Administration of Atrial Natriuretic Peptide Attenuates Reperfusion Phenomena and Preserves Left Ventricular Regional Wall Motion After Direct Coronary Angioplasty for Acute Myocardial Infarction

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To evaluate the effects of synthetic human atrial natriuretic peptide (hANP) on myocardial reperfusion injury and left ventricular remodeling, 19 patients within 12 h of a first attack of anterior myocardial infarction (AMI) underwent intracoronary injection of 25μg of hANP immediately after coronary angioplasty, combined with intravenous infusion of 0.025μg·kg⁻¹·min⁻¹ of hANP initiated on admission for 1 week (hANP group); 18 similar patients had saline administered (control group). The incidences of premature ventricular contraction, ventricular tachycardia and/or fibrillation in the hANP group were significantly less than in the control group after coronary angioplasty. Left ventricular ejection fraction was significantly greater and left ventricular end-diastolic volume index was significantly smaller 6 months after coronary angioplasty. Left ventricular regional wall motion of the infarcted segments significantly increased. Thus, hANP remarkably suppressed reperfusion phenomena and preserved left ventricular function through improvement of regional wall motion of the infarcted segments after coronary angioplasty. (Circ J 2003; 67: 443–448)

Key Words: Intracoronary administration; Left ventricular ejection fraction; Left ventricular end-diastolic volume index; Persistent ST-segment elevation; Ventricular tachycardia

Beneficial effects of atrial natriuretic peptide (ANP) on experimentally induced ischemia–reperfusion myocardial injury have been recently reported. It is known that ANP decreases sympathetic activity, suppresses the renin–angiotensin–aldosterone system and dilates the coronary artery. In addition, ANP protects against neutrophil-induced endothelial cytotoxicity, inhibits endothelin-1 secretion and reduces oxygen radical-induced cell damage and calcium overload in human hepatic stellate cells. These effects of ANP sufficiently cover the multiple mechanisms causing reperfusion injury and so it can be anticipated that intracoronary administration of ANP would reduce reperfusion injury. However, there does not appear to be any report of the effects of intracoronary administration of ANP in the clinical setting.

Hayashi et al have reported that ANP administration, combined with acute revascularization, prevented left ventricular remodeling 1 month after AMI. That result may be caused by the effects of ANP, and in addition, by its suppressive effects on collagen synthesis and inhibition of angiotensin II–induced proliferation of cardiac fibroblasts by blocking endothelin-1 gene expression, which has been shown to take place in rat. Thus, beneficial effects of ANP on the late outcome of AMI also can be anticipated.

The aim of the present study was to evaluate the effects of the combination of intracoronary administration and intravenous infusion of ANP on reperfusion phenomena with myocardial damage and left ventricular remodeling in patients with AMI after acute revascularization.
Patient Enrolment
We enrolled 40 consecutive patients satisfying the inclusion criteria of a first attack of anterior AMI within 12 h of symptom onset, without cardiogenic shock (Killip class 4)29 and/or ventricular tachycardia/fibrillation (VT/VF). Patients were judged eligible to have anterior AMI if they had chest pain accompanied by ST segment elevation of 2 mm or more in precordial leads V1–3 and/or V4 of the electrocardiogram (ECG) on admission. Because a preconditioning effect influences the prognosis of the patient after revascularization therapy,30 we excluded patients who had anginal chest pain within 1 week before admission. We obtained informed consent to a form authorized by the Review Board of the University Hospital from all subjects. The patients were randomized into 2 groups of 20 patients who received either recombinant human atrial natriuretic peptide (hANP; carpelitide, Suntory, Ltd, Osaka, Japan) or physiological saline. One patient in the hANP group and 2 patients in the saline group were excluded from the study because they had Thrombolysis in Myocardial Infarction (TIMI) grade 0 coronary blood flow31 in the culprit artery because they had hANP, human atrial natriuretic peptide; CK, serum creatine kinase concentration; CCU, coronary care unit; PDE, phosphodiesterase.

### Methods

#### Study Protocol
Continuous intravenous infusion of hANP (0.025 µg·kg\(^{-1} \cdot \text{min}^{-1}\)) or the same volume (1 ml/h) of saline was initiated immediately after admission in each group, and continued for 1 week. Coronary angiography was carried out immediately after initiation of the intravenous infusion of hANP or saline. Intracoronary injection of hANP (25 µg/min) or the same volume (10 ml/min) of saline for 1 min was performed via the balloon catheter immediately after successful coronary angioplasty. Revascularization was determined to be successful if a coronary blood flow of TIMI grade 3 was achieved. Left ventriculography was carried out under 30-degree right anterior oblique projection after intracoronary injection of hANP or saline. Follow-up coronary angiography and left ventriculography were performed 1 and 6 months after coronary angioplasty.

#### Parameters
Reperfusion Phenomena We counted the number of premature ventricular contractions (PVC), defined as the appearance of isolated successive ventricular beats32 within the infarct-related lesion of the proximal left anterior coronary artery was successfully performed. No cardiac event or re-stenosis of the stenting site detected by follow up angiography at 1 and 6 months after coronary angioplasty occurred in the subjects during the follow up period of 6 months. Consequently, the results in 19 patients with hANP (hANP group) and 18 patients with saline administration (control group) were analyzed.

#### Table 1 Clinical Characteristics and Medications of the Patients in the 2 Groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>hANP n=19, (%)</th>
<th>Control n=18, (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60 (11)</td>
<td>58 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>Male gender</td>
<td>15 (78)</td>
<td>13 (72)</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)*</td>
<td>97±10</td>
<td>95±10</td>
<td>NS</td>
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<tr>
<td>Systolic blood pressure (mmHg)*</td>
<td>121±28</td>
<td>125±32</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)*</td>
<td>80±21</td>
<td>84±26</td>
<td>NS</td>
</tr>
<tr>
<td>Revascularization time (h)*</td>
<td>6.2±1.8</td>
<td>6.3±1.7</td>
<td>NS</td>
</tr>
<tr>
<td>TIMI flow grade‡</td>
<td>0.5±0.52</td>
<td>0.5±0.51</td>
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</tr>
<tr>
<td>Rentrop grade of collateral flow§</td>
<td>0.3±0.47</td>
<td>0.3±0.46</td>
<td>NS</td>
</tr>
<tr>
<td>Killip class§</td>
<td>1.2±0.43</td>
<td>1.2±0.44</td>
<td>NS</td>
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<tr>
<td>CK on admission (IU/ml)</td>
<td>1,436±849</td>
<td>1,060±701</td>
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</tr>
<tr>
<td>Time to PTCA from admission (min)</td>
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<td>24.8±2.9</td>
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<td>Risk factors</td>
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<tr>
<td>Diabetes mellitus</td>
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<td>12 (67)</td>
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<td>8 (44)</td>
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<tr>
<td>Smoking</td>
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<td>8 (44)</td>
<td>NS</td>
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<td>In-CCU therapies</td>
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<td></td>
</tr>
<tr>
<td>Catecholamines</td>
<td>7 (37)</td>
<td>9 (50)</td>
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</tr>
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<td>PDE inhibitor</td>
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<td>1 (6)</td>
<td>NS</td>
</tr>
<tr>
<td>Diuretics</td>
<td>5 (26)</td>
<td>11 (61)</td>
<td>0.03</td>
</tr>
<tr>
<td>Nitrates</td>
<td>19 (100)</td>
<td>17 (94)</td>
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<td>Anti-arrhythmic agents</td>
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<td>9 (50)</td>
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</tr>
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<td>Enalapril (5–10 mg/day)</td>
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<td>18 (100)</td>
<td>NS</td>
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<tr>
<td>Aspirin (81 mg/day)</td>
<td>19 (100)</td>
<td>18 (100)</td>
<td>NS</td>
</tr>
<tr>
<td>In-hospital and follow up medications until 6 months after discharge from CCU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enalapril (5–10 mg/day)</td>
<td>19 (100)</td>
<td>18 (100)</td>
<td>NS</td>
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<tr>
<td>Aspirin (81 mg/day)</td>
<td>19 (100)</td>
<td>18 (100)</td>
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<td>I-blocker</td>
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<tr>
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<td>NS</td>
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<tr>
<td>Carvix channel blocker</td>
<td>14 (73)</td>
<td>13 (72)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Values measured on admission; † symptom onset-revascularization time; ‡ coronary flow grade of Thrombolysis in Myocardial Infarction before revascularization; § collateral flow grade of Rentrop; clinical severity of Killip classification. Data are number of patients (percentage) or mean±SD.

**Note:** This information is based on the content of the image and the context provided. Additional details and further analysis may be necessary for a comprehensive understanding.
Method was used for the measurement of LVEF and 6 months after coronary angioplasty. The area–length by left ventriculography, immediately and at 1 month and index (LVEDVI) and LV regional wall motion (LVRWM) who was unaware of the patient group category, measured LVEDVI and the centerline method was used to estimate LVRWM of each segment in each group were compared between the 2 groups by unpaired Student's t-test. Discrete variables were expressed as mean ± SD, and the 2 groups were compared by unpaired Student’s t-test. The change in the number of PVC in each group was analyzed by ANOVA. The incidence of VT/VF (baseline = 0) and ST>50% after coronary angioplasty were expressed as percentages and compared by Fisher’s exact test. The LVEF and LVEDVI were compared at each measurement time by unpaired Student’s t-test, which was also used to compare between the 2 groups the LVRWM of each segment at each measuring time point. The changes in LVEF, LVEDVI and LVRWM of each segment in each group were analyzed by ANOVA. The difference of mean values of BNP at each measuring time point was compared between the 2 groups by unpaired Student’s t-test, which was also used to compare the difference of mean values of cumulative CK release between the 2 groups. A value of p<0.05 was regarded as significant.

Results

The clinical characteristics of the patients are shown in Table 1. The percentage of patients receiving diuretics in the coronary care unit (CCU) in the hANP group was significantly less than in the control group, There was no difference in the other factors between the 2 groups. Medications in the CCU, while in-hospital and during the follow up period after discharge are shown in Table 1. Nitrate, angiotensin-converting enzyme inhibitor (enalapril 5–10 mg/day) and aspirin (81 mg/day) were used in all subjects from the 2nd day of admission and continued until 6 months after discharge from the CCU. No adverse effects, such as hypotension or bradycardia, were seen after intravenous or intracoronary administration of hANP.

There was no difference in the mean PVC number before coronary angioplasty between the hANP and control groups (6±2 vs 5±4 beats/10 min). The number of PVC after coronary angioplasty in the hANP group was significantly (p<0.01) less than in the control group (7±5 vs 194±78 beats/10 min). An increase in this value in the control group was significant (p<0.01), whereas no change was observed in the hANP group (Fig 1).

The incidence of VT/VF in the hANP group was significantly (p<0.05) less than in the control group (0 vs 33%), and the incidence of ST>50% in the hANP group was also significantly (p<0.05) less than in the control group (0 vs 44%) (Fig 2).

LVEF immediately and at 1 month after coronary angioplasty showed no significant difference between the hANP

Statistical Analyses

Continuous variables in the clinical characteristics were expressed as mean±SD, and the 2 groups were compared by unpaired Student’s t-test. Discrete variables were expressed in terms of patient number (percentage) and a comparison was made by Fisher’s exact test. The numbers of PVC before and after coronary angioplasty in each group were compared between the 2 groups by unpaired Student’s t-test. The change in the number of PVC in each group was analyzed by ANOVA. The incidence of VT/VF (baseline = 0) and ST>50% after coronary angioplasty were expressed as percentages and compared by Fisher’s exact test. The LVEF and LVEDVI were compared at each measurement time by unpaired Student’s t-test, which was also used to compare between the 2 groups the LVRWM of each segment at each measuring time point. The changes in LVEF, LVEDVI and LVRWM of each segment in each group were analyzed by ANOVA. The difference of mean values of BNP at each measuring time point was compared between the 2 groups by unpaired Student’s t-test, which was also used to compare the difference of mean values of cumulative CK release between the 2 groups. A value of p<0.05 was regarded as significant.
and control groups (immediately: 53.1±12.3% vs 52.2±14.2%, 1 month: 55.3±13.5% vs 53.8±13.9%). However, at 6 months after coronary angioplasty the LVEF in the hANP group was significantly (p<0.05) greater than that in the control group (61.8±14.2% vs 55.2±15.1). The increase in LVEF from immediately after to 6 months after coronary angioplasty in the hANP group, whereas no change was observed in the LVRWM of the other segments in either group and there was no difference between the 2 groups.

The only significant difference between the 2 groups was diuretic usage in the CCU and may have been the diuretic effect of hANP. There were no other differences in the clinical characteristics of the patients or their medications either in the CCU or during the 6-month follow-up period between the 2 groups.

**Effects of hANP on Reperfusion Phenomena**

Arrhythmias, such as frequent PVC and/or VT/VF, have attracted attention as indicators of successful revascularization. However, Wehrens et al reported that in patients in whom reperfusion arrhythmias developed, the serum CK concentration was significantly higher than in those without arrhythmias, which suggests that acceleration of ventricular arrhythmias indicates the reperfusion injury that...
Effect of ANP After Direct Coronary Angioplasty

Effect of ANP After Direct Coronary Angioplasty

Takata et al reported that administration of exogenous ANP prevented reperfusion arrhythmia and also avoided the decrease in high-energy phosphates in the inner layers of the myocardium in animal models of ischemia–reperfusion. Thus, the remarkable reduction of reperfusion arrhythmias in the hANP group suggests a protective effect of hANP with regard to the development of myocardial reperfusion injury.

Claeyssens et al reported that ST>50% after coronary angioplasty implies coronary microvascular injury. The present study showed that hANP almost totally prevented ST>50% measured at 10 min after coronary angioplasty. Because reperfusion microvascular injury develops abruptly, not gradually, after reperfusion, the estimation in the present study at 10 min likely reflects accurately the development of microvascular injury. Thus, its intracoronary administration might play a large role in the inhibitory effect of hANP.

LV Global Function and LVRWM

The present results showed that LVEF was significantly greater in the hANP group than in the control group at 6 months after coronary angioplasty, which was caused by the remarkable improvement in the LVRWM of the infarcted segment. The LVEDVI was significantly smaller in the hANP group than in the control group at 1 and 6 months after coronary angioplasty, indicating that hANP improved the late outcome of the patients. It is known that infarct expansion followed by subsequent ventricular remodeling after AMI develops within 1 week of onset, so the first week of treatment of AMI is critically important for avoiding LV remodeling. Therefore, we ensured the intravenous infusion of hANP occurred during this period. This volume reduction presumes that intravenous infusion of hANP might modify the process of infarct expansion and suppress subsequent ventricular remodeling. It is also likely that improvement of the contractile function of the infarcted segment plays an important role in the suppression of LV remodeling.

The analysis of LVRWM revealed significant improvement in the infarcted segments at 1 and 6 months after coronary angioplasty in the hANP group in accordance with suppressed CK release, which was indicated by the difference in the cumulative CK release between the 2 groups.

The results of the analysis of the serial changes in BNP concentration in blood suggested that deterioration of LV function during the early stage of the post-infarction process was suppressed in the hANP group. These results also suggest that administration of hANP helped to salvage jeopardized myocardium better than in the control group, an effect that is presumably mainly the result of the preventive effect of intracoronary administration of hANP on reperfusion injury, which destroys myocardium abruptly after reperfusion.

Comparison With Previous Reports

Herrmann et al assessed the effects of intracoronary continuous infusion of ANP in normal subjects, by increasing the dosage from 1.75 to 84 μg/min, and reported that ANP dilated epicardial coronary arteries. Dubois-Rande et al infused 0.06–0.8 μg/min of ANP for 8 min into the left coronary arteries of congestive heart failure patients and normal subjects, and stated that this dose of ANP did not alter coronary circulation or LV contractility, whereas there was a hemodynamic improvement with a decrease in cardiac afterload at high dosages. Kai et al investigated the effect of intracoronary administration of ANP (0.03 μg/min for 15 min) on pacing-induced myocardial ischemia in patients with effort angina, and reported that ischemia was improved by the dilatation of coronary collateral vessels.

Kugiyama et al compared the effect of intracoronary infusion of nitroglycerin and ANP (0.5 μg·kg⁻¹·min⁻¹ for 2 min) in patients with coronary spastic angina and normal subjects, and reported equal dilatation of coronary arteries in both groups. The dose of hANP we used was similar to that used in the 2 later studies. Although we did not directly evaluate the coronary dilating effect of hANP, it is presumable that the beneficial effect shown in our study was partially because of coronary artery and collateral vessel dilatation.

Study Limitations

The intracoronary administration of hANP was done after coronary angioplasty in combination with intravenous infusion initiated before the procedure. Therefore, the role of intracoronary administration of hANP in suppressing reperfusion phenomena is unclear with specific regard to the role of the effect of intravenous infusion. Secondly, the role of intravenous infusion of hANP is unclear in terms of its beneficial effects on LV remodeling, in relation to its role in the suppression of reperfusion phenomena. Furthermore, although the suppressive effect of hANP on reperfusion phenomena was significant, the mechanisms involved can only be presumed. Further studies are necessary to clarify the role, and the mechanisms of its effect, of intracoronary administration of hANP.

References


