Antidiuretic Effect of Non-Renal Venous Congestion on Renal Water Excretion by the Hydrated Rat. (18932)

WILLIAM O. REINHARDT.*†

From the Division of Anatomy, University of California School of Medicine, Berkeley, Calif.

An experimental technic for measuring renal excretion after water loading has provided a method of studying the effects of disturbances in normal homeostatic mechanisms in altering renal function. In this study, this technic has been employed to assess the effects of increased venous pressure in altering renal water excretion. This problem has been investigated, using other technics, and has recently been reviewed in detail(1-4). The problem has been a matter of greatest concern in the evaluation of the relative importance of renal and non-renal factors in chronic passive congestion and edema formation.

The present experiments were carried out to evaluate the effects of acute hemorrhage, unilateral nephrectomy, obstruction of lymphatic drainage, and hypophysectomy, in rats in which the venous congestion was produced by one stage complete ligation of the inferior vena cava. A principal finding of note is that the acute passive congestion produced by ligation of the inferior vena cava causes antidiuresis in the presence of a single kidney with unobstructed venous drainage. It is further demonstrated that the hypophysis is not a necessary component in the production of this type of antidiuresis. Finally, the important role of lymphatic drainage in the maintenance of effective circulatory mechanisms in the presence of acute venous obstruction is reemphasized.

Methods and materials. Male rats of the Long-Evans strain, maintained under uniform experimental conditions, fed Diet XIV, were fasted for 18 hours but allowed access to water. The animals were hydrated after various operative interventions by the method described by Birnie *et al.*(5). Each animal received, by gastric intubation, 3 ml tap water/100 sq cm surface area, at hourly intervals for 3 hours. Urine output was collected in metabolism cages and measured at hourly intervals for 3½ hours after the first dose of water. The total urine excretion in this period of time was calculated as % of the water administered. Operative procedures were carried out under ether anesthesia, using clean technics, with the least possible trauma. Inferior vena cava ligations, nephrectomy, and thoracic lymph duct ligations were carried out through ventral abdominal incisions. The anatomical relationships of the renal veins in the rat allowed ligation of the inferior vena cava in different groups of animals at 3 different levels: (1) caval ligation was carried out midway between the right renal vein and the liver (prerenal); (2) caval ligation was carried out midway between the right and left renal veins (interrenal); (3) ligations were made just caudal to the left renal vein (postrenal). Care was taken to include only the vena cava in the ligature, and the animals were examined postmortem to verify that no other vessels or nerve trunks had been included in the ligatures. Left nephrectomy was carried out by ligation of the renal artery and vein distal to the site of entrance into the

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1. Smith, H. W., *The Kidney*, 1951, Oxford University Press, New York, pp. 663-694.

2. Various authors. *Am. J. Med.*, 1949, v6, 84, 232, 357, 470, 651, 722.

3. Youmans, W. B., and Huckins, A. R., *Hemodynamics in Failure of the Circulation*, American Lecture Series, 1951, Thomas, Springfield.

4. Wolf, A. V., *The Urinary Function of the Kidney*, 1950, Grune and Stratton, New York.

5. Birnie, J. H., Eversole, W. J., Boss, W. R., Osborn, C. M., and Gaunt, R., *Endocrinol.*, 1950, v47, 1.

TABLE I. Effect on Water Excretion by the Hydrated Rat of Hemorrhage, Unilateral Nephrectomy, Hypophysectomy, and Thoracic Lymph Duct Ligation, Separately, and Combined with Inferior Vena Cava Ligation.

Procedure	No. of rats	Avg BW, g	Water excreted as % of water administered Avg % ± SE	(Range)	Mortality in group (24 hr period)
Controls					
a. Sham-operated	10	290	72 ± 9	(52–94)	0
b. Acute hemorrhage	4	319	46 ± 4	(34–50)	0
c. External jugular vein ligation	6	296	72 ± 5	(60–83)	0
Inferior vena cava ligation					
a. Prerenal	8	236	.4 ± .4	(0–3)	0
b. Interrenal	8	229	11 ± 3	(1–23)	0
c. Postrenal	4	188	49 ± 4	(37–57)	0
Nephrectomy, unilateral					
a. Left nephrectomy	10	267	70 ± 3	(57–82)	0
b. Left nephrectomy and interrenal caval ligation	9	227	12 ± 5	(1–45)	0
c. Right nephrectomy and prerenal caval ligation	6	264	0	(0)	0
Hypophysectomy					
a. Hypophysectomy	12	132	33 ± 1	(30–35)	0
b. Hypophysectomy and pre- or interrenal caval ligation	9	158	1 ± 1	(0–4)	6 in 24 hr
Thoracic duct ligation					
a. Thoracic duct ligation	6	223	46 ± 5	(34–68)	0
b. Thoracic duct and prerenal caval ligation	6	235	0	(0)	6 in 6 hr

renal vein of the tributary left adrenal vein. The thoracic duct was ligated at the level of the left crus of the diaphragm, at the point of entrance of the duct into the thoracic cavity. Hypophysectomy was carried out in unfasted animals by the parapharyngeal approach. Completeness of operation was verified at autopsy by inspection of the sella under the binocular microscope. Both external jugular veins were ligated at their points of junction with the subclavian veins in an attempt to produce cephalic and cervical congestion. Animals subjected to hemorrhage were bled from the external jugular vein to the extent of 1.5% of the body weight. All animals recovered quickly from the anesthetized state and were subjected to the hydration test within a period of 2-3 hours after operation.

Results. The experimental data are presented in Table I. Normal or sham-operated animals excreted approximately 70% of an administered water load in 3½ hours. The normal rat tolerates ligation of the inferior vena cava at any level caudal to the liver and does not exhibit any obvious signs of shock. Prerenal ligation of the inferior vena cava is a routine first stage procedure in preparation for the operation of evisceration. If, however, such animals (prerenal cava ligated) are subjected to a post-operative hydration test, it is noted that urine formation falls to a negligible quantity in the time interval studied. In such animals, an increased venous pressure exists in the cava, and in the renal, and adrenal veins as manifested by direct inspection and by actual manometric measurement. This increased venous pressure, however, gradually returns to normal as evidenced by the gross appearance of collateral circulatory channels. One also finds a more normal response to the hydration test within a period of 2-3 days postoperatively (unpublished data).

If, on the other hand, cava ligation is carried out midway between the renal veins (interrenal ligation), the increased venous pressure affects only the left kidney and adrenal gland, the right kidney and adrenal gland being situated proximal to the site of ligation. In this preparation, with an unobstructed venous return from the right kidney, 11% of an administered dose of water is ex-

creted. Postrenal ligations of the inferior vena cava result in an excretion of 45% of the administered water in the same time interval.

The above results obtained with different levels of caval ligation suggested that increased renal pressure might be responsible for the failure of diuresis after water loading. To test this hypothesis, similar water loading was carried out in unilaterally nephrectomized rats, with and without caval ligation. It was noted that removal of the left kidney alone did not alter the diuretic response, which was in the control range (70%), whereas if interrenal caval ligation was carried out simultaneously, a procedure which does not obstruct right kidney venous drainage, diuresis fell to a level of the same magnitude (12%) as with interrenal caval ligation alone (11%).

The occurrence of an antidiuresis, in the presence of an unobstructed kidney, suggested that an antidiuretic material (ADH) might be liberated from the pituitary as a resultant of disturbance of the normal homeostatic mechanisms induced by caval ligation. To test this hypothesis, rats were hypophysectomized and subjected to the same hydration test. In the time interval studied, hypophysectomized rats excreted a smaller % of the administered water than did control rats. If, however, hypophysectomy was combined with either prerenal or interrenal caval ligation, excretion of administered water fell to zero. It should be noted, however, that hypophysectomy rendered the rat extremely susceptible to hydration after caval ligation, more than 2/3 of the rats succumbing within 24 hours. Evidently ADH is not an essential element in the production of the marked antidiuresis seen in these animals. It should be noted, however, that these rats were subjected to simple hypophysectomy, *i.e.*, no attempt was made to remove the stalk or related neural tissue known to contain (or secrete) ADH.

In the presence of acute venous obstruction as produced by caval ligation, one of the remaining unobstructed pathways for the return of fluid to the blood is by way of the lymphatic trunks. In order to determine the influence of the pathway, the caval ligation experiments were repeated in animals with ligated thoracic ducts. Depression of water excretion to 46% occurred after hydration of animals with ligated thoracic ducts, but when this procedure was combined with caval ligation, water excretion fell to zero, and strikingly, all animals died within a period of 6 hours. This observation emphasizes the role of the lymphatics in restoring fluid to the effective circulating blood volume in the presence of venous congestion. On the other hand, in control experiments, loss of 30% of the blood volume (arbitrarily estimated at 5% of the body weight) did not produce a remarkable antidiuresis after water loading, the level of excretion being diminished to the level noted after thoracic duct ligation alone. It is noteworthy solely as a control observation that obstruction of the largest venous channels (external jugular veins) draining the head and neck did not produce any degree of antidiuresis.

Discussion. The role of increased venous pressure in relationship to renal excretory activity has been of concern in understanding the mechanisms of retention of sodium and water by the kidney in varied states, as after assumption of the erect posture, exercise, hemorrhage, shock, hypoproteinemia, nephrotic syndrome, and in chronic passive congestion. The present experiments were designed to test the hypothesis that increased caval and renal venous pressure would cause a marked antidiuresis, presumably as the direct result of increase in renal venous pressure, and possibly mediated by increased secretion of ADH by the posterior lobe of the pituitary. Evidence has been presented to show that an antidiuretic material (nature not identified) is present in the body fluids of patients with congestive failure(6). On the other hand, Blake *et al.*(7), have shown that unilateral increase in renal venous pressure in the anesthetized laparotomized dog affected only sodium and water excretion of the affected kidney, thus excluding a humoral

6. Bercu, B. A., Rokaw, S. N., and Massie, E., *Am. Heart Assn.*, Trans., 1949 (June 3).

7. Blake, W. D., Wegria, R., Keating, R. P., and Ward, H. P., *Am. J. Physiol.*, 1949, v157, 1.

or neural pathway for the production of this effect. The mechanism of this sodium and water retention was ascribed to a local action, although no marked changes in glomerular filtration or total renal plasma flow were shown. Contrariwise, Selkurt *et al.*(8), noted, under similar experimental conditions, a progressive reduction in these functions, not sufficient, however, according to these authors, to account for the sodium retention, and, in their opinion, requiring the invokement of mechanisms other than increased renal venous pressure to account for congestive failure. Similar results to those of Selkurt *et al.*, have been obtained by Bradley and Bradley(9), in studying the effects of abdominal compression in man. This subject has recently been reviewed by Smith(1), with the tentative conclusion that the reduction in renal filtration rate cannot be entirely attributed to increase in renal venous pressure, and that other factors, endocrine or hemodynamic, must be invoked to account for the train of events in congestive failure with particular reference to the role of the kidney.

The present experiments provide evidence that the increase in renal venous pressure as produced by ligation of the inferior vena cava(10) is not an obligatory or sole cause of the impairment of diuresis noted, since that antidiuresis occurs to the same degree in animals with a single kidney with unobstructed venous return. Furthermore, in these acute experiments, the antidiuresis is not dependent on the presence of a functioning posterior lobe of the pituitary gland, since it occurs in the hypophysectomized rat with either one or both renal veins obstructed by caval ligation. It is interesting to note that ligation of both external jugular veins in the rat, as might be expected, does not produce sufficient increase in intracranial venous pressure to alter renal function. The present experiments do provide decisive evidence of the necessity for patency of the main lymphatic trunks in the presence of venous obstruction.

The evidence is believed to justify the conclusion that venous obstruction may alter diuretic activity by mechanisms entirely independent of (and additional to) local effects produced by increased renal venous pressure. Hemodynamic effects are more likely important in terms of decrease in effective circulating blood volume, although neurogenic and humoral effects (other than from the posterior lobe of the pituitary) have not been negated by the experimental data presented.

Summary. (1) Water excretion by hydrated rats has been studied to ascertain the alterations after ligation of the inferior vena cava at 3 levels in relationship to the renal veins. In addition, the effects of unilateral nephrectomy, hypophysectomy and thoracic lymph duct ligation, and various other control procedures have been observed. (2) The antidiuretic effect of inferior vena cava ligation in the hydrated rat is shown to be independent of increased renal venous pressure, and is also shown to occur in the absence of the pituitary gland. (3) The critical importance of the lymphatic pathway in maintaining an effective circulating blood volume in the presence of acute venous obstruction is demonstrated by showing the lethal effects of hydration in animals with combined caval and thoracic duct ligation, procedures which are separately tolerated by the rat.

8. Selkurt, E. E., Hall, P. W., and Spencer, M. P., *Am. J. Physiol.*, 1949, v157, 40.

9. Bradley, S. E., and Bradley, G. P., *J. Clin. Invest.*, 1947, v26, 1010.

10. Addis, T. and Lew, W., *J. Clin. Invest.*, 1939, v18, 777.

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