Usefulness of Carperitide for the Treatment of Refractory Heart Failure due to Severe Acute Myocardial Infarction

Migaku KIKUCHI, 1 MD, Motoyuki NAKAMURA, 1 MD, Tomomi SUZUKI, 1 MD, Madoka SATO, 1 MD, Toshitake TAKINO, 1 MD, and Katsuhiko HIRAMORI, 1 MD

SUMMARY

Carperitide (synthetic atrial natriuretic peptide) is a newly developed drug for the treatment of heart failure. Although this drug has been used for various types of heart failure, it remains unknown whether it has additive effects on hemodynamic parameters or renal excretory function during intensive treatment for acute refractory heart failure. We have examined the cardiorenal and hormonal effects of carperitide (0.05-0.10 µg/min/kg) in 9 patients (mean age: 67±8 years) with severe heart failure complicated with acute myocardial infarction, in which a range of intensive treatments have already been started. Hemodynamic parameters were determined before and 4, 24 and 48 hours after initiation of carperitide. Pulmonary capillary wedge pressure (mean±SD) had decreased dramatically from 21±6 to 11±5 mmHg (p<0.01) 4 hours after the treatment without significant renal effects. Heart rate and systemic blood pressure were not significantly changed. These beneficial effects were maintained for at least 24 hours. Plasma aldosterone levels fell significantly in response to the drug (from 148±68 to 56±29 pg/ml; p<0.05). However, mean hourly urine output remained unchanged after carperitide. In conclusion, intravenous infusion of carperitide promptly and persistently reduces left ventricular filling pressure without diuresis, hypotension, reflex tachycardia, or neurohormonal activation in patients with refractory heart failure due to severe acute myocardial infarction.

(Jpn Heart J 2001; 42: 271-280)

Key words: Atrial natriuretic peptide, Myocardial infarction, Hemodynamics, Preload, Aldosterone

Several studies have demonstrated that synthetic atrial natriuretic polypeptide (ANP) facilitates multifarious effects such as vasodilation,1) water-sodium diuresis,2) an anti-renin-aldosterone effect,3,4) and coronary vasodilation.5) All of these pharmacological effects seem to be beneficial for the treatment of heart failure. However, several clinical studies in patients with chronic congestive heart
failure have suggested that these cardiovascular and humoral effects were blunted because, in this chronic disorder, elevated circulating levels of ANP due to cardiac dysfunction may be sufficient to down-regulate ANP receptors. On the other hand, this type of down-regulation may not be apparent in acute heart failure and myocardial infarction because, in these conditions, the receptors may not be exposed to high ANP levels for long enough to initiate down-regulation. Therefore, although administration of synthetic ANP may not be sufficiently beneficial for the treatment of chronic heart failure, it may be hypothesized that its use would be effective in acute severe heart failure. As previously reported, we have proved that administration of a low-dose synthetic ANP infusion to patients with acute myocardial infarction (AMI) produces significant water-sodium diuresis and inhibits plasma aldosterone levels. However, it remains unclear whether these hemodynamic, diuretic and neurohumoral effects would persist for several hours or days during long-term infusion of synthetic ANP in patients with severe AMI complicated with heart failure.

In the present study, we investigated the usefulness of supplementary administration of synthetic ANP (carperitide) for more than 24 hours in patients with AMI complicated with severe heart failure in whom standard intensive medical therapy had already been started.

**Subjects and Methods**

All patients were admitted to Iwate Medical University's coronary care unit. A diagnosis of AMI was made based on a typical history of chest pain, typical electrocardiogram changes, and an increase in circulating levels of cardiac enzymes. After the baseline conventional intensive treatments (i.e., intravenous administration of diuretics, vasodilators, catecholamines, phosphodiesterase inhibitor, and/or intra-aortic balloon pumping) were performed, patients with AMI complicated with pulmonary congestion, who met the hemodynamic criteria, i.e., a mean pulmonary capillary wedge pressure (PCWP) exceeding 15 mmHg, were enrolled in this study.

Nine patients (5 males and 4 females) with a mean age of 67 years were recruited (Table). Their infarcted region was anterior wall in 5 patients, inferior wall in 2, anterolateral wall in one and posterior wall in one. On Forrester's classification, 7 and 2 patients were categorized as subsets II and IV, respectively. Although left ventricular ejection fraction averaged 39%, one patient had an ejection fraction of 60% complicated with severe ischemic mitral regurgitation. Primary coronary angioplasty was performed on 7 of the 9 patients, and recanalization was successfully achieved in these patients. As baseline therapy, all patients received intravenous furosemide and continuous intravenous nitrate
In all patients, continuous intravenous infusion of carperitide was started at a dose of 0.025 µg/kg/min, and then maintained at 0.05-0.1 µg/kg/min after confirmation of no blood pressure reduction. Infusion was discontinued when hemodynamic stability was achieved, in addition to improvement of clinical signs. Patients in whom doses of drugs used in the initial therapy were changed after carperitide administration were excluded from the study. Patients who were diagnosed with inferior AMI complicated with right ventricular infarction were also excluded. Furosemide use was permitted whenever necessary.

Blood pressure, heart rate, pulmonary arterial pressure, mean PCWP, mean right atrial pressure and cardiac index were measured in all patients through a Swan-Ganz catheter. These hemodynamic parameters were determined before and 4, 24 and 48 hours after initiation of carperitide. Plasma concentrations of renin and aldosterone were measured before and approximately 9 hours after the start of carperitide administration. Urine volumes collected by bladder catheter were also measured from the start of baseline therapy to immediately before the start of carperitide administration, and to the end of carperitide administration. Urine volumes were calculated and analyzed in terms of volume per hour.

**Statistical Analysis:** Data are shown as mean±standard deviation. The data obtained were analyzed using a paired t-test, Wilcoxon's rank sum test, and analysis of variance. A p value<0.05 was considered statistically significant.

### Table. Baseline Characteristics of Patients with Severe Heart Failure due to Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age/sex</th>
<th>Site of MI</th>
<th>Killip/Forrester Subset</th>
<th>Peak CK (IU/ml)</th>
<th>EF (%)</th>
<th>Preceding treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65/m</td>
<td>inf-lat</td>
<td>2/2</td>
<td>3036</td>
<td>60**</td>
<td>PTCA, IABP, drug, duration</td>
</tr>
<tr>
<td>2</td>
<td>66/m</td>
<td>ant</td>
<td>2/4</td>
<td>4203*</td>
<td>20</td>
<td>F, N</td>
</tr>
<tr>
<td>3</td>
<td>79/f</td>
<td>ant</td>
<td>3/2</td>
<td>5330</td>
<td>38</td>
<td>F, N</td>
</tr>
<tr>
<td>4</td>
<td>71/m</td>
<td>inf</td>
<td>2/2</td>
<td>5419</td>
<td>51</td>
<td>C, F</td>
</tr>
<tr>
<td>5</td>
<td>58/f</td>
<td>ant</td>
<td>2/2</td>
<td>6361</td>
<td>41</td>
<td>C, F</td>
</tr>
<tr>
<td>6</td>
<td>59/m</td>
<td>inf</td>
<td>2/2</td>
<td>5016</td>
<td>40</td>
<td>A, F, N</td>
</tr>
<tr>
<td>7</td>
<td>66/f</td>
<td>ant</td>
<td>4/2</td>
<td>10038</td>
<td>41</td>
<td>A, B, C, F</td>
</tr>
<tr>
<td>8</td>
<td>61/m</td>
<td>ant</td>
<td>2/4</td>
<td>11980</td>
<td>32</td>
<td>B, C, F, N</td>
</tr>
<tr>
<td>9</td>
<td>80/f</td>
<td>ant-lat</td>
<td>4/2</td>
<td>10596</td>
<td>30</td>
<td>A, B, C, F, N, P</td>
</tr>
</tbody>
</table>

* on admission, ** with ischemic mitral regurgitation.
A=dopamine; B=dobutamine; C=nicorandil; EF=left ventricular ejection fraction; F=furosemide; IABP=intraaortic balloon pumping; MI=myocardial infarction; N=nitrate; P=phosphodiesterase inhibitor; PTCA=percutaneous transluminal coronary angioplasty; ant=anterior; inf=inferior; lat=lateral.
RESULTS

The baseline conventional intensive therapy lasted for 1.0 to 86.5 hours (Table). Carperitide was then administered at a maintenance dose of 0.05 µg/kg/min in 8 patients and at 0.1 µg/kg/min in one. Carperitide administration was continued for more than 48 hours in 3 patients, for more than 24 hours in 3 patients, and for more than 8 hours in 3 patients.

Hemodynamics: Figure 1 shows the changes in hemodynamic parameters. Blood pressure (systolic / diastolic) was 117±25 / 68±16 mmHg before the start of carperitide infusion and had decreased slightly to 107±14 / 61±8 mmHg at 4 hours after infusion (NS). Heart rate showed no significant changes during carperitide administration, compared to pre-carperitide. Pulmonary vascular resis-

![Graphs showing changes in hemodynamic parameters over time](image-url)

**Figure 1.** Changes in hemodynamic parameters. Hemodynamic parameters were determined before and 4, 24 and 48 hours after initiation of carperitide. The data are the mean±standard deviation. *p<0.05, **p<0.01 versus before carperitide. BP=blood pressure; HR=heart rate; PVR=pulmonary vascular resistance; SVR=systemic vascular resistance.
tance and systemic vascular resistance also did not significantly change at 4 hours after carperitide infusion, compared to pre-carperitide (PVR, from 105±41 dyn•sec/cm$^5$ to 127±45 dyn•sec/cm$^5$; NS: SVR, from 1386±496 dyn•sec/cm$^5$ to 1447±391 dyn•sec/cm$^5$; NS). As shown in Figure 2, at 4 hours after carperitide administration, pulmonary artery pressure (systolic / diastolic) had decreased significantly from 40±8 / 21±5 to 26±6 / 13±4 mmHg ($p<0.01$). Mean right atrial pressure also decreased slightly from 10±3 to 7±3 mmHg ($p<0.05$). PCWP was halved from 21±6 to 11±5 mmHg ($p<0.05$). These significant decreases were maintained for more than 48 hours. Although the cardiac index decreased temporarily at 4 hours after carperitide infusion compared to pre-infusion, this posed no clinical problems such as preshock, tachycardia or oliguria, and it returned to baseline by the 24 hour time point.

**Urine volume:** Although mean urine volumes per hour before carperitide varied widely, no statistically significant difference was observed in urine volumes before and during administration of the drug. The dose of furosemide per hour decreased somewhat during carperitide infusion, but the dose was maintained at $>5$ mg/hr (Figure 3).

![Graphs](image-url)
Neurohumoral factors: Plasma renin concentrations showed no significant change approximately 9 hours after carperitide administration compared with pre-treatment values. However, plasma aldosterone concentrations had decreased significantly from 148±68 to 56±29 pg/ml (p<0.05) at this time point (Figure 4).

![Figure 3](image1.png) Changes in urine volume (left) and dose of furosemide (right) before and during use of carperitide.

![Figure 4](image2.png) Changes in plasma concentrations of renin (left) and aldosterone (right) before and during use of carperitide.
DISCUSSION

This study has demonstrated that intravenous infusion of carperitide promptly and persistently reduces left ventricular filling pressure without diuresis, hypotension, reflex tachycardia or neurohormonal activation in patients with severe acute heart failure in which routine intensive treatments have already been started.

In contradiction of our hypothesis, no diuretic effects were obvious during the study, although the use of furosemide decreased slightly after carperitide infusion. Cody, et al. observed that ANP significantly increases sodium and water excretion in patients with congestive heart failure, but the magnitude of sodium or water excretion was not commensurate with clinically effective diuresis. Other reports in patients with chronic heart failure have also shown that a bolus injection of synthetic ANP is not potent enough to induce a renal excretory effect comparable to that of furosemide and that a single dose of furosemide and ANP does not enhance diuresis or sodium excretion. This suggests that the renal effect of ANP is attenuated irrespective of the type of severe heart failure. In hemodynamically compromised heart failure, as seen in patients in the present study, renal effects may be blunted due to reduction in renal blood flow and insufficient renal perfusion pressure. These mechanisms may result in a blunted renal response to carperitide in severe heart failure. On the other hand, Kitashiro, et al. have recently reported that concomitant administration of carperitide increases diuresis in patients with acute refractory heart failure, and then decreases PCWP and increases the cardiac index for 48 hours to 7 days. Further studies will be needed to determine whether renal excretory function is improved by carperitide in this disorder.

Although this study could not determine the exact mechanism by which carperitide lowered left ventricular filling pressure at 4 hours after administration despite the lack of a diuretic effect, several possible explanations are worthy of consideration. First, ANP has been reported to decrease the volume of circulating plasma by increasing vascular permeability, possibly leading to hemodynamic improvement. Second, ANP acts as a vasodilator mainly on veins rather than arteries under high plasma norepinephrine concentrations in patients with heart failure, although its vasodilator action has been reported to be less than nitrates. Carperitide may decrease preload without changes in systemic vascular resistance. Third, as ANP receptors are abundantly present in the pulmonary vascular bed, ANP has a particularly potent vasodilatory effect on the pulmonary artery. However we could not find a significant change in pulmonary vascular resistance in our patients. Finally, ANP has coronary vasodilatory effects and increases myocardial perfusion to the ischemic area. ANP also ameliorates
myocardial dysfunction by preventing reperfusion injury. Therefore ANP might improve left ventricular diastolic dysfunction by reducing myocardial injury due to ischemia and reperfusion.

While conventional diuretics and vasodilators reduce pulmonary congestion by decreasing cardiac preload, they may also generate problems such as decreased cardiac output, abnormal electrolyte balance, activation of neurohumoral factors, and induction of drug resistance. Indeed, although nitrates have been widely used in the acute phase of myocardial infarction, they can potentially induce adverse reflex tachycardia with a reduction in blood pressure, and may facilitate neurohumoral activation. It has been reported that ANP has a counteractive effect on nitrate-induced neurohumoral activation when given to patients with AMI. Use of furosemide in patients with chronic heart failure induces mild systemic vasoconstriction and stimulates neurohumoral factors, but these undesirable effects seem to be inhibited when furosemide is given in conjunction with ANP. We have previously reported that the use of ANP in uncomplicated AMI has an inhibitory effect on aldosterone. The present study also revealed that administration of ANP in addition to a nitrate, furosemide, and/or a catecholamine in patients with AMI complicated with severe heart failure significantly inhibited circulating levels of aldosterone. This phenomenon that carperitide infusion is associated with reduced plasma aldosterone concentrations without decreasing the plasma renin concentration may support the findings of a previous study by Atarashi, et al who reported that synthetic ANP inhibits aldosterone production from rat adrenal cells. This effect may be beneficial in terms of the prognosis of AMI because several recent reports have suggested that this mineralocorticoid is a potent stimulator of cardiac fibrosis and remodeling.

Limitation: The present study was not a randomized placebo-controlled study. It is therefore possible that the hemodynamic and hormonal changes seen after carperitide infusion were part of the natural course of this disorder or were effects of preceding treatments. However, hemodynamic amelioration, especially of ventricular filling pressure, occurred consistently within 4 hours of carperitide infusion irrespective of the interval between preceding treatments and the commencement of carperitide (Figures 1, 2 and Table). The reduction in plasma aldosterone levels was dissociated from changes in plasma renin concentrations (Figure 4). This type of change in plasma aldosterone coincides with our previous placebo-controlled study in patients with uncomplicated AMI. We therefore believe that these hemodynamic and endocrine effects were due to carperitide.

In conclusion, supplementary administration of carperitide to patients with AMI complicated with severe heart failure after the start of standard intensive medical therapy decreased ventricular filling pressure and reduced plasma aldosterone levels. In addition, no side effects such as serious arrhythmia, excessive
blood pressure reduction or reflex tachycardia were observed in any of our patients during carperitide infusion. This type of drug may thus be useful for the treatment of refractory heart failure due to severe AMI.

REFERENCES