentation of diastolic blood flow and coronary blood flow similar to the intraaortic balloon pump, utilizing the serial inflation of three sets of cuffs that wrap around the calves, the thighs, and the buttocks. Inflation and deflation are timed to the patient's electrocardiogram (ECG), and the arterial pressure waveform is monitored noninvasively. The overall hemodynamic effect is to provide diastolic augmentation and thus increase coronary perfusion pressure; to unload systolic cardiac workload and therefore decrease myocardial oxygen demand; and to increase venous return and, subsequently, cardiac output. This exciting new therapy is being explored as a treatment for chronic angina, but it has many possible therapeutic utilities in acute ischemic syndromes and cardiac dysfunction.

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History of Counterpulsation

In 1953, Kantrowitz and Kantrowitz initially described the concept of diastolic augmentation as a technique to improve coronary flow, which had been known to be primarily diastolic. Early work by Birtwell and others showed that the ECG QRS complex could be utilized to time an external pumping device that provided a synchronous pulse wave, thereby increasing the development of coronary collaterals in experimental models. In the 1960s, S.D. Malopoulis, of the Cleveland Clinic, developed an experimental protocol for the intraaortic balloon pump, wherein a pulse wave was delivered via an intraaortic balloon device timed to the cardiac cycle to increase diastolic pressure and flow. Soroff and colleagues[2] then described how these types of assistive devices could not only produce increased coronary flow but also reduce left ventricular work and oxygen demand.

Soroff, Hui, and Gorlin[3] first coined the term "counterpulsation" to describe the 2-fold effect of the rapid displacement and reduced resistance of volume in the lower arterial circuit. The principle believed to be in effect is that, via persistent augmentation of diastolic flow, stimulation of collaterals to ischemic territories occurs with improvement in symptoms and clinical measures of ischemia. It has been shown that external counterpulsation improves ischemic physiology by increasing myocardial oxygen supply (with increased diastolic perfusion pressure) and reducing cardiac workload by decreasing left-ventricular afterload.[3]

Adrian Kantrowitz began clinical work with an internal system in 1968 using a 15 French device that was employed via surgery with a chimney graft on the femoral artery.[4] This technique was developed to become the modern intraaortic balloon pump that is part of the standard

armamentarium of cardiologists and cardiovascular surgeons today.[4] The present-day intraaortic balloon pump is available in 8 French and 9 French sizes and can be placed via a transfemoral approach in 90%–95% of patients in whom coronary perfusion or cardiac assistance is needed.

Soroff et al.[5,6] first described how the application of a positive pressure pulse to the lower extremities during diastole could raise diastolic pressures 40%–50% and lower systolic pressures as much as 30%. By the early 1960s, three groups (Birtwell and Soroff, Dennis, and Osborn) independently developed hydraulically activated external counterpulsation devices. They found that the technique was effective in improving survival after myocardial infarction complicated by cardiogenic shock.[5,6] Initial experience with a crude external counterpulsation device used in stable angina included relief of angina symptoms with angiographic evidence of increased vascularity.[7] In a large, randomized trial, 258 acute myocardial infarction patients were assigned to treatment with external counterpulsation for 3 hours within 24 hours of presentation. Mortality was reduced significantly in patients over 46 years of age (8.3% vs. 17.5%, $p < 0.05$).[8] Despite some of these very positive early findings, other studies showed no benefit with external counterpulsation when it was studied in the 1970s and 1980s. The great variability in clinical benefit seemed to correlate with the achieved level of diastolic augmentation.

In the early 1980s, a Chinese group led by Z.S. Zheng[9,10] began reporting on a large experience using a sequential three-cuff external counterpulsation system that provided a pressure wave by sequentially inflating from calf to thigh to buttock (Figures 1 and 2). The group's clinical experience led to the installation of more than 1,500 external counterpulsation units in China during the past 15 years, subsequently leading to the development and refinement of the EECP technique and device.

Stony Brook Experience

A commercially available EECP system (EECP®, Vasomedical Inc., Westbury, N.Y.) similar to the Chinese device has been approved by the U.S. Food and Drug Administration as of 1995 and has been utilized recently in clinical studies by Lawson and Cohn and the group at the State University of New York (SUNY) at Stony Brook.[11,12,13] Lawson et al. examined this outpatient therapy when it was performed for 1 hour each day for 7 weeks in 18 patients. Subjects had symptomatic angina despite medical and surgical interventions and evidence of ischemia by exercise thallium testing. In all 18 patients, there was symptomatic improvement in angina; and, in 16 of 18, activities of daily living could be performed asymptomatically. Thallium-201 imaging showed resolution of thallium defects in 12 patients (67%), a decrease in ischemic area in 2 patients (11%), and no change in 4 patients (22%).[11] Exercise treadmill tests showed an improvement in exercise duration without a significant change in double product.[11] A sustained benefit was seen in most of these patients, as 13 of 18 reported being angina free at the 3-year follow up without interval coronary events.[12] Repeat thallium-201 imaging in 10 of the 14 original patients showed persistent improvement in comparison with pre-EECP studies in 8 patients and worsening in only 2.[12] Recently reported, unpublished 5-year follow-up data on 33 patients treated at Stony Brook suggest that this positive effect continues in the long term.

It has been postulated that this collateral development is dependent on the patency of neighboring vessels. It appears that an open, nonobstructed conduit, via either native coronary flow or bypass graft, provides the milieu for greatest benefit from EECP, thus placing greater importance in the angiographic findings in patients in predicting who will benefit most from this treatment.[13] In analyzing the 50-patient experience at the SUNY Stony Brook medical center, it appears that patients with residual 1- or 2-vessel coronary artery disease appear to derive more benefit from EECP, and those with residual 3-vessel disease may derive less benefit when only 35 hours of therapy are applied. The clinical benefit seen in 80% of patients in this series was inversely related to the extent of residual coronary disease.[13] Thus it appeared that transmission of diastolic pressure and distal vessel effects are dependent on a patent proximal conduit.

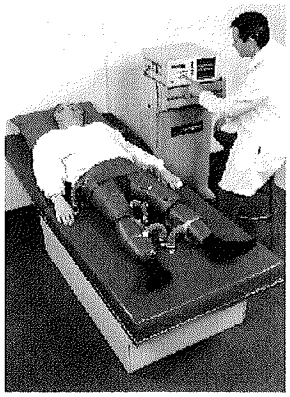

Figure 1. EECP device.

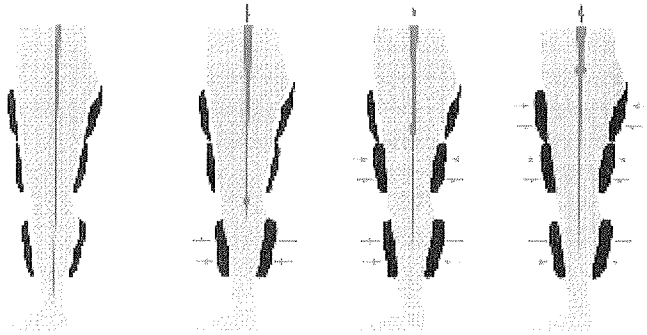

Figure 2. Sequential application of cuff inflations. A series of three cuffs, timed with the cardiac cycle, inflate at the calf, the thigh, and the buttock levels.

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MUST-EECP

The first multicenter, randomized, sham-controlled trial comparing the effect of full EECP treatment versus sham on exercise treadmill scores and subjective angina in stable chronic angina patients was recently completed. The Multicenter Study of Enhanced External Counterpulsation (MUST-EECP) study results were presented at the 1997 Annual Scientific Sessions of the American Heart Association.[14] Seven centers enrolled in this study: University of California–San Francisco Moffitt-Long Hospitals, Columbia Presbyterian Medical Center, Yale New Haven Medical Center, and Beth Israel Deaconess Hospitals of Harvard Medical School, University of Pittsburgh Medical Center, and Grant/Riverside Methodist Hospitals of Columbus, Ohio.

In this study, 139 patients (mean age: 63 years, range 35–81 years) with angina pectoris (typical Canadian Cardiovascular Society Classes I, II, and III angina) and documented coronary ischemia were equally randomized to hemodynamically inactive counterpulsation (CP) with EECP versus active CP. Endpoints on exercise treadmill testing included time to ST-segment depression by ECG, frequency of angina attacks by questionnaire, and on-demand oral nitrate use. Time to ST-segment depression was significantly different between groups (p=0.01) with active-CP patients improving (337 ± 18 seconds to 379 ± 18 seconds [mean ± standard deviation]); p<0.002) versus no improvement for sham (326 ± 21 seconds to 330 ± 20 seconds; p>0.7). Total exercise duration was significantly higher after treatment in the active-CP group (426 ± 20 seconds to 470 ± 20 seconds; p<0.001) compared with the inactive-CP (432 ± 22 seconds to 464 ± 22 seconds; p<0.03). Between-group difference was not significant (p>0.3). Angina frequency in the active-CP group was decreased (0.76 ± 0.15 to 0.55 ± 0.27; p<0.001) but not in the inactive-CP group (0.76 ± 0.13 to 0.77 ± 0.2; p>0.4). More active-CP patients showed a decrease, and fewer experienced an increase in angina as compared with inactive-CP patients (p<0.05). Nitroglycerine usage did not change in the inactive-CP patients (0.51 ± 0.15 tablets to 0.45 ± 0.19; p>0.4) but decreased in the active-CP patients (0.47 ± 0.13 to 0.19 ± 0.07; p<0.001); the difference was not significant (p>0.7). There were no serious complications from treatment in either group. Initial data at 1-year follow up suggests a sustained effect.

The MUST-EECP data suggest that the experience of the Chinese investigators as well as the preliminary results from the Stony Brook trial are accurate. In a well-controlled, randomized, clinical trial, multicenter data now suggest that EECP can effectively and safely improve exercise treadmill parameters as well as medication usage and subjective angina pectoris complaints in patients with chronic stable angina.

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Current and Future Directions

Currently, the primary indication for EECP treatment is chronic stable angina. Patients who are accepted for treatment must be prepared to undergo 35 hours of EECP therapy. Treatment is administered 1 or 2 hours daily at least 5 days per week. If 2 hours daily is planned, then the first week of treatment is best limited to 1 hour daily to facilitate familiarization and to monitor patient tolerance before increasing the daily treatment time. Two hours of treatment on the same day should be separated by a rest period. Precautions for therapy (see Table 1) include recent catheterization, arrhythmia that would preclude accurate timing of the device, active cardiac dysfunction, aortic insufficiency, and limiting peripheral vascular disease.

Clearly, EECP has potential for treatment of patients with angina. In the absence of an indication for revascularization on the basis of survival benefit or as an alternative to percutaneous transluminal coronary angioplasty or coronary artery bypass grafting, EECP may be of particular utility in patients at high risk for revascularization or for whom revascularization is not technically possible.

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Table 1. Precautions for EECP treatment

- Cardiac catheterization within 1–2 weeks to minimize the likelihood of bleeding at the femoral puncture site
- Arrhythmia that might interfere with the triggering of the EECP system (e.g., atrial fibrillation, atrial flutter, ventricular tachycardia)
- Congestive heart failure (In some patients, left ventricular unloading may be insufficient to compensate for increased venous return during EECP.)
- Aortic insufficiency when regurgitation would prevent diastolic augmentation
- Limiting peripheral vascular disease (PVD) and/or phlebitis because of increased risk of thromboembolus (Severe PVD with reduced vascular volume and diminished musculature of the lower extremities can compromise effective counterpulsation.)
- Severe hypertension (≥180/110 mm Hg) (Under these circumstances, EECP could produce diastolic blood pressure levels surpassing acceptable limits.)
- Bleeding diathesis, coumadin therapy with prothrombin time ≥ 15, because the pressure of cuff inflations might cause bleeding in the leg muscles
- Pregnant women and women of child-bearing potential who do not employ a reliable contraceptive method to avoid possible danger to fetus

Note: Current experience indicates that EECP presents little or no danger to patients. Nevertheless, before EECP, patients should be evaluated in keeping with usual practices when planning intervention. A complete medical history and physical examination, including a 12-lead electrocardiogram, is recommended at the time of patient enrollment and at the completion of treatment.

Potential use of the current EECP system in chronic heart failure, unstable cardiogenic shock syndromes, and acute ischemic syndromes is also being explored. Historical data suggest that there is great potential for its use in acute coronary syndromes. Application in the field, the emergency ward, and the intensive care unit requires the development of a smaller mobile system that replicates the dependable augmentation that the present system produces. Such a system is in development.

Conclusions

The intractable angina patient who fails to respond to conventional treatment with bypass surgery or catheter-based techniques has options. EECP is a noninvasive technique that has a long history of providing relief from angina in China and has shown promise in U.S. experience to date. Recently completed, randomized trial data suggest that EECP is a real and viable alternative for patients who have no other interventional options. More trials are under way to evaluate the true efficacy of this exciting technology and the precise role that it will play in the broader treatment of coronary artery disease.

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EDITOR'S COMMENTS

Dr. Chou summarizes a therapy for patients with chronic ischemic heart disease that has, in my opinion, great potential. Its potential could be particularly applicable in patients who are not candidates for revascularization but who continue to have repetitive episodes of myocardial ischemia. The principle of counterpulsation makes great sense because it increases diastolic pressure and thus influences coronary perfusion. Systolic pressure may be lowered in these patients because of reflex arc related to higher diastolic pressure. This technique has now been studied quite well and deserves consideration in patients who continue to present difficult management problems. I do not believe this technique is first-line therapy. We still should progressively optimize the pharmacologic therapy that is available to us in 1998.

—C. Richard Conti, MD, MACC