Experimental inappropriate ADH secretion caused by positive-pressure respirators

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A laboratory model was developed for studying antidiuretic hormone (ADH) secretion during mechanical respiratory assist of paralyzed rats. Inappropriate ADH secretion occurred during the use of positive-pressure respirators but did not occur when negative-pressure respirators were used.

Key Words • respirator • vasopressin • inappropriate ADH secretion • rats

The clinical syndrome of inappropriate antidiuretic hormone secretion (SIADHS), first described by Schwartz, et al., in 1957, has been associated with numerous causative factors that include head injury, polyneuropathy, various neoplasms, and general anesthesia. Recently, Sladen, et al., reported water retention secondary to SIADHS in patients receiving prolonged positive-pressure ventilation. It was suggested by these authors that mechanical ventilators may decrease central venous blood volume, activate stretch receptors in the atria of the heart, and trigger the reflex release of antidiuretic hormone (ADH).

Previous laboratory studies concerned with SIADHS have yielded controversial results. In the dog and in the rat, positive-pressure ventilators have been associated with inappropriate ADH secretion. Recent work has questioned the role of positive-pressure respirators, as a diuresis, and measurably less plasma ADH has been noted when the end expiratory pressure is maintained at zero. Further investigation has related the mechanism of ADH secretion to changes in blood carbon dioxide.

The experiments we are reporting used paralyzed rats and were designed to compare positive-pressure ventilators to negative-pressure ventilators in the production of SIADHS.

Method

Respirators

Two types of rat respiratory devices were used, and ADH secretion was studied during their use. A Harvard rodent respirator (No. 680), similar to volume respirators used in clinical medicine, was selected to inspire curare-paralyzed rats in Group 1 (20 rats). In Group 2 (20 rats), the animals were similarly paralyzed but maintained on a specially constructed tank-type negative-pressure respirator, somewhat similar to the Drinker respirator.

To contrast the mechanical effects of the two types of respirators, selected individual rats were switched between respirators after catheters had been placed in the right heart, aorta, and pleural cavity. Continuous pressure recordings were obtained with each type of ventilator as well as during spontaneous respiration. These recordings included blood
Inappropriate ADH due to positive-pressure respirator

Fig. 1. Experimental model. \( R = \) positive pressure respirator; \( TC = \) temperature controller; \( O = \) dual beam oscilloscope; \( IP = \) infusion pump; \( S = \) Phipps bird switch; \( V = \) vacuum; \( CC = \) cooling coil; \( U = \) urine; \( Air = \) air pressure source; \( H_2O = \) water source.

pressure, intrapleural pressure, and central venous pressure.

**Positive-Pressure vs Negative-Pressure Respiration**

Litter mate 300-gm male albino rats were matched for weight, fasted overnight, and then lightly anesthetized with ether for a maximum duration of 10 min. While anesthetized, an external catheter was placed for urine collection, a gastric tube for continuous fluid maintenance, and a tracheostomy performed. The anesthetic was then discontinued, and D-tubocurarine-chloride pentahydrate (curare) was given intramuscularly, and in Group 1, the rats were connected to the Harvard positive-pressure respirator via tracheostomy tube. In Group 2, the animals were placed within a cylindrical tank and the tracheostomy tube led to atmosphere through an outlet in the side of the tank.

In both groups of animals the fluid intake was controlled at 6 cc of 5% D/W per hour by means of a Harvard syringe infusion pump (No. 975); EKG's were monitored with a Tektronix dual-beam oscilloscope; temperature was maintained at 37° by a YSI 73TA temperature controller that regulated a heat lamp and a cooling coil; end-expiratory CO₂ was maintained at 3% by varying the respiratory rate and excursion; and all urine was collected for the 6-hour duration of the experiment (Fig. 1). At the conclusion of the experiment the animals were sacrificed, the blood collected for plasma studies, and the pituitary glands removed for vasopressin assay.

These two groups of 40 rats were compared for urine osmolality and electrolytes, plasma osmolality and electrolytes, total body weight change, brain water, and vasopressin remaining in pituitary glands. Osmolarities were determined by an Advanced freezing point osmometer, electrolytes by a flame photometer, and brain water was calculated from brain weights before and after oven dehydration at 60°C. End-expiratory CO₂ levels were determined with a Beckman infrared gas analyzer. A modification of De-
All data were subjected to statistical analysis with T-tests and probability determined for significant differences between the groups and controls.

Results

Respirators

The mechanical differences between the positive-pressure ventilator and negative-pressure ventilator can be seen in Fig. 2. During spontaneous respiration, pleural pressure measures -5 to -10 cm of water. During negative-pressure ventilation, pleural pressure is generally on the negative scale, measuring between +2 and -10 cm of water. During positive-pressure ventilation, however, pleural pressure is abnormally positive, varying between +5 and +10 cm of water.

Central venous pressure during spontaneous respiration and negative-pressure ventilation are approximately 5 cm of water. During positive-pressure respiration, however, central venous pressure is abnormally elevated to 15 cm of water.

Positive-Pressure vs Negative-Pressure

As shown in Table 1, positive-pressure respiration (Group 1) caused an increase in urine osmolality and sodium, a decrease in plasma osmolality and sodium, an increase in body weight, and an increase in brain water. All of these measurements are consistent with the diagnosis of SIADHS. Moreover, the amount of ADH within the pituitaries of these animals after death was measurably less than that in the control animals, thus providing direct evidence that ADH was released during positive-pressure ventilation.

In contrast, negative-pressure respirators (Group 2) caused a slight decrease in urine osmolality and sodium, no change in plasma osmolality and sodium, a decrease in body weight, and no change in brain water. The amount of ADH found in the pituitaries of these animals was no different from that in the control animals.

ADH Injections

In animals given vasopressin during negative-pressure ventilation, there was an increase in body weight, an increase in urine osmolality and sodium, and a decrease in

Statistical Analysis

Fro. 2. Pressure recordings in Rat 24A.
Inappropriate ADH due to positive-pressure respirator

TABLE 1
Results of positive- and negative-pressure ventilation

<table>
<thead>
<tr>
<th>Physiological Parameters</th>
<th>Control (10 rats)</th>
<th>Group 1 (20 rats)</th>
<th>Group 2 (20 rats)</th>
<th>P* Control and Group 1</th>
<th>P Group 2 and Group 2</th>
<th>P Group 1 and Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>plasma:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>osmolality (mOsm/kg)</td>
<td>307 ± 2</td>
<td>277 ± 7</td>
<td>304 ± 13</td>
<td>&lt; .001</td>
<td>NS†</td>
<td>&lt; .1</td>
</tr>
<tr>
<td>sodium (mEq/L)</td>
<td>136 ± 1</td>
<td>125 ± 1.6</td>
<td>136 ± 1</td>
<td>&lt; .001</td>
<td>NS</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>urine:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>osmolality (mOsm/kg)</td>
<td>291 ± 32</td>
<td>523 ± 60</td>
<td>228 ± 30</td>
<td>&lt; .01</td>
<td>&lt; .01</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>sodium (mEq/L)</td>
<td>11 ± 1.7</td>
<td>17 ± 3</td>
<td>7 ± 1</td>
<td>&lt; .10</td>
<td>&lt; .10</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>brain water: (%)</td>
<td>78.01 ± .09</td>
<td>78.42 ± 1</td>
<td>77.93 ± 1</td>
<td>&lt; .02</td>
<td>NS</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>weight gain: (gm)</td>
<td>-0-</td>
<td>+19 ± 2</td>
<td>-8 ± 2</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>pituitary ADH: (milliunits)</td>
<td>512 ± 57</td>
<td>299 ± 24</td>
<td>-16 ± 1</td>
<td>&lt; .01</td>
<td>NS</td>
<td>&lt; .01</td>
</tr>
</tbody>
</table>

* P = significance of difference of means.
† NS = not significant.

plasma sodium (Table 2). These changes mirror the changes seen in animals maintained on positive-pressure ventilation and lend indirect evidence to the thesis that the measured alterations seen with positive-pressure ventilation were caused by inappropriate ADH secretion.

Brattleboro Rats

The Brattleboro rats, genetically unable to secrete ADH, did not show any of the weight changes or alterations in urine and blood that were seen in Group 1 animals despite maintenance on positive-pressure ventilators (Table 2). The absence of change in these animals suggests that a normal ADH-secreting pituitary is necessary for the development of SIADHS and again supports the thesis that positive-pressure respirators cause fluid and electrolyte shifts by virtue of ADH release, not from other alterations in cardiac output, renal flow, etc.

Water Restriction

It is emphasized that no changes occurred in positive-pressure rats unless the animals

TABLE 2
Results of additional studies

<table>
<thead>
<tr>
<th>Physiological Parameters</th>
<th>Control (10 rats)</th>
<th>Brattleboro Rats (6 rats)</th>
<th>P* Control and Bratt.</th>
<th>P Group 2 and Bratt.</th>
<th>ADH-Injected Rats (8 rats)</th>
<th>P Control and ADH-Injected</th>
<th>P Group 1 and ADH-Injected</th>
</tr>
</thead>
<tbody>
<tr>
<td>plasma sodium (mEq/L)</td>
<td>136 ± 1</td>
<td>136 ± 1</td>
<td>NS†</td>
<td>NS</td>
<td>125 ± 2</td>
<td>&lt; .001</td>
<td>NS</td>
</tr>
<tr>
<td>urine sodium (mEq/L)</td>
<td>11 ± 1.7</td>
<td>4 ± 1</td>
<td>&lt; .01</td>
<td>&lt; .20</td>
<td>20 ± 3</td>
<td>&lt; .02</td>
<td>NS</td>
</tr>
<tr>
<td>urine osmolality (mOsm/kg)</td>
<td>291 ± 32</td>
<td>195 ± 30</td>
<td>&lt; .05</td>
<td>NS</td>
<td>647 ± 76</td>
<td>&lt; .001</td>
<td>NS</td>
</tr>
<tr>
<td>weight gain (gm)</td>
<td>-0-</td>
<td>-2 ± 1</td>
<td>&lt; .10</td>
<td>&lt; .01</td>
<td>+16 ± 1</td>
<td>&lt; .001</td>
<td>NS</td>
</tr>
</tbody>
</table>

* P = significance of difference of means.
† NS = not significant.

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were water-loaded. The 15 animals maintained on positive-pressure respirators but with normal fluid intake did not develop the changes of SIADHS.

**Discussion**

The mechanisms for the inappropriate release of vasopressin have not been determined although we suspect volume control mechanisms as identified by Gauer and Henry. Stretch receptors in the left atrium are activated upon relaxation; the relatively empty left atrium seen in shock or hypovolemia triggers the activity of these receptors. Conversely, the full or stretched left atrium seen in congestive failure or hypervolemia stays the activity of these receptors. Information from these receptors is conveyed, presumably by the vagus, to the brain stem and eventually to the hypothalamus. The reflex arc ends in the posterior pituitary where ADH is released into the systemic circulation. Share has summarized the extensive and, at times, controversial research that has identified this reflex arc.

During positive-pressure respiration, venous pressure is elevated in an unphysiological manner and the left atrium is presumably more empty. It must be emphasized that the elevated venous pressure is a consequence of the elevated intrapleural pressure and the left atrium is probably smaller despite the elevated central venous pressure. In this setting the stretch receptors are activated, as they might be during shock or hypovolemia, and thus the SIADHS begins.

We have attempted to relate ADH secretion to the mechanical differences between the respirators tested. Therefore, the variable in our initial experimental design was limited to the use of either a positive or a negative-pressure respirator. Age, sex, weight, anesthetics, surgical procedures, drugs, hydration, temperature, end expiratory CO2, and the period of respiratory assist were all controlled identically for both test groups. Variations in any of these factors could possibly alter ADH secretion and obscure the vasopressin's relationship to the use of a respiratory assist device.

Our findings show that inappropriate ADH secretion results from positive-pressure respirators but not from negative-pressure devices. The development of similar fluid and electrolyte shifts with ADH injection during negative-pressure ventilation and the lack of fluid and electrolyte shifts in the Brattleboro rats during positive-pressure ventilation are further substantiating evidence that inappropriate ADH release underlies the fluid and electrolyte shifts noted during positive-pressure respiration.

It would be preferable to measure the amount of circulating ADH during the course of these experiments. This is not feasible for several reasons: blood removal is a potent stimulus to ADH release; ADH has a short biological half-life (from 2 to 8 min) and the amount of ADH circulating in the blood (1 to 6 microunits per mL) is difficult to assay with dependable accuracy.

Accordingly, we chose to measure the amount of ADH remaining in the pituitary at the end of the experiment. This avoids the problem of blood removal, variation in blood levels, and above all, permits bioassay in the 350,000 to 530,000 microunit range rather than the 1 to 6 microunit range of plasma.

The finding of ADH depletion in the pituitary only after positive-pressure ventilation is perhaps the most convincing evidence that the fluid and electrolyte changes result directly from ADH release.

The lack of SIADHS during negative-pressure ventilation implies that this type of mechanical ventilation is more physiological. The early measurements by Maloney and Whittenberger revealed no pressure differences between positive and negative-pressure devices. Our respirators produced dramatic differences in intrapleural pressure and central venous pressure (Fig. 2). Perhaps the variation between the observations of Maloney and Whittenberger and our own reflects basic engineering differences in the respiratory devices as well as physiological differences in the test animals.

There are basic differences between the tank respirator used in this experiment and the tank respirator originally developed by Drinker and Shaw. Our tank respirator has no constricting cuff about the neck which all tank models in current clinical use do have; this cuff partially obstructs venous blood return from the head which may affect ADH
Inappropriate ADH due to positive-pressure respirator

secretion. Cuirass devices are no exception as they constrict a patient’s trunk with essentially the same effect.

We observed no reduction in blood pressure during the use of either respirator; this differs from the findings of Tarak and Chaudhury. Rather, after 4 hours of use there appeared a relative hypertension during the use of each. This laboratory finding is similar to the clinical finding of McDowell and Plum who noted hypertension in patients with acute anterior poliomyelitis, especially in those requiring respirator therapy.

Summary

In paralyzed rats maintained on a positive-pressure ventilator and given a water-load, the syndrome of inappropriate antidiuretic hormone secretion (SIADHS) occurs.

In paralyzed rats maintained on a negative-pressure ventilator and given a water-load, SIADHS does not develop.

If paralyzed rats are maintained on the positive-pressure ventilator, but given a normal amount of fluid, SIADHS does not develop.

Brattleboro rats, congenitally unable to produce ADH, maintain a normal pattern of fluid and electrolyte balance despite positive-pressure ventilation and waterloading.

We feel that the syndrome of inappropriate ADH secretion during mechanical ventilation occurs more often than is generally recognized. The results of these experiments do not justify alterations in the type of respiratory assist devices used in clinical medicine, yet do justify greater attention directed toward the recognition and treatment of SIADHS during mechanical ventilation.

References


2. Baratz RA, Philbin DM, Patterson RW: Urinary output and plasma levels of antidiuretic hormone during intermittent positive-pressure breathing in the dog. Anesthesiology 32:17-22, 1970


13. Share L: Rate of disappearance of arginine vasopressin from circulating blood in the dog. Amer J Physiol 204:1179-1181, 1962


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