The Effect of Carbon Dioxide on Plasma Antidiuretic Hormone Levels during Intermittent Positive-pressure Breathing

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Spontaneously breathing dogs on intermittent positive-pressure breathing (IPPB) had measurable decreases in plasma levels of antidiuretic hormone (ADH), with ensuing diuresis. The hypothesis that alteration in ADH secretion resulted from IPPB-induced changes in Pa_{CO_2} was investigated. During constant hyperventilation, plasma ADH, urinary output, cardiac output (CO) and blood gas determinations were made as Pa_{CO_2} was altered by addition or subtraction of carbon dioxide in inspiratory gas. Hyperventilation to Pa_{CO_2} 19 mm Hg produced an increase in the flow of urine. Addition of CO_2 to match control conditions decreased urinary flow. Further increases in the CO_2 concentration in the airway increased plasma ADH concentration, accompanied by oliguria. When CO_2 administration was discontinued, Pa_{CO_2} reverted to 18 mm Hg, and was accompanied by a 66 per cent decrease in ADH levels and diuresis. Therefore, plasma ADH levels and urinary flow are related to Pa_{CO_2} rather than to IPPB. (Key words: Carbon dioxide; Antidiuretic hormone; Urinary output; Intermittent positive pressure breathing.)

STIMULATION OF STRETCH RECEPTORS in the left atrium, causing the release of antidiuretic hormone (ADH) from the hypothalamico–hypophyseal tract, has been considered to be the mechanism of suppression of renal function during positive-pressure breathing observed by several investigators.[1, 2, 3] However, studies in the dog [4] and in man [5] have demonstrated that if the end-expiratory pressure is zero, intermittent positive-pressure breathing (IPPB) is associated with low plasma ADH levels and diuresis. Therefore, IPPB, under these conditions, does not stimulate the left atrial receptor mechanism. There are, however, several other physiologic changes brought about by hyperventilation which could afford explanations for diuresis during IPPB. The present investigation was undertaken to see if plasma ADH concentration and renal function are affected by one such ventilation-dependent change, alteration in Pa_{CO_2}.

Methods

Six female mongrel dogs, weighing between 13.6 and 19 kg were anesthetized with intravenous sodium pentobarbital (Nembutal). The initial dose was 50 mg/kg. The trachea was intubated with a wide-bore endotracheal tube and the cuff inflated to a gas-tight fit. Halothane, 0.5 per cent, subsequently was administered via a Copper Kettle, with room air as the carrier. Inspired halothane concentration was monitored continuously by means of an A.S.C. Fluothane monitor and end-tidal CO_2 concentration by an infrared CO_2 analyzer (Beckman Model LB-4).

The tip of a cardiac catheter was introduced through the jugular vein into the right ventricle or pulmonary artery (as indicated by the pulse-pressure contour). An indwelling teflon catheter was placed in the femoral artery. These were connected to Statham PR-23-2D-300 transducers and a direct-writing recorder (Electronics for Medicine, Inc.) for continuous monitoring of pressures. Arterial and mixed venous blood samples were obtained from the same catheters. Blood gases were analyzed with a modified Clark O_2 electrode (Model 133, Instrumentation Laboratory, Boston, Mass.) and with a Severinghaus electrode for P_{CO_2} at 37 C. Blood *p*H was

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TABLE 1. Cardiorespiratory and Renal Data*

	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6
Urinary flow (ml/min)	3.51±1.3	3.58±1.4	4.93±1.4	3.73±0.9	2.68±0.7	4.30±1.1
Plasma ADH (μU/ml)	11.8±3.9	14.8±3.5	9.8±3.5	8.3±3.3	23.8±4.5	8.0±4.5
Cardiac output (l/min)	3.9±0.4	4.0±0.4	3.2±0.2	3.5±0.3	4.2±0.5	2.6±0.3
Pa_{O_2} (mm Hg)	77.3±3.7	77.9±1.3	78.0±5.4	106.7±5.4	118.6±4.0	83.3±6.3
Pa_{CO_2} (mm Hg)	43.7±3.2	40.9±2.7	18.6±1.4	38.8±1.7	59.8±1.9	17.9±1.2
*p*H	7.36±0.03	7.37±0.03	7.67±0.03	7.36±0.02	7.21±0.03	7.66±0.03

* Mean ± SE.

measured with an Instrumentation Laboratory *p*H meter. Blood P_{O_2} was corrected for membrane blood–gas differences by tonometry at 37 C.

Cardiac output (CO) was measured using the standard dye-dilution technique with indocyanine green and a Beckman recording densitometer. The densitometer was calibrated with samples of each dog's blood containing a known amount of dye. The dye was injected through the venous catheter and densitometer sampling done from the catheter in the femoral artery.

Following a period of measurement during spontaneous respiration, each dog was connected to a volume-controlled ventilator (Ohio) with a one-way valve to eliminate rebreathing. Tidal volume of the ventilator was adjusted so that end-tidal CO_2 ($F_{ET_{CO_2}}$) corresponded to that during spontaneous respiration. In subsequent periods, tidal volume was increased so that the $F_{ET_{CO_2}}$ was approximately half the original value. This tidal volume was maintained throughout the study.

The dogs were hydrated intravenously with 25 ml/kg/hr of lactated Ringer's solution until a urinary flow of at least 2 ml/kg/min was obtained; then, the infusion was continued at a rate of 15 ml/kg/hr. Urine was collected continuously from an indwelling bladder catheter. At the end of each period of collection, the bladder was evacuated by aspiration and 10 ml of air. Plasma osmolality and urinary osmolality were measured by freezing-point depression in an Advanced Osmometer and osmolal (C_{osm}) and free water clearance (C_{H_2O}) values were calculated. Plasma levels of antidiuretic hormones were determined as described by Yoshida,[6] using a four-point assay for each sample.

After a stable urinary output had been achieved, measurements were made during six periods, as follows:

Period 1. Spontaneous respiration, $F_{ET_{CO_2}}$ approximately 4 per cent.

Period 2. IPPB, maintaining $F_{ET_{CO_2}}$ at 4 per cent.

Period 3. IPPB increased, $F_{ET_{CO_2}}$ approximately half that in period 2.

Period 4. IPPB as in period 3, but with addition of CO_2 to maintain $F_{ET_{CO_2}}$ at 4 per cent.

Period 5. IPPB as in period 3, but with addition of CO_2 to maintain $F_{ET_{CO_2}}$ at 8 per cent.

Period 6. IPPB as in period 3, with $F_{ET_{CO_2}}$ approximately half that in period 2.

All periods were 30 minutes long. Measurements were made during the second 15 minutes of each period.

Results

The cardiorespiratory and renal data are listed in table 1. There was little difference between the values in periods 1 and 2, indicating a close adjustment of IPPB to spontaneous ventilation. During period 3, Pa_{CO_2} decreased by 50 per cent following the increase in minute ventilation. Cardiac output mirrored Pa_{CO_2} changes throughout the study. There was a decrease in plasma ADH levels with the institution of hyperventilation during period 3. Average urinary outflow increased to 4.9 ml/min, an increase of 38 per cent over the previous period.

Minute ventilation was not changed during the remaining 90 minutes of the study. During period 4, $F_{ET_{CO_2}}$ and Pa_{CO_2} were increased

to control levels by addition of 4–6 per cent CO_2 to the inspired gas. This produced a decrease in urinary flow and an increase in CO similar to the values obtained during the control period, demonstrating that the changes were not due to the mechanics of IPPB or hyperventilation, except insofar as Pa_{CO_2} was altered. Increasing inspired CO_2 to above 6 per cent (period 5) led to a rise in Pa_{CO_2} to 60 mm Hg, and increased plasma ADH to 102 per cent above the control value, with oliguria. Free-water clearance declined from -0.77 ± 0.5 ml/min in period 4 to -1.16 ± 0.4 in period 5. Ventilation with room air during the sixth and final period, with the CO_2 washout, led to a decrease in plasma ADH within 30

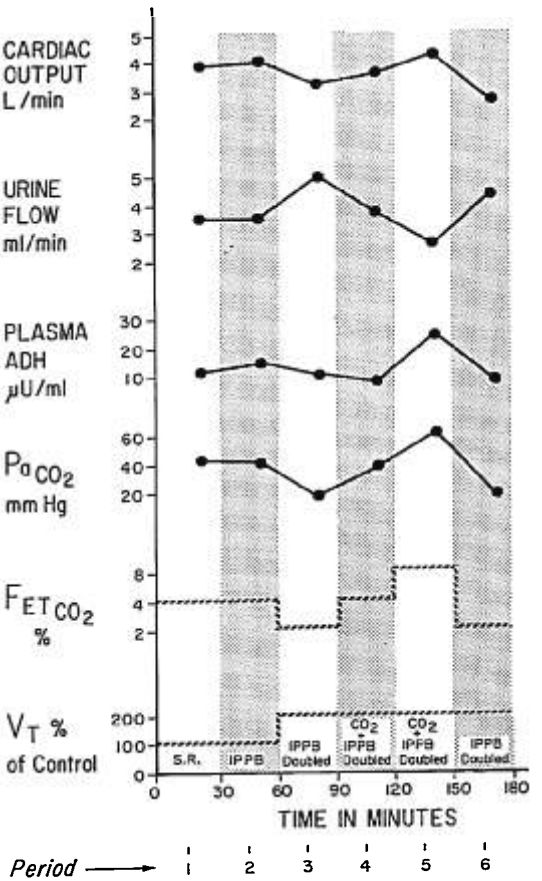

FIG. 1. Relationship of carbon dioxide (Pa_{CO_2} and $F_{ET CO_2}$) to urinary flow (ml/min), plasma ADH (μU/ml) and cardiac output (l/min). Points plotted represent mean values.

minutes, accompanied by massive diuresis. There were no significant changes in plasma osmolality during the period of the study.

Figure 1 summarizes the variables studied. The points plotted represent mean values for six dogs. Urinary flow exhibited an inverse relationship to Pa_{CO_2} throughout the six periods. Cardiac output, to some degree, varies directly with Pa_{CO_2}, as previously demonstrated.[7] Plasma ADH levels rose significantly in period 5 with the addition of approximately 6 per cent F_{ICO_2}.

Discussion

Most of the previous work on fluid exchange in anesthetized animals has been done using as the anesthetic chloralose, a drug shown to have no apparent inhibitory effect on water diuresis or renal hemodynamics.[8] In the present study, the dogs were anesthetized with sodium pentobarbital, then maintained on 0.4–0.5 per cent halothane in room air for the remainder of the experiment, which lasted as long as six hours. Inasmuch as there was no difference between the effects of hyperventilation on plasma ADH levels and urinary output during this series with halothane and the effects of hyperventilation in the previous series with chloralose,[4] we conclude that halothane has no specific effect on the release of ADH from the posterior hypophysis. This is in agreement with the work of Moran *et al.*,[9] who have also shown that halothane in man does not stimulate the release of ADH. On the contrary, Christoforo and Brody[10] have suggested that halothane may be important in controlling peripheral vasoconstriction through the release of vasopressin. However, as Price[11] points out, this is unlikely, considering that the levels of vasopressin needed to produce vasoconstriction are much higher than that needed to produce selective reabsorption of water from the distal nephron.

There were no significant changes in urinary output or plasma ADH levels when IPPB was adjusted to maintain $F_{ET_{CO_2}}$ and Pa_{CO_2} at approximately the same levels as those found during spontaneous ventilation. However, when the tidal volume was increased to reduce Pa_{CO_2} to half of control values, plasma ADH decreased and urinary output increased. As this increase in V_T has been shown to have minimal effects on pulmonary mechanics and pulmonary arterial pressure, other ventilation-dependent changes were sought to explain the results obtained. Thus, the effects of changes in Pa_{CO_2} on renal function were studied. It was apparent in each experiment that the addition of significant amounts of CO_2 to inspired air consistently produced increases in plasma ADH and decreases in urinary output. The accompanying decline in free-water clearance during period 5 reflected the role of the elevated ADH. Removal of the CO_2 just as readily improved urinary output, with a concomitant decrease in plasma ADH. There were no significant changes in plasma osmolality, indicating that osmoreceptors did not play a role in changes in urinary output.

During period 5, when the Pa_{CO_2} was elevated, cardiac output was also high, in agreement with the reports of Prys-Roberts *et al.*[7] Therefore, it appears that changes in renal or cerebral perfusion are not contributory, because with cardiac output high the urinary output was decreased and plasma ADH elevated. Elimination of the CO_2 in period 6 brought about abrupt declines in both CO and plasma ADH, but urinary output rose significantly.

The regulation of water excretion and formation of urine is the function of a complex system involving stimuli from reflex arcs as well as humoral factors. Thus, differing conditions may produce the same end-result, whether oliguria or diuresis. For instance, Barbour *et al.*[12] measured renal function in awake recumbent men breathing 5–7 per cent CO_2. They observed diuresis which could be nullified by change in position, such as sitting up. Subsequently, Valtin *et al.*[13] found a similar diuretic response to CO_2 but could not relate the diuresis to left atrial stretch receptor mechanism. Neither study attempted to quantitate plasma ADH levels; therefore, the receptor site for the induced CO_2 diuresis was not evident.

In the present experiments, in dorsally recumbent hydrated dogs, addition of CO_2 to the inspired gas mixture produced an increase in plasma ADH levels and an accompanying

antidiuresis. While antidiuretic hormone secretion appears to be the result of an efferent limb of a reflex arc, the afferent limb still is not clearly defined. There may be peripheral receptors responding to the elevated Pa_{CO_2} or accompanying *p*H changes, or a direct central effect resulting in the release of ADH. Changes in Pa_{CO_2} are known to affect renal blood flow and glomerular filtration directly, and possibly reflexly, via sympathetic stimulation, but our data indicate that in these studies ADH plays the dominant role.

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Surgery

HYPERPYREXIA Sudden unexplained hyperpyrexia during general anesthesia is often fatal. In some instances there is associated tonic contraction of the musculature. The evidence suggests that muscle rigidity, tonic muscle contractions, and abnormal posturing are the result rather than the cause of the hyperthermia. They are common findings in heat stroke. It is essential to monitor the temperatures of patients continuously during anesthesia. (*Thomford, N. R., and others: Sudden Hyperpyrexia during General Anesthesia, Surgery 66: 850 (Nov.) 1969.*)

HEAD INJURIES Patients with acute hematomas ordinarily require little or no anesthesia, but an endotracheal tube must be inserted and an anesthetist must be present throughout the procedure to monitor vital functions, maintain respiratory exchange, and regulate fluid administration. For the cooperative patient with chronic subdural hematoma, local infiltration anesthesia may be adequate, but general anesthesia is necessary for the confused or anxious patient. (*Craigmile, T. K.: Operative Treatment of Acute Craniocerebral Injuries, Surg. Clin. N. Amer. 49: 1425 (Dec.) 1969.*)