Beneficial Effects of Atrial Natriuretic Peptide on Exercise-Induced Myocardial Ischemia in Patients With Stable Effort Angina Pectoris

Cha-Po Lai, MD; Kensuke Egashira, MD; Hideki Tashiro, MD; Hideki Narabayashi, MD; Samon Koyanagi, MD; Tsutomu Imaizumi, MD; and Akira Takeshita, MD

Background. It has been shown that atrial natriuretic peptide (ANP), an endogenous vasodilator, dilates coronary arteries and decreases coronary vascular resistance. The purpose of this study was to determine whether an intravenous administration of ANP attenuated exercise-induced myocardial ischemia in 14 patients with stable effort angina pectoris.

Methods and Results. The first 12 patients (patients 1–12) who had exercise-induced ST segment depression underwent treadmill exercise testing and the last seven patients (patients 8–14) underwent the exercise 201Tl–single-photon emission computed tomography (SPECT) study while synthetic 28–amino acid α-human ANP (0.1 μg/kg per minute) or saline was intravenously infused in a double-blind, cross-over manner. The duration of exercise testing was the same during ANP and saline infusion, which was determined in preliminary exercise testings in each patient to cause a transient perfusion defect and/or ischemic ST segment depression. During saline infusion, all 12 patients developed exercise-induced ischemic ST segment depression, whereas no significant ST segment depression appeared during ANP infusion. Average ST segment depression during ANP infusion was significantly less (p < 0.01) than that during saline infusion (0.8±0.1 vs. 0.2±0.1 mV, mean±SD). The averaged extent and severity scores assessed by 201Tl–SPECT during ANP infusion were significantly lower than those during saline infusion (extent score: 0.22±0.20 vs. 0.42±0.20; severity score: 18.77±23.45 vs. 38.24±24.04, respectively). ANP decreased resting systolic blood pressure from 125±15 to 110±15 mm Hg (p < 0.01) but did not alter resting heart rate. At peak exercise, systolic blood pressure, heart rate, and the rate–pressure products did not differ during ANP and saline infusion. At peak exercise, plasma ANP increased from 98±45 to 4,383±2,782 pg/ml and cGMP increased from 3.6±1.7 to 34.5±16.1 pmol/ml during ANP infusion; values were significantly higher than those during saline infusion (from 96±42 to 133±66 pg/ml and from 3.4±1.8 to 4.6±2.1 pmol/ml, respectively).

Conclusions. An intravenous administration of ANP attenuated exercise-induced myocardial ischemia in patients with stable effort angina pectoris. Although the mechanism by which ANP attenuated myocardial ischemia was not defined, increased myocardial perfusion to the ischemic region might be an important factor.

Key Words • atrial natriuretic peptide • angina pectoris, effort • testing, treadmill exercise • 201Tl–SPECT

Twenty-eight–amino acid α-human atrial natriuretic peptide (ANP), which is mainly released from atrial myocytes in a physiological condition, plays an important role in regulation of body fluid homeostasis and blood pressure.1–6 In addition, ANP causes vasodilatation by activating particulate guanosine cyclase, which increases cGMP in vascular smooth muscle cells, resulting in the decrease in intracellular free calcium ions producing vascular relaxation.7,8 Recent studies in animals and humans have indicated that an intravenous or intracoronary administration of ANP results in vasodilation of large epicardial and small resistance coronary arteries.9–12 Chu et al13 have shown that in chronically instrumented conscious dogs with flow-limiting coronary stenosis, ANP increased regional coronary blood flow and the ratio of subendocardial to subepicardial myocardial blood flow in the ischemic myocardium. Furthermore, it has been suggested that ANP has little direct effect on myocardial contractility and energetics and that ANP decreases left ventricular end-diastolic pressure by reducing venous return.12,15 In addition, a reflex increase in heart rate during hypotension induced by ANP is less prominent than during hypotension caused by nitrates.16,17 These findings suggest that ANP may improve myocardial perfusion to the ischemic area with no increase in myocardial oxygen...
consumption in ischemic heart disease. However, the efficacy of ANP in the treatment of angina pectoris has not been examined.

The present study aimed to determine whether an intravenous infusion of ANP attenuated exercise-induced myocardial ischemia in patients with stable effort angina pectoris. Exercise testing was done while ANP or saline was intravenously infused in a double-blind, cross-over manner. The magnitudes of ST segment depression and the extent and severity scores of myocardial ischemia assessed by 207TI–single-photon emission computed tomography (SPECT) were compared during ANP and saline infusion.

Methods

Subjects

This study was done in 14 patients (13 men and one woman; age, 43–73 years) with stable effort angina pectoris who had significant fixed stenosis in one or more coronary arteries. Patients who had unstable angina, previous myocardial infarction, valvular heart disease, or heart failure were excluded. Patients who had ST segment abnormalities at rest were also excluded. No patient was taking digitalis. All patients underwent preliminary exercise testings by the Bruce protocol at least on two occasions before the drug study, and 12 of 14 patients showed horizontal or downsloping ST segment depression of ≥0.1 mV at least in two leads and/or chest pain on those testings. All patients also underwent the 207TI–SPECT study before the drug study, and all had the exercise-induced transient perfusion defect in the area perfused by the stenotic coronary artery. No patient had the perfusion defect on 207TI–SPECT at rest. Two patients who did not show significant ST segment depression on exercise testings had the exercise-induced perfusion defect on 207TI–SPECT.

Selective coronary arteriography and biplane left ventricular angiography were performed by the Judkins technique in all patients. The degree of coronary artery stenosis (percentage of diameter stenosis) was assessed by cineangangiograms taken immediately after intracoronary infusion of isosorbide dinitrate at a dose of 2 mg. A stenosis of 75% or more in the luminal diameter was considered significant stenosis. Left ventricular ejection fraction was calculated by the area-length method.18

Exercise Testing and Thallium Myocardial Scintigraphy

Exercise testing was performed by the Bruce protocol. Cuff blood pressure (STBP-680, Nihon Colin, Tokyo), heart rate, and 12-lead ECG were recorded at every 1-minute interval throughout exercise testing. In addition, three ECG leads (aVF, V1, and V5) were continuously monitored. A computer-assisted system (Marquette Case 12, Marquette Electronics Inc., Milwaukee, Wis.) was used for displaying the trends of heart rate, rate-pressure products, and ST segments of the three monitored leads. Exercise testing was terminated when significant ST segment depression and/or chest pain occurred. Criteria for significant ST segment depression were horizontal or downsloping ST segment depression of ≥0.1 mV at 0.08 seconds after the J point in more than two leads.

207TI (111 MBq) was injected at the maximum level of treadmill exercise testing, and the patients continued to exercise for 1 minute after injection. The patients were imaged with a rotating gamma camera at 10 minutes and 3 hours after injection of 207TI. The system of SPECT consisted of a large field of view gamma camera with a high-resolution, parallel-hole collimator mounted on a gantry (Shimadzu SNC-500, Shimadzu Inc., Tokyo) and interfaced to a dedicated computer system (Scintipack 700, Shimadzu Inc.). Thirty-six projections at every 5° were obtained for 30 seconds each in the 180° arc around the long axis of each patient from the 45° right anterior oblique to the left posterior oblique projection. The short-axis tomographic images that encompassed the entire left ventricle were reconstructed at a 6.0-mm interval.

The computerized 207TI tomographic method, which was described by Garcia et al.,19 was used to quantify the size of myocardial perfusion defect. The circumferential profiles for each short-axis tomographic image were constructed automatically from the most apical to the most basal image. Each point in the maximal-count profiles represented the maximum count value per pixel in each 60 radii, which were along a radius extending from the center of the left ventricle to the limit of the radius of search. The profile was then constructed by the computer from the values of 60 radii spaced at 5° intervals plotted clockwise. Each profile was normalized to the maximum pixel value in the profile of each image. The resulting profiles were arranged as a series of concentric circles that formed a single two-dimensional polar map with the apex at the center and the base at the periphery. Activity from the inferior wall was located at the bottom of the two-dimensional polar map, activity from the septum was located on the left, and activity from the lateral wall was located on the right. To formulate a polar map, the normalized maximum pixel value at each point was compared with the normal value at the corresponding point, which had been derived from 20 normal subjects. Two types of polar maps were generated for quantitative analysis of abnormal myocardial perfusion: one map for the extent of abnormal myocardial perfusion and the other for its severity. In the extent polar map, the circumferential profiles are compared with the lower limit of normal range (<2.0 SD of the mean), and thus the fraction of left ventricular myocardium with perfusion defect is indicated. In the severity polar map, the pixel values within normal range are shown as red, and the pixel values below the normal limit are shown in blue–white levels, depending on the severity. The severity score was determined by dividing the sum of total difference between normalized maximum pixel values and the pixel values below the normal range in the abnormal area by the number of abnormal pixel points on the severity map.

Study Protocol

The study was done while the patients were on nitrates and/or calcium antagonists (two patients on nitrates and 12 patients on both nitrates and calcium antagonists). However, the drugs were not changed during the study period, and exercise testings were performed in the morning, strictly 2 hours after the last medication. No patients were taking β-blockers.
TABLE I. Clinical Characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)/sex</th>
<th>Duration of exercise (minutes)</th>
<th>Ischemic ECG change*</th>
<th>Chest pain</th>
<th>Exercise-induced perfusion defect</th>
<th>SPECT</th>
<th>Coronary artery disease (% diameter stenosis)</th>
<th>Visualized collateral†</th>
<th>Left ventricular ejection fraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63/M</td>
<td>5.5</td>
<td>II, III, aVF</td>
<td>+</td>
<td>Apex</td>
<td>RCA</td>
<td>90</td>
<td>None</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>62/M</td>
<td>7</td>
<td>II, III, aVF, V4, V5, V6</td>
<td>−</td>
<td>Apex</td>
<td>LAD</td>
<td>77 84 100</td>
<td>Fair</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>71/M</td>
<td>6</td>
<td>II, III, aVF, V4, V5, V6</td>
<td>−</td>
<td>Lateral</td>
<td>LCx</td>
<td>100 99</td>
<td>Fair</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>62/M</td>
<td>9</td>
<td>II, III, aVF, V4, V5, V6</td>
<td>−</td>
<td>Posterolateral</td>
<td>LCx</td>
<td>89</td>
<td>None</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>73/M</td>
<td>5.5</td>
<td>V5, V6</td>
<td>+</td>
<td>Anteroseptal</td>
<td>LCx</td>
<td>100 100</td>
<td>Well</td>
<td>56</td>
</tr>
<tr>
<td>6</td>
<td>68/M</td>
<td>4</td>
<td>II, III, aVF, V5, V6</td>
<td>−</td>
<td>Posterolateral</td>
<td>LCx</td>
<td>99</td>
<td>Fair</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>63/M</td>
<td>8</td>
<td>II, III, aVF, V5, V6</td>
<td>−</td>
<td>Posterolateral</td>
<td>LCx</td>
<td>99</td>
<td>Fair</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>58/M</td>
<td>4</td>
<td>II, III, aVF, V5, V6</td>
<td>+</td>
<td>Anteroseptal</td>
<td>LCx</td>
<td>99</td>
<td>Well</td>
<td>84</td>
</tr>
<tr>
<td>9</td>
<td>48/M</td>
<td>6.5</td>
<td>II, III, aVF, V5, V6</td>
<td>+</td>
<td>Anteroseptal</td>
<td>LCx</td>
<td>100 99</td>
<td>Well</td>
<td>56</td>
</tr>
<tr>
<td>10</td>
<td>59/M</td>
<td>5</td>
<td>II, III, aVF, V5, V6</td>
<td>+</td>
<td>Inferoposterior</td>
<td>LCx</td>
<td>100 100</td>
<td>Well</td>
<td>56</td>
</tr>
<tr>
<td>11</td>
<td>59/M</td>
<td>3</td>
<td>II, III, aVF, V5, V6</td>
<td>+</td>
<td>Anteroseptal-interoposter</td>
<td>LCx</td>
<td>99</td>
<td>Well</td>
<td>89</td>
</tr>
<tr>
<td>12</td>
<td>48/M</td>
<td>5.5</td>
<td>II, III, aVF, V4, V5, V6</td>
<td>+</td>
<td>Apex</td>
<td>LCx</td>
<td>99</td>
<td>Well</td>
<td>89</td>
</tr>
<tr>
<td>13</td>
<td>51/F</td>
<td>4</td>
<td>No change</td>
<td>+</td>
<td>Anteroseptal</td>
<td>LCx</td>
<td>71 83</td>
<td>None</td>
<td>74</td>
</tr>
<tr>
<td>14</td>
<td>43/M</td>
<td>9</td>
<td>No change</td>
<td>+</td>
<td>Anteroseptal</td>
<td>LCx</td>
<td>78</td>
<td>None</td>
<td>72</td>
</tr>
</tbody>
</table>

SPECT, ²⁰¹TI-single-photon emission computed tomography; RCA, right coronary artery; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery.

*ECG leads that denoted ST segment depression ≥0.1 mV.
†Reading of visualized collateral filling: None, no visible filling of collateral channels; poor, collateral filling of branches of the stenotic vessel without any depth reaching the epicardial segment of this vessel; fair, partial collateral filling of the epicardial segment of the stenotic vessel; well, complete collateral filling of the stenotic vessel.

Twelve patients (patients 1–12, Table 1) who had exercise-induced ST segment depression underwent exercise testing to examine exercise-induced ECG changes during intravenous infusion of ANP (0.1 μg/kg per minute) (Suntory Ltd., Osaka, Japan) or saline. Seven patients (patients 8–14, Table 1) underwent the ²⁰¹TI-SPECT study to evaluate the exercise-induced perfusion defect during intravenous infusion of ANP or saline. Exercise testing and the ²⁰¹TI-SPECT studies during infusion of ANP and saline were done at a week interval in a double-blind, cross-over manner. The duration of exercise during ANP and saline infusion was the same, which was determined in each patient in preliminary exercise testing done before the drug study to cause transient myocardial ischemia. The order of ANP and saline was randomized. ANP and saline were infused with an infusion pump (Nipro SP-60, Techtoron Inc., Osaka, Japan). Drug infusion was begun 10 minutes before beginning exercise testing and continued until peak exercise. We selected this dose of ANP because it had been used for the treatment of congestive heart failure.¹⁴,²⁰

The results of ²⁰¹TI-SPECT were analyzed individually and blindly by three experienced observers (H.T., H.N., and S.K.) without knowledge of the treatment of ANP or saline. The location of myocardial perfusion defect was diagnosed in SPECT images. There was no difference in opinion on location of significant myocardial perfusion defect among three observers. The extent and severity of myocardial perfusion defect were diagnosed in polar maps, where the area of abnormal perfusion was indicated as the area of thallium counts <2.0 SD of the mean.

Plasma ANP and cGMP Assay

Venous blood was sampled from the contralateral arm for the measurements of plasma ANP and cGMP before infusion and at the end of exercise testing during saline and ANP infusion.

Plasma ANP levels were determined by radioimmunoassay (RIA) using the method described previously.²¹ Briefly, the RIA assay buffer was 0.1 M Tris acetate, pH 7.4, containing 0.1% bovine serum albumin and 1 mM Na₂ EDTA. The RIA incubation mixture consisted of 100 μl of standard ANP, 100 μl of antisera diluted in the assay buffer, 100 μl of ¹²⁵-I-ANP (10,000 cpm), and 200 μl of assay buffer. The mixture was incubated for 24 hours at 4°C. The antibody-bound and free tracer peptide were separated by adding 100 μl each of anti-rabbit IgG antiserum (1:20), normal rabbit serum (1:200), and 15% polyethylene glycol in assay buffer.

Blood samples collected in chilled tubes containing Na₂ EDTA (4 mM) and aprotinin (500 kallikrein inactivator units/ml) were separated by centrifugation at
**Figure 2.** Graph of exercise-induced ST segment depression during atrial natriuretic peptide (ANP) and saline infusion. During ANP infusion, exercise-induced ischemic ST depression did not develop in any patient (n=12). The average degree of ST segment depression during ANP infusion was significantly smaller than that during saline infusion (0.2±0.0 vs. 0.2±0.1 mV; p<0.01). *p<0.01 vs. saline infusion.

**Statistical Analysis**

Data are expressed as mean±SD. A paired t test was used for comparing the results between saline and ANP infusion. Clinical characteristics of patients were analyzed with the Fisher's exact test. A probability value of <0.05 was considered significant.

**Results**

Table 1 shows the clinical characteristics of the patients. Twelve of 14 patients showed exercise-induced ST segment depression and the myocardial perfusion defect. Two patients (patients 13 and 14) did not show

---

**Table 2. Exercise-Induced Myocardial Perfusion Defect**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Extent score</th>
<th>Severity score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saline</td>
<td>ANP</td>
</tr>
<tr>
<td>8</td>
<td>0.15</td>
<td>0.00</td>
</tr>
<tr>
<td>9</td>
<td>0.47</td>
<td>0.17</td>
</tr>
<tr>
<td>10</td>
<td>0.18</td>
<td>0.19</td>
</tr>
<tr>
<td>11</td>
<td>0.61</td>
<td>0.57</td>
</tr>
<tr>
<td>12</td>
<td>0.37</td>
<td>0.28</td>
</tr>
<tr>
<td>13</td>
<td>0.55</td>
<td>0.00</td>
</tr>
<tr>
<td>14</td>
<td>0.61</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Mean±SD 0.42±0.20 0.22±0.20* 38.24±24.04 18.77±23.45*

ANP, atrial natriuretic peptide.

*p<0.05 vs. saline infusion.
A

**LONG-AXIS VIEW**

**SALINE**  
**ANP**

**EXERCISE**

**SHORT-AXIS VIEW**

**SALINE**  
**ANP**

**REDISTRIBUTION**

B

**EXERCISE**

**SALINE**

**ANP**

**EXTENT SCORE**

- **Severity Score**: 0.15
- **Severity Score**: 0.00

**REDISTRIBUTION**

**EXTENT SCORE**

- **Severity Score**: 5.01
- **Severity Score**: 0.01
significant ST segment depression during exercise, but they had exercise-induced anginal pain and the myocardial perfusion defect.

All had significant coronary artery stenosis in one or more coronary arteries. Left ventricular ejection fraction assessed by left ventriculography was within normal range (>55%) in all patients.

Effects of ANP on Exercise-Induced ST Segment Depression and Anginal Pain

The representative ECGs on exercise testing in a patient (patient 3) are shown in Figure 1. Figure 2 summarizes exercise-induced ST segment depression during ANP and saline infusion in 12 patients who underwent exercise ECG recordings. During saline infusion, all 12 patients developed significant ST segment depression on exercise testing, but significant ST segment depression did not occur during ANP infusion at the same level of exercise. Mean ST segment depression during ANP infusion was significantly less than that during saline infusion (0.0±0.0 versus 0.2±0.1 mV, p<0.01).

Anginal pain occurred in nine of 14 patients at the preliminary exercise tests. During saline infusion, exercise-induced anginal pain appeared in all nine patients. During ANP infusion, only one patient (patient 5) developed anginal pain, which was considerably milder than that during saline infusion.

### Table 3. Hemodynamic Changes on Exercise Testing

<table>
<thead>
<tr>
<th></th>
<th>ANP</th>
<th>Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest (before infusion)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>125±15</td>
<td>122±13</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>65±9</td>
<td>68±8</td>
</tr>
<tr>
<td>RPP (mm Hg×bpm)</td>
<td>8,824±1,688</td>
<td>8,280±1,469</td>
</tr>
</tbody>
</table>

After 10 minutes of infusion

<table>
<thead>
<tr>
<th></th>
<th>ANP</th>
<th>Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>110±15**</td>
<td>120±10</td>
</tr>
<tr>
<td>HR</td>
<td>68±9</td>
<td>66±7</td>
</tr>
<tr>
<td>RPP</td>
<td>7,259±1,839*</td>
<td>7,903±948</td>
</tr>
</tbody>
</table>

Peak exercise

<table>
<thead>
<tr>
<th></th>
<th>ANP</th>
<th>Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>170±24*</td>
<td>168±16*</td>
</tr>
<tr>
<td>HR</td>
<td>114±15*</td>
<td>110±15*</td>
</tr>
<tr>
<td>RPP</td>
<td>19,539±4,642*</td>
<td>18,453±3,484*</td>
</tr>
</tbody>
</table>

Data are mean±SD. ANP, atrial natriuretic peptide; SBP, systolic blood pressure; HR, heart rate; bpm, beats per minute; RPP, rate-pressure product.

*p<0.01 vs. value before infusion.

Effects of ANP on Myocardial Perfusion Defect

Table 2 shows the results of 201Tl-SPECT during ANP and saline infusion in seven patients (patients 8–14). The exercise-induced perfusion defect with complete redistribution at the delayed imaging was observed in all seven patients during saline infusion and in five patients during ANP infusion at the area related to the stenotic coronary artery. The size of the perfusion defect (the extent score) and the severity of ischemia (the severity score) during exercise were significantly less during ANP than those during saline infusion. The mean extent score was 0.42±0.20 during saline and 0.22±0.20 during ANP (p<0.05). The mean severity score was 38.24±24.04 counts during saline and 18.77±23.45 counts during ANP (p<0.05). Figure 3 shows the images and two-dimensional polar maps of 201Tl-SPECT in patient 8, in whom the exercise-induced perfusion defect was noted during saline infusion but not during ANP infusion.

### Table 4. Plasma Levels of ANP and cGMP

<table>
<thead>
<tr>
<th></th>
<th>ANP</th>
<th>Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before infusion</td>
<td>Peak exercise</td>
<td>Before infusion</td>
</tr>
<tr>
<td>ANP (pg/ml)</td>
<td>98±45</td>
<td>4,383±2,782*</td>
</tr>
<tr>
<td>cGMP (pmol/ml)</td>
<td>3.6±1.7</td>
<td>34.5±16.1*</td>
</tr>
</tbody>
</table>

Data are mean±SD. ANP, atrial natriuretic peptide.

*p<0.01 vs. before infusion.

### Discussion

The major finding of this study is that in patients with stable effort angina pectoris, an intravenous infusion of synthetic α-human ANP at a dose of 0.1 μg/kg per minute significantly reduced exercise-induced myocardial ischemia assessed by exercise ECG recordings and the exercise 201Tl-SPECT studies.

Previous studies in animals and humans have shown that ANP causes coronary vasodilation and increases coronary blood flow.9-12 In chronically instrumented dogs, an intracoronary injection of ANP (10 μg) dilated large epicardial coronary arteries and increased coronary blood flow.10 The dilation of epicardial coronary...
artery evoked with ANP at this dose was comparable to that evoked with an intracoronary injection of nitroglycerin (1 μg). It also has been shown that in dogs with flow-limiting coronary artery stenosis, an intravenous injection of ANP (3 μg/kg) improved regional myocardial perfusion to the ischemic area. In humans, intra-
vaneous or intracoronary ANP dilated large epicardial coronary arteries and increased coronary blood flow. These findings suggest the possibility that ANP may be efficacious in improving myocardial perfusion in the ischemic region in patients with coronary artery disease. Furthermore, in addition to the effects on coronary circulation, the systemic effects of ANP are expected to improve myocardial ischemia by reducing myocardial oxygen consumption. It has been shown in humans that ANP decreased arterial pressure and left ventricular end-diastolic pressure by reducing venous return. Lack of reflex tachycardia with ANP-induced hypotension is beneficial in preventing an increase in oxygen consumption. However, no study has examined whether ANP is effective in reducing myocardial ischemia in patients with angina pectoris.

This study was designed to examine whether an intravenous infusion of ANP reduced the magnitude of exercise-induced myocardial ischemia in patients with stable effort angina pectoris. The patients underwent exercise testing during infusion of ANP and saline in a double-blind, cross-over manner. The duration of exercise varied among patients but was the same during ANP and saline infusion in each patient. The duration of exercise was determined in each patient in preliminary exercise testing before the drug study to cause exercise-induced myocardial ischemia. Among 12 patients who underwent exercise ECG recordings during ANP and saline infusion, all developed significant ST segment depression (≥0.1 mV) during saline infusion, whereas no patient showed significant ST segment depression during ANP infusion (Figure 2). The exercise-induced myocardial perfusion defect was noted during saline infusion in all seven patients who underwent the exercise 201Tl-SPECT studies during drug infusion. Five of those patients developed the exercise-induced perfusion defect and two patients did not develop perfusion defect during ANP infusion. However, the extent score and severity score of the exercise-induced perfusion defect were significantly less during ANP infusion than during saline infusion (Table 2). Furthermore, nine patients developed anginal pain on exercise testing during saline infusion, whereas only one patient had anginal pain during ANP infusion, which was milder than that during saline infusion. These results indicate that intravenous infusion of ANP at a dose of 0.1 μg/kg per minute reduced exercise-induced myocardial ischemia in patients with stable effort angina pectoris.

In two patients, the extent score and severity score of the exercise-induced myocardial perfusion defect did not differ during ANP and saline infusion (patients 11 and 12, Table 2). In these two patients, exercise-induced ST segment depression and anginal pain developed during saline infusion but did not occur during ANP infusion. The mechanism to account for these results is not clear, but it may be plausible that mild improvement of myocardial perfusion, which was not detectable by the 201Tl-SPECT study, was sufficient to ameliorate ST segment depression and anginal pain in these patients.

The study was done while the patients were on the antianginal drugs, which included calcium antagonists and/or nitrates. These antianginal drugs might have influenced the effects of ANP on systemic hemodynamics and coronary circulation. However, exercise testing was done strictly 2 hours after the last medication so that the difference in the results between ANP and saline infusion could not be accounted for by the treatment with antianginal drugs per se. Taking nitrates might have reduced the magnitude of beneficial effects of ANP per se, and thus the anti-ischemic effects of ANP could be underestimated because nitrates and ANP share the intracellular mechanism that causes vasorelaxation. It is also unlikely that a training effect of repeated exercise testings affected the results. The patients underwent at least two exercise testings before the drug study, which demonstrated reproducible ST segment depression after the same duration of exercise. Moreover, the order of the study with ANP and saline infusion was randomized.

The precise mechanisms by which ANP reduced exercise-induced myocardial ischemia in our patients with stable effort angina pectoris are not known. As previously discussed, ANP may improve coronary perfusion in the ischemic region and may reduce myocardial oxygen consumption. We calculated the rate-pressure products at peak exercise, which did not differ during ANP and saline infusion (Table 3). Although factors other than blood pressure and heart rate that influence myocardial oxygen consumption are not considered, the latter results may suggest that myocardial oxygen consumption at peak exercise was similar during ANP and saline infusion. Thus, it appears that ANP improved exercise-induced myocardial ischemia largely by increasing coronary perfusion to the ischemic region in our patients with stable effort angina pectoris. In this regard, eight of our 14 patients had variable degrees of visible collateral anastomosis. In these patients with collateral vessels, ANP might have reduced exercise-induced myocardial ischemia by increasing myocardial perfusion through collateral vessels. Therefore, whether the anti-ischemic effects of ANP are mediated by dilating collateral vessels, stenotic segments of coronary artery, or both awaits further studies.

Finally, we infused one dose of ANP (0.1 μg/kg per minute), which was comparable to that used for the treatment of congestive heart failure. Infusion of ANP at this dose raised plasma ANP level from 98 to 4,385 pg/ml and cGMP level from 3.6 to 34.5 pmol/ml. Thus, it should be noted that attained concentrations of plasma ANP were pharmacological rather than physiological levels. Increased plasma cGMP indicates that ANP activated particulate guanylate cyclase in vascular smooth muscle. Because the effects of multiple doses of ANP were not examined, we do not know the plasma level of ANP that is needed to decrease exercise-induced myocardial ischemia.

Summary

An intravenous infusion of ANP at a dose of 0.1 μg/kg per minute decreased exercise-induced myocardial ischemia assessed by exercise ECG recordings and the 201Tl-SPECT study in patients with stable effort
angina pectoris. Because ANP must be given intravenously, it may not be useful as a drug to control effort angina pectoris in daily life. However, the results of this study suggest the possibility that intravenous administration of ANP may be efficacious in the treatment of severe angina pectoris in patients such as those who require intravenous infusion of nitrates. It is also possible that an inhibitor of neutral endopeptidase, which metabolizes endogenous ANP, may be useful for the treatment of effort angina pectoris. 37, 28 These possibilities need to be examined in future studies.

References
Beneficial effects of atrial natriuretic peptide on exercise-induced myocardial ischemia in patients with stable effort angina pectoris.
C P Lai, K Egashira, H Tashiro, H Narabayashi, S Koyanagi, T Imaizumi and A Takeshita

_Circulation_. 1993;87:144-151
doi: 10.1161/01.CIR.87.1.144

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/87/1/144

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at: http://circ.ahajournals.org/subscriptions/