Increased Release of Alpha-atrial Natriuretic Peptide during Controlled Mechanical Ventilation with Positive End-expiratory Pressure in Humans

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The objective of this study was to test the hypothesis that a release of alpha-artrial natriuretic peptide (ANP) is depressed resulting in the reduction of urinary output in patients receiving controlled mechanical ventilation (CMV) with positive end-expiratory pressure (PEEP). Five normovolemic patients with no apparent cardiac, renal, endocrine, or pulmonary dysfunctions were included in this study. After the patients were mechanically ventilated using a volume-cycled ventilator with zero cmH_2O PEEP for one hour, hemodynamic variables were measured. Urine and blood samples were collected after the measurements. Plasma alpha-ANP levels were determined on blood samples taken from radial artery using specific radioimmunoassay. Then PEEP levels were changed to 5, 10, 15 and, finally, 0 cmH_2O in four consecutive one-hour periods. At the end of each period, the measurements and collection of the samples were repeated. With increasing levels of PEEP, central venous pressure (CVP), pulmonary artery wedge pressure (PAWP), and heart rate were pressure-dependently increased. On the other hand, cardiac output and urinary output were decreased. Plasma levels of alpha-ANP were also increased by the institution of PEEP. These changes occurred in a pressure-dependent fashion. Urinary sodium excretion, potassium excretion, fractional excretion of sodium and free water clearance remained unchanged. It is concluded that a release of alpha-ANP was augmented rather than depressed with PEEP. This suggests that a decrease in urinary excretion in patients with PEEP may not be due to a reduced release of alpha-ANP. (Key words: controlled mechanical ventilation, alpha-atrial natriuretic peptide, PEEP (positive end-expiratory pressure), diuresis)

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CMV with PEEP is commonly used in patients with respiratory failure to increase arterial oxygen content. It is well known that PEEP causes a decrease in urinary output[1]. Although the mechanisms of the complication is not fully understood, two main factors, i.e. hemodynamic and humoral factors, have been suggested to be responsible[2]. First, PEEP may suppress cardiovascular function and thereby decrease renal blood flow or reduce renal perfusion pressure resulting in the reduction of urinary output. Second, an increase in intra-thoracic pressure by PEEP increases a release of antiduretic hormone (ADH) which is responsible for water retention.

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Table 1. Clinical characteristics of subjects

Subjects number	Age (Yrs)	Sex	Diagnosis
1	18	M	Guillain-Barre syndrome
2	63	F	Ovarian carcinoma
3	55	M	Myasthenia gravis
4	58	F	Acute respiratory failure
5	67	M	Acoustic neurinoma

Alpha-atrial natriuretic peptide (alpha-ANP) is a polypeptide hormone with diuretic and natriuretic properties and synthesized and stored in atrial muscle cells. Alpha-ANP has been shown to be increased by distending the atrium in hyper-volemic patients with congestive heart failure or renal failure[3]. It would be, therefore, reasonable to speculate that the institution of CMV with PEEP may decrease ANP levels, thus resulting in the reduced renal excretory function found in the patients with respiratory support. In this study, we investigated the effects of different levels of PEEP on hemodynamic changes, diuresis, natriuresis, and plasma alpha-ANP levels in patients.

Subjects and Methods

Five patients with mean age of 52.2 ± 20.0 (29–63yr.) were included in this study (table 1). The studies were performed on the day when patients were without apparent renal, cardiac, endocrine, or pulmonary dysfunction as assessed by clinical, radiological, and routine laboratory tests. All patients were mechanically ventilated by a volume-cycled ventilator (Engstrom Erica, Engstrom Medical AB, Sweden) with a tidal volume of 10–12 ml per kg of body weight, at a respiratory rate of 15–18 breaths per min. A fractional concentration of inspired oxygen ($F_{I_{O_2}}$) was initially adjusted to obtain arterial oxygen tension (Pa_{O_2}) between 90 and 120 mmHg. Arterial carbon dioxide tension (Pa_{CO_2}) was maintained between 35 and 40 mmHg to avoid hypo- or hyper-ventilation. The ventilation settings except the level of PEEP were unchanged throughout the study.

Blood pressure was monitored via a catheter placed in the radial artery. Central venous, mean pulmonary artery, and pulmonary artery wedge pressure (CVP, MPA, PAWP, respectively) were measured using a pulmonary artery catheter (702-K200H-7F, American Edwards Laboratories, Anasco, Puerto Rico). Cardiac output was measured by thermodilution (78551A cardiac output module, Hewlett Packard Co. Paroalto, Ca, USA), taking the mean of five successive determinations, and cardiac index (l/min/m^2) was calculated.

Blood was drawn from the radial artery. Urine was collected through an intravesical catheter. Blood and urinary samples were simultaneously obtained to determine creatinine, electrolytes, and osmolality (Fiske OS osmometer, Fiske Associate, Needham Hights, Mass, USA).

Plasma alpha-ANP levels were determined using specific radioimmunoassay without extraction (Kitasato Biochemical Lab., Sagamihara, Japan) on arterial blood samples drawn into an ice-cold syringe containing EDTA and aprotinin (final concentration; 100 units per ml).

Experimental Protocol

All patients were initially ventilated with zero cmH_2O PEEP. Then the level of PEEP was successively changed to 5, 10, 15 and finally zero cmH_2O with each one hour period. Hemodynamic measurements, blood sampling, and urine collection were done at the end of CMV with each level of PEEP.

Statistics

All values were expressed as the mean ± the standard error of the mean for each point. Statistical analyses were performed between the values at initial zero cmH_2O PEEP and those at each levels of PEEP thereafter by Student's t-test for paired data. $P<0.05$ was considered to be statistically significant.

Results

Cardiac index was pressure-dependently decreased from 3.80 ± 0.38 at a zero PEEP level to 3.12 ± 0.43 l/kg/min ($P<0.05$) at

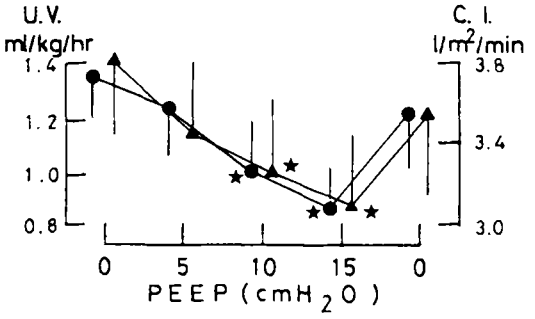

Fig. 1. Effects of PEEP on urinary output (•) and on cardiac index (▲) in patients (n=5) during CMV.

* Significant difference ($P<0.05$) with respect to values at initial zero PEEP.

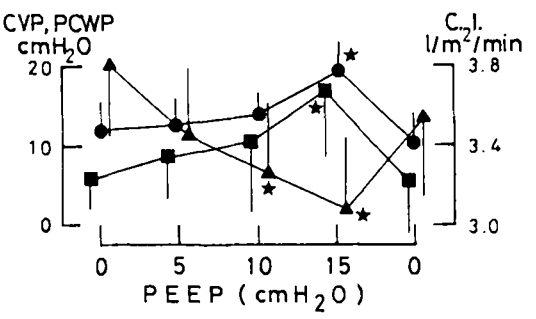

Fig. 2. Effects of PEEP on hemodynamics (CVP:▪, PAWP:•, cardiac index:▲) in patients during CMV.

* Significant difference ($P<0.05$) with respect to values at initial zero PEEP.

a 15cmH_2O PEEP level (fig. 1). PEEP reduced, in a pressure-dependent fashion, urinary output (fig. 1, 1.34 ± 0.16 ml/kg/hr at zero PEEP and 0.83 ± 0.07 ml/kg/hr at 15cmH_2O, $P<0.05$). The changes of cardiac index and urinary output were parallel (fig. 1). With increasing levels of PEEP, CVP and PAWP were increased. Thus, CVP and PAWP at zero PEEP were 6.25 ± 0.41, 12.00 ± 1.08 cmH_2O and they reached to 13.00 ± 0.25 ($P<0.05$), 18.2 ± 1.02 ($P<0.05$) cmH_2O at a 15 cmH_2O PEEP level, respectively (fig. 2). There was a significant, pressure-dependent increase in heart rate (fig. 3, from 92.6 ± 2.7 at zero cmH_2O PEEP to 116.0 ± 3.7 beats/min at 15 cmH_2O PEEP, $P<0.02$). Plasma level of alpha-ANP before the application of PEEP was 31.7 ± 1.97 pg/ml. When a level of PEEP was increased, elevation of the hormone level was observed (fig. 3). Plasma concentrations of the hormone at 5, 10, 15 and 0 cmH_2O were, respectively, 38.2 ± 1.96, 44.9 ± 3.53 ($P<0.05$), 48.9 ± 4.92 ($P<0.05$), and 33.6 ± 2.12 pg/ml. All the changes that occurred by the application of PEEP were reversed when PEEP was returned to zero cmH_2O. There were no significant changes in free water clearance, and fractional excretion of sodium and potassium.

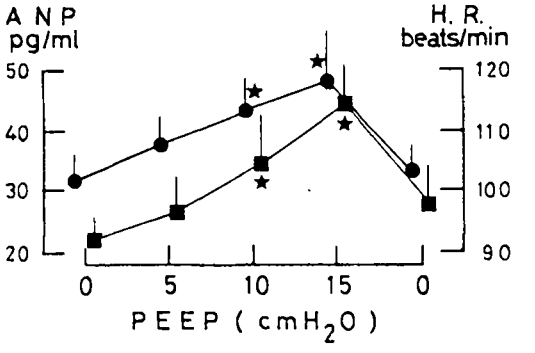

Fig. 3. Effects of PEEP on heart rates (▪) and plasma alpha-ANP (•) levels in patients during CMV.

* Significant difference ($P<0.05$) with respect to values at initial zero PEEP.

Discussion

The results in this study show that urinary-output and cardiac-output in patients receiving CMV with PEEP were reduced while plasma alpha-ANP levels were increased. These reductions of urinary- and cardaic-outputs and the increase in alpha-ANP were pressure-dependent. On the other hand, in a similar study Leithner et al.[4] reported decreased release of alpha-ANP in patients suffering from acute respiratory failure as well as in healthy volunteers during CMV with 15 cmH_2O PEEP. Main difference between the two studies is that the most subjects in the latter study were volume-expanded before the institution of PEEP. One of their subjects, who was thought to be free of edema, failed to have a PEEP-induced reduction of plasma alpha-ANP level. They speculated that PEEP could depress alpha-

ANP only in volume-expanded subjects. All subjects in this study seemed to be normovolemic: because they had no edema, and their CVP, PAWP, and urinary output and osmolality before the application of PEEP were within normal limits.

It has been shown that plasma alpha-ANP levels are increased in volume-expanded subjects[3], patients with congestive heart failure[3], and chronic renal failure[5]. These studies suggest that a release of alpha-ANP may be regulated via activation of stretch receptors on atrium in response to atrial distension. In the present study we found that PEEP induced rises in CVP and PAWP. Although the determination of transmural right and left atrial pressure was not made in our study, it is reported that PEEP may increase a transmural right atrial pressure[6]. Therefore, it is possible that PEEP induced atrial distension resulting in the increased release of alpha-ANP.

In this study with unsedated patients, heart rate was pressure-dependently increased during the application of PEEP. The increase in heart rate may indicate a rise in plasma levels of catecholamines, as reported by Chernow et al.[7] and by Venus et al.[8] Infusion of epinephrine was shown to increase plasma immunoreactive alpha-ANP through beta-adrenergic mechanisms in humans[9]. Tunny et al.[10] found a significant positive correlation between changes in circulating norepinephrine and changes in alpha-ANP levels in man. Therefore, it is also possible that increased release of alpha-ANP was due to an increased level of catecholamines in response to PEEP.

A decrease in urinary output has been attributed, at least in part, to an elevated levels of ADH[11]. We observed no change in free water clearance throughout the study. The result indicates that ADH is unlikely to be involved in the decrease of urinary output. Payen et al. also suggested that antidiuretic effect of PEEP is mainly due to systemic and renal hemodynamic changes[12].

In summary, plasma alpha-ANP levels were increased in normovolemic, unsedated humans during CMV with PEEP despite the decreased urinary output. Alpha-ANP may not contribute to a reduction of urinary output in response to the increased airway pressure. Further studies are needed to elucidate the mechanisms responsible for the impairment of renal excretory function during respiratory support.

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