Circ J 2004; **68:** 1030 – 1034

Effects of Enhanced External Counterpulsation on Hemodynamics and Its Mechanism

— Relation to Neurohumoral Factors —

Isao Taguchi, MD; Kenichi Ogawa, MD; Tomoaki Kanaya, MD; Ryuko Matsuda, MD*; Hideyo Kuga, MD; Masatoshi Nakatsugawa, MD

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. (*Circ J* 2004; **68:** 1030 – 1034)

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

Enhanced external counterpulsation (EECP) is a noninvasive 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[1] In the United States, the effectiveness of this method in chronic angina has been reported[2,3] and its effectiveness has been confirmed in a large-scale clinical trial[4] 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[5,6] 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[7] 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.

(Received November 25, 2003; revised manuscript received August 12, 2004; accepted August 23, 2004)
*Departments of Cardiology and Pneumology, and *Clinical Laboratory Medicine, Dokkyo University School of Medicine, Tochigi, Japan*
Mailing address: Isao Taguchi, MD, Department of Cardiology and Pneumology, Dokkyo University School of Medicine, 880 Kitakibayashi, Mibu, Tochigi 3212-0293, Japan. E-mail: taguchi@dokkyomed.ac.jp

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 12 h 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 pa-

Table 1 Characteristics of the Patients With Acute Myocardial Infarction

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

LAD, left anterior descending branch; LCX, left circumflex branch; RCA, right coronary artery; CK, creatine kinase; LVEF, left ventricular ejection fraction.

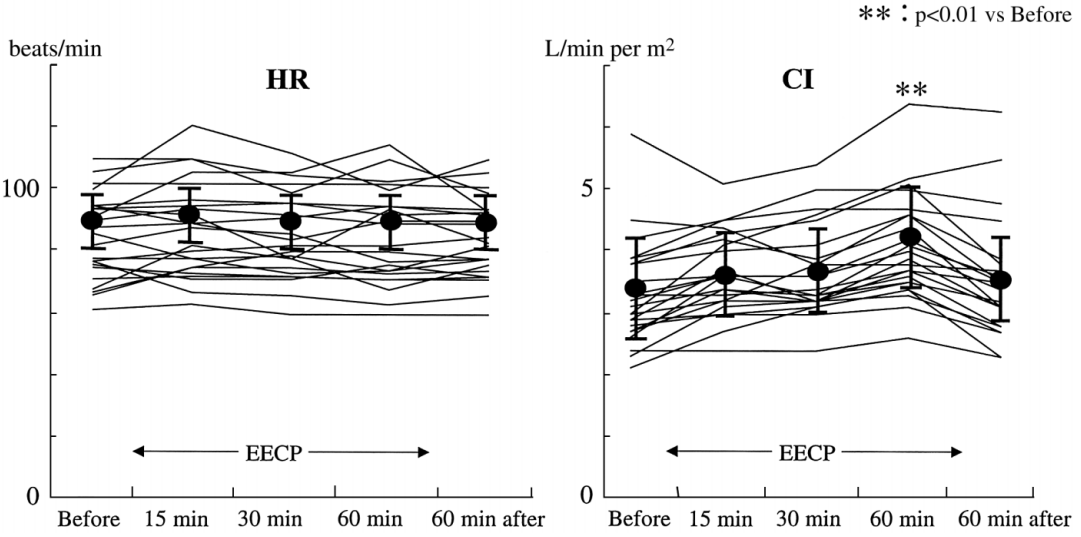

Fig 1. The mean heart rate (HR) did not change significantly after enhanced external counterpulsation (EECP) treatment, but the mean cardiac index (CI) was significantly increased after 60 min of treatment ($p<0.01$).

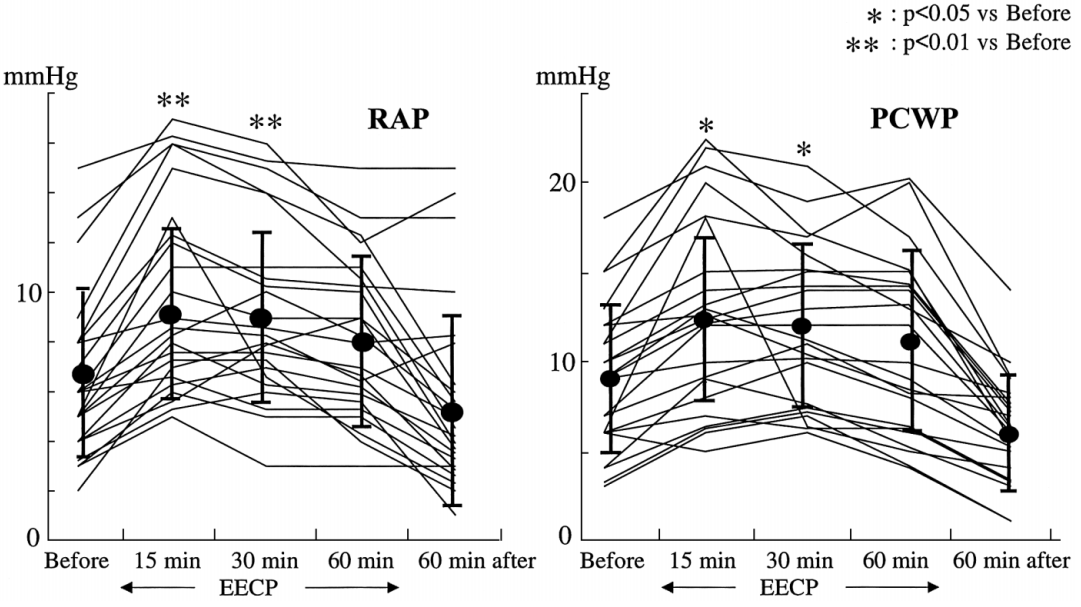

Fig 2. The mean right atrial pressure (RAP; Left) was significantly increased at 15 and 30 min of enhanced external counterpulsation (EECP) treatment compared with control ($p<0.01$) and was decreased at 60 min after ceasing the treatment. The mean pulmonary capillary wedge pressure (PCWP; Right) in the EECP group was increased at 15 and 30 min after starting treatment and was decreased 60 min after cessation.

tients 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

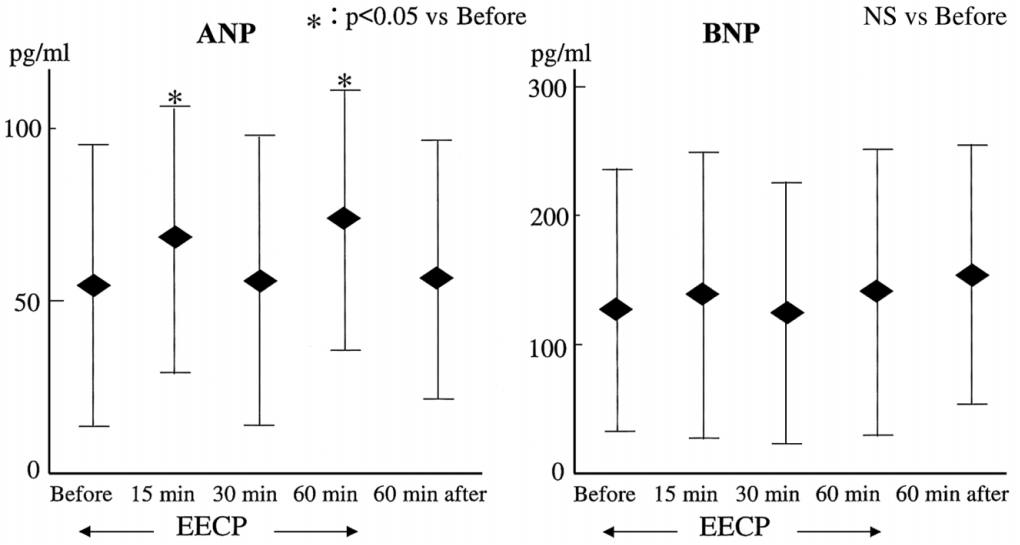

Fig 3. The mean concentration of atrial natriuretic peptide (ANP; Left) was significantly increased at 15 and 60 min after starting enhanced external counterpulsation (EECP) treatment whereas the mean concentration of BNP (Right) did not change significantly.

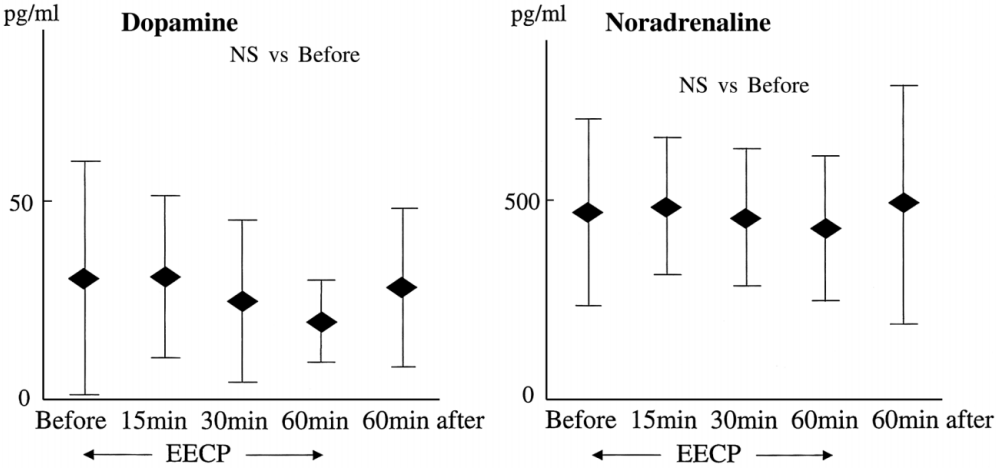

Fig 4. The mean concentrations of dopamine (Left) and noradrenaline (Right) did not change significantly after enhanced external counterpulsation (EECP) treatment.

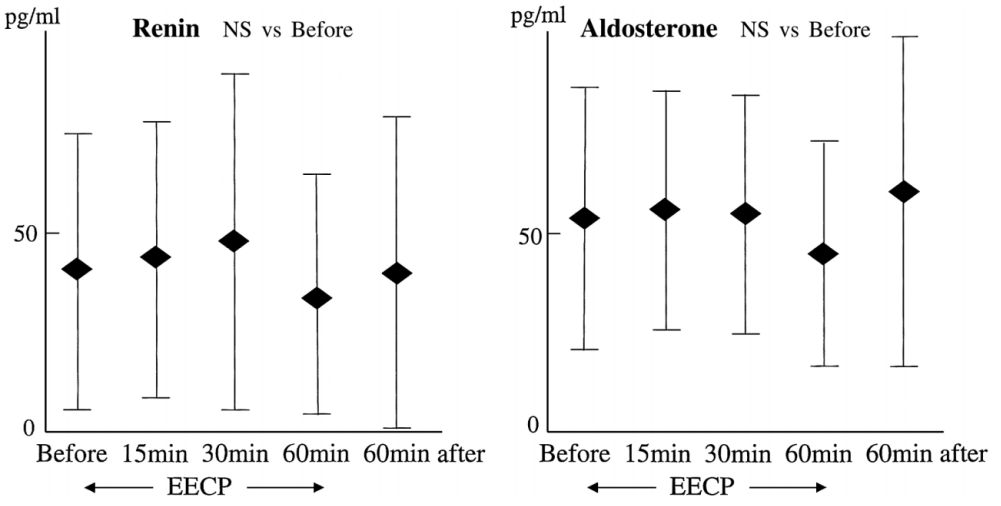

Fig 5. The mean concentrations of renin (Left) and aldosterone (Right) did not change after enhanced external counterpulsation (EECP) treatment.

(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 m^2 before treatment and gradually increased to 4.1±0.8 L/min per m^2 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/m^2, 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).

Table 2 Changes in Left Ventricular Function After EECP

	Acute phase	*Subacute phase*	*p value*
LVEF (%)	*50.6±10.0*	*54.2±10.8*	*NS*
LVEDVI (ml/m²)	*59.3±3.7*	*58.2±2.3*	*NS*
LVEDP (mmHg)	*18.6±1.6*	*13.8±6.4*	*<0.05*

EECP, enhanced external counterpulsation; LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end diastolic volume index; LVEDP, left ventricular end diastolic pressure.

Discussion

We previously reported that EECP treatment increased cardiac output, but did not adequately explain its mechanism[7] 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[8] 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[9] 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[10–12] at the same time as IABP[3,1] 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[14] 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.[15,16] 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.[4,17–19] Recently, Stys et al[20] and other researchers[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,[23] and EECP treatment has shown a beneficial effect in patients with heart failure, which has been considered a contraindication.[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 associated with right ventricular infarction. In addition, EECP might be better than IABP in patients with acute obstruction after coronary bypass surgery or catheter intervention, because it is noninvasive, can be used immediately and produces greater diastolic augmentation than IABP.[25,26]

Study Limitation

The subjects were limited to patients with stable hemodynamics, as this study was the first to use EECP treatment 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

The authors appreciate the help given by Professor Noboru Kaneko.

References

1. Zheng ZS, Yu LQ, Cai SR, Kambic H, Li TM, Ma H, et al. New sequential external counterpulsation for the treatment of acute myocardial infarction. *Artif Organs* 1984; **8:** 470–477.
2. Lawson WE, Hui JCK, Soroff HS, Zheng ZS, Kaydan DS, Sasvary D, et al. Efficacy of enhanced external counter-pulsation in the treatment of angina pectoris. *Am J Cardiol* 1992; **70:** 859–862.
3. Lawson WE, Hui JCK, Zheng ZS, Oster Z, Katz JP, Diggs P, et al. Three-year sustained benefit from enhanced external counterpulsation in chronic angina pectoris. *Am J Cardiol* 1995; **75:** 840–841.
4. Arora RR, Chou TM, Jain D, Fleishman B, Crawford L, MacKiernan T, et al. The multicenter study of enhanced external counterpulsation (MUST-EECP): Effect of EECP on exercise-induced myocardial ischemia and anginal episodes. *J Am Coll Cardiol* 1999; **33:** 1833–1840.
5. Shiraishi R, Okazaki Y, Naito K, Itoh T. Perforation of the descending aorta by the tip of an intra-aortic balloon pump catheter. *Circ J* 2002; **66:** 423–424.
6. Hikosaka T, Ito K, Takuji T, Zen K, Adachi Y, Kato S, et al. Surgical removal of intra-aortic balloon catheter with fractured nitinol central lumen: A case report. *Circ J* 2002; **66:** 419–422.
7. Taguchi I, Ogawa K, Kaneko N, Oida A, Abe S, Sakio H. Comparison of hemodynamic effects of enhanced external counterpulsation and intra-aortic balloon pumping in patients with acute myocardial infarction. *Am J Cardiol* 2000; **86:** 1139–1141.
8. Kuga H, Ogawa K, Oida A, Taguchi I, Nakatsugawa M, Kaneko N, et al. Administration of atrial natriuretic peptide attenuates reperfusion phenomena and preserves left ventricular regional wall motion after direct coronary angioplasty for acute myocardial infarction. *Circ J* 2003; **67:** 443–448.
9. Arakawa N, Nakamura M, Aoki H, Hiramori K. Plasma brain natriuretic peptide concentration predicts survival after acute myocardial infarction. *J Am Coll Cardiol* 1996; **27:** 1656–1661.
10. Denis C, Moreno JR, Hall DP, Crosz C, Ross SM, Wesolowski SA, et al. Studies on external counterpulsation as a potential measure for acute left heart failure. *Trans Am Soc Artif Int Organs* 1963; **9:** 186–191.
11. Moulopoulos SD, Topaz S, Kolff WL. Diastolic balloon pumping (with carbon dioxide) in aorta: A mechanical assistance to failing circulation. *Am Heart J* 1962; **63:** 669–675.
12. Osborn JJ, Main FB, Gerbode FL. Circulatory support by leg or airway pulses in experimental mitral insufficiency. *Circulation* 1963; **28**(Suppl)**:** 781.
13. Osborn JJ, Russi M, Selel S, Bramson ML, Gerbode FL. Circulatory assistance by external pulsed pressures. *Am J Med Electronics* 1964; **111:** 87–90.
14. Soroff HS, Hui J, Giron F. Current status of external counterpulsation. *Crit Care Clin* 1986; **2:** 277–295.
15. Leuptow RM, Karlen JM, Kamm RD, Shapiro AH. Circulatory model studies of external cardiac assist by counterpulsation. *Cardiovasc Res* 1981; **15:** 443–455.
16. Cohen LS, Mullins CB, Mitchell JH, Alsobrook HD. Sequenced external counterpulsation and intraaortic balloon pumping in cardiogenic shock. *Am J Cardiol* 1973; **32:** 656–666.
17. Arora RR, Chou TM, Jain D, Fleishman B, Crawford L, MacKiernan T, et al. Effect of enhanced external counterpulsation on health-related quality of life continues 12 months after treatment: A substudy of the Multicenter Study of Enhanced External Counterpulsation. *J Invest Med* 2002; **50:** 25–32.
18. Corn PF. External counterpulsation for the treatment of myocardial ischemia. *Heart Dis* 1999; **1:** 221–225.
19. Barsness G, Feldman AM, Holmes DR Jr, Holubkov R, Kelsey SF, Kennard ED. The International EECP Patient Registry (IEPR): Design, methods, baseline characteristics, and acute results. *Clin Cardiol* 2001; **24:** 435–442.
20. Stys TP, Lawson WE, Hui JC, Fleishman B, Manzo K, Strobec JE, et al. Effects of enhanced external counterpulsation on stress radionuclide coronary perfusion and excercise capacity in chronic stable angina pectoris. *Am J Cardiol* 2002; **89:** 822–824.
21. Masuda D, Nohara R, Inada H, Hirai T, Li-Guang C, Sasayama S. Improvement of regional myocardial and coronary blood flow reserve in a patient treated with enhanced external counterpulsation: Evaluation by nitrogen-13 ammonia PET. *Jpn Circ J* 1999; **63:** 407–411.
22. Lawson WE, Hui JC, Cohn PF. Long-term prognosis of patients with angina treated with enhanced external counterpulsation: Five-year follow-up study. *Clin Cardiol* 2000; **23:** 254–258.
23. Urano H, Ikeda H, Ueno T, Matsumoto T, Murohata T, Imaizumi T. Enhanced external counterpulsation improves exercise tolerance, reduces exercise-induced myocardial ischemia and improves left ventricular diastolic filling in patients with coronary artery disease. *J Am Coll Cardiol* 2001; **37:** 93–99.
24. Lawson WE, Kennard ED, Holubkov R, Kelsey SF, Strobec JE, Soran O, et al. Benefit and safety of enhanced external counterpulsation in treating coronary artery disease patients with a history of congestive heart failure. *Cardiology* 2001; **96:** 78–84.
25. Michaels AD, Accad M, Ports TA, Grossman W. Left ventricular systolic unloading and augmentation of intracoronary pressure and Doppler flow during enhanced external counterpulsation. *Circulation* 2002; **106:** 1237–1242.
26. Lawson WE, Hui JC, Guo T, Burger L, Cohn PF. Prior revascularization increases the effectiveness of enhanced external counterpulsation. *Clin Cardiol* 1998; **21:** 841–844.