Blood volume and interstitial fluid pressure in the development and reversal of renal hypertension in rats

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Summary

1. During the development and maintenance of one-kidney, one-clip hypertension in rats, there were no significant differences in blood volume or interstitial fluid pressure compared with one-kidney control rats.

2. Rats with one-kidney, one-clip hypertension of 25 days’ duration were either unclipped, sham-operated or nephrectomized. Over 24 h the changes in arterial pressure, blood volume and interstitial pressure in the sham and nephrectomized groups were insignificant. In the unclipped group arterial pressure decreased 50 mmHg to normal by 24 h and was associated with increased diuresis and a small decrease in blood volume (9.8%). Unclipped rats with the greatest urine outputs showed the largest decreases in interstitial pressure \( r = 0.70, P < 0.02 \).

3. Thus, in the reversal of this hypertension, changes in blood volume played only a partial role; decreased interstitial pressure was secondary to tissue fluid depletion from increased diuresis and normalization of arterial pressure required the presence of the unclipped kidney.

Key words: blood volume, Goldblatt rats, interstitial tissue pressure, renal hypertension.

Introduction

The pathogenesis of chronic experimental renovascular hypertension is incompletely understood (Davis, 1977). One approach to study possible mechanisms involved in this form of hypertension is to examine the physiological events that occur during its rapid reversal. Haemodynamic studies have shown that after removal of a constricting clip from the renal artery in renal hypertensive rats there was a rapid decrease in arterial pressure associated with decreased cardiac output (Ledingham & Cohen, 1962). Others have reported that, during the reversal of this form of hypertension, there was a decrease in plasma volume along with an apparent shift of fluid from the plasma compartment into the interstitium (Lucas & Floyer, 1974). It was suggested that this decrease in intravascular volume played an important role in the decreased cardiac output and consequent decrease in arterial pressure after removal of the renal artery constriction (Lucas & Floyer, 1974). However, these studies on changes in blood volume and interstitial fluid pressure during reversal of renal hypertension have neither been refuted nor confirmed. The purpose of the present study was to examine the changes in blood volume and interstitial fluid pressure during the development and reversal of one-kidney, one-clip hypertension in rats.

Methods

All surgical procedures were performed with ether as the anaesthetic agent. Acute experiments were conducted in conscious rats 3 or 24 h after surgical placement of appropriate catheters. One-kidney, one-clip hypertension was induced in male Wistar rats by removing surgically the left kidney and applying a tantalum clip (0.18–0.20 mm internal diameter) to the right renal artery. Rats serving as controls only had the left kidney removed. Tissue capsules (Guyton, 1963) were implanted, along with an attached catheter, in the subcutaneous tissue dorsal to the shoulder. Terminal experiments were conducted on samples of rats at 3, 28 or 56 days after renal artery clipping and/or unilateral nephrectomy and 2–4 weeks after capsule implantation.
Mean arterial pressure was measured from an indwelling catheter in the common carotid artery and interstitial fluid pressure was measured from the catheter connected to the tissue capsule. The transducer-recorder channel used for measuring interstitial fluid pressure was calibrated by using the centre of the capsule as the zero-pressure reference point and the fluid-filled catheter connected to the transducer as a water manometer. Plasma volume was measured by dilution of 125I-labelled human albumin (10 μCi/kg) and a single 10 min arterial blood sample, 0-1 ml in volume. Duplicate plasma samples (0.004 ml) obtained from this blood sample were used for radioactivity determination. Erythrocyte volume was measured by indwelling catheter in the common carotid artery erythrocyte volumes.

Reversal of hypertension

In a separate series of experiments, rats were implanted with tissue capsules and subjected to the one-kidney, one-clip procedure as described above. At 25 days post-clipping, mean arterial pressure, blood volume and interstitial fluid pressure were measured as described above. The hypertensive rats were then divided into three groups: unclipped (surgical removal of the renal artery clip); sham (surgical exposure of the renal artery, but the clip left in place); nephrectomy (removal of the sole clipped kidney). Changes in the above variables and urine output were measured as described above. The clip left in place); sham (surgical exposure of the renal artery, but the clip left in place); nephrectomy (removal of the sole clipped kidney). Changes in the above variables and urine output were measured as described above. The hypertensive rats were then divided into three groups: unclipped (surgical removal of the renal artery clip); sham (surgical exposure of the renal artery, but the clip left in place); nephrectomy (removal of the sole clipped kidney). Changes in the above variables and urine output were measured as described above. The hypertensive rats were then divided into three groups: unclipped (surgical removal of the renal artery clip); sham (surgical exposure of the renal artery, but the clip left in place); nephrectomy (removal of the sole clipped kidney). Changes in the above variables and urine output were measured as described above. The hypertensive rats were then divided into three groups: unclipped (surgical removal of the renal artery clip); sham (surgical exposure of the renal artery, but the clip left in place); nephrectomy (removal of the sole clipped kidney). Changes in the above variables and urine output were measured as described above.

Statistics

All groups consisted of 8–11 rats, except the control group studied at 56 days after operation, which consisted of five rats. All values are expressed as means ± SEM. Statistical significance was assessed by paired and unpaired t-tests. P < 0·05 was considered significant.

Results

In the samples of rats studied 3 days after clipping and/or unilateral nephrectomy, mean arterial pressure was significantly increased in the one-kidney, one-clip hypertensive group compared with the one-kidney control group (153 ± 5 and 127 ± 3 mmHg, P < 0·001). Mean body weight was 366 ± 12 and 358 ± 12 g in the hypertensive and normotensive groups respectively. Interstitial fluid pressure tended to be increased in the one-kidney, one-clip hypertensive group (−1·0 ± 0·2 mmHg) compared with that in the one-kidney control group (−1·4 ± 0·3 mmHg), but not significantly. Likewise, there was no significant difference in blood volume between the two groups (67·7 ± 2·7 in the one-kidney, one-clip hypertensive group and 67·6 ± 2·6 ml/kg in the one-kidney control group).

In the samples of rats studied at 28 days, mean arterial pressure was also significantly (P < 0·001) increased in the one-kidney, one-clip hypertensive group (162 ± 9 mmHg) compared with the one-kidney control group (122 ± 4 mmHg), and there were no significant differences between the hypertensive and normotensive groups respectively in body weight (365 ± 9 and 376 ± 15 g), interstitial fluid pressure (−1·2 ± 0·2 and −1·2 ± 0·2 mmHg) or blood volume (66·8 ± 1·8 and 65·5 ± 2·0 ml/kg).

Similar results were observed in the samples of rats studied at 56 days. Mean arterial pressure was significantly (P < 0·01) increased in one-kidney, one-clip hypertensive animals (164 ± 9 mmHg) compared with the one-kidney controls (120 ± 6 mmHg), and there were no significant differences between the hypertensive and normotensive groups respectively in body weight (410 ± 17 and 433 ± 20 g), interstitial fluid pressure (−1·3 ± 0·2 and −1·3 ± 0·4 mmHg) or blood volume (59·7 ± 1·8 and 57·6 ± 1·9 ml/kg).

Reversal of hypertension

The changes in variables that occurred after unclipping, sham unclipping or nephrectomy in rats with one-kidney, one-clip hypertension (25 days duration) are shown in Fig. 1. Only the rats undergoing unclipping showed a significant decrease in mean arterial pressure. Six hours after unclipping mean arterial pressure was decreased by 30 mmHg; but the changes in blood volume and interstitial fluid pressure were minimal and not significant. Twenty-four hours after unclipping mean arterial pressure was decreased by 50 mmHg. Blood volume was decreased...
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FIG. 1. Changes observed in one-kidney, one-clip hypertensive rats after unclipping (O---O), sham operation (■-----■) or nephrectomy (○-----○). Means values ± SEM; n = 8–11 per group. Body weights in the unclip, sham-operated and nephrectomized groups were 338 ± 7, 315 ± 10 and 334 ± 7 g respectively.

significantly by 2.3 ml (9.8%) and interstitial fluid pressure tended to be decreased, but not significantly, although in two animals showing very large urine outputs (21 and 29 ml/24 h) interstitial fluid pressure decreased by 5.4 and 12.3 mmHg respectively. Furthermore, there was a significant correlation between the 24 h urine output and the 24 h decrease in interstitial fluid pressure in the unclipped group (r = 0.70, P < 0.02).

Discussion

Surgical removal of the constricting clip from the renal artery in animals with one- or two-kidney hypertension almost invariably results in a rapid return of arterial pressure to normal levels within 2–24 h. Presently it is not known what mechanisms are responsible for this reversal of hypertension, although several factors have been shown to be relatively unimportant. Changes in plasma renin activity (Ten Berg, Leenen & De Jong, 1979), urinary kalikrein (Gulati, Carretero, Morino & Oza, 1976), prostaglandins (Romero, Ott, Aguilo, Torres & Strong, 1975) and sodium/potassium excretion (Neubig & Hoobler, 1975; Otsuka, Carretero, Albertini & Binia, 1979) have been shown to be of little importance or only partly responsible for lowering arterial pressure after unclipping in one-kidney, one-clip hypertension.

On the other hand, haemodynamic studies during the reversal of renal hypertension in rats showed that the decreased arterial pressure was associated with an early decrease in cardiac output (Ledingham & Cohen, 1962), and it was suggested that a reduction in plasma volume was at least partly responsible. In a later study, Lucas & Floyer (1974) reported that immediately after removal of the clip in rats with one-kidney, one-clip hypertension the decrease in arterial pressure was indeed associated with a decrease in plasma volume and decreased venous pressure; interstitial fluid pressure also decreased despite an increase in interstitial fluid volume. From these findings the authors suggested that the reduction in plasma volume was the result of fluid migration into the interstitium due to a primary decrease in interstitial fluid pressure, which could only have been brought about by an abrupt increase in interstitial compliance (Lucas & Floyer, 1974).

In the present study we found no evidence of altered interstitial fluid pressure or blood volume during the development and maintenance phases of one-kidney, one-clip hypertension in rats. Furthermore, during the reversal of this form of hypertension, large decreases in interstitial fluid pressure occurred only in some animals and appeared to be secondary to tissue fluid depletion resulting from increased diuresis. Thus these results do not suggest that the decrease in interstitial fluid pressure was a primary event during hypertension reversal.

In the unclipped group, blood volume decreased only slightly during the first 6 h (less than 5%) and could not account for the 30 mmHg drop in arterial pressure. Likewise, by 24 h after removal of the clip, blood volume was decreased by only 9.8%, and it is unlikely that it was totally responsible for the 50 mmHg drop in mean arterial pressure (Gauer, Henry & Behn, 1970). Thus mechanisms other than decreased blood volume must also play an important role in the reversal of renal hypertension.

Since extracellular fluid volume was not measured in these experiments, it was not certain whether or not there was a fluid shift into the interstitium, as suggested by Lucas & Floyer (1974). However, our finding of a small decrease
in blood volume could be explained by the increased diuresis and does not require the hypothesis of an internal fluid transfer. Indeed, the observation that the greatest decrease in interstitial fluid pressure occurred in those animals with the largest increase in urine output suggested that fluid was actually lost from the interstitium.

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References


