Study of Renovascular Hypertension in Rats: I. The Role of the Contralateral, Non-clipped Kidney in Two-kidney, One-clip Hypertension in Rats

Kazuo MATSUSHITA

Department of Urology, Tokyo Hospital, Tokai University School of Medicine

(Received June 18, 1984)

We attempted to produce two-kidney one-clip renovascular hypertension in SD rats, using hemoclips 0.2mm in diameter. After 12 weeks, 10 of the 16 rats were hypertensive. At this point, one-kidney, ond-clip models were prepared by contralateral nephrectomy in five of the 10 hypertensive rats and in all six normotensive rats. Postoperatively, these 11 rats developed hypertension. Four to 6 weeks later, the clip was removed from the renal artery in five two-kidney and 11 one-kidney hypertensive rats. After unclipping, all the rats became normotensive although the extent of the fall in blood pressure in the one-kidney model was significantly greater than in the two-kidney model.

The roles of the contralateral non-clipped kidney in the evolution of two-kidney, one-clip Goldblatt hypertension appear to be dual; sometimes depressing elevated blood pressure and sometimes maintaining it. Thus, it is postulated that in the six initially normotensive rats, its action was predominantly anti hypertensive, while in the other 10 hypertensive rats, the presence of a contralateral non-clipped kidney served to develop and maintain hypertension even after unclipping.

(Key Words: Two-kidney, one-clip hypertension, Contralateral nephrectomy, Unclipping)

INTRODUCTION

In 1939 Wilson and Byrom produced renovascular hypertension in rats by applying a stenotic clip to the renal artery on one side with the opposite kidney untouched (10), as did Goldblatt in dogs. Since then, a number of studies have been undertaken using two-kidney one-clip models in various animals with the aim of understanding the mechanism of renovascular hypertension. In the two-kidney, one-clip Goldblatt hypertension model (2 KGH) in rats, it is postulated that the renin-angiotension system is responsible for development of early phase hypertension since the plasma renin concentration and angiotension II level are elevated within hours following application of a clip to the renal artery (7, 9), and that in this early stage, any one of the inhibitory agents of the renin-angiotension system usually depresses elevated blood pressure (4, 8). In the course of 8 or more weeks after clipping, hypertension becomes established. However, the plasma levels of renin and angiotensin II are not always increased (7, 1). In the chronic phase of hypertension of more than 12 weeks' duration, saralasin, an angiotensin receptor antagonist, causes a significant fall in blood pressure in salt-depleted rats, but not in salt-repleted rats (2). The mechanism of 2 KGH in rats has not been fully explained by angiotensin-induced vasoconstriction alone, particularly in the late stage. Altered excretory function of the non-clipped kidney induced by elevated levels of angiotensin II has been suggested as one of the potential causes (9).

The present study was undertaken to investigate the roles of the contralateral, non-clipped kidney in the chronic phase of a two KGH model rat with respect to effects of nephrectomy (contralateral nephrectomy) and removal of the clip from the clipped renal artery.
MATERIALS AND METHODS (Fig. 1)

A total of 16 male SD rats weighing 180 to 200g were used. They were anesthetized with intraperitoneal injections of 0.3 ml of nembutal. The right femoral artery was exposed and cannulated with a 23-gauge needle which was connected to a pressure transducer (MPU-0.5, Nihon Koden Co. Ltd.) for direct measurement of arterial systolic pressure. Through upper median laparotomy, the left renal artery was clipped with a tantalum hemoclip of 0.2 to 0.25mm in diameter. The right kidney was untouched. Five sham-operated rats underwent arterial cannulation, laparotomy and exposure of the left renal artery only.

Twelve weeks after production of the two KGH model, the femoral artery was cannulated and the blood pressure (BP) was recorded under pentobarbital anesthesia. At this point, the animals were divided into two groups, an elevated BP group and an unchanged BP group. Five rats with elevated BP and all rats with unchanged BP underwent contralateral right nephrectomy. Four to 6 weeks later, right iliac arterial cannulation was performed and 800μg/kg of 1-Sar-8-Ieu angiotensin II (Daiichi Seiyaku Co. Ltd.) was infused through it. The BP was continuously monitored and recorded for 30 minutes. The angiotensin II analog was also administered to five other rats with elevated BP but without contralateral nephrectomy. At the end of this test, the clip on the left renal artery was removed in all rats. Seven days after unclipping, the animals were anesthetized, the left iliac artery cannulated, the BP recorded and finally the remaining kidneys removed for histologic studies.

RESULTS

Twelve weeks after preparation of the two KGH model, elevation of BP was observed in 10 of the 16 rats (mean: 148 ± 7.5mmHg SD), while in six, it was unchanged (116 ± 8.0mmHg). Five of the 10 elevated BP group rats and all six unchanged BP group rats underwent contralateral nephrectomy. Four to 6 weeks thereafter, they were all hypertensive (150 ± 9.8 and 148 ± 14.8mmHg respectively, Figs. 2 and 3). Infusion of 1-Sar-8-Ieu angiotensin II caused no significant change in BP. Removal of the clip from the left renal artery in 9 of these 11 rats resulted in a fall of BP to 102 ± 9.1mmHg (Fig. 2). Unclipping in the other five hypertensive rats with no contralateral nephrectomy reduced the BP to a pre-clipping normal level, 126 ± 8.0mmHg. The extent of the fall in BP was more significant in one-kidney, one-clip rats than in two-KGH rats (P<0.01, Fig. 4).

In two KGH model rats which had been hypertensive for more than 16 weeks, the arteriolar wall of the contralateral, non-clipped kidneys was thickened to a mild degree (Fig. 5).

In the sham-operated group, no remarkable change in blood pressure was caused by contralateral nephrectomy or infusion of the angiotensin II analog.

DISCUSSION

It is known that in two-KGH models produced by application of a stenotic clip to one renal artery, all rats do not develop hypertension, while in the one-KGH model with a clip on one renal artery followed by contralateral nephrectomy, almost all rats become hypertensive. The incidence of sustained hypertension in two-KGH rats was reported to range between 60 and 80 per cent (5). The severity of hypertension is believed to be determined by the diameter of the stenotic clip (6).

We succeeded in establishing hypertension in 10 of 16 rats of the two-KGH model (62.5 per cent) using a stenotic clip of 0.25mm in diameter. The size of the clips was sufficient to induce renovascular hypertension as proved by the development of hypertension in all six initially normotensive rats following contralateral nephrectomy which was performed 12 weeks after preparation of the two-KGH model (Fig. 3B). These results suggested that in some two-KGH rats, non-clipped untouched kidneys may have antihypertensive action opposing the stimulated renin-angiotensin system. In contrast, the role of the non-clipped kidneys of the 10 rats which became hypertensive soon after clipping of one renal artery might be quite different from that mentioned above. It can be partially explained by altered excretory function induced in the non-clipped kidneys due to elevated plasma angiotensin II levels which causes sodium and water retention with resultant hypertension (8).
Thus, it was suggested that the non-clipped kidneys in two-KGH rats had a dual action, i.e., sometimes hypertensive and sometimes antihypertensive. In the two-KGH model in any case, development of hypertension is dependent on the condition of the contralateral non-clipped kidney and not on the ipsilateral clipped kidney. Intrarenal arteriolar changes, functional or organic, have been regarded as one of the potential causes. In fact, in our experiment, removal of the stenotic clip restored the blood pressure to the pre-clipping normal level in one-KGH model rats but not in two-KGH model rats. This may be attributed to an arteriolar narrowing lesion which was demonstrated in the contralateral non-clipped kidney and seemingly had resulted from long-standing hypertension (Fig. 5).

The determinant factors in the behavior of the opposite non-clipped kidney in the two-KGH model remains to be investigated, particularly how and when antihypertensive action occurs.

REFERENCES
6) Leen FHH, Dejong W: A solid silver clip for induction of predictable levels of renal hypertension in the rat. J. Appl. Physiol. 31: 142-144, 1971
METHODS

Two-kidney, one-clip model in 16 male SD rats

Contralateral nephrectomy

Blockade with Sar¹, Ileu⁶ angiotensin II

Unclip

Fig. 1  Summary of methods.

Preoperative blood pressure in rats
110 ± 6.4 mmHg

12 weeks after renal artery stenosis

BP elevated

BP unchanged

(A) 148 ± 7.5
n = 10

116 ± 8.0
n = 6

4-6 weeks after contralateral nephrectomy

Unclip

150 ± 9.8
p < 0.01
n = 5

148 ± 4.8
n = 6

102 ± 9.1
n = 9*

126 ± 8.0
n = 5

Fig. 2  Summary of results.
*Two rats died after contralateral nephrectomy.
**EFFECT OF CONTRALATERAL NEPHRECTOMY**

![Graph showing blood pressure levels after contralateral nephrectomy](image)

- **A**: Elevated BP Group after 12 weeks
- **B**: Unchanged BP Group after 12 weeks

**Fig. 3** The animals were divided into two groups after 12 weeks according to blood pressure.

**EFFECT OF UNCLIPPING**

![Graph showing blood pressure levels after unclipping](image)

- **Two-kidney model**: 126 ± 8.0
- **One-kidney model**: 102 ± 9.1

**Fig. 4** Although unclipping restored the elevated blood pressure to a normal level, the mean value was significantly different between the two-kidney model and one-kidney model.
Fig. 5  Contralateral non-clipped kidney. Arteriolar wall thickness with resultant narrowing of the lumen. (×400)