

# Urinary Antidiuretic Hormone Excretion during Mechanical Ventilation and Weaning in Man

Margaret Hemmer, M.D.,\* Christian E. Viquerat, M.D.,† Peter M. Suter, M.D.,‡ and Michel B. Vallotton, M.D.§

The authors measured antidiuretic hormone (ADH) excretion, and renal and cardiovascular function in eight patients with flail chest during four ventilatory conditions: continuous positive-pressure ventilation (CPPV), intermittent positive-pressure ventilation (IPPV), spontaneous breathing with continuous positive airway pressure (CPAP) and spontaneous breathing (SB). Each condition was maintained for six to eight days. ADH excretion was significantly greater during CPPV ( $181 \pm 14$  ng/24 h, mean  $\pm$  SE) than during IPPV ( $86 \pm 10$ ), CPAP ( $83 \pm 7$ ), and SB ( $44 \pm 6$ ). Free-water clearance was more negative during mechanical ventilation than during CPAP and SB, resulting in significant fluid retention during CPPV and IPPV ( $440 \pm 88$  and  $547 \pm 70$  ml/day) and a negative water balance during SB ( $-154 \pm 80$  ml/day). Arterial and central venous pressures and cardiac output (measured in four patients) did not change significantly among ventilatory conditions. It is concluded that ADH excretion is increased during CPPV, and this could represent one possible mechanism of water retention with this type of ventilation. (Key words: Hormones, antidiuretic. Kidney: function. Ventilation, mechanical.)

DECREASED URINARY OUTPUT and fluid retention are frequently observed in patients treated with prolonged mechanical ventilation.<sup>1</sup> Intermittent positive-pressure ventilation (IPPV) is known to decrease venous return and intrathoracic blood volume,<sup>2</sup> and the addition of positive end-expiratory pressure (PEEP) enhances this effect.<sup>3,4</sup> Those hemodynamic alterations presumably activate mechanisms responsible for water retention and changes in urinary output.<sup>5,6</sup> Two mechanisms, suggested by Drury *et al.*,<sup>7</sup> have been studied most: release of antidiuretic hormone (ADH) and changes of renal function. Increases in plasma ADH during continuous positive-pressure ventilation (CPPV) have been observed in dogs,<sup>8</sup> rats,<sup>9</sup> patients in respiratory failure,<sup>10</sup> and conscious subjects during IPPV.<sup>11</sup> It has been postulated that there are stretch receptors in

the left atrium that are sensitive to changes of transmural pressure and vascular volume and influence the flow of urine by modifying ADH release.<sup>12,13</sup> Decreased cardiac filling pressures during mechanical ventilation may diminish the neural activity of these receptors and increase the secretion of ADH. The role of the atrial stretch receptors has been challenged, since plasma ADH has been shown to increase during CPPV in dogs whose vagi have been transected.<sup>14</sup>

All of these investigations of the cardiocirculatory and neurohormonal effects of mechanical ventilation on water and electrolyte handling have been of short duration (hours), and little is known about long-term adaptation. The purpose of this study was to investigate the effects of mechanical ventilation of several weeks' duration and of different ventilatory conditions on ADH excretion, water and electrolyte balance, and renal response to ADH.

## Methods

Eight patients, seven men and one woman, ranging in age from 34 to 65 years (mean 56 years) were included in this study. Mechanical ventilation was needed for respiratory failure due to severe flail chest. Trauma and pulmonary dysfunction were of similar severities in all cases. Patients who had head trauma, central nervous system disease, severe infections, or cardiac, hepatic or renal failure were excluded from the study. Informed consent was obtained from the patient's personal physician and from the patient's closest relative, and the study protocol was approved by the committee for ethics in human research of our institution. The measurements were started on the third day after admission of the patient to the intensive care unit in order to eliminate as much as possible the effects of stress of the first posttraumatic days on ADH secretion.

Volume-controlled ventilators were used in the assisted mode to deliver tidal volumes of 12 to 15 ml/kg body weight. Studies were performed during four ventilatory conditions, each applied for six to eight consecutive days to every patient: 1) CPPV with PEEP 7 cm H<sub>2</sub>O; 2) IPPV; 3) spontaneous breathing with continuous positive airway pressure (CPAP) 7 cm H<sub>2</sub>O; 4) spontaneous breathing (SB).

The sequence of these conditions was 1-2-3-4 for four patients and 2-1-3-4 for the other four, established

\* Research Associate.

† Research Assistant.

‡ Médecin responsable, Surgical Intensive Care Unit.

§ Professor of Medicine, Head, Division of Endocrinology.

Received from the Soins intensifs chirurgicaux de l'Institut d'Anesthésiologie and the Division d'Endocrinologie du Département de Médecine Interne, Hôpital cantonal universitaire, Genève, Switzerland. Accepted for publication November 23, 1979. Supported in part by the Swiss National Science Foundation (grant No. 3.845-0.77 and 3.564-0.75). Presented in part at the Annual Meeting of the American Society of Anesthesiologists, San Francisco, October 9-12, 1976.

Address reprint requests to Dr. Suter: Hôpital cantonal universitaire, 1211 Genève 4, Switzerland.

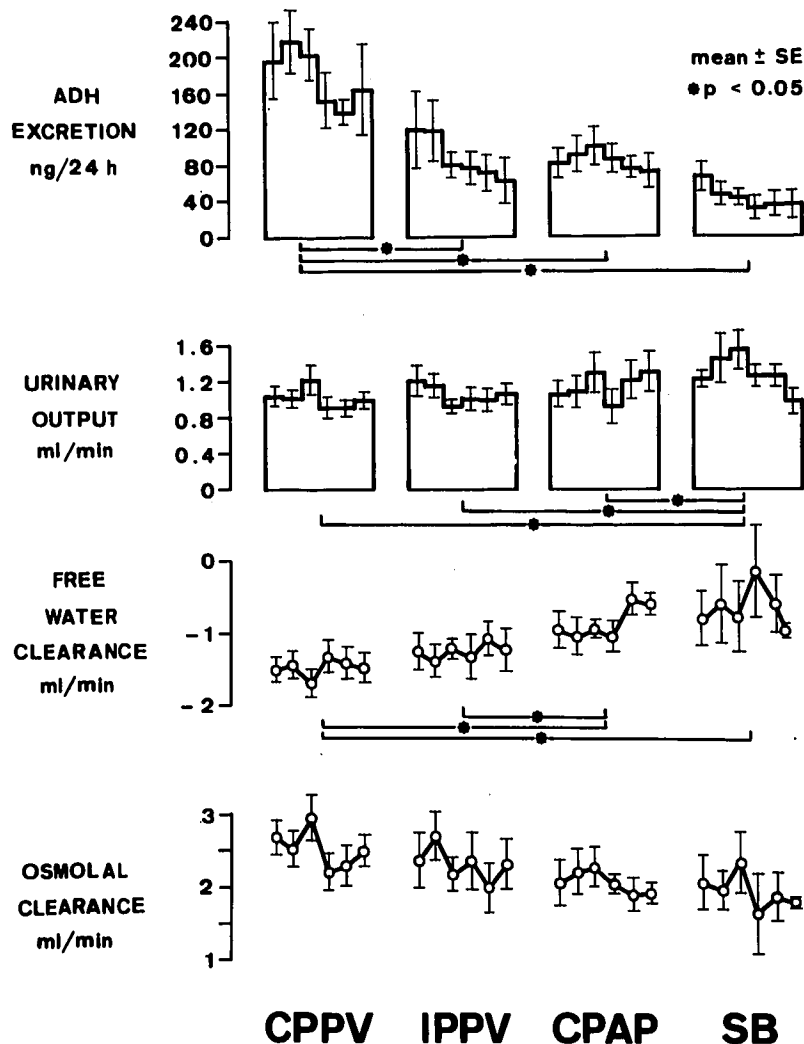


FIG. 1. Effects of the four ventilatory conditions on ADH excretion and water handling. The normal value of ADH excretion in our laboratory is  $71 \pm 11$  ng/24 h (mean  $\pm$  SE). Shown are mean values  $\pm$  SE for the eight patients studied during the six days of each ventilatory condition. Statistically significant differences are indicated by the asterisks.

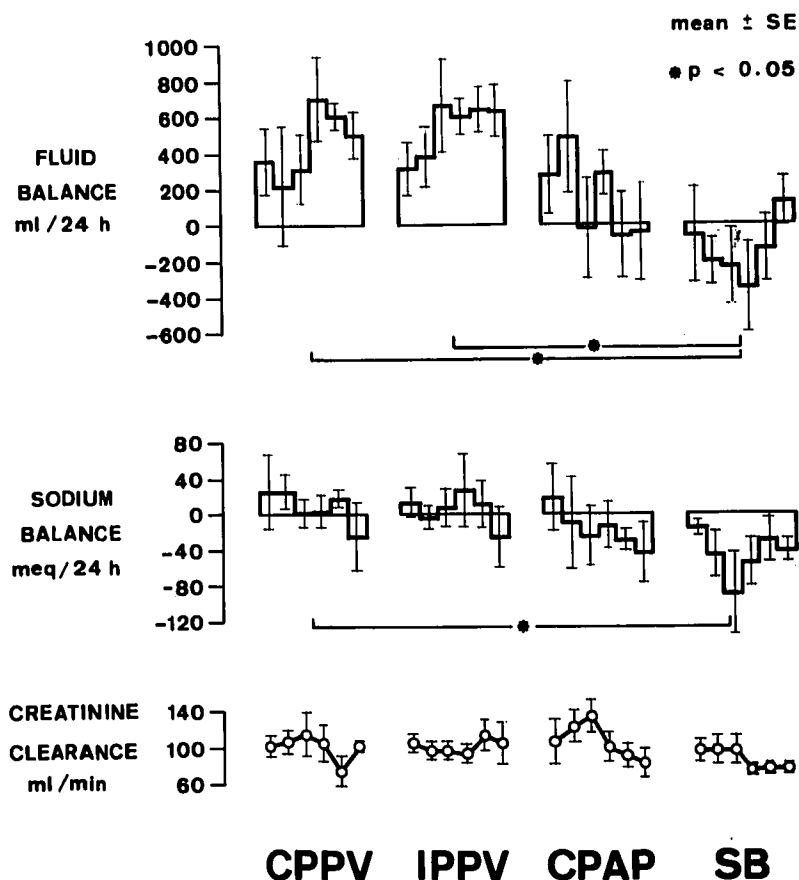
in a random fashion. Measurements were not obtained in one patient during CPAP and in three patients during SB. Of these, one patient had fatal gram-negative septicemia during the CPAP period, and two other patients had to be transferred to another unit before the end of the study. All patients underwent tracheostomy within 48 hours of admission to the hospital. Radial-artery and superior-vena-cava catheters were placed percutaneously to monitor arterial and central venous pressures. Arterial blood-gas and pH values were measured several times daily by standard electrode techniques. The inspired oxygen concentration was adjusted to obtain an arterial oxygen tension ( $P_{aO_2}$ ) between 70 and 90 torr. Arterial carbon dioxide tension ( $P_{aCO_2}$ ) was maintained between 35 and 40 torr to avoid the effects of hyper- and hypoventilation on ADH secretion and renal function.<sup>15,16</sup>

All patients received intravenous (glucose, amino acid and lipid solutions) and intragastric nutrition to ensure an adequate caloric intake (30–40 kcal/kg/day). Water balance was calculated from fluid intake minus urinary output and estimated insensible losses. During

mechanical ventilation a 300-ml volume was added daily to the water intake as the average gain from the main-line humidifier.<sup>1</sup> Mean body surface insensible loss was calculated as 15 ml/hour<sup>17</sup> plus 3 ml/kg body weight/degree C above 37 C.<sup>18</sup> A positive or negative water balance was defined as a difference between input and output after all the above corrections had been applied. Sodium and potassium balance were calculated as intake minus urinary output. For each 24-hour period plasma and urinary electrolytes and osmolality, plasma protein, blood and urinary urea nitrogen values, and urinary and plasma creatinine concentrations were measured by standard laboratory techniques. Creatinine, free water and osmolal clearances were then calculated.

Daily urinary excretion of ADH was measured using a radioimmunoassay for (arginine<sup>8</sup>)-vasopressin as reported previously.<sup>19</sup> This assay makes use of an antiserum raised in the author's laboratory whose specificity has been thoroughly tested.<sup>20</sup> It is specific for the C-terminal tripeptide chain of arginine-vasopressin and does not bind fragments of this hormone after it

FIG. 2. Effects of the four ventilatory conditions on daily water and electrolyte balance (mean  $\pm$  SE) in the eight patients studied.



has been incubated with kidney homogenate, thus making highly unlikely any interference by urinary metabolites. The arginine-vasopressin labelled with iodine-125<sup>19</sup> or serving as standard was synthetic arginine-vasopressin $\ddagger$  at a biological concentration of 150 IU/ml. The application of this radioimmunoassay to measurement of urinary antidiuretic hormone has been validated.<sup>21</sup> The mean recovery of unlabelled arginine-vasopressin added to urine and extracted on Amberlite<sup>®</sup> CG 50 (100–200 mesh) was  $70 \pm 2$  (SE) per cent with a blank value of  $0.29 \pm 0.21$  pg/ml. The value for normal adults in our laboratory is  $71 \pm 11$  ng/24 h.

The results for the first six days of each ventilatory condition were analyzed for each variable by the two-way analysis of variance.<sup>22</sup> Linear regression analysis was performed by the method of least squares.

### Results

The daily fluid volume received by the patients was  $32 \pm 0.1$  ml/kg (mean  $\pm$  SE) intravenously or orally. The mean sodium intake was 107 mEq per day and the mean potassium intake,  $96 \pm 3$  mEq per day.

We observed a marked increase in ADH excretion during CPPV (fig. 1). Urinary output was greater during SB than during the other periods. No significant

difference in free-water clearances was noticed between CPPV and IPPV, but an increase was observed when CPAP and SB were instituted. Osmolal clearance did change in the opposite direction compared with free-water clearance. The fluid balance was positive during mechanical ventilation and negative during spontaneous breathing (fig. 2). The sodium balance was negative during spontaneous breathing without noticeable sodium retention during the previous periods. There was no significant change in potassium balance. Creatinine clearance remained in the normal range throughout the study period. We found no significant difference in heart rates, arterial blood pressures, cardiac outputs, and arterial blood-gas values among the four ventilatory conditions (table 1). Central venous pressure was lower during spontaneous breathing than during CPPV or IPPV. During the transition from IPPV to CPPV (in four patients) or from CPPV to IPPV (in the other four patients) there was a marked change in ADH excretion (fig. 3), which was greater during CPPV than during IPPV. The regression lines calculated for the correlation between free-water clearance and ADH excretion during spontaneous breathing (fig. 4) were similar in our study group and a group of healthy subjects during a salt-loading test.<sup>21</sup> However, the slope of the regression line was significantly different for the data obtained during CPPV.

$\ddagger$  Ferring A. B., FACK 200-60 Malmö 30, Sweden.

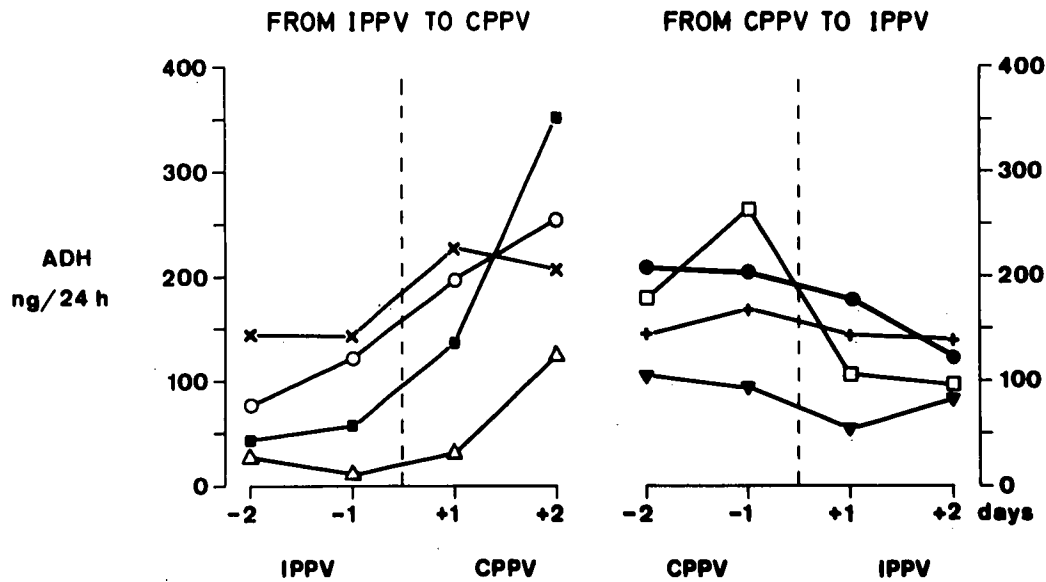


FIG. 3. ADH excretion during the transitions from IPPV to CPPV in four patients and from CPPV to IPPV in four others. The values of the two days before and after the changes of the ventilatory condition are represented, and the changes are significant (Wilcoxon rank test).

Plasma osmolality was higher during CPPV and IPPV than during CPAP (table 2). Plasma sodium concentration was higher during CPPV than during CPAP and SB, but no difference between CPPV and IPPV was observed. There was no significant change in plasma proteins or blood urea nitrogen during the study. Urinary osmolality was higher during CPPV and IPPV than during the other two periods. A significant decrease was also noticed between CPAP and SB. Urinary sodium excretion was greater during SB than during CPPV, urea nitrogen excretion was significantly higher during CPPV and IPPV than during SB, and the total osmolal excretion was higher during CPPV than during SB.

### Discussion

We have observed a sustained increase in urinary ADH excretion during prolonged use of CPPV in adults with chest trauma. Although stress, fear and pain are factors that may increase ADH release in conscious, critically ill patients submitted to mechani-

cal ventilation, these stimuli should not have been different between CPPV and IPPV in our study group. The clinical conditions of the patients were similar during the two ventilatory conditions: there was no difference in pulmonary or cardiovascular status. Thereby we assume that changes in urinary excretion of ADH reflect changes in its secretion from the neurohypophysis, but changes in its metabolic fate cannot be excluded by the present data. We have demonstrated in the rat that ADH injected by micropuncture of the proximal or the distal tubules is recovered intact to the extent of  $89 \pm 3$  or  $94 \pm 4$  per cent, respectively, indicating that once filtered, ADH is not significantly degraded.<sup>23</sup>

The following mechanisms may underlie the augmentation of ADH excretion during CPPV. First, an osmotic stimulation may have contributed to the increase in ADH release. A positive correlation ( $r = 0.57$ ,  $P < 0.001$ ) existed between the mean values of plasma osmolality and mean urinary ADH levels. The regression function describing this relationship: urinary

TABLE 1. Hemodynamic Variables (Means  $\pm$  SE)

	Ventilatory Condition			
	CPPV	IPPV	CPAP	SB
Pulse rate (/min)	101 $\pm$ 4	98 $\pm$ 4	97 $\pm$ 7	94 $\pm$ 8
Arterial blood pressure (torr)				
Systolic	142 $\pm$ 6	131 $\pm$ 3	139 $\pm$ 8	128 $\pm$ 10
Diastolic	78 $\pm$ 3	74 $\pm$ 3	77 $\pm$ 3	71 $\pm$ 4
Central venous pressure (cm H <sub>2</sub> O)	10 $\pm$ 1*	10 $\pm$ 1*	8 $\pm$ 2	4 $\pm$ 2*
Cardiac output (l/min) (four patients only)	6.0 $\pm$ 1.6	6.5 $\pm$ 1.8	7.0 $\pm$ 2.0	6.4 $\pm$ 1.5
PaO <sub>2</sub> (torr)	78 $\pm$ 5	72 $\pm$ 3	79 $\pm$ 3	74 $\pm$ 5
Paco <sub>2</sub> (torr)	37 $\pm$ 1	36 $\pm$ 1	38 $\pm$ 1	38 $\pm$ 1
pH	7.43 $\pm$ 0.01	7.42 $\pm$ 0.01	7.40 $\pm$ 0.01	7.42 $\pm$ 0.01

\*  $P < 0.05$ , difference between CPPV and SB, or between IPPV and SB. Cardiac output was measured with the indicator dilution

technique, using Cardiogreen®. All vascular pressures were obtained at end-expiration.

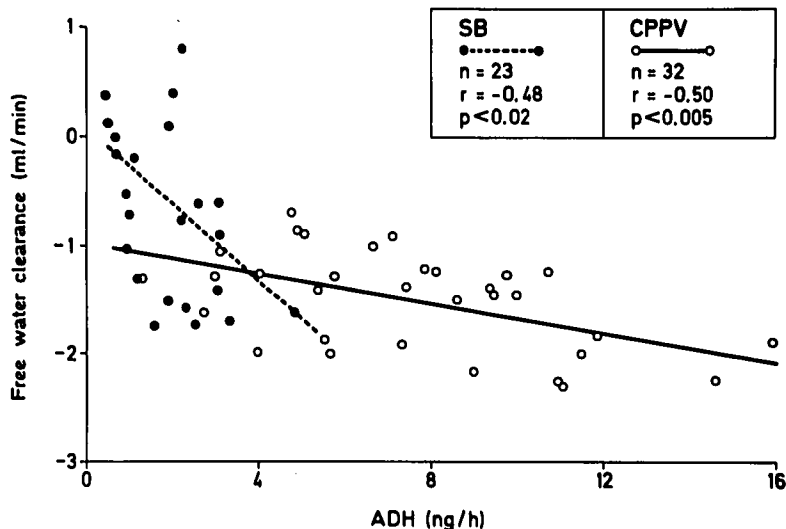


FIG. 4. Relationship between free-water clearance and urinary ADH excretion. For CPPV and SB individual points as well as the calculated linear regression lines are indicated. Regression equation for CPPV: free-water clearance =  $(-0.065 \times \text{ADH}) - 1.014$ ; for SB: free water clearance =  $(-0.337 \times \text{ADH}) + 0.063$ .

ADH excretion per 24 hours = 6.7 (plasma osmolality 272) was similar to that obtained by Fressinaud *et al.*<sup>24</sup>: 5.9 (plasma osmolality -275), who used a different urinary assay in healthy men. However, the changes observed cannot be explained by this mechanism alone, since the major change in ADH excretion occurring between CPPV and IPPV was not accompanied by a significant difference in total plasma osmolality, plasma sodium concentration, water and electrolyte balance, or renal function.

Second, ADH secretion and its renal effects can be affected during mechanical ventilation by the application of PEEP. The resulting changes in intrathoracic pressure and blood volume, and the decrease in cardiac filling pressure, may increase ADH release through pressor<sup>25</sup> or volume-dependent mechanisms.<sup>8</sup> There is evidence indicating that a hemodynamic stimulus does not interfere with concurrent osmotic stimuli for ADH release.<sup>26</sup> However, the application of PEEP during mechanical ventilation not only affects central blood volume and cardiac output, but may

also alter the distribution of cardiac output to and within different organ systems. For instance, there is evidence that PEEP may decrease blood flow to the central nervous system,<sup>\*\*</sup> and the possibility that a decreased flow to the hypothalamus itself might be a stimulus for ADH release during CPPV<sup>27</sup> cannot be excluded. In our patients the renal responses during the four ventilatory conditions were characterized by more negative free-water clearance during mechanical ventilation (CPPV and IPPV) than during spontaneous breathing (SB and CPAP). Since greater ADH excretion was actually observed during CPPV and IPPV it is conceivable that the water retention observed during mechanical ventilation and the negative water balance during spontaneous breathing could have

\*\* Pontoppidan H: personal communication (Stene JK, Snider MT, Boucher R, et al: Effects of PEEP on regional blood flow in the awake sheep during spontaneous and mechanical ventilation. Abstracts, Annual Meeting of the American Society of Anesthesiologists, 1977, p 711).

TABLE 2. Biochemical Data from Six Daily Measurements for Each of the Eight Patients during Four Ventilatory Conditions

	Ventilatory Condition			
	CPPV	IPPV	CPAP	SB
Plasma				
Osmolality (mOsm/kg)	291 ± 2‡	291 ± 2‡	285 ± 2*†	284 ± 2
Sodium (mEq/l)	138 ± 1‡§	137 ± 1	135 ± 1*	133 ± 1*
Potassium (mEq/l)	4.6 ± 0.1	4.5 ± 0.1	4.2 ± 0.1	4.2 ± 0.1
Proteins (g/l)	62 ± 1	64 ± 1	66 ± 1	65 ± 1
Urea nitrogen (mg/l)	191 ± 7	193 ± 10	175 ± 9	179 ± 11
Urinary				
Osmolality (mOsm/kg)	765 ± 37‡§	667 ± 38‡§	548 ± 40*†	458 ± 59*†‡
Sodium (mEq/24 h)	93 ± 18§	90 ± 12	120 ± 18	118 ± 19*
Potassium (mEq/24 h)	96 ± 5	79 ± 6	85 ± 7	76 ± 8
Urea (g/24 h)	12.9 ± 1.2§	12.4 ± 1.1§	9.5 ± 1.1	7.0 ± 1.0*†‡
Osmolal excretion (mOsm/24 h)	1058 ± 54§	972 ± 66	847 ± 63	779 ± 89*

\* P < 0.05 vs. CPPV.  
† P < 0.05 vs. IPPV.

‡ P < 0.05 vs. CPAP.  
§ P < 0.05 vs. SB.

been at least partly due to modifications in free-water clearance secondary to changes in ADH release. In addition, for most values of ADH above 5 ng/hour during CPPV, the free-water clearance was less negative than would have been expected by linear extrapolation from the relation observed in controls and during spontaneous breathing.<sup>21</sup> The disparity between the renal antidiuretic response and the high ADH levels during CPPV have also been observed in the dog<sup>14</sup> and in critically ill patients<sup>10</sup> in short-term experiments. The urinary excretions of ADH are considerably greater than those observed during induced hyperosmolarity,<sup>21</sup> and therefore possibly above the range for maximal antidiuretic action. They may reflect plasma concentration at which ADH exerts a vasoconstrictor action,<sup>28</sup> and this could influence the renal response. In addition, the hemodynamic changes induced by CPPV, such as modifications in cardiac output, total renal plasma flow, renal perfusion pressure and a redistribution of intrarenal blood flow,<sup>10,20-31</sup> may also alter renal function and its response to ADH.

In conclusion, prolonged mechanical ventilation with PEEP is associated with an important and sustained increase of urinary ADH excretion. Fluid retention during prolonged mechanical ventilation and negative water balance after the resumption of spontaneous breathing may be partly due to variations in ADH secretion and consequent changes in free-water clearance. Free-water clearance is not proportionate to the high ADH levels during CPPV.

The authors are indebted to Ms. Mary-Claude Dubied for technical assistance, and to M. D. Grossiord for the statistical analysis.

### References

- Sladen A, Laver MB, Pontoppidan H: Pulmonary complications and water retention in prolonged mechanical ventilation. *N Engl J Med* 279:448-453, 1968
- Cournand A, Motley HL, Werko L, et al: Physiological studies of the effects of intermittent positive pressure breathing on cardiac output in man. *Am J Physiol* 152:162-174, 1948
- Lenfant C, Howell BJ: Cardiovascular adjustments in dogs during continuous pressure breathing. *J Appl Physiol* 15:425-428, 1960
- Kumar A, Falke KJ, Geffin B, et al: Continuous positive-pressure ventilation in acute respiratory failure. Effects on hemodynamics and lung function. *N Engl J Med* 283:1430-1436, 1970
- Murdaugh HV Jr, Sicker HO, Mandredi F: Effect of altered intrathoracic pressure on renal hemodynamics, electrolyte excretion and water clearance. *J Clin Invest* 38:834-843, 1959
- Davis JT: The influence of intrathoracic pressure on fluid and electrolyte balance. *Chest* 62:118s-125s, 1972
- Drury DR, Henry JR, Goodman J: The effects of continuous pressure breathing on kidney function. *J Clin Invest* 26:945-951, 1947
- Baratz RA, Ingraham RC: Renal hemodynamics and antidiuretic hormone release associated with volume regulation. *Am J Physiol* 198:565-570, 1960
- Tarak TK, Chaudhury RR: The mechanism of positive pressure respiration induced antidiuresis in the rat. *Clin Sci* 28:407-415, 1965
- Kumar A, Pontoppidan H, Baratz RA, et al: Inappropriate response to increased plasma ADH during mechanical ventilation in acute respiratory failure. *ANESTHESIOLOGY* 40:215-221, 1974
- Khambatta HJ, Baratz RA: IPPB, plasma ADH, and urine flow in conscious man. *J Appl Physiol* 33:362-364, 1971
- Henry JP, Gauer OH, Reeves JL: Evidence of the atrial location of receptors influencing urine flow. *Circ Res* 4:85-90, 1956
- Brennan LA Jr, Malvin RL, Jochim KE, et al: Influence of right and left atrial receptors on plasma concentrations of ADH and renin. *Am J Physiol* 221:273-278, 1971
- Baratz RA, Philbin DM, Patterson RW: Plasma antidiuretic hormone and urinary output during continuous positive-pressure breathing in dogs. *ANESTHESIOLOGY* 34:510-513, 1970
- Kilburn KH, Dowell AR: Renal function in respiratory failure. *Arch Intern Med* 127:754-762, 1971
- Philbin DM, Baratz RA, Patterson RW: The effect of carbon dioxide on plasma antidiuretic hormone levels during intermittent positive-pressure breathing. *ANESTHESIOLOGY* 33:345-349, 1970
- Newburgh LD, Johnston MW: Insensible loss of water. *Physiol Rev* 22:1-18, 1942
- Kinney JM, Egdahl RH, Zuidema GD: Manual of Pre-operative and Post-operative Care. Second edition. Philadelphia, W. B. Saunders, 1971
- Czernichow P, Merkelbach U, Vallotton MB: Radioimmunoassay of 8-arginine-vasopressin. I. Methodology. *Acta Endocrinol* 80:444-452, 1975
- Czernichow P, Reinharz A, Vallotton MB: Immunochemical analysis of rabbit antibodies against vasopressin. *Immunochemistry* 11:47-53, 1974
- Merkelbach U, Czernichow P, Gaillard RC, et al: Radioimmunoassay of 8-arginine-vasopressin. II. Application to determination of antidiuretic hormone in urine. *Acta Endocrinol* 80:453-464, 1975
- Snedecor GW, Cochran WG: Statistical Methods. Sixth edition. Ames, Iowa, Iowa State University Press, 1967
- Lindheimer MD, Reinharz A, Grandchamp A, et al: Fate of vasopressin (AVP) perfused into nephrons of Wistar and Brattleboro (diabetes insipidus) rats. *Clin Sci* (in press)
- Fressinaud P, Corvol P, Menard J: Radioimmunoassay of urinary antidiuretic hormone in man: Stimulation-suppression tests. *Kidney Int* 6:184-190, 1974
- Share L, Levy MN: Carotid sinus pulse pressure, a determinant of plasma antidiuretic hormone concentration. *Am J Physiol* 211:721-724, 1966
- Robertson GL, Shelton RL, Athar S: The osmoregulation of vasopressin. *Kidney Int* 10:25-37, 1976
- Guyton AC: Textbook of Medical Physiology. Fourth edition. Philadelphia, W. B. Saunders, 1971, p 883
- Möhring J: Neurohypophysial vasopressor principle: Vasopressor hormone as well as antidiuretic hormone? *Klin Wochenschr* 56(Suppl I):71-79, 1978
- Hall SV, Johnson EE, Hedley-Whyte J: Renal hemodynamics and function with continuous positive-pressure ventilation in dogs. *ANESTHESIOLOGY* 41:452-461, 1974
- Laver MB: Dr. Starling and the "ventilator" kidney (editorial). *ANESTHESIOLOGY* 50:383-386, 1979
- Marquez JM, Douglas ME, Downs JB, et al: Renal function and cardiovascular responses during positive airway pressure. *ANESTHESIOLOGY* 50:393-398, 1979