Cardiovascular design after ‘reversal’ of long-standing renal hypertension in rats

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Summary

1. After 4.5 months of renal hypertension in rats renal artery ‘declipping’ was performed. Eight weeks afterwards paired hindquarter perfusions were performed on the declipped rats and normotensive control rats, exploring the relationships between mean arterial pressure and flow, from maximal vasodilatation to maximal vasoconstriction, induced by graded noradrenaline infusions. Left ventricular weights were measured.

2. Declipping caused a fall in mean arterial pressure from 180 to 135 mmHg, though still after 8 weeks the mean pressure was 19% higher than in normotensive control rats.

3. All parameters reflecting design and reactivity of the resistance vessels and left ventricular weight decreased significantly, but not as much as mean arterial pressure, and were still significantly increased compared with those of control rats.

4. Thus neither mean arterial pressure nor cardiovascular design was normalized 8 weeks after ‘reversal’ of long-standing renal hypertension, in contrast to short-standing renal hypertension where both are completely normalized 3 weeks after declipping.

Key words: pressure–flow, renovascular hypertension, resistance vessels.

Abbreviations: MAP, mean arterial pressure; NA, noradrenaline.

Introduction

The importance of the duration of hypertension for normalization of the cardiovascular design after reduction of blood pressure is of great interest in analysing the effects of antihypertensive treatment.

After reversal of established renal hypertension of short duration in rats mean arterial pressure decreased rapidly, followed by complete normalization of cardiovascular design after 3 weeks (Lundgren, 1974). In spontaneously hypertensive (SH) rats it seems more difficult to achieve structural cardiovascular normalization, even if reduction in mean pressure occurs early in life. Further, the greater the age of SH rats and the more longlasting their hypertension, the more difficult it is to induce regression of hypertensive structural cardiovascular changes (Weiss, 1974).

The present study was performed in order to investigate how rapidly, and to what extent, hypertensive cardiovascular changes show regression after ‘reversal’ of long-standing renal hypertension in rats.

Methods

Renal hypertension was induced in 13 7-week-old male normotensive Wistar rats by left renal artery clipping, leaving the right kidney intact. After 4.5 months the clip was removed. Mean arterial pressure (MAP) during conscious resting conditions was measured in the caudal artery before and at different intervals after declipping.

Eight weeks after declipping paired perfusion experiments were performed on the hindquarter vascular beds of the declipped renal hypertensive (D–RH) rats and matched normotensive controls (NC rats) (Lundgren, 1974). Pressure–flow relationships during complete vasodilatation were examined. Flow was then set to 10 ml min⁻¹ 100 g⁻¹ and resistance responses to increasing noradrenaline (NA) concentrations were investigated. Maximal pressor response was achieved by supra-
maximal doses of vasopressin and barium chloride. Resistance at maximal dilatation, threshold NA concentration, M50 (i.e. the NA concentration producing 50% of the maximal NA pressor response), steepness of the resistance curve and maximal pressor response were deduced for each pair of dose–response curves. Means ± se were calculated and the differences between D–RH and NC rats were analysed by paired t-test.

Left heart ventricles were weighed and means ± se of the percentage left ventricular weight/body weight were calculated.

Results

MAP during awake conditions before declipping, i.e. 4–5 months after clipping, was 180 ± 5 mmHg. One day after declipping MAP was 110 ± 8 mmHg but it then increased gradually, being 135 ± 6 mmHg after 8 weeks. Though MAP was then significantly decreased compared with RH rats, it was significantly higher (19%) than in matched NC rats.

Resistance to flow during maximal vasodilatation was 11% higher in D-RH rats than in NC rats (3.29 ± 0.08 vs 2.96 ± 0.09; P < 0.03 at 10 ml min⁻¹ 100 g⁻¹ and 1.95 ± 0.08 vs 1.76 ± 0.07; N.S. at 30 ml min⁻¹ 100 g⁻¹). No significant differences in NA ‘thresholds’ or in M50 were found between D-RH and NC rats. Steepness of the resistance curve for D-RH rats was increased 40% and maximal pressor response 24% (P < 0.002 and P < 0.001 respectively; Fig. 1).

Percentage left ventricular weight/body weight was 29% higher in D-RH rats than in NC rats (0.206 ± 0.004 and 1.160 ± 0.003 respectively; P < 0.001).

Discussion

The degree of reversibility of hypertensive cardiovascular changes after reversal of hypertension is of great importance for judging the true effects of antihypertensive treatment. Perfusion studies after reversal of established renal hypertension of short duration in rats reveal that complete normalization of MAP as well as of cardiovascular design has occurred by 3 weeks after declipping (Lundgren, 1974). This is not the case in SH rats, where cardiovascular design is not completely normalized even if MAP is reduced very early in life. Further, if antihypertensive treatment is first started at 12 months of age in SH rats it influences hypertensive cardiovascular changes so little that they appear to be largely irreversible at that stage (Weiss, 1974).

The present results showed that MAP was reduced but not normalized 8 weeks after declipping in rats with long-standing renal hypertension.

![Fig. 1](image)
Cardiovascular changes in long-standing hypertension

Also the hypertensive cardiovascular changes showed significant regression (Fig. 1), but not to the same extent as MAP and all parameters reflecting design remained significantly increased compared with values in NC rats. Steepness of the resistance curve, reflecting average wall/lumen ratio of the resistance vessels, was the least affected by MAP reduction, being 40% increased 8 weeks after declipping compared with NC rats. Thus 'reversal' of long-standing renal hypertension does not cause complete regression of cardiovascular changes, as is the case after shortlasting renal hypertension (Lundgren, 1974).

Hence, the higher the age of animals and the more longlasting the hypertension, the less complete the regression of hypertensive structural cardiovascular changes. This may at least in part be due to structural changes in heart and vessels such as collagen endowment, which develops more gradually than muscle hypertrophy and which shows far less of regression than muscle hypertrophy upon pressure normalization (Wolinsky, 1971).

Together, these results illustrate the advantage of early therapy. Thus, if MAP is normalized in early phases, structural cardiovascular changes may disappear completely, at least in secondary hypertension. However, once collagen invasion has further added to wall thickness in the heart and vessels this component tends to remain, thereby decreasing the chances for full reversal of the hypertension.

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References

