Clinical Investigation and Reports

Coronary Reperfusion Enhances Recovery of Atrial Natriuretic Peptide Secretion

Salvaging Endocrine Function in Patients With Acute Right Ventricular Infarction

Satoshi Yasuda, MD; Hiroshi Nonogi, MD; Shunichii Miyazaki, MD; Yoichi Goto, MD; Kazuo Haze, MD

Background The heart has been demonstrated not only to be a pumping organ but also an endocrine organ secreting atrial natriuretic peptide (ANP). We hypothesized that myocardial ischemia may affect ANP secretion and that reperfusion therapy for acute myocardial infarction can preserve endocrine function of the heart.

Methods and Results Twenty patients with acute right ventricular infarction were examined who underwent reperfusion therapy on admission. These patients had proximal occlusion of the dominant right coronary artery involving the right atrial branches: 9 patients with successful reperfusion (SRP group) and the remaining 11 patients with unsuccessful reperfusion (URP group). Within 24 hours after the onset of infarction, a volume loading test was performed after reperfusion therapy with measurements for plasma ANP levels and hemodynamics. Before the volume loading test, the plasma ANP level and mean right atrial pressure were similar between these two groups. However, in the URP group, percent increase in ANP in response to volume loading was strikingly smaller (URP, 45±18% versus SRP, 133±25%; P<.01) despite similar percent increase in mean right atrial pressure (URP, 100±46% versus SRP, 86±23%). The peak ANP level occurred significantly later in the URP group (69±16 hours) than in the SRP group (28±9 hours, P<.001) after the onset of infarction.

Conclusions The response of ANP release to volume loading is attenuated in patients with right ventricular infarction without coronary reperfusion. However, successful reperfusion induces a rapid recovery of cardiac endocrine function as well as its mechanical function. A sufficiently elevated plasma ANP level may be a useful predictor of hemodynamic improvement in patients with right ventricular infarction. (Circulation. 1994;89:558-566.)

Key Words • infarction • peptides • reperfusion

Reperfusion therapy in acute myocardial infarction has been shown to salvage myocardial tissue and to reduce mortality and ventricular irritability. This therapy also has been reported to result in a rapid improvement in right ventricular function and resolution of atrioventricular block complicated with acute inferior infarction. Recently, the heart has been demonstrated not only to be a pumping organ but also an endocrine organ secreting atrial natriuretic peptide (ANP). This peptide appears to influence circulatory homeostasis through vasoactive and natriuretic activities, which are clinically useful for the treatment of congestive heart failure.

Acute right ventricular infarction is a unique clinical model to study both ANP secretion after acute myocardial infarction and the response of ANP secretion to volume loading, which is usually applied as a treatment in this setting. It is well known that hormone synthesis or release is an energy-dependent process and therefore sensitive to ischemia. Serra et al reported that the response of ANP release to volume loading was attenuated in patients with acute right ventricular infarction. However, because their study was performed in patients without reperfusion therapy, the effect of coronary reperfusion on ANP secretion has never been clarified. Therefore, the goal of this study was to examine our hypothesis that (1) myocardial ischemia affects ANP secretion, (2) reperfusion therapy for acute myocardial infarction can preserve endocrine function of the heart, and (3) this salvaged endogenous peptide is of some help to enhance the functional recovery process from acute right ventricular infarction.

Methods

Study Patients

Patient selection is shown in Fig 1, and the sequence of events is shown in Fig 2. From November 1991 through March 1993, 43 consecutive patients with acute inferior transmural myocardial infarction were prospectively recruited for this study who were admitted to the coronary care unit at National Cardiovascular Center and underwent reperfusion therapy to the proximal right coronary artery within 24 hours after the onset of infarction. Acute inferior transmural myocardial infarction was diagnosed by the presence of all the following criteria: (1) typical chest pain with a duration >30 minutes suggestive of acute myocardial infarction; (2) ST segment elevation of ≥1.0 mm in at least two of ECG leads II, III, and aVF, and (3) subsequent elevation of creatine phosphokinase more than twofold the normal range. Twenty-eight of 43 patients had right ventricular infarction, which was determined by at least two of the four following criteria: (1) ST segment elevation of >1.0 mm in right precordial leads, (2) ECG evidence of right ventricular asynergy, (3) mean right atrial pressure >10 mm Hg and the difference between mean pulmonary capillary wedge pressure and mean right atrial...
pressure <5 mm Hg either in the basal period or after volume expansion.10 (4) a noncompliant pressure pattern in the right atrium either in the basal period or after volume expansion.10 Eight of the 28 patients with right ventricular infarction were excluded from the study because of (1) clinical or hemodynamic evidence of left ventricular failure, (2) history of previous myocardial infarction, (3) chronic atrial tachyarrhythmias, (4) severe hypertension, (5) chronic renal failure, (6) valvular heart disease, or (7) cor pulmonale. Thus, the study group comprised 20 patients (RVi [right ventricular infarction] group); 16 were men and 4 were women, mean age was 64±7 years. Fifteen of the 43 patients had inferior myocardial infarction but no right ventricular involvement, and 4 of these 15 patients did not succeed in reperfusion therapy. Thus, the remaining 11 patients (10 men and 1 woman; mean age, 60±10 years) with successful reperfusion therapy served as controls (control group).

**Hemodynamic Measurements**

Right atrial, pulmonary arterial, and pulmonary capillary wedge pressures were measured by using a Swan-Ganz thermodilution catheter (model 93A-431H-7.5Fr, Baxter Healthcare Co). These pressures were recorded with ECGs on a multichannel recorder (San-ei 2318, San-ei Co). Cardiac output (CO) was calculated by the thermodilution method with a Baxter Edwards REF-1 cardiac output computer (Baxter Healthcare Co). Blood pressure was measured by sphygmomanometry. Total systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were calculated by standard formulas: SVR=(mAo−mRA)/CO×80 dyne · sec · cm⁻²; PVR=(mPA−mPC)/CO×80 dyne · sec · cm⁻²; mAo is mean aortic pressure, mRA is mean right atrial pressure, and mPC is mean pulmonary arterial pressure. These hemodynamic parameters were measured at the time of admission and every 3 to 6 hours after admission with blood sampling for hormonal assay. A catheter was placed for collecting urine for 1 hour, which was averaged over 24 hours as urine volume rate.

**Volume Loading Test**

To establish the diagnosis of right ventricular infarction, a volume loading test was performed under steady-state condition at 2 to 3 hours after the reperfusion therapy and within 24 hours after the onset of myocardial infarction in all 20 patients in the RVi group and 6 patients in the control group. A rapid intravenous infusion of dextran was performed at a rate of 200 mL/5 min, and pulmonary capillary wedge pressure was monitored so that it did not exceed 18 mm Hg. Pressures, cardiac output, and plasma ANP levels were measured before and immediately after the volume loading test. In 5 patients in the right RVi group, a second volume loading test was performed at the clinically recovered period.

**Treatment Protocol**

**Reperfusion Therapy**

Left heart catheterization and reperfusion therapy were performed in all patients as rapidly as possible after determining the diagnosis of acute myocardial infarction. The delay between the diagnosis and the reperfusion therapy was usually less than 1 hour. Coronary arteriography and left ventriculography were performed using the Judkins technique. Left ventricular ejection fraction was calculated using the area-length method. After occlusion (total or subtotal) of

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**Fig 1.** Flow chart of patient selection. AMI indicates acute myocardial infarction; RV, right ventricular; RVi, right ventricular infarction; Urp, unsuccessful reperfusion group; and Srp, successful reperfusion group. *All patients underwent reperfusion therapy to the proximal right coronary artery within 24 hours after the onset of AMI. **Exclusion criteria were left ventricular failure, previous myocardial infarction, chronic atrial tachyarrhythmias, severe hypertension, chronic renal failure, valvular heart disease, or cor pulmonale.

**Fig 2.** Flow chart of study protocol. The initial volume loading test was performed at 2 to 3 hours after reperfusion therapy. The second volume loading was performed at the clinically recovered period in 5 patients in the unsuccessful reperfusion group.
the vessel supplying the infarct zone had been confirmed, tissue-type plasminogen activator (Hapase KOWA inj, KOWA Co) was administered through the selective coronary catheter at a rate of 160 000 U/min with a maximum of 6 400 000 U. Fifteen patients with unsuccessful thrombolysis (Thrombolysis in Myocardial Infarction [TIMI] flow grade 0 to 2) underwent the rescue coronary angioplasty. Successful reperfusion was defined as coronary blood flow improved to TIMI flow grade 3. A second cardiac catheterization was performed before hospital discharge in all patients except two in the RVI group in whom reperfusion therapy was unsuccessful on admission.

**Therapeutic Choices**

Volume loading therapy was the initial choice of treatment in patients with right ventricular infarction, in whom normal saline infusion was continued when the pulmonary capillary wedge pressure was <15 mm Hg. When volume loading therapy did not increase cardiac output or correct hypotension, dobutamine was infused at a starting rate of 1.0 μg·kg⁻¹·min⁻¹ and increased to a maximum of 10 μg·kg⁻¹·min⁻¹. A vasodilator agent was administered to patients in the RVI group. When pulmonary capillary wedge pressure reached 18 mm Hg, a small amount of diuretic agent (furosemide, 5 mg) was sometimes used to prevent left heart failure.

**Fig. 3.** Graphs show results of volume loading test. ANP indicates atrial natriuretic peptide; mRA, mean right atrial pressure. Left, Initial volume loading test performed within 24 hours after the onset of acute myocardial infarction (at the acute period). Closed circles represent values of patients with unsuccessful reperfusion (Urp, n=11), open circles, values of patients with successful reperfusion (SrP, n=9); crosses (X), control (n=6); and squares, mean±SD. Right, Comparison between the initial volume loading test performed at the acute period and the second volume loading test performed at the clinically recovered period in 5 patients in the Urp group. Closed circles represent values of the initial volume loading test; dotted circles, values of the second volume loading test; and squares, mean±SD.
Blood Sampling and Hormonal Assays

Blood samples were drawn from the pulmonary artery through a Swan-Ganz catheter into the tube containing ethylenediaminetetraacetic acid and aprotinin in the same manner as reported previously. Plasma was stored frozen immediately at −80°C in polyethylene tubes until assay. Plasma levels of ANP were determined by specific radioimmunoassay (Eiken Chemical Co) after extraction with octadeylsilane cartridges, as described previously. Samples from each patient were analyzed as a batch within 1 week after collection. Normal values in our institute were 29 to 74 pg/mL. Creatine phosphokinase was also measured at the same sampling point as ANP. The highest level of serial changes of plasma ANP was defined as peak ANP in the present study.

Statistical Analysis

Results were expressed as mean±1 SD. Differences in characteristics among patient groups were compared by one-way ANOVA or χ² analysis. Repeated-measures ANOVA was used for comparison of the serial data followed by the multiple comparison test. A value of P<.05 was considered significant.

Results

Comparison of Baseline Characteristics

In 9 of 20 patients in the RVI group, reperfusion therapy was successful, and its patency was verified at the chronic stage (SRP). In the remaining 11 patients, reperfusion therapy was unsuccessful (URP).

Table 1 compares baseline characteristics of the SRP, URP, and control groups. There were no differences in age, sex, left ventricular ejection fraction, peak serum creatine phosphokinase, and pulmonary capillary wedge pressure on admission among those three groups. Systolic blood pressure and cardiac index were significantly lower, and right atrial pressure was higher in the RVI group than in the control group, which was compatible with the characteristics of right ventricular infarction. Although plasma ANP level on admission was higher in the RVI group than in the control group, the level was within the normal range (29 to 74 pg/mL) in 19 of 20 patients in the RVI group. Both the elapsed time to admission and the time to peak serum creatine phosphokinase were much longer in the URP than in the other two groups with successful reperfusion. Atrial tachyarrhythmias and atrioventricular block were recorded more frequently in the URP group than in the other two groups, but the difference did not reach statistical significance.

Angiographic studies showed that all 20 patients in the RVI group had proximal occlusion near the ostium of the dominant right coronary artery involving right atrial branches as well as right ventricular branches. In the control group, right ventricular branch involvement was shown only in 3 patients (27%, P<.05 versus RVI).

Volume Loading Test

The initial volume loading test was performed at the acute stage, 14±6 hours after the onset of myocardial infarction. The results were summarized in Fig 3 (left panel). Before the volume loading test, both plasma ANP level (SRP, 45.3±11.8 pg/mL versus URP, 45.3±11.7 pg/mL) and mean right atrial pressure (SRP, 5.7±2.0 mm Hg versus URP, 7.4±2.9 mm Hg) were similar between the SRP and URP groups. In the control group, plasma ANP level (24.7±6.8 pg/mL) and mean right atrial pressure (4.0±2.2 mm Hg) were lower (P<.05) than in the SRP and URP groups. After volume loading, pulmonary capillary wedge pressures were similar among the three groups. Although percent increases in mean right atrial pressure were similar among the three groups (URP, 100±46%; SRP, 86±28%; control, 66±19%), percent increase in ANP was strikingly smaller in the URP group (URP, 45±18% versus SRP, 133±25%, control, 130±25%; P<.01), indicating that the response of ANP release to volume loading was blunted in the URP group. In contrast, percent increases in ANP were similar between the SRP and control groups, indicating that successful reperfusion preserved the ability of ANP release in response to volume loading.

In 5 patients in the URP group, a second volume loading test was performed at the clinically recovered period (119±40 hours after the onset of infarction). The results were summarized in Fig 3 (right panel). Before the second volume loading test, both plasma ANP level (46.4±5.4 pg/mL) and mean right atrial pressure were not different among the three groups. After volume loading, both plasma ANP level and mean right atrial pressure in the URP group were lower (P<.05) than in the SRP group. ANP and mRA levels were increased in the SRP group, whereas they decreased in the URP group. The results were summarized in Fig 4.
(6.6±2.4 mm Hg) were similar to those before the initial volume loading test. After the second volume loading test, mean right atrial pressure increased to 11.6±2.6 mm Hg, which was lower than the value after the initial volume loading test (16.2±2.2 mm Hg, P<.05). Plasma ANP level increased to 100.0±8.9 pg/mL, significantly higher than that after the initial volume loading test (70.2±25.3 pg/mL, P<.05). Consequently, after the second volume loading test, percent increase in ANP (117±40%) was proportional to that in mean right atrial pressure (90±37%), indicating that the response of ANP release to volume loading was restored at the clinically recovered period.

Relation Between Plasma ANP Levels and Hemodynamics

**URP Group**

To correct persistent hypotension, saline infusion was performed after the initial volume loading test in the URP group. Although right atrial pressure increased sufficiently due to saline infusion by 27±9 hours after the onset of myocardial infarction (equal to before dobutamine infusion), plasma ANP level remained disproportionately low (Fig 4). During this period of hyposcerection of ANP, patients suffered from a low cardiac output and oliguria with a high right atrial pressure (Table 2). Both the systemic and the pulmonary vascular resistance abnormally increased. The upper panel of Fig 5 demonstrates a representative case in the URP group that shows the discrepancy between the increment in plasma ANP level and that in right atrial pressure with a low cardiac output condition. Because of the low cardiac output state, the administration of dobutamine was required in all 11 patients of the URP group (versus 0% in SRP or control, P<.01). During the steady state with dobutamine infusion (42±12 hours after the onset of infarction), ANP release remained unchanged (Fig 4 and Table 2). Cardiac output increased slightly, but its change was not statistically significant. Subsequently, plasma ANP level gradually increased and formed its peak at 69±16 hours after the onset of myocardial infarction. It is of note that the ratio of peak ANP value to mean right atrial pressure in the URP group (12.3±2.3) was comparable to that in the SRP group (13.1±2.3), although the time to peak ANP differed significantly (URP, 69±16 hours versus SRP, 28±9 hours after the onset of infarction; P<.001) (Fig 4). At peak ANP, mean pulmonary arterial pressure (25±3 to 20±3 mm Hg, P<.05), mean pulmonary capillary wedge pressure, and pulmonary vascular resistance were ameliorated significantly without changes in

**Table 2.** Mean Hemodynamic Data in 11 Patients With Unsuccessful Reperpusion on Admission, Immediately After the Volume Loading Test, Before Dobutamine Infusion, During Dobutamine Infusion, at Peak ANP, and at the Clinically Recovered Period

<table>
<thead>
<tr>
<th></th>
<th>Admission</th>
<th>After VL Test</th>
<th>Before DOB</th>
<th>During DOB</th>
<th>Peak ANP</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANP, pg/mL</td>
<td>39.5±19.6</td>
<td>65.5±20.2</td>
<td>53.0±17.7</td>
<td>78.1±16.4</td>
<td>170.0±50.5†‡</td>
<td>80.2±20.5‡</td>
</tr>
<tr>
<td>mRA, mm Hg</td>
<td>8.4±3.1</td>
<td>14.0±3.0‡</td>
<td>15.0±3.3‡</td>
<td>14.2±3.2</td>
<td>13.9±2.9</td>
<td>7.0±3.8†</td>
</tr>
<tr>
<td>mPC, mm Hg</td>
<td>11.7±2.5</td>
<td>14.2±2.1</td>
<td>14.0±3.0‡</td>
<td>12.6±2.8</td>
<td>10.3±3.1*</td>
<td>10.1±3.8*</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>3.2±1.1</td>
<td>...</td>
<td>3.1±1.1</td>
<td>3.5±1.8</td>
<td>3.7±1.4‡</td>
<td>4.7±1.0‡</td>
</tr>
<tr>
<td>SVR, dyne·sec·cm⁻⁵</td>
<td>1668±376</td>
<td>1820±388</td>
<td>1709±382</td>
<td>1560±377</td>
<td>1338±338*</td>
<td>99±37†</td>
</tr>
<tr>
<td>PVR, dyne·sec·cm⁻⁵</td>
<td>176±68</td>
<td>246±54‡</td>
<td>212±62</td>
<td>196±70*</td>
<td>114±66‡</td>
<td></td>
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<tr>
<td>UV, mL/h</td>
<td>35±20</td>
<td>...</td>
<td>42±38</td>
<td>69±42</td>
<td>292±126‡</td>
<td>114±66‡</td>
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<tr>
<td>Time, h</td>
<td>12±5</td>
<td>18±4</td>
<td>27±9</td>
<td>42±12</td>
<td>69±16</td>
<td>122±30</td>
</tr>
</tbody>
</table>

VL indicates volume loading; DOB, dobutamine; ANP, atrial natriuretic peptide level; mRA, mean right atrial pressure; mPC, mean pulmonary capillary wedge pressure; CO, cardiac output; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; UV, urine volume rate over 24 hours; Time, time from the onset of myocardial infarction to obtaining data.

*P<.05, †P<.01 vs before dobutamine infusion; ‡P<.01 vs admission.
mean aortic pressure (84±9 to 82±10 mm Hg, NS) compared with those in the period of hyposecretion of ANP (equal to before dobutamine infusion). Cardiac output increased moderately by 19%, and urine volume rate over 24 hours increased strikingly by fivefold to eightfold. After the occurrence of peak ANP, hemodynamic variables returned to the normal range progressively as demonstrated in the upper panel of Fig 5.

**SRP Group**

Patients' conditions on admission in the SRP group were similar to those observed in the URP group, ie, a low cardiac output and increased vascular resistance (Table 3). Consequently, volume loading therapy with normal saline was also performed after the initial volume loading test. Because patients in the SRP group had a favorable response to volume loading therapy alone, they did not require dobutamine infusion. After volume loading therapy, plasma ANP levels reached peak value concomitantly with the increase in right atrial pressure (Fig 4). Urine volume rate over 24 hours increased strikingly by eightfold, and cardiac output was augmented by 31% (Table 3). This increment in urine volume was disproportionately larger than that in cardiac output, suggesting that this increase in urine volume was due to a direct effect of ANP rather than the secondary effect of an increase in cardiac output. The lower panel of Fig 5 demonstrates a representative case in the SRP group showing that cardiac output and urine volume increased more quickly after the earlier peak of plasma ANP level compared with the case in the URP group shown in the upper panel.

**Discussion**

The present study has demonstrated that (1) the response of ANP release to volume loading was attenuated in patients with right ventricular infarction without coronary reperfusion and (2) successful coronary reperfusion preserved cardiac endocrine function from an ischemic insult.

**Attenuated ANP Secretion in Right Ventricular Infarction**

Atrial natriuretic peptide is synthesized and stored in atrial myocyte granules. It is rapidly induced and released within minutes and increases in plasma acutely by 10 to 15 pmol/L for each 1 mm Hg increment of atrial pressure. However, in the present study, the blunted response to volume loading was observed after the onset of right ventricular infarction in patients without coronary reperfusion. This finding suggests that a pressure sensitivity of ANP release is attenuated in acute right ventricular infarction with an occluded right coronary artery. The mechanism of such attenuation is unclear. However, several explanations are possible, such as (1) a depletion of ANP storage caused by an excessive release, (2) a reduced rate of synthesis or translocation of ANP caused by right atrial ischemia or necrosis, or (3) a reduced compliance of the ischemic atrium.

A depletion of ANP has been reported to be due to a long-term pronounced ANP secretion under some conditions such as hypertension or chronic severe heart failure. However, the condition in the present study was different from the previous reports because (1) all patients who had any diseases associated with chronic high plasma ANP levels were excluded from the study, (2) the initial volume loading test was performed soon after the onset of myocardial infarction, and (3) the plasma ANP level before the initial volume loading test remained within the normal range. Thus, it is unlikely that ANP storage is exhausted in patients of the present study.

It is well known that hormone synthesis or release is an energy-dependent process. In the present study, all patients had right coronary artery occlusion near the ostium, suggesting the presence of right atrial ischemia or infarction. During ischemia, the production of high-energy phosphate declines and its stores deplete progressively. Thus, the decreased intracellular energy supply during atrial ischemia probably impairs the ability of ANP synthesis or translocation to the release site, which may play a role in the blunted response of this peptide release to volume loading.

Myocardial ischemia alters chamber compliance, which determines chamber volume at a given pressure. Atrial distension has been reported to be the primary mechanism controlling ANP release. Therefore, the ischemic atria may have released less hormone because of a reduction in atrial compliance because less compli-
ant atria respond to a given pressure with a lesser degree of distension.

Pressure sensitivity of ANP secretion recovered a few days after the onset of myocardial infarction as demonstrated in Figs 3 and 4. This delayed restoration may be ascribed to the recovery of ANP synthesis/release or the improvement of atrial compliance from the ischemic insult. A ventricular recruitment of ANP synthesis may contribute in part to this situation. The ventricle, including only 1% to 2% of atrial ANP level in normal heart,22,23 can be recruited as another ANP production site in the volume- and/or pressure-overloaded heart.24,25 By 24 to 72 hours after the onset of acute myocardial infarction, ANP gene expression has been observed in the human ventricle.26 Thus, in the present study, an enhanced ventricular recruitment of ANP synthesis may contribute to the delayed elevation of plasma ANP levels at 69±16 hours after the onset of infarction. However, it may also be possible that the ventricular ANP gene expression itself is impaired by ventricular infarction.

The Role of ANP Secretion in Right Ventricular Infarction

Elevated plasma ANP levels have been proposed to play a role in the clinical deteriorations of right ventricular infarction because the diuretic and vasorelaxant effects would easily reduce right ventricular preload.27 However, in the present study, we have shown that both urine volume and cardiac output increased significantly with a decrease in vascular resistance during the phase of peak ANP in patients without coronary reperfusion. These findings suggest that increased plasma ANP is not mainly responsible for the low cardiac output condition in right ventricular infarction. In contrast, the hemodynamic deterioration was observed during the period of hyposcretion of ANP, that is, when the level of ANP was not sufficient for the elevated filling pressure. Thus, we speculate that a relative deficiency of ANP despite a high level of right atrial pressure may contribute to the hemodynamic deterioration in acute right ventricular infarction and that ANP release may have potentially beneficial effects for the hemodynamics in this setting.

Goto et al28 reported that a low cardiac output during right ventricular ischemia primarily is due to the reduction of left ventricular end-diastolic volume. Increased right ventricular volume after volume loading may produce further compression of the left ventricular cavity. Atrial natriuretic peptide has a natriuretic effect, which is highly dependent on sodium or water balance. Therefore, this endogenous peptide might serve as an important regulator to prevent excessive circulatory volume overload in right ventricular infarction.

A low cardiac output condition leads to activation of the vasoconstrictive neurohumoral system such as the renin-angiotensin-aldosterone system, arginine vasopressin, and the sympathetic nervous system. Although ANP is considered to be an ideal endogenous agent to counterbalance the detrimental effects of those vasoconstrictive systems,29-31 the vasodilatory effect of ANP seems to be modest even during peak ANP release in the present study. This is probably because the effects of ANP are masked by the stimulation of the more potent vasoconstrictive system.32,33 Our results also suggest that this peptide may cause vasodilation of the pulmonary vascular bed34 in right ventricular infarction, which is advantageous for right ventricular systolic performance.

Effects of Coronary Reperfusion on ANP Secretion

Reperfusion therapy has been shown to decrease infarct size1 and to reduce mortality2 and ventricular irritability.3 For acute right ventricular infarction, reperfusion therapy is beneficial because it induces rapid improvement of right ventricular function4 or resolution of atrioventricular block.5 Furthermore, in the present study, we have shown that coronary reperfusion preserved cardiac endocrine function as well as its mechanical function. This preserved ANP secretion might help to maintain sodium-water excretion and promote vasodilation, which may contribute in part to the enhancement of the hemodynamic recovery after acute right ventricular infarction.

In the present study, patients without coronary reperfusion suffered from a refractory low cardiac output condition coupled with vasoconstriction during the phase of hyposcretion of ANP. However, such a detrimental condition associated with an ANP deficiency did not last long because of the delayed but spontaneous recovery of ANP synthesis or release. Like an exogenous ANP infusion for the treatment of congestive heart failure,6,7 enhanced ANP secretion appeared to have improved the hemodynamics of acute right heart failure. If a deficiency of ANP is continued, hemodynamic deterioration would be accelerated. Fig 6 shows one patient with acute right ventricular infarction without coronary reperfusion who was not entered into the study group because of a history of anterior nontransmural myocardial infarction. This patient died of severe low cardiac output on the sixth hospital day with a persistent failure of ANP release without responding to the high filling pressure. At autopsy, the right atrium was dilated and histological specimens revealed extensive necrosis of the atrial wall, suggesting irreversible endocrine failure of the right atrium. In a similar case, a patient who died of acute right ventricular infarction has been reported to be accompanied by the functional defect of ANP release.27 These findings support the hypothesis that persistent ANP deficiency may indicate a poor prognosis in patients with right ventricular infarction. Salvaging endocrine function by the reperfusion therapy may have a beneficial effect in these patients.

Clinical Implications

Robalino et al27 suggest that an elevated plasma ANP level may be used as an early diagnostic marker of right ventricular involvement. However, plasma ANP level would not be elevated soon after the onset of myocardial infarction if right atrial pressure remains within the normal range or if a secretion of ANP is impaired by the ischemic insult. Thus, it would be difficult to establish the diagnosis of right ventricular infarction only by the plasma ANP level. In contrast, the present study has shown that the hemodynamic improvement follows the occurrence of peak ANP (Fig 5 and Table 2), suggesting that an elevated ANP level can be used as a useful predictor of the functional recovery from acute right ventricular infarction.

The highest reported incidence of atrial infarction by the autopsy study is 42%.35 However, its antemortem
diagnosis is commonly difficult. This is probably because the findings in electrocardiography, which is the primary instrument for antemortem diagnosis, are subtle and nonspecific or may be masked by changes associated with concomitant ventricular infarction. In the present study, supraventricular tachyarrhythmias, one of the criteria for diagnosis of atrial infarction, was recorded in only 6 (55%) of the 11 patients without coronary reperfusion whose angiography revealed the atrial branch involvement in the dominant right coronary artery. Goldstein et al reported previously that the loss of atrial booster function caused by the ischemic right atrial dysfunction or atrioventricular asynchrony contributed to severe low cardiac output in patients with acute right ventricular infarction. Therefore, in this setting, the diagnosis of atrial infarction is of clinical importance. The present study suggests that the ANP response to volume loading could help in part to identify patients with atrial infarction.

Study Limitations
A limitation of the present study is the lack of direct evidence for the beneficial effect of ANP in right ventricular infarction. To demonstrate the direct effect of ANP release on the hemodynamics of right ventricular infarction, specific antagonists of ANP should be used in patients with successful reperfusion, or inhibitors of degradation or exogenous ANP should be administered during the phase of hyposcretion of this peptide in patients without coronary reperfusion. Another limitation of this study is the predictive value of plasma ANP levels, because ANP levels cannot be obtained rapidly. Further studies will be needed to address this issue.

Conclusions
The present study demonstrates that ANP secretion in response to volume loading is attenuated by ischemic insult. Coronary reperfusion induces a rapid recovery of endocrine function and hemodynamic improvement. These findings suggest that reperfusion therapy contributes to the enhanced hemodynamic recovery by salvaging endocrine function as well as mechanical function.

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