Anesthesiology
66:17-23, 1987

# *No Involvement of Antidiuretic Hormone in Acute Antidiuresis During PEEP Ventilation in Humans*

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**Decreased urinary output ($\dot{V}_u$ ml/min) after institution of PEEP is attributed to a variety of mechanisms including decreased cardiac output and renal blood flow (RBF), activation of neurohormonal reflexes, increased catecholamines, plasma renin activity (PRA), and antidiuretic hormone (ADH) release. To evaluate these factors, seven normovolemic patients (36 yr ± 13 SD), free of preexisting lung, cardiac, or renal disease, requiring continuous mandatory ventilation for neurologic reasons were studied. The authors measured or calculated: total blood volume (TBV) ($^{51}Cr$); right atrial, pulmonary arterial, pulmonary wedge, and systemic pressures, cardiac index (CI); renal plasma flow (RPF) (iodohippurate sodium $^{131}I$ [$^{131}I$ PAH] clearance); glomerular filtration rate (GFR) (creatinine clearance), free water clearance ($\dot{C}_{H_2O}$), osmolal clearance ($\dot{C}_{osm}$), fractional excretion of sodium ($FE_{Na^+}$) and potassium ($FE_{K^+}$); and plasma renin activity (PRA) ($ng \cdot ml^{-1} \cdot h^{-1}$), plasma ADH (pg/ml; radioimmunoassay), epinephrine (E in pg/ml), and norepinephrine (NE in pg/ml) (double-isotope radioenzymatic assay). Two conditions were studied after 90-min steady state: 1) zero PEEP (ZEEP); and 2) 15 $cmH_2O$ PEEP. PEEP caused a significant decrease in CI (−21%; $P < 0.01$) and RPF (−19%; $P < 0.05$) without significant decrease in GFR. A significant decrease in $\dot{V}_u$ (−55%; $P < 0.05$), $FE_{Na^+}$ (−39%; $P < 0.05$) and $\dot{C}_{osm}$ (−36%; $P < 0.25$) occurred without modification in $\dot{C}_{H_2O}$. Plasma ADH remained in the normal range and did not increase when PEEP was applied. NE increased significantly ($P < 0.05$) in parallel with PRA ($r = 0.80$; $P < 0.01$). Within the limits of this study, acute antidiuresis during PEEP ventilation appears to result from systemic and renal hemodynamic changes with simultaneous sympathetic activation and high PRA. Moreover, at constant plasma osmolality and TBV, ADH remained in the normal low range. This study demonstrates the absence of any ADH release during PEEP-induced antidiuresis. (Key words: Hormones: antidiuretic; catecholamines; plasma renin activity. Kidney: renal hemodynamics; renal function. Ventilation: PEEP.)**

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Received from the Departement d'Anesthésie Réanimation, Hôpital Lariboisiere, Paris; the Service d'Explorations Fonctionnelles, Hôpital Louis Mourier, Colombes; the Service de Réanimation Médicale and the Departement de Médecine Núcleaire, Hôpital Henri Mondor, Créteil, France. Accepted for publication August 7, 1986. Supported in part by the Institutionnal grant program of Faculté de Médecine, Lariboisiere—Saint-Louis, and Université Paris VII. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, San Francisco, October 1985.

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IN PATIENTS TREATED with continuous mandatory ventilation (CMV), the addition of positive end-expiratory pressure (PEEP) induces a decrease in urinary output.[1,2] Several factors may explain these alterations of renal function and fluid balance. First, PEEP may affect cardiovascular function[3] and thereby decrease renal blood flow or reduce renal perfusion pressure.[1] Second, decreased cardiac output (CO) and systemic arterial pressure (SAP) due to PEEP could initiate neurohormonal reflexes *via* central cardiopulmonary receptors[4] and high pressure baroreceptors[5] and, in turn, cause antidiuresis.[1] It has been shown that increased sympathetic activity or renal nerve stimulation contributes to changes in renal function.[6,7] However, to our knowledge, no previous clinical study has reported a relationship between plasma catecholamines or renal sympathetic activity and renal function during CMV with PEEP in humans.[1] In addition, other hormonal factors, such as antidiuretic hormone (ADH) and the renin angiotensin system, may also modify renal function during PEEP.[1,8,9]

The present study was performed to assess the relative roles of hemodynamic change and neurohormonal release (ADH, plasma catecholamines, and renin angiotensin) on renal function during PEEP ventilation in humans when total blood volume (TBV) remained constant.

## Materials and Methods

### PATIENTS

Seven male patients, aged 36 yr ± 13 SD (22–59 yr), were studied. Written, informed consent was obtained from each patient's closest relative, and the protocol was approved by the University Research Ethical Committee. Criteria for inclusion were the absence of apparent lung, cardiac, and renal dysfunction as assessed by clinical, radiologic, and routine laboratory tests. The studies were performed in patients who required CMV because of neurologic disease. None of them had evidence of significant cerebral edema or intracranial hematoma on computerized tomography (CT) scan performed the day before the study. No patient had undergone any previous surgery, or had any fluid or electrolyte abnormalities or inappropriate secretion of ADH. A fractional inspired $O_2$ concentration ($FI_{O_2}$) (32 ± 6% SD) was selected that would maintain arterial oxygen tension higher than 90 mmHg throughout the procedure. All patients were sedated by

TABLE 1. Clinical Characteristics of Patients

| Patient | Age | Diagnosis by CT Scan | Outcome | $FIO_2$ |
|---|---|---|---|---|
| 1 | 23 | Head trauma, nonhemorrhagic hemispheric contusion | Alive | 0, 4 |
| 2 | 36 | Subarachnoid hemorrhage (grade III) | Alive | 0, 3 |
| 3 | 27 | Head trauma, bifrontal nonhemorrhagic contusion | Alive | 0, 3 |
| 4 | 42 | Recovery from Guillain Barré syndrome | Alive | 0, 4 |
| 5 | 59 | Encephalitis | Dead | 0, 3 |
| 6 | 22 | Head trauma, right hemispheric contusion | Alive | 0, 3 |
| 7 | 43 | Head trauma, occipital nonhemorrhagic contusion | Alive | 0, 3 |

CT = computerized tomography; $FIO_2$ = fractional inspired $O_2$ concentration.

continuous iv infusion of flunitrazepam and paralyzed with pancuronium bromide during the study. All patients were studied while hemodynamics were stable, and none required any vasoactive drugs. No patients received any diuretic, analgesic, or antiinflammatory drugs prior to or throughout the study. Clinical data and diagnosis concerning the patients are shown in table 1.

All patients were mechanically ventilated *via* an endotracheal tube by a volume-cycled ventilator (CPU-1, Ohmeda, Maurepas, France), with a tidal volume of 10–12 ml/kg of body weight at a respiratory rate of 16–18 breaths/min.

## Hemodynamic Study

SAP was monitored *via* a radial artery catheter. Intraluminal right atrial pressure (RAP), pulmonary arterial pressure (PAP), and pulmonary arterial wedge pressure (PAWP) were measured *via* a triple-lumen, balloon-tipped catheter (Swan Ganz) inserted into the pulmonary artery *via* the right internal jugular vein. Position of the catheter tip was verified by a chest x-ray, which also confirmed the absence of radiologic abnormalities. All pressures were measured at end expiration with Bentley® transducers positioned at the midaxillary level connected to a Thomson Telco® amplifier and a multichannel recorder (Honeywell). Heart rate (HR) was recorded from a standard electrocardiogram lead. CO was obtained by averaging three successive thermodilution determinations (CO computer, 9510 A, Edwards Laboratory) performed in random order during the respiratory cycle, and cardiac index (CI) ($l \cdot min^{-1} \cdot m^2$) was calculated.

Inferior vena cava pressure (PIVC) was measured through an indwelling catheter. The tip of the catheter was advanced to the level of the renal veins under fluoroscopic control. Renal driving pressure (DP) was calculated as:

$$DP = SAP - PIVC$$

Systemic vascular resistance index (SVRI) = [SAP − RAP]/CI in $mmHg \cdot min \cdot m^2 \cdot l^{-1}$ (IU) and stroke index (SI = CI/HR in $ml \cdot beat^{-1} \cdot m^2$) were obtained from pressure and CO measurements. Arterial blood gas measurements were performed with an ABL 30® apparatus (Radiometer, Copenhagen).

## Renal Hemodynamics

Renal plasma flow (RPF) measurement was carried out by iv bolus injection of iodohippurate sodium ($^{131}I$ PAH) as described by Burbank *et al.*[10] and Tauxe.[11] Sterile serum chloride $^{131}I$ PAH (Biomedica Italia) was injected ($q_0$) at $t_0$. Plasma samples were collected at 1, 5, 10, 15, 20, 25, 30, 40, 50, 60, and 90 min. Plasma concentration, expressed as counts per s per ml (Ct) at any time, was measured using a gamma counter (Kontron, France) and plotted against time on semilog paper. An aliquot of the injected dose was also counted, and total injected counts per s were determined and designated $q_0$. The disappearance of radioactivity proved to be a biexponential function of time, and the second segment of curve was used to calculate RPF as follows:

$$RPF = k \cdot \text{Volume of distribution}$$

where k is the rate constant equal to $0.693/T_{1/2}$. The volume of distribution was measured by extrapolating the second segment of curve back to give concentration at zero time. This value was then expressed as $Ct_0$ ($\mu$Ci/ml). The injected dose $q_0$ was then divided by this latter value to give diluting volume according to:

$$\text{Volume of distribution} = q_0/Ct_0$$

The first iv bolus injection of $^{131}I$ PAH contained 27 $\mu$Ci in 5 ml, and the second injection 150 $\mu$Ci in 15 ml. Therefore, total body irradiation was $6.10^{-3}$ rad and kidney irradiation was 0.2 rad.

Using each patient's hematocrit (Hct) value, we calculated RBF according to the formula:

$$RBF\,(ml \cdot min^{-1}) = RPF \times \frac{1}{1 - Hct}$$

Renal vascular resistance index (RVRI) was calculated as:

$$RVRI = DP/RBF \text{ index in } mmHg \cdot min \cdot m^2 \cdot l^{-1}\,(IU)$$

TBV was measured using the subject's red blood cells tagged with a radioisotope of chromium ($^{51}Cr$) at the control point and at the end of PEEP measurements.

## Renal Function Study

Urine was collected through an intravesical catheter and urinary output ($\dot{V}_u$) was expressed as $ml \cdot min^{-1}$. Blood and urine samples were drawn simultaneously to determine urea, creatinine, and electrolytes using standard

laboratory techniques. Osmolality was measured with a Fisk® osmometer. Creatinine clearance ($\dot{C}_{creat}$), free water clearance ($\dot{C}_{H_2O}$) and osmolal clearance ($\dot{C}_{osm}$) were calculated and expressed in ml · min$^{-1}$. Glomerular filtration rate (GFR) was evaluated as the $\dot{C}_{creat}$ in ml · min$^{-1}$. Filtration fraction (FF) was expressed in per cent as the ratio GFR/RPF. Fractional excretion of $Na^+$ ($FE_{Na^+}$) and $K^+$ ($FE_{K^+}$) were then calculated and expressed in per cent.

### Hormonal Study

Plasma ADH levels were determined by radioimmunoassay on venous blood samples drawn into chilled syringes containing dipotassium EDTA. Blood samples were centrifuged at 3,000 rpm for 15 min at +4° C and plasma was stored at −20° C and extracted within 2 weeks with acetone, according to Robertson *et al.*[12] Plasma ADH was measured by radioimmunoassay with an antibody obtained in our laboratory, as previously described.[13] Mean plasma ADH value observed in normal subjects under conditions of moderate antidiuresis was 3.6 ± 0.16 pg/ml (mean ± SEM). Intraassay and interassay variations were 12.5% and 17.9%, respectively. The antibody used did not recognize oxytocin even at 1 ng/ml and cross-reacted slightly with 1-deamino-8-D-AVP (0.6%).

Plasma norepinephrine (NE) and epinephrine (E) concentrations were measured using a double-isotope radioenzymatic assay.[14] Pulmonary artery blood samples were collected in chilled tubes containing lithium heparin. After 20 min centrifugation (4,000 rpm) at +4° C, plasma was separated and stored at −20° C until the assay. Sensitivity of this technique was 1.5 pg/ml for both E and NE. Coefficients of variation were 3.1% (420 ± 13 pg/ml) and 3.3% (80 ± 2.6 pg/ml) (intraassay) and 4.2% and 4.5% (interassay) for NE and E, respectively.

Plasma renin activity (PRA) was determined on pulmonary arterial blood after centrifugation by the CEA Sorin® kit. PRA measurement was based on the radioimmunoassay by angiotensin I,[15] and expressed as ng of angiotensin I generated per ml of plasma per h of incubation (ng · ml$^{-1}$ · h$^{-1}$).

### Protocol

All patients were initially mechanically ventilated with ZEEP, followed by ventilation with PEEP. The studies were conducted at the therapeutic level of $FI_{O_2}$ used before the study. Steady-state conditions were confirmed by serial hemodynamic and CO measurements. Three patients initially included in the study had to be withdrawn because CO varied greater than 15% during this time. After 30 min of steady state at zero PEEP level, the first iv bolus of $^{131}$I PAH was injected to measure RPF. At the end of $^{131}$I PAH clearance time (*i.e.*, 90 additional min of CMV with ZEEP), hemodynamic parameters and blood samples were collected and $\dot{V}_u$ was measured. Then 15 cm $H_2O$ PEEP was added, and after a 30-min stabilizing period the second measurement of RPF was made. As before, at the end of $^{131}$I PAH clearance time, blood samples were collected and hemodynamic parameters and $\dot{V}_u$ measured.

TABLE 2. Hemodynamic Variables

| Variable | ZEEP | PEEP | *P* value |
|---|---|---|---|
| SAP (mmHg) | 84 ± 22.2 | 80.4 ± 16.9 | NS |
| RAP (mmHg) | 7.7 ± 1.7 | 12.5 ± 4.2 | <0.01 |
| PAP (mmHg) | 20.1 ± 4.94 | 27.7 ± 7.1 | <0.01 |
| PAWP (mmHg) | 9 ± 1.8 | 17.6 ± 4.3 | <0.001 |
| CI (l · min$^{-1}$ · m$^{-2}$) | 5.22 ± 1.48 | 3.96 ± 1.12 | <0.01 |
| HR (beats/min) | 112 ± 18 | 117 ± 16 | NS |
| SI (ml · m$^{-2}$) | 47 ± 12.3 | 36.4 ± 8.9 | <0.025 |
| PIVC (mmHg) | 6.3 ± 3.8 | 11.3 ± 4.9 | <0.001 |
| DP= SAP−PIVC (mmHg) | 77.6 ± 21.4 | 69.1 ± 13.3 | NS |
| RPF (ml · min$^{-1}$) | 643 ± 131 | 525 ± 141 | <0.05 |
| RBFI (ml · min$^{-1}$ · m$^{-2}$) | 526 ± 155.9 | 436 ± 153 | <0.005 |
| SVR (IU) | 15.2 ± 4.65 | 17.9 ± 3.9 | <0.05 |
| RVRI (IU) | 65.3 ± 35.8 | 73.3 ± 34.2 | NS |
| RBF/CI (%) | 25.7 ± 10.9 | 26.4 ± 7.5 | NS |
| TBV (ml) | 4638 ± 914 | 4697 ± 982 | NS |

Values are mean ± SD. NS = not significant.

SAP = systemic arterial pressure; RAP = right atrial pressure; PAP = pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; CI = cardiac index; HR = heart rate; SI = stroke index; PIVC = inferior vena cava pressure; DP = driving pressure; RPF = renal plasma flow; RBFI = renal blood flow index; SVR = systemic vascular resistance; RVRI = renal vascular resistance index; TBV = total blood volume.

TBV was maintained stable by replacing urinary loss with isotonic saline serum infusion (0.9% sodium chloride). Because urinary loss was not large, the 0.9% sodium chloride solution required to maintain TBV did not modify the serum electrolytes as assessed by the second TBV and serum electrolytes determination. Total duration of the protocol did not exceed 4 h, and we assumed that no significant changes occurred in the clinical condition of the patients during this time.

### Statistical Analysis

Statistical analysis was performed using a paired Wilcoxon test. All data are expressed as the mean ± SD. Differences with $P < 0.05$ are considered statistically significant. Correlations were calculated using the least-squares method.

## Results

### Hemodynamic and Blood Gas Data (tables 2 and 3)

Cardiac index (CI) decreased significantly from 5.22 ± 1.48 to 3.96 ± 1.12 l · min$^{-1}$ · m$^2$ ($P < 0.01$) as did SI from 47 ± 12.3 to 36.4 ± 8.9 ml · beat$^{-1}$ · m$^2$ ($P < 0.025$)

TABLE 3. Arterial Blood Gas Parameters

| | ZEEP | PEEP | *P* value |
|---|---|---|---|
| $Pa_{O_2}$ (mmHg) | 103 ± 34 | 119 ± 45 | <0.03 |
| $P\bar{v}_{O_2}$ (mmHg) | 39 ± 6 | 37 ± 6 | NS |
| $Pa_{CO_2}$ (mmHg) | 32 ± 8 | 32 ± 8 | NS |
| *p*H | 7.48 ± 0.07 | 7.47 ± 0.05 | NS |
| $Sa_{O_2}$ (%) | 96.2 ± 2.9 | 97.2 ± 2.2 | NS |
| Hematocrit (%) | 27.6 ± 6.3 | 28 ± 5.2 | NS |

Values are mean ± SD. NS = not significant.

after application of PEEP. SAP did not change significantly from ZEEP to PEEP, whereas SVR increased from 15.2 ± 4.65 to 17.9 ± 3.9 IU ($P < 0.05$). PEEP was accompanied by an increase in cardiac filling pressures: intraluminal RAP from 7.7 ± 1.7 (ZEEP) to 12.5 ± 4.2 mmHg (PEEP) ($P < 0.01$), and PAWP from 9 ± 1.8 to 17.6 ± 4.3 ($P < 0.001$) and an increase in mean PAP from 20.1 ± 4.9 to 27.7 ± 7.1 ($P < 0.01$). $Pa_{O_2}$ increased slightly but significantly ($P < 0.03$). Blood *p*H and $Pa_{CO_2}$ were unaffected by PEEP (table 3).

## RENAL HEMODYNAMIC AND FUNCTION (TABLES 2 AND 4)

Plasma osmolality, serum electrolytes values, and TBV were not changed by institution of PEEP, whereas there was a 55% reduction in $\dot{V}_u$ from 3.1 ± 0.9 to 1.44 ± 0.7 ml · min$^{-1}$ ($P < 0.05$). RPF was diminished significantly: 643 ± 131 *versus* 525 ± 141 ml · min$^{-1}$ ($P < 0.05$). PIVC

TABLE 4. Effect of ZEEP and PEEP on Renal Function

| Variable | ZEEP | PEEP | *P* value |
|---|---|---|---|
| Plasma | | | |
| Sodium (mmol/l) | 132 ± 6 | 131 ± 6 | NS |
| Potassium (mmol/l) | 3.9 ± 0.3 | 3.9 ± 0.4 | NS |
| Osmolality (mosm/kg) | 280.7 ± 13.1 | 280.4 ± 13.2 | NS |
| Urinary | | | |
| Urinary output (ml/min) | 3.1 ± 0.9 | 1.44 ± 0.7 | <0.05 |
| Sodium excretion (mmol · min · $10^{-3}$) | 195.4 ± 186 | 111 ± 97.2 | <0.01 |
| Potassium excretion (mmol · min · $10^{-3}$) | 119 ± 31 | 73.2 ± 29 | <0.02 |
| Osmolality (mosm/kg) | 454.4 ± 220.5 | 520.1 ± 191.3 | NS |
| GFR (ml/min) | 139.5 ± 41.9 | 119.8 ± 34.7 | NS |
| $\dot{C}_{osm}$ (ml/min) | 3.9 ± 0.9 | 2.5 ± 1 | <0.025 |
| $\dot{C}_{H_2O}$ (ml/min) | −0.93 ± 1.32 | −0.80 ± 0.52 | NS |
| FF (%) | 23.1 ± 7.8 | 22.3 ± 6.2 | NS |
| $FE_{Na^+}$ (%) | 1.19 ± 1.3 | 0.72 ± 0.73 | <0.05 |
| $FE_{K^+}$ (%) | 0.21 ± 0.06 | 0.15 ± 0.03 | <0.025 |

Values are mean ± SD. NS = not significant.
GFR = glomerular filtration rate; $\dot{C}_{osm}$ = osmolal clearance; $\dot{C}_{H_2O}$ = free water clearance; FF = filtration fraction; $FE_{Na^+}$ = fractional excretion of $Na^+$; $FE_{K^+}$ = fractional excretion of $K^+$.

TABLE 5. Plasma Hormonal Values from Seven Patients during CMV with ZEEP and PEEP

| Variable | ZEEP | PEEP | *P* value |
|---|---|---|---|
| ADH (pg/ml) | 3.11 ± 1.47 | 3.38 ± 1.69 | NS |
| PRA (ng · ml · h$^{-1}$) | 9.1 ± 7.5 | 16.1 ± 12.6 | <0.025 |
| NE (pg/ml) | 509 ± 301 | 594 ± 298 | <0.05 |
| E (pg/ml) | 62.5 ± 27.5 | 90.2 ± 74.3 | NS |

Values are mean ± SD. NS = not significant.
CMV = continuous mandatory ventilation; ADH = antidiuretic hormone; PRA = plasma renin activity; NE = norepinephrine; E = epinephrine.

increased significantly following PEEP application ($P < 0.001$) and calculated driving pressure (DP = SAP − PIVC) was unchanged.

$\dot{C}_{H_2O}$ did not change significantly from ZEEP to PEEP and remained constantly negative during CMV. $\dot{C}_{osm}$ was 3.9 ± 0.9 ml · min$^{-1}$ with ZEEP and fell significantly to 2.5 ± 1 ml · min$^{-1}$ with PEEP ($P < 0.025$). When PEEP was applied, $FE_{Na^+}$ diminished 39% ($P < 0.05$) and $FE_{K^+}$ 29% ($P < 0.025$).

## HORMONAL STUDY (TABLES 5 AND 6)

Plasma osmolality was in the low normal range, but did not vary during CMV with ZEEP or PEEP. Plasma ADH concentrations also remained in the normal range (2–6 pg/ml) throughout the study. Plasma NE level rose significantly following the application of PEEP from 509 ± 301 pg/ml to 594 ± 298 pg/ml ($P < 0.05$). In contrast, plasma E was unchanged during both ZEEP and PEEP ventilation. PRA increased significantly during PEEP (16.1 ± 12.6 ng · ml$^{-1}$ · h$^{-1}$) when compared with control ZEEP levels (9.1 ± 7.5 ng · ml$^{-1}$ · h$^{-1}$).

Figure 1 shows the positive linear correlation between PRA and plasma NE variations: r = 0.80, $P < 0.025$.

## Discussion

The present study was conducted in patients free of apparent cardiovascular, lung, or renal disease, and in the absence of any drug likely to modify the hormonal systems under investigation. Continuous sedation and paralysis prevented intraindividual variations in chest wall or lung distensibility. Intravascular volume was normal and kept constant as was plasma osmolality. Therefore, a steady state was present for all patients during CMV with both ZEEP and PEEP. Patients were ventilated for neurologic reasons, and coma itself might have changed the activity and/or reactivity of the neuroendocrine system. Except for PRA, mean NE and E were in the normal range with a relatively large scattering of individual values. However, despite the large standard deviation, the increase in NE was significant using the nonparametric Wilcoxon test because for each patient, NE concentrations

TABLE 6. Absolute Values of Individual Hormonal Changes Induced by PEEP Referred to ZEEP Condition (−)*

| Patient No. | PRA ($ng \cdot ml^{-1} \cdot hr^{-1}$) | NE (pg/ml) | E (pg/ml) | ADH (pg/ml) |
|---|---|---|---|---|
| 1 | 15 | 14 | −69 | 0.9 |
| 2 | 0.6 | 8 | 15 | −1.25 |
| 3 | 11.2 | 162 | 13 | −1.35 |
| 4 | 9.6 | 67 | −3 | −0.1 |
| 5 | 0.4 | 51 | 73 | 0.75 |
| 6 | 1.25 | 71 | 178 | 1.25 |
| 7 | 11.5 | 117 | −13 | 1.7 |
| Mean ± SD | 7.08 ± 6.14 | 70 ± 54.8 | 27.7 ± 78.4 | 0.27 ± 1.2 |
| *P* value | <0.025 | <0.05 | NS | NS |

NS = not significant.
* Implies that PEEP induced a decrease. *P* value tests the null hypothesis for average value of changes.

increased when PEEP was applied. Thus, we assumed that the observed modifications were induced by the application of PEEP during CMV.

As expected, $Pa_{O_2}$ increased slightly during PEEP, whereas *p*H and $Pa_{CO_2}$ remained unchanged. Moreover, the hemodynamic changes following PEEP were also as expected: CI and SVI decreased without any change in heart rate.[3,16] These hemodynamic consequences of PEEP may induce reflex activation mediated by low- and high-pressure baroreceptor deactivation.[1,5,17-19] Although renal extraction coefficient of $^{131}I$ PAH is not 100% and may change during the renal vasoconstriction induced by PEEP, we consider the RPF results valid. In this study, as in previous studies during PEEP,[1] RPF decreased in parallel with the reduction in CI (table 2).

GFR remained in the normal range throughout the experiment, and FF was not significantly modified. Although increased PIVC might be deleterious for renal hemodynamics, it did not significantly change renal DP. The minor physiologic importance of increased PIVC on observed antidiuresis was previously demonstrated by Priebe *et al.*[20] Therefore, modifications of systemic and renal hemodynamics alone were not sufficient to explain the antidiuresis and impaired renal function during PEEP.

A significant decrease in $\dot{V}u$ with PEEP was associated with decreased $FE_{Na^+}$ and $C_{osm}$. These results suggested enhanced renal sodium-sparing effect during PEEP, as previously demonstrated by other studies.[5,19,21,22] Similar to other reports[9,19] we found negative $\dot{C}_{H_2O}$ during ZEEP ventilation, but it was not further decreased with PEEP, although we observed enhanced antidiuresis. Moreover, there was no significant variation in plasma ADH levels, which remained in the normal range throughout the study. To our knowledge, this finding has not been previously reported during PEEP-induced acute antidiuresis in humans at constant TBV and blood osmolality. Elevation of plasma ADH was previously reported during positive-pressure ventilation in animals.[8,23,24] Some data in humans have also demonstrated elevated plasma ADH levels during CMV with ZEEP[25,26] or the occurrence of urinary ADH excretion during positive-pressure breathing.[27] However, most of these studies failed to demonstrate parallel changes in free water clearance and ADH. Such results have been questioned because urinary rather than plasma ADH concentrations were measured.[16,27]

Lack of ADH reactivity in healthy subjects has recently been shown by Goldsmith *et al.*[28,29] Using lower body negative pressure (LBNP),[28] central venous pressure (CVP) was decreased without changing SAP or HR. This maneuver induced a large sympathetic stimulation (NE increase) without any change in plasma ADH levels, despite unloading of cardiopulmonary receptors. At a more intense LBNP, they showed that a further decrease in CVP was closely associated with further increase in sym-

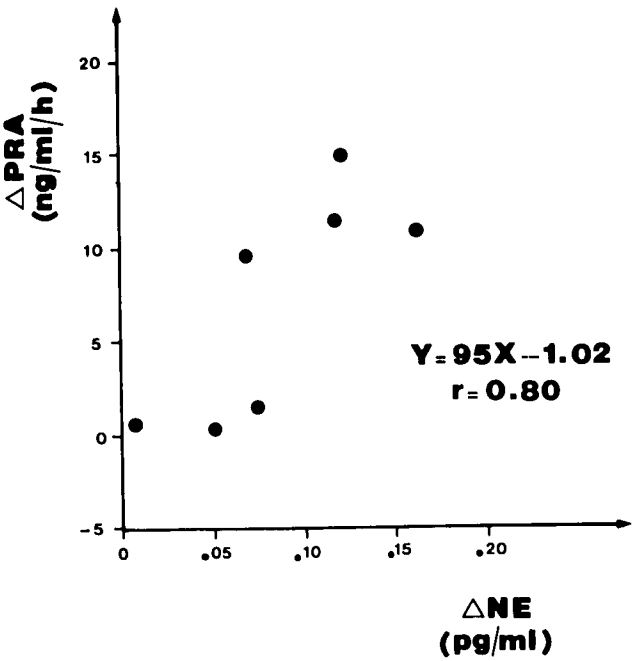


FIG. 1. Relationship between plasma norepinephrine (Δ NE) increase and plasma renin activity variations (Δ PRA) between zero PEEP (ZEEP) and 15 $cmH_2O$ PEEP (PEEP).

pathetic nervous system activity; ADH again did not increase. In a more recent study, the same authors performed the counterexperiment.[29] Cardiopulmonary receptors and high-pressure baroreceptors loading by saline infusion and lower body positive pressure (LBPP) failed to alter ADH levels. Similar results were found with a more prolonged stimulation using 1-h head-down tilt. They concluded that in humans, ADH is poorly responsive to moderate changes in tone of low- and high-pressure baroreflexes under unstressed, isoosmotic conditions.

Neurohormonal responses to decreased intrathoracic blood volume, SAP, and/or CO were commonly thought to be a consequence of[4]: 1) increased sympathetic tone and catecholamine release; 2) activation of the renin angiotensin system[30]; and 3) release of vasopressin. Our study confirmed these physiologic changes, except for vasopressin.

Preexisting sympathetic activation was absent in these patients as shown by low-average baseline catecholamine values.[31] When PEEP was applied, both PRA and NE increased in comparison with controls, whereas E did not change significantly (tables 5 and 6). Hall *et al.* previously demonstrated that positive-pressure ventilation increased sympathetic activity or plasma catecholamines in dogs.[19,32] Sympathetic activation was generally attributed to reflex mechanisms originating from high-pressure baroreflex[5] or atrial stretch receptors.[1,4,33] In addition, we recently demonstrated in patients with acute respiratory distress syndrome that when cardiopulmonary blood volume and systemic hemodynamics were corrected by application of LBPP, NE and PRA returned to ZEEP values.[34]

Despite the relative scattering of PRA values (from 1 to 18 $ng \cdot ml^{-1} \cdot h^{-1}$), all patients had an increase in PRA, suggesting a normal response of this system to stimulation. Recently, London *et al.*[35] demonstrated a significant negative correlation between cardiopulmonary blood volume and PRA variations and suggested that this reflex-mediated inverse relationship was due to the sympathetic system. Although our data do not prove a cause–effect relationship, they do suggest that sympathetic stimulation was involved in the response of PRA to PEEP (fig. 1). This finding, to our knowledge, had not been previously reported. This hypothesis is consistent with the finding in dogs that prior administration of propranolol or baroreflex denervation[23,36] prevents stimulation of PRA during PEEP ventilation. Such results would suggest an underlying adrenergic mechanism involved in PEEP activation of the renin angiotensin system, and will require further experimental and clinical studies.

Although aldosterone $Na^+$ retaining effect might become effective during long-term application of PEEP,[37] in the present experiment, plasma aldosterone was not measured because this hormone must first induce new protein synthesis to be effective.[38] Moreover, a significant fall in $FE_{K^+}$ reinforces the absence of a major aldosterone effect in this short-term study.

In conclusion, the present study demonstrated that: 1) ADH secretion was not stimulated and did not mediate the short-term antidiuretic effect of PEEP in normovolemic patients; and 2) decrease in CI and RBF induced consequent reflex sympathetic stimulation with activation of the renin angiotensin system, which appeared to be the main factors causing PEEP-induced antidiuresis and $Na^+$ retention in humans.

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