NEW THERAPIES

New Therapy Provides Non-Invasive Revascularization

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A newly developing field of therapy, enhanced external counterpulsation (EECP), increases the range of services for patients with symptomatic coronary artery disease. EECP is a non–invasive, atraumatic procedure for the treatment of angina pectoris. Hospitals and free-standing clinics are beginning to offer enhanced external counterpulsation outside of clinical studies for the first time.

Definition of EECP

EECP provides sustained relief to patients suffering chronic angina. The FDA has given marketing clearance to enhanced external counterpulsation for indications including stable and unstable angina pectoris, acute myocardial infarction and cardiogenic shock. Currently, the focus is on the treatment of stable angina pectoris.

The treatment system uses fundamental hemodynamic principles to relieve angina — by increasing coronary blood flood to ischemic areas of the myocardium. EECP compresses and decompresses the large vascular beds of the lower extremities by inflating and deflating a series of compressive cuffs wrapped around the patient's legs and buttocks. Timed by the patient's ECG signal, a microprocessor controls inflation and deflation of the cuffs at specific points during the cardiac cycle. During diastole, the cuffs sequentially compress vascular beds, thereby creating a retrograde pressure wave, greatly increasing coronary perfusion pressure, blood flow and oxygen supply. During systole, the cuffs are deflated simultaneously to produce significant systolic unloading, and consequently, decreasing oxygen demand. Venous return is also increased, improving cardiac output.

EECP offers an alternative for patients suffering with angina pectoris who are refractory to conventional treatment. It is appropriate for patients who do not respond to medical management and who are not good candidates for coronary revascularization. Often, these patients have undergone multiple invasive procedures that have either failed or no longer suffice. EECP can be used safely in patients who have undergone one or more CABG or PTCA procedures, irrespective of whether they are suitable for further procedures. Additional interventions may be too risky, not feasible or refused by the patient. Also, EECP may be used before invasive procedures when they are not unequivocally indicated.

Enhanced external counterpulsation non–invasively increases blood supply to the heart, which provides similar, and possibly superior, effects to intra–aortic balloon pumping (IABP), according to research recently presented at the American College of Cardiology (ACC) 45th Scientific Session. According to researchers, enhanced external counterpulsation increases blood pressure in the aorta and blood flow in the coronary arteries during diastole. These effects increase perfusion in the heart, which may stimulate development of collateral circulation.

Coronary Collateral Circulation

The purpose of coronary collaterals — a network of minute vessels within the heart — has been continuously debated. These vessels are so small that they measure only 20 to 250 millionths of a meter. In a normal heart, collaterals seem to serve little or no purpose. However, when an artery becomes blocked, these channels expand in a few seconds. By increasing in diameter, they provide an alternative source of blood flow to the heart muscle jeopardized by insufficient blood flow.

Animal experiments have shown that repeated, brief periods of ischemia stimulate the formation of collateral vessels. Collaterals began developing almost immediately after coronary occlusion. It is possible to detect blood flow in collaterals as soon as five minutes after occlusion. This flow rises progressively over the next 24 to 48 hours, reflecting the recruitment of collateral blood vessels.

An abnormal pressure gradient appears to contribute to the formation of collaterals. When blood flow is obstructed in a coronary artery, there is a decrease in perfusion pressure distal to the obstruction. However, collateral vessels, which are proximal to the stenosis, are still subject to the same blood pressure as before. Therefore, the pressure gradient across a latent collateral vessel is increased — causing the vessel to dilate. For this process to occur, the artery supplying blood to the collateral vessel must remain patent.

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This natural process of opening new collaterals to compensate for insufficient supply of oxygen to heart muscle may be simulated by enhanced external counterpulsation. In clinical trials, EECP was shown to be most effective in patients who have single or double vessel disease, and least effective in those with generalized triple vessel disease. This finding is consistent with the presumption that EECP stimulates collateral vessel formation.

Before– and after–treatment thallium scans indicate that EECP, when given in a series of 35 hour-long treatments, facilitates the development of a permanent collateral circulation, and thus a natural bypass of occluded arteries is achieved.

Clinical Benefits

Clinical response to EECP shows improved myocardial function. Based on observed response in clinical trials of patients with angina pectoris, EECP can reduce the frequency and intensity of chest pain, decrease the need for antianginal medication, improve myocardial perfusion of ischemic areas and greatly improve the ability of the patient to participate in everyday activities. As a result of symptomatic and clinical improvements, patients report an overall improvement in the quality of their lives.

Patients often begin to experience alleviation of angina after 15 or 20 hours of the recommended 35-hour treatment regimen. The sustained benefits following a course of treatment have been documented by clinical studies.

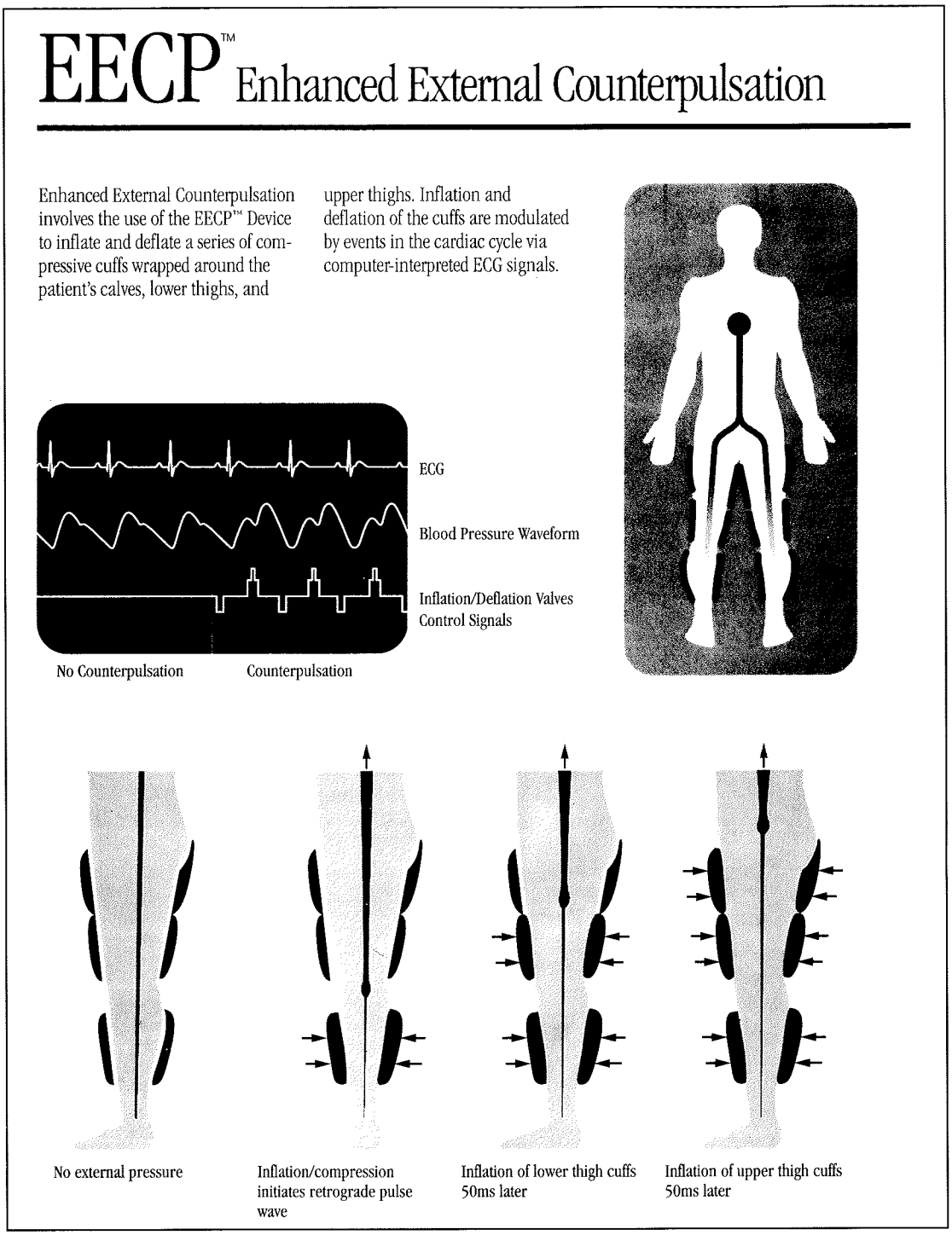

Figure 1. *Enhanced external counterpulsation (EECP). Diagram courtesy of Vasomedical, Inc.*

Studies

The technique of counterpulsa-

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Figure 2. *Patient receiving EECP™ treatment.*

tion was conceived by heart surgeons at Harvard University in the 1950s. However, researchers encountered many difficulties in designing practicable equipment. During the intervening decades, researchers in the United States continued to conduct studies that guided the development of EECP.

Clinicians in China adopted external counterpulsation as a means of providing practical treatment to large numbers of people at a lower cost than invasive procedures. EECP has been used extensively in China during the past 15 years.

Favorable results reported by Chinese investigators led scientists at the Health Sciences Center at the State University of New York at Stony Brook to reassess this procedure. In 1989, researchers at the University Medical Center at Stony Brook, New York began clinical studies of EECP, which provided initial confirmation of the benefits to patients with chronic stable angina pectoris refractory to standard therapy. Follow-up studies have shown that this effect can last at least three years.

The efficacy and tolerability of EECP was studied in 18 patients with chronic, stable exertional angina pectoris. All patients had incapacitating symptoms, refractory to medical therapy, and exertional myocardial ischemia documented by thallium–201 perfusion imaging. Eight patients had previously undergone a total of 19 attempts at revascularization by coronary bypass or angioplasty. Following an initial symptom–limited stress thallium study, subjects received a total of 36 one–hour treatments with EECP over a 7–week period. Antianginal medications were continued at the initial or reduced doses. At the end of the treatment period, thallium testing was repeated, followed by routine maximal stress testing.

In all patients, treatment with EECP was associated with a substantial improvement in symptoms, and 16 patients reported a complete absence of angina during their usual activities. Repeat thallium testing showed a reduction in myocardial ischemia in a significant proportion of patients: 12 (67%) demonstrated a complete absence of perfusion defects, and 2 (11%) demonstrated a reduction in the area of ischemia at the level of exercise achieved in the baseline study. The mean duration of exercise during maximal stress testing, using the Bruce protocol, increased by 1.58 minutes ($p<0.005$). In the subgroup of patients with improved thallium scans an increase in mean exercise duration of 1.86 minutes ($p<0.001$) was observed; this was accompanied by a significant increase in the double product (heart rate x systolic pressure at peak exercise). There were no reported adverse effects of treatment with EECP.

Data from an initial follow-up study were available for 17 of the original 18 patients studied, including 13 of 14 patients who had previously shown a reduction in myocardial ischemia. One of the 13 patients suffered a myocardial infarction, and another underwent a revascularization procedure during the intervening period. Of the remaining 11 patients, all remained free of limiting angina. Ten patients underwent repeat stress thallium testing. In these patients, the mean double product at 3 years was not significantly different from the baseline value; however, eight patients (80%) demonstrated persistent improvements in the results of thallium scintigraphy.

Data from an additional group of 50 angina patients treated with EECP are consistent with initial open trial results. All of these patients reported a reduction in symptoms, and 80% demonstrated improvement by radionuclide testing. Patients with one- or two-vessel disease were significantly more likely to respond than those with three–vessel disease.

In a study of 10 outpatients at rest and while receiving enhanced external counterpulsation, clinical benefits, including a 63 percent increase in cardiac output and a 135 percent increase in retrograde diastolic flow, were demonstrated. These hemodynamic effects provide a physiologic basis for the observed long-term benefits of enhanced external counterpulsation. The

study demonstrated that cardiac support with EECP is comparable to that of the IABP. Unlike IABP, EECP increases venous return and increases cardiac output more effectively than IABP.

Currently, four leading medical centers are engaged in a 120-patient controlled clinical study with EECP to confirm clinical benefits observed in studies at Stony Brook. These centers are University of California San Francisco, Columbia University College of Physicians & Surgeons at Columbia-Presbyterian Medical Center in New York, Deaconess Hospital (a teaching affiliate of Harvard Medical School) in Boston and Yale University School of Medicine in New Haven.

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Role of EECP

The first line of treatment for patients with angina pectoris is medication. In most cases, medical management is effective for a period of time, but for some patients further intervention eventually becomes necessary. EECP can be used safely in patients who are receiving nitrates, beta–blockers or calcium channel blockers or who are refractory to these drugs.

CABG or PTCA are sometimes recommended if medication fails to ease angina or if the risk of heart attack is high. These procedures often provide relief of symptoms and a favorable prognosis. However, they too can fail, are not without risk and are very expensive.

Reocclusion is a major concern for PTCA. The rate of restenosis following PTCA remains as high as 25 to 40 percent after 6 months. Repeat procedures are not uncommon, and restenosis rates after repeat PTCA are as high as 50 percent. Emergency surgery is required occasionally in patients undergoing elective PTCA and is associated with higher mortality and morbidity than with routine CABG.

For patients who have undergone CABG, repeat procedures are also possible. Six to 10 percent of CABG procedures are now reoperations. Late survival is usually good, with 85-95 percent of patients surviving at 5 years. However, reoperative mortality rates are two to three times those of the initial procedure and range from 2 to 10 percent for second operations and up to 15 percent for third and subsequent operations. Patients undergoing repeat procedures generally have more advanced coronary artery disease rendering the revascularization process less effective.

Mechanism of Effect

Normal heart function depends on maintaining a balance between oxygen supply and oxygen demand. Myocardial oxygen consumption is determined by heart rate, contractility and systolic wall tension. Oxygen supply is proportional to coronary blood flow, which is determined by diastolic blood pressure and coronary perfusion pressure. Approximately 80 percent of the blood flow to the myocardium occurs during diastole. Increasing the ratio of oxygen supply to oxygen demand by decreasing systolic pressure (systolic unloading), and increasing diastolic pressure (diastolic augmentation) is the basis for the technique of counterpulsation.

EECP increases diastolic pressure, coronary perfusion pressure and coronary flow because the diastolic blood pressure achieved during treatment exceeds the autoregulatory range in patients with stenosed coronary arteries. EECP also augments diastolic perfusion pressure in these patients. Experience has shown conclusively that effective counterpulsation is directly related to the magnitude of diastolic augmentation.

Conclusion

Based on evidence that EECP improves perfusion of previously ischemic myocardium, the alleviation of angina symptoms is presumed to be related to the development of collaterals, creating a natural bypass.

Enhanced external counterpulsation has been found to be a noninvasive alternative to percutaneous transluminal coronary angioplasty and coronary bypass surgery in the treatment of coronary artery disease.

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