Enhanced external counterpulsation improved myocardial perfusion and coronary flow reserve in patients with chronic stable angina

Evaluation by \(^{13}\)N-ammonia positron emission tomography

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Aims The mechanism by which enhanced external counterpulsation therapy exerts its beneficial effects on chronic and symptomatic stable angina is largely unknown. To clarify the mechanism of action of enhanced external counterpulsation, we used \(^{13}\)N-ammonia positron emission tomography to evaluate myocardial perfusion.

Methods and Results This was not a randomized controlled study. Eleven patients (eight male, age: 61·6 ± 9·7) with angina pectoris underwent enhanced external counterpulsation therapy for 35 1 h sessions. They underwent a treadmill exercise test and \(^{13}\)N-ammonia positron emission tomography, both at rest and with dipyridamole, before and after enhanced external counterpulsation therapy. Neurohumoral factors and nitric oxide were also evaluated. Myocardial perfusion increased at rest after therapy (0·69 ± 0·27 to 0·85 ± 0·47 ml.min\(^{-1}\)g\(^{-1}\), \(P<0·05\)). In ischaemic regions, particularly the anterior region, myocardial perfusion at rest and with dipyridamole and coronary flow reserve improved significantly after therapy (at rest: 0·71 ± 0·26 to 0·86 ± 0·31; \(P<0·05\), with dipyridamole: 1·26 ± 0·65 to 1·84 ± 0·94; \(P<0·02\), coronary flow reserve: 1·75 ± 0·24 to 2·08 ± 0·28; \(P<0·04\)). Exercise time was prolonged and the time to 1-mm ST depression improved markedly (\(P<0·01\)). After therapy, nitric oxide levels increased (\(P<0·02\)) and neurohumoral factors decreased.

Conclusions Enhanced external counterpulsation therapy improved myocardial perfusion at rest and with dipyridamole and was associated with an increased exercise tolerance with \(^{13}\)N-ammonia positron emission tomography and increased nitric oxide levels. These results suggest that one of the enhanced external counterpulsation mechanisms is development and recruitment of collateral vessels.

Key Words: Enhanced external counterpulsation, ischaemic heart disease, \(^{13}\)N-ammonia positron emission tomography, myocardial perfusion, coronary flow reserve, endothelial function.

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chronic stable angina who are resistant to medication and repeat interventions, including coronary artery bypass grafting (CABG). The exact mechanisms by which enhanced external counterpulsation exerts its beneficial effects are unknown, but one of its effects is considered to be the development and recruitment of collateral vessels. However, it may be difficult to demonstrate changes in myocardial flow and collateral vessels on coronary angiography. No previous study of enhanced external counterpulsation has investigated quantitatively coronary perfusion and coronary enhanced external counterpulsation therapy has investigated quantitatively coronary perfusion and coronary flow reserve. Therefore, we therefore evaluated changes in coronary perfusion and coronary flow reserve by 13N-ammonia positron emission tomography, exercise tolerance testing, and by levels of nitric oxide and neurohumoral factors, in an attempt to clarify some of the mechanisms of the beneficial effects of enhanced external counterpulsation.

### Methods

#### Study population

Eleven patients with chronic stable angina met the following inclusion criteria: (1) age between 21 and 81 years; (2) symptoms consistent with Canadian Cardiovascular Society Classification angina level I, II, or III; (3) evidence of coronary artery disease, with angiographically proved >90% stenosis in at least one or more major coronary arteries; (4) past history of myocardial infarction documented by elevation of creatine phosphokinase and/or development of abnormal Q waves on the electrocardiogram; (5) nuclear exercise stress test, positive for myocardial infarction or ischaemia.

Patients were excluded if they had the following: (1) myocardial infarction or CABG in the preceding 3 months; (2) intervention in the preceding 2 weeks; (3) unstable angina; (4) overt congestive heart failure; (5) left ventricular ejection fraction <30%; (6) significant valvular disease; (7) blood pressure >180/100 mmHg; (8) a permanent pacemaker or implantable cardioverter defibrillator; (9) non-bypassed left main stenosis >50%; (10) severe peripheral vascular disease, phlebitis, deep vein thrombosis, etc.; (11) bleeding diathesis, warfarin use with International Normalized Ratio >2.0; (12) atrial fibrillation or frequent ventricular premature construction, etc. that interferes with enhanced external counterpulsation triggering; (13) were pregnant; (14) were enrolled in cardiac rehabilitation; (15) were enrolled in another research programme.

Medications, apart from nitroglycerin, remained unchanged during this study. Patients underwent a treadmill test, 13N-ammonia positron emission tomography, and blood collection, before and within 4 weeks of enhanced external counterpulsation therapy. Patients’ characteristics are shown in Table 1.

### Enhanced external counterpulsation therapy

The enhanced external counterpulsation machine (Vasomedical, Westbury, New York) is composed of an air compressor, a computer console, a set of cuffs and a treatment table. Before treatment, the cuffs are wrapped around both calves, and the lower and upper thighs (including the buttocks) of the patient. The enhanced external counterpulsation machine inflates the cuffs with air and then deflates them, in a sequence that is synchronized with the patient’s cardiac cycle, so that the pressure is applied sequentially from the calves to the buttocks, starting in early diastole. At the end of diastole, the compressed air is released rapidly from the cuffs to remove the externally applied pressure.

Enhanced external counterpulsation therapy was applied in 1-h sessions, once or twice daily, over a period of 18 to 35 days, to provide a total of 35 h of treatment, which is comparable with a randomized controlled trial. During each session, the change in the patient’s blood pressure wave was monitored by finger plethysmography. A cuff pressure of approximately 250 mmHg was applied, so that the ratio of plethysmographically measured diastolic peak pressure to systolic peak pressure was 1–5 times or higher.

### Exercise tolerance test

All patients performed an exercise tolerance test following the standard Bruce protocol, before and after the treatment period. During the exercise-tolerance test, ECG and blood pressure were monitored. The double
product was calculated as heart rate times systolic blood pressure. Exercise time, the time to 1 mm ST depression, and the double product were measured during exercise. The values of these parameters, measured before and after the therapy, were compared.

**Positron emission tomography study**

The $^{13}$N-ammonia positron emission tomography studies, both before and after enhanced external counterpulsation therapy, were performed at rest and after dipyridamole infusion. All patients underwent the positron emission tomography study at rest first; the image was acquired immediately after intravenous administration of $^{13}$N-ammonia tracer. One hour later, the positron emission tomography study was repeated after dipyridamole infusion.

Dipyridamole (0·56 mg · kg$^{-1}$ body weight) was administered intravenously over 4 min. Three minutes after the end of the dipyridamole administration, $^{13}$N-ammonia tracer was injected intravenously again and the corresponding image was acquired immediately. The average value of $^{13}$N-ammonia tracer was about 11 mCi both at rest and with dipyridamole. The regions of interest on each myocardial wall were drawn manually on the positron emission tomography images acquired both at rest and with dipyridamole, before and after enhanced external counterpulsation therapy. Myocardial perfusion, both at rest and with dipyridamole, was calculated for the regions of interest. The method of calculation has been described previously.$^{[10]}$ Coronary flow reserve was calculated by dividing the myocardial perfusion with dipyridamole by that at rest. The investigators interpreting the results did not have access to clinical information regarding the patients.

Values of myocardial perfusion obtained on positron emission tomography were classified in two ways. First by myocardial region (overall, anterior, septal, lateral, and inferior). The ‘overall’ value was computed as the average of the values obtained for the anterior, septal, lateral, and inferior walls. Second, a classification was made according to the presence or absence of coronary artery stenosis. Coronary artery disease was defined as a region with a stenotic coronary artery, and ‘non-coronary artery disease’ as a region with a normal coronary artery. Coronary artery stenosis was defined as a stenosis of over 90% in a major coronary artery demonstrated by coronary angiography.

**Statistical analysis**

All values were expressed as mean ± SD. Paired t-tests were used to compare the values of parameters before and after enhanced external counterpulsation therapy. One-way ANOVA repeated measure with multiple comparison test, followed by Scheffé’s test, was used to compare data on nitric oxide and neurohumoral factors. A value of $P<0.05$ was considered significant statistically.

This enhanced external counterpulsation study was approved by the Ethical Committee of Kyoto University.

**Results**

**Myocardial perfusion and coronary flow reserve in myocardial wall regions**

As shown in Table 2, myocardial perfusion at rest increased overall, and in anterior walls after enhanced external counterpulsation therapy. Myocardial perfusion with dipyridamole significantly improved in the anterior wall after enhanced external counterpulsation therapy.

Coronary flow reserve increased significantly only in the anterior region, from 1·75 ± 0·24 ratio to 2·08 ± 0·28 ratio (Table 3).

**Myocardial perfusion and coronary flow reserve in regions with and without coronary artery disease**

As shown in Table 4, resting myocardial perfusion in the regions with coronary artery disease increased after enhanced external counterpulsation therapy, from 0·71 ± 0·26 ml · min$^{-1} · g^{-1}$ to 0·87 ± 0·41 ml · min$^{-1} · g^{-1}$, $P<0.05$. Myocardial perfusion with dipyridamole increased after enhanced external counterpulsation therapy only in the region of the coronary artery disease (1·39 ± 0·70 ml · min$^{-1} · g^{-1}$ vs 1·73 ± 1·21 ml · min$^{-1} · g^{-1}$, $P<0.05$). As a result, coronary flow reserve showed no significant change after enhanced external counterpulsation therapy in either the coronary artery disease or non-coronary artery disease region.

**Exercise tolerance test**

As compared with baseline, the time to 1 mm ST depression was prolonged significantly from 190·5 ± 115·5 s to
**Table 2**  **Myocardial perfusion at rest and with dipyridamole in myocardial wall regions**

<table>
<thead>
<tr>
<th></th>
<th>Overall (ml. min⁻¹.g⁻¹)</th>
<th>Anterior (ml. min⁻¹.g⁻¹)</th>
<th>Septal (ml. min⁻¹.g⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>REST</strong></td>
<td>0.69 ± 0.27</td>
<td>0.71 ± 0.26</td>
<td>0.81 ± 0.37</td>
</tr>
<tr>
<td></td>
<td>1.39 ± 0.27</td>
<td>1.26 ± 0.65</td>
<td>1.59 ± 0.68</td>
</tr>
<tr>
<td><strong>DIP</strong></td>
<td>0.85 ± 0.47*</td>
<td>0.86 ± 0.31*</td>
<td>0.86 ± 0.50</td>
</tr>
<tr>
<td></td>
<td>1.85 ± 1.33</td>
<td>1.85 ± 0.94**</td>
<td>1.52 ± 0.99</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Lateral (ml. min⁻¹.g⁻¹)</th>
<th>Inferior (ml. min⁻¹.g⁻¹)</th>
</tr>
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<tbody>
<tr>
<td><strong>REST</strong></td>
<td>0.64 ± 0.28</td>
<td>0.73 ± 0.30</td>
</tr>
<tr>
<td></td>
<td>1.45 ± 0.98</td>
<td>1.56 ± 0.97</td>
</tr>
<tr>
<td><strong>DIP</strong></td>
<td>0.84 ± 0.56</td>
<td>0.84 ± 0.52</td>
</tr>
<tr>
<td></td>
<td>1.92 ± 1.80</td>
<td>2.11 ± 1.66</td>
</tr>
</tbody>
</table>

Baseline = before enhanced external counterpulsation therapy; post-EECP = after enhanced external counterpulsation therapy; overall = the average of the values obtained for the anterior, septal, lateral and inferior walls; anterior = myocardial perfusion at anterior wall; septal = myocardial perfusion at septal wall; lateral = myocardial perfusion at lateral wall; inferior = myocardial perfusion at inferior wall; REST = the value of myocardial perfusion at rest; DIP = the value of myocardial perfusion with dipyridamole.

*P<0.05 compared with baseline; **P<0.02 compared with baseline.

**Table 3**  **The change in coronary flow reserve in myocardial wall regions**

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Anterior</th>
<th>Septal</th>
<th>Lateral</th>
<th>Inferior</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>1.98 ± 0.24</td>
<td>1.75 ± 0.24</td>
<td>2.03 ± 0.10</td>
<td>2.22 ± 0.54</td>
<td>2.05 ± 0.48</td>
</tr>
<tr>
<td><strong>Post-EECP</strong></td>
<td>2.01 ± 0.36</td>
<td>2.08 ± 0.28*</td>
<td>1.82 ± 0.83</td>
<td>1.96 ± 0.63</td>
<td>2.19 ± 0.59</td>
</tr>
</tbody>
</table>

Baseline = before enhanced external counterpulsation therapy; post-EECP = after enhanced external counterpulsation therapy; overall = the average of the values obtained for the anterior, septal, lateral and inferior walls; anterior = myocardial perfusion at anterior wall; septal = myocardial perfusion at septal wall; lateral = myocardial perfusion at lateral wall; inferior = myocardial perfusion at inferior wall.

#P<0.04 compared with baseline.

375.5 ± 202.4 s, P<0.01 after enhanced external counterpulsation therapy (Fig. 1). The double products at peak exercise did not change significantly (Fig. 1).

**Nitric oxide and neurohumoral factors**

In 1 month after enhanced external counterpulsation therapy, the nitric oxide level increased to 107.9 ± 59.9 µmol (P<0.02, vs baseline) (Fig. 2). Figure 3 shows the changes in human atrial and brain natriuretic peptide levels before and after enhanced external counterpulsation therapy. The value of human atrial natriuretic peptide 1 week after enhanced external counterpulsation therapy was decreased significantly compared with that of control (P<0.02). The brain natriuretic peptide levels significantly decreased from the baseline value of 36.2 ± 36.5 pg . ml⁻¹ to 24.1 ± 26.0 pg . ml⁻¹ (P<0.05) at 1 week after completion of enhanced external counterpulsation therapy.

**Discussion**

In this study, we have demonstrated, by non-invasive methods, that enhanced external counterpulsation therapy for patients with chronic stable angina pectoris increased myocardial perfusion and enhanced dipyridamole-induced coronary vasodilatation. On exercise testing, the time to 1-mm ST depression was increased significantly, with a similar trend in exercise duration. Nitric oxide levels, measured at rest, were increased, while human atrial natriuretic peptide and brain natriuretic peptide levels were decreased, following the course of enhanced external counterpulsation treatments.

**Myocardial perfusion by¹³⁷N-ammonia positron emission tomography study**

In several previous studies, the beneficial effects of enhanced external counterpulsation therapy were
<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>CAD (58 segments)</th>
<th>Non-CAD (28 segments)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>REST (ml. min(^{-1}). g(^{-1}))</td>
<td>DIP (ml. min(^{-1}). g(^{-1}))</td>
<td>CFR (ratio)</td>
</tr>
<tr>
<td>Baseline</td>
<td>0.69 ± 0.27</td>
<td>1.39 ± 0.77</td>
<td>1.98 ± 0.24</td>
</tr>
<tr>
<td>Post-EECP</td>
<td>0.85 ± 0.47*</td>
<td>1.85 ± 1.33</td>
<td>2.01 ± 0.36</td>
</tr>
</tbody>
</table>

Baseline = before enhanced external counterpulsation therapy; post-EECP = after enhanced external counterpulsation therapy; overall = the average of the values obtained for the anterior, septal, lateral and inferior walls; CAD = defined as a region with a stenotic coronary artery; non-CAD = defined as a region with normal coronary artery; REST = the value of myocardial perfusion at rest; DIP = the value of myocardial perfusion with dipyridamole; CFR = the value of coronary flow reserve.

*P < 0.05 compared with baseline.
attributed to the development and recruitment of the collateral vessels\textsuperscript{[4–9]}. However, it may be difficult to demonstrate changes in the collateral circulation on coronary angiography. In a previous study of 11 patients after enhanced external counterpulsation therapy, five patients had increased myocardial vascularity, four had equivocal changes, and two had no visible change on coronary angiography\textsuperscript{[12]}. The present study evaluated the collateral vessels non-invasively and directly with \textsuperscript{13}N-ammonia positron emission tomography, a technique that allows an assessment of myocardial perfusion and coronary flow reserve.

Myocardial perfusion at rest increased after enhanced external counterpulsation therapy; the increases overall, and for specific regions (anterior wall and coronary artery disease) were statistically significant. These results are consistent with the development and recruitment of the collateral vessels, not only in an ischaemic area but also in a wider area in the heart. This is likely to be the result of increased shear stress throughout the whole body.

Figure 1 Left graph: changes in exercise test and double product before and after enhanced external counterpulsation therapy; right graph: change in the time to 1 mm ST depression, before and after enhanced external counterpulsation therapy. \#\textit{P}<0.01 compared with before enhanced external counterpulsation (EECP) therapy.

Figure 2 Control: before enhanced external counterpulsation therapy, next day: 1 day following completion of therapy, 1 week: 1 week after completion of therapy, 1 month: 1 month after completion of therapy. \#\textit{P}<0.02 vs control and \textit{P}<0.01 vs next day.

Figure 3 Control: before enhanced external counterpulsation therapy, next day: 1 day following completion of therapy, 1 week: 1 week after completion of therapy, 1 month: 1 month after completion of therapy. \#\textit{P}<0.05 vs control, \*\textit{P}<0.02 vs control. ■=human ANP; ■=BNP.
coronary artery, produced by enhanced external counterpulsation treatment.

Improvements in myocardial perfusion with dipyramidole after enhanced external counterpulsation therapy were statistically significant in the 'anterior wall' and 'coronary artery disease' regions. The slight decrease in perfusion noted in the 'septal wall' was attributed to the 'blood steal' phenomenon with dipyramidole[13]. These results suggested that enhanced external counterpulsation therapy enhanced dipyramidole-induced vasodilatation, especially in 'anterior' and 'coronary artery disease' areas. This is consistent with the absence of change in coronary flow reserve after enhanced external counterpulsation: since enhanced external counterpulsation increases myocardial perfusion at rest and after dipyramidole infusion, the ratio of perfusion with dipyramidole/perfusion at rest (coronary flow reserve) remains constant.

This study, using 13N-ammonia positron emission tomography, is the first non-invasive study to support the concept that enhanced external counterpulsation increases the development and recruitment of the collateral vessels and enhances coronary artery dilatation.

**Exercise tolerance test**

This study was not a randomized controlled study. However, the increase in exercise time after enhanced external counterpulsation seemed to be similar to the findings in the multicentre trial of enhanced external counterpulsation (MUST-EECP)[29]. The lack of statistical significance of the change in exercise time in this study may be owing to the small number of patients enrolled. Another possible reason may be related to development and recruitment of collateral vessels. Although the change of the time to 1 mm ST depression was statistically significant, it is recognized that collateral vessels cannot necessarily compensate completely for deficiencies in blood flow in a major coronary artery[14,15]. Therefore, we concluded that the exercise time, as an index of overall exercise tolerance, might not show a statistically significant increase under the conditions of this study.

**Nitric oxide and neurohumoral factors**

Nitric oxide levels increased and human atrial natriuretic peptide and brain natriuretic peptide levels decreased with enhanced external counterpulsation therapy. The raised level of nitric oxide at rest was considered to be due to an increase of endothelial enzyme nitric oxide synthase. A previous study showed that exercising for 10 days increased the gene expression of endothelial nitric oxide synthase in a dog[16]. Enhanced external counterpulsation therapy was applied over 3 to 7 weeks. During this period, every time enhanced external counterpulsation is applied, the drastic haemodynamic changes induced by the therapy can be expected to produce significant changes in shear stress. Therefore, we hypothesized that the increased shear stress induced by enhanced external counterpulsation during the treatment period triggers the gene expression of endothelial nitric oxide synthase. Further, the influence of the increase in nitric oxide can be expected to extend not only to coronary arteries but also to systemic arteries.

Human atrial and brain natriuretic peptide levels decreased after enhanced external counterpulsation therapy and this change was maintained for 1 month after completion of the course of enhanced external counterpulsation. Although the improvement of the results of the myocardial perfusion test on enhanced external counterpulsation therapy had been shown to persist for 3 years[6], no previous study has reported changes in the levels of neurohumoral factors. These results suggest that cardiac workload decreased and the effect of enhanced external counterpulsation therapy persisted for at least 1 month after completion of the course of treatment. These data suggest that enhanced external counterpulsation therapy not only improves myocardial perfusion but also decreases cardiac workload.

**Mechanisms of action of enhanced external counterpulsation**

Coronary blood flow is subject to autoregulation. Vasodilatation is a major component of the autoregulation process, and the endothelium plays an important role in influencing the degree of dilatation of arteries. Dipyridamole dilates vessels via the cAMP pathway[17], while nitric oxide does so via the cGMP pathway[18].

Our observations of increased myocardial perfusion with dipyridamole and nitric oxide at rest suggest that enhanced external counterpulsation produces improvements in coronary endothelial function; it is possible that this is accompanied by increased release of nitric oxide (due to increased endothelial nitric oxide synthase activity) in peripheral arteries[19], leading to a decrease of peripheral vascular resistance.

Lawson et al[20] reported that enhanced external counterpulsation therapy appeared to induce a ‘training’ effect, decreasing peripheral vascular resistance and the heart rate response to exercise. Soran et al.[21] reported little change in maximum oxygen intake, with a remarkable change in peak exercise time after enhanced external counterpulsation; this suggests that the efficiency of peripheral oxygen utilization increased after enhanced external counterpulsation therapy. These two reports[20,21] support our contention that enhanced external counterpulsation therapy has a peripheral effect in addition to its cardiac effect.

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Conclusions

This study provides evidence, by non-invasive methods, of increased myocardial perfusion at rest and after dipyridamole infusion on enhanced external counterpulsation therapy in patients with chronic stable angina pectoris, most probably related to the development and recruitment of collateral coronary vessels and the improvement of coronary dilatation. Coronary flow reserve was maintained. Nitric oxide levels were increased, decreasing peripheral resistance and cardiac workload.

Thus, there is a scientific rationale for the use of enhanced external counterpulsation therapy in such patients.

The improvement in myocardial perfusion and coronary flow reserve, the improving coronary endothelial function, and the prolongation of the time to 1-mm ST depression further validate using enhanced external counterpulsation therapy for patients with coronary artery disease.

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References