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A New Treatment Modality in Heart Failure

Enhanced External Counterpulsation (EECP)

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Abstract

Heart failure remains a significant health problem in the United States and in the world. Despite a surfeit of recent diagnostic and therapeutic advances, patients with heart failure remain inadequately helped. The overwhelming need for new and better therapies continues to stimulate scientists to investigate new technologies. Over the past several years the use of enhanced external counterpulsation as a treatment for chronic angina has steadily increased. Recently, its potential role in heart failure management has been shown. We review the role of enhanced external counterpulsation in heart failure management as an emerging noninvasive outpatient therapy.

Key Words: EECP, heart failure, noninvasive

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Heart failure has reached epidemic proportions in the United States and is becoming increasingly prevalent as the population ages. Approximately 4.9 million Americans experience heart failure, with 550,000 new cases per year reported.[1] Heart failure accounts for between 5% and 10% of all hospital admissions and is the most frequent cause of hospitalization in the elderly. Comparison of reports of 1979 with those of 2000 reveals that the hospital discharges for heart failure has risen from 377,000 to 999.000.[1] Heart failure is also associated with significant mortality, contributing to approximately 262,300 deaths each year.[1]

In addition, heart failure imposes a large economic burden on the United States, primarily from repeated hospitalizations as a result of worsening heart failure. In 2003, the total direct and indirect cost of congestive heart failure is estimated at $24.3 billion.[1] A new understanding of the pathophysiology of heart failure as a continuum, rather than a series of discrete events, has led to the realization that early identification and treatment of the disease can significantly reduce morbidity and costs.

The therapeutic goals for the treatment of heart failure are to slow or reverse cardiac remodeling, thus prolonging the patient's life, as well as to improve the patient's overall quality of life. Therapies most frequently used for the outpatient treatment of heart failure include diuretics, angiotensin-converting enzyme (ACE) inhibitors, digoxin, and more recently β-blockade.[2] Once contraindicated, the use of β-blockers in mild to moderate heart failure is now strongly advocated by ACTION HF (Action of Heart Failure) Consensus Recommendations and the Heart Failure Society of America (HFSA) Practice Guidelines.[2]

A novel treatment modality being investigated for the treatment of heart failure is enhanced external counterpulsation (EECP). Although EECP is known to decrease symptoms in patients with angina, its role in the treatment of patients with heart failure has only recently been investigated. The purpose of this article is to describe the current role of EECP for the treatment of heart failure.

WHAT IS EECP?

EECP is a noninvasive, outpatient therapy consisting of ECG-gated sequential leg compression, which produces hemodynamic effects similar to those of an intraaortic balloon pump (IABP). Unlike IABP, however, EECP also increases venous return. A computer-controlled pneumatic system acts to inflate and deflate a series of compressive cuffs enclosing the lower extremities and but-

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tocks. Inflation and deflation are triggered by events in the cardiac cycle through microprocessor-interpreted electrocardiographic signals. A finger plethysmogram is used throughout treatment to monitor diastolic and systolic pressure waveforms. A typical treatment course consists of 35 treatments administered as 1-hour a day over 7 weeks.

EFFICACY AND SAFETY OF EECP FOR ANGINA IN SEVERE LEFT VENTRICULAR DYSFUNCTION

EECP has been shown to improve both angina and stress myocardial perfusion in patients with coronary artery disease (CAD).[3–15] However, a primary concern is that the increased venous return resulting from EECP could precipitate pulmonary edema in angina patients with severe left ventricular dysfunction (LVD) or an exacerbation of heart failure in patients experiencing angina who have a history of heart failure. Strobeck et al. evaluated the safety and efficacy of EECP in patients with angina and severe LVD (ejection fraction [EF] $<35\%$).[16] The outcomes of EECP treatment were followed in 466 patients enrolled in the International Enhanced External Counterpulsation Registry (IEPR), an international multicenter study of EECP for the treatment of patients with chronic angina.[16] EECP was observed to be a safe and effective treatment of angina in patients with severe LVD who were not considered good candidates for revascularization by coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI). Importantly, there was a significant reduction in Canadian Cardiovascular Association angina class, and quality of life improved approximately 70% for all patients completing treatment. The magnitude of improvement in angina classification and quality of life produced by EECP was observed to be independent of the degree of LVD before treatment.[16] These benefits were maintained for at least 2 years after EECP treatment.[17,18]

Lawson et al. also used the International EECP Registry to examine the benefit and safety of EECP treatment in patients with a history of congestive heart failure. A total of 1957 patients, 548 with a history of heart failure, were followed for 6 months after receiving EECP therapy. The heart failure cohort consisted of an older patient population with a greater duration of CAD and higher frequency of prior infarcts and revascularizations. Although exacerbation of heart failure was more frequent in patients with a history of heart failure, the incidence of major adverse cardiac events (eg, death, myocardial infarction, revascularization) during treatment was not significantly different between groups. Notably, the angina class improved in 68% with a comparable quality-of-life benefit in the heart failure patient group. At 6 months, patients with heart failure maintained their reduction in anginal symptoms but were more likely to experience an adverse cardiac event.[19] Factors predisposing to the development of heart failure during the EECP treatment course include female gender, a history of heart failure, low ejection fraction, and diabetes.[20]

Lawson et al. evaluated refractory angina patients with preserved left ventricular function ([PLV]; EF $>35\%$) and with severe left ventricular dysfunction ([SLVD]; EF $\leq 35\%$) who were treated with a 35-hour course of EECP. Bioimpedance measurements of cardiovascular function were obtained before the first and again after the 35th hour of EECP. Twenty-five patients were enrolled, 20 with PLV and 5 with SLVD. Angina class improved similarly in both groups. The SLVD group, in contrast to the PLV group, increased cardiac power, stroke volume, and cardiac index and decreased systemic vascular resistance with treatment. This study suggests that EECP could benefit patients experiencing CAD with SLVD directly by improving cardiac power and indirectly by decreasing SVR.[21]

EFFICACY AND SAFETY OF EECP IN HEART FAILURE

Most of the data on efficacy and safety of EECP in heart failure is from small studies.

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A pilot study of clinically stable patients diagnosed with mild to moderate heart failure (NYHA class II or III) and a left ventricular ejection fraction (LVEF) <35% found EECP treatment to be safe with no unexpected adverse events during the application of EECP treatment.[22] A multicenter feasibility study, in which stable heart failure (New York Heart Association class II–III) patients with LVEF <35% were treated with 35 1-hour sessions of EECP therapy over a 7-week period and followed over a 6-month period demonstrated that EECP was safe and well-tolerated in this group of patients. In addition, EECP was associated with significant improvements in exercise capacity as measured by peak oxygen uptake and exercise duration and in quality of life at 1 week and 6 months after EECP treatment. Although safety was the primary end point of this feasibility study, the efficacy results suggest that EECP can increase peak oxygen uptake, improve exercise capacity and functional status, as well as the patient's quality of life, for both the short-term and long-term (6 months) after the completion of EECP therapy. Study subjects benefited from EECP to a similar degree regardless of ischemic or nonischemic etiology of their heart failure.[15]

To test the hypothesis that EECP could have beneficial effects on LV function in patients with heart failure, Gorcsan et al. studied the effects of EECP on LV function in patients with NYHA class II or III heart failure with an LVEF <35%.[23] Preload-adjusted maximal power (PAMP) was assessed as a relatively load-independent measure of LV performance before and after EECP treatment consisting of 35 1-hour sessions over a 7-week period. Pressure volume relationships were simultaneously estimated using echocardiographic automated border detection as a surrogate for LV volume and photoplythesmography as a surrogate for LV ejection pressure to calculate PAMP noninvasively. PAMP was calculated using the following equation:

$$(\text{pressure} \times \text{flow}) / (\text{end-diastolic area}).[24]$$

EECP was associated with a significant improvement in LV function, as measured by increases in both PAMP and LVEF, as well as a significant decrease in heart rate. In addition, these beneficial effects were sustained for 6 months after EECP therapy. Thus, preliminary data shows that EECP improves LV function in patients experiencing heart failure and could be a useful adjunct to medical therapy in these patients.[23]

MECHANISM OF EECP

On diastole, cuffs inflate sequentially from the calves, raising diastolic aortic pressure proximally and increasing coronary perfusion pressure. Compression of the vascular beds of the legs also increases venous return. Instantaneous decompression of all cuffs at the onset of systole significantly unloads the left ventricle, thereby lowering vascular impedance and decreasing ventricular workload. This latter effect, when coupled with augmented venous return, raises cardiac output. In summary, EECP increases venous return, raises cardiac preload, increases cardiac output, and decreases systemic vascular resistance.[25,26]

Mode of action studies have shown that EECP increases angiogenesis factors such as hepatocyte growth factor, vascular endothelial growth factor, and basic fibroblast growth factor. Enhanced diastolic flow increases shear stress, increased shear stress activates the release of growth factors, and augmentation of growth factor release activates angiogenesis[27] (Fig. 1).

In addition, EECP improves endothelial function and enhances vascular reactivity. Like athletic training, the vascular effects of EECP can be mediated through changes in the neurohormonal milieu. Wu et al. showed that EECP therapy has a sustained, dose-related effect in stimulating endothelial cell production of the vasodilator nitric oxide (NO) and in decreasing production of the vasoconstrictor endothelin (ET-1).[28] Qian et al. showed in another study that the NO level

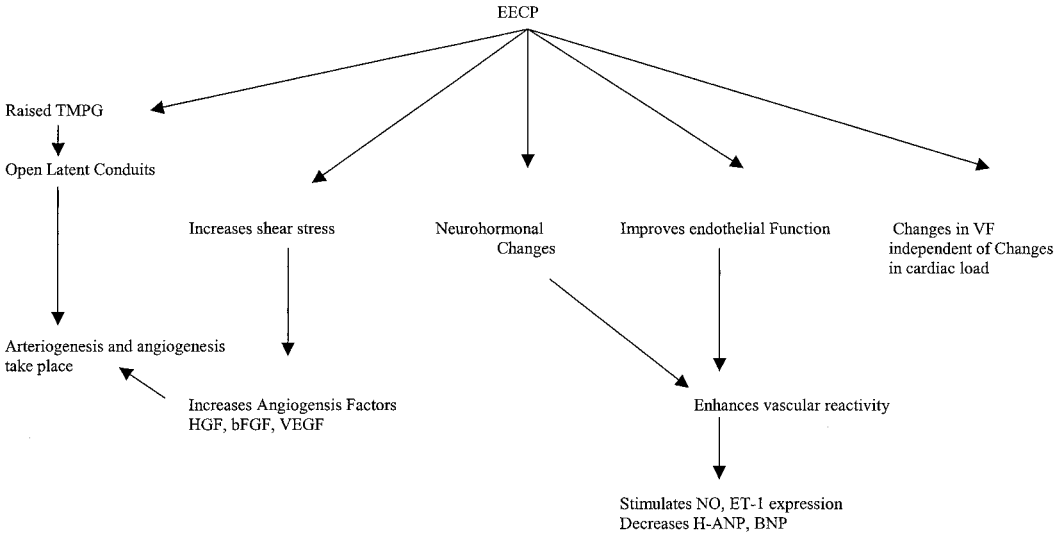

FIGURE 1. Mechanism of enhanced external counterpulsation.

increased linearly in proportion to the hours of EECP treatment.[29]

Masuda et al. demonstrated that EECP therapy increased myocardial perfusion and enhanced dipyridamole-induced coronary vasodilation. On exercise testing, the time to 1-mm ST-segment depression was increased significantly with a similar trend in exercise duration. NO levels measured at rest were increased, whereas human atrial natriuretic peptide and brain natriuretic peptide levels were decreased after the course of EECP treatment.[8]

Urano et al. further showed that plasma brain natriuretic peptide levels decreased after EECP and were positively correlated with LV end diastolic pressure and negatively correlated with peak filling rate. They concluded that EECP reduces exercise-induced myocardial ischemia in association with improved LV diastolic filling in patients with CAD.[7]

Another possible mechanism to explain the mode of action of EECP is that it could effect changes in ventricular function independent of changes in cardiac load. Gorscan et al. evaluated the effects of EECP on left ventricular function in patients with class II or III heart failure with an EF $<40\%$.[23] Their results showed that EECP treatment was associated with improvements in PAMP, a relatively load-independent measure of LV performance and EF, along with a decrease in heart rate in these patients experiencing heart failure.

FOOD AND DRUG ADMINISTRATION-CLEARED INDICATION

Labeled indications for the use of EECP include treatment of patients with congestive heart failure, stable or unstable angina pectoris, acute myocardial infarction, or cardiogenic shock.

WHICH GROUP OF PATIENTS EXPERIENCING HEART FAILURE COULD BENEFIT FROM EECP?

1. Patients with stable heart failure; NYHA class II, III (patients with any evidence of decompensation should not be treated until they are stable with the use of medical therapy).

2. Patients with ischemic or idiopathic cardiomyopathy.

3. Patients in stable condition with manageable peripheral edema.

4. Patients with LVD (EF $<35\%$).

5. Patients with heart failure and other comorbid states that increase their surgical risks such as diabetes or pulmonary disease.

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SUGGESTIONS TO FOLLOW DURING THE TREATMENT OF PATIENTS EXPERIENCING HEART FAILURE

1. Verify that the subject is in stable condition.

2. Obtain vital signs.

3. Initiate pulse oximetry measurements and record oxygen saturation.

4. Initiate EECP treatment. Raise the applied treatment pressure to the recommended level (approximately 260 mm Hg) within 5 minutes.

5. Record a during-session plethysmography tracing.

6. Record oxygen saturation every 20 minutes. Discontinue treatment if the oxygen saturation decreases by 3% or more from the initial measurement and the patient begins to experience symptoms of fluid in the lungs.

7. Terminate the session 60 minutes after initiating the application of the device.

CONCLUSION

Studies show that EECP is a promising new therapy for the treatment of heart failure. EECP has been demonstrated to improve myocardial perfusion, angina symptoms, exercise tolerance, and quality of life in patients with CAD. In addition, EECP has been proven to be safe and effective in patients with angina and severe LVD. Although more data from prospective, randomized, controlled trials are needed, early studies suggest EECP increases exercise capacity by increasing peak oxygen uptake and exercise duration, improves functional status, and improves quality of life in patients with heart failure. Currently, a multicenter, prospective, randomized, controlled clinical trial (*P*rospective *E*valuation of *E*ECP in *C*ongestive *H*eart Failure [PEECH]) is ongoing to verify the efficacy of EECP as an adjunctive therapy in the management of patients with chronic stable heart failure.

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