Studies of the Mechanism of Antidiuretic Hormone Secretion and the Post-Commissurotomy Dilutional Syndrome *

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PREVIOUS STUDIES in our laboratory have dealt with the hormonal mechanisms responsible for alterations in water balance in surgical patients. Recently the development of a highly sensitive method for the estimation of antidiuretic hormone (ADH) in whole blood made it possible to study changes in the circulating level of ADH at frequent intervals and to demonstrate that operative procedures caused rapid elevations to concentrations many times that of the preoperative base line.[14-16] Depending upon the magnitude of the surgical procedure, these levels remained elevated from 2 to 5 days following operation and could be correlated with changes in water balance. Thus, hypersecretion of ADH provided a logical explanation for the intolerance of surgical patients to the administration of excessive amounts of hypotonic solutions and for the occasional occurrence of "postoperative water intoxication."[24] The studies referred to demonstrated that certain aspects of the operative procedure could be correlated closely with an abrupt increase in blood ADH levels. These factors included tissue trauma, visceral manipulation and abrupt changes in hemodynamic equilibrium occurring with hemorrhage or total cardiopulmonary bypass. Subsequent studies have been directed toward the elucidation of mechanisms by which these stimuli effect ADH secretion.

Cardiac volume receptors have been of interest because of their presumed role in the regulation of extracellular fluid volume[7] and their possible association with the occurrence of water retention and hyponatremia in patients whose hemodynamics have been altered suddenly by the reopening of a strictured mitral valve.[8, 23] D'Angelo *et al.*[5] postulated that "post-commissurotomy hyponatremia" was the result of an excessive secretion of ADH secondary to the acute reduction of left atrial pressure. They cited the work of Henry, Gauer and Reeves[10]—who had reported that inflation of a balloon within the left atrium of dogs would produce a diuresis—as evidence for the existence of atrial receptors capable of influencing renal water excretion. Baisset and Montastruc[2] obtained plasma samples for ADH assay prior to and once during each inflation of the balloon and concluded that the 50 per cent reduction in plasma antidiuretic activity observed during inflation was responsible for the diuresis. However, Ledsome *et al.*[12] questioned the role of ADH in production of this reflex since they were unable to abolish the diuresis by the infusion of Pitressin. Arndt, Reineck and Gauer[1] dem-

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onstrated changes in inulin and p-aminohippurate clearance as well as free water clearance and concluded that both hormonal and renal hemodynamic factors were responsible for the diuresis. Lydtin and Hamilton[13] reported that the atrial reflex was active in chronically prepared animals and that Pitressin infusion could modify the diuresis in prehydrated dogs.

In order to clarify the role of atrial receptors in the regulation of ADH secretion, frequent blood levels of ADH were obtained prior to and during the inflation of the left atrial balloon as well as following its deflation. This was made possible by the development in this laboratory of an extremely sensitive method which could be applied to frequent small samples.[14-16] ADH levels were also obtained in a second series of experiments in which acute mitral stenosis was produced by tightening of an annular ligature.

Methods

Female mongrel dogs (10–20 Kg.) were premedicated with 15 mg. of morphine and anesthetized with an intravenous dose of 8 to 10 ml./Kg. of 1 per cent chloralose in 0.6 per cent sodium chloride solution. Hydration and light anesthesia were maintained by infusion of 3 ml./Kg./hr. of the chloralose-saline solution throughout the entire experiment. In two dogs (6 and 30), nembutal was substituted for chloralose. Prior to thoracotomy an endotracheal tube was inserted and connected to a mechanical positive pressure respirator. An atrial balloon was inserted in nine dogs according to the technic of Reeves *et al.*[19] The chest wall was closed, air was aspirated through a chest tube which was subsequently clamped, and the mechanical respirator was detached from the endotracheal tube. Bilateral cervical vagotomy was performed in two of these animals following placement of the atrial balloon.

In three dogs, acute mitral stenosis was produced by placing a heavy silk ligature around the annulus of the mitral valve as described by Ellison *et al.*[6] The ends of the purse strings were brought through the chest wall through a Teflon cannula so that constriction of the mitral valve could be achieved externally after the chest was closed. Care was taken to avoid the orifice of the inferior vena cava and aortic valve during this procedure.

In all experiments, plastic catheters had been placed into the left femoral artery and left atrium in order to monitor continuously and record central aortic and left atrial pressures. Catheters had also been placed through both femoral veins for collection of inferior vena cava blood samples, facilitation of blood replacement and administration of fluid. Urine was collected at 5-minute intervals from an indwelling Foley catheter leading to a mechanical fraction collector.

Two or three hours were allowed to elapse between skin closure and the beginning of the experimental procedure. After control blood samples had been withdrawn, the atrial balloon was inflated with enough saline to increase the atrial pressure 15 to 20 cm. of water. Venous sampling was continued throughout the period of inflation and after release of the atrial balloon. The same procedure was followed in the three animals with annular ligatures, except that the periods of atrial hypertension were of shorter duration. Blood losses resulting from sampling were immediately and accurately replaced to avoid the effect of hemorrhage on ADH secretion.

In Dogs 15, 16, 17, 22, 26, 29 and 47, blood and urine analyses were performed for determination of endogenous creatinine, osmolal and free water clearances. Osmolality was determined by freezing point depression with the Fiske osmometer. Creatinine levels were estimated by the Technicon Auto-Analyzer system. Sodium and potassium concentrations were measured with an internal standard flame photometer.

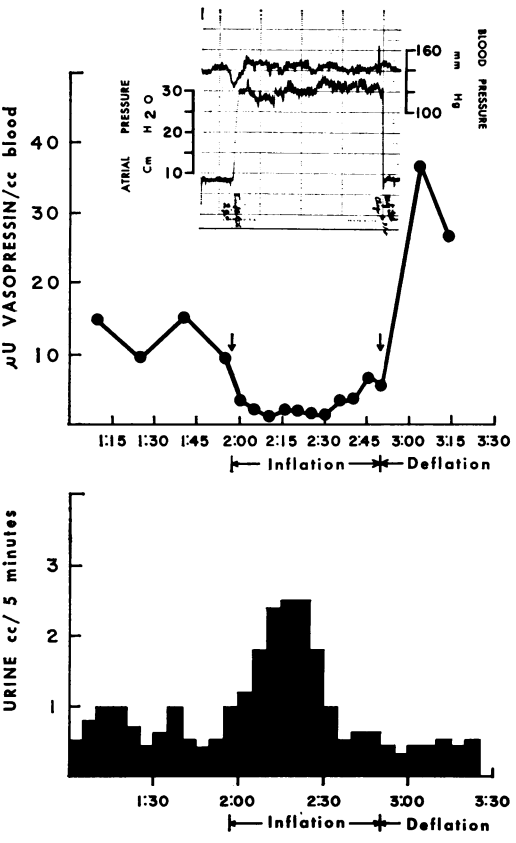

FIG. 1. Portion of experiment on Dog 15 showing effect of inflation and deflation of atrial balloon on blood pressure, atrial pressure, blood ADH and urine flow in Dog 15.

The 10 ml. blood samples obtained from the vena cava for ADH estimations were precipitated with cold trichloracetic acid. The ether-washed supernatant was adsorbed on a column of CG-50 resin (1 cm. in diameter and 1.5 cm. high) at pH 4.5. The antidiuretic peptide was eluted with a solution of 75 per cent ethanol (adjusted to a pH of 2.0 with hydrochloric acid) and brought to dryness in vacuo at 20° C. The residue was redissolved in 1.0 ml. of "injection solution" consisting of 0.2 per cent sodium chloride, 0.0285 per cent acetic acid and 10^{-3}M disodium ethylenediaminetetra-acetate. This sample was diluted further if the resulting ADH concentration exceeded 20.0 μU./200 ul. Assay of antidiuretic activity was carried out in intravenously hydrated ethanolized rats. Constant hydration is maintained by a balance photoelectrically coupled to a balance which supports the assay animal. The logarithm of maximal urine conductance divided by initial urine conductance was used as the response parameter and rate of urine formation was used for verification of antidiuretic activity. For the latter the cumulated urine volume was measured in a glass cylinder with a pressure transducer, the direct current signal from which was led to an on-line analog computer unit to differentiate the volume curve and produce a voltage proportional to the rate of urine flow. Blood ADH concentration was calculated by averaging the activity from four or five 200 μl. doses of sample concentrate which had been compared with standards prepared from U.S.P. Posterior Pituitary Reference Powder. The assay has been described in detail elsewhere.[15, 16]

Normal values obtained with this method in hydrated dogs (serum osmolality = 283–287 mOsm./Kg.) excreting hypotonic urine (55–145 mOsm./Kg.) average 0.14 μU./ml. Average levels of 0.57 μU./ml. are found if these animals excrete hypertonic urine (287–553 mOsm./Kg.).

All computations performed on the data from the bioassay procedures, as well as those relating to the clearance studies, were carried out by programs written in Fortran II for the IBM 1620 digital computer.

Results

One hundred fifty-six blood samples were assayed in conjunction with this experiment. The values are graphically represented along with mean left atrial pressures and urinary flows in Figures 1–4. Table 1 summarizes these results.

To determine the length of time required for ADH to return to reasonable levels before undertaking the experimental procedure, 13 additional blood ADH determinations were obtained at 15-minute

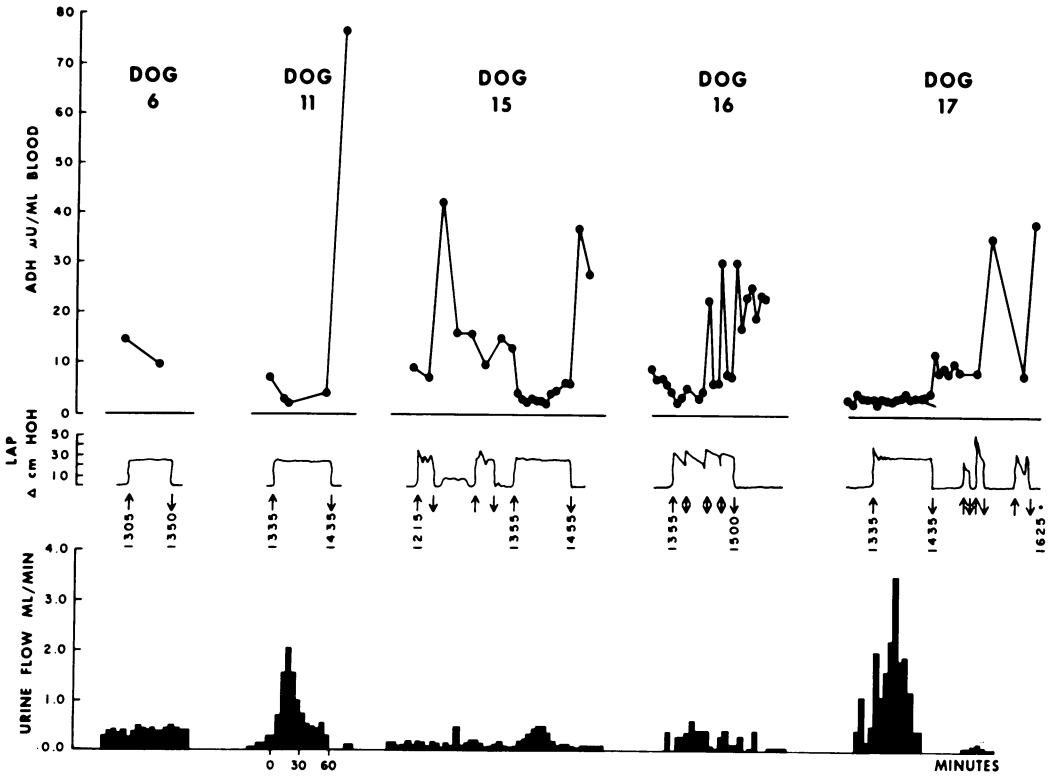

FIG. 2. Effect of inflation (↑) and deflation (↓) of a left atrial balloon on blood antidiuretic hormone (ADH), left atrial pressure (LAP) and urine flow. Dogs 15, 16 and 17 illustrate reversal of hypersecretion caused by reinflation of balloon.

intervals throughout the surgical procedure and early postoperative period in Dog 15.[15] The response was similar to that observed in our studies on surgical patients. A maximum ADH level of 53.0 μU./ml. was reached when the balloon was inserted in the left atrium, and the level gradually declined to 5.1 μU./ml. 40 minutes following skin closure. During the next 45 minutes respiration and left atrial pressure gradually increased, and ADH gradually increased to 69.6 μU./ml. At that time air and blood were aspirated from the chest catheter and a transfusion was given. The ADH level fell to 8.8 μU./ml. within 15 minutes.

Serum osmolality varied from 295 to 304 mOsm./Kg. This degree of dehydration was probably the result of preoperative withholding of food and water. Experimental manipulations of atrial pressure did not affect serum osmolality.

Inflation of Atrial Balloon. Fig. 1 illustrates the typical response to a single inflation and deflation. An increase of 20 cm. of water in atrial pressure was associated with a transient reduction of 10 mm. of Hg in mean arterial pressure. The ADH level started to decrease within 5 minutes, reaching a minimum in 15 to 20 minutes. This was associated with a corresponding increase in urine output. Both ADH and urinary flow started to return to the preinflation level in 30 to 40 minutes, although the atrial pressure was still elevated.

A decrease in blood ADH was observed in each of the 10 inflations for which values were available (range = − 9 to − 88%, mean = − 0.46%) (Fig. 2). Two of these

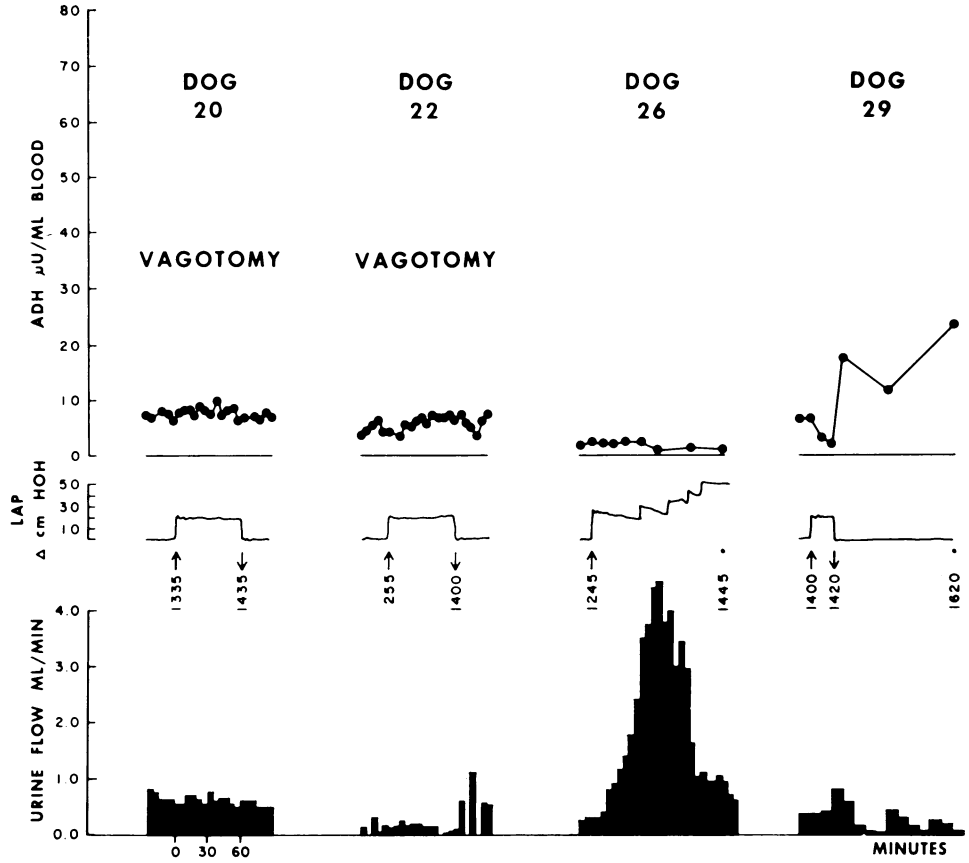

FIG. 3. Vagotomy completely abolishes effect of distention and release of atrial balloon (Dogs 20, 22). Dog 26 illustrates effect of prolonged distention without release. Dog 29 demonstrates that postdeflation hypersecretion lasts for more than 2 hours (see text).

changes (-9% and -10%) in Dog 17 were smaller than the expected coefficient of variation of the analytical technic at their respective levels ($\pm 30\%$ and $\pm 15\%$).

A significant increase in urinary flow was observed in only six of these ten inflations (range = 2 to 15 fold). Minimum ADH levels found during inflation in those whose urinary flow did not significantly increase were 6.6, 6.7, 9.0 and 9.6 μU./ml. The maximum ADH level observed during inflations associated with a significant increase in urinary flow was 2.2 μU./ml.

Clearance data was available for eight of these inflations. Urinary flow was compared to osmolal clearance. Figure 5 is representative of those inflations which were associated with a diuresis. The counterclockwise circling of consecutive points with their return to control base line following deflation was observed in each inflation associated with a significant increase of urinary flow. This behavior is consistent with a diuresis produced by a decrease in ADH.

The period of inflation could be divided into two phases (Fig. 6). During the first 10 to 15 minutes a transient increase in osmolal clearance and the urinary excretion rates of creatinine, sodium and potassium were noted. The urinary flow, osmolal serum/urine ratio and urinary creatinine, sodium and potassium concentration changed very little. There was a transient decrease

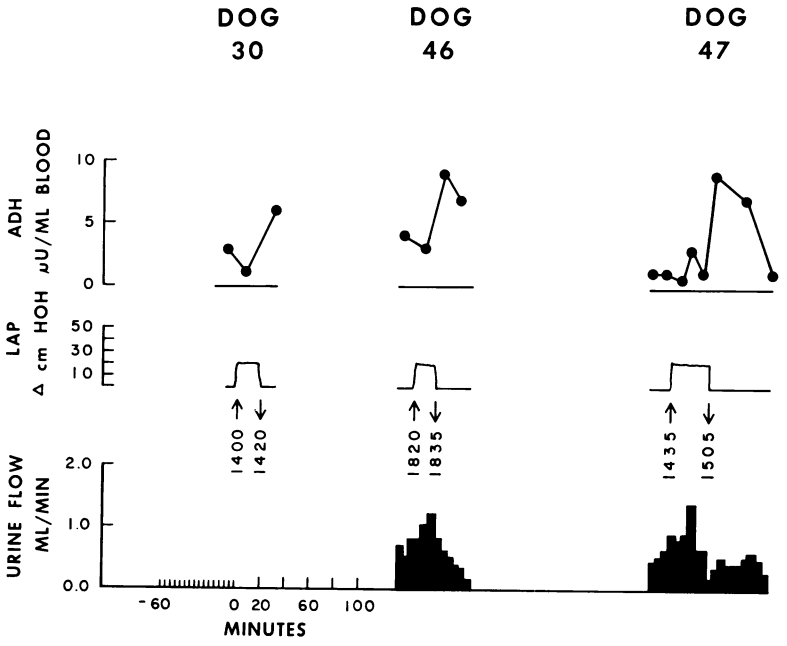

FIG. 4. Effect of mitral stenosis (↑) and release of stenosis (↓) on blood ADH, left atrial pressure (LAP) and urine flow.

in free water clearance. The second period was associated with an increase in osmolal serum/urine ratio, free water clearance and urinary flow; a decrease in solute concentration; and return of solute and creatinine excretion to control levels. After 30 to 40

TABLE 1. *Summary of Changes in Blood ADH Levels and Urinary Flow During Acute Changes in Left Atrial Pressure*

	Control		Tension		Release of Tension	
Dog	Blood μU. ADH/ml.	Urine ml./min.	Blood μU. ADH/ml.	Urine ml./min.	Blood μU. ADH/ml.	Urine ml./min.
6	14.8	0.38	9.6	0.50		
11	6.9	0.30	1.8	2.06	76.3	0.00
15	8.8	0.10	6.6	0.08	42.0	0.04
	15.4	0.16	9.0	0.14	14.8	0.10
	12.6	0.08	1.5	0.50	36.8	0.06
16	3.9	0.20	1.9	0.30	*4.6	0.38
			*2.7	0.60	*22.0	0.40
			*5.0	0.40	*29.7	0.04
			*6.7	0.42	29.4	0.12
17	2.2	0.50	2.0	3.50	11.6	0.00
	8.4	0.00	7.6	0.16	34.9	0.02
			*6.9		37.5	
26	2.6	0.30	1.1	4.50		
29	6.8	0.40	2.2	0.80	17.5	0.03
20 CV	7.4	0.69	8.3	0.62	8.0	0.55
22 CV	5.1	0.15	4.6	0.22	6.0	0.60
30 MS	2.6		1.6		5.6	
46 MS	3.9	0.70	3.5	1.16	7.7	0.28
47 MS	1.6	0.64	1.1	1.36	9.4	0.32

CV = cervical vagotomy; MS = mitral stenosis; * = Secondary inflations.

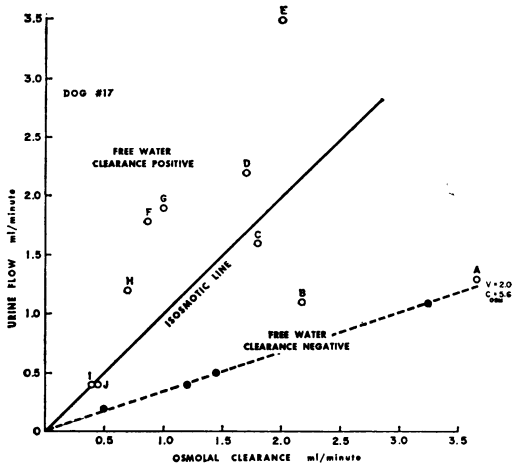

FIG. 5. Relationship between urine flow (V) and osmolal clearance (C_{HOH}) during diuresis induced by inflation of arterial balloon.

Solid points: Control periods.
Open Circles A-J: Successive 5 min. intervals during period of inflation.

minutes the urinary flow, free water clearance and solute concentration began to return toward control levels.

The parallel changes in excretion of these solutes without comparable alterations in solute concentration suggested that the initial phase might be the result of dead space in urinary collecting system. This would not allow changes in solute concentration to reach the test tube in the fraction collector until sometime after transmitted volume changes. The computer program used in the calculation of clearance data was altered and the clearance values recomputed while the urine volume was moved ahead 5 minutes at a time. The transient peak of solute excretion was reduced by this calculation but not eliminated completely, and the possibility remains that the transient increase in solute excretion observed in these experiments may well be an artifact secondary to the dead space of urinary collecting system rather than an index of changes in renal clearance.

Deflation of Atrial Balloon. A 12.4-fold (range = 1.6–42 times base line) increase in blood ADH levels was noted within 5 minutes of the deflation of the atrial balloon (Fig. 1, 2). These levels were 5.3 times the preinflation levels and appeared to be maximal at this time. The urinary output following deflation was from 0 to 75 per cent of preinflation values. The maximum ADH concentration observed during these 8 deflations was 76.3 μU./ml.

The elevated ADH levels following deflation could be suppressed by immediate reinflation as illustrated in Dog 16 (Fig. 2). In this dog the atrial catheter was deflated and immediately reinflated three times in order to compensate for a falling left atrial pressure. There was no elevation of ADH in Dog 26 whose atrial catheter was defective and could not be deflated after several attempts (Fig. 3).

We do not know how long hypersecretion of ADH can persist after release of atrial tension. The longest period in which this was followed with frequent samples obtained in Dog 29 in which the level was still elevated after 2 hours (Fig. 3).

Effect of Vagotomy. Neither inflation nor deflation of the atrial balloon in vagotomized animals induced any significant changes in urinary flow or blood levels of ADH (Fig. 3).

Acute Mitral Stenosis. The desired elevation of 20 cm. of water in mean atrial pressure was achieved readily by acute constriction of the annulus as described above. The mean arterial pressure fell approximately 10 mm. Hg and the pulse rate increased 10 beats per minute. With acute stenosis, the ADH level decreased an average of 26 per cent and the urinary flow doubled from the prestenosis control. Release of stenosis resulted in a 2.2 to 8.5-fold increase over values obtained during stenosis and a 2.0 to 5.9 fold increase over control values. Urinary flow was decreased. The maximum ADH level achieved by release of stenosis was 9.4 μU./ml.

Discussion

Volume Regulation. Acute alterations in left atrial pressure induced changes in the blood antidiuretic hormone levels and parallel adjustments in urine flow. Distension of the left atrium caused a decrease in the ADH activity which was in agreement with the findings of Baisset and Montastruc and an increase in urine flow which was comparable to the findings of Henry *et al.*[10, 11] and Arndt *et al.*[1]

The blood ADH concentrations in the dog before inflation were high as a result of surgical manipulations. This was comparable to the findings in surgical patients.[15] Three patterns of response were seen following inflation. The first was a reduction of ADH from a high to a lower level which was still more than 2.0 μU./ml. This was associated wtih a slight or no change in urine flow. The second response occurred when the drop was to a level lower than 2.0 μU./ml. This in addition to a substantial decrease in ADH caused a brisk increase in urine flow. The third pattern was seen when the ADH level was already low, and a slight decrease in its concentration produced a significant diuresis.

The increase in free water clearance following inflation confirmed the work of Arndt *et al.* and gave further evidence to support the role of ADH in the diuresis which follows distention of the left atrium.[1, 11]

The effect of release of atrial distension on urine flow and blood ADH was unexpected, and the phenomenon would not have been recognized had urine flow alone been measured. After the initial observation, hypersecretion of ADH and reduction of urine flow were observed in every experiment in which the atrial balloon was deflated. In this connection, it is of interest that Baratz and Ingraham [3] found abrupt increase of ADH concentration of comparable magnitude following hemorrhage and positive pressure breathing and that

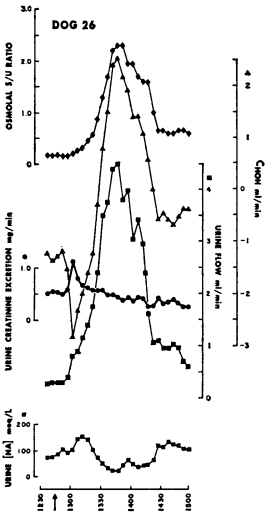

FIG. 6. Effect of inflation of an atrial balloon (↑) on osmolal serum/urine (S/U ratio), sodium and creatinine urine excretion, urine flow, and free water clearance (C_{H_2O}).

Share [21] demonstrated a similar increase following reduction of the extracellular volume by peritoneal lavage with hypertonic solution. Salem *et al.*[20] showed that the elevated blood and urine ADH levels caused by positive pressure were abolished by vagotomy.

The present studies confirm the atrial location of "volume receptors" and demonstrate their importance in the regulation of blood level of ADH and urine flow.[10] Such receptors were found by the histologic and physiologic studies of Coleridge *et al.*[4] to be in the atrio-venous tissues on the right and left sides of the heart. Paintal [17] described two types of receptors—a type B which discharges during stretch and a type A which responds during atrial systole. The type B receptors are apparently sensitive to stretch caused by mechanical distension, negative pressure breathing or isotonic expansion of the extracellular volume.[3, 10] Inhibitory afferent impulses travel along the vagus to the hypothalamic-neurohypophyseal system and cause a drop in ADH level and increase in urine flow.[2, 11] Cooling of the vagus or vagotomy abolishes these impulses.[11, 12] The nature of the hypersecretory response on release of distension deserves further study. It may represent simply cessation of inhibitory impulse.

This has been described by Henry and Pearce [11] to occur following hemorrhage. The possibility exists, however, that this response could be the result of discharge along the vagus from a "Paintal Type A" receptor, and that the mechanism is comparable to that shown by Pearce and Henry [18] to occur following hemorrhage and adrenalin injection. In either case, the vagus carries the impulses and vagotomy prevents the occurrence of any change in ADH level or urine flow following release of distension. Gauer and Henry [7] suggest that the volume receptor might be the first and most sensitive regulatory mechanism to respond to moderate blood loss or redistribution of blood volume, as in erect posture, application of cuffs to the thighs or positive pressure breathing. If hemorrhage is moderate, the atrial receptors are influenced and hypersecretion of ADH occurs. If it is more severe with a seven to ten per cent loss of blood volume, cardiac output is decreased and arterial baroreceptors are stimulated.

Mitral Stenosis. Although experimental mitral stenosis and atrial balloon inflation produced comparable changes in urine flow and ADH level, the effect of the former was less pronounced, presumably because the balloon applied more stretch to the atrial wall than could be achieved by obstruction alone. The fact that release of stenosis was associated with a rise in ADH level has clinical significance in that it simulates the reduction in atrial pressure which follows surgical relief of mitral stenosis. D'Angelo *et al.*[5] reviewed the problem of water and electrolyte disturbances which follow mitral commissurotomy, added five cases to those previously described by the Peter Bent Brigham and Yale groups [8, 23] and reaffirmed the tendency to water retention and oliguria with a resultant dilutional hyponatremia. The serum sodium level decreased 7 to 20 mEq./L. and the plasma osmolality dropped 6 to 20 mOsm./Kg. Hyponatremia and water retention were more pronounced and prolonged than following other operations. Since there was a favorable response to the administration of alcohol, D'Angelo and associates concluded that a sustained elevation of ADH level was the underlying mechanism and suggested that a reduction in atrial pressure might be the stimulus for the hypersecretion of ADH.

Our data support this theory and give an explanation for the postcommissurotomy hyponatremic syndrome. It shows that release of atrial hypertension produces a striking hypersecretion of ADH. This unquestionably adds to that caused by the trauma of surgery, causes a prolonged postoperative elevation of the blood level of ADH and accounts for the metabolic alterations seen after commissurotomy.[15, 8, 23] These changes are enhanced when excessive amounts of fluids are given.

Summary

Inflations of balloons in the left atrium of dogs produced a 2- to 15-fold increase in rate of urine flow associated with a significant decrease in the blood level of ADH.

The diuresis was associated with an increase in free water clearance and osmolal S/U ratio.

Release of distension of the atrial balloon performed nine times was associated with a pronounced elevation of ADH. The mean increase was 30.7 μU./ml. This rise in ADH was associated with antidiuresis. Repetative inflations and deflations produced reciprocal effects.

Bilateral cervical vagotomy abolished the effect of inflation and deflation on blood level of ADH and urine flow.

Experimental mitral stenosis caused a drop of 0.6 μU./ml. in the level of ADH and an increase in urine flow. Release of mitral stenosis caused a mean increase of 6.0 μU./ml. in ADH and antidiuresis.

It is concluded that the diuresis which follows distension of the left atrium is caused by a decrease in blood ADH. Re-

lease of tension, as in mitral commissurotomy, causes a remarkable increase in ADH offering a reasonable explanation for water retention in the so called "post-commissurotomy syndrome."

Acknowledgment

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References

1. Arndt, J. O., H. Reineck and O. H. Gauer: Ausscheidungsfunktion und Hamodynamik der Nieren bei Dehnung des linken Vorhofes am narkotisierten Hund. Arch. Ges. Physiol., 277:1, 1963.
2. Baisset, A. and P. Montastruc: Modifications De La Diurese Apres Distension De L'Oreillette Gauche Role De L'Hormone Antidiuretique. Path. Biol., 7:1691, 1959.
3. Baratz, R. A. and R. C. Ingraham: Renal Hemodynamics and Antidiuretic Hormone Release Associated with Volume Regulation. Amer. J. Physiol., 198:565, 1960.
4. Coleridge, J. C. G., A. Hemingway, R. L. Holmes and R. J. Linden: The Location of Atrial Receptors in the Dog; A Physiological and Histological Study. J. Physiol., 136:174, 1957.
5. D'Angelo, G. J., H. V. Murdaugh and W. C. Sealy: The Nature and Treatment of the Post-Commissurotomy Hyponatremic Syndrome. Surg. Gynec. & Obstet., 106:87, 1958.
6. Ellison, R. G., R. C. Major, R. W. Pickering and W. F. Hamilton: Techniques of Producing Mitral Stenosis of Controlled Degree. J. Thor. Surg., 24:154, 1952.
7. Gauer, O. H. and J. P. Henry: Circulatory Basis of Fluid Volume Control. Physiol. Rev., 43:423, 1963.
8. Goodyer, A. V. N. and W. W. L. Glenn: Observations on the Hyponatremia Following Mitral Valvulotomy. Circulation, 11:584, 1955.
9. Grage, T., J. Winter and B. Zimmermann: Studies of Extracellular Volume in the Regulation of Antidiuretic Hormone. Surg. Forum, 11:129, 1960.
10. Henry, J. P., O. H. Gauer and J. L. Reeves: Evidence of the Atrial Location of Receptors Influencing Urine Flow. Circulation, 4:85, 1956.
11. Henry, J. P. and J. W. Pearce: The Possible Role of Cardiac Atrial Stretch Receptors in the Induction of Changes in Urine Flow. J. Physiol., 131:572, 1956.
12. Ledsome, J. R., R. J. Linden and W. J. O'Connor: The Mechanisms by which Distension of the Left Atrium Produces Diuresis in Anesthetized Dogs. J. Physiol., 159:87, 1961.
13. Lydtin, H. and W. F. Hamilton: Effect of Acute Changes in Left Atrial Pressure on Urine Flow in Unanesthetized Dogs. Amer. J. Physiol., 207:530, 1964.
14. Miltenberger, F. W. and W. H. Morgan, Jr.: Peripheral Blood Levels of Vasopressin (ADH) During Surgical Procedures. Surg. Forum, 14:54, 1963.
15. Moran, W. H., F. W. Miltenberger, W. A. Shu'ayb and B. Zimmermann: The Relationship of Antidiuretic Hormone Secretion to Surgical Stress. Surgery, 56:99, 1964.
16. Moran, W. H., Jr. and F. W. Miltenberger: Use of the Intravenous Route for Maintenance of Water Balance in the Alcoholized Rat Bioassay of Vasopressin. Fed. Proc., 22: 386, 1963.
17. Paintal, A. S.: The Conduction Velocities of Respiratory and Cardiovascular Afferent Fibres in the Vagus Nerve. J. Physiol., 121: 341, 1953.
18. Pearce, J. W. and J. P. Henry: Changes in Cardiac Afferent Nerve-Fiber Discharges Induced by Hemorrhage and Adrenalin. Amer. J. Physiol., 183:650, 1955.
19. Reeves, J. L., J. P. Henry and O. H. Gauer: Three Methods of Inducing Graded Obstruction of the Pulmonary Circulation. Amer. J. Vet. Res., 17:98, 1956.
20. Salem, M. R., D. Ginsburg, C. Rattenborg and D. A. Holaday: The Effect of Continuous Positive Pressure and Negative Pressure Breathing on the Urine Formation. Fed. Proc., 23:362, 1964.
21. Share, L.: Vascular Volume and Blood Level of Antidiuretic Hormone. Amer. J. Physiol., 202:791, 1962.
22. Share, L. and M. N. Levy: Cardiovascular Receptors and Blood Titer of Antidiuretic Hormone. Amer. J. Physiol., 203:425, 1962.
23. Wilson, G. M., I. S. Edelman, L. Brooks, J. A. Myrden, D. E. Harken and F. D. Moore: Metabolic Changes Associated with Mitral Valvuloplasty. Circulation, 9:199, 1954.
24. Zimmermann, B. and O. H. Wangensteen: Observations on Water Intoxication in Surgical Patients. Surgery, 31:654, 1952.

Discussion

Dr. Francis D. Moore (Boston): It has long been suspected that postoperative cardiac patients had a factor operative, producing a defect in water excretion which was over and beyond their operation. We thought that it had to do with the fact that they were often of small body weight, that they had been dehydrated and desalted by their preoperative medical treatment. Even very modest oral water loads did produce a severe hyponatremia.

But there is something else, and that something else is atrial stretch receptors. Dr. Zimmermann has shown this to be an important mechanism in cardiac surgery.