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Reviews

An Update on Enhanced External Counterpulsation

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Summary

The development of advanced revascularization techniques has resulted in the growth of a subset of patients with coronary artery disease who are nonrevascularizable and are considered to have refractory angina. Enhanced external counterpulsation (EECP) has been developed for the management of these patients with chronic, refractory disease. Evidence has shown that through improvement of vascular endothelial function and recruitment of collateral vessels, EECP provides many clinical benefits. These patients experience sustained decreases in angina, improvement in exercise time, improved myocardial perfusion, and enhanced quality of life. Furthermore, EECP appears to be safe and effective in the treatment of angina in patients with impaired systolic function and has similar potential in patients with congestive heart failure.

Key words: angina pectoris, refractory angina, enhanced external counterpulsation

Introduction

The growth of a population of patients who have persistent angina despite multiple surgical or interventional procedures and optimal medical management has incited efforts to develop new treatment methods. With these nonrevascularizable patients with refractory angina in mind, the concept of counterpulsation has been revisited. In 1983, a model of enhanced external counterpulsation (EECP) was developed in China based on experience involving over 6,000 patients with angina. This was the basis for the current technique of EECP, involving electrocardiographic-gated, sequentially inflated pneumatic compression cuffs.[1–3]

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Enhanced External Counterpulsation Technique

Currently, EECP consists of three pneumatic compression cuffs applied to each of the patient's legs. The mechanism is synchronized with the patient's electrocardiogram such that with each cardiac cycle pressure is sequentially applied distally to proximally in early diastole, resulting in an increase in diastolic blood pressure (diastolic augmentation) and retrograde aortic diastolic blood flow. At end diastole, pressure is released simultaneously from all cuffs, resulting in systolic unloading and afterload reduction. The degree of hemodynamic effect is monitored by the ratio of systolic to diastolic pressures, monitored by finger plethysmography. A usual course of EECP treatment consists of 35 one-hour sessions.

Immediate Effects

The mechanism by which EECP transmits its hemodynamic effect is similar to an intra-aortic balloon pump (IABP). The degree of diastolic augmentation produced is comparable with that of IABP. However, EECP also increases venous return and cardiac preload through the compression of capacitance veins, leading to increased right atrial pressure, pulmonary capillary wedge pressure, cardiac index, and cardiac output.[4] In addition, other noninvasive studies have shown increased stroke volume and cardiac output, decreased systemic vascular resistance, and relative bradycardia.[5,6]

Physiologic Effects of Enhanced External Counterpulsation

Catheterization performed during EECP has demonstrated augmentation of the diastolic aortic pressure resulting in increased intracoronary diastolic peak pressure (93%) and mean pressure (16%). Intracoronary Doppler studies also showed an increase in peak velocity (150%). Correspondingly, the corrected Thrombolysis In Myocardial Infarction (TIMI) frame count on angiography revealed a 28% increase in coronary flow. In addition, these studies confirmed that systolic unloading results in decreased peak intracoronary systolic pressure (15%) and peak aortic systolic pressure (11%), lowering left-ventricular (LV) afterload.[7]

Patients who achieve greater diastolic augmentation obtain greater reduction in angina class[8,9] and greater improvement of wall motion abnormalities on dobutamine stress echocardi-

ography following EECP.[10] On this basis, it has been hypothesized that EECP may recruit preformed collaterals, resulting in improved myocardial perfusion. Correspondingly, canine studies have shown an increase in femoral collateralization following external counterpulsation.[11]

Reactive hyperemia-peripheral artery tonometry (RH-PAT), a measure of peripheral arterial endothelial function, detects pulsatile arterial volume changes following the induction of reactive hyperemia. Assessment of RH-PAT in patients with refractory angina demonstrates impaired endothelial function prior to the initiation of EECP. Following each session of EECP, there was an acute increase in the average RH-PAT index. There was also a sustained increase in the average RH-PAT index at 1 month after completion of EECP, indicating improvement of endothelial function. Moreover, there was a correlation between increased RH-PAT index and improvement in average Canadian Cardiovascular Society (CCS) angina class and functional capacity.[12]

Similar results were demonstrated by flow-mediated vasodilatation (FMD), measured by Doppler ultrasound of the brachial artery in response to induction of sudden increased flow by release of a pneumatic tourniquet. Findings of increased FMD from baseline ($1.7 \pm 0.1\%$) immediately following a 7-week course of EECP were not seen in a control group ($0.1 \pm 0.1\%$), suggesting improved vascular endothelial function. This study also demonstrated no increase in FMD following administration of exogenous nitric oxide (NO), suggesting improved endothelial function to be related to endogenous production of and improved endothelial response to NO.[13] Furthermore, ^{13}N-ammonia positron emission tomography (PET) has demonstrated improved myocardial perfusion at rest and in response to dipyridamole and NO in patients with angina following a course of EECP.[14]

Further supporting an effect on endothelial function, a patient with angina demonstrating recurrent, objective findings of cardiac ischemia was treated with a course of EECP. Diagnostic workup demonstrated structurally normal coronary arteries and coronary spasm. Intracoronary adenosine administration resulted in normal endothelium-independent microvascular response and flow reserve. With infusion of graded acetylcholine, an endothelium-dependent vasodilator, angiography demonstrated paradoxically decreasing coronary blood flow and coronary occlusion with accompanying angina, consistent with endothelial dysfunction. Despite maximal medical therapy, the patient experienced worsening symptoms consistent with CCS class IV angina. Due to refractory symptoms, the patient underwent a course of EECP. At completion of treatment the patient was asymptomatic and remained so at 3-month follow-up.[15]

The mechanism by which EECP improves endothelial function remains largely unknown. The most prominent theory is that regulation of factors affecting endothelial function is modulated by arterial shear forces that are increased by diastolic augmentation.[7, 16] Fluid shear stresses have been shown to induce phosphorylation and activation of endothelial NO synthetase and thus induce arterial vasodilatation.[17, 18] This is especially marked in patients with coronary artery disease (CAD) who have low baseline NO levels. Immediately and 1 month following a course of EECP, NO levels are significantly increased.[14, 19]

Coronary shear stress and mechanical pressure, as provided by EECP, also reduced the release of endothelin-1, a potent arterial vasoconstrictor and smooth muscle mitogen;[19] however, in experimental models, mechanical forces have had variable effects on endothelin release.[20–22]

Shear forces may also enhance the production of angiogenic factors, thus enhancing collateral vessel formation. Among patients with chronic stable angina, there was a demonstrable increase in basic fibroblast growth factor, vascular endothelial growth factor, and hepatocyte growth factors following a course of EECP.[23]

Clinical Outcomes

The Multicenter Study of Enhanced External Counterpulsation (MUST-EECP) trial was the first prospective, randomized, blinded, sham-controlled trial of EECP in the management of 139 patients with chronic stable angina and a positive exercise treadmill test. Although there was no significant difference in exercise duration or decrease in sublingual nitroglycerin use, more patients receiving active counterpulsation reported a > 50% improvement in the number of anginal episodes, and there was a significant improvement in the time to ST-depression on stress testing following EECP.[24]

In addition to objective measures of ischemia, participants in the MUST-EECP trial provided information on health-related quality of life (HQOL) at baseline, at the end of treatment, and at 1 year. The HQOL data demonstrated significant improvements in both cohorts with a trend toward greater improvement in those who received active counterpulsation. At 1-year follow-up, the HQOL scores for bodily pain, social functioning, and cardiac-specific health and functioning showed greater improvement in the group that received active counterpulsation.[25]

Another long-term follow-up study evaluated 1,097 patients from the International EECP Patient Registry (IEPR). Immediately following EECP, 73% of patients improved by at least one CCS angina class, and the number of patients with CCS Class III or IV angina decreased from 86.9 to 26.8%. Improvement of angina by at least one CCS class (74.9%) and decrease in the percentage of patients with class III or IV angina (24.1%) was maintained at 2-year follow-up. There were also improvements in weekly anginal episodes and sublingual nitroglycerin use. In addition, health status, quality of life, and satisfaction with life improved in 54.5, 53.2, and 57.8% of patients, respectively, and were maintained at 2-year follow-up.[26]

In another cohort of 1,532 patients from the IEPR, data on angina class, cardiac events, and quality of life were determined for 1 year following EECP. Comparison of those with and without diabetes mellitus (DM) revealed that those with DM were more likely to have a history of congestive heart failure, noncardiac vascular disease, and were less likely to be a candidate for revascularization. Outcomes demonstrated a similar percentage of patients with improvement of angina by

at least 1 CCS class immediately following EECP in nondiabetic (72%) and diabetic (69%) groups. At 1 year, although there were more episodes of death and congestive heart failure in the DM group, there was maintenance of reductions in angina class, angina episodes, sublingual nitroglycerin use, and improvement in quality of life measured by the Likert scales.[27]

Improvement of cardiac perfusion by EECP has been further demonstrated by stress cardiac imaging. Fifty patients with exercise-induced, reversible radionuclide perfusion defects were stratified by number of involved coronaries on angiography and underwent EECP followed by repeat radionuclide stress testing. All patients reported a decrease in angina symptoms following treatment. Radionuclide imaging demonstrated that response was best in patients with one (95%) or two (90%) coronary arteries affected compared with those with triple-vessel (42%) disease. Finding that a patent vessel is required for achieving reliable benefits from EECP supports the hypothesis that development of collaterals is one mechanism by which such patients experience improved myocardial perfusion and clinical benefit.[28]

Another study evaluated radionuclide perfusion treadmill stress testing in 175 patients refractory to medical therapy and ineligible for further revascularization procedures. Results showed 85% of patients reporting an improvement by at least one CCS angina class and 15% with improvement by two or more CCS angina classes following EECP. At the same level of exercise, 83% of patients had improvement in radionuclide perfusion defects. Patients who underwent maximal treadmill stress testing showed a significant improvement in exercise duration, without significant change in the double product.[29] Another analysis found that 93% of patients had improvement in CCS angina class following EECP, with a significant increase in average exercise time on maximal stress testing from 5.95 ± 1.55 to 7.48 ± 1.62 min. Of patients who had ST-segment depression, 80% had no ST-depression or increased time to ST-depression on stress testing following EECP.[30]

Patients have also been evaluated for myocardial perfusion by dobutamine stress echocardiography. Twenty-three patients with CAD and a dobutamine stress echocardiogram demonstrating inducible ischemia were treated with EECP. Stress echocardiograms before and after EECP were evaluated for regional wall motion abnormalities of the contractile function of each of 16 segments of the left ventricle, resulting in a wall motion score between 16 and 64. Following EECP, 43% of patients with positive dobutamine stress echocardiograms had normal tests or wall motion score improved by at least two points.[10]

In evaluating EECP as primary intervention, angina symptoms and major cardiac events were evaluated in 323 patients from the IEPR who were candidates for percutaneous coronary intervention (PCI) and 448 patients who underwent PCI. At baseline, candidates for PCI undergoing EECP were more likely to be male and had more severe disease (i.e., congestive heart failure, previous PCI, or coronary artery bypass graft [CABG], or prior myocardial infarction) than did patients who underwent PCI. Survival rates at 1 year were similar in the group of patients treated with EECP (98.7%) and those who underwent PCI (96.8%). However, the PCI group had greater improvement in angina and there was a greater proportion of patients achieving complete resolution of symptoms: 73.4 versus 43.7% in the EECP group. The proportion of patients with no anginal symptoms 1 year after treatment was also significantly greater in the PCI group. It was observed that patients treated with EECP also had improvements in CCS angina class, and there was a resolution of angina in a number of patients.[31]

Congestive Heart Failure

As EECP has been more seriously considered as a viable treatment for reduction of symptoms in patients with refractory stable angina, the feasibility of using it in other populations has been considered.

Initial studies using EECP demonstrated safety in congestive heart failure from the theoretical risk of acutely increasing preload and precipitating pulmonary edema. Analysis of baseline characteristics has shown that patients with impaired LV function tended to have more severe angina and other comorbidities than patients without impaired ventricular function. Accordingly, these patients had more adverse events during and following EECP. However, assessment of major adverse event rates demonstrated that most events were related to underlying illness rather than to treatment. These preliminary studies observed the effects of EECP on ventricular function rather than on angina and demonstrated improved Canadian Functional Class, Minnesota score of quality of life, peak oxygen consumption, and treadmill time following EECP; these improvements were maintained at 6 months. Enhanced external counterpulsation was determined to be safe and effective in the treatment of heart failure, justifying further studies.[32, 33] Other studies comparing echocardiography in a small number of patients with class II–III heart failure demonstrated improvement in ejection fraction and preload adjusted maximal power following EECP, a measure of the maximal hydraulic power generated by the left ventricle.[34, 35]

In addition to using EECP in treating heart failure, utility in the management of angina in patients with ventricular dysfunction has been evaluated. In all, 312 patients from the IEPR with moderately reduced LV ejection fraction were compared with those with preserved LV systolic function post EECP and after 6 months. Similar to other studies comparing equivalent populations, patients with reduced ejection fraction had more severe disease prior to therapy, including more with prior congestive heart failure, myocardial infarction, longer history of CAD, and more severe baseline angina. Immediately following EECP, both groups showed considerable improvement. However, there were more patients in the group without LV systolic dysfunction who improved by at least one CCS angina class (76.2 vs. 67.8%). A similar percentage of patients in each group discontinued sublingual nitroglycerin. There was a higher rate of major events in the follow-up period including congestive heart failure exacerbation (9.9 vs. 3.7%), death (9.3 vs. 2.2%), and composite outcome of death, myocardial infarction, CABG, and PCI (15.4 vs. 8.3%) in patients with LV systolic dysfunction. There was no significant difference in the

percentage of patients who maintained improvement in angina at 6 months. Thus, patients with LV systolic dysfunction did demonstrate an improvement, although not as substantial as patients with preserved systolic function, and improvement was maintained in both groups at 6 months.[36] The results from a prospective, randomized study in patients with heart failure and cardiomyopathy (Prospective Evaluation of EECP in Congestive Heart Failure [PEECH] study) are awaited.

Conclusion

As advancements in revascularization techniques continue, there will likely be a continued growth in a population of patients who have undergone several revascularization procedures and have persistent disease. This population of patients with chronic, stable angina who are not eligible for further revascularization is left with few treatment options. Enhanced external counterpulsation appears to be a safe method of treatment for patients with normal and those with reduced LV systolic function. Furthermore, it has been associated with improvement in angina, longer exercise duration, and improved quality of life, sustained for up to 2 years following the treatment course.

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