Interactions Between Hemodynamic and Hormonal Modifications During Peep-Induced Antidiuresis and Antinatriuresis*

Dominique Farge, MD, MSc; Jean E. De La Coussaye, MD; Sadek Beloucif, MD; Marie D. Fratacci, MD; and Didier M. Payen, MD, PhD

The interactions between hemodynamic and hormonal modifications during antidiuresis and antinatriuresis induced by positive end-expiratory pressure (PEEP) were studied in six patients under 15 cm H2O PEEP before PEEP and after the addition of lower body positive pressure (LBPP) to PEEP (PEEP+LBPP). We measured or calculated the following: cardiac index, systemic arterial, right atrial, pulmonary arterial, and pulmonary artery occlusive pressures; indexed renal blood flow (iodohippurate 131 sodium clearance); total blood volume (chromium 51 radiolabeled RBCs); glomerular filtration rate; urinary output; fractional excretion of sodium (FE Na+); plasma concentrations of antidiuretic hormone (ADH), plasma renin activity (PRA), norepinephrine and epinephrine; urinary concentration of PGE2 (PGE2u). Although LBPP application corrected PEEP deleterious effects on systemic and renal hemodynamics, sustained fall in Vu and in FE Na+ were observed. Antidiuresis was not due to ADH release. Sympathetic activation and high PRA appeared the main determinants of renal function alterations in PEEP ventilation.

(Ches 1995; 107:1095-1100)

\[ \text{ADH=antidiuretic hormone; CI=cardiac index; CO=cardiac output; FE Na}^+ = \text{fractional excretion of sodium; GFR=glomerular filtration rate; HR=heart rate; } \text{BNP} = \text{brain natriuretic peptide; PV=positive } \text{volume in } \text{lung; PRA=plasma renin activity; PAP=pulmonary artery pressure; SBP=systolic blood pressure; SBP= systemic blood pressure; SI=stroke index; SVRI=systemic vascular resistance index} \]

**Key words:** antidiuresis; antinatriuresis; lower body positive pressure; positive pressure breathing; renal function

Positive pressure breathing, especially during positive end-expiratory pressure (PEEP), induces rapid and intense antidiuresis with fall in fractional excretion of sodium (FE Na+).\(^1,2\) whereas negative pressure breathing is associated with increased urinary flow.\(^3\) Although PEEP is commonly used for symptomatic treatment of patients with acute respiratory failure, the respective roles of direct and indirect factors involved in renal function modifications are still debated.\(^4\) PEEP decreases cardiac output (CO),\(^5\) blood pressure,\(^1\) and renal plasma flow (RPF).\(^6,7\) It also leads to indirect cardiovascular reflex activation or deactivation of high\(^8\) and low\(^9\) pressure baroreflexes and to vasoactive hormonal release of antidiuretic hormone (ADH),\(^10\) renin,\(^6\) and norepinephrine.\(^11\)

In spontaneously breathing healthy volunteers, it has been shown that water immersion,\(^12\) fluid loading,\(^7\) head down passive tilt,\(^13\) as well as lower body positive pressure (LBPP)\(^14\) induce water and sodium diuresis. We also have shown that LBPP with mild inflation of military anti-shock trousers corrected PEEP deleterious systemic hemodynamic effects, via an increase in venous return, in patients suffering from acute respiratory failure.\(^15\) We, therefore, used the same nonpharmacologic and isovolumic maneuver to evaluate the effects of LBPP on renal hemodynamics and function during PEEP and to analyze subsequent modifications of plasma ADH, renin activity, norepinephrine, and epinephrine levels.

**Materials and Methods**

**General Data**

Patients were studied after written informed consent had been obtained from their closest relative. Protocol was approved by the University Research Ethical Committee. All patients were mechanically ventilated via an endotracheal tube by a volume-cycled ventilator (CPU1, Ohmeda; Maurepas, France), with a tidal volume of 10 to 12 mL·kg\(^{-1}\) body weight at a respiratory rate of 16 to 18 breaths·min\(^{-1}\).

**Patients:** Because 5 h of hemodynamic steady state was needed...
to collect the data, we selected patients mechanically ventilated for neurological reasons 23 ± 6 days after the acute injury. The following criteria for preinclusion were used: normal lung, cardiac or renal function as assessed by routine clinical, radiologic, and biological tests with a mean serum creatinine clearance of 142 ± 45 mL/min at that time; no administration of diuretic, anti-infective, or anti-inflammatory drugs before or throughout the study; hemodynamic stability as assessed by serial hemodynamic measurements: only patients with CO variations less than 15% in the 90 min of each step of the protocol were kept in the study. Three patients with the initial criteria for preinclusion were taken out of the study because CO variations were greater than 15%.

Finally, six male patients, aged 35 ± 14.2 years old, were selected. None of them had cerebral edema or intracranial hematomata evidenced on a CT scan performed the day before the study. No patient had undergone any previous surgery, nor suffered from any fluid or electrolyte abnormality, including inappropriate ADH secretion. Fio2 (0.33 ± 0.05) was adapted to maintain PaO2 higher than 90 mm Hg throughout the procedure. To limit metabolic variations and hemodynamic instability during data collection, all patients were sedated by continuous intravenous infusion of flunitrazepam and were paralyzed with pancuronium bromide.

**Hemodynamic Study:** Systemic arterial pressure (SAP) was monitored via a radial artery catheter. Intraluminal right atrial (RAP), pulmonary artery (PAP), and pulmonary artery occlusive (PAOP) pressures were measured via a triple-lumen balloon-tipped Swan-Ganz catheter inserted into the pulmonary artery via the right internal jugular vein. Position of the catheter tip was verified by a chest x-ray film, which also confirmed the absence of radiologic abnormalities. All pressures were measured and averaged over one respiratory cycle with the patient breathing spontaneously, in order to maintain the tidal volume of the hypoventilated patient at the midaxillary level, connected to a Thomson Telco amplifier and to a multichannel recorder (Gould ES 1000). Heart rate (HR) was recorded from a standard ECG lead. The 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·min⁻¹·m⁻²)] was calculated.

For both ethical and practical reasons, direct true measurement of renal perfusion pressure (RPP) could not be performed and RPP was calculated as: RPP=SAP−RAP. Systemic vascular resistance index (SVRI) was calculated with the following equation: SVRI=(SAP−RAP)/CI in international unit. Stroke index (SI) also was determined: SI=CI/HR in mL·beat⁻¹·m⁻². Values were obtained from pressures and CO measurements. Arterial blood gas measurements were performed with an ABL 30 apparatus (Radiometer; Copenhagen, Denmark), and SaO₂ was measured.

**Renal Hemodynamics:** Renal plasma flow measurement was carried out by intravenous bolus injection of iodohippurate I31 sodium (131IPAH) as described by Burbank et al.18 and Tauxe.17 Sterile serum chloride 131IPAH (Biomedica Italia) was injected at time zero t₀. Plasma concentration was expressed as counts per second per millilitre (Cl) when measured with a gamma counter (Kontron, France) and plotted vs time on semilog paper. An aliquot of the injected dose also was measured, and the amount of injected counts per second was determined and designated q₀. Radioactivity disappearance proved to be a biexponential function of time, and the second segment of the curve was used to calculate RPF as follows: RPF=K·VD, where K is the rate constant equal to 0.693/T¹/₂ and VD is the distribution volume. Retrospective extrapolation of the second segment of the curve was used to determine concentration at time zero (t₀, Bq/ml). The injected dose, q₀, was then divided by this latter value to determine the distribution volume VD=q₀/C₀. The first intravenous bolus injection of 131IPAH contained 50 μCi in 10 mL, and the second contained 150 μCi in 15 mL. Thus, total body irradiation was 5.4 x 10⁻² mGy and kidney irradiation was 1.8 mGy.

Using each patient’s hematocrit value, we calculated renal blood flow (RBF) according to the formula: RBF (mL·min⁻¹)= RPF×(1−hematocrit). Total blood volume was measured using RBC tagged with a chromium radioisotope (51Cr) at the beginning of the protocol and at the end of PEEP+LBPP measurements. Before this study, reproducibility of the RBF measurement technique had been assessed by three successive measurements performed in two healthy volunteers kept under stable hemodynamic conditions. Intraindividual variations were less than 8%.

**Renal Function Study:** Urine was collected through an intravesical catheter, and urinary output was expressed in mL·min⁻¹. Blood and urine samples were drawn to determine the concentrations of urea, creatinine, and electrolytes using standard laboratory techniques. Osmolality was measured with a Fick osmometer. Creatinine clearance, free water clearance, and osmolar clearance were calculated and expressed in mL·min⁻¹. Glomerular filtration rate (GFR) was evaluated as the creatinine clearance filtration fraction was expressed in a percentage using the ratio GFR to RPF. The FE Na⁺ was calculated and expressed in a percentage.

**Hormonal Study:** Plasma ADH levels were determined by radioimmunoassay on venous blood samples drawn into chilled syringes containing dipotassium ethylene diaminetetraacetic acid. Blood samples were centrifuged at 3,000 revolutions per minute (rpm) for 15 min at 4°C, and plasma was stored at −20°C and extracted within 2 weeks with aceton. Plasma ADH was measured by radioimmunoassay.18 The mean plasma ADH value observed in normal subjects under conditions of moderate antidiuresis was 5.6 ± 0.16 (SEM) pico gram (pg)/mL. Intraassay and interassay variations were 12.5 and 17.9%, respectively. The antibody used did not recognize oxytocin (Ocytocin) even at 1 ng/mL and cross-reacted slightly with 1-deamino-8-D-AVP (0.6%).

Plasma norepinephrine and epinephrine concentrations were measured using a double-isotope radioenzymatic assay.19 Pulmonary artery blood samples were collected in chilled tubes containing lithium heparin. After 20 min of centrifugation (4,000 rpm) at −4°C, plasma was separated and stored at −20°C until the assay was done. Sensitivity of this technique was 1.5 pg/mL for both epinephrine and norepinephrine. Variation coefficients were 3.1% (420 ± 13 pg/mL) and 3.3% (80 ± 2.6 pg/mL) for intraassay and 4.2 and 4.5 for interassay for norepinephrine and epinephrine, respectively.

Plasma renin activity (PRA) was determined on pulmonary arterial blood after centrifugation by CEA Sorin kit. The PRA measurement was based on the radioimmunoassay of angiotensin I20 and was expressed as nanogram of angiotensin I generated per milliliter of plasma per hour of incubation.

Urinary PGE₂ concentration was measured by radioimmunoassay using the extraction and assay procedures previously described elsewhere.21 Results were expressed in picogram per milliliter. Urine (5 mL) was acidified to pH 3.0 to 3.5, extracted twice with 3 volumes of a solution of cyclohexane and ethylacetate in a ratio of 1 to 1, and chromatographed on silicic acid columns. Recoveries were calculated using (3H) PGE₂ additions to the original sample. Antiserum to PGE₂ was obtained from Institut Pasteur, Paris. Standard curves were established for every assay, and all samples were assayed in triplicate. Fifty percent displacement of the radiolabeled PGE₂ from the antibody was obtained with 10 pg PGE₂. Recoveries varied from 50 to 80%. All values were corrected for the measured recoveries.

**Protocol**

Two successive sets of measurements were performed, using the same sequence for all patients at the same level of fraction of inspired oxygen per patient. Baseline values were obtained at 15
cm H₂O PEEP (PEEP), and mild LBPP was then added to PEEP (PEEP+LBPP). We used a classic anti-G suit device (Gladiator; Jobst, Ohio) inflated first around the lower limbs at 40 mm Hg, and then around the abdomen at 20 mm Hg to maintain a positive pressure gradient from the periphery to the heart. Special attention was paid to avoid any compression of the lower thorax to conserve rib cage mechanics.

An initial period of 30 min was first allowed to assess hemodynamic stability. After this initial 30-min steady-state period, a first intravenous bolus of 131IIPAH was injected to measure RPF. After the 131IIPAH injection, PEEP ventilation was maintained during 90 min, at the end of which blood samples were collected and hemodynamic parameters, mean urinary output, and 131IIPAH clearance were measured (PEEP). This sequence (30-min stabilization period followed by a 90-min acquisition period) was repeated when LBPP was added to PEEP (PEEP+LBPP).

Total blood volume was maintained at a stable level by exact compensation of urinary loss (455 ± 50 mL) with 5% dextrose in water with 92 mEq/L sodium chloride. Stability of volemic status in the procedure was assessed by measuring blood volume before and after the data collection. Total duration of the protocol did not exceed 5 h, and we assumed that no significant evolution of the patients’ clinical conditions occurred within this time.

### Statistical Analysis

All data are expressed as mean ± SD. The raw and calculated data were compared by the paired t test. Linear correlations were calculated by the least squares method. A probability value less than 0.05 was considered statistically significant.

### RESULTS

#### Systemic Hemodynamic and Gazometric Study

The HR and SAP did not vary under the two conditions of the protocol (Table 1). The LBPP application during PEEP increased CI (p<0.001) and SI (p<0.001), via an increase in RAP and PAoP, with a consequent decrease in SVRI (p<0.02). Blood pH, PaCO₂, and hematocrit values remained stable.

#### Renal Hemodynamic and Function

Total blood volume, serum electrolytes, and plasma osmolality did not change throughout the study (Table 2, Fig 1). The PEEP-induced antidiuresis and antinatriuresis were sustained in PEEP+LBPP with no change in GFR.

The LBPP application increased index RBF (IRBF [p<0.01]) with no change in RPP. Figure 1 shows the significant correlation between CI and IRBF in the two sets of measurements (r=0.85, p<0.001).

#### Hormonal Study

Plasma ADH concentrations were in the normal range according to plasma osmolality during PEEP ventilation and did not vary in PEEP+LBPP (Table 3). The PRA levels were elevated during PEEP ventilation and remained elevated after LBPP application. Plasma epinephrine values were within the normal range during PEEP and remained unchanged.

### Table 1—Effect of PEEP and PEEP+LBPP on Systemic Hemodynamics*

<table>
<thead>
<tr>
<th>Variables</th>
<th>PEEP</th>
<th>PEEP+LBPP</th>
<th>Probability Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beat·min⁻¹</td>
<td>117±18.1</td>
<td>114±15.2</td>
<td>NS</td>
</tr>
<tr>
<td>Mean SAP, mm Hg</td>
<td>83.8±15.7</td>
<td>87.6±14.1</td>
<td>NS</td>
</tr>
<tr>
<td>RAP, mm Hg</td>
<td>13.1±3.6</td>
<td>15.1±2.72</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>PAP, mm Hg</td>
<td>28.1±7.67</td>
<td>27.3±4.32</td>
<td>NS</td>
</tr>
<tr>
<td>PAoP, mm Hg</td>
<td>18.5±4.08</td>
<td>21.7±4.36</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CI, L·min⁻¹·m⁻²</td>
<td>4.2±1.10</td>
<td>5.1±1.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SI (mL·beat⁻¹·m⁻²)</td>
<td>35.6±9.70</td>
<td>44.8±10.47</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>SVRI, IU</td>
<td>17.7±4.23</td>
<td>14.8±4.16</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

*Values are mean ± SD.
†NS=not significant.

### Table 2—Effect of PEEP and PEEP+LBPP on Renal Hemodynamics and Function*

<table>
<thead>
<tr>
<th>Variables</th>
<th>PEEP</th>
<th>PEEP+LBPP</th>
<th>Probability Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total blood volume, mL</td>
<td>4,823±847</td>
<td>4,900±901</td>
<td>NS</td>
</tr>
<tr>
<td>RPP, mm Hg</td>
<td>71±13.3</td>
<td>73±12.5</td>
<td>NS</td>
</tr>
<tr>
<td>IRBF, mL·min⁻¹·m⁻²</td>
<td>433±151</td>
<td>540±177</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Plasma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na⁺, mmol/L</td>
<td>131±6</td>
<td>130±4</td>
<td>NS</td>
</tr>
<tr>
<td>K⁺, mmol/L</td>
<td>4.0±0.3</td>
<td>3.8±0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Osmolality, mOsm·kg⁻¹</td>
<td>283±11.4</td>
<td>281±13.8</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary output, mL·min⁻¹</td>
<td>1.47±0.62</td>
<td>1.05±0.34</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Na⁺ excretion mmol·min⁻¹·10⁻³</td>
<td>129±91</td>
<td>81±48</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>K⁺ excretion mmol·min⁻¹·10⁻³</td>
<td>86±28</td>
<td>95±44</td>
<td>NS</td>
</tr>
<tr>
<td>Osmolality, mOsm·kg⁻¹</td>
<td>529±208</td>
<td>611±169</td>
<td>NS</td>
</tr>
<tr>
<td>GFR, mL·min⁻¹</td>
<td>129±25</td>
<td>137±51.5</td>
<td>NS</td>
</tr>
<tr>
<td>Osmolar clearance, mL·min⁻¹</td>
<td>2.76±0.82</td>
<td>2.61±1.23</td>
<td>NS</td>
</tr>
<tr>
<td>Free H₂ clearance, mL·min⁻¹</td>
<td>-1.19±0.88</td>
<td>-1.41±1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Filtration fraction, %</td>
<td>23±6.6</td>
<td>19±6.5</td>
<td>NS</td>
</tr>
<tr>
<td>FE Na⁺, %</td>
<td>0.85±0.72</td>
<td>0.59±0.53</td>
<td>&lt;0.03</td>
</tr>
</tbody>
</table>

*Values are mean ± SD.
†NS=not significant.
during PEEP+LBPP. Plasma norepinephrine levels were elevated during PEEP as opposed to normal plasma epinephrine values and did not decrease during PEEP+LBPP. Urinary concentration of PGE₂ was elevated during PEEP and increased after LBPP application (p<0.05).

**DISCUSSION**

**Study Data**

Alternations in renal function and in fluid balance during mechanical ventilation may constitute an adverse prognostic factor. Whatever the underlying disease or the ventilatory mode, increased intrathoracic pressure always induces antidiuresis and antinatriuresis. Several mechanisms have been proposed to explain the relationship between the increase in intrathoracic pressure and renal function alterations, including systemic or renal hemodynamic alterations or both, reflex activation of the sympathetic outflow, increase in ADH secretion or in plasma renin activity. However, the respective roles of systemic and renal hemodynamic modifications and their relationships with the release of vasoactive hormones as well as the exact stimulus of sympathetic outflow activation remain to be elucidated.

In the present study, we hypothesized that application of LBPP during PEEP should improve systemic and renal hemodynamics and might in turn correct the antidiuresis and antinatriuresis observed during PEEP ventilation. Lower body positive pressure during PEEP effectively corrected hemodynamic alterations and allowed us to study the direct relationship between systemic and renal hemodynamics and function under controlled conditions: (1) at constant total blood volume, (2) in the absence of pharmacologic interaction, (3) with little impact on high and low pressure baroreflexes; systemic arterial blood pressure did not vary, and we assumed that the usual decrease in cardiopulmonary blood volume during PEEP was corrected by LBPP. Antidiuresis and antinatriuresis, however, were sustained after LBPP application, and thus hemodynamic factors per se did not explain the observed modifications of renal function. Sustained elevation in PRA rather appeared to be the main determinant of water and sodium retention during PEEP ventilation. We considered that data collection was valid since ADH was in the low-normal range according to plasma osmolality and the steady state was effective during the procedure with maintenance of normal total blood volume and plasma osmolality.

**Systemic and Renal Hemodynamics**

Few human studies have reported simultaneous measurements of systemic and renal hemodynamic parameters with control of total blood volume. Annat et al observed a parallel decrease in renal plasma flow, GFR, and CO and suggested that renal hemodynamic alteration induced by PEEP was a consequence of a decrease in CO. This hypothesis had been previously tested using plasma volume expansion to increase CO during PEEP, but conflicting results concerning an improvement in urine flow have been published. It has been shown that dopamine improved urinary output, an effect that could result from renal vasodilation, from CO increase, or from both. But none of these studies showed a direct relationship between PEEP systemic hemodynamic alterations and renal hemodynamics and function.

The application of LBPP induced a significant in-

---

**Table 3—Hormonal Values During PEEP and PEEP+LBPP**

<table>
<thead>
<tr>
<th>Variables</th>
<th>PEEP</th>
<th>PEEP+LBPP</th>
<th>Probability Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH, pg·mL⁻¹</td>
<td>2.96±1.39</td>
<td>3.5±1.14</td>
<td>NS</td>
</tr>
<tr>
<td>PRA (ng·mL⁻¹·h⁻¹)</td>
<td>16.4±10.1</td>
<td>14.2±8.9</td>
<td>NS</td>
</tr>
<tr>
<td>Epinephrine, pg·mL⁻¹</td>
<td>68±40</td>
<td>88±41</td>
<td>NS</td>
</tr>
<tr>
<td>Norepinephrine, pg·mL⁻¹ (n=5)</td>
<td>526±134</td>
<td>480±124</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Urinary PGE₂, pg·mL⁻¹</td>
<td>481±227</td>
<td>618±261</td>
<td>&lt;0.03</td>
</tr>
</tbody>
</table>

*Values are mean ± SD.
†NS = not significant.

---

**1098 Hemodynamic and Hormonal Modifications During PEEP-Induced Antidiuresis and Antinatriuresis (Farge et al)**
crease in CI and IRBF when compared with PEEP values. Systemic and renal blood flow variations during PEEP and PEEP+LBPP were parallel as shown by the linear correlation between IRBF and CI (Fig 1). According to the methodology used for RPF determination, this increase in RBF can be considered as valid since p-aminohippuric acid extraction coefficient is not modified in patients without renal failure. Despite improved systemic and renal hemodynamics by LBPP during PEEP, antidiuresis and antinatriuresis persisted. These results are in contrast with those of Priebel and al who used blood transfusions to correct RBF in dogs. Although total blood volume was not measured in their study, the magnitude of CI decrease (44.8%) during 10 cm H2O PEEP suggested a relative hypovolemic status, whereas in our study, baseline filling pressures and total blood volume were within the normal range. The anesthetics used in the study of Priebel et al could also have altered physiologic responses and baseline cardiovascular parameters, as suggested by the elevation of control heart rate (157 BPM). Our patients’ baseline hemodynamic conditions were close to normal, and anesthesia induced sedation without hypotension, vasoplegia, or both. Within the limits of our study, we concluded that renal and systemic hemodynamic modifications per se did not explain impaired renal function in PEEP.

Hemodynamic variations may have altered renal function by indirect mechanisms, such as reflex activation, hormonal effects, or both. Renal sympathetic innervation has been considered as one of the main determinants of renal sodium handling since antinatriuresis has been observed during renal nerve stimulation, whereas acute renal denervation increases natriuresis. Renal sympathetic outflow was shown to follow the efferent pathway of numerous reflexes, and some of these are initiated by an increase in intrathoracic pressure: (1) changes in the activity of carotid sinus and aortic arch baroreceptors; (2) a decrease in low pressure baroreflex discharge via receptors located in the right and left atrium; and (3) activation of low threshold pulmonary stretch receptors mediated by the vagal afferent response. The role of a renal sympathetic outflow mediation for PEEP-induced RBF decrease and for decreases in natriuresis and diuresis was initially showed by Fewell and Bond. They showed that PEEP decreased CO and pulse pressure in dogs. Decreased firing of carotid sinus baroreceptors with consequent increase in renal sympathetic activity was associated with a decrease in urine flow, effective RPF, FE Na+, GFR, and osmolar clearance. Moreover, they showed mediation via the renal nerves since renal function was not altered during PEEP in the denervated kidney, whereas the normally innervated contralateral kidney exhibited the usual antidiuresis and antinatriuresis.

Whatever the afferent stimulus, increased sympathetic outflow was observed during PEEP as shown by high values of PRA and norepinephrine. This confirms previous results obtained in patients with ARDS. Positive end-expiratory pressure ventilation can decrease central cardiopulmonary blood volume and activate low pressure stretch receptors, which are another afferent pathway of the sympathetic outflow. Receptor denervation by cervical vagotomy in dogs, however, did not change renal function alterations during PEEP, showing the minor role of this mechanism. In addition, LBPP has been shown to increase cardiopulmonary blood volume in patients, and in our study it did not enhance renal sodium and water excretion during PEEP ventilation. Within the limits of our study, we concluded that both high and low pressure baroreflexes were not sufficient per se to explain the observed modifications of renal function. Further studies will be necessary to investigate the role of lung inflation vasodepressor reflex because of activation of low-threshold pulmonary stretch receptors by increased functional residual capacity during PEEP.

Hormonal Study

Elevation in plasma ADH has been reported during positive pressure ventilation. However, most studies failed to show parallel changes in free water clearance and ADH. In the present study, there was no significant variation in ADH plasma levels, which remained in the normal range throughout the study. We, therefore, confirm that ADH did not play any role in renal function alteration induced by PEEP.

PRA modifications have been shown to depend on two intrarenal mechanisms: (1) renal vascular baroreceptor and distal sodium delivery mediated by macula densa receptor and (2) extrarenal beta-mediated sympathetic stimulation. In our study, basal sympathetic tone was normal in these unstressed patients, as shown by normal plasma epinephrine values, which did not vary during LBPP. We had shown in patients ventilated with 0 and 15 cm H2O PEEP a sympathetic mediation for renin release during PEEP ventilation. In the present study, partial sympathetic deactivation during PEEP+LBPP allowed a decrease in norepinephrine levels. High PRA during PEEP, however, was only slightly reduced by LBPP. This suggested the presence of several stimuli for PRA elevation, which appeared the main determinant of the sustained antidiuresis and antinatriuresis.

Whatever its primary determinant, increased urinary PGE2 concentration during LBPP could be interpreted as enhancement of renal prostaglandin synthesis, while urinary output decreased. Similar
results have been observed during renal hypoperfusion and ischemia. The present data did not allow us to determine the impact of such prostaglandin release on renal hemodynamics and function nor its role on renin release, although PGE2 could have modulated the angiotensin-induced vasoconstriction. However, the increase in urinary PGE2 release observed with LBPP failed to counterbalance antidiuresis and antinatriuresis.

In summary, this study showed that antidiuresis and antinatriuresis during PEEP were not entirely dependent on systemic and renal hemodynamic modifications. Moreover, deactivation of high and low pressure baroreflexes in this model did not relieve alterations in renal function. Whatever the stimuli, sustained high PRA and sympathetic outflow were the main factors contributing to failure of LBPP to correct water and sodium retention during PEEP ventilation. Further studies will be needed to elucidate the potential therapeutic benefit of converting enzyme inhibitors in this setting and to find out if the observed release of water and sodium retaining vasoactive hormones is appropriately counterbalanced by plasma atrial natriuretic factor secretion.

REFERENCES

8. Fewell JE, Bond GC. Role of sinoaortic baroreceptors in initiating the renal response to continuous positive-pressure ventilation in the dog. Anesthesiology 1981; 52:408-13