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Original article

Effect of external counterpulsation on cardiac work following cardiac surgery: Implications of the mechanism responsible for clinical benefits

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Summary
Background: External counterpulsation (ECP) has been recognized as a non-invasive treatment for chronic refractory angina or heart failure. However, the mechanisms responsible for the clinical benefits of ECP therapy remain elusive. Moreover, the clinical significance of ECP therapy for postoperative patients has not been established yet.
Methods: Six adult patients received ECP therapy for 60 min under pulmonary artery catheter monitoring after cardiac surgery. Hemodynamic data were obtained before ECP therapy (pre-ECP), 20 min after ECP was commenced (20-min-ECP), 40 min after ECP was commenced (40-min-ECP), and after ECP therapy (post-ECP).
Results: The mean right atrial pressure (pre-ECP: 9 ± 4 mmHg; 20-min-ECP: 12 ± 5 mmHg; 40-min-ECP: 12 ± 4 mmHg; and post-ECP: 9 ± 4 mmHg), pulmonary wedge pressure (16 ± 6 mmHg, 20 ± 7 mmHg, 20 ± 7 mmHg, and 17 ± 7 mmHg, respectively), cardiac index (2.4 ± 0.4 l/min/m^2, 2.8 ± 0.6 l/min/m^2, 2.7 ± 0.5 l/min/m^2, and 2.5 ± 0.4 l/min/m^2, respectively), cardiac work index (2.5 ± 0.4 kg m/m^2, 3.3 ± 0.8 kg m/m^2, 3.1 ± 0.8 kg m/m^2, and 2.6 ± 0.5 kg m/m^2, respectively), and left ventricular stroke work index (32 ± 7 g m/m^2, 41 ± 12 g m/m^2, 39 ± 12 g m/m^2, and 33 ± 8 g m/m^2, respectively) significantly ($p < 0.05$) increased after ECP was commenced (pre-ECP vs. 20-min-ECP) and decreased after ECP was discontinued (40-min-ECP vs. post-ECP). Significant ($p < 0.001$) diastolic augmentation (20-min-ECP: $24 \pm 6\%$, 40-min-ECP: $23 \pm 5\%$) and systolic unloading ($3 \pm 1\%$, and $3 \pm 1\%$, respectively) were obtained. No clinical adverse effects were observed.

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Conclusions: ECP increases venous return, cardiac output, and cardiac work in addition to diastolic augmentation and systolic unloading. These actions may play important roles in the clinical benefits of ECP therapy. Our data also suggest that ECP is beneficial for patients undergoing cardiac surgery.

Introduction

External counterpulsation (ECP) is a non-invasive treatment that utilizes diastolic inflation of a series of lower-extremity cuffs to increase diastolic intracoronary pressure and flow. Simultaneous cuff deflation at the end of diastole decreases left-ventricular afterload. ECP was initially evaluated in patients with cardiogenic shock. Since the advent of intra-aortic balloon pumping (IABP), IABP has been a standard care for cardiogenic shock or acute coronary syndrome. On the other hand, ECP is a non-invasive treatment, which can be performed daily on an outpatient basis. Repeated administration of ECP, consisting of a standard treatment regimen of 35 1-h sessions over 7 weeks, has been shown to have benefits in patients with chronic refractory angina [1,2]. ECP improves the angina class immediately after a treatment regimen, and these beneficial effects are mostly sustained for a few years [3]. Moreover, ECP therapy can be applied for patients with chronic heart failure because ECP improves the quality of life and functional classification in patients with mild-to-moderate heart failure [4,5]. However, the mechanisms responsible for the clinical benefit of ECP have not been fully elucidated yet.

Moreover, the clinical significance of ECP therapy for postoperative patients has not been established. In this study, ECP was performed immediately after cardiac surgery. Patients generally have mild-to-moderate cardiac dysfunction, due to cardioplegic cardiac arrest or surgical stress after cardiac surgery. Patients commonly receive pharmacological treatments, such as catecholamine administration. Mechanical support, such as IABP, is a treatment option for patients with low cardiac output syndrome or severe heart failure. The aim of the study was to evaluate the hemodynamic effects of ECP on postoperative patients without severe heart failure.

Methods

Between July 2009 and June 2010, 6 patients were studied (Table 1). All 6 patients underwent ECP therapy under pulmonary catheter monitoring in the intensive care unit immediately after cardiac surgery. No patients had a surgical incision on their legs or groins. Patients were intubated and sedated. ECP was performed using a Compact CP system (model NT-CCP, Nishimura Kikai Co. Ltd., Kyoto, Japan and the University of Tokyo, Tokyo, Japan). The system profile has been reported previously [6]. Briefly, the main feature of this system is the double lumen cuff; the contact cuff is attached to a leg with a constant pressure of 0—10 kPa, the main cuff is inflated and deflated with a driving pressure of 20—80 kPa. The cuff inflation and deflation are synchronized with the patient's cardiac cycle at a ratio of 2:1. In this study, the contact cuff pressure was set at 8 kPa and the driving pressure at 40 kPa. Cuffs were wrapped around the patient's calves, thighs, and buttocks and connected to a driving console with an air compressor (Fig. 1). ECP was performed for 60 min. The radial artery pressure wave forms were analyzed, and peak or average systolic and diastolic pressure were obtained using a wave-form analysis software (Multi Trace CC, Medical Try System Co. Ltd., Tokyo, Japan). Percent diastolic augmentation, percent systolic unloading, and diastolic/systolic pressure ratio were calculated using the equations shown in Fig. 2. Hemodynamic data were collected 10 min before ECP commenced (pre-ECP), 20 min after it commenced (20-min-ECP), 40 min after ECP commenced (40-min-ECP), and 10 min after ECP discontinued (post-ECP). We calculated means ± standard deviation (SD) for continuous variables and compared them using paired Student's *t* test. A *p*-value of <0.05 was considered to indicate statistical significance. The ethics committee approved our study, and written informed consent was obtained from each patient.

Results

All patients were transferred from the operating room without critical heart failure or low output syndrome. About 1 h later, ECP therapy was commenced. During the treatment, the patients were on a fixed dosage of dopamine (1—3 μg/kg/min) and nitroglycerin (0.3—1.4 μg/kg/min). The fluid balance ranged between −226 and 112 ml (−40 ml on average) and the blood balance ranged between −40 and 65 ml (−10 ml on average) during ECP therapy. No adverse effects, including bleeding problems or leg injuries, were

Table 1 Patient characteristics.

Number of patients	6
Age (years)	68 ± 10
Male:female	3:3
Body surface area (m^2)	1.57 ± 0.17
Diagnosis	
Mitral regurgitation	3
Aortic valve disease	2
Coronary artery disease	1
Functional class (New York Heart Association)	
I	2
II	3
III	1
Left ventricular ejection fraction	58 ± 7%
Pulmonary hypertension	
None	3
Mild	3
Operation	
Mitral valve repair /replacement	3
Aortic valve replacement	2
Coronary artery bypass	1

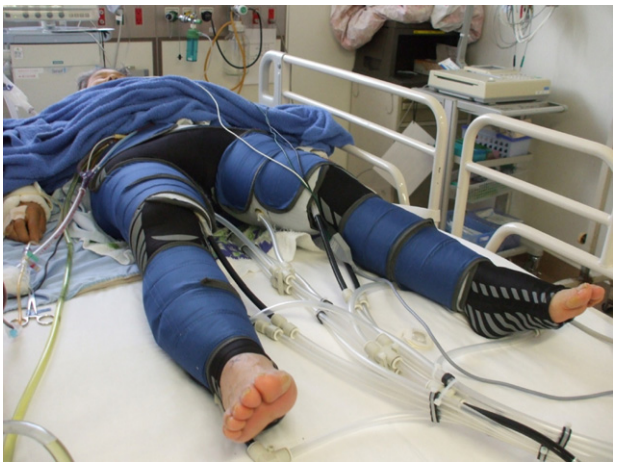

Figure 1 External counterpulsation performed in the intensive care unit immediately after cardiac surgery. Cuffs are wrapped around the patient's calves, thighs, and buttocks and are connected to an air compressor with tubes.

observed during or after ECP therapy. The patients were extubated within a few hours after ECP therapy.

During ECP therapy (Fig. 3), the diastolic/systolic pressure ratio significantly increased with significant diastolic augmentation and systolic unloading. The diastolic/systolic pressure ratio calculated from peak pressure was 0.85 and from mean pressure was 0.87—0.89 on average. Mean arterial (systemic) pressure, mean pulmonary pressure, right atrial pressure, pulmonary capillary wedge pressure, cardiac index, stroke volume index, cardiac work index, left and right ventricular work index, and left and right ventricular stroke work index significantly increased after ECP was commenced (pre-ECP vs. 20-min-ECP) and decreased after ECP was discontinued (40-min-ECP vs. post-ECP). Systolic systemic vascular resistance index, which was calculated ($S2_{mean}$ − right atrial pressure) × 79.92/cardiac index, significantly ($p = 0.003$) decreased after ECP was commenced, while the systemic and pulmonary vascular resistance index remained relatively constant (Tables 2 and 3).

Discussion

Like IABP, ECP provides diastolic augmentation and systolic unloading. Unlike IABP, ECP enhances venous return by squeezing the venous system [7]. Therefore, the primary concern of the initial investigators was that increased venous return during ECP therapy could precipitate pulmonary edema in patients with left ventricular dysfunction. However, it has been reported that ECP therapy is safe and effective in angina patients with severe left ventricular systolic dysfunction with an ejection fraction less than 0.35 [8]. Moreover, the Prospective Evaluation of Enhanced External Counterpulsation in Congestive Heart Failure (PEECH) trial [4] demonstrated that ECP improves exercise tolerance, quality of life, and functional classification without an accompanying increase in peak oxygen consumption (VO_2) in patients with ischemic or non-ischemic heart failure. Subgroup analysis of the PEECH trail found that ECP has a beneficial effect in older patients with chronic, stable, and mild-to-moderate heart failure with an accompanying increase in peak VO_2 [5].

However, the mechanisms responsible for the clinical benefits associated with ECP therapy have not been fully elucidated. Recent evidence suggests that ECP may improve symptoms through various mechanisms. One of these possible mechanisms is promotion of myocardial collateralization via opening preformed collateral vessels, arteriogenesis, and angiogenesis by increasing coronary flow [9]. This could be a contributing factor to reduced ischemia and improved myocardial perfusion in angina patients with or without left ventricular dysfunction. Additionally, ECP is also associated with improved diastolic filling and decreased plasma brain natriuretic peptide levels in patients with stable coronary artery disease [10]. This could be another contributing factor to improved symptoms in patients with chronic heart failure.

In this study, right atrial, pulmonary artery, and pulmonary capillary wedge pressure significantly increased during ECP, resulting in increased cardiac output. We calculated cardiac work and demonstrated that the cardiac work index, including the left and right ventricular work index,

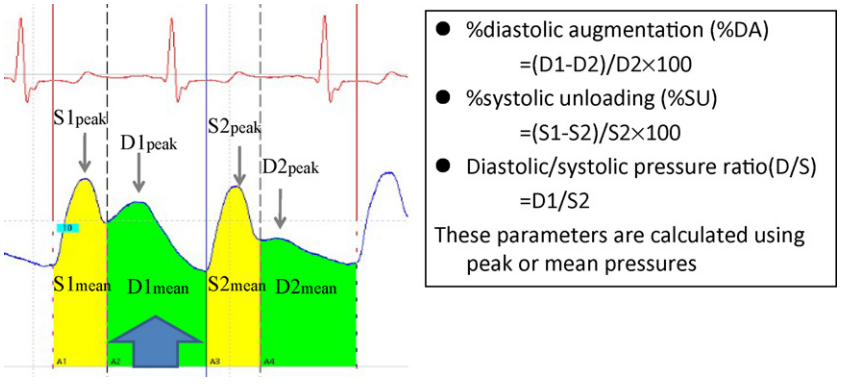

Figure 2 External counterpulsation applied at a ratio of 2:1. An arrow shows cuff inflation. $S1_{peak}$, peak systolic pressure without systolic unloading; $D1_{peak}$, peak diastolic pressure with diastolic augmentation; $S2_{peak}$, peak systolic pressure with systolic unloading; $D2_{peak}$, peak diastolic pressure without diastolic augmentation; $S1_{mean}$, mean systolic pressure without systolic unloading; $D1_{mean}$, mean diastolic pressure with diastolic augmentation; $S2_{mean}$, mean systolic pressure with systolic unloading; $D2_{mean}$, mean diastolic pressure without diastolic augmentation.

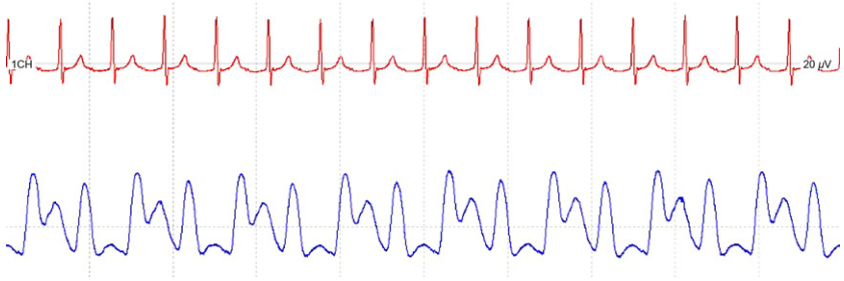

Figure 3 Pressure wave forms during external counterpulsation with 2:1 assist ratio. A 64 year-old patient underwent external counterpulsation after mitral valve plasty ($\%DA_{peak}$ 31, $\%SU_{peak}$ 5, D/S_{peak} 0.92, $\%DA_{mean}$ 22, $\%SU_{mean}$ 8, D/S_{mean} 1.00, see Fig. 2 for abbreviations).

Table 2 Systolic and diastolic pressure and external counterpulsation (ECP).

	Pre-ECP	20 min-ECP	*p*	40 min-ECP	Post-ECP	*p*
Peak pressure						
Peak systolic pressure without systolic unloading (S1peak: mmHg)	130 ± 14	144 ± 16	**0.003**	140 ± 20	128 ± 15	**0.026**
Peak diastolic pressure with diastolic augmentation (D1peak: mmHg)	92 ± 11	118 ± 13	<**0.001**	114 ± 15	91 ± 13	<**0.001**
Peak systolic pressure with systolic unloading (S2peak: mmHg)	130 ± 14	140 ± 17	**0.019**	135 ± 20	128 ± 15	0.126
Peak diastolic pressure without diastolic augmentation (D2peak: mmHg)	93 ± 11	95 ± 14	0.248	93 ± 15	90 ± 13	0.452
%diastolic augmentation	−0.7 ± 1.9%	24.2 ± 6.2%	<**0.001**	23.3 ± 5.4%	0.2 ± 1.5%	<**0.001**
%systolic unloading	−0.1 ± 1.0%	3.4 ± 1.4%	<**0.001**	3.2 ± 1.1%	−0.1 ± 0.6%	<**0.001**
Diastolic/systolic pressure ratio (D1peak/S2peak)	0.71 ± 0.03	0.85 ± 0.06	<**0.001**	0.85 ± 0.07	0.70 ± 0.05	<**0.001**
Mean pressure						
Mean arterial pressure	93 ± 11	103 ± 14	**0.004**	100 ± 14	90 ± 11	**0.013**
Mean systolic pressure without systolic unloading (S1mean: mmHg)	109 ± 13	123 ± 16	**0.005**	119 ± 18	107 ± 13	**0.026**
Mean diastolic pressure with diastolic augmentation (D1mean: mmHg)	97 ± 14	102 ± 13	<**0.001**	81 ± 11	83 ± 10	**0.002**
Mean systolic pressure with systolic unloading (S2mean: mmHg)	108 ± 12	114 ± 15	**0.022**	112 ± 18	105 ± 12	0.158
Mean diastolic pressure without diastolic augmentation (D2mean: mmHg)	82 ± 10	86 ± 13	0.054	83 ± 12	80 ± 11	0.181
%diastolic augmentation	0.7 ± 0.6%	18.2 ± 3.3%	<**0.001**	16.7 ± 2.0%	1.3 ± 1.4%	<**0.001**
%systolic unloading	1.1 ± 1.8%	7.3 ± 1.0%	**0.001**	5.4 ± 2.3%	0.9 ± 1.4%	**0.008**
Diastolic/systolic pressure ratio (D1mean/S2mean)	0.77 ± 0.05	0.89 ± 0.06	<**0.001**	0.87 ± 0.07	0.77 ± 0.05	**0.001**

Table 3 Hemodynamic change.

	Pre-ECP	20 min-ECP	*p*	40 min-ECP	Post-ECP	*p*
Heart rate (beats/min)	79 ± 11	80 ± 9	0.660	79 ± 8	78 ± 7	0.731
Mean pulmonary artery pressure (mmHg)	16 ± 6	20 ± 7	**0.031**	20 ± 7	17 ± 7	**0.003**
Pulmonary capillary wedge pressure (mmHg)	9 ± 3	12 ± 5	**0.026**	12 ± 4	9 ± 4	**0.010**
Right atrial pressure	7 ± 4	9 ± 5	**0.037**	9 ± 4	7 ± 5	**0.009**
Cardiac index (l/min/m^2)	2.4 ± 0.4	2.8 ± 0.6	**0.041**	2.7 ± 0.5	2.5 ± 0.4	**0.043**
Stroke volume index (ml/m^2)	31 ± 7	36 ± 10	**0.037**	35 ± 9	32 ± 7	0.108
Systemic vascular resistance index (dynes sec/cm^5/m^2)	2958 ± 921	2788 ± 900	0.179	2750 ± 786	2760 ± 617	0.918
Pulmonary vascular resistance index (dynes sec/cm^5/m^2)	238 ± 129	232 ± 146	0.833	235 ± 148	268 ± 148	0.155
Cardiac work index (kg m/m^2)	2.8 ± 0.4	3.6 ± 0.8	**0.018**	3.4 ± 0.9	2.8 ± 0.5	**0.029**
Left ventricular work index (kg m/m^2)	2.7 ± 0.3	3.5 ± 0.7	**0.016**	3.3 ± 0.8	2.7 ± 0.5	**0.026**
Left ventricular stroke work index (g m/m^2)	35 ± 7	44 ± 12	**0.025**	42 ± 13	35 ± 9	**0.050**
Right ventricular work index (kg m/m^2)	0.30 ± 0.07	0.40 ± 0.11	**0.021**	0.40 ± 0.09	0.36 ± 0.09	**0.017**
Right ventricular stroke work index (g m/m^2)	3.8 ± 0.7	5.0 ± 1.0	**0.016**	5.0 ± 0.9	4.6 ± 1.0	**0.029**
Systolic systemic vascular resistance index without systolic unloading (dynes sec/cm^5/m^2)	3526 ± 1095	3364 ± 1044	0.289	3294 ± 847	3314 ± 680	0.850
Systolic systemic vascular resistance index with systolic unloading (dynes sec/cm^5/m^2)	3477 ± 1049	3102 ± 978	**0.003**	3114 ± 885	3277 ± 641	0.259

ECP, external counterpulsation.

significantly increased during ECP therapy. Cardiac afterload significantly decreased immediately after cuff deflation as a result of systolic unloading, while systolic blood pressure increased mainly caused by an increase in cardiac output. These results obtained from our study are mostly consistent with previous investigations. Werner and associates [11] showed that during ECP therapy, there was an augmentation in flow volume in the carotid, renal, and hepatic arteries from 20% to 25% and in the coronary arteries from 20% to 40%, as well as a 12% increase in stroke volume, using duplex scanning and echocardiography.

Taguchi et al. [12] compared the hemodynamic effects of IABP and enhanced external counterpulsation (EECP, Vasomedical Co. Ltd., NY, USA) and reported that right atrial pressure, pulmonary capillary wedge pressure, and cardiac output significantly increased during ECP treatment while no significant change was observed in the IABP group. They also reported that the areas under arterial pressure during systole did not significantly change during ECP. We speculate that the left ventricular work index, which was not calculated in their study, might have increased during their ECP therapy. Because left ventricular work is calculated by the product of cardiac output and the difference between mean arterial pressure and pulmonary capillary wedge pressure. Blood pressure during ECP generally depends on the conditions; some studies [13] reported its increase, others [12,14] reported no significant difference.

These hemodynamic changes observed during ECP therapy are similar to those observed during mild physical exercise. Exercise training improves exercise capacity, functional class, quality of life [15], and survival [16] in patients with chronic heart failure or angina. The mechanisms responsible for the clinical benefits of exercise training involve both central and peripheral effects, such as improved endothelial function, reduced peripheral resistance, and improved diastolic filling [17]. Similar mechanisms have been reported in ECP therapy [5,10,18,19]. Ochoa and colleagues [14] found that VO_2 at rest was increased to the same degree during an ECP treatment session. Their results suggested that the simulation of a very low level of exercise by ECP might promote increased exercise tolerance and improved clinical benefits.

Increased cardiac output is associated with increased systemic arterial shear stress [18] and release of nitric oxide

from endothelial cells [19]. Improved endothelial function is associated with relaxation of underlying vascular smooth muscle [20]. Consequently, ECP improves arterial stiffness [21] and peripheral artery flow-mediated dilatation [22]. Moreover, a 35-h course of ECP improves hypertension [23,24]. These data suggest that the daily acute effect of ECP can cause chronic vasodilation and cardiac afterload reduction. Therefore, cardiac work will be decreased after the completion of ECP treatment, although the cardiac work is increased during a 60-min ECP treatment. We also believe that ECP is unlikely to cause ischemia, even in increased myocardial oxygen consumption, because coronary flow was also increased by diastolic augmentation. In contrast, physical exercise does not provide diastolic augmentation and systolic unloading. Therefore, ECP is particularly beneficial in patients with ischemic cardiomyopathy and muscle weakness, paralysis or extremely decreased activities of daily living.

ECP can also be a treatment option for postoperative heart failure after cardiac surgery or other acute heart diseases. However, the significance of ECP for acute heart failure or acute coronary syndrome has not been established yet. Cohen et al. [13] applied ECP to 10 patients with unstable angina, acute myocardial infarction, or cardiogenic shock and showed the safety and feasibility of ECP therapy in these patients. In our study, the right atrial and pulmonary capillary wedge pressure mildly increased during ECP. The increase in cardiac preload resulted in 10—20% increased cardiac output. Significant diastolic augmentation and systolic unloading were observed. These effects could have been beneficial for the studied patients although they had no critical symptoms of heart failure. Additionally, as systolic blood pressure tends to increase during ECP, administration of a vasodilator may be helpful for reducing systolic blood pressure during ECP therapy. In case of critical myocardial ischemia or decompensated heart failure, increased cardiac preload or work may cause adverse effects on patients undergoing ECP therapy despite significant diastolic augmentation. For these patients, IABP should be indicated.

From the other point of view, ECP may be useful for patients undergoing cardiac surgery. Because ECP mildly increases cardiac work and VO_2 with an accompanying increase in coronary flow, ECP can be performed as part of postoperative cardiac rehabilitation protocols. Cardiac rehabilitation has numerous beneficial effects for postoperative patients after cardiac surgery [25]. In addition, ECP may prevent deep vein thrombosis (DVT) after cardiac surgery by intermittent compression of lower legs [26]. DVT is a significant complication after cardiac surgery [27].

This study has several limitations. First, the number of studied patients was small. Second, the basic design of the ECP system used in our study was different from that of the ECP system used in the previous investigations, such as the Vasomedical EECP mentioned earlier. The Vasomedical system consists of single-chamber cuffs. In contrast, our system has double-chamber cuffs, which reduce the size of the air compressor and the impact of cuff inflation/deflation. Therefore, the capacity of the system compressor was limited. The maximum assist rate was approximately 60/min. For this reason, we applied ECP in 2:1 ratio, which might have affected the results of our study.

Third, ECP therapy was performed in about one hour after transfer to the ICU because patients were usually extubated in a few hours postoperatively. As most patients were in the hyper-diuretic phase after cardiopulmonary bypass, we often needed to increase fluid volume in order to maintain the water in-out balance during ECP therapy. Hypovolemia may reduce the effect of ECP. Moreover, both low cardiac output and hypothermia are known to increase systemic vascular resistance after cardiac surgery. Vasoconstriction may also reduce the effect of ECP. Indeed, the D/S ratio obtained in this study was relatively less than that obtained in our previous pilot study [6]. The response to ECP may be reduced in perioperative periods in some patients.

Fourth, patients undergoing coronary artery bypass are generally considered to be good candidates for postoperative ECP therapy. However, they are often excluded because of a lower leg incision. Finally, the ECP system is basically designed for out-patient treatments, with each treatment period limited to 1 or 2 h. It is possible that longer or more continuous treatment might be feasible for the treatment of acute heart ischemia or failure.

In conclusion, ECP increases venous return and cardiac output during counterpulsation in addition to diastolic augmentation and systolic unloading. Consequently, cardiac work load increases during ECP therapy. These acute actions, which are rare in intra-aortic balloon pumping, may play important roles in the clinical benefits of ECP therapy, especially in patients with chronic ischemia or heart failure. Our data also suggest that ECP is effective in patients with mild-to-moderate acute heart failure or ischemia following cardiac surgery. Moreover, ECP may be performed as part of postoperative cardiac rehabilitation. Further investigations are needed to confirm the significance of ECP therapy for such patients.

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