Effects of Long-term Infusion of Synthetic Atrial Natriuretic Factor on Hemodynamics and Water Input-output Balance in Patients with Acute Myocardial Infarction

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SUMMARY

The administration of atrial natriuretic factor (ANF) increases coronary blood flow and decreases coronary vascular resistance. However, little is known about the feasibility and reliability of intravenous long-term infusion of ANF in patients with coronary heart disease. We therefore examined the effects on hemodynamic parameters and water input-output balance of 24-hour administration of synthetic ANF [ANF-[99–126]: 20–50 ng/kg/min] in 8 patients with acute myocardial infarction (6 men and 2 women; mean age 55 years). The ANF infusion significantly decreased pulmonary capillary wedge pressure to a maximum of greater than 50% 4 hours after infusion (from 16±2 to 7±2 mmHg; p<0.01), and the effect was sustained throughout the 24-hour infusion without diuresis (mean water balance, +25±12 ml/hr). This reduction was significantly correlated with the baseline value before infusion (r=−0.85, p<0.01). The effect on pulmonary capillary wedge pressure was accompanied by small reductions (approximately 20%) in systemic blood pressure and cardiac index, without significant changes in systemic vascular resistance and heart rate. These results indicate that prolonged administration of low to medium doses of synthetic ANF causes potent and sustained left ventricular unloading without reflex tachycardia and volume depletion, and may thus be safe and have potential benefits for patients with coronary heart disease. (Jpn Heart J 34: 707–716, 1993)

Key Words:
Atrial natriuretic factor Heart failure Myocardial infarction
Hemodynamics Vein Human Coronary circulation Myocardial ischemia

ATRIAL natriuretic factor (ANF), a peptide secreted from the heart, is thought to play a pivotal role in the regulation of body fluid balance and
vessel tone in both healthy and diseased states. Pharmacological doses of ANF have been reported to dilate the epicardial coronary artery in animal hearts and isolate coronary vascular strips. In a canine experimental model of myocardial infarction, ANF has been demonstrated to increase coronary blood flow due to dilation of the proximal coronary artery and the collateral vessels. In a human study, Rosenthal et al showed that intracoronary administration of ANF resulted in an increase in coronary blood flow and a decrease in coronary vascular resistance. It has been suggested that these effects of ANF on coronary hemodynamic parameters may be comparable to those of nitroglycerin.

However, few studies to date have examined the suitability and efficacy of intravenous synthetic ANF infusion in patients with ischemic heart disease. We have reported previously that a short-term low dose infusion enhanced renal water-sodium excretion without significant hemodynamic changes in patients with acute myocardial infarction. The present study examined the clinical feasibility of long-term administration of synthetic ANF on hemodynamic parameters and body fluid balance in patients with acute mild heart failure due to myocardial infarction.

**Subjects and Methods**

Patients

Eight patients with acute myocardial infarction who had been admitted to the coronary care unit of Iwate Medical University Hospital were enrolled (six men and two women; mean age 55 years; Table I). Three of the eight patients showed pulmonary congestion which was confirmed by physical examination and chest x-ray. The diagnosis of MI was based on a history of typical chest pain, typical electrocardiographic changes and an increase in serum creatine kinase levels. Excluded from the study were those patients with cardiogenic shock.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age and sex</th>
<th>Sites of infarction</th>
<th>Pulmonary congestion</th>
<th>Cardiac rhythm</th>
<th>History</th>
<th>Starting time (mg/24hrs)</th>
<th>Total infusion rate (mg/24hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>43M</td>
<td>lateral</td>
<td>-</td>
<td>AF</td>
<td>—</td>
<td>0.50</td>
<td>2.2</td>
</tr>
<tr>
<td>2</td>
<td>59M</td>
<td>non-Q wave</td>
<td>-</td>
<td>SR</td>
<td>HT</td>
<td>15:00</td>
<td>1.6</td>
</tr>
<tr>
<td>3</td>
<td>54M</td>
<td>inferior</td>
<td>-</td>
<td>SR</td>
<td>HT</td>
<td>14:00</td>
<td>2.1</td>
</tr>
<tr>
<td>4</td>
<td>81M</td>
<td>anterior</td>
<td>-</td>
<td>SR+AF</td>
<td>HT</td>
<td>17:15</td>
<td>1.6</td>
</tr>
<tr>
<td>5</td>
<td>20M</td>
<td>anterior</td>
<td>-</td>
<td>SR</td>
<td>—</td>
<td>8:00</td>
<td>2.3</td>
</tr>
<tr>
<td>6</td>
<td>65F</td>
<td>inferior</td>
<td>+</td>
<td>3º-AVB</td>
<td>HT</td>
<td>08:00</td>
<td>1.6</td>
</tr>
<tr>
<td>7</td>
<td>42M</td>
<td>anterior</td>
<td>+</td>
<td>SR</td>
<td>OMI</td>
<td>18:00</td>
<td>5.2</td>
</tr>
<tr>
<td>8</td>
<td>78F</td>
<td>non-Q wave</td>
<td>+</td>
<td>AF</td>
<td>DM, HT</td>
<td>14:15</td>
<td>4.0</td>
</tr>
</tbody>
</table>

AF=atrial fibrillation; SR=normal sinus rhythm; HT=hypertension; AVB=atrio-ventricular block; OMI=old myocardial infarction; DM=diabetes mellitus.
tolic blood pressure <90 mmHg), or with life-threatening arrhythmias. Patients with right ventricular infarction were also excluded, as volume expansion was usually required for their treatment. All patients gave informed consent before participating in this study, which was approved by the ethics committee of our hospital.

All patients received routine oxygen inhalation throughout the study protocol. Four patients were examined by cardiac catheterization, and two were given a thrombolytic agent before the study began. One patient with inferior infarction who showed complete AV block was treated by temporary cardiac pacing (patient 6; Table I).

Protocol

A Swan-Ganz catheter was inserted through the subclavian vein for serial measurement of hemodynamic parameters (pulmonary capillary wedge pressure, right atrial pressure, pulmonary arterial pressure and cardiac output), and an automatic blood pressure monitoring system was attached to the upper arm for measurement of systemic blood pressure and heart rate. Cardiac index and systemic vascular resistance were calculated by standard formulae. For measurement of urinary volume, a bladder catheter was inserted in all patients.

At least 3 hours after these procedures were completed, a half-hour run-in phase was initiated, followed by a 24-hour period of ANF administration as follows: 5000 mcg of synthetic ANF (ANF-[99-128]; Suntory, Tokyo, Japan) were dissolved in 500 ml of vehicle (Haemaccel; Behringwerke AG, Marburg, Germany), and infused into the right atrium via the catheter at a rate of 20 or 50 ng/kg/min (infusion volume; 0.12 or 0.30 ml/kg/hr) by a microsyringe pump. The dose of ANF was selected according to the pulmonary capillary wedge pressure (>20 mmHg, higher dose; ≤20 mmHg, lower dose).

Baseline hemodynamic measurements were taken at the beginning and the end of the run-in period. After these were completed, serial measurements were made 1, 4, 18 and 24 hours after the commencement of the ANF infusion, and 1 hour after the infusion had ceased. Throughout the ANF administration, water input-output balance was calculated at 4-hourly intervals (water balance = water intake + infusion volume − urine volume). Subjects were allowed a maximum water intake of 600 ml per 24 hours ad libitum.

Statistics

Data are presented as mean ± standard error of the mean, and were analyzed by one-way analysis of variance (ANOVA) with repeated measurements. When the ANOVA indicated a significant treatment effect, planned comparisons between mean baseline data and the value at each time point were made using a t test with the error mean square from the ANOVA. The relationship between
the baseline value and the maximal decrease in pulmonary capillary wedge pressure was examined by Pearson's correlation coefficients. All calculated p values were two-tailed, and a value of 0.05 or less was considered significant.

**Results**

The infusion of synthetic ANF was sustained for the full 24 hours in all patients without any adverse effects such as progression of heart failure, shock, arrhythmias, or new onset of chest pain.

As shown in Figure 1 and Table II, systolic and diastolic blood pressures declined, with a maximal decrease of approximately 20% observed 24 hours after the onset of ANF infusion (systolic blood pressure; from 128±5 to 104±7 mmHg, p<0.01: diastolic blood pressure; from 73±9 to 60±6 mmHg, p<0.01). This effect was sustained one hour after the infusion was discontinued. However, heart rate did not change significantly during the experimental infusion (Fig. 1 and

![Graph showing the effects of 24-hour infusion of synthetic atrial natriuretic peptide on systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) in 8 patients with acute myocardial infarction. Baseline data are the mean of two measurements in the predose period. Subsequent pressures are expressed as percentage change from baseline. **p<0.01, *p<0.05 vs baseline value.](image-url)
Table II. Effects of 24-hour Infusion of Synthetic Atrial Natriuretic Factor on Hemodynamic Parameters and Hematocrit in Patients with Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>1 hr</th>
<th>4 hr</th>
<th>18 hrs</th>
<th>24 hrs</th>
<th>25 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>87±7</td>
<td>82±7</td>
<td>79±5</td>
<td>81±5</td>
<td>87±5</td>
<td>79±5</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>128±5</td>
<td>113±3*</td>
<td>110±4*</td>
<td>115±4*</td>
<td>114±7**</td>
<td>115±7*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>73±9</td>
<td>67±7</td>
<td>64±4*</td>
<td>66±4</td>
<td>60±6**</td>
<td>63±4*</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mmHg)</td>
<td>16±2</td>
<td>10±2**</td>
<td>7±2**</td>
<td>9±1**</td>
<td>9±2**</td>
<td>12±2</td>
</tr>
<tr>
<td>Right atrial pressure (mmHg)</td>
<td>7±1</td>
<td>6±1</td>
<td>5±2*</td>
<td>8±1</td>
<td>7±2</td>
<td>8±1</td>
</tr>
<tr>
<td>Mean pulmonary arterial pressure (mmHg)</td>
<td>23±3</td>
<td>17±2*</td>
<td>15±2**</td>
<td>17±2*</td>
<td>18±2*</td>
<td>19±2</td>
</tr>
<tr>
<td>Cardiac index ($l/min/m^2$)</td>
<td>3.4±0.2</td>
<td>2.9±0.3</td>
<td>2.8±0.2*</td>
<td>2.7±0.1**</td>
<td>2.7±0.1**</td>
<td>3.0±0.1</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (dynes-sec-cm $^{-5}$)</td>
<td>34±67</td>
<td>296±58</td>
<td>270±63</td>
<td>329±69</td>
<td>311±44</td>
<td>385±57</td>
</tr>
<tr>
<td>Systemic vascular resistance (dynes-sec-cm $^{-5}$)</td>
<td>1017±96</td>
<td>1303±109</td>
<td>1246±95</td>
<td>1291±62</td>
<td>1089±71</td>
<td>1075±62</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>43.3±1.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>40.4±1.9</td>
</tr>
</tbody>
</table>

Mean±SE, *p<0.05, **p<0.01 vs baseline value.

Fig. 2. Effects of 24-hour infusion of synthetic atrial natriuretic peptide on pulmonary capillary wedge pressure (PCWP), cardiac index (CI), and systemic vascular resistance (SVR) in 8 patients with acute myocardial infarction. Baseline data are the mean of two measurements in the predose period. Subsequent pressures are expressed as percentage change from baseline. **p<0.01, *p<0.05 vs baseline value.
As demonstrated in Figure 2 and Table II, left ventricular filling pressure, as determined by mean pulmonary capillary wedge pressure, decreased rapidly and remained low throughout the study. A maximal reduction of more than 50% was observed 4 hours after the onset of infusion (from 16±2 to 7±2 mmHg; p<0.01), and the decrease was maintained for one hour after the cessation of ANF administration (12±2 mmHg). A significant correlation was found between baseline pulmonary capillary wedge pressure and the maximal decrease in this parameter (r = −0.85, p<0.01; Fig. 3). Right atrial pressure also declined during the infusion (from 7±1 to 5±2 mmHg 4 hours after onset; p<0.05), but the level returned to the baseline value thereafter (Table II). Mean pulmonary arterial pressure decreased by a maximum of 35% 4 hours after ANF administration began (from 23±3 to 15±2 mmHg; p<0.01; Table II). Pulmonary vascular resistance did not change significantly throughout the study (Table II).

Cardiac index declined gradually to a maximal decrease of approximately 20% at 18 hours (from 3.4±0.2 to 2.7±0.1 l/min/m²; p<0.01; Fig. 2), and returned to baseline values after infusion ceased. No significant change was observed in systemic vascular resistance (Fig. 2 and Table II).

The serial water input-output balance is shown in Table III. Although there

**Table III.** Serial Water Input-output Balance during 24-hour Administration of Synthetic Atrial Natriuretic Factor

<table>
<thead>
<tr>
<th>Time after infusion</th>
<th>Baseline</th>
<th>0-4 hr</th>
<th>5-8 hr</th>
<th>9-12 hr</th>
<th>13-16 hr</th>
<th>17-20 hr</th>
<th>21-24 hr</th>
<th>25 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine volume (ml/hr)</td>
<td>10±19</td>
<td>106±20</td>
<td>91±21</td>
<td>61±17</td>
<td>89±17</td>
<td>123±29</td>
<td>101±13</td>
<td>66±14</td>
</tr>
<tr>
<td>Water input (ml/hr)</td>
<td>62±15</td>
<td>101±18</td>
<td>140±23</td>
<td>111±15</td>
<td>123±22</td>
<td>144±15</td>
<td>149±22</td>
<td>98±19</td>
</tr>
<tr>
<td>Total balance (ml/hr)</td>
<td>−45±25</td>
<td>−4±15</td>
<td>+57±15*</td>
<td>+50±26</td>
<td>+34±16</td>
<td>+21±23</td>
<td>+47±17*</td>
<td>+32±17</td>
</tr>
</tbody>
</table>

Mean±SE, * p<0.05 vs zero balance.
was no significant loss of body fluids during the initial 4 hours (−5±18 ml/hr; N.S.), a slight positive water balance was evident in the latter phase of the study. Throughout the study, mean urine output was 94±12 ml/hr and mean water input (water intake plus infusion volume) was 119±15 ml/hr, giving a mean water balance of +25±12 ml/hr. The mean water balance in patients using contrast medium was not significantly different from that in those without the agent (+27±12 versus +24±12 ml/hr, respectively).

**DISCUSSION**

This study has demonstrated that long-term synthetic ANF infusion induced potent and sustained hemodynamic unloading due to preload reduction without diuresis in patients with acute mild heart failure due to coronary heart disease. This effect was accompanied by small reductions (approximately 20%) in systemic blood pressure and cardiac output but without significant changes in systemic vascular resistance and heart rate.

In contrast to these observations, we have previously reported that short-term low-dose infusion of synthetic ANF (10 ng/min/kg for one hour) induced a transient increase in water-sodium excretion without changing systemic hemodynamic parameters in patients with uncomplicated myocardial infarction. These discrepancies may be explained by the fact that the doses of synthetic ANF employed in the present study were two or five times larger than those in our previous study. A short-term low-dose infusion (less than 10 ng/min/kg) in healthy volunteers or a small bolus dose (70 mcg) in patients with chronic heart failure has been shown to induce transient water-sodium excretion without significant hemodynamic changes. On the other hand, larger doses have been found to cause a significant reduction in pulmonary capillary wedge pressure and systemic blood pressure in patients with chronic congestive heart failure.

However, no data are available regarding the hemodynamic and renal effects of long-term administration of synthetic ANF in patients with acute heart failure. In patients with chronic heart failure, Munzel et al have demonstrated that during a 20-hour infusion of synthetic ANF (75 ng/kg/min) a significant renal excretion effect was observed only during the initial 4 hours, with no significant renal effects occurring thereafter. A similar transient increase in water-sodium excretion was reported in a prolonged ANF-infusion study in healthy volunteers. Although the present study did not examine sodium excretion during the infusion, previous studies demonstrated that ANF-induced diuresis was consistently associated with natriuresis. Thus, our present data suggest that the water-sodium excretion effects of exogenous ANF are transient, whereas its hemodynamic effects are long-lasting.
In the present study, synthetic ANF infusion provoked sustained left ventricular unloading without significant effects on systemic vascular resistance and volume depletion in patients with myocardial infarction. These results may be related to a volume shift from the intravascular to the extravascular compartment due to an increase in capillary permeability, and/or may be caused by the venous blood pooling induced by the venous dilating effect of ANF. These pharmacological characteristics of potent preload reduction resemble those of nitroglycerin. However, the infusion of nitroglycerin is known to induce adverse reflex tachycardia with a reduction in blood pressure, and nitrate tolerance tends to develop within 24 hours of the initiation of treatment, whereas in the present study, no significant reflex tachycardia or development of the tolerance indicated by a minimum hemodynamic change was found. These favorable effects may be due to ANF’s inhibitory effects on sympathetic nerve activity and the renin-angiotensin system.

It is unlikely that ANF would bring about an adverse decrease in venous return or a deterioration in heart failure in cases of severe left ventricular dysfunction, because unloading of the ventricle due to preload reduction may depend on the level of basal cardiac load. The present protocol employed a higher dose of ANF for patients with elevated ventricular filling pressures of more than 20 mmHg. The possibility that higher doses of ANF may facilitate the reduction in pressure in these patients cannot be excluded, although the mean maximal decrease in pressure versus baseline data after the higher dose of ANF was not significantly different from the value after the lower dose (52±7 versus 60±7%, N.S.).

Negative inotropic effects of ANF have been suggested by several experimental studies, however, direct intracoronary ANF administration studies in humans have shown no effect on left ventricular contractility. The decrease in mean cardiac output found in our study may have been due to the small number of patients with severe congestive heart failure. The effect of different vasodilators on left ventricular stroke volume varied with the presence or absence of left ventricular failure. The hemodynamic subgroup of patients without evidence of left ventricular failure demonstrated a decrease in both stroke volume and cardiac output after vasodilator therapies. Thus, further studies are needed for to investigate whether cardiac output is increased by prolonged ANF infusion in patients with severe acute congestive heart failure.

Limitations: Since the present study did not include a placebo-control group, one may speculate that these hemodynamic changes were due to circadian variation. However, the starting time of ANF infusion varied greatly (Table I). Thus, the circadian changes may not directly affect the present results. Previous medications and water-sodium intake obviously could not be standardized
because of the sudden and unexpected nature of the subject’s condition. However, it seems unlikely that the effects of previously administered drugs or water-sodium intake would have lasted throughout the 24-hour study period because the mean duration from the onset of symptoms to the commencement of the study was more than eight hours. It remains unknown whether cardiac catheterization and coronary intervention before the study had any influence on the results. Four of the eight patients were examined by coronary angiography and left ventriculography. The contrast medium used in these examinations may have caused a deterioration in renal function and overwhelmed the diuretic effect of ANF. However, mean water input-output balance in patients examined with a contrast medium was not different from that in patients examined without the agent (+27±12 versus +24±12 ml/hr, N.S.).

In conclusion, long-term administration of a low to medium dose of synthetic ANF caused potent and sustained left ventricular unloading without reflex tachycardia and volume depletion in patients with acute myocardial infarction. These effects of ANF combined with its previously demonstrated favorable effects on coronary hemodynamics may indicate the potential benefits and safety of prolonged synthetic ANF infusion for ischemic heart disease.

**REFERENCES**


