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Reversal of Chronic Renal Hypertension: Role of Salt and Water Excretion (39014)

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Hypertension can be induced in rats and other animals by constricting the blood flow to one kidney and removing the contralateral kidney (1). This type of hypertension has two different phases in which the blood pressure is maintained by separate mechanisms (2, 3). In the acute phase, blood pressure is lowered by removal of the clipped kidney (2, 4) or by renin–angiotensin-system inhibitors (3, 5), suggesting that renin may be maintaining the high blood pressure. In the chronic phase, nephrectomy and renin–angiotensin inhibitors do not lower blood pressure, indicating that an extrarenal pressor mechanism is operating. Removal of the clip causes a rapid fall in blood pressure. This must be due to an antihypertensive action of the kidney rather than the removal of a hypertensive one, because the kidney is not maintaining the elevated blood pressure. The fall in blood pressure correlates well with the sodium excretion following unclipping (6). Liard and Peters (6) have suggested a causal role for the excretion of excess salt and water in the fall in blood pressure after unclipping. The present work attempts to assess the role of salt and water excretion in the reversal of chronic one-kidney hypertension in the rat.

Materials and methods. Male Sprague–Dawley rats, initially weighing 150 g, were maintained on Purina rat chow and water *ad lib*. They were made hypertensive in two operations. The left renal artery was constricted with a silver clip (i.d., 0.2 mm), and 2 weeks later the right kidney was removed. Both operations were performed through flank incisions under halothane anesthesia.

Mean blood pressure was measured in conscious, unrestrained rats by means of an indwelling PE 50 catheter in the carotid artery. The catheter was exteriorized at the back of the neck and attached to a Statham P23D6 transducer recording on a Gilson polygraph. The catheters were heparinized by the following procedure: Soaked 20–24 hr in 3% (w/v) TDMAC (tridodecylmethylammonium chloride) in 50:50 toluene–hexane, vacuum dryed, soaked 1–2 hr in 0.25% (w/v) heparin in 50% aqueous ethanol, washed with fresh ethanol, and stored in sterile saline (7).

Fourteen to seventeen days after nephrectomy, the carotid artery catheter was implanted under sodium pentobarbital anesthesia. The following day, an initial blood pressure measurement was made in conscious animals. Those rats with a mean blood pressure in excess of 135 mm Hg were divided into three groups: Group A (six rats) underwent a sham unclipping in which the clip was exposed but not removed; Group B (seven rats) were unclipped; Group C (nine rats) were unclipped and placed in metabolic cages. Every 15–30 min, 0.9% saline was infused through the carotid artery cannula to replace the volume of urine excreted during that period. Blood pressure was measured hourly for 3 hr, then the urine from the rats in Group C was collected for Na^+ measurement.

Results. The volume of saline infused in Group C was equal to the volume of urine excreted, so the rats were maintained at even fluid balance. Sodium balance was calculated and the results are presented in Table I. Seven of the nine rats were in positive sodium balance, and the other two rats were kept to a loss of less than one-twentieth of total excreted sodium.

Figure 1 shows the change in blood pressure after the operation for all three groups. Group A (sham unclipped) showed a small but not significant fall in blood pressure at 1 hr which may be attributed to the operation and to the pentobarbital. By the 2nd hr, blood pressure was back to preoperative levels, showing that the operation itself did not cause a prolonged effect on blood pressure. Group B (unclipped) and Group C (unclipped and reinfused) exhibited virtually

TABLE 1. URINE OUTPUT AND SODIUM BALANCE IN GROUP C.[a]

Rat number	Urine volume (ml/kg)	Na^+ excretion (mequiv/kg)	Na^+ balance (mequiv/kg)
1	96	15.65	−0.86
2	91	13.38	+0.64
4	79	9.16	+3.00
7	67	10.18	+0.13
5	41	6.60	−0.29
6	33	0.69	+4.39
9	17	2.25	+0.32
8	13	1.09	+0.91
3	13	1.18	+0.88

[a] Salt and water excretion and calculated sodium balance for the 6-hr period following unclipping in Group C (unclip and reinfuse). Normal saline (154 mequiv of Na†/l) was infused every 15–30 min so that the volume excreted during that period was exactly replaced. In all but two rats sodium balance was positive.

identical blood pressure behavior. At 1 hr after unclipping, there was a large, significant fall in blood pressure ($P < 0.025$), but at 2 hr there was a partial recovery which brought the blood pressure to the level at which it remained for the rest of the 6-hr period. At the end of the 6 hr, the blood pressures of Groups B and C were significantly lowered from hypertensive levels, -28.4 ± 5.2 ($P < 0.005$) and -34.0 ± 9.5 ($P < 0.01$), respectively, while Group A was not significantly changed from the preoperative level, $+8.5 \pm 6.8$ ($P < 0.20$).

Discussion. The possibility that an expansion of body fluid volume is responsible for the elevation of blood pressure in one-kidney Goldblatt hypertension (1-KGH) is suggested by the fact that total exchangeable sodium is elevated in 1-KGH (8). This would make excretion of the excess salt and water a likely mechanism for the reversal of the hypertension. Further support for this hypothesis comes in the experiments of Liard and Peters (6), who showed that the fall in blood pressure after unclipping is highly correlated with the 6-hr sodium and water excretion. Also, the fall in cardiac output, which is associated with the decline in blood pressure (9), could be caused by loss of excess body fluid. The present work opposes this viewpoint.

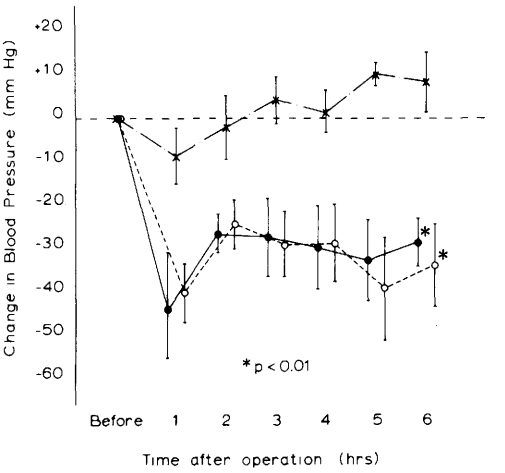

FIG. 1. Change in blood pressure in one-kidney Goldblatt hypertension after Unclipping (solid circles, $n = 7$), ($n = 7$), sham unclipping (cross, $n = 6$), and unclipping with replacement of excreted salt and water (open circles, $n = 9$). Replacement of excrete fluid did not prevent the fall in blood pressure after unclipping.

It is possible that a pressor factor unrelated to water and electrolytes is excreted by the kidney. However, experiments by Floyer (4) in rats and by ourselves in rabbits (unpublished observations) have shown that returning the urine to the vena cava by means of a ureterocaval anastomosis does not prevent the reversal of hypertension by unclipping.

Some possible mechanisms by which unclipping the kidney could lower blood pressure are 1) release of vasodilators, 2) metabolism of an extrarenal pressor factor, 3) release of some cardiac or cardiovascular center depressant, or 4) internal shifts of fluid compartments. The presence of vasodilators such as prostaglandin PGE_2 in the kidney medulla is well established (10), but the fact that the fall in blood pressure is reported to be mediated by a fall in cardiac output (9) makes this explanation unlikely. The absence of evidence for a humoral factor in chronic 1-KGH (11) or for a renal hormone capable of affecting cardiac output prevents us from seriously considering the second and third hypotheses. There is evidence to suggest that the kidney can control the compliance of the extracellular fluid compartment (12). Thus, removal of the clip in

chronic 1-KGH has been shown to increase extracellular fluid volume compliance, thus allowing a shift of fluids out of the plasma volume (13). Venodilation would produce the same effect on the cardiac output by decreasing venous pressure and end diastolic filling pressure. These hypotheses are attractive but have not been tested.

Excretion of fluid and electrolytes cannot be the sole mechanism of the reversal of the hypertension. In fact, it is probable that no simple explanation can account for the dramatic reduction in blood pressure that follows unclipping in rats with 1-KGH.

Summary. Rats with chronic one-kidney Goldlatt hypertension underwent an unclipping procedure with and without maintenance of body fluid volume through administration of iv salt solution. The blood pressure declined equally in the two groups. It is concluded that external loss of salt and water is not the mechanism for the reversal of this form of hypertension

1. Goldblatt, H., J. Exp. Med. **59,** 347 (1934).
2. Pickering, G. W., Clin. Sci. **5,** 229 (1945).
3. Brunner, H. R., Kirshman, J. D., Sealey, J. E., and Laragh, J. H., Science **174,** 1344 (1971).
4. Floyer, M. A., Clin. Sci. **14,** 163 (1955).
5. Bumpus, F. M., Sen, S., *et al.*, Clin. Sci. Mol. Med. **47** (1974).
6. Liard, J. F., and Peters, G., Experientia **26,** 743 (1970).
7. Grode, G. A., Trans. Amer. Soc. Artif. Organs **15**-(1970).
8. Tobian, L., Coffee, K., and McCrea, P., Amer. J. Physiol. **217,** 457 (1969).
9. Ledingham, J. M., and Cohen, R. D., Clin. Sci. **22,** 69 (1962).
10. Lee, J. B., J. Clin. Invest. **45,** 1036 (1966).
11. Koletsky, S., and Pritchard, W. H., Clin. Res. **13,** 552 (1963).
12. Lucas, J., and Floyer, M. A., Clin. Sci. **44,** 397 (1973).
13. Lucas, J., and Floyer, M. S., Clin. Sci. Mol. Med. **47** (1974).

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