Effects of Graded Renal Artery Constriction on Blood Pressure, Renal Artery Pressure, and Plasma Renin Activity in Goldblatt Hypertension

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SUMMARY: One-kidney, one clip (1K1C) and two-kidney, one clip (2K1C) Goldblatt hypertension was produced in rats by placing 0.30, 0.25, or 0.20 mm silver clips on the left renal artery. Mean arterial pressure (MAP) and plasma renin activity (PRA) were measured in conscious rats 24 to 28 days after clipping. The MAP in control rats (n = 38) was 116 ± 1 mm Hg (mean ± SEM). The 0.30, 0.25, and 0.20 mm clips produced MAPs of 133 ± 2, 161 ± 5, and 189 ± 5 mm Hg, respectively, in 1K1C rats, and 123 ± 2, 129 ± 3, and 172 ± 5 mm Hg in 2K1C rats (n = 17–20). When 1K1C and 2K1C groups were compared, MAP was significantly greater in 1K1C rats at all clip sizes. No treatment group's PRA was different than control (4.8 ± 0.4 ng Al/ml/hr), except for the 0.20 mm 2K1C rats (16.2 ± 3.1 ng Al/ml/hr). Renal artery pressure (RAP) was measured in another series of experiments and was not different from control in all but the 0.20 mm 1K1C rats. With identical clip sizes, 2K1C rats showed smaller pressure gradients than 1K1C across the clips: 0.30 mm, 8.5 ± 1.7 vs 10.7 ± 1.9 mm Hg; 0.25 mm, 16.5 ± 1.2 vs 42.1 ± 7.5 mm Hg; 0.20 mm, 51 ± 5.3 vs 79.1 ± 5.7 mm Hg (n = 8–12). Therefore, both the increase in MAP and the pressure gradient across the clip were greater in the 1K1C rats at every clip size. In total, these data indicate that RAP is controlled to maintain a normal pressure in both models of Goldblatt hypertension. In 1K1C rats, RAP is normalized in conjunction with a rise in MAP. In the 2K1C rats, we propose that an increase in the clipped kidney's renal vascular resistance, secondary to renal atrophy, acts to increase RAP without hypertension. With severe renal artery clipping in 2K1C animals, renal atrophy alone may not fully restore RAP; in this case the hypertension is required to normalize RAP. (Hypertension 6:68-74, 1984)

KEY WORDS: • Goldblatt hypertension • two-kidney, one clip • one-kidney, one clip

BOTH the one-kidney, one clip (1K1C) and two-kidney, one clip (2K1C) models of Goldblatt hypertension result from renal artery constriction, yet the etiology and ultimate severity of the hypertension is different for each model. With equivalent renal artery constriction, 1K1C animals usually show a greater increase in blood pressure compared to 2K1C animals. The degree of hypertension in 1K1C animals is generally predictable; however, hypertension development in the 2K1C model is frequently variable, with some animals never becoming hypertensive. For instance, researchers often prepare many 2K1C rats and then select only those rats with pronounced hypertension. The 2K1C animals that do develop significant hypertension often enter into a malignant phase of hypertension; this transition to malignant hypertension does not occur as readily in 1K1C animals.

Renal artery constriction has different effects on the renin-angiotensin system in each of the two Goldblatt hypertension models. Initially following renal artery constriction, plasma renin activity (PRA) increases in the 1K1C model, but returns to normal in the established phase of hypertension. Blockade of the renin-angiotensin system does not prevent 1K1C hypertension in the rat, but does affect the final level of hypertension by 10 to 15 mm Hg. In 2K1C animals, PRAs are also acutely elevated following renal artery constriction. Some investigators have found that PRAs remained elevated in the chronic phase of 2K1C hypertension, while others have reported that PRAs returned to normal. The importance of the renin-angiotensin system in 2K1C Goldblatt hypertension is underscored by the fact that chronic converting-
enzyme inhibition prevents the hypertension and will reverse existing 2K1C hypertension.2,3

In 1K1C hypertension, both renal artery pressure (RAP) and renal blood flow (RBF) initially fall following renal artery constriction and later return to normal in established hypertension.4,5 The hypertension, in effect, offsets the constriction and returns the kidneys' pressure and/or flow to normal. The hemodynamic factors underlying the development of 2K1C Goldblatt hypertension have not been as well documented. It is commonly assumed that a chronically subnormal RAP distal to the renal artery constriction is the reason for the increased PRA and angiotensin II (AII) levels associated with 2K1C hypertension. As the arterial pressure begins to rise in the 2K1C animal, the unclipped contralateral kidney will excrete more salt and water,6 and for this reason the unclipped kidney will oppose the rise in arterial pressure. It has therefore been hypothesized that pressure and flow are never fully restored to the constricted kidney; this abnormality theoretically remains as the stimulus to renin release and perpetuates the hypertension.7,8

The purpose of this study was to compare and contrast 1K1C and 2K1C animals subjected to equivalent degrees of renal artery constriction in an attempt to determine which factors are critical to hypertension development. The effects of graded renal artery constriction on blood pressure, renal artery pressure distal to the constriction, plasma renin activity, and kidney mass have been examined in both 1K1C and 2K1C models. From these data we have been able to address several questions concerning the development of hypertension in each of the Goldblatt models.

Methods

Male Sprague-Dawley rats weighing 140 to 190 g were anesthetized with sodium pentobarbital (50 mg/kg). A midline abdominal incision was performed to provide access to both the left and right kidneys. In 1K1C animals, a small U-shaped silver clip was placed on the left renal artery, and the right kidney was removed. The left renal artery was similarly clipped in 2K1C animals, while the contralateral kidney remained untouched. Procaine penicillin-G (30,000 U) was applied to the clipped renal artery, and the incision was then closed. Three clip sizes were used in the study: a loose clip (0.30 mm I.D.), an intermediate sized clip (0.25 mm I.D.), and a tight clip (0.20 mm I.D.). Two sham-clipped groups were also prepared to serve as controls: a one-kidney, no clip (1KNC) group and a two-kidney, no clip (2KNC) group. Along with the 1KNC and 2KNC groups, a "normal" control group of rats, not subjected to prior anesthesia or surgery, was included in the first series of experiments. Rats were maintained on standard laboratory rat chow (Purina) and provided water ad libitum.

In the first series of experiments, previously clipped or control rats were reanesthetized approximately 3½ weeks following the initial surgery, and the left femoral artery was catheterized with P.E. 50 tubing. Catheters were tunneled subcutaneously to exit in the interscapular region on the rat's back. Arterial pressure was measured in conscious rats 24 to 28 days after renal artery clipping and within 2 days following femoral artery catheterization. Animals that showed signs of hindlimb ischemia following catheterization or exhibited less than full recovery from the surgery were excluded from the study. Arterial pressures were recorded in a quiet room, and normally it took 20 to 30 minutes before a stable basal arterial pressure was attained. Pressures were measured using a Statham P23ID transducer and recorded on a Glass Model 7 polygraph. The arterial pressure signal was electronically averaged, and mean arterial pressure (MAP) values are presented in the text. After recording MAP, a 3 ml blood sample was drawn for the determination of plasma renin activity; samples were drawn via the indwelling arterial catheter within 15 seconds. Samples were collected in chilled tubes containing 5 mg sodium EDTA. PRA was measured by radioimmunoassay using a Squibb Angiotensin I Immunotope kit.

Renal artery pressure was measured in a second series of animals during the study. Rats were reanesthetized 24 to 28 days after clipping, and a P.E. 50 catheter was advanced via the left femoral artery into the aorta to approximately the level of the kidneys. The left kidney was approached by a midline abdominal incision and under a dissecting microscope (Wild-Heerbrugg, M8) 2 to 3 mm of renal artery distal to the silver clip was carefully cleared of connective tissue and adventitia using fine forceps. RAP was measured by direct puncture of the renal artery using a glass micropipette with a tip diameter of approximately 100 μ. The micropipette was fitted into a three-way stopcock attached to an ultra-low displacement pressure transducer (Century Technology Company, Model CP-01) mounted on a micromanipulator. The RAP signal was also electronically meaned and RAP refers to a mean renal artery pressure distal to the clip. This technique for measuring RAP does not alter renal blood flow (RBF),9,10 and typically RAP is 3 to 4 mm Hg lower than simultaneously recorded MAP.

MAP and RAP data from each rat are an average of 10 observations taken at 10-second intervals after the preparation had stabilized. Group values presented in the text are means ± 1 SEM. The number of animals per group is indicated in each figure in parentheses.

Comparisons between 1K1C and 2K1C groups with the same size clip were performed using the Student's t test. In cases where all treatment groups were compared to a control group, Dunnett's test for multiple comparisons was used to determine significance levels. Analysis of variance and the Bonferroni method for multiple comparisons were used to determine whether there was a statistical difference among the 2KNC, 1KNC, and "normal" control groups. Comparisons between MAP and RAP were tested for significance using the paired t test.
**Results**

The NC (no clip) control values for MAP and PRA plotted in Figures 1 and 2 represent a compilation of the 1KNC, 2KNC, and "normal" control groups. The MAP in the 1KNC group was 117 ± 3 mm Hg (n = 10), 120 ± 2 mm Hg in the 2KNC rats (n = 10), and 114 ± 1 mm Hg in the "normal" control animals (n = 18). The PRA for the 1KNC, 2KNC, and "normal" control groups was 3.7 ± 0.4, 4.6 ± 0.7, and 5.6 ± 0.7 ng Al/ml/hr, respectively. All possible comparisons among the three control groups were tested (1KNC vs 2KNC, 1KNC vs "normals," 2KNC vs "normals"), and the groups were not found to be statistically different with respect to either MAP or PRA. Data from the three groups were combined into a single control group (n = 38) with a MAP of 116 ± 1 mm Hg and a PRA of 4.8 ± 0.4 ng Al/ml/hr. This combined control data will be referred to in the text simply as the control data.

MAP data measured in conscious 1K1C and 2K1C rats at the three levels of renal artery constriction are presented in Figure 1. In all six groups with renal artery constriction, the MAPs were significantly greater than those in the control rats for all clip sizes (p < 0.01). The 1K1C rats were also found to have significantly higher MAPs at each clip size than comparable 2K1C rats (p < 0.05).

The effect of renal artery constriction on PRA in both Goldblatt hypertension models is shown in Figure 2. None of the three 1K1C groups had PRAs significantly different from control. In the 2K1C rats, neither the 0.30 mm nor the 0.25 mm clip groups had PRAs statistically different from control. However, PRA was found to be significantly greater in the 0.20 mm 2K1C group (p < 0.01); PRA was 16.2 ± 3.1 ng Al/ml/hr, some threefold greater than control. The PRA in the 0.20 mm 2K1C group was also significantly higher than the corresponding PRA in the 0.20 mm 1K1C rats (p < 0.01). The 0.20 mm 2K1C animals could almost be evenly divided into two subgroups on the basis of PRA. Nine animals had a MAP of 186 ± 7 mm Hg with a PRA of 30.4 ± 1.7 ng Al/ml/hr. The other 11 rats were less hypertensive, with a MAP of 160 ± 5 mm Hg, but with PRAs in the normal range (4.5 ± 1.3 ng Al/ml/hr).

In the 1K1C rats presented in Figure 3, all three groups plus the control 1KNC group had significantly higher MAPs than simultaneously recorded RAPs (p < 0.01). Although the difference between the aortic and renal artery pressures in the 1KNC rats was only 3 ± 1 mm Hg, this difference was significant and agreed with preliminary work from this laboratory using rats without renal artery constriction. Compared to the RAPs in 1KNC controls (133 ± 4 mm Hg), RAPs in neither
FIGURE 3. Aortic pressure at kidney level and simultaneously measured renal artery pressure in 1KIC rats. All comparisons are to control. *p < 0.05; **p < 0.01.

FIGURE 4. Aortic and renal artery pressure in 2KIC rats. RAP was not different from control in any of the groups. All comparisons are to control. *p < 0.05; **p < 0.01.

The 0.30 mm nor the 0.25 mm clip groups were statistically different from control. The RAP in the tightly clipped 0.20 mm 1K1C group was found to be significantly less than control (p < 0.05). MAPs recorded in anesthetized 0.20 mm and 0.25 mm 1K1C rats were significantly greater than in 1KNC controls (p < 0.01), while MAPs in the 0.30 mm group were not different than control. In the 2K1C rats (Figure 4), none of the groups with renal artery constriction had RAPs statistically different from the 2KNC controls (132 ± 5 mm Hg). MAPs in anesthetized 2K1C 0.30 mm clipped rats were not statistically greater than control, whereas for the 0.25 mm (p < 0.05) and the 0.20 mm (p < 0.01) 2K1C groups, the MAPs were higher than control. Like the 1K1C animals, MAPs in the 2KNC rats were all greater than simultaneously measured RAPs for all clip sizes (p < 0.05).

The pressure gradients across each renal artery clip in both 1K1C and 2K1C rats are presented in Figure 5. The recorded difference between MAP and RAP in the 1KNC (3.2 ± 1.1 mm Hg) and the 2KNC (2.9 ± 0.9 mm Hg) control groups was nearly equal. The pressure gradient produced by mild renal artery constriction (0.30 mm clip) was small and not statistically different when 1K1C (10.7 ± 1.9 mm Hg) and 2K1C (8.5 ± 1.7 mm Hg) animals were compared. In the case of the 0.25 mm clip, the pressure drop across the clip in the

FIGURE 5. Pressure gradient (aortic-renal artery pressure) across each clip in 1K1C and 2K1C rats.
FIGURE 6. Kidney weights in 1K1C and 2K1C rats at each clip size and controls (NC). Comparisons are to the appropriate control kidney. *p < 0.05; **p < 0.01.

1K1C rats was 42.1 ± 7.5 mm Hg, which was significantly greater than the resulting 16.5 ± 1.2 mm Hg pressure gradient in 2K1C rats (p < 0.01). The pressure gradient across the 0.20 mm clip in the 1K1C rats was 79.1 ± 5.7 mm Hg; the 0.20 mm clip’s pressure gradient in the 2K1C rats was 51.6 ± 5.3 mm Hg, nearly 30 mm Hg less than that in the 1K1C rats (p < 0.01).

Animal growth of the 1KNC and 2KNC controls did not differ 24 to 28 days following sham clipping; their weights were 343 ± 9 g and 346 ± 5 g, respectively. None of the 2K1C groups was significantly different in body weight compared with the 2KNC controls. Of the 1K1C rats, only the 0.20 mm clip rats weighing 311 ± 6 g were found to be significantly smaller than the 1KNC controls (p < 0.05).

Renal artery constriction produced large changes in kidney mass in both models of Goldblatt hypertension. Right renal nephrectomy in the 1KNC rats was responsible for a 48% increase in left kidney mass compared to the left kidneys of the 2KNC rats (p < 0.01). Kidney weights, normalized per 100 g body weight, are presented in Figure 6. None of the three 1K1C groups had normalized kidney weights different from the 1KNC controls. The difference between left and right kidney weights in the 2KNC group was not significant, but significant changes in 2K1C kidney weights did develop after clipping. All of the contralateral unclipped kidneys displayed significant hypertrophy (p < 0.05); increases in kidney weight ranged from 14% to 22% compared to the 2KNC right kidneys. Whereas the unclipped kidneys hypertrophied following renal artery constriction, the clipped kidneys showed a reduction in mass. The left kidneys in the 0.30 mm 1K1C rats were 10% smaller, but not statistically different, than control. Left kidneys in the 2K1C 0.25 mm and 0.20 mm clipped rats were 21% and 23% smaller than control (p < 0.01).

Discussion

Both models of Goldblatt hypertension can be readily produced in the rat, in contrast to the dog where the 2K1C model has often been difficult to produce. The techniques used to produce 2K1C Goldblatt hypertension in the dog require severe renal artery constriction, and normotension may return with the development of collateral renal circulation. The rat is not prone to the development of collateral circulation following renal artery constriction.

Goldblatt hypertension has been traditionally produced in the rat by applying a small silver clip to the renal artery. The degree of renal artery constriction can be precisely controlled by adjusting the internal dimensions of the silver clip. We chose the rat as our experimental animal because of this ability to produce the same degree of renal artery constriction (RAC) easily and repeatedly and because 2K1C hypertension has been reliably produced in the rat by other researchers.

Blood pressures in 1K1C animals were significantly greater than in 2K1C rats for all clip sizes. Whereas the tighter clips caused a progressive MAP increase in the 1K1C rats, pressures increased only slightly in 2K1C rats with the 0.30 mm and 0.25 mm clips. The increase in MAP was statistically significant in all 2K1C groups compared to control; however, only in the 0.20 mm animals was there a substantial increase in MAP. Our data suggest that a critical degree of stenosis must be reached before pronounced hypertension occurs in the 2K1C model. In contrast, Leenan and de Jong17 saw a progressive rise in blood pressure with increasingly severe RAC in 2K1C Goldblatt rats. When recording systolic blood pressures by the tail-cuff method, they found that pressures at each clip size were much higher than control. The difference between our findings and those of Leenan and de Jong probably lies in how the blood pressures were recorded. The tail-cuff measurement technique is known to produce stress, which would cause the recorded systolic pressures to be artificially high. Bunag18 has reported that 2K1C rats, which exhibited only mild hypertension (115 ± 9 mm Hg) when MAP was recorded by an indwelling catheter, became very hypertensive when blood pressure was measured by the tail-cuff technique (185 ± 8 mm Hg).

Plasma renin activities were not found to be statistically different from control in any of our 1K1C groups. In the 2K1C animals, PRAs were not increased in
either the 0.30 mm or 0.25 mm clip groups, although a small increase in MAP was evident in both groups. In the 2K1C 0.20 mm clipped group, the average of the PRAs was approximately threefold higher than that of controls; however, only half of the animals actually showed an increase in PRA. Similar findings have been reported by Oates et al. in 2K1C Goldblatt rats. PRAs have been found to be chronically elevated in 2K1C hypertensive dogs by some investigators, while other researchers have reported normal or near normal PRAs in 2K1C hypertensive dogs.

These results again bring into question the importance of the renin-angiotensin system in the chronic phase of 2K1C Goldblatt hypertension. In the initial phase of 2K1C Goldblatt hypertension, the pressure increase is dependent on the renin released by the clipped kidney and on increased circulating levels of All. The increased All levels have an antinatriuretic effect on the contralateral kidney, which is thought to cause the hypertension. The chronic mechanisms behind 2K1C Goldblatt hypertension are less clear. One hypothesis is that an All-mediated retention of salt and water is responsible for chronic 2K1C hypertension. This hypothesis, however, does not explain 2K1C hypertension when PRAs are not elevated. After renal artery clipping, the contralateral kidney is exposed to increased arterial pressure and shows a decreased renin content. The bulk of the circulating renin in 2K1C animals is presumably released from the clipped kidney. We can only speculate that the renin-depleted unclipped kidney becomes supersensitive to circulating All. A supersensitivity to circulating All would explain how an All-dependent 2K1C hypertension could occur with normal or only slightly elevated plasma renin levels.

Following RAC, both PRA and renal perfusion pressure return to normal in the 1K1C model, but it is generally assumed that in the 2K1C model RAP is chronically subnormal. The reduced RAP is thought to be the stimulus for the higher PRAs in 2K1C hypertension. Acutely, reductions in RAP are well correlated with renin secretion, but there have been no studies on the effects of chronically reduced RAP on renin secretion or PRA. Guyton et al. have proposed a simple model to explain both 1K1C and 2K1C Goldblatt hypertension; one of the basic assumptions of the model is that the pressure gradient across the renal artery stenosis is fixed and constant in both 1K1C and 2K1C animals. In this explanation, the 1K1C animals’ MAP increases enough to fully restore a normal renal perfusion pressure, whereas in the 2K1C animals the full development of hypertension is opposed by the function of the contralateral kidney. Because the clip’s pressure gradient has been fixed, RAP remains chronically subnormal in such a 2K1C animal.

Results from the few studies that have measured RAP in 2K1C animals distal to a renal artery constriction are not in total agreement. Schwietzer and Gertz report that RAPs distal to renal artery clips in 2K1C rats are normal when measured 1 month after RAC. Bounous and Schumacker reported normal RAPs in 2K1C dogs 3 months following renal artery constriction, whereas Lupu and Maxwell found that RAPs were still low 1 month after RAC in 2K1C dogs. In the present study, RAPs distal to renal artery clips in 2K1C rats were not different from control in any of the three clip groups. While it has been proposed that RAP in subnormal in the 2K1C model, we have found that RAP returns to normal even in cases of severe renal artery constriction.

Perfusion pressure distal to the renal artery clip in 1K1C rats was not different from control in either the 0.30 mm or 0.25 mm groups. In the 0.20 mm 1K1C rats, RAP was found to be significantly lower than control. The low RAP in the 1K1C 0.20 mm group (Figure 3) may be a valid observation or may be related to the absence of an increase in arterial pressure that occurred in the other groups following surgical preparation for the measurement of RAP. MAPs in the anesthetized 1K NC and 2K NC controls were 136 ± 3 mm Hg and 135 ± 5 mm Hg, approximately 20 mm Hg higher than MAPs in the conscious control rats. It seems that the stress of surgery produced somewhat higher MAPs and RAPs in the anesthetized rats compared to the conscious rats, with the exception of the 0.20 mm 1K1C rats. In the 0.20 mm 1K1C rats, the lack of an increase in arterial pressure with surgery probably relates to the already high MAPs in this group (189 ± 5 mm Hg in conscious rats).

Although RAPs were comparable in the 2K1C and 1K1C rats, the hypertension was not as severe in 2K1C rats at any given clip size (Figure 1). Because RAP returns to normal, the pressure gradient across a renal artery clip is less in 2K1C rats compared to 1K1C rats. A renal artery clip cannot be thought of as producing a fixed pressure gradient in this situation. If the clip acts like an ohmic resistance, then changes in RBF and the clip’s pressure gradient will be proportional. With severe clipping the stenosis may act like an orifice, and the pressure drop will be proportional to the square of the flow velocity; in this case the clip will act like a variable resistance. In either case, the clip’s pressure gradient will be a function of renal blood flow. It is possible that increasing renal vascular resistance (RVR) causes a decrease in RBF and a decrease in the pressure gradient across the stenosis. The normal renal artery pressure and attenuated stenosis pressure gradient seen in the 2K1C rats suggest such an increased RVR distal to the renal artery clip.

In the 2K1C model the clipped kidney atrophies after RAC in what appears to be a matching of renal tissue mass to renal blood flow while the contralateral kidney hypertrophies (Figure 6). Other studies have shown that RAC in 2K1C rats results in a chronic reduction in RBF to the clipped kidney and an increase in flow to the contralateral unclipped kidney. These changes in blood flow were approximately proportional to changes in renal mass. Like the clipped kidney in a 2K1C rat, the sole kidney in a 1K1C animal hypertrophies to compensate for the loss of contralateral renal mass. The exact mechanisms surrounding renal
hypertrophy or atrophy in Goldblatt hypertension are not critical to this study. However, these changes in renal mass do occur following renal artery constriction, and they will alter blood flow through the renal artery clip, the pressure gradient across the clip, RAP, and, ultimately, MAP.

If RBF does change in proportion to a change in tissue weight, this means that flow across a given renal artery clip (and therefore the pressure gradient across the clip) will be greater in 1K1C rats compared to 2K1C rats. This conjecture agrees with the data presented in Figure 5 and fits with our observation that 1K1C rats with the same size clip develop a more severe hypertension compared to 2K1C rats.

We have shown that RAP beyond the clip is well regulated in Goldblatt hypertension and usually returns to normal in both the 1K1C and 2K1C models. This need to maintain a normal RAP appears to be common to both models, but the mechanisms by which RAP is normalized may be different in each case. RAP appears to increase in 1K1C animals solely through a rise in MAP. Ipsilateral hypertrophy in the 1K1C animal may amplify the impact of the clamp and the need for increased MAP. In 2K1C animals with mild-to-moderate renal artery constriction, it appears that renal atrophy of the clipped kidney (with an associated decrease in RBF) acts to restore RAP without a large concomitant increase in MAP. The hypertrophied contralateral kidney in this situation can compensate to provide normal excretory function. In 2K1C animals with severe RAC, RAP appears to be normalized partially through renal atrophy and partially through an increase in blood pressure. Whether hypertension occurs in the 2K1C animal may depend on the degree to which the clipped kidney can atrophy. Ultimately, the severity of the hypertension will depend on the clip size, the presence or absence of a contralateral kidney, and possibly the changes in renal mass occurring in the clipped kidney.

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