Disturbances in hormonal systems involved in sodium and water homeostasis are common during respiratory insufficiency. To investigate the role of hypercapnia, we designed a study to examine the hormonal response to acute hypercapnia induced at constant cardiac filling pressures and without hypoxemia. Seven sedated patients with COPD receiving mechanical ventilation were studied during five successive periods. Hemodynamics, arterial blood gases, and plasma hormone levels (atrial natriuretic peptide, renin, angiotensin II, aldosterone, vasopressin) were measured three times during 60 min of acute hypercapnia (52 ± 5 mm Hg) and at control periods, before (36 ± 4 mm Hg) and after (42 ± 3 mm Hg) acute hypercapnia. During acute hypercapnia, mean pulmonary arterial pressure and cardiac output were increased without variation of other measured cardiorespiratory data and hormonal levels when compared with control values. After acute hypercapnia, cardiorespiratory variables returned to control values without variations of hormonal levels. Our results show that moderate acute hypercapnia does not significantly influence the hormonal levels when cardiac filling pressures and sympathetic tone remain stable. We suggest that changes in those plasma hormones involved in salt and water homeostasis during acute hypercapnia are secondary to hemodynamic changes induced by acute respiratory failure and not to acute hypercapnia per se.

**Key words:** acute hypercapnia; atrial natriuretic peptide; chronic obstructive pulmonary disease; renin angiotensin aldosterone system; vasopressin

Disturbances in hormonal systems involved in sodium and water homeostasis are common during acute respiratory failure in patients with chronic obstructive pulmonary disease (COPD). Various organs are involved such as the heart, the brain, the kidney, and the adrenal cortex that release atrial natriuretic peptide (ANP), vasopressin (ADH), renin, angiotensin II, and aldosterone, respectively. As ANP is usually regarded as an antagonist of the renin-angiotensin-aldosterone system (RAAS) and ADH, the neurohormonal control of sodium and water homeostasis and of vascular tone depends on the balance existing between these peptides. Various studies have shown a rise in ANP, renin, aldosterone, and ADH plasma levels during hypercapnia. Experimental data demonstrated an increase in plasma ANP and ADH concentrations and a RAAS stimulation during acute hypercapnia in dogs. Similar variations were noticed in patients with COPD with acute and chronic hypercapnia. When applying these observations to patients with COPD, however, one has to keep in mind that hypercapnia was not the sole stimulus since it was associated with other factors able to influence the hormonal system, like cardiac filling pressures and hypoxemia. Moreover, ex-
trapolating from animal to human studies may be questionable because of interspecies differences. Finally the magnitude of hypercapnia varied from one study to another.

The aim of the present study was to further examine the hormonal responses to acute hypercapnia induced by an additional dead space at constant cardiac filling pressures and without hypoxemia in anesthetized patients with COPD who were receiving mechanical ventilation (MV) because of acute respiratory failure.

METHODS

Patients

The study involved seven male patients with COPD with acute respiratory failure, 64±2 years old, and referred to the Critical Care Unit for ventilatory support. The diagnosis of COPD was established from a history of chronic bronchitis and the evidence of airflow limitations on pulmonary function tests, ie, forced expiratory volume in 1 s (FEV1) less than 40% predicted13 and a ratio of FEV1 to forced vital capacity (FEV1/FVC) less than 60%. At the time of hospital admission, all patients had infectious bronchitis or pneumonia and showed fluid retention with peripheral edema. Their clinical data at hospital admission and the results of spirometry and blood gas determinations observed before acute respiratory failure or after recovery are shown in Table 1. Patients with persistent bronchitis or pneumonia, or plasma creatinine level over 150 μmol/L at the time of the study, were excluded from the protocol.

The patients had been mechanically ventilated for 5 to 15 days (mean: 9 days) prior to the study. Cardiorespiratory variables were stable. PaO2 was over 100 mm Hg with a fractional inspired O2 (FiO2) less than 0.5 or the PaO2/FiO2 ratio was above 200. PaCO2 was 40±4 mm Hg, systolic systemic arterial pressure was above 100 mm Hg, and heart rate was less than 100 beats/min. No edema was present and no diuretic or vasoactive drugs had been administered within the 24 h prior to the study. The clinical state had required cardiovascular monitoring with radial and pulmonary artery catheterization, as well as end-tidal CO2 analysis (PetCO2) and transcutaneous oximetry. The study was performed after written informed consent had been obtained from the patients and it was approved by the institute’s ethics committee.

Protocol

The patients rested in a supine position overnight and in the morning before the study, which was performed in the afternoon. To keep a stable intrathoracic pressure regimen during the whole study, the patients were sedated (flunitrazepam, 1 mg intravenously [IV] then 1 mg/h) and paralyzed (pancuronium bromide, 4 mg IV then 1 mg/h). The FIO2 was adjusted to raise oxygen hemoglobin saturation above 95%. The breathing pattern set on the ventilator remained unchanged throughout the study. The measurements were performed in five periods. The control 1 period was achieved 30 min after sedation induction. Then three or four tubes, 60 mL of volume each, were successively added to the ventilator’s circuit, between the endotracheal tube and the ventilator Y piece, thus increasing the dead space without altering the tidal gas volume delivered to the patient. The volume of dead space was chosen to obtain an increase in PetCO2 from 6 to 10 mm Hg. The second, third, and fourth measurements (hypercapnia 1, 2, 3) were performed respectively after 20, 40, 60 min breathing with the additional dead space. The additional dead space was then removed and the fifth measurement (control 2) was performed 20 min later. All patients underwent the protocol without complication.

<table>
<thead>
<tr>
<th>Patient No./Age, yr</th>
<th>PaCO2* (mm Hg)</th>
<th>O2 Ratio*</th>
<th>pH*</th>
<th>MV, d</th>
<th>FVC,† (L)</th>
<th>FEV1,† (L)</th>
<th>PaCO2† (mm Hg)</th>
<th>PaO2† (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/60</td>
<td>71</td>
<td>177</td>
<td>7.28</td>
<td>9</td>
<td>2.4</td>
<td>0.9</td>
<td>45</td>
<td>67</td>
</tr>
<tr>
<td>2/66</td>
<td>84</td>
<td>152</td>
<td>7.19</td>
<td>15</td>
<td>1.8</td>
<td>0.7</td>
<td>50</td>
<td>56</td>
</tr>
<tr>
<td>3/53</td>
<td>66</td>
<td>148</td>
<td>7.21</td>
<td>12</td>
<td>1.3</td>
<td>0.6</td>
<td>52</td>
<td>54</td>
</tr>
<tr>
<td>4/65</td>
<td>69</td>
<td>173</td>
<td>7.34</td>
<td>5</td>
<td>1.4</td>
<td>0.7</td>
<td>47</td>
<td>50</td>
</tr>
<tr>
<td>5/72</td>
<td>80</td>
<td>171</td>
<td>7.27</td>
<td>13</td>
<td>2.9</td>
<td>1</td>
<td>47</td>
<td>54</td>
</tr>
<tr>
<td>6/69</td>
<td>75</td>
<td>160</td>
<td>7.25</td>
<td>5</td>
<td>1.2</td>
<td>0.7</td>
<td>50</td>
<td>63</td>
</tr>
<tr>
<td>7/63</td>
<td>78</td>
<td>221</td>
<td>7.30</td>
<td>7</td>
<td>1.1</td>
<td>0.4</td>
<td>50</td>
<td>38</td>
</tr>
</tbody>
</table>

*Values obtained on admission to the critical care unit. O2 ratio=PdCO2/FIO2.
†Values obtained before acute respiratory failure or after recovery. Arterial blood gases were measured in room air. Spirometry: numbers in parentheses are percent of predicted.15

Table 1—Study Population

Heart rate (HR) was measured continuously from an electrocardiogram. A radial artery catheter (Seldicath, Plastimed, Saint Lou la Forêt, France) allowed systemic arterial pressure monitoring and blood sampling for hormonal dosages and blood gases. A Swan-Ganz catheter 7F (Edwards Laboratories, Santa Ana, Calif) was inserted into the pulmonary artery via an internal jugular vein. Pressures were measured using quartz pressure transducers (Hewlett Packard, Palo Alto, Calif). The transducers were referenced to the midpoint level with patients in the supine recumbent position. Mean systemic (Psa) and pulmonary (Ppa) arterial pressures were obtained by electronic integration. Pulmonary arterial wedge (Paw) and right atrial pressures (Pres) were read at end-expiration and averaged over at least three respiratory cycles. Cardiac output (CO) was determined by the thermal dilution method with 10 mL of 5% dextrose serum cooled.

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Table 2—Mean (±SEM) Cardiopulmonary Data Obtained During Acute Hypercapnia in Seven Sedated Patients With COPD Receiving Mechanical Ventilation

<table>
<thead>
<tr>
<th></th>
<th>Control 1</th>
<th>Hypercapnia 1 20 min</th>
<th>Hypercapnia 2 40 min</th>
<th>Hypercapnia 3 60 min</th>
<th>Control 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaCO₂, mm Hg</td>
<td>36±2</td>
<td>47±3*</td>
<td>50±4*</td>
<td>52±5*</td>
<td>42±3*</td>
</tr>
<tr>
<td>pH</td>
<td>7.48±0.02</td>
<td>7.39±0.03</td>
<td>7.36±0.03</td>
<td>7.35±0.03</td>
<td>7.43±0.03</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>124±12</td>
<td>125±15</td>
<td>121±16</td>
<td>121±13</td>
<td>118±12</td>
</tr>
<tr>
<td>PAW, mm Hg</td>
<td>7.0±0.7</td>
<td>6.7±0.6</td>
<td>6.6±0.6</td>
<td>6.6±0.6</td>
<td>7.1±0.6</td>
</tr>
<tr>
<td>V̇E, L·min⁻¹</td>
<td>9.0±1.1</td>
<td>8.4±1.1</td>
<td>8.6±1.2</td>
<td>8.6±1.2</td>
<td>8.6±1.2</td>
</tr>
<tr>
<td>HR, bpm/min</td>
<td>86±6</td>
<td>87±6</td>
<td>88±6</td>
<td>90±6</td>
<td>87±6</td>
</tr>
<tr>
<td>CO₂, L·min⁻¹</td>
<td>3.8±0.4</td>
<td>4.4±0.5</td>
<td>5.1±0.7*</td>
<td>4.7±0.6*</td>
<td>3.9±0.4†</td>
</tr>
<tr>
<td>Psa, mm Hg</td>
<td>68±6</td>
<td>71±5</td>
<td>73±5</td>
<td>80±5*</td>
<td>74±5</td>
</tr>
<tr>
<td>Ppma, mm Hg</td>
<td>24±2</td>
<td>29±4*</td>
<td>30±3*</td>
<td>32±4*</td>
<td>27±3*</td>
</tr>
<tr>
<td>Ppaw, mm Hg</td>
<td>10±2</td>
<td>10±2</td>
<td>10±1</td>
<td>11±2</td>
<td>11±2</td>
</tr>
<tr>
<td>Pfa, mm Hg</td>
<td>6±2</td>
<td>7±2</td>
<td>7±2</td>
<td>7±2</td>
<td>6±2</td>
</tr>
<tr>
<td>SVR, dyn·s·cm⁻⁵</td>
<td>1,510±120</td>
<td>1,290±90</td>
<td>1,170±120*</td>
<td>1,400±150</td>
<td>1,550±110</td>
</tr>
<tr>
<td>PVR, dyn·s·cm⁻⁵</td>
<td>305±40</td>
<td>355±35</td>
<td>330±45</td>
<td>380±60</td>
<td>350±45</td>
</tr>
</tbody>
</table>

*p<0.05 with reference to control 1.
†p<0.05 with reference to values measured during hypercapnia 3.

at 2 to 4°C using a bedside computer (Edwards 9520-A); each result was taken as the mean of three determinations at least.

Derived hemodynamic variables were calculated according to standard formulas: Systemic vascular resistance (SVR)=80(Psa-Pfma)/CO₂; pulmonary vascular resistance (PVR): 80(Ppma-Ppaw)/CO₂; where pressures are expressed in mm Hg, cardiac output in L·min⁻¹ and resistances in dyn·s·cm⁻⁵.

Gas Exchange and Ventilation Measurements

The following parameters were obtained at each step of the protocol: pH, PaCO₂, and PaO₂ (ABL 30, Radiometer, Copenhagen, Denmark); minute ventilation (V̇E), mean airway pressure (Paw), and PETCO₂ measurements from the ventilator (EV-Ä, Dräger, Lübeck, Germany).

Hormone Measurements

Blood samples were drawn into heparinized tubes for renin determinations. Additional blood was drawn into chilled tubes containing 10 mg of ethylene-diamine-tetraacetic acid (EDTA) and 0.1 mg of aprotinin, and centrifuged for 15 min at 2,500 rpm for other hormonal determinations. The supernatant was stored at −80°C until assay.14

Alpha ANP, angiotensin II, and vasopressin were extracted from plasma on cartridges (SEP-PAK C18, Amersham RPN 1902; Amersham Corp, Arlington Heights, Ill). The dry extracts were stored at −20°C until radioimmunoassay was performed.

The assay of alpha ANP resides in the competition between the alpha ANP found in the sample and a radioactive tracer (3,125Iodo-tirosyl-28 alpha ANP, Amersham) in the presence of polyclonal rabbit anti-alpha ANP antibodies. Separation of bound antibody from free fraction is achieved with a second antibody preparation (Amerlex-M second antibody), thus allowing a simple magnetic separation. Assay sensitivity is 1 fmol per tube, and within-assay and between-assay variability are 7.6% and 11.6%, respectively. There is a complete cross-reaction with angiotensin II and angiotensin III and 1.5 to 2% cross-reaction with angiotensin I. This substantial cross-reactivity with angiotensin III results in a final value that is the sum of angiotensin II and III concentrations. In a control group of healthy resting subjects in our laboratory, angiotensin II plasma levels ranged from 5 to 35 pg/mL.

Vasopressin assay was carried out using a standard radioimmunologic method.15 A polyclonal antivasopressin antibody and a radioiodinated vasopressin tracer were used. Assay sensitivity is 1.0 pg per tube, and within-assay and between-assay variability are 1.4% and 12%, respectively. In a control group of healthy subjects in our laboratory, vasopressin plasma levels ranged from 2 to 6 pg/mL.

Renin assay involved a radioimmunometric technique (Renate IRMA Pasteur, ERIA Diagnostics Pasteur, Marne la Coquette, France) using a human antirenin monoclonal antibody couple. The first monoclonal antibody (Acml, clone 3 ES) is covalently bound to a solid magnetic phase (Magnogel) consisting of acrylamide and reticulated agarose beads surrounding an iron oxide particle. This antibody binds to both active and inactive renin. The second monoclonal antibody (Acml, clone 4 G1) is 125I-labeled. This antibody only specifically binds active-renin. Determination of solid magnetic phase bound activity is performed following elimination of the free fraction using an ordinary magnet. Assay sensitivity is 1.25 pg per tube, and within-assay and between-assay variability are 4.4% and 6.2%, respectively. In a control group of healthy resting subjects in our laboratory, renin plasma levels of 35±15 ng/L were determined.14

Aldosterone assay was performed using a radioimmunologic method (RIA CIS, Gif-sur-Yvette, France) based on a polyclonal antibody and a radioiodinated tracer. The technique proposed involves the separation of the free fraction from that bound to the inner surface of antibody-coated tubes. Assay sensitivity was 15 pg/mL, and within-assay and between-assay variability are 8.2% and 14%, respectively. In a control group of healthy resting subjects in our laboratory, plasma levels ranged from 15 to 150 pg/mL.14

Statistical Analysis

Results are expressed as the mean ± standard error of the mean (m ± SEM). One-way analysis of variance with repeated measures was performed to compare the changes in cardiorespiratory and
hormonal values, and this was followed by the Fisher exact test when statistical significance was detected. Linear regression analysis was used to determine if any significant correlation existed between the different parameters observed. The criterion of significance was \( p < 0.05 \).\(^{16}\)

**RESULTS**

Results are shown in Tables 2 (cardiorespiratory data) and 3 (hormonal data).

**Basal State (Control 1)**

All patients showed moderate alcalosis without hypoxemia (\( \text{PaO}_2 = 124 \pm 12 \text{ mm Hg} \) with \( \text{FiO}_2 = 0.4 \pm 0.1 \)). Pulmonary hypertension (\( \text{Ppa} > 20 \text{ mm Hg} \)) and an increase in PVR (\( > 150 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5} \)) were present in six patients. The mean levels of ANP concentrations were in normal range in six patients and increased in one patient. The mean levels of the other hormones were slightly higher than in normal subjects.

**Effects of Hypercapnia (Hypercapnia 1,2,3)**

The additional dead space produced hypercapnia with moderate respiratory acidosis. The slight but nonsignificant increase in \( \text{PaCO}_2 \) from hypercapnia 1 to hypercapnia 3 was related to sedation that kept \( \text{VE} \) constant and prevented an adaptive increase of ventilation. \( \text{PaO}_2 \) and \( \text{Paw} \) did not change. Hypercapnia increased \( \text{Ppa} \). The cardiac output increase was significant at hypercapnia 2 and that of \( \text{Psa} \) at hypercapnia 3. SVR decreased significantly only at hypercapnia 2. Other hemodynamic data and hormonal levels did not change.

**Removal of Dead Space (Control 2)**

This decreased \( \text{PaCO}_2 \). All cardiorespiratory data returned to their previous control values. The correction of hypercapnia did not induce a variation of the studied hormones. During the whole study, no significant variation of \( \text{PaO}_2, \text{VE}, \text{heart rate}, \text{cardiac filling pressures}, \text{and hormone levels} \) was observed. The control 2 values did not differ significantly from the control 1 values.

Some significant relationships were observed between variations induced by hypercapnia (from control 1 to hypercapnia 3): variations of angiotensin II plasma levels with those of renin (\( r = 0.84, p < 0.02 \)); and variations of aldosterone plasma levels with those of renin (\( r = 0.94, p < 0.01 \)). No relationship was observed between the slight variations of ANP plasma levels and the hemodynamic data during the same periods.

**DISCUSSION**

This study showed no variation of plasma hormones involved in the circulatory and body fluid homeostasis, during an isolated acute hypercapnia, in patients with COPD sedated under mechanical ventilation. It should be emphasized that hypercapnia was really the sole variable parameter in the study: \( \text{Paco}_2 \) was maintained above 100 mm Hg and cardiac filling pressures did not change during the whole study. In the absence of variation in \( \text{VE} \) and airway pressure, since these patients were sedated and paralyzed, intrathoracic pressure was stable. Under these conditions, intravascular pressure variations can be considered as transmural pressure variations.

During the control period, PVR was increased in all patients. Six of them had pulmonary hypertension. Like other authors,\(^{5,11}\) we found no correlation between ANP plasma levels and the hemodynamic variables studied. Circulating ANP was found increased in the only patient with congestive heart failure.\(^{3}\) In the other patients, normal ANP plasma levels were observed. This contrasts with increased ANP plasma levels previously reported in hypoxic, spontaneously breathing patients with COPD.\(^{2,5,10,11,17,18}\) This difference could be due to the lack of increased transmural right atrial pressure as well as to the absence of hypoxemia observed in our patients. Indeed intermittent positive pressure breathing induces an increase in intrathoracic pressure and a decrease in cardiac filling pressures,\(^{19}\) whereas the main stimulus for the ANP release is the increase in transmural right atrial pressure, \( ie \), atrial stretch, not intra-auricular pressure in itself.\(^{20,21}\) Moreover, in the present study, hypoxemia had been corrected for an average of 9 days by mechanical

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**Table 3—Mean (±SEM) Hormonal Data Obtained During Acute Hypercapnia in Seven Sedated Patients With COPD Receiving Mechanical Ventilation**

<table>
<thead>
<tr>
<th></th>
<th>Control 1</th>
<th>Hypercapnia 1</th>
<th>Hypercapnia 2</th>
<th>Hypercapnia 3</th>
<th>Control 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{PaCO}_2, \text{mm Hg} )</td>
<td>36 ± 2</td>
<td>47 ± 3*</td>
<td>50 ± 4*</td>
<td>52 ± 5*</td>
<td>42 ± 3†</td>
</tr>
<tr>
<td>ANP, fmol·mL(^{-1} )</td>
<td>20 ± 5</td>
<td>17 ± 2</td>
<td>20 ± 3</td>
<td>19 ± 3</td>
<td>17 ± 3</td>
</tr>
<tr>
<td>Renin, ng·mL(^{-1} )</td>
<td>91 ± 54</td>
<td>82 ± 27</td>
<td>77 ± 19</td>
<td>78 ± 24</td>
<td>89 ± 38</td>
</tr>
<tr>
<td>Angio II, pg·mL(^{-1} )</td>
<td>63 ± 15</td>
<td>63 ± 3</td>
<td>58 ± 9</td>
<td>60 ± 13</td>
<td>60 ± 18</td>
</tr>
<tr>
<td>Aldo, ng·mL(^{-1} )</td>
<td>22 ± 15</td>
<td>19 ± 10</td>
<td>17 ± 7</td>
<td>24 ± 11</td>
<td>21 ± 9</td>
</tr>
<tr>
<td>ADH, pg·mL(^{-1} )</td>
<td>5.6 ± 0.8</td>
<td>4.4 ± 0.8</td>
<td>4.9 ± 1.1</td>
<td>4.4 ± 1</td>
<td>5.6 ± 1.1</td>
</tr>
</tbody>
</table>

\( *p < 0.05 \) with reference to control 1.

\( †p < 0.05 \) with reference to values measured during hypercapnia.
ventilation. These results are consistent with those reported by Stockmann et al\textsuperscript{22} who showed that the rise in ANP release due to right ventricular hypertrophy induced by hypoxemia was reversible within 3 days, despite persistent right ventricular hypertrophy.

At control 1, the RAAS was slightly stimulated. The ADH levels were in the normal range. In patients with COPD, high plasma levels of ADH,\textsuperscript{9} renin, and aldosterone\textsuperscript{9} are common but inconstant\textsuperscript{11} also during acute respiratory failure.\textsuperscript{7} Moreover, positive pressure ventilation can increase plasma levels of ADH, renin, and aldosterone by hemodynamic alterations.\textsuperscript{19,23} However, in our study, the improvement of the cardiorespiratory function and body fluid volume homeostasis resulting from the treatment of acute respiratory failure could explain the absence of important stimulation of these hormonal systems.\textsuperscript{19}

The consequences of hypercapnia on hormonal release have been examined previously in animal and human studies with controversial results. Methodologic differences must be considered. In fact, the discussion of these data should take into account hemodynamic and gasometric data. The present study evaluated the hormonal responses to a short period of hypercapnia. The hypercapnia stimulus was unique and moderate. The heart rate stability is in favor of the constancy of adrenergic tone during the whole protocol. This could be attributed either to the moderate hypercapnic stimulus or to sedation.\textsuperscript{24-26} As previously reported, hypercapnia dilated systemic vessels and increased cardiac output and pulmonary arterial pressure.\textsuperscript{25} The effect on pulmonary artery pressure was inconstant.\textsuperscript{27}

In our study, isolated hypercapnia was unable to elicit ANP release. This result differs from previously reported high ANP plasma levels observed during respiratory failure.\textsuperscript{2,8,18} However, high ANP levels could be related to the increase in cardiac filling pressures due to hypoxemia and hypercapnia. Our results demonstrate that acute hypercapnia did not induce ANP plasma level variation when cardiac filling pressures remained stable. Animal studies have been performed in conscious dogs with hypercapnia stimulus as high as 70 and 80 mm Hg.\textsuperscript{4} Under these conditions, plasma ANP concentrations increased by more than 100\% and returned to baseline at the end of hypercapnia.\textsuperscript{4} However, in these experiments, hypercapnia increased cardiac filling pressures and V\textsubscript{E}. Hyperpnea decreased pleural pressure which in turn increased cardiac filling transmural pressures.\textsuperscript{28} Therefore, a rise in left atrial transmural pressure could explain the ANP rise described by Clozel et al.\textsuperscript{4} As in our study, Rose et al\textsuperscript{29} recently reported that less severe hypercapnia, i.e., 58 mm Hg, a level close to that induced in the present study, did not significantly rise plasma ANP. Conversely, when acute hypoxemia was combined with hypercapnia, the increase in plasma ANP was significant. This could be due to a rise in cardiac filling pressures (not measured in the study of Rose et al). In patients with COPD in a stable clinical condition, plasma ANP concentrations were positively related to the mean pulmonary arterial pressure\textsuperscript{30} and PaCO\textsubscript{2}.\textsuperscript{11,30} Conversely, in acute hypoxemic and hypercapnic respiratory failure, plasma ANP level did not correlate with PaCO\textsubscript{2}.\textsuperscript{2,18}

In unanesthetized dogs, plasma ADH concentration increased during acute hypercapnic acidosis. Increased ADH release was induced by a nonosmotic stimulus, probably left atrial or arterial baroreceptors stimulation.\textsuperscript{31} In hypercapnic edematous patients with COPD,\textsuperscript{9} plasma ADH level was also often increased. However, in COPD with acute respiratory failure, plasma ADH concentration was not correlated with PaCO\textsubscript{2}.\textsuperscript{7} Our results did not show any change in ADH concentration during acute hypercapnia. This is probably related to the hemodynamic stability maintained during the protocol,\textsuperscript{23} particularly the constancy of left atrial pressure\textsuperscript{31} and also the lack of stress provided by the sedation.\textsuperscript{23}

Acute hypercapnia did not induce any change in the hormones released by the kidney and by the adrenal cortex, i.e., renin, angiotensin II, and aldosterone. These results are not in agreement with those observed in other studies. Indeed, experimental hypercapnic acidosis increased renin\textsuperscript{6,32} and angiotensin II plasma levels.\textsuperscript{9} Renin secretion was mediated by the β-adrenergic system.\textsuperscript{32} Sympathetic tone was a major compensatory mechanism opposing the deleterious systemic hemodynamic and cardiac effects of acute hypercapnic acidosis.\textsuperscript{26} In conscious dogs, during an acute hypercapnic acidosis with increased heart rate, norepinephrine plasma concentrations increased mildly.\textsuperscript{26} In patients with COPD with acute hypercapnic respiratory failure, plasma levels of catecholamines, ADH, renin, angiotensin II, and aldosterone were often increased.\textsuperscript{2,9} Anand et al\textsuperscript{2} stated that this neurohormonal activation was due to the vasodilator properties of carbon dioxide. In our study, the absence of change in plasma hormones could be explained by the stability of sympathetic tone, as reflected by the heart rate constancy during the whole study. However, we did not measure norepinephrine plasma levels to confirm this hypothesis. Hypercapnic stimulus was lower than in the study by Anand et al\textsuperscript{2} (52 vs 60 mm Hg). The decrease in SVR, although significant, was limited and unassociated with a decrease in mean systemic arterial pressure, thus explaining the absence of RAAS stimulation.
Changes in cardiovascular function and renal perfusion are usually responsible for the hormonal effects of the anesthetic drugs. However, a hormonal reaction to a stimulus can be blunted by some anesthetic drugs, independently of their cardiovascular actions. However, benzodiazepines as midazolam or flunitrazepam do not affect significantly the adrenocortical response to ACTH and they do not suppress the stress-related norepinephrine increase. Muscle relaxants do not influence the adrenal function. In addition, Andrivet et al investigated patients receiving mechanical ventilation who were sedated and paralyzed with the same drugs as in our study, i.e., flunitrazepam and pancuronium given as continuous infusion and at the same dose (1 mg/h). They did observe changes in plasma ANP levels in response to hemodynamic variations induced by changes in intrathoracic pressures. All these data support the idea that flunitrazepam and pancuronium bromide did not blunt or modify the secretion of those hormones.

In our study, acute hypercapnia with moderate hemodynamic changes without variation in cardiac filling pressures did not induce significant changes in plasma levels of the hormones involved in circulatory and body fluid volume homeostasis. Arterial carbon dioxide tension cannot be considered as a stimulus acting directly on the endocrine function of the heart, brain, kidney, and adrenal. Our results can be related to those of Adnot et al who did not observe changes in plasma levels of ANP, renin activity, and aldosterone during brief variations in the level of oxygenation in patients with COPD. They reported that variations in the level of oxygenation were associated with hemodynamic changes without change in cardiac filling pressures. Our conclusions are in agreement with those of Anand et al who stated that the neurohormonal activation in patients with COPD is due to the hemodynamic consequences of hypercapnia. Therefore, during respiratory insufficiency, changes in hormones involved in circulatory and body fluid volume homeostasis are not directly induced by blood gas variations but are rather due to the changes in cardiac filling pressures and sympathetic tone caused by the blood gas variations.

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REFERENCES
24. Vatner SF, Braunwald E. Cardiovascular control mechanisms...
28 Schrijen F, Ehrlich W, Permutt S. Cardiovascular changes in conscious dogs during spontaneous deep breaths. Pflügers Arch 1975; 355:205-15
29 Rose CE, Ragsdale NV, Carey RM. Combined acute hypoxemia and hypercapnic acidosis increases atrial natriuretic polypeptide in conscious dogs. Miner Electrolyte Metab 1992; 18:24-34