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Research Article

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The mechanisms involved in the marked sodium retention observed in such clinical states as congestive heart failure and advanced portal cirrhosis continue to pose a challenging problem. The role of increased renal venous pressure and of efferent nervous pathways to the kidney in effecting sodium retention, and the role of the adrenal nerves in the hypersecretion of aldosterone observed in such states demands further clarification. In investigating the role of increased venous pressure in experimental ascites produced by thoracic inferior vena caval constriction in the dog, Whelan, McCoord and Schilling (1) have reported that the kidney transplanted to the neck failed to exhibit the same degree of sodium retention as the normal kidney following thoracic caval constriction; however, the fact that one of their four experimental animals did show virtually complete sodium retention following caval constriction suggests the kidney removed from the congested circulation may respond just as the normally located kidney does to thoracic inferior vena caval constriction. In studying the mechanisms of sodium retention in dogs with experimental congestive heart failure, Barger, Muldowney and Liebowitz (2) have suggested that increased sympathetic tone of the renal nerves is an important factor in severe chronic sodium retention; other investigators (3–6) have, however, concluded that complete renal denervation has no consistent effect on sodium chloride excretion. In an investigation of the role of the adrenal nerves in the control of aldosterone secretion, Fleming and Farrell (7) have pointed out that the acutely transplanted adrenal released aldosterone at a normal or slightly

elevated rate. Denton, Goding and Wright (8) have demonstrated that the adrenal chronically transplanted to the neck in sheep increased the rate of aldosterone secretion in response to sodium depletion. Quantitative measurements of aldosterone secretion by the transplanted adrenal gland in animals with chronic sodium retention have, however, not before been reported.

In the present study, two experiments have been performed. The first experiment was designed to investigate the role played by the renal nerves and by increased renal venous pressure in the marked sodium retention observed after thoracic inferior vena caval constriction in the dog. The second experiment was aimed to determine whether efferent nervous pathways to the adrenal are essential to the hypersecretion of aldosterone observed in the dog after thoracic caval constriction and superimposed acute hemorrhage. In the first experiment, studies have been made of the response of the animal with a single transplanted kidney to thoracic inferior vena caval constriction. In the second experiment, the response of the animal with a single transplanted adrenal gland to chronic thoracic inferior vena caval constriction and to superimposed acute hemorrhage has been investigated. The secretion rates of aldosterone and corticosterone have been determined after thoracic caval constriction, and chronic electrolyte balance studies have been carried out in both experiments.

MATERIAL AND METHODS

Experiments were performed on mongrel dogs weighing 15 to 20 kg. In Experiment I (6 dogs), the left kidney and adrenal were transplanted to the neck by the procedure described by Levy and Blalock (9). Approximately one week later, right nephrectomy was performed.

One week after nephrectomy the thoracic inferior vena cava was constricted. In 3 of these animals, after two weeks of observations, the right adrenolumbar vein was cannulated under sodium pentobarbital anesthesia, and the adrenal venous effluent was collected.

In Experiment II (3 dogs), initially the left kidney and adrenal were transplanted to the neck. Approximately one week later, the left (cervical) kidney was carefully dissected out and excised, with preservation of the renal artery and vein; at the same time the right (abdominal) adrenal was removed. Two to three weeks following the latter procedure, thoracic inferior vena caval constriction was performed. One to two weeks later, the left external jugular vein was cannulated under sodium pentobarbital anesthesia, and adrenal venous blood was obtained both before and 30 to 90 minutes after removal of 250 ml of blood via the femoral vein.

Each animal was kept in a metabolic cage throughout the experiments and received (by forced feeding when necessary) a synthetic diet containing 60 mEq sodium and 18 mEq potassium per day. All animals were allowed water *ad libitum*. In Experiment I urine dripped from the open end of the ureter, which was transplanted to the surface of the neck, to the collecting pan of the metabolic cage. This pan was washed with 500 ml of distilled water immediately prior to removal of the 24-hour collection jar. Urinary and fecal sodium and potassium excretion was determined throughout the experiments, and in Experiment II plasma sodium and potassium concentrations were measured at frequent intervals by flame photometry. Inferior vena caval pressures were determined with a water manometer. Arterial pressures were measured by direct puncture of the femoral artery; a

Statham strain gage and a Sanborn recording system were used for recording of pressures. Ascites was removed by paracentesis at frequent intervals.

Adrenal venous aldosterone and corticosterone concentrations were determined by the double isotope derivative technique (10), and secretion rates of these steroids were calculated by a method described previously (11). In one animal, urinary aldosterone was determined by a modification of the double isotope technique with the addition of a fourth chromatographic step to provide better purification (12). Secretion rates of 17,21-dihydroxy-20-ketosteroids were determined by a modification of the Porter-Silber method as described by Peterson, Karrer and Guerra (13).

For pathological studies, transplanted kidneys and adrenal glands were fixed in 10 per cent formalin. Following fixation of the adrenal gland, extraneous tissues were carefully removed and the adrenals were weighed. Frozen microtome sections of adrenal glands were stained with Sudan IV. Paraffin sections of adrenal and renal tissue were stained with hematoxylin and eosin, and with azure-eosin (pH 4.5).

RESULTS

Experiment I: Effects of chronic constriction of the thoracic inferior vena cava following transplant of the left kidney to the neck and right nephrectomy. Following transplantation of the left kidney and adrenal gland to the neck and right nephrectomy, all six animals achieved sodium balance within two days. The average daily urinary

TABLE I

Effects of thoracic caval constriction on sodium and potassium excretion in dogs following transplantation of the left kidney to the neck and right nephrectomy

Dog no.	Before constriction					After constriction				
	Na excretion		K excretion		Fecal Na/K	Na excretion		K excretion		Fecal Na/K
	Urine	Feces	Urine	Feces		Urine	Feces	Urine	Feces	
	mEq/day		*mEq/day*			*mEq/day*		*mEq/day*		
1	43.1 [6]†	3.5	18.7	0.9	3.9	2.5* [7]	1.6	13.8	2.2	0.7
2	48.2 [6]	7.0	18.8	1.4	5.0	1.6 [9]	0.4	15.5	5.2	0.1
3	31.0 [7]	1.6	13.1	0.7	2.3	1.9 [7]	0.8	17.4	4.4	0.2
4	47.1 [6]	5.4	19.1	1.4	3.9	3.9 [9]	3.4	14.4	7.6	0.5
5	38.8 [6]	1.3	20.8	2.2		0.8 [6]		5.4		
6	31.8 [1]		17.7			1.5 [5]		14.8		

* The values presented for sodium and potassium excretion after thoracic caval constriction in Dog 1 represent the average values for the first 7 days after caval constriction (see Figure 2).
† The numbers in brackets indicate the number of days that measurements were made for urinary and fecal electrolyte excretion. Values represent averages for each period.

Aldosterone secretion by the normally located right adrenal following transplantation of the left kidney and adrenal to the neck, right nephrectomy and thoracic inferior vena caval constriction

Dog no.	Aldosterone secretion	Corticosterone secretion
	μg/min	μg/min
3	0.090	3.31
	0.085	5.08
5	0.054	1.78
	0.044	0.79
6	0.147	1.78
	0.132	1.97
Normal dogs stressed by laparotomy (n = 10)	0.024 ±0.017	2.13 ±0.65
Dogs with thoracic caval constriction stressed by laparatomy (n = 16)	0.135 ±0.056	3.11 ±1.78

volume produced by the cervical kidney ranged from 237 to 474 ml in the six dogs. All animals appeared in excellent health at the time of thoracic caval constriction. After caval constriction, inferior vena caval pressures increased from an average normal value of 51 mm of water (14) to the range of 178 to 320 mm of water; virtually complete so-

dium retention was observed in every animal, and urinary potassium excretion was decreased in five of the six dogs (Table I and Figures 1 and 2). The low fecal sodium/potassium ratio resulted in each animal from an increase in fecal potassium as well as from a decrease in fecal sodium excretion. Aldosterone secretion by the normally located right adrenal gland, determined two weeks after thoracic inferior vena caval constriction, was elevated in the three animals in which determinations were made. In each of these three dogs, aldosterone secretion was in the range previously observed in dogs subjected to thoracic inferior vena caval constriction (Table II) and was adequate to account for the observed sodium retention. Corticosterone secretion was in the same range as that of normal animals stressed by laparotomy and adrenolumbar vein cannulation (Table II). Urinary aldosterone excretion was very low (less than 0.1 μg per day) prior to caval constriction and increased strikingly to a level of 1.65 μg per day after caval constriction (Figure 1). Arterial pressure remained at the normal level throughout the experiment in all animals.
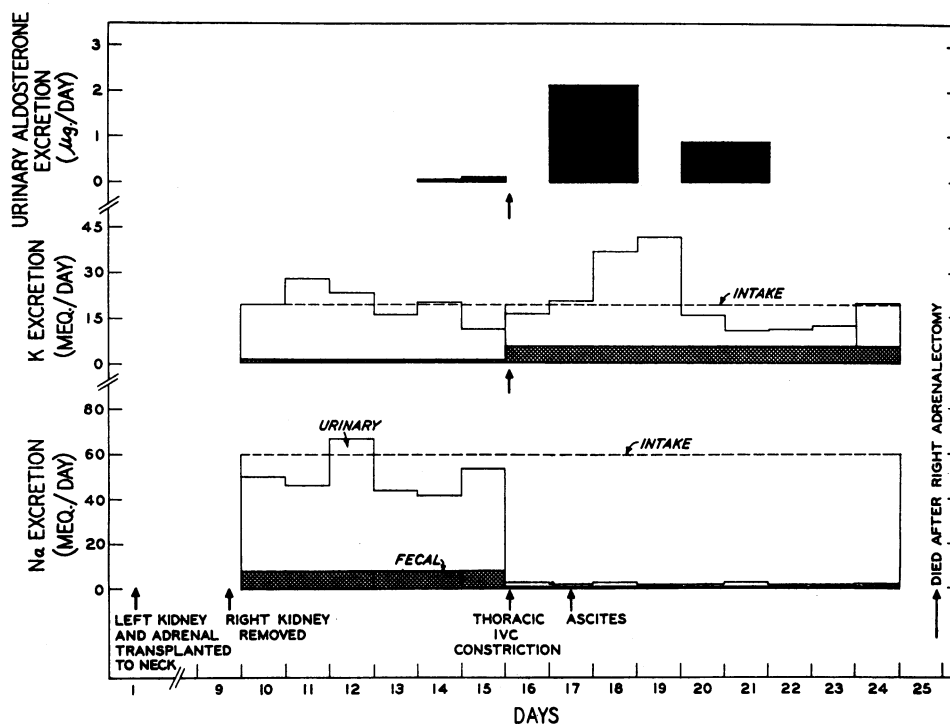

FIG. 1. EFFECTS OF CHRONIC THORACIC INFERIOR VENA CAVAL CONSTRICTION FOLLOWING TRANSPLANT OF LEFT KIDNEY AND ADRENAL TO THE NECK AND RIGHT NEPHRECTOMY IN DOG 2, TABLE I.

In Dog 3, the right (abdominal) adrenal gland
was removed after collection of adrenal venous
blood. Metabolic studies were continued during
the following week, at a time when neither the kid-
ney nor the adrenal gland was in the normal ab-
dominal position. During this period, the marked
sodium retention continued (Table III).

In one dog (Figure 2), thoracic inferior vena
caval pressure, which was 255 mm of water on the
sixth day after caval constriction, fell to 210 on
the twelfth postoperative day, presumably sec-
ondary to venous collateralization. Concomitant
with the fall in vena caval pressure, a marked in-
crease in sodium excretion occurred. At this time,
reconstriction of the thoracic inferior vena cava
resulted in a rise in venous pressure to 320 mm of
water, and almost complete sodium retention again
occurred.

Pathological examination of the transplanted
kidneys was performed in three cases (Dogs 1, 3
and 5). Each of these kidneys appeared grossly
normal. On microscopic examination, focal areas

of necrosis were observed, but in no instance did
the necrosis involve more than 10 per cent of the
renal parenchyma.

*Experiment II: Effects of chronic thoracic in-
ferior vena caval constriction following transplant
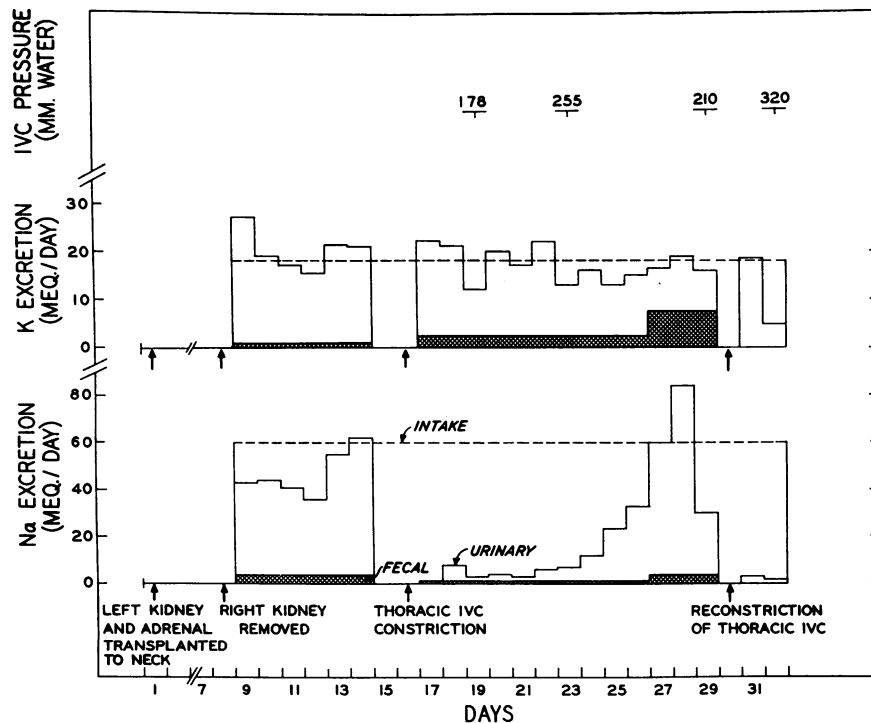of the left adrenal and kidney to the neck, right*

TABLE III

*Effects of thoracic caval constriction and subsequent removal
of the right (abdominal) adrenal gland on sodium and
potassium excretion following transplant of left kidney
and adrenal gland to the neck and right nephrectomy
(Dog 3, Table I)*

Dog 3		Before caval con-striction	After caval con-striction	After removal of right (abdominal) adrenal
Na excretion (mEq/day)	Urine	31.0 [7]*	1.9 [7]	1.0 [5]
	Feces	1.6	0.8	0.6
K excretion (mEq/day)	Urine	13.1	17.4	14.0
	Feces	0.7	4.4	2.0

* The number in brackets indicates the number of days in which
measurements were made for urinary and fecal electrolyte excretion.
Values represent averages for each period.

FIG. 2. EFFECTS OF CHRONIC THORACIC INFERIOR VENA CAVAL CONSTRICTION FOL-
LOWING TRANSPLANT OF LEFT KIDNEY AND ADRENAL TO THE NECK AND RIGHT NEPHREC-
TOMY IN DOG 1, TABLE I. Note the natriuresis concurrent with the fall in inferior
vena caval (IVC) pressure and the almost complete sodium retention following re-
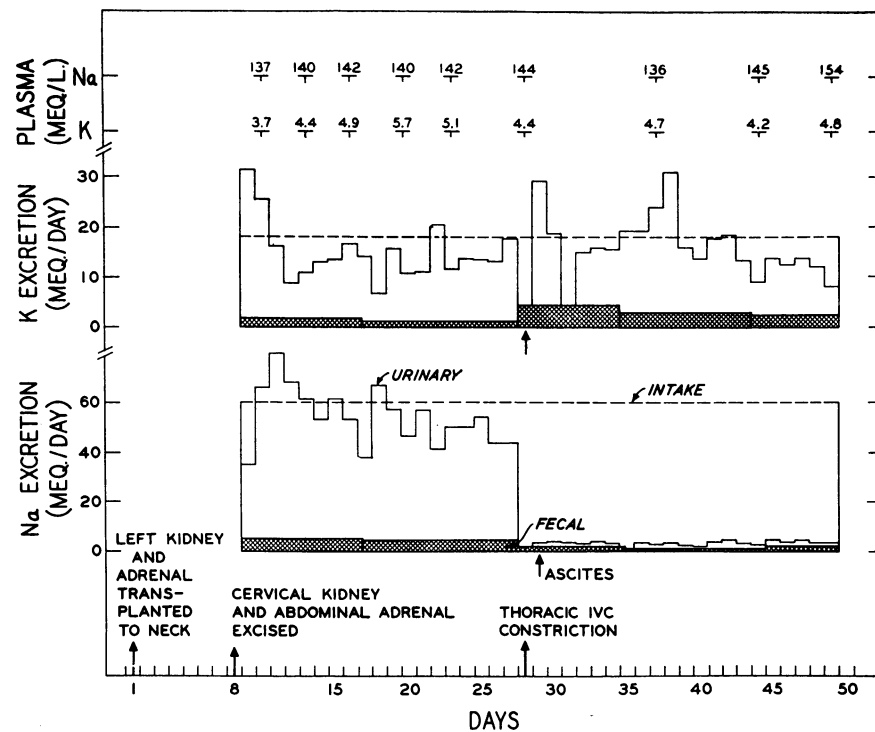tightening of caval ligature.

FIG. 3. EFFECTS OF CHRONIC THORACIC INFERIOR VENA CAVAL CONSTRICTION FOL-
LOWING TRANSPLANT OF LEFT ADRENAL AND KIDNEY TO THE NECK, RIGHT ADRENALEC-
TOMY AND CERVICAL NEPHRECTOMY IN DOG 7, TABLE IV.

adrenalectomy and left (cervical) nephrectomy. After right adrenalectomy and cervical nephrectomy, sodium balance was rapidly achieved by all animals (see Figure 3). Plasma sodium and potassium levels and mean arterial pressures remained within normal limits. Subsequent to thoracic inferior vena caval constriction, marked sodium retention occurred (Table IV) and ascites

accumulated rapidly in all dogs. The fecal sodium/potassium ratio decreased, and urinary potassium excretion declined in two of the three animals following caval constriction.

In two animals, adrenal venous blood was obtained by cannulation of the left external jugular vein proximal to the site of its anastomosis with the left renal vein. Aldosterone, corticosterone,

TABLE IV

*Effects of thoracic inferior vena caval constriction on sodium and potassium excretion in dogs following trans-
plantation of the left adrenal and kidney to the neck, right adrenalectomy and cervical nephrectomy*

Dog no.	Before constriction					After constriction				
	Na excretion		K excretion		Fecal Na/K	Na excretion		K excretion		Fecal Na/K
	Urine	Feces	Urine	Feces		Urine	Feces	Urine	Feces	
	mEq/day		*mEq/day*			*mEq/day*		*mEq/day*		
7	50.7 [19]*	4.7	17.6	1.6	3.0	1.2 [21]	1.8	14.8	3.1	0.6
8	42.1 [17]	7.8	15.0	1.6	4.7	0.7 [14]	0.9	9.7	2.0	0.5
9	50.3 [13]		18.8			2.1 [12]		18.0		

* The numbers in brackets indicate the number of days on which measurements were made for urinary and fecal electrolyte excretion. Values represent averages for each period.

TABLE V

Steroid secretion by the cervical adrenal gland in dogs with thoracic caval constriction before and 30 to 90 minutes after hemorrhage

Dog no.	Time	Aldosterone secretion	Corticosterone secretion	Porter-Silber chromogen secretion
	min	*μg/min*	*μg/min*	*μg/min*
8	0	0.078	0.23	0.39
	10	0.049	0.06	3.91
	30 → bled			
	70	0.077	0.84	5.87
	100	0.103	1.04	6.65
	120	0.103	0.98	
9	0	0.005	0.15	0.90
	10	0.006	0.17	0.86
	20 → bled			
	60	0.036	0.85	1.99
	70	0.033	0.60	3.82
Conscious unstressed normal dogs (n = 5)		0.006 ± 0.002	0.29 ± 0.20	0.80 ± 0.20
Normal dogs stressed by laparotomy		0.024 ± 0.017 (n = 10)	2.13 ± 0.65 (n = 10)	7.34 ± 2.69 (n = 7)

and Porter-Silber chromogen secretion rates were determined. The results are presented in Table V. In one animal, the rate of aldosterone secretion was clearly elevated. In the other dog, aldosterone secretion appeared to be low; this was probably because only a fraction of the adrenal venous effluent was returning via the left external jugular vein. Corticosterone and Porter-Silber chromogen secretion rates were low in both dogs; the values were in the same range as those observed in unstressed conscious normal dogs with chronic adrenal venous catheters (12), and were far below the secretion rates of normal dogs stressed by laparotomy (15).

Following collection of the control samples of adrenal venous blood, both dogs were subjected to acute hemorrhage. An increase in the secretion rates of aldosterone, corticosterone, and Porter-Silber reacting chromogens occurred within 40 to 70 minutes after the blood loss (Table V). It is noteworthy that even in Dog 8, in which the control secretion rate of aldosterone was elevated as the result of chronic inferior vena caval constriction, a further increase in aldosterone secretion rate occurred following hemorrhage. The increments in secretion rates of corticosterone (fourfold) and of Porter-Silber chromogens (two-

to fourfold) were similar for each of the two animals.

Each of the three transplanted adrenal glands in Experiment II was examined for pathological changes. The transplanted adrenals appeared normal grossly and ranged in weight from 1.0 to 1.9 g. On microscopic examination, small areas of necrosis, involving both cortex and medulla, were present in each gland; the necrosis did not involve more than 25 per cent of the adrenal parenchyma in any instance. Normal zonal adrenocortical architecture was observed. The zona glomerulosa was easily distinguished from the outer and inner fasciculata and juxtamedullary regions. In areas where only a portion of the thickness of the cortex remained, the zona glomerulosa was most often preserved.

DISCUSSION

All animals in Experiment I remained in good clinical condition following transplantation of the left kidney to the neck and right nephrectomy. This observation is in accord with the work of Dempster (16), who noted survival of dogs in apparent good health for over a year after unilateral nephrectomy and transplantation of the remaining

kidney to the neck. However, the marked polyuria, which was observed following removal of the normal kidney in the cases reported by Dempster, failed to occur in any of the present experimental animals. Urinary volume from the neck kidney after uninephrectomy was not significantly different from the normal total urinary output.

Renal hemodynamic function studies were not performed in the present experiments. On the basis of the observations of Bricker, Straffon, Mahoney and Merrill (3), the possibility must be considered that both renal plasma flow and glomerular filtration rate (GFR) in the cervical kidney were reduced. In each animal, however, the cervical kidney consistently demonstrated the ability to maintain normal sodium and potassium balances during the period prior to thoracic inferior vena caval constriction. In one animal the brisk natriuresis which accompanied the fall in venous pressure indicated that the cervical kidney was capable of excreting sodium at a rate adequate to produce a negative sodium balance. Hence, it appears that the renal hemodynamic alterations attendant upon transplantation of the kidney to the neck played no essential role in the sodium retention observed after caval constriction in the present experimental animals. The observed hypersecretion of aldosterone in the presence of elevated venous pressure secondary to thoracic caval constriction provides an adequate explanation for the sodium retention (17), but a possible contributory influence of a decreased GFR cannot be excluded.

In an investigation of the role of increased renal venous pressure in the sodium retention produced by thoracic caval constriction, Whelan and associates (1) performed experiments similar to those of the present study, although in two of their four dogs, thoracic caval constriction was carried out prior to removal of the abdominal kidney. Their results, however, were inconclusive, since one animal failed to show a positive sodium balance after thoracic caval constriction, and varying degrees of sodium retention were observed in the other three dogs; only one of their four animals showed the virtually complete sodium retention which was characteristic of all the animals described in the present study. Although Whelan and co-workers attributed their results to a diminished ability of the transplanted kidney to retain sodium, it appears more likely that the elevation in

inferior vena caval pressure was inadequate in their experimental dogs. The present observations demonstrate that the kidney transplanted to the neck exhibited the same marked sodium retention as do normally located kidneys following thoracic inferior vena caval constriction (18).

In investigating the role of the renal nerves in the sodium retention of congestive heart failure, Barger and associates (2) have pointed out that the infusion of 10 μg of aldosterone into the renal artery of a normal dog failed to cause a unilateral antinatriuresis, whereas a much smaller dose of aldosterone injected into the renal artery of an animal with experimental tricuspid insufficiency exerted a definite antinatriuretic effect. They have further observed that norepinephrine injected into the renal artery of a normal dog caused a unilateral decrease in renal sodium excretion, whereas Dibenzyline (phenoxybenzamine hydrochloride) injected into the renal artery of a dog with experimental tricuspid insufficiency caused marked natriuresis. On this basis, Barger and co-workers have postulated that the renal nerves or the renal response to circulating norepinephrine play an important role in the severe sodium retention of congestive heart failure. The almost complete sodium retention in the present experimental dogs with denervated, transplanted kidneys demonstrates that the renal nerves are not essential to the profound chronic sodium retention which follows thoracic inferior vena caval constriction. Our present experimental results are in accord with those and Bricker and associates (3) who found, in studying the function of the kidney transplanted to the femoral region in the dog, that the "complete denervation occurring during the transplantation procedure did not result in any consistent abnormality in the tubular transport of sodium chloride."

The results obtained from Experiment II, in which the left adrenal gland was transplanted to the neck and the right adrenal was excised, confirm the observations of Levy and Blalock (9) that the transplanted adrenal gland in the dog secretes adequate steroid to maintain the animal in excellent health. Actual measurements of the basal secretion rates of steroids in the present experiment further demonstrate that the secretion rates of corticosterone and Porter-Silber chromogens by the transplanted adrenal were in the same

range as those of the abdominal adrenal of normal unstressed conscious dogs (12).

In investigating the role played by the adrenal nerves in the regulation of aldosterone secretion, Fleming and Farrell (7) acutely transplanted the adrenal gland of a donor animal to the thigh of a recipient dog. They measured the aldosterone and cortisol output by the transplanted adrenal and found the secretion rates to be as high as, or higher than, the secretion rates by the normal adrenal gland of the anesthetized dog stressed by laparotomy. However, they did not subject the recipient animal to any stimulation to determine whether the transplanted adrenal would respond to an appropriate stimulus with an increase in aldosterone secretion. In their extensive studies on the adrenal gland transplanted to a cervical pouch in sheep, Denton and associates (8) have shown that the transplanted gland, in response to sodium depletion, exhibited at least a fivefold increase in secretion rate of aldosterone. The present experimental data show that the transplanted adrenal gland not only responded to thoracic caval constriction by hypersecretion of aldosterone, but also responded to superimposed acute hemorrhage by a further increase in rate of aldosterone secretion. As in the studies of Denton and associates, the hypersecretion occurred after complete adrenal denervation, a finding which supports the thesis of Yankopoulos, Davis, Kliman and Peterson (15) that a humoral factor, an aldosterone-stimulating hormone, provides the immediate stimulus to hypersecretion of aldosterone in experimental secondary hyperaldosteronism.

The present experiments indicate that acute hemorrhage stimulates the secretion not only of aldosterone, but also of other corticosteroids. The increase in secretion of corticosterone and Porter-Silber chromogens demonstrates that increased ACTH release is an important part of the response of the animal to hemorrhage. In hypophysectomized dogs, corticosterone and Porter-Silber chromogen output either failed to increase or increased only slightly following hemorrhage (personal observations). It has previously been recognized that acute hemorrhage causes an increase in the secretion rate of aldosterone in both the normal (19) and the hypophysectomized (20, 21) dog, and it has been assumed that the increase in normal animals is mediated via a volume receptor system ac-

tivated by the decreased blood volume (22). The fact that acute hemorrhage causes also an increased release of ACTH in the normal dog has previously been obscured because the animals studied have been subjected to the stress of laparotomy and adrenolumbar vein cannulation (19), and consequently, control secretion rates of corticosteroids have approached maximal levels. In the two animals here described, the cervical adrenal venous effluent was collected after a simple skin incision, so that the control corticosterone and Porter-Silber chromogen secretion rates were very low; therefore, increased ACTH release in response to hemorrhage was clearly demonstrable by the striking increase in corticosteroid output.

SUMMARY AND CONCLUSIONS

The response of a single transplanted cervical kidney to chronic thoracic inferior vena caval constriction has been investigated in six dogs. In each animal, the transplanted kidney responded to caval constriction in essentially the same manner as a normally located kidney, with virtually complete sodium retention. The response of a single transplanted cervical adrenal gland to chronic thoracic caval constriction and to superimposed acute hemorrhage has been studied in three dogs. In each animal, the transplanted adrenal gland secreted adequate aldosterone to effect the almost complete sodium retention and the very low fecal sodium/potassium ratio which is characteristic of the response of the animal with normally located adrenals to thoracic caval constriction. The transplanted adrenal gland responded to acute hemorrhage with marked increases in secretion rates of aldosterone, corticosterone and Porter-Silber chromogens. The present data demonstrate that neither intact renal and adrenal nerves nor increased renal venous pressure are essential to the hypersecretion of aldosterone and virtually complete sodium retention which follow thoracic inferior vena caval constriction. They further indicate that increased ACTH release is an important part of the response of the animal to acute hemorrhage.

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