Enhanced External Counterpulsation: U.S. Clinical Research

In U.S. clinical research, EECP (Vasomedical) has been shown to be an effective treatment for angina pectoris, with reported response rates ranging from a 75% success rates in unselected patients to 92% in patients with single vessel CAD (Table; Fig.). EECP effectively augments diastolic pressure and retrograde aortic flow, thereby increasing transmyocardial perfusion pressure. Demonstrable improvement of myocardial perfusion achieved by EECP may be due to collateral formation or recruitment. One or more proximally patent conduits (e.g., native coronary or bypass graft) improves the success of EECP, and is consistent with the concept that distal transmission of diastolic flow and pressure is necessary. Improvement in exercise tolerance after EECP may also be augmented by peripheral effects. The effects of EECP have been shown to be maintained in a majority of responders over a 3 year period. Over a 4–7 year period, the majority of treated patients remained free of interim events or need for hospitalization, with mortality results comparable to reported historical medical and surgical treatment. The patients enrolled in the reported clinical trials present the full spectrum of CAD severity; from the patient with single vessel disease and good left ventricular function to the triple vessel disease patient with stenotic grafts and compromised left ventricular function. The reported findings support the effectiveness of EECP used in three strategies of CAD treatment. EECP is highly effective in lessening ischemic symptoms in the patient with single or double vessel disease who wishes to defer more aggressive means of revascularization. Also, it is effective as an adjunct to angioplasty or bypass grafting in patients with incomplete revascularization, further decreasing the ischemic burden. EECP finds its third clinical role in treating patients who are poor revascularization candidates because of comorbidity and technical reasons, though results in this group are less impressive.

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Background

EECP is a novel noninvasive outpatient treatment for CAD. Originating in the U.S., the concept of counterpulsation has its roots in a seminal paper by Drs. Arthur and Adrian Kantrowitz[1] in 1953. Early U.S. trials by Dr. Ezra Amsterdam et al,[2] that utilized a cumbersome hydraulic system with a single chamber unit enclosing the lower extremities showed improved mortality in patients treated for acute MI. Use of and interest in external counterpulsation waned in this country with the advent and widespread dissemination of the ABP.

The current device used for EECP was developed by Dr. Zhen-Shen Zheng at Sun Yat Sen University in China and brought to this country by Drs. Harry Soroff and John Hui in 1989 for clinical research trials at the State University of New York at Stony Brook. The device uses 3 pairs of external pneumatic cuffs (calves, thighs, upper thighs, buttocks) that are sequentially inflated during diastole using EKG timing to produce effective diastolic augmentation. The action of EECP is in many respects similar to IABP. Qualitatively, EECP differs from IABP hemodynamically in directly increasing venous return, thereby benefiting cardiac output.

Early Trials

Reported in 1992, the early Stony Brook experience[3] comprised treatment of the first 18 patients treated with EECP in this country. These patients had chronic angina refractory to medical therapy (8 patients had 19 prior revascularization attempts; 7 had 14 prior myocardial infarcts between them).

ABBREVIATIONS AND ACRONYMS

CABG	Coronary artery bypass graft
CAD	Coronary artery disease
EECP	Enhanced external counterpulsation
IABP	Intraaortic balloon pump
MI	Myocardial infarction
PAIS-R	Psychosocial Adjustment to Illness Scale-Revised
PTCA	Percutaneous transluminal coronary angioplasty

The patient received a total of 36 one-hour treatments with EECP treatments. All patients had pre and posttreatment thallium treadmill stress tests to identical cardiac work loads and a posttreatment maximal routine treadmill stress test.

Over the course of treatment, all patients reported improvement in anginal symptoms, with 16 patients experiencing no angina during usual activities. Use of cardiac medication decreased or remained constant and there were no complications from treatment. Thallium scintigraphy, read in a blinded-fashion posttreatment, demonstrated stress-associated reversible perfusion defect resolution in 67% (12 patients), improvement in 11% (2 patients), and no change in 22% (4 patients). Average maximal treadmill time improved an average of 1.6 minutes on a Bruce protocol, with no significant change in double product. The 14 patients with improved thallium scans demonstrated an average increase of 1.9 minutes in exercise duration as well as a significant increase in treadmill peak double product. The improvement in myocardial perfusion after EECP was hypothesized to be collateral recruitment or development.

Psychosocial testing was performed before and after EECP treatment[4] on 12 of the initial group of patients using the PAIS-R and a pain, exercise, and medication questionaire. In this subgroup, 75% (9 patients) demonstrated improved thallium perfusion and exercise tolerance. The only significant difference on the PAIS-R posttreatment was in the extended family subscale, with patients demonstrating an overall good adjustment to illness. The 3 patients who did not improve objectively with treatment still demonstrated significantly lower values on the psychological distress PAIS-R subscale. All patients reported improvement in ability to work and in overall well being. In summary, EECP was well tolerated with perceived benefits for patients who did and did not demonstrate objective improvement.

Subsequent clinical follow up of the initially treated 18 patients was reported after 3 years.[5] In patients free of interim events (i.e., revascularization, MI, and death), a repeat stress thallium was performed to the same duration as the initial study. Of the 14 patients initially responding to EECP with a decrease in ischemia demonstrated by thallium perfusion imaging, one had an interim myocardial infarction, another had surgical revascularization, and one patient was lost to follow up. The other 11 patients demonstrating initial improvement with EECP remained free of limiting angina. Of the 10 patients undergoing repeat stress testing (one patient refused), improvement in thallium imaging was maintained in 8 (80%). At 3 years, most of the initially responding patients remaine event-free and without limiting angina. Continuea improvement in thallium imaging was demonstrable in the majority of initial responders over the 3-year period.

A 5 year follow up addressing the issue of morbidity and mortality in the first 33 angina patients treated with EECP recently was completed.[6] In this group of patients, angiography demonstrated multivessel coronary disease in 16 out of 18 patients, 10 had prior MI, and 13 had undergone prior revascularization (i.e., bypass surgery, angioplasty, or both). At a mean follow up period of 5 years (range 4–7 years), 4 patients had died (2 sudden death, 1 congestive heart failure, 1 status post stent) and 9 patients had required hospitalization (4 acute MI, 6 CABG or PTCA, 1 unstable angina, 1 other cardiac surgery).

Over 60% (20/30) of these CAD patients remained alive, healthy, and without interim cardiac events or need for hospitalization. This demonstrates that the benefits of EECP may be sustained over a 4–7 year period. The 5 year survival of 88% of patients treated with EECP is comparable to the survival of similar studied populations as reported in the CABG metaanalysis (medical mortality 84% and CABG mortality 90%)[7] and in the BARI revascularization trials (PTCA mortality 86% and CABG mortality 89%).[8]

Optimizing Patient Selection

Using the Stony Brook database, 50 consecutive patients demonstrating >70% stenosis in a major native coronary artery or bypass graft by coronary angiography prior to EECP, were analyzed for response to treatment.[9] Patients were divided into groups based on residual extent of CAD,(i.e., single, double, triple vessel residual disease), after allowing for graft patency in those patients previously bypassed. Of the 50 patients, 31 had prior revascularization attempts (6 CABG alone, 15 PTCA alone, 10 both PTCA and CABG). Pre and post EECP radionuclide stress images were evaluated independently by two masked interpreters, and the results of the 3 groups were compared.

There was a significant correlation between the extent of residual CAD and response to EECP. More than 90% of patients with residual single and double vessel disease showed improvement or reso lution of reversible radionuclide perfusion defects, while 41% of patients with residual triple vessel dis-

ease demonstrated an improvement. The results support the hypothesis that a proximally "patent conduit" is necessary to allow transmission of the augmented diastolic pressure and flow to the distal coronary circulation. The presence of one or more native coronary arteries or bypass grafts without significant stenoses appears to increase substantially the effectiveness of EECP.

The effect of prior surgical revascularization on improved stress radionuclide perfusion after EECP was examined further in 25 bypassed and 35 unrevascularized CAD patients who had undergone previous coronary angiography. In the group without revascularization, patients with significant single and double vessel disease were much more likely to respond to EECP than those with triple vessel disease (85% and 92% respectively vs. 22%, $p<0.05$). Previously bypassed patients responded similarly to patients with single and double vessel CAD.[10] A comparison of radionuclide stress improvement was performed for 19 post EECP patients (unrevascularized patients with three vessel disease vs. previously bypassed patients with triple-vessel disease and >70% stenosis of all grafts).[10] While 80% (8/10) of the post bypass patients demonstrated improvement in myocardial perfusion post EECP, only 22% (2/9) of the unbypassed patients improved.

Prior surgical revascularization may improve distal transmission of pressure and flow augmented due to EECP by providing a conduit to the distal coronary circulation. Because of common bypass vein/coronary artery size mismatch, a >70% vein graft stenosis may not be as compromising to distal flow as a similar lesion in a proximal native coronary artery. Prior revascularization appears to increase substantially the probability of a positive response to EECP in patients with triple vessel CAD and suggests a role for EECP as an effective adjunct to incomplete surgical revascularization (Table; Fig.).

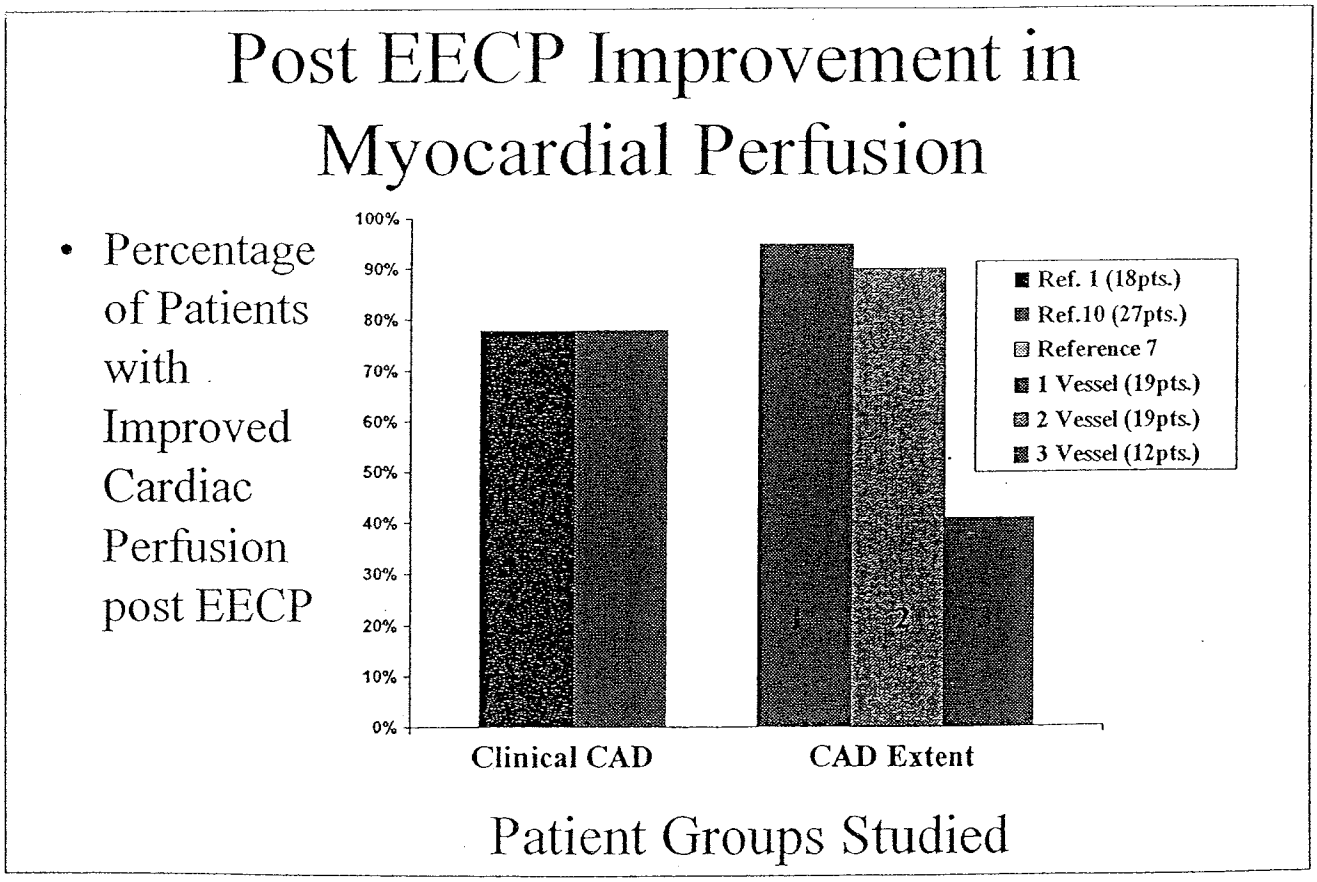

Figure. Percentage of patients showing improvement in myocardial perfusion by radionuclide stress testing post EECP based on extent of CAD (single, double, or triple vessel) and on prior surgical revascularization (CABG) reported in clinical research trials.[9,10,11] Post-CABG patients are categorized into single, double, triple-vessel residual disease as described in the text.

TABLE. ANGIOGRAPHIC PREDICTION OF EECP EFFECTIVENESS

CAD EXTENT	NO CABG (N=35)	CABG (N=25)	ALL PATIENTS(N=60)
1 vessel (N=21)	11/13 (85%)	7/8 (88%)	18/21 (86%)
2 vessel (N=20)	12/13 (92%)	5/7 (71%)	17/20 (85%)
3 vessel (N=19)	2/9 (22%) *	8/10 (80%)	10/19 (53%)
All CAD	25/35 (71%)	20/25 (80%)	45/60 (75%)

Percentage of coronary patients demonstrating improvement in radionuclide perfusion on stress testing after EECP based on extent of CAD (single, double, or triple vessel) and on prior revascularization[9,10,11] Percentage of 3 vessel CAD without revascularization responding to EECP is significantly less by chi square testing ($p<0.05$) than patients with single and double vessel disease or previously bypassed patients.

Mechanism of Action

EECP has been demonstrated by radionuclide scintigraphy to improve myocardial perfusion in a majority of treated patients. Effectiveness has been shown to be directly related to the number of patent coronary vessels in the treated patient. Counterpulsation with the intraaortic balloon pump [11,12] has been shown to increase distal coronary blood flow velocity, pressure, and volume in the absence of significant proximal stenoses and after successful angioplasty of a proximal stenosis. It is hypothesized that EECP similarly increases coronary blood flow, promoting collateral recruitment or development over time to maintain the augmented coronary perfusion. Expectations that effectiveness could be predicted in the presence of proximally patent vessels has been substantiated in clinical trials.

The effect of EECP on exercise hemodynamics[13] was examined in a group of 27 patients with chronic stable angina. A maximal radionuclide stress test was performed before a 35 hour course of EECP. Post EECP, a radionuclide stress test to the same workload as baseline and a maximal routine stress test were performed. Most patients (78%) showed improved stress radionuclide perfusion images and exercise tolerance (81%) post EECP. Increases in exercise time correlated with increases in double product and heart rate. However, blood pressure response and, to a lesser extent, heart rate response to exercise were blunted post EECP, suggesting a training effect. This alteration in exercise hemodynamics suggests that improved exercise tolerance post EECP may be a consequence of both improved myocardial perfusion and decreased peripheral vascular resistance.

A case report[14] of a patient with triple vessel CAD suggests that proposed explanations for the efficacy of EECP may be inadequate. The patient continued to experience persistent effort angina and thallium perfusion defects despite 7 multivessel angioplasties, and 2 surgical revascularizations over a 21 month period. After high pressure (up to 275 mm Hg) prolonged EECP (>120 hours), both angina and thallium perfusion defects resolved. The patient has remained free of angina for 5 years since receiving EECP. The ability of EECP to stabilize what had become a virulent biological process may suggest that EECP has an effect in normalizing endovascular function and demonstrates that EECP may be effective as an adjunct to revascularization.

The effects of EECP on descending aortic flow[15] were examined in a group of 10 subjects. The effect of EECP on the Doppler echocardiographic waveform appearing qualitatively similar to that produced by IABP. The retrograde aortic diastolic time velocity integral increased from a baseline average of 1.7 cm to 8.3 cm with EECP diastolic augmentation. The antegrade aortic systolic time velocity integral also increased with EECP from a baseline average of 14.2 cm to 21.5 cm. These changes in aortic flow are consistent with effective diastolic augmentation and increased cardiac output during EECP.

The effect of increasing external cuff pressure (from 100–275 mm Hg) on descending aortic blood flow was evaluated in a group of 15 patients.[16] As assessed by finger phlethysmography, systolic and diastolic time velocity integrals both increased in a linear fashion as diastolic augmentation (peak diastolic to peak systolic ratio) increased to the 1.5–2.0 range. Above this range, further increases in diastolic augmentation resulted in little, if any, change in systolic or diastolic aortic volume. Therefore, an optimal range for diastolic augmentation is identifiable for maximizing the hemodynamic effects of EECP while minimizing the applied external pressure.

Safety

To date, clinical research has demonstrated the safety of EECP. No major morbidity or mortalities have been reported at this writing. The most com-

nonly noted adverse effect skin trauma secondary to application of external pressure and friction. This effect can be largely prevented by wearing proper clothing (e.g., spandex leggings) and with proper cuff application (i.e., tight and without padding). Reported clinical trials have excluded patients with: clinical congestive heart failure, aortic insufficiency, recent MI or unstable angina, significant ventricular ectopy, atrial fibrillation, permanent pacemakers, severe peripheral arterial disease, active or recurrent deep vein thrombophlebitis, uncontrolled hypertension (BP>180 /110), bleeding diathesis, and nonischemic cardiomyopathy.

Current Initiatives

A multicenter, placebo (low vs. full augmentation) controlled, single masked study of the effectiveness of EECP in treating angina began in 1994 (MUST-EECP, Multi-Center Study of EECP). The vanguard centers of Columbia-Presbyterian Medical Center (Dr. Rohit Arora), Yale University (Dr. Diwaker Jain), University of California San Francisco (Dr. Tony Chou), and Beth Israel-Deaconess Medical Center (Dr. Richard Nesto) have been joined in their efforts by the University of Pittsburgh (Dr. Lawrence Crawford), Loyola University of Chicago (Dr. Thomas McKiernan), and Grant/Riverside Methodist Hospitals (Dr. Bruce Fleishman) in Columbus, Ohio. Study endpoints include: exercise tolerance (treadmill time), time to ischemia (by ST changes on treadmill), anginal frequency, and nitroglycerin use. Enrollment and treatment of participants was completed in the spring of 1997 and results will be available later this year.

The University of Pittsburgh has been chosen to serve as coordinator for the newly-formed National EECP Patient Registry. Dr. Sheryl Kelsey is director of the registry coordinating center and Dr. Jonathan Jaffe is chair of the national EECP Patient Registry. This centralized database will standardize data collection and analysis and allow rapid acquisition and dissemination of information relevant to EECP in the future.

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