Beneficial Effect of Atrial Natriuretic Peptide on Pulmonary Gas Exchange in Patients With Acute Lung Injury*

Chieko Mitaka, MD; Yukio Hirata, MD; Takashi Nagura, MD; Yukio Tsunoda, MD; and Keisuke Amaha, MD

Study objectives: The purpose of this study was to investigate the effect of IV infusion of atrial natriuretic peptide (ANP) on hemodynamics, pulmonary gas exchange, and urine volume during mechanical ventilation with positive end-expiratory pressure (PEEP) in patients with acute lung injury.

Design: Prospective, randomized, comparable study.

Setting: ICU of a university hospital.

Patients: Forty patients with moderate acute lung injury (lung injury score ≥2.0) who required mechanical ventilation with PEEP were studied.

Interventions: The patients were randomly divided into two groups: ANP group (n=20) and control group (n=20). The ANP group received genetic recombination α-human ANP (carperitide) at the rate of 0.1 μg/kg/min for 24 h. The control group did not receive ANP.

Measurements and results: Hemodynamic and blood gas parameters, and urine volume were measured at baseline, 3 h, and 24 h after initiating the ANP infusion. Plasma ANP concentrations markedly (p<0.01) increased from 112.0±27.0 to 1,868.3±385.3 pg/mL after 24 h in the ANP group, whereas they remained unchanged in the control group. In the ANP group, hemodynamic parameters did not change, but PaO2/FI02 (fraction of inspired oxygen) and thoracic compliance significantly (p<0.01) increased at 24 h after initiating the ANP infusion, associated with significant (p<0.01) decreases in lung injury score and shunt. Urine volume significantly (p<0.01) increased during 0 to 3 h after initiating the ANP infusion. In the control group, hemodynamics, pulmonary gas exchange, and urine volume did not significantly change during the study period. There were significant differences in PaO2/FI02 (24 h), thoracic compliance (24 h), lung injury score (24 h), and urine volume (3 h) between the two groups.

Conclusion: The results suggest that ANP infusion induces diuresis and improves pulmonary gas exchange in patients with acute lung injury during mechanical ventilation with PEEP.

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Key words: acute lung injury; atrial natriuretic peptide; drugs; hemodynamics; infusion; pharmacology; pulmonary function; urine volume

Abbreviations: ANP=atrial natriuretic peptide; CeO2=pulmonary capillary oxygen content; FI02=fraction of inspired oxygen; MPAP=mean pulmonary arterial pressure; Paw=airway pressure; PEEP=positive end-expiratory pressure

Plasma concentrations of atrial natriuretic peptide (ANP), one of the key hormones involved in the regulation of body fluid and BP, have been shown to be correlated with the severity of acute lung injury. Although the exact pathophysiologic role of ANP in acute lung injury remains unknown, accumulating evidence suggests that ANP has a beneficial effect on injured lung. It has been reported that significant diuresis associated with increase in plasma ANP levels preceded the improvement of pulmonary function in infantile respiratory distress syndrome. We have shown previously that plasma ANP concentrations increased in patients with acute lung injury, which were positively correlated with urine volume, urinary sodium excretion, and excreted fraction of filtered sodium. These findings suggest that increased secretion of endogenous ANP may be a homeostatic mechanism during acute lung injury that improves pulmonary function. Exogenous application of ANP has been shown to prevent lung edema in vitro. In addition, ANP infusion has been

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shown to improve hypoxemia and pulmonary hypertension in a lung injury model. These observations led us to propose that ANP may have a beneficial effect on acute lung injury in humans.

Mechanical ventilation with positive end-expiratory pressure (PEEP) acutely depresses urine output and natriuresis by 30 to 50%. The mechanism of antidiuresis/antinatriuresis in response to PEEP may be clinically important because fluid retention could oppose the expected beneficial effect of PEEP by worsening pulmonary edema. One possible explanation of this antidiuresis and antinatriuresis has been suggested by the fact that PEEP decreases plasma ANP concentration. Since ANP is mainly released from atrium by stimulation with mechanical stretch, the major cause of the decreased ANP release during PEEP has been shown to be due to the atrial compression by the distended lungs and the reduced venous return. Therefore, exogenous ANP may counteract the detrimental effect of PEEP on fluid retention. However, the clinical trials of ANP infusion in patients with acute lung injury have not been performed thus far. Accordingly, the present preliminary study was designed to determine the effect of ANP infusion on hemodynamic parameters, pulmonary gas exchange, and urine volume during mechanical ventilation with PEEP in patients with acute lung injury.

**Materials and Methods**

**Patients**

The study was approved by the institutional committee on human research, and appropriate informed consent was obtained from the subjects or their nearest relatives. Forty patients with acute lung injury (30 male, 10 female; range, 47 to 84 years) were selected for this study. The severity of acute lung injury was determined using a lung injury score by Murray et al. This score is based on four components: the chest radiograph, oxygenation (PaO₂/fraction of inspired oxygen [FIO₂]), PEEP, and thoracic compliance, each scoring from zero to four points. The final value is obtained by dividing the aggregate sum by the number of components used. All four components were recorded in 37 patients and three components except for thoracic compliance were recorded in 3 patients. A score >2.5 represents severe injury, a score between 0.1 and 2.5 represents mild-to-moderate injury, and a zero score means no lung injury. The lung injury score of each patient was >2.0 at entry into the study. Patient characteristics, etiology of acute lung injury, duration of ICU stay, and the mortality are shown in Table 1. The patients are randomly divided into two groups: ANP group and control group. The ANP group and the control group consisted of 20 patients each. During the study, all patients were mechanically ventilated with PEEP 5 to 12 cm H₂O and sedated with continuous infusion of midazolam. PEEP was not changed in individual patients during the 24-h observation period. Dopamine and/or dobutamine were used in all patients except for four.

<table>
<thead>
<tr>
<th>Table 1—Clinical Characteristics of 40 Patients With Acute Lung Injury</th>
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<tbody>
<tr>
<td>Age, yr, mean±SEM</td>
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<tr>
<td>Gender, No.</td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
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<td>Etiologies, No.</td>
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<tr>
<td>Sepsis</td>
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<td>Postoperative</td>
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<td>Pneumonia</td>
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<td>Multiple blood transfusions</td>
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<tr>
<td>ICU stay, d, mean±SEM</td>
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<tr>
<td>Mortality, No.</td>
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**Measurements of Hemodynamics, Pulmonary Gas Exchange, and Urine Volume**

A catheter was inserted into the radial artery for measurement of systemic arterial pressure and for blood sampling in all patients. A Swan-Ganz catheter (93A-750H-7.5F; Baxter HealthCare; Irvine, Calif) was inserted into the pulmonary artery in 11 patients in the ANP group and in 13 patients in the control group. Heart rate was monitored with ECG. Mean arterial pressure, mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure, and right atrial pressure were measured at the end-expiratory phase on a monitoring system (Lifescope 14; Nihon Kohden; Tokyo, Japan) connected to the pressure line through transducers (Baxter; Deerfield, Ill). Cardiac output was obtained by the thermodilution method using the average of three measurements calculated by computer (Explorer; Baxter Healthcare). Cardiac index, systemic vascular resistance index, and pulmonary vascular resistance index were calculated by standard formula. Arterial and mixed venous blood gases were measured by an analyzer (Stat Profile 5; NOVA Biomedical; Waltham, Mass). Shunt was calculated by the following equation:

\[ \text{Cc'0₂=CaO₂}/(\text{Cc'O₂-CVO₂}) \]

where \( \text{Cc'0₂} \) = pulmonary capillary oxygen content \( (1.39\times\text{Hb})+\text{PaO₂}/0.0031 \), \( \text{CaO₂} \) = arterial oxygen content, and \( \text{CVO₂} \) = mixed venous oxygen content. Thoracic compliance was monitored by the ventilator (Evita; Dräger; Lübeck, Germany) in all patients except for three patients who were ventilated with pressure support ventilation; the mean values during 10 respiratory cycles were calculated. The ventilator (Evita) has a computer-assisted multipoint method for breath-by-breath calculation of thoracic compliance and airway resistance. Thus, static thoracic compliance and airway resistance were calculated from airway pressure (Paw), expiratory flow, and expiratory volume at various times (t) during expiration by the following formula:

\[ \text{Plateau Paw}=\text{Paw}(t)+\text{volume}(t)/\text{compliance}+\text{resistance} \times \text{flow}(t) \]

\[ t_1=80, 88, 96, 104 \text{ ms from the start of expiration} \]

\[ t_2=3/4 \text{ of expiration time} \]

Each value of Paw \( (t_1) \), volume \( (t_1) \), and flow \( (t_1) \) is the average of four measurements at 80, 88, 96, and 104 ms from the start of expiration, and each value of Paw \( (t_2) \), volume \( (t_2) \), and flow \( (t_2) \) is the measurement at 3/4 of expiration time. Urine samples were collected by a balloon catheter and urine volume was measured at 1-h intervals.

**Study Protocol**

After stable resting period, baseline parameters were measured. Genetic recombination α-human ANP (carpetide; Zeira/...
Suntory Co Ltd; Tokyo, Japan) was IV infused at the rate of 0.1 μg/kg/min for 24 h (ANP group). Hemodynamic and pulmonary parameters were measured after 3 and 24 h. Urine volume was measured during 3 to 0 h, 0 to 3 h, and 3 to 24-h intervals. In the control group, the above parameters were measured at the same time interval. Infusion rates of inotropic agents and sedative drugs were kept constant during the study, and diuretics were not used.

**Blood Sampling and Assay of ANP**

Blood samples for ANP assay were obtained from a radial artery at baseline and after 24 h. Blood was collected into chilled glass tubes containing EDTA-2K and aprotinine, immediately centrifuged at 4°C, and the plasma was stored at −80°C until assayed. Plasma ANP concentration was measured by a specific radioimmunoassay as previously described. Plasma ANP concentrations in healthy subjects were 31.7±1.1 pg/mL.

**Statistical Analysis**

Values were expressed as mean±SEM. Statistical analysis was performed by analysis of variance for repeated measures followed by Tukey’s multiple comparison test when F value indicated significant differences. Statistical comparisons between groups were performed by one-way analysis of variance and post hoc multiple comparison with the use of Tukey’s test. A p value <0.05 was considered significant.

**RESULTS**

**Plasma ANP Concentrations**

Plasma ANP concentrations markedly and significantly (p<0.01) rose 24 h after initiating the ANP infusion, while they remained unchanged in the control group (Table 2).

**Hemodynamic Changes**

In both groups, no hemodynamic parameters changed during the study period (Table 2).

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**Pulmonary Gas Exchange**

In the ANP group, PaO₂/FIq2 and thoracic compliance increased significantly (p<0.01) associated with significant (p<0.01) decrease in shunt after 24 h (Fig 1). Lung injury score was significantly (p<0.01) decreased 24 h after initiating the ANP infusion (Fig 2). In the control group, PaO₂/FIq2, shunt, thoracic compliance, or lung injury score did not change during the study period (Figs 1 and 2). There were significant differences (p<0.05) in PaO₂/FIq2 (24 h), thoracic compliance (24 h), and lung injury score (24 h) between the two groups.

**Urine Volume**

In the ANP group, urine volume increased significantly (p<0.01) from 55±6 mL/h (3 to 0 h) to 105±16 mL/h (0 to 3 h), 82±7 mL/h (3 to 24 h), while in the control group, urine volume did not change during the study period; 64±7 mL/h (3 to 0 h), 61±6 mL/h (0 to 3 h), and 70±5 mL (3 to 24 h). Urine volume during 0 to 3 h in the ANP group was significantly (p<0.01) greater than that in the control group.

**DISCUSSION**

An intriguing and novel finding in the present preliminary study is that ANP infusion improved arterial oxygenation and lung injury score in patients with acute lung injury during mechanical ventilation with PEEP, as evidenced by an increase in PaO₂/FIq2 with a concomitant increase in thoracic compliance, even though urine volume and plasma ANP concentrations have been reported to decrease during mechanical ventilation with PEEP.11–13

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**Table 2—Changes in Hemodynamic Parameters of Patients With Acute Lung Injury With or Without ANP Infusion**

<table>
<thead>
<tr>
<th></th>
<th>ANP Group (n=11)</th>
<th>Control Group (n=13)</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 h</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>98±4</td>
<td>103±3</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>87±5</td>
<td>82±3</td>
</tr>
<tr>
<td>MPAP, mm Hg</td>
<td>24±2</td>
<td>21±2</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>14±1</td>
<td>12±1</td>
</tr>
<tr>
<td>RAP, mm Hg</td>
<td>9±1</td>
<td>8±1</td>
</tr>
<tr>
<td>CI, L/min/m²</td>
<td>4.03±0.32</td>
<td>4.31±0.41</td>
</tr>
<tr>
<td>SVRI, dyne·s·cm⁻⁵·m²</td>
<td>1,689±156</td>
<td>1,513±145</td>
</tr>
<tr>
<td>PVRI, dyne·s·cm⁻⁵·m²</td>
<td>214±29</td>
<td>184±27</td>
</tr>
<tr>
<td>Plasma ANP levels, pg/mL</td>
<td>112.0±27.0 (n=20)</td>
<td>1568.3±385.3¹¹</td>
</tr>
</tbody>
</table>

*Values are mean±SEM. HR=heart rate; MAP=mean arterial pressure; PCWP=pulmonary capillary wedge pressure; RAP=right atrial pressure; CI=cardiac index; SVRI=systemic vascular resistance index; PVRI=pulmonary vascular resistance index.

¹¹p<0.01, compared with baseline.

¹p<0.01, compared with control.
Improvement of pulmonary oxygenation by ANP suggests that ANP may reduce the pulmonary transcapillary filtration, perhaps by decreasing vascular permeability and/or hydrostatic pressure. It has been shown that ANP directly prevented pulmonary edema by arachidonic acid,6 thrombin,17 and oxidant,18 possibly by blocking water movement from blood vessels to the interstitial space. Taken together, it is suggested that ANP improves the barrier function of endothelial cells to reduce edema formation. It has been shown that oxygen saturation increased in healthy mountaineers after ANP infusion, and the alveolar arterial oxygen difference decreased during hypoxia despite hemococoncentration.19 Collectively, these data support the hypothesis that ANP may selectively prevent the permeability of the pulmonary circulation to improve pulmonary gas exchange.

In the present study, hemodynamic parameters did not significantly change during ANP infusion. It has been shown that ANP decreased MPAP in patients with COPD,20 and that ANP caused pulmonary vasodilation against angiotensin II-induced pulmonary vasoconstriction in healthy volunteers.21 The apparent discrepancy between our study and others may be due to the subject population studied. It remains unknown whether ANP plays a counterregulatory role as a pulmonary vasodilator against pulmonary hypertension in acute lung injury.

In the present study, thoracic compliance significantly increased and shunt significantly decreased 24 h after ANP infusion in patients with acute lung injury. Since a decrease in circulating volume by phlebotomy reduces the intrapulmonary shunt and improves pulmonary gas exchange in canine oleic acid-induced pulmonary edema,22 a decrease in shunt after ANP infusion may be due to a reduction in circulating volume. In the present study, ANP infusion immediately induced diuresis, followed by improvement of oxygenation. In infantile respiratory distress syndrome, a significant diuresis preceded the improvement of the pulmonary function,3,4 suggesting the removal of excess lung water via diuresis. We have also shown in a previous study that in-

**Figure 1.** Changes in pulmonary gas exchange in patients with acute lung injury with (n=20) or without (n=20) ANP infusion (0.1 μg/kg/min). PaO2/FI02 (top), shunt (center), and thoracic compliance (bottom) at baseline, 3 h, and 24 h. Each point with bars shows mean±SEM. Asterisk: p<0.05, double asterisk: p<0.01, compared with baseline; dagger: p<0.05, double dagger: p<0.01, compared with the control group.

**Figure 2.** Change in lung injury score at baseline and 24 h in patients with acute lung injury with (n=20) or without (n=20) ANP infusion (0.1 μg/kg/min). Each column with bar shows mean±SEM. Double asterisk: p<0.01, compared with baseline; dagger: p<0.05, compared with control group.
increased circulating ANP concentrations in patients with acute lung injury were correlated with diuresis/natriuresis. Furthermore, injection of anti-ANP antibody reduced diuresis/natriuresis and increased wet lung in a rat pulmonary injury model. These data suggest that ANP may function to attenuate lung edema in part through its diuretic/natriuretic action.

It has been shown that ANP infusion was more effective in increasing PaO₂ than furosemide even after its discontinuance in a porcine lung injury model. These results are in agreement with those of ours showing that the improvement of pulmonary gas exchange occurred later after diuresis. The reason why the delayed onset of improvement of thoracic compliance and shunt was observed after ANP infusion remains unknown, because plasma ANP concentrations would have reached steady-state by 3 h. Although ANP promptly induced diuresis/natriuresis and a subsequent decrease in intravascular blood volume, slow transition of extracellular lung water from interstitial space of lung into circulation may occur, thereby leading to an increase in thoracic compliance and a decrease in shunt. Taken together, it may take a longer time to improve pulmonary function by ANP infusion in acute lung injury. In fact, PaO₂/FIO₂ and thoracic compliance in the ANP group significantly improved after 24 h compared with those in the control group. Therefore, it appears likely that the changes observed after 24 h reflect improvement by ANP rather than general treatment.

However, Andrivet et al. have reported that ANP infusion did not improve arterial oxygenation in patients with COPD, suggesting that the impaired oxygenation is due to an increase in blood flow perfusing poorly ventilation-perfusion abnormality and/or an increase in pulmonary shunt. The apparent difference between their study and ours may be due to patient population and/or duration and dose of ANP used. The patient population of their study had COPD, whereas ours had acute lung injury. Duration of ANP infusion in their study was shorter (30 min) and dose of ANP was smaller (0.01 and 0.03 µg/kg/min) than those in our study (24 h and 0.1 µg/kg/min). Although it is unknown whether ANP increases ventilation-perfusion mismatch, a reduction of excess lung water by ANP may have led to improvement of oxygenation and thoracic compliance as observed in our study.

We and other investigators have shown that the severity of lung injury correlated with elevated plasma ANP concentrations that decreased after improvement of lung injury. Although PEEP has been shown to decrease ANP secretion because of impaired atrial stretch and decreased venous return, plasma ANP concentrations increased even during PEEP application in acute lung injury as previously reported, suggesting its excessive secretion and/or decreased clearance by organs other than atrium. Because lungs are the major site of ANP production as well as its clearance, elevated plasma ANP level in acute lung injury was most likely derived from its overproduction and/or decreased clearance by the injured lungs. Therefore, the severity of the lung injury should be correlated with plasma ANP concentrations, and after improvement of lung injury, enhanced ANP secretion and/or impaired ANP clearance could be normalized. These data strongly suggest that elevated circulating ANP level plays a compensatory role for acute lung injury to improve pulmonary function.

Despite elevation of endogenous ANP secretion, infusion of exogenous ANP improved pulmonary function in our patients, suggesting that increased endogenous ANP levels in acute lung injury are still insufficient to correct the impaired pulmonary function. Accordingly, the administration of exogenous ANP to further augment circulating ANP concentrations may improve pulmonary oxygenation in acute lung injury.

It should be noted that our patients with severe injury (lung injury score >2.5) were only three in the ANP group and two in the control group; thus, most patients had moderate lung injury. Although lung injury score significantly decreased 24 h after ANP infusion in our study, the moderate lung injury did not decrease to mild or no lung injury. Therefore, a larger study treating more patients with severe lung injury score with ANP infusion and its beneficial effect on survival rate is necessary. Some dispute against the usefulness of the lung injury score for assessment of outcome in acute lung injury. Among the four components of lung injury score examined, the chest radiograph and PEEP did not change after initiating the ANP infusion, and the major factors for improvement of lung injury score appeared to be PaO₂/FIO₂ and thoracic compliance in the present study.

**Conclusion**

The present study demonstrated that ANP infusion induced diuresis and improved pulmonary oxygenation and thoracic compliance, thus decreasing lung injury score in patients with acute lung injury even during mechanical ventilation with PEEP. A more extensive study is necessary to justify whether ANP infusion is a useful therapeutic agent in acute lung injury.
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