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Ongoing and Planned Studies of Enhanced External Counterpulsation

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Summary: There is strong, continued interest in enhanced external counterpulsation (EECP) as evidenced by current, ongoing clinical trials. Many of these have been designed to support the current indications of EECP, mainly its application in the treatment of symptomatic coronary artery disease. An exciting area in this regard is how EECP may help control blood glucose in patients with angina and diabetes mellitus. A variety of planned or ongoing exploratory studies are also helping to explain the mechanism of action behind EECP. Two clinical trials are now investigating a new indication for EECP in patients with congestive heart failure, including the important randomized Prospective Evaluation of EECP in Congestive Heart failure (PEECH) trial.

Key words: angina pectoris, congestive heart failure, coronary artery disease, enhanced external counterpulsation, myocardial infarction, PEECH trial

Introduction

Current and future clinical trials of enhanced external counterpulsation (EECP) are focusing on three areas of research. First, some of these trials continue to investigate current indications for EECP. Second, other trials are being designed to develop prospective new indications. Finally, other studies are exploratory in nature.

Clinical trials will also focus on various aspects of EECP. For example, there will be a number of trials looking at the mechanism of EECP, which is still not thoroughly understood. In terms of disease application, randomized, controlled studies will investigate the efficacy of EECP for the treatment of congestive heart failure. At present, there is a company-sponsored pilot study examining perfusion in patients with chronic stable angina. These pilot data will be used later to reinforce the application to the National Institutes of Health (NIH) for a large, multicenter trial.

The International EECP Patient Registry

The International EECP Patient Registry (IEPR) continues to investigate the use of EECP in patients with symptomatic coronary artery disease. Phase II of the registry will add an additional 2,500 patients to achieve a total of 7,500 patients. This phase will allow a series of substudies in addition to those already carried out in Phase I.

This registry Phase II study will include a "treat-to-target" option, where patients are treated until achieving a preset goal of symptom reduction instead of a standard 35-h course of EECP-II. Clinical event data will be captured, along with data from the Duke Activity Status Index (DASI) for health quality of life before treatment, after treatment, and at 6 and 12 months following treatment.

In one substudy, there will be microalbuminuria testing for 500 consecutive patients with type II diabetes to determine the specific benefit of EECP in diabetics. Another substudy will measure sexual function in men after EECP treatment by using a validated questionnaire. This will be used with 500 patients to determine whether there is a benefit in this regard for those with coronary artery disease. Finally, another substudy will investigate the benefit of EECP in patients with peripheral artery disease. Consecutive patients with concomitant intermittent claudication will be tested before and after treatment using ankle-brachial index, 6-min walk test, Edinburgh Claudication Scale, medication changes, and physical examinations.

Other Coronary Artery Disease Studies

Two multicenter, prospective studies are currently underway to investigate EECP also in patients with symptomatic coronary artery disease. In the first, which is a single-blind, single-group study, the purpose will be to determine how EECP affects myocardial perfusion and regional wall motion. Six centers will treat a total of 40 class II and III patients with

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angina with 35 h of EECP. Using quantitative techniques, a core laboratory will blindly access changes in stress/rest radionuclide (technetium 99 single-photon emission computed tomography) myocardial perfusion scans baseline to 1 month post treatment. Testing will consist of segmental perfusion, regional wall motion, time to > 1 mm ST depression, double product, health quality of life (using the SF 36 and Seattle Angina Questionnaire), and safety. This study began in May 2001.

The other clinical trial is a single-arm study of approximately 30 patients with concomitant angina and type II diabetes mellitus. Its purpose is to verify in-clinic observations that EECP can help control blood glucose in angina patients with diabetes. Patients will be tested for insulin resistance using the Euglycemic Clamp technique before and after a course of EECP treatment. Testing will consist of measuring glycosylated hemoglobin (HbA1c) and fructosamine.

Exploratory Studies

A number of exploratory studies are also underway. Two of these studies are investigating the application of EECP in patients with myocardial infarction. The first one is a prospective, nonrandomized, case-control trial of 20 patients with acute inferior infarction complicated by involvement of the right ventricle. The purpose is to test the feasibility of EECP to augment right ventricular performance by increasing left ventricle preload and cardiac output, thereby eliminating or reducing the need for fluid loading.

Within 12 h of symptom onset, all qualified presenting patients are invited to enroll in the study. Patients declining EECP are asked to enter the control group. Both groups will have the usual Swan-Ganz catheter measurements. The EECP group, however, will have repeat determinations at 0, 30, 90, and 120 min during their EECP treatment. Measurements will include right atrial pressures, pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), mean arterial pressure (MAP), pulmonary vascular resistance (PVR), systemic vascular resistance (SVR), cardiac index (CI), total intravenous fluids during the first 48 h, right ventricle wall motion, tricuspid valve flow velocities, length of stay in the intensive care unit, and mortality. This study began recently.

A second exploratory study of EECP in patients with myocardial infarction is a prospective, controlled, patient-blind study of 30 patients with recent infarction and residual myocardial ischemia. The purpose is to discover whether EECP affects large-vessel functionality (compliance, hyperemic reflex) and whether responses correlate with ETT findings.

Carotid arteries will be examined by ultrasound/laser Doppler using the Phillips-ATL 5000 for diastolic diameter and systolic distention, intimal and medial thickening, plaque formation, endothelial shear, blood viscosity, and red cell aggregation. Measurements will be exercise tolerance test (ETT), brachial arterial pressure via Dinamap (Baxter), carotid/femoral pulse dimension, platelet activation, nitric oxide, renin, and angiotensin II.

A variety of other exploratory studies are also either ongoing or being planned (Table I). It is hoped these studies will help explain the mechanisms of action behind EECP. In addition, these studies will also provide initial data on which to base future clinical trials.

Prospective New Indications Trials

An important trial investigating a new indication for EECP is the Prospective Evaluation of EECP in Congestive Heart Failure (PEECH) study. This is a multicenter, prospective, randomized, single-blind, controlled trial. The purpose is to determine conclusively the efficacy of EECP as treatment for chronic congestive heart failure (New York Heart Association [NYHA] II/III).

Patients will be randomized on a 50/50 basis at more than 20 centers. The goal is to have 180 subjects who have NYHA class II/II heart failure, left ventricle ejection fraction ≤ 35%, and are either ischemic or idiopathic. Subjects will be under optimal medical care to receive either 35 h of EECP or continued medical care without EECP. Testing will consist of peak VO_2, exercise duration, NYHA class change, health quality of life (SF36 and Minnesota Living with Heart failure (MLWHF) questionnaire), circulating markers (plasma norepinephrine [PNE], angiotensin II [AII], brain natriuretic peptide [BNP], C-reactive protein [CRP], preproendothelin, nitric oxide), and safety. There will also be an echocardiogram substudy. Follow-up will be at 1 and 26 weeks post treatment, with some measurements also taken at 12 weeks. This trial began in March 2001.

A more recently begun trial for prospective new indications is also examining the role of EECP in the treatment of congestive heart failure using cine magnetic resonance (CMR). Called the EECP CHF CineMRI Evaluation (ECCE)-1 Trial, it is a multicenter, prospective, single-blind, single-group pilot study. The trial will determine the feasibility of conducting a multicenter controlled trial using CMR to demonstrate the effects of EECP on cardiac performance in patients with congestive heart failure.

TABLE I Areas of interest for planned or ongoing exploratory studies of enhanced external counterpulsation

Central hemodynamics during treatment (cath. lab)
Renal function
Cognition
Effects on baroreceptors & neurohomones
Effects on heart rate variability and silent ischemia: 48-h Holter monitoring
Vascular reactivity
Microcirculatory responses (arteriolar & capillary) in brain, eye fundus, kidney, skin
Endothelial function and growth factors
Platelet responses & coagulation factors
Myocyte metabolic responses

Enhanced external counterpulsation will be delivered for 35 h to subjects with NYHA class II/III heart failure who have a left ventricle ejection fraction of ≤ 35% (ischemic or idiopathic). Measurements will be CMR global and regional indices of left ventricle systolic and diastolic function and structural status, peak VO_2, exercise duration, NYHA class change, health quality of life (SF36 and MLWHF questionnaire), BNP, and safety. Follow-up will be conducted at 1, 12, and 26 weeks post treatment, with no CMR performed at 12 weeks.

Summary

Enhanced external counterpulsation continues to be investigated on several fronts. The International EECP Patient Registry continues to investigate current indications for patients with symptomatic coronary artery disease. Exploratory studies are delving into exciting applications of EECP in patients with myocardial infarction who may have right ventricle involvement or residual myocardial ischemia. Other studies in this category are furthering our understanding of the mechanism behind EECP and its physiologic effects. Finally, a number of trials are examining prospective new indications for EECP, particularly in patients with congestive heart failure. Given the current momentum in current and future studies of EECP, the future looks bright for expanded applications and indications for this novel form of treatment.

Discussion

Participant: If the effectiveness of EECP is about 70 percent of an intra-aortic balloon pump, wouldn't it be logical to have the machine in the emergency room? If a patient comes in with pulmonary edema or acute myocardial infarction, you could just hook them up. We have a big hospital with a trauma service. The noise wouldn't bother us; it would be relatively minor compared to what the noise is there. It seems like it would be quite logical as a treatment for acute MI or severe heart failure. Nurses could be trained to just hook them up and start the balloon pump going while the physician is doing conventional therapy. I imagine you could even do thrombolytic therapy with EECP going and a lot of other things that might make it helpful to have it initially and immediately available. Does the panel have any experience with this or any thoughts?

Conti: Well, I have thoughts on it, but I think what the companies need to do is make a device that is mobile. This way, one could move it around, just like you move an echocardiogram machine down there if you need one. Right now, the EECP machine costs money. You can't have 10 of these all over the place. But your point is well taken. You need to have it where you are going to use it for whatever it is you want to use it for, and if it is for acute coronary syndromes, it has got to be either in the coronary care unit, the catherization lab, or the emergency room, not in the outpatient suite.

Beller: For preshock patients or those with failing blood pressures, the cath lab is not available, and you are going to give them thrombolytic therapy. There are abundant data to suggest that you get better improvement in terms of thrombolysis if you are able to raise the pressure and get more penetration of the clot, so I think that is a good idea.

DeMaria: You need to keep in mind also that, while this instrument is relatively easy to use, it is not without the required technical expertise. There are little tricks of the trade that people learn along the way, such as how to optimize the inflation and deflation cycles. So, within an emergency room, you would really need trained personnel who use it frequently enough so they could quickly get it on the patient and optimize the situation.