EECP Symposium

Acute hemodynamic effects of enhanced external counterpulsation

Bhavananda T. Reddy, Andrew D. Michaels

Department of Medicine, Division of Cardiology, University of Utah, Salt Lake City, Utah, United States.

Key Words Enhanced external counterpulsation; diastolic augmentation; hemodynamics; angina; heart failure.

Introduction

In the United States, there are about 17.6 million patients suffer from symptomatic coronary artery disease (CAD), affecting 7.9% of adults ≥ 20 years of age. An estimated 10.2 million patients have angina, and 500,000 patients will develop new angina pectoris each year. A subset of angina patients are categorized as refractory when symptoms continue despite optimal medical therapy and revascularization. Routine daily activities become impossible without experiencing chest pain in this patient population.

Heart failure is a most common diagnosis in Medicare patients and nearly 5 million Americans are diagnosed with heart failure and nearly 550,000 new cases are reported every year. Despite maximal medical therapy, many patients continue to be symptomatic and restrict their activities and anticipate a reduced life expectancy.

Several non-pharmacological treatment options are available for these patients with refractory angina, including neurostimulation, enhanced external counterpulsation (EECP), transmyocardial laser revascularization, gene therapy, percutaneous in situ coronary venous arterializations, and percutaneous in situ coronary artery bypass. Of these options, EECP therapy is the only Food and Drug Administration (FDA)-approved noninvasive technique proven to reduce angina symptoms, improve objective measures of myocardial ischemia, and improve left ventricular systolic and diastolic function.

Historical perspective

Researchers at Harvard University conducted experiments with external counterpulsation about one-half century ago showing that this technique significantly reduced cardiac workload and thus left ventricular oxygen consumption. In 1953, Kantrowitz and Kantrowitz described diastolic augmentation as a means of improving coronary blood flow. Initially, external counterpulsation was given through hydraulic-driven water-filled chambers that squeezed the lower extremities. These research programs investigated the utilization of these devices in patients with acute ischemic heart disorders, specifically cardiogenic shock and acute myocardial infarction. Soroff was the first investigator who applied external counterpulsation in man. Among 20 patients with cardiogenic shock treated with external counterpulsation, the mortality rate of 65% was reported to be lower than contemporary rates for those treated with an intra-aortic balloon pump (IABP). It was felt that these early external counterpulsation devices improved hemodynamics and myocardial metabolism in cardiogenic shock, but was not powerful enough to fully reverse shock hemodynamics.

Early external counterpulsation devices were evaluated in patients with acute myocardial infarction. External counterpulsation appeared to prevent the hypotension caused by nitroprusside vasodilator therapy, providing left ventricular systolic unloading pharmacologically while maintaining coronary perfusion by external counterpulsation. In a large multicenter study of 258 patients with acute myocardial infarction, patients were randomized to external counterpulsation within 24 hours of presentation or usual care. Patients assigned to the external counterpulsation group had a trend toward lower hospital mortality rate (8.4%) compared with controls (14.7%; P=NS). Patients in the external counterpulsation group had lower rates of recurrent chest pain, progression of heart failure (HF), ventricular fibrillation, and improved cardiac functional status at discharge.

However, there were significant limitations of these early external counterpulsation devices. First, the water-driven leg compression bags were not powerful enough to result in effective systolic unloading. In direct comparisons between IABP and external counterpulsation, the latter did not lower systolic pressure. Studies of cardiac metabolism showed that IABP decreased myocardial oxygen consumption resulting in improved myocardial metabolism, whereas external counterpulsation increased oxygen consumption. In studies measuring coronary sinus blood flow and changes during atrial pacing stress testing, external coun-
terpulsation had no acute beneficial metabolic or hemodynamic effects. There are no clinical trials to date have evaluated the efficacy of the pneumatic-driven EECP device in patients with acute coronary syndrome or cardiogenic shock.

**Acute hemodynamic effects of enhanced external counterpulsation**

Various authors have assessed acute hemodynamic effects of EECP through both noninvasive (finger plethysmography, thoracic electrical bioimpedance, echocardiography, and radial tonometry) as well as invasive (right heart catheterization, radial artery catheterization, intracoronary pressure and Doppler flow, and simultaneous right and left heart catheterization techniques).

A study published by Taguchi et al. assessed the hemodynamic effects of EECP and compared it with IABP in 39 patients with uncomplicated acute myocardial infarction who underwent successful balloon coronary angioplasty within 12 hours after onset of chest pain. The radial artery and subclavian vein were cannulated to measure right atrial pressure, pulmonary capillary wedge pressure (PCWP), cardiac index, and systemic vascular resistance. Radial artery pressure tracing was used to measure area under arterial pressure curves in systolic and diastolic phases.

Sixty minutes treatment was administered to the patients in the EECP group. All parameters were measured before EECP, at 15, 30, 45, and 60 minutes after starting EECP, and 60 minutes after stopping EECP. After starting IABP support, measurements were obtained at 15, 30, 45, and 60 minutes.

There were no significant changes in heart rate in either group before, during, and after treatments. Right atrial pressure increased significantly at 15 and 30 minutes after starting EECP, and then decreased gradually. There was no significant increase in right atrial pressure at 45 and 60 minutes after starting EECP compared with baseline. Right atrial pressure did not change in the IABP group, and there was no significant difference between 2 groups, except at 15 minutes after starting treatment.

In the EECP group the PCWP significantly increased at 15 and 30 minutes, and then decreased gradually, but no significant change was seen in IABP group. Between two groups, there were no significant differences at baseline and during treatment. However, 60 minutes after stopping treatment, PCWP was significantly lower in the EECP group. The cardiac index in EECP group increased significantly at 45 and 60 minutes compared with the baseline, but no significant change was noted in IABP group. The increase in cardiac index at 60 minutes in the EECP group was significantly greater than that in the IABP group.

Mean values of the area under the arterial pressure curves during the diastolic phase increased significantly in both groups, and there was no significant difference between two groups at any measuring point. Mean values of the areas under the artery pressure curves during the systolic phase decreased significantly during treatment compared with baseline in the IABP group. No significant change was observed in the EECP group. In both groups, systemic vascular resistance decreased significantly during treatment compared with baseline, but no significant difference was seen between two groups.

In summary, this study showed that the hemodynamic effects of EECP were similar to those of IABP for diastolic augmentation (DA) and systemic vascular resistance. However, right atrial pressure, PCWP, and cardiac index increased during EECP in contrast to IABP. These effects suggest that EECP increases venous return, raises cardiac preload, and increases cardiac output.

In 2004, Taguchi et al. reported both hemodynamic as well as neurohormonal changes during EECP. They have performed 60 minutes of EECP in 24 stable acute myocardial infarction patients who underwent success percutaneous coronary intervention (PCI). Right heart catheterization and neurohormonal parameters were assessed before, during 15, 30 and 60 minutes after EECP. Blood levels of atrial natriuretic peptide (ANP), brain (or B type) natriuretic peptide (BNP), renin, aldosterone, dopamine, and noradrenaline were assessed. Left ventricular ejection fraction (LVEF) and size were assessed invasively during the admission and between days 13 to 16.

Cardiac index increased from $3.3 \pm 0.8$ L/min before treatment to $4.1 \pm 0.8$ L/min at 60 minutes ($P<0.01$). Right atrial pressure increased from 6.4 ± 3.3 mmHg at baseline to 9.8 ± 4.0 mmHg at 15 minutes ($P<0.01$), and PCWP increased from 8.9 ± 4.0 mmHg to 12.6 ± 5.3 mmHg ($P<0.05$). The blood levels of ANP increased from 54 ± 42 pg/ml at baseline to 70 ± 46 pg/ml at 60 minutes, which returned to baseline level 60 minutes after EECP treatment. The pre-treatment concentrations of BNP, dopamine, noradrenaline, renin and aldosterone did not change during or after EECP treatment. Left ventricular end-diastolic pressure (LVEDP) decreased from 18.6 ± 1.6 mmHg during the acute stage to 13.8 ± 6.4 mmHg during subacute follow-up, but there was no change in LVEF or end-diastolic volume (EDV) index.

Blood concentrations of ANP increased at 15 minutes after initiation of EECP, which suggested that EECP treatment increased the volume of venous return, resulting in an increased atrial load. EECP significantly improved cardiac index with a significant increase in blood ANP concentration but without increase in heart rate (HR) or BNP. These findings suggest that there is an increased atrial preload without any significant change in ventricular preload.

The study published by Michaels and colleagues in 2002 used an invasive approach to measure intracoronary, central aortic, and left ventricular pressure and intracoronary Doppler flow to assess the acute hemodynamic effects of EECP. Ten patients who were referred for cardiac catheter-
ization (5 with suspected coronary artery disease, 3 with severe mitral regurgitation, and 2 with heart transplant patients) were included in the study. Key exclusion criteria included severe aortic insufficiency, decompensated heart failure, significant arrhythmia, systolic blood pressure more than 180 mmHg, and symptomatic peripheral arterial disease. EECP was performed at external cuff pressures ranging from 100 to 300 mmHg. At baseline and during EECP, simultaneous central aortic and intracoronary pressure, intracoronary Doppler flow velocity, and corrected thrombosis in Myocardial Infarction study (TIMI) frame count (CTFC) were measured.

Peak aortic systolic pressure decreased 11% from 114 ± 19 mmHg at baseline to 101 ± 28 mmHg during EECP (P=0.02). These findings indicate that EECP acutely reduces ventricular afterload. LVEDP decreased during EECP (15 ± 7 mmHg at baseline, 13 ± 6 mmHg during EECP; P=0.17). Aortic diastolic pressure increased 92% from 71 ± 10 mmHg to 136±22 mmHg (P<0.0001), and mean aortic pressure (MAP) increased 16% from 88 ± 10 mmHg to 102 ± 14 mmHg during EECP (P=0.0007), indicating significant.

Intracoronary pressure was measured in an unobstructed epicardial coronary artery using the micromanometer-tipped 0.014-inch pressure wire. There was a 93% increase in intracoronary peak diastolic pressure (71 ± 10 mmHg at baseline to 137±21 mmHg during EECP; P<0.0001; Fig 1).

![Representative simultaneous hemodynamic tracings of central aortic pressure from the coronary catheter and intracoronary pressure from the PressureWire.][22] In tracings of both phasic and mean pressure (bottom) obtained at the beginning of EECP (A), there is a gradual increase in peak diastolic (dashed arrows) and mean pressure with a decrease in peak systolic pressure (solid arrows) attributable to systolic unloading as the inflation pressure is increased in the EECP device. In another patient, diastolic augmentation (DA) is demonstrated during EECP at a cuff pressure of 300 mmHg (B). The intracoronary coronary pressure was 5 mmHg lower than central aortic pressure, attributable to diffuse coronary atherosclerosis. The paper speed is 25 mm/sec. (Reproduced with permission).
Mean pressure increased by 16% from 88 ± 9 mmHg at baseline to 102 ± 16 mmHg during EECP (P=0.006). EECP decreased peak systolic pressure by 15% from 116 ± 20 mmHg at baseline to 99 ± 26 mmHg during EECP (P=0.002). Planimetry of the intracoronary pressure tracings showed a 28% increase in diastolic pressure (42 ± 9 mmHg · sec at baseline; 54 ± 15 mmHg · sec during EECP; P=0.0003) and a 12% decrease in systolic pressure (33 ± 6 mmHg · sec at baseline; 29 ± 7 mmHg · sec during EECP; P=0.008).

Intracoronary Doppler flow velocity was measured using a 0.014-inch FloWire (Fig 2). The average peak velocity (APV) increased 109% from 11 ± 5 cm/s at baseline to 23 ± 5 cm/s during EECP (P=0.001). The peak diastolic velocity increased 150% from 18 ± 7 cm/s at baseline to 45 ± 14 cm/s during EECP (P=0.0004). The diastolic-to-systolic velocity ratio (DSVR) increased 100% from 1.0 ± 0.3 to 2.0 ± 0.7 during EECP (P=0.003). There was no significant change in peak systolic velocity. The CTFC, another measure of coronary flow velocity, significantly decreased 28% from 37 ± 18 at baseline to 27 ± 13 during EECP (P=0.001).

This study provides solid evidence of the increase in directly measured aortic and coronary diastolic pressure and flow velocity from EECP DA. There is a significant reduction in LV afterload and left ventricle (LV) work secondary to systolic unloading. Hemodynamic effects of this EECP study are roughly comparable to the data reported in a study of IABP (Table 1). An important difference in these studies being, IABP study examined critically ill patients in cardiogenic shock where as this EECP study enrolled stable outpatients who were referred for elective catheterization. It is likely that EECP may displace more blood compared with 30 to 40 ml displaced by IABP.

In 2009, Michaels et al. described acute changes in invasive left ventricular energetics during EECP using left ventricular pressure-volume conductance catheter technique. The main goals of this study included 1) assessment of left ventricular contractility, diastolic function, and mechanical efficiency during EECP, and 2) assessment of the contribution of inflation cuff pressure, and 3) examination of the roles of four lower extremity cuff combinations. Ten patients who were referred for right and left heart catheterization were enrolled in this study. The right internal jugular vein and right radial artery were used for right and left heart catheterization.

Invasive hemodynamics were recorded at baseline and during five different external cuff inflation pressure levels (80, 160, 260 and 300 mmHg) and four different cuff combinations (calf cuff only, calf and lower thigh cuffs termed 2-cuff low; lower and upper thigh termed 2-cuff high, and all 3 cuffs). At each setting, central aortic pressure was

<table>
<thead>
<tr>
<th>Variable</th>
<th>EECP</th>
<th>IABP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic pressure</td>
<td>92%</td>
<td>80%</td>
</tr>
<tr>
<td>Mean aortic pressure</td>
<td>16%</td>
<td>42%</td>
</tr>
<tr>
<td>Systolic pressure</td>
<td>11%</td>
<td>6%</td>
</tr>
<tr>
<td>Mean coronary flow velocity</td>
<td>109%</td>
<td>67%</td>
</tr>
<tr>
<td>Diastolic flow velocity</td>
<td>150%</td>
<td>103%</td>
</tr>
</tbody>
</table>
measured by a 6F MPA1 guiding catheter, left ventricular hemodynamics using 4F pressure-volume 12-electrode conductance catheter, and right atrial pressure from the right internal jugular venous catheter. Offline analysis of data from LV catheter yielded following variables; stroke volume, tau, maximal positive and negative dP/dt, end-diastolic pressure (EDP), EDV, end-systolic pressure (ESP), end-systolic volume (ESV) and stroke work. Conductance catheter ventricular volumes were calibrated using ventricular volume measured by echocardiography.

With increasing cuff pressure, right atrial pressure increased significantly only in 3-cuff setting. DA and MAP increased gradually with increasing cuff pressure as well as with change in cuff setting from the 1-cuff to 3-cuff setting. The greatest increase in MAP was noted in the 2-cuff high and 3-cuff settings. Systolic unloading was noted in the 2-cuff high setting. LVEDP was reduced in both 2-cuff high and 3-cuff settings, but not with the 1-cuff or 2-cuff low settings. The greatest reduction in LVEDP was noted in the 2-cuff high setting. Left ventricular ESV and EDV increased with the 2-cuff and 3-cuff settings, but the greatest increase was noted with 2-cuff low and 3-cuff settings. Significant decreases in stroke work were noted only with the 2-cuff high setting. There was a slight decrease in myocardial efficiency in the 2-cuff setting, but no significant change in 3-cuff setting.

This study showed that during EECP there is an acute increase in right atrial pressure leading to increased left ventricular preload and a load-dependent increase in contractility measured by increase in maximum positive dP/dt. The traditional 3-cuff EECP system resulted in an effective counterbalance between increased preload and afterload reduction, resulting in an overall beneficial reduction in LVEDP. Using a low inflation cuff pressure, there is the potential to increase preload (from venous compression) without effective afterload reduction; this may result in elevated left ventricular diastolic pressure. In contrast, 2-cuff high EECP resulted in less venous return, greater reduction in LVEDP and stroke work, and greater increase in maximum positive dP/dt. Therefore, it is acceptable to remove the calf cuffs in patients who do not tolerate calf compression. The 2-cuff low setting resulted in no decrease in LVEDP and stroke work, minimal DA and modest increase in maximal positive dP/dt, suggestive that this setting provided only little hemodynamic support. This finding has implications for EECP in the cardiac catheterization laboratory with femoral arterial access; this technique of withholding the highest cuff does not provide maximal EECP hemodynamic support.

The data from this study have direct clinical implications in treating HF patients with EECP. Lower inflation pressure EECP may be unsafe in volume-overloaded HF patients as this result in increased preload without effective afterload reduction. In euvolemic HF patients, higher inflation pressure EECP may yield greater hemodynamic effects to the left ventricle, resulting in increased contractility and systolic unloading.

Clinical implications

Investigators examined the relationship between DA ratios and clinical outcomes in patients undergoing EECP therapy. This study reviewed data from 1 004 patients enrolled in International EECP Patient Registry (IEPR) for treatment of chronic angina and completed 35 one-hour treatments. Blood pressure waveforms were recorded from finger plethysmography on the final day of EECP. Six-month clinical outcomes were obtained by telephone interview. The ratio of DA is calculated as the area under the diastolic curve divided by the area under systolic curve. At the end of EECP treatment, 370 (37%) had higher DA (defined as ≥ 1.5) and 634 (63%) had lower DA (defined as <1.5).

Factors associated with lower DA ratio include age ≥ 65 (P<0.001), female gender (P<0.001), LVEF <35% (P<0.05), hypertension (P<0.01), prior coronary bypass surgery (P<0.01), nonvascular cardiac surgery (P<0.001), multivessel disease (P<0.01), congestive heart failure (P<0.01), current smoking (P<0.01), unsuitability for further revascularization (P<0.001), and higher baseline angina class (P<0.001). At 6-month follow-up, patients with a DA ratio ≥ 1.5 had a lower incidence of HF exacerbation (P<0.05) and unstable angina (P<0.05), a higher rate of PCI (P<0.05), a lower angina class (P<0.01), and a higher quality-of-life score (P<0.001) than those with lower augmentation. Both groups of patients (with higher and lower DA ratios) had a significant reduction in angina class (P<0.001). Patients with higher DA ratios were in lower angina class than those with lower DA ratios (P<0.05). There was no significant difference in death, myocardial infarction and coronary artery bypass graft (CABG) between the two groups. The independent predictors of a lower DA at the end of EECP therapy were current smoking (odds ratio 3.3), non-cardiac vascular disease (2.3), female gender (2.2), no prior EECP (1.9), multivessel disease (1.7), age ≥65 years, and unsuitability of patients for revascularization (1.6). The authors concluded that higher DA ratios are associated with improved short or long-term clinical outcomes, suggesting that clinical benefits from EECP be associated with the magnitude of DA.

In 2005, investigators reported benefits of EECP in patients with HF and reduced LVEF. Data from Cardiomedics EECP Patient Registry, which included 127 New York Heart Association (NYHA) class II-IV CHF patients with a comorbidity of Canadian Cardiovascular Society Functional class III-IV angina, consecutively treated with EECP at six clinical sites in the United States were retrospectively analyzed. All patients received standard medical therapy [angiotensin converting enzyme inhibitors (ACEI) in 64% and β-blockers (BB) in 31%] and 35 hours of EECP treatment. Unconventionally low peak diastolic to peak systolic pres-
sure (D/S) ratios were applied, starting as low as 0.1 : 1, and gradually increased in small increments in stages over the 35-hour, 7-week ECP regimen, under a new "Graduated Pressure Regimen".

There were 54 patients in Low D/S ratio group (average D/S ratio of 0.7 : 1 and range 0.40:1-0.99 : 1), 39 patients in Mid D/S ratio group (average D/S ratio of 1.08 : 1 and range 1.00 : 1-1.29 : 1) and the 34 patients in High D/S ratio group (average D/S ratio 1.32 : 1 and range 1.30 : 1-1.60 : 1). The pressure used in high D/S ratio group was comparable to the D/S ratios commonly used in the treatment of angina. The study endpoints were comparative changes in mortality, LVEF, NYHA class, and incidence of all-cause hospitalization during 1-year following ECP therapy.

The 1-year mortality following ECP therapy was 1.85% (1/54), 7.69% (3/39) and 8.82% (3/34) respectively in low, mid and high D/S ratio groups. In the low D/S ratio group patients with NYHA functional class II - III HF, the 1-year mortality was zero compared with 8.5% (1-year adjusted mortality) in 1,232 MADIT II (Multicenter Automatic Defibrillator Implantation Trial II) patients. The mortality was 2.1% in the low D/S ratio group (one out of 48 patients with NYHA class II - IV HF symptoms) compared to 12.2% (82.8% reduction with a P-value of <0.0001) in COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) study of 595 NYHA class III - IV HF patients. In the low D/S ratio group, the mortality is decreased by 75.3% compared with mid D/S ratio group (P<0.001) and 77.8% compared with high D/S ratio group (P<0.0001).

The LVEF improved from 32.6 to 40.1% (P<0.05) in the low D/S ratio group. But the improvement in LVEF was not statistically significant in both the mid (31.3 to 37.5%) and high D/S ratio (32.6 to 38.3%) groups. The NYHA class improved by 36.6%, from a mean class of 3.0 ± 1.0 to 1.9 ± 0.5 (P<0.0001) in the low D/S ratio group, by 29.6% (P<0.005) from a mean class of 2.7 ± 1.3 to 1.9 ± 0.5 in the mid D/S ratio group and by 29.6% (P<0.01) from a mean class of 2.7 ± 1.3 to 1.9 ± 0.5 in the high D/S ratio group. The average incidence of all-cause hospitalization has decreased significantly by 87.5% (P<0.0001) from a mean of 2.8 to 0.3 per patient per year in the low D/S ratio group, by 83.2% (from 2.4 to 0.4, P<0.001) in the mid D/S ratio group, and 46.2% (from 1.3 to 0.7, P<0.01) in the high D/S ratio group. The decrease in the incidence of hospitalization was seen across all NYHA classes in both the low and mid D/S ratio groups but not in NYHA class II and less significantly in NYHA class III - IV HF patients of the high D/S ratio group.

This is the first study to report significant reduction in all-cause mortality and hospitalizations and improvement in NYHA functional class with EECP in NYHA class II - IV HF patients. There was also statistically significant improve-ment LVEF in the low D/S ratio group. The benefits in this study were thought to be related to EECP regimen’s theoretical potential to train the heart to accept and eject increasing volumes of blood, training ventricles to beat synchronously, improvement in endothelial function related to increased shear forces and release of endogenous growth factors. Other hypotheses for the efficacy of EECP proposed were enhancement of vascular reactivity, neurohormonal alteration, and stimulation of protein kinases and alteration of myocyte metabolism.

Lastly, given the potent acute hemodynamic effects of EECP in terms of DA and systolic unloading, this therapy was examined as an adjunct for patients with acute coronary syndrome and cardiogenic shock in a pilot study.27 In this feasibility pilot study, a portable EECP device provided effective hemodynamic support in an intensive care setting. Further research is warranted to assess its role in ambulances, emergency departments, and intensive care units.

Conclusions

EECP provides DA and systolic unloading comparable to an IABP. In addition, venous compression leads to increased preload and increased cardiac output. In patients with HF, it is important to balance any increased venous return with systolic unloading, which is usually achieved with high cuff pressure. In euvolemic HF patients, a low pressure algorithm may be associated with improved outcomes.

References


