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Changes in the Extracellular Fluid Volume and Cardiac Output During the Development of Experimental Renal Hypertension

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THE purpose of this communication is to describe certain changes observed in body fluids and in circulatory dynamics during the development of experimental renal hypertension.

During a study of water and electrolyte distribution in experimental renal hypertension in 1953, the observation was made that the extracellular fluid volume (E.C.F.V.) was expanded in hypertension of short duration, and fell to within the normal range as the duration of hypertension was prolonged.[1] This suggested that circulatory changes, leading to hypertension, might be associated with or even caused by this expansion of volume, and that these circulatory changes in early hypertension might differ from those in established hypertension.

The first part of the present study concerns changes in extracellular fluid and plasma volumes (P.V.) during the phase of developing hypertension from the time of renal artery constriction. E.C.F.V. and P.V. were estimated by the thiocyanate and Evans blue spaces respectively in rats subjected to right renal artery constriction and left nephrectomy.

To establish a group of normotensive controls, a loose clip was used in one series of rats. In the experimental group a tighter clip was used; this group showed a rise in blood pressure within three days, and all except one had at some time a blood pressure of 145 mm. Hg or over (Fig. 1). None of the rats with the loose clip developed hypertension. In Fig. 2 is shown the E.C.F.V., three, seven and 14 days after operation in the two groups of clipped animals, in a group of normals, and in a group of animals subjected to unilateral nephrectomy alone, seven days previously. Both the clipped groups showed a significant increase in E.C.F.V. at three and seven days, the differences between the two groups also being significant; by 14 days the E.C.F.V. had fallen in both these groups, and returned to the normal range in the normotensive rats. Within the hypertensive group there was no correlation between the increase in blood pressure and the expansion of the E.C.F.V. Changes in plasma volume measured by Evans blue paralleled those in the E.C.F.V. In the group subjected to unilateral nephrectomy there was no change in E.C.F.V.

It was concluded that transient expansion of the E.C.F.V. accompanies the development of this form of experimental hypertension, but it is not possible to assess its role in the pathogenesis of the hypertension. The large overlap with the normotensive control group and the lack of correlation between the increase in blood pressure and the expansion of the E.C.F.V. suggest that other factors are involved.

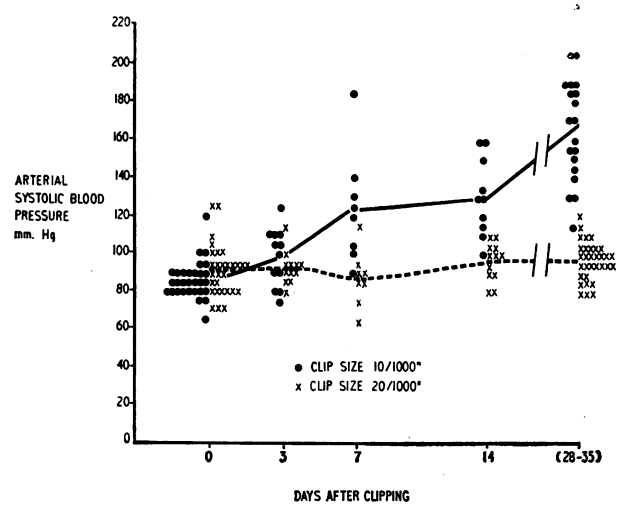

Fig. 1.—Arterial systolic blood pressure in two groups of rats after right renal artery constriction by clips of different sizes and contralateral nephrectomy.

The second part of this investigation concerns hemodynamic changes during the development of hypertension, studied by means of an electromagnetic flow transducer implanted on the ascending aorta of the rat. This method made possible measurements of cardiac output after renal artery

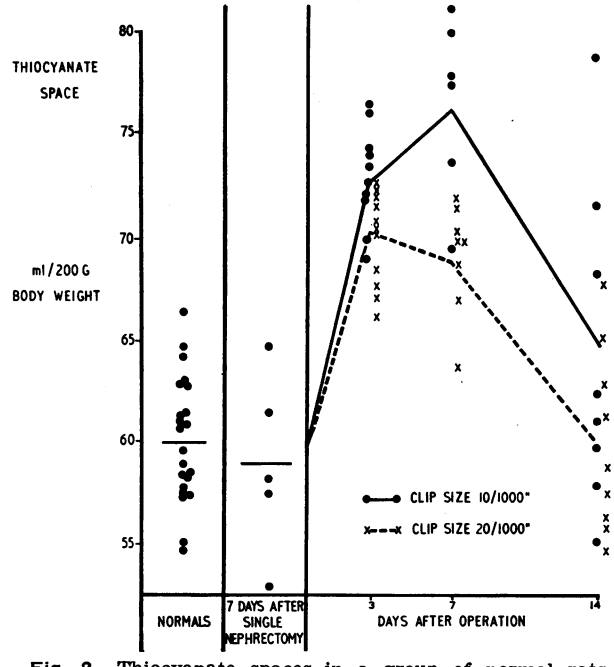

Fig. 2.—Thiocyanate spaces in a group of normal rats, in a group of rats subjected to unilateral nephrectomy seven days previously, and in two groups of rats at varying intervals after right renal artery constriction and contralateral nephrectomy.

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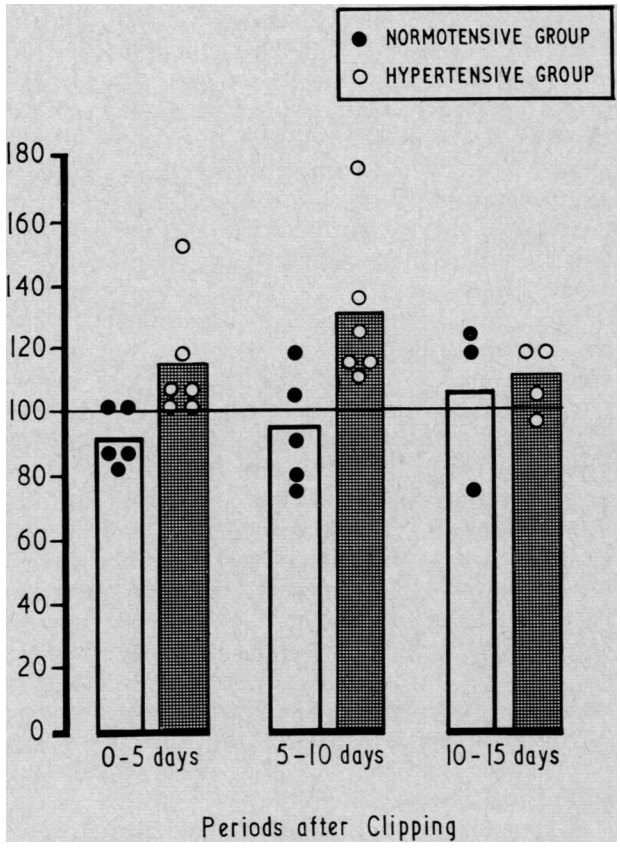

Fig. 3.—Changes in cardiac output after renal artery constriction and contralateral nephrectomy in normotensive (solid circles) and hypertensive (open circles) rats expressed as a percentage of the mean cardiac output before clipping. Each point represents the mean of between two and five observations each made on different days. The means for the groups are shown by the heights of the columns.

constriction in unanesthetized rats. Blood pressure measurements have so far only been made by the tail plethysmographic method under ether anesthesia immediately following the measurement of resting cardiac output. These blood pressure measurements thus give only a guide to the rate of development of hypertension and do not enable exact

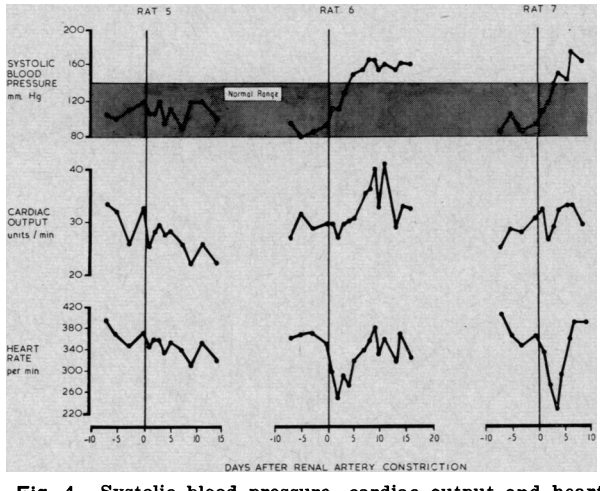

Fig. 4.—Systolic blood pressure, cardiac output and heart rate before and after right renal artery constriction and left nephrectomy in one animal remaining normotensive (Rat 5) and in two animals developing hypertension (Rats 6 and 7), showing the severe reduction of heart rate in the immediate postoperative phase in the hypertensive animals.

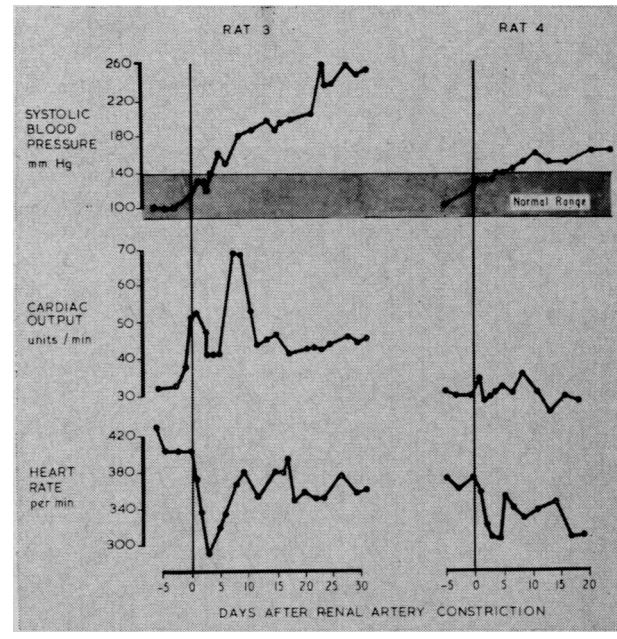

Fig. 5.—Observations on one rat (Rat 3) developing hypertension rapidly, showing a steep rise in cardiac output as the heart rate returned to normal and on another rat (Rat 4) developing hypertension slowly, showing a reduction in heart rate.

changes in the peripheral resistance to be calculated. After at least seven days of control observations, a silver clip of between 8½ and 20 thousandths of an inch was placed on the right renal artery, and left nephrectomy was performed. Serial observations were then made on 11 rats for periods of from seven to 31 days after clipping.

In Fig. 3 the mean cardiac output during successive five-day periods after clipping has been expressed as a percentage of the mean preoperative control observations. Five animals remained normotensive throughout the period of observation and in these no significant change in cardiac output took place, nor was there any sudden change in heart rate. Six animals developed hypertension (B.P. > 140) and showed a moderate rise in cardiac output. In comparison with the normotensive group the cardiac output was significantly increased ($P < .001$) by 24% and 35% in the first two five-day periods. In the third five-day period there was no significant difference in cardiac output between the groups, suggesting a return to the normal level, but the number of animals under observation in this period was fewer. All save one of the animals developing hypertension showed a great reduction in heart rate (e.g. from 380 to 260 per min.) which reached a minimum between the second and fourth day and returned to normal by the fifth to eighth day (Fig. 4: Rats 6 and 7). This fall in rate was accompanied by some rise in cardiac output, but the major increase in output usually occurred as the rate rose to normal (Fig. 5: Rat 3). The heart rate in one animal did not fall and in this case the rise in cardiac output was immediate (Fig. 6: Rat 2).

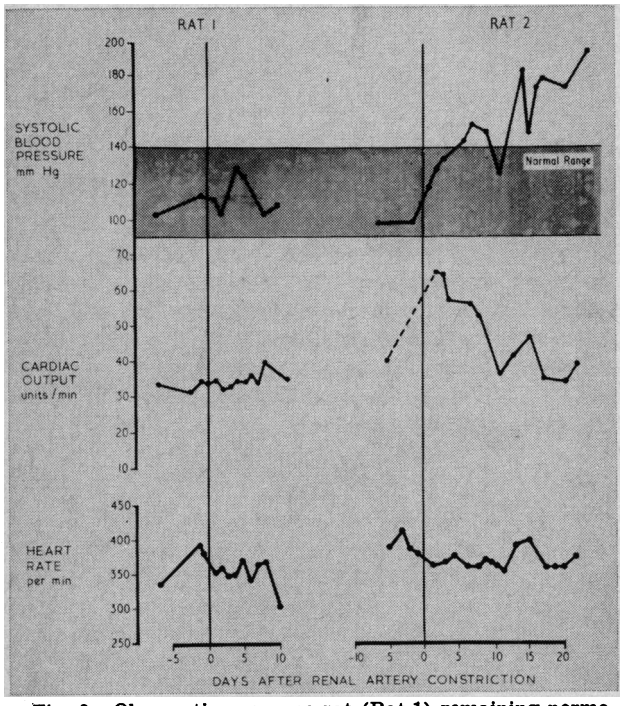

Fig. 6.—Observations on one rat (Rat 1) remaining normotensive and on another (Rat 2) developing hypertension rapidly. The latter showed an immediate rise in cardiac output and no reduction in rate.

DISCUSSION

If the primary change in the development of hypertension is an increase in peripheral resistance mediated by some agent acting solely on the arterioles, it would be expected that nervous baroreceptor reflexes would in the first place bring about bradycardia accompanied by a reduction in both stroke volume and cardiac output, as demonstrated in dogs by Daly and Luck.[2] Angiotensin infusions in unanesthetized dogs have been reported to cause similar changes.[3] The findings reported here are not consistent with the action either of angiotensin or of any other agent acting solely on the peripheral vessels in this developmental stage of hypertension. On the other hand, the data are compatible with the suggestion[4-6] that a rise in cardiac output may be the primary circulatory disturbance in the development of experimental renal hypertension. An increase in cardiac output, if sufficiently prolonged, would result in a rise of blood pressure, since accommodation of nervous baroreceptor responses is rapid.[7, 8] It has previously been suggested[4, 5] that the increased peripheral resistance in hypertension may be brought about by an inherent myogenic response of the arterioles[9] to the increased arterial pressure produced by such an increase in cardiac output. This response would cause the blood pressure to rise further. The pressure at the renal pressor receptors distal to the clip will consequently rise, and the stimulus to increased cardiac output will be removed. The situation known to exist in chronic hypertension, with normal cardiac output and raised peripheral resistance, would then be observed.

Possible mechanisms whereby cardiac output might be elevated in developing hypertension include increased atrial filling pressure and increased myocardial contractility. Previous studies of the circulatory changes during the *reversal* of experimental renal hypertension after release of renal artery constriction have suggested that both these factors may have contributed to the sharp reduction in cardiac output observed in this phase.[5]

The expansion of E.C.F.V. and P.V. that occurs during the development of experimental renal hypertension could be a factor in causing an increase in cardiac output and thus lead to hypertension. However, the overlap with the normotensive controls and the lack of correlation between expansion of the E.C.F.V. and the level of blood pressure, referred to earlier, suggest that this expansion cannot be the sole factor involved and it may not have any causal relation to the rise in blood pressure. The transient expansion may perhaps be mediated through the renin-angiotensin-aldosterone system, and the observations of Haynes and Dexter[10] on the level of circulating renin after renal artery constriction suggest that this hormone is transiently increased over the same period as has been found for E.C.F.V. Experiments are planned to clarify this point.

Recent observations by Floyer and Richardson[11] on renal hypertension in parabiotic rats suggest that an increase in capillary pressure follows renal artery constriction. However, it is generally agreed that angiotensin has no effect on capacity vessels.[12] Aldosterone on the other hand has been reported to increase myocardial contractility in hypodynamic heart muscle,[13] but the relevance of this property in the present context is uncertain.

SUMMARY

Evidence has been advanced which suggests that hypertension may be a new equilibrium state achieved by a process of transient elevation of cardiac output and maintained by an increased myogenic response to pressure in the arterioles. The role of renin in this process remains unknown.

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REFERENCES

1. LEDINGHAM, J. M.: *Clin. Sci.*, 12: 337, 1953.
2. DALY, M. DE B. AND LUCK, C. P.: *J. Physiol. (London)*, 143: 343, 1958.
3. PAGE, I. H. AND BUMPUS, F. M.: *Physiol. Rev.*, 41: 331, 1961.
4. LEDINGHAM, J. M.: Extrarenal factors in the pathogenesis of hypertension. *In*: Hypotensive drugs, edited by M. Harington, Pergamon Press, Inc., London, 1956, p. 183.
5. LEDINGHAM, J. M. AND COHEN, R. D.: *Clin. Sci.*, 22: 69, 1962.
6. *Idem*: *Lancet*, 1: 887, 1963.
7. KUBICEK, W. G. *et al.*: *Amer. J. Physiol.*, 175: 380, 1953.
8. MCCUBBIN, J. W., GREEN, J. H. AND PAGE, I. H.: *Circ. Res.*, 4: 205, 1956.
9. FOLKOW, B.: *Acta Physiol. Scand.*, 27: 99, 1952.
10. HAYNES, F. W. AND DEXTER, L.: *Amer. J. Physiol.*, 150: 190, 1947.
11. FLOYER, M. A. AND RICHARDSON, P. C.: *Lancet*, 1: 253, 1961.
12. FOLKOW, B., JOHANSSON, B. AND MELLANDER, S.: *Acta Physiol. Scand.*, 53: 99, 1961.
13. TANZ, R. D.: *J. Pharmacol. Exp. Ther.*, 135: 71, 1962.