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Inappropriate Response to Increased Plasma ADH during Mechanical Ventilation in Acute Respiratory Failure

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The effect of mechanical ventilation (IPPV) and positive end-expiratory pressure (PEEP) on plasma ADH was studied in eight patients with acute respiratory failure. The study was divided into two 60-minute periods, PEEP of 10 cm H_2O being added to IPPV during first or second hour in random order. Mean decreases in urinary flow from 1.11 to 0.78 ml/min ($P < 0.05$) and cardiac index (determined in six patients) from 4.3 to 3.4 l/min/m² ($P < 0.01$) were observed with PEEP. Although a twofold increase in plasma ADH (mean 8.1 to 18.8 μU/ml, $P < 0.05$) following PEEP was associated with a decrease in urinary flow, inconsistent changes in free-water and osmolal clearance and urinary osmolality point to an inappropriate response to increased ADH. The decrease in urinary flow and concurrent reduction in urinary sodium excretion suggest an overriding influence of the decrease in cardiac index on renal function. (Key words: Ventilation: mechanical; Ventilation: positive end-expiratory pressure; Hormones: antidiuretic hormone; Kidney: urinary output; Heart: cardiac index; Fluid balance: water; Ions: sodium, excretion.)

IN A RETROSPECTIVE STUDY, Sladen *et al.*[1] demonstrated that 19 of 100 patients receiving prolonged mechanical ventilation (IPPV) developed positive water balances, with an average weight gain of 2.6 kg. Concomitantly, there were significant reductions in serum sodium concentration and hematocrit, with deterioration of pulmonary mechanics, blood–gas exchange, and radiologic changes consistent with pulmonary edema. After induced diuresis and fluid restriction, all the observed changes were reversed. A combination of a decrease in central blood volume, activation of left atrial volume receptors, and ultimately augmented secretion of antidiuretic hormone (ADH) was suggested as one of the several possible mechanisms for water retention. However, none of these physiologic variables was measured.

Studies in dogs by Baratz *et al.*[2] and in anesthetized patients without pulmonary disease by Verma *et al.*[3] have failed to demonstrate increased ADH during IPPV, compared with spontaneous ventilation. In fact, decreased ADH and increased urinary flow have been demonstrated. These investigators conclude that the use of IPPV did not impose sufficient stress on the circulatory system to cause a decrease in intrathoracic blood volume and subsequent stimulation of the left atrial volume receptor mechanism.

Recent reports indicate that IPPV with PEEP causes a significant improvement in oxygenation in certain patients with severe, acute respiratory failure not responding to IPPV alone.[4-5-6] PEEP is now widely used as an adjunct to IPPV in acute respiratory failure. Although the cardiovascular response to PEEP has been described, its effect on renal function in patients has not been studied.

It has generally been assumed that water retention during the course of mechanical ventilation is the result of inappropriate ADH secretion, although it has not been demonstrated that there is an appropriate response to increased ADH secretion. The study reported here was undertaken to determine the acute effects of addition of PEEP to IPPV on plasma ADH, urinary composi-

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TABLE 1. Clinical Data

	Age (Years), Sex	Diagnosis	Duration of IPPV (Days)	Duration of PEEP (Days)
Patient 1	52, M	Bilateral pneumonia	1	7
Patient 2	70, M	Resection of aneurysm of abdominal aorta; pulmonary edema; chronic obstructive pulmonary disease	1	2
Patient 3	78, M	Resection of aneurysm of abdominal aorta; postoperative acute respiratory failure; atrial fibrillation	None	1
Patient 4	51, M	Salt water aspiration, pulmonary congestion and edema, chronic bronchitis	2	1
Patient 5	50, M	Chronic obstructive pulmonary disease, cor pulmonale	15	4
Patient 6	17, F	Stab wound of abdomen, septicemia, positive water balance, pulmonary edema	5	5
Patient 7	68, M	Myasthenia gravis, bilateral pneumonia	7	1
Patient 8	18, F	Crushed-chest injury, pulmonary contusion, splenectomy	None	1

tion, and cardiac index in patients with acute respiratory failure.

Methods

SELECTION OF PATIENTS

We have studied eight patients, all of whom had been receiving mechanical ventilation with a volume-preset, time-cycled ventilator. In the cases of Patients 1, 2, 4, 5, 6, and 7, PEEP was added after various durations of IPPV, while for Patients 3 and 8 PEEP was used from the initiation of mechanical ventilation. Clinical data are given in table 1.

Patients with histories of head injuries or with poor renal function (BUN more than 25 mg/100 ml) were excluded from the study. Patients 2, 4, and 5 had pre-existing chronic obstructive pulmonary disease (COPD). Patients 2, 3, and 8 were studied in the early postoperative period, when plasma ADH levels are known to be high.[7,8] Diuretic agents were withheld for 4 to 6 hours before study, but given during the course of mechanical ventilation when indicated.[1] Consequently, no significant change in body weight, hematocrit, or serum Na^+ concentration was seen from initiation of treatment to the day of study.

During study periods, the patient lay supine, with a 15-degree head-up tilt. Five per cent dextrose in water was infused at a rate of 60 ml/hour. Diuretics and drugs known to alter plasma ADH levels (*e.g.*, morphine) were withheld prior to study for periods exceeding their estimated durations of action (4–6 hours).

VENTILATION PATTERN

Ventilation was controlled with an Emerson postoperative ventilator via a cuffed endotracheal or tracheostomy tube. As part of routine clinical care, the inspired oxygen concentration was adjusted to maintain Pa_{O_2} in the normoxemic range, but for the purpose of this study, all measurements were performed at the end of 30-minute periods of ventilation with 100 per cent oxygen. A positive end-expiratory plateau pressure was obtained using a pressurized Bennett gas-collecting manifold attached to the expiratory port of the ventilator. PEEP's were 10 cm H_2O, except for Patients 1 and 7, for whom they were 15 and 5 cm H_2O, respectively.

Tidal volume, respiratory rate, and inspiratory-to-expiratory time ratio were constant in the individual patient during the study. When necessary, *d*-tubocurarine was used to facilitate controlled ventilation.

In every patient, catheters were inserted percutaneously into a radial artery and the superior vena cava for continuous pressure recording of arterial and central venous pressures using a Hewlett-Packard Model 267AC transducer and an amplifier recorder system. Airway pressure was also recorded. Mean

pressures were obtained by electronic integration.

The study was divided into two 60-minute periods, PEEP being added to IPPV during the first or second hour in random order. The first 30 minutes of each study period were allowed for stabilization and urine was collected from an indwelling Foley catheter during the second 30-minute period only. Samples for plasma ADH assay and for analysis of arterial blood gases, serum electrolytes, and osmolality were drawn into heparinized syringes during the last 15 minutes of each study period. Arterial blood-gas analysis was by standard electrode techniques. Serum and urinary electrolytes were determined with a flame photometer,¶ and plasma and urinary osmolalities by freezing-point osmometer.** During the last 15-minute period, cardiac output was measured in duplicate in six patients, using the dye-dilution technique with indocyanine green dye and a Beckman densitometer (model 350172).

ADH Assay

Plasma levels of ADH were determined by a modification of the method described by Yoshida.[9] Blood was withdrawn in heparinized syringes and centrifuged. Plasma was kept frozen until the time of extraction, when it was deproteinized sequentially using 12.5, 10, and 5 per cent trichloroacetic acid (TCA). TCA was removed with ether and the supernatant adjusted to *p*H 4.1 using 1 N ammonium hydroxide. The resultant solution was concentrated on an ion-exchange column of Amberlite CG 50 resin, which was found to be more specific than the XE-64 resin column used by Yoshida. The octapeptide was eluted from the column using 50 per cent (V/V) acetic acid, which was sequentially evaporated in a vacuum evaporator. The concentrated material was dissolved in 0.2 ml saline solution and injected intravenously into a water-loaded ethanol-anesthetized rat. Urinary flow for 10 minutes following injection was compared with urinary flow for the 10 minutes preceding injection. In every case, a four-point assay for each sample was performed as described by Sawyer.[10] The standard used was U.S.P. posterior pituitary reference standard. Using this method, plasma ADH levels in normal human subjects averaged 1.9 μU/ml; during periods of dehydration the values averaged 6.5 μU/ml.

All results were analyzed by Student's t test for paired data.

Results

Experimental data for each patient are summarized in table 2; mean values during the two study periods are shown in figure 1. With PEEP, urinary flow decreased in seven of eight patients from a mean of 1.11 to 0.78 ml/min ($P < 0.05$), or an average of 29 per cent. Increases in plasma ADH were also seen in seven of eight patients with the use of PEEP. Mean ADH during IPPV was 8.1 μU/ml and increased to 18.8 μU/ml ($P < 0.05$) with the addition of PEEP.

The mean cardiac index (determined in six patients) decreased by 21 per cent from 4.3 to 3.4 l/min/m^2 when mean airway pressure was increased from 12 to 22 cm H_2O with addition of PEEP. Greater decreases of 41 and 44 per cent occurred in Patients 2 and 5, who had pre-existing COPD, respectively. Mean arterial pressure remained unchanged with application of PEEP. A small but significant rise in mean central venous pressure (determined in six patients) from 7 to 8 cm H_2O was observed. The "effective compliance" changed insignificantly, and there was no correlation between patients with initially low or high compliance and changes in central venous pressure.

No consistent or significant change in serum sodium or osmolality occurred. Sodium excretion rates decreased in Patients 1, 2, 4, and 5, but the changes were not significant. Urinary osmolality increased minimally in six patients. Free-water clearance decreased in Patients 6 and 8, the only patients with positive free-water clearance during IPPV.

Discussion

The principal finding of this study was that institution of PEEP in patients receiving IPPV led to increases in plasma ADH from initially elevated values. In addition, cardiac index decreased and there was a moderate decrease in urinary flow. At first glance, it is tempting to attribute the decrease in urinary flow to the elevated plasma ADH. As discussed below, changes in urinary

¶ Model 143 Instrumentation Laboratory, Inc.
** Advanced Digimatic osmometer; Model 3D. Advanced Instruments, Inc.

TABLE 2. Experimental Data with

	Mode of Ventilation	Mean Airway Pressure (cm H_2O)	"Effective"* Compliance (ml/cm H_2O)	Pa_{O_2} (mm Hg)	Pa_{CO_2} (mm Hg)	Cardiac Index (l/min/m²)	Central Venous Pressure (cm H_2O)
Patient 1	IPPV	9.5	45	420	37	5.3	5.5
	IPPV with PEEP	23.5	60	463	39	4.4	10
Patient 2	IPPV†	12.5	49	254	34	3.4	4.5
	IPPV with PEEP	19.5	57	425	33	2.4	9
Patient 3	IPPV	10	47	399	37	‡	14.5
	IPPV with PEEP	20	46	467	40		18.0
Patient 4	IPPV	12	45	232	41	‡	3
	IPPV with PEEP	25	42	290	45		3.5
Patient 5	IPPV†	8.5	52	119	35	4.2	‡
	IPPV with PEEP	17	53	386	36	2.9	
Patient 6	IPPV†	12.5	28	135	57	3.86	5.5
	IPPV with PEEP	24	25	465	46	3.25	6.5
Patient 7	IPPV†	17.5	28	97	44	4.0	11
	IPPV with PEEP	23.5	26	96	44	3.6	13
Patient 8	IPPV	11.5	33	427	32	4.8	4.5
	IPPV with PEEP	20.5	37	443	33	3.5	7.5
Mean ± SE							
	IPPV	12±1	41±3.4	260±49	39.6±2.8	4.2±0.3	6.9±1.6
	IPPV with PEEP	22±1	43±4.7	379±46	39.5±1.8	3.3±0.3	9.6±1.8
P (significant values only)		<0.001		<0.05		<0.01	<0.05

* "Effective" compliance was calculated as the ratio of tidal volume to peak inspiratory pressure minus end-expiratory pressure.
† Indicates that IPPV with PEEP was used first, followed by IPPV only in these patients.
‡ Data not available.

volume and composition did not support this assumption.

Changes in Renal Hemodynamics with PEEP

The effects of alterations in airway pressure on renal function and ADH activity have been studied in animals and in healthy human subjects during positive-pressure breathing (spontaneous ventilation with PEEP). Drury *et al.*[11] implicated circulatory stress and possible secretion of ADH as a cause for a reduction in urea clearance and urinary flow in human volunteers, although plasma ADH was not determined. The decreases in glomerular filtration rate and renal plasma flow were proportional to the decline in cardiac output produced by positive-pressure breathing. Baratz and Ingrahm[12] obtained similar effects in dogs. An increase in plasma ADH and a decrease in urinary flow in dogs with PEEP unaffected by bilateral vagotomy were reported by Baratz *et al.*[13] They suggested the decrease in urinary flow to be a direct effect of the decline in cardiac output with PEEP. It is fair to assume that the 21 per cent diminution in cardiac index associated with the use of PEEP in the present study probably resulted in altered renal hemodynamics, as indicated by changes in the quality and quantity of urinary flow. That ADH levels were not in the pressor range (except possibly in Patient 2) presumably rules out a direct renal vasoconstrictor effect.

Role of Sodium

In a study of healthy trained human subjects, Cox *et al.*[14] showed a significant decrease in the urinary sodium/potassium (Na/K) ratio and an increase in aldosterone excretion after half an hour of PEEP during spontaneous respiration. In another long-term metabolic study[15] of seven patients, IPPV was used to treat respiratory failure. Sodium retention correlating with periods of pul-

IPPV and Following Addition of PEEP

Plasma ADH (μU/ml)	Plasma Osmolality (mOsm/l)	Serum Na (mEq/l)	Urinary Flow (ml/min)	Urinary Osmolality (mOsm/l)	Na Excretion Rate (mEq/min)	Urinary Na/K Ratio	Osmolal Clearance (ml/min $C_{[osm]}$)	Free-water Clearance (ml/min $C_{[H_2O]}$)
8	302	140	1.17	960	0.090	0.96	3.72	−2.5
14	304	139	0.77	1014	0.032	0.58	2.57	−1.8
15	312	142	1.43	558	0.020	0.12	2.56	−1.1
55	306	141	1.17	586	0.005	0.04	2.24	−1.1
11	277	133	0.80	551	0.006	0.06	1.59	−0.8
23	272	136	0.56	558	0.007	0.10	1.15	−0.6
9	281	132	0.47	890	0.075	1.84	1.49	−1.0
19	277	134	0.50	875	0.065	1.43	1.58	−1.1
1	294	130	0.83	†	0.023	0.27	—	†
7	289	134	0.67		0.012	0.17	—	
9	282	138	2.10	255	0.086	1.57	1.90	+0.2
15	283	138	1.73	443	0.166	2.00	2.71	−1.0
2	310	151	0.47	623	0.001	0.06	0.94	−0.5
10	312	145	0.20	629	0.001	0.06	0.40	−0.2
10	273	131	1.60	139	0.008	0.21	0.81	+0.8
7	271	131	0.66	623	0.018	0.25	1.52	−0.9
8.1±1.6	291±5	137±2.5	1.11±0.20	568±114	0.039±0.013	0.64±0.26	1.86±0.4	−0.70±0.4
18.8±5.5	289±6	137±1.6	0.78±0.17	675±75	0.038±0.019	0.58±0.26	1.74±0.3	−0.96±0.2
<0.05			<0.05					

monary edema occurred in all seven patients. During IPPV, administration of a diuretic caused natriuresis, followed by a reduction in signs of pulmonary edema. In our study the urinary Na/K ratio decreased in Patients 1, 2, 4, and 5, minimally increased in Patients 3 and 6, and remained unchanged in Patient 7. Any tendency to sodium retention was probably prevented by intermittent use of diuretics that caused natriuresis.

Blood–Gas Exchange and Urine Flow

Consistent increases in Pa_{O_2} were observed in all patients except Patient 7 (for whom only 5 cm H_2O PEEP was used). Hyperoxia and hypoxia may diminish glomerular filtration rate, renal plasma flow, urinary flow, and sodium excretion.[16] With the possible exception of Patients 5 and 6, neither the absolute values nor the variations in Pa_{O_2} with the addition of PEEP in this study are likely to have caused such alterations in renal function.

Elevation of Pa_{CO_2} to above 50 mm Hg has been shown to increase plasma ADH[17] and consequently to reduce urinary flow. However, minimal changes in Pa_{CO_2} in our study, except in Patient 6, were insufficient to account for the increase in plasma ADH.

Role of ADH

The primary physiologic functions of ADH are regulation of osmotic pressure of extracellular fluid and regulation of blood volume. The complex mechanism of ADH release has recently been reviewed.[8-18]

Plasma ADH levels during IPPV (mean 8.1 ± 1.6 μU/ml) were significantly above those measured in normal human subjects in the laboratory of one of us (R.A.B.). This is in contrast to previous studies in dogs[2] and anesthetized patients with normal lungs[3] where IPPV was associated with a decrease in plasma ADH and an increase in urine flow. In a recent study[19] of conscious patients during the period of weaning from

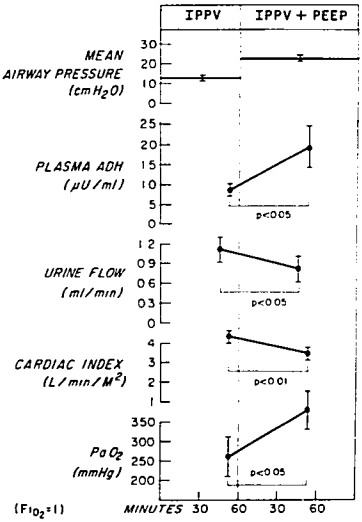

FIG. 1. Changes in mean airway pressure, plasma ADH, urinary flow, cardiac index, and Pa_{O_2} with the application of PEEP to IPPV. Results are mean values for eight patients, except for cardiac index (determined in six patients). Vertical bar represents 1 SEM. Mean airway pressure increased from 12 to 22 cm H_2O with the application of PEEP to IPPV. Mean plasma ADH increased from 8.1 to 18.8 μU/ml. Mean urinary flow was reduced from 1.11 ml/min during 30-minute period of IPPV to 0.8 ml/min during 30-minute period following use of PEEP. With IPPV the mean cardiac index was 4.2 l/min/m²; it decreased to 3.3 l/min/m² with PEEP. Mean Pa_{O_2} with IPPV was 260 mm Hg and increased to 337 mm Hg after a 30-minute period of PEEP. All changes were statistically significant, as indicated by *P* values.

the ventilator, an increase in plasma ADH and diminished urine flow have been reported with IPPV following control periods of spontaneous ventilation. Psychogenic factors such as anxiety and stress associated with IPPV were proposed as contributing to the release of ADH and corticotropin. In the present study of conscious, critically ill patients, it is reasonable to assume that similar factors may have been responsible for high ADH levels. Pain and early postoperative status in Patients 2, 3, and 8 may have contributed to initially high plasma ADH levels during IPPV.[8] In addition, changes in position and environmental temperature alter ADH activity.[20] Since patients in respiratory failure receiving prolonged mechanical ventilation have a tendency to develop water retention,[1] water restriction and intermittent administration of diuretic drugs are now common practice. Thus, a contraction in extracellular volume without an alteration in tonicity of body fluids in patients in this study could also contribute to initially high ADH levels.

With the addition of PEEP, significant increases in plasma ADH were observed in seven of the eight patients. Activation of osmoreceptors is unlikely to account for this change, since no consistent or significant alteration in plasma osmolality was observed. Release of ADH may occur as a result of non-osmotic stimuli acting via aortic and carotid baroreceptors sensitive to tension in the left atrium and great pulmonary veins. Institution of PEEP led to a decrease in cardiac output and an increase in mean airway pressure. Thus, the increase in plasma ADH following the use of PEEP could be the result of stimulation of baroreceptor as well as volume receptor mechanisms.

Conclusions

In this study, a variety of stimuli resulted in initially high plasma ADH levels, but in none of these patients were clinical features of "syndrome of inappropriate ADH secretion" present. Patients 6 and 8 had positive free-water clearance despite high initial ADH levels, thus suggesting a decreased renal response to ADH. A failure to demonstrate a significant increase in urinary osmolality or a consistent change in free-water clearance with addition of PEEP to IPPV leads us to conclude that the increase in plasma ADH and the decrease in urinary flow are unrelated. A concurrent reduction in urinary sodium excretion points to an overriding influence of the decrease in cardiac index on renal function. It is possible that the ADH system was disabled because of certain nonspecific stimuli, other neurohormonal control mechanisms, altered state of hydration, sustained high levels of plasma ADH, and functional or organic disorders of the renal tubules in these critically ill patients. This explains the inappropriate response to plasma ADH in terms of urinary flow, urinary osmolality and free-water clearance during IPPV as well as following institution of PEEP.

This is a short-term study, and whether

these changes persist needs to be investigated. The oft-assumed "inappropriate ADH secretion" as a source of water retention in critically ill patients who need mechanical ventilation does not receive support from our study. Conclusions as to the mechanism of handling of water and electrolytes by critically ill patients cannot be drawn in the absence of measurements of renal blood flow. This is particularly important in view of the fact that substantial alterations in cardiac index can occur with changes in ventilatory pattern despite the absence of a change in mean arterial blood pressure or pulse rate.[5-12]

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