Enhanced external counterpulsation (EECP) is a non-invasive method of assisting the circulation, which enhances diastolic augmentation and systolic unloading by means of a pressurized air cuff around the patient’s legs that is maintained at approximately 300 mmHg during diastole. In the United States, the effectiveness of this method in chronic angina has been reported, and its effectiveness has been confirmed in a large-scale clinical trial. It has been concluded that the increase in coronary blood flow by EECP treatment is mainly through diastolic augmentation, which is similar to the effect on the arterial system by intraaortic balloon pumping (IABP), but EECP also has an effect on venous return. It can be implemented immediately, and is noninvasive without risk of bleeding or infection, which is a great advantage compared with IABP. It is anticipated that EECP will help improve the circulation in patients with acute heart failure and acute coronary syndrome. We previously reported that in patients with acute myocardial infarction (AMI) EECP produced diastolic augmentation similar to IABP, but increased preload and the cardiac index (CI) with increased venous return, which is different to IABP. In this study, we used EECP in patients with AMI and observed the changes in neurohumoral factors, as well as the hemodynamic effects, to investigate its mechanism and effects on left cardiac function.

**Methods**

**Study Population**

The subjects were 24 patients (20 male, 4 female; mean age: 61±8 years) with AMI who were treated successfully with reperfusion therapy (percutaneous transluminal coronary angioplasty) within 12h of onset (Table 1). All patients were in a stable condition 48–72 h after the onset and were expected to be discharged from the coronary care unit. The exclusion criteria were heart failure of Killip Class III or higher, serum creatinine concentration of 2.0 mg/dl or higher, and arteriosclerosis obliterans. In addition, 4 patients were excluded because of technical difficulties with the EECP device. The study was approved by the institutional review board, and informed consent was obtained from all patients.

**Key Words:** Acute myocardial infarction; Enhanced external counterpulsation; Neurohumoral factors

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**Background** The hemodynamic effects of enhanced external counterpulsation (EECP) and its mechanism(s) were investigated in relation to neurohumoral factors in patients with acute myocardial infarction (AMI).

**Methods and Results** Twenty-four patients with AMI were studied before, during and after EECP treatment for 60 min. Heart rate (HR), right atrial pressure (RAP), pulmonary capillary wedge pressure (PCWP) and cardiac index (CI) were determined. In addition, circulating concentrations of neurohumoral factors were determined at each time point. HR did not change following EECP treatment. However, RAP and PCWP increased significantly and CI was significantly elevated during EECP and thereafter. Blood atrial natriuretic peptide (ANP) concentration was significantly increased 15 and 60 min after the start of EECP treatment, but brain natriuretic peptide (BNP) did not change. Renin, aldosterone and catecholamine concentrations also did not change.

**Conclusion** Treatment with EECP resulted in an increased preload because of increased venous return, and CI was increased thereafter. In patients with AMI, EECP increased blood ANP concentration, but not BNP, which suggests that an increase in ANP without an increase in BNP is an important mechanism for the effects of EECP treatment.

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**Table 1 Characteristics of the Patients With Acute Myocardial Infarction**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD), years</td>
<td>61±8</td>
</tr>
<tr>
<td>Male</td>
<td>20 (83.3%)</td>
</tr>
<tr>
<td>Culprit coronary artery</td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>15 (62.5%)</td>
</tr>
<tr>
<td>LCX</td>
<td>2 (8.3%)</td>
</tr>
<tr>
<td>RCA</td>
<td>7 (29.2%)</td>
</tr>
<tr>
<td>Max CK (U/L)</td>
<td>3,100±2,469</td>
</tr>
<tr>
<td>LVEF</td>
<td>50.6±10.0%</td>
</tr>
<tr>
<td>Killip grade on admission</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>19 (79.2%)</td>
</tr>
<tr>
<td>II</td>
<td>5 (20.8%)</td>
</tr>
<tr>
<td>III</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
</tr>
</tbody>
</table>

LAD, left anterior descending branch; LCX, left circumflex branch; RCA, right coronary artery; CK, creatine kinase; LVEF, left ventricular ejection fraction.
Patients who complained about the vibration caused by EECP and could not tolerate the treatment for 60 min were also excluded. All patients gave written informed consent. Because the therapy and device (EECPR; Vasomedical Inc, USA) were not covered by medical insurance, approval was obtained from the institutional review board of the hospital. The conduct of the study conformed with the Helsinki declaration.

**Study Protocol**

All patients underwent EECP for 60 min. Before, during (15, 30 and 60 min after the start of treatment) and 60 min after the treatment, the following hemodynamic and neurohumoral factors were determined sequentially. For hemodynamics, heart rate (HR), right atrial pressure (RAP), pulmonary capillary wedge pressure (PCWP) and CI were determined using a Swan-Ganz catheter. A blood sample was collected from an arterial line and centrifuged. Serum and plasma samples were cryopreserved at −20°C until analysis of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), renin and aldosterone by rasioimmunoassay, and dopamine and noradrenaline by high-performance liquid chromatography.

Patients underwent cardiac catheterization during admission (acute stage) and on one of Disease Days 13–16 (during the subacute stage). To evaluate left cardiac function, left ventricular ejection fraction (LVEF) and left ventricular end-diastolic volume index (LVEDVI) were determined by left ventriculography in all patients using an area–length method. In addition, left ventricular end-diastolic pressure.
Fig 3. The mean concentration of atrial natriuretic peptide (ANP; Left) was significantly increased at 15 and 60 min after starting enhanced external counterpulsation (EECP) treatment whereas the mean concentration of BNP (Right) did not change significantly.

Fig 4. The mean concentrations of dopamine (Left) and noradrenaline (Right) did not change significantly after enhanced external counterpulsation (EECP) treatment.

Fig 5. The mean concentrations of renin (Left) and aldosterone (Right) did not change after enhanced external counterpulsation (EECP) treatment.
(LVEDP) was determined using a pressure transducer inserted into the left ventricle via a catheter.

**Statistical Analysis**

Measured and calculated values are presented as the mean ± standard deviation. Changes in each value relative to the pretreatment value were tested using paired t-test, and differences with p<0.05 were considered significant.

**Results**

**Hemodynamics**

The mean baseline HR was 90±8 beats/min and was unchanged by EECP treatment. The CI was 3.3±0.8 L/min per m² before treatment and gradually increased to 4.1±0.8 L/min per m² at 60 min after the start of EECP treatment, which was a significant increase (p<0.01), and decreased after the completion of EECP treatment (Fig 1). The RAP was 6.4±3.3 mmHg before treatment and 9.8±4.0 mmHg at 15 min after the start of EECP treatment, showing a significant increase (p<0.01), and decreased thereafter. The PCWP was 8.9±4.0 mmHg before treatment and 12.6±5.3 mmHg at 15 min after the start of EECP treatment, showing a significant increase (p<0.05), and decreased thereafter (Fig 2).

**Neurohumoral Factors**

The blood ANP concentration was 54±42 pg/ml before treatment and significantly increased to 68±46 pg/ml at 15 min after the start of EECP treatment. Thereafter, the concentration transiently decreased and then increased to 70±46 pg/ml at 60 min after the start of EECP treatment, but at 60 min after the completion of EECP treatment the blood ANP concentration was decreased. The respective BNP concentrations were 129±118, 127±117 and 135±120 pg/ml, before treatment, and 30 and 60 min after the start of EECP treatment, showing no changes and there was no change at 60 min after the completion of EECP treatment (Fig 3). The pretreatment concentrations of dopamine, noradrenaline, renin and aldosterone were 30±27, 472±231, 40.9±35.0 and 54±33 pg/ml, respectively, showing no significant change during or after EECP treatment (Figs 4, 5).

**Left Cardiac Function**

The LVEF and LVEDVI were 50.6±10.0% and 59.3±3.7 ml/m², respectively, in the acute stage (during admission) and showed no significant change during the subacute stage. LVEDP was 18.6±1.6 mmHg in the acute stage, but decreased significantly to 13.8±6.4 mmHg in the subacute stage, which was within the normal range (Table 2).

**Discussion**

We previously reported that EECP treatment increased cardiac output, but did not adequately explain its mechanism. In the present study, we determined the contribution of neurohumoral factors to the effect of EECP treatment. We found a significant increase in the blood ANP concentration at 15 min after the start of EECP treatment, concomitant with an elevation of RAP and PCWP, which suggested that EECP treatment increased the volume of venous return, resulting in an increased atrial load. RAP and PCWP, as indices of preload, were increased in the early stage of EECP treatment, but decreased gradually and returned to the pretreatment levels. The results of this study show that EECP treatment increases the CI without an increase in HR. The effects of ANP, including diuretic and vasodilating effects and inhibitory effects on the sympathetic nervous system and renin–angiotensin system, were verified. It has been reported that EECP treatment had the clinical effect of protecting the myocardium in patients with AMI, and on the basis of that finding and our present results we propose that the mechanism of the changes in cardiac function following EECP treatment are an increased urine volume as a result of increased renal blood volume caused by an increase in venous return together with an effect on cardiac output, and the direct diuretic and vasodilating effects of ANP.

The finding that EECP treatment significantly improved CI with a significant increase in the concentration of ANP, but not of BNP, is very interesting. The increase in ANP indicates increased atrial preload, whereas BNP is a prognostic factor in patients with AMI and an increase suggests an increase in ventricular preload, which is associated with worsening cardiac function. Therefore, EECP treatment significantly increased atrial, but not ventricular, preload and neurohumoral factors such as ANP may have an important role in the hemodynamic changes that occur during EECP treatment. In addition, increased concentrations of neurohumoral factors such as dopamine, noradrenaline, renin and aldosterone are also indicative of worsening cardiac function and the absence of a significant change in BNP or these factors in the present study suggests that EECP treatment does not have an adverse effect on hemodynamics. Improved cardiac function because of the increase in ANP may have also suppressed BNP. We did not include patients with pulmonary congestion and none of the present patients showed a change in the Killip classification.

In this study, the ANP concentration peaked twice (ie, at 15 and 60 min) after the start of EECP treatment, with a decrease in concentration at 30 min, which suggests there is a time-lag between the secretion and the production of ANP in the early stage of EECP treatment.

With respect to cardiac function during the subacute stage, LVEF and LVEDVI were unchanged, and LVEDP decreased significantly and almost returned to the normal range. These findings are considered to be the result of drug treatment and the natural course of healing, suggesting that there are no adverse effects of EECP treatment and that this treatment can be used for patients with heart failure or AMI.

EECP was developed approximately 30 years ago at the same time as IABP and was expected not only to be a less invasive treatment, but also to have the same degree of effectiveness in hemodynamic improvement. However, at that time, the results of clinical studies of EECP treatment were insufficient and varied considerably because there was a lack of uniformity in the devices and insufficient
technical development. Subsequently, the EECP device was improved and a better effect was obtained.\textsuperscript{13,16} Further upgrades of the current device were made to reduce patient discomfort.

Multicenter studies in the United States have reported that EECP treatment improves the symptoms and exercise tolerance of patients with chronic stable angina, and the effectiveness of EECP treatment has been verified.\textsuperscript{17-19} Recently, Stys et al\textsuperscript{20} and other researchers\textsuperscript{21,22} used radioisotopic examinations to evaluate EECP treatment and reported that it improved myocardial blood flow in the perfused area of the stenotic coronary artery in 83\% of patients. Urano et al reported that EECP treatment improved not only dilation of the left ventricle, but also myocardial blood flow,\textsuperscript{23} and EECP treatment has shown a beneficial effect in patients with heart failure, which has been considered a contraindication.\textsuperscript{24} The results of the present study contribute significantly to the explanation of the mechanism(s) of EECP. At present, EECP treatment is not used for patients with acute coronary syndrome, but as shown by our study EECP is superior to IABP in increasing cardiac output and may be effective in patients with heart failure for patients with AMI in the acute phase. An increase in preload after EECP treatment may exacerbate pulmonary congestion in patients with severe heart failure. Further studies are necessary to evaluate the effectiveness of EECP treatment as a circulatory aid in patients with heart failure and acute coronary syndrome.

Conclusion

EECP treatment in patients with AMI increased preload through an increase in venous return, increased the blood concentration of ANP and improved CI. The blood concentrations of BNP, renin, aldosterone and catecholamines were unchanged. These results suggest that EECP treatment can assist in improving the cardiac function of patients with AMI.

Acknowledgment

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References