Pathophysiology of Renovascular Hypertension

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Renovascular hypertension has its experimental counterpart in the two-kidney, one clip model (Goldblatt hypertension). From the study of this model, a general pathophysiological scheme has evolved suggesting that temporal stages in the development and maintenance of hypertension are regulated by complicated hormonal and neural interrelations. The central roles played by the renin-angiotensin system and the renal nerves is discussed as they relate to other hormones. In addition, the possible contribution of converting enzyme inhibitors to understanding the pathophysiology of this condition is discussed. (Hypertension 1991;17:707-719)

Science is usually perceived as practical and cold, therefore ugly. Yet its ample beauty can be perceived in many ways. One way is the well-designed experiment. Harry Goldblatt and his associates performed such a feat in the 1930s when they first demonstrated that reduction of blood flow to the kidneys can produce hypertension, as it did in the cases presented here. Science was so beautified by these studies that the Goldblatt "look" has been the subject of imitation ever since. Goldblatt hypertension is one of the most frequently studied models in medical science and one that still harbors rewards in our attempts to understand the mechanisms of the genesis and sustenance of hypertension.

Goldblatt hypertension includes the two-kidney, one clip (2K1C) as well as the one-kidney, one clip (1K1C) models of experimental hypertension. This review relates almost exclusively to the 2K1C model, which seems to be a counterpart for renovascular hypertension in humans. The 1K1C model is referred to early on in the discussion only to illustrate the differences in the relative contributions of the renin-angiotensin-aldosterone system and expansion of the extracellular fluid volume to the generation and maintenance of hypertension in the two models.

I will review some of the enormous body of information that has accumulated in relation to the renin-angiotensin system and other hormones in the pathophysiology of the Goldblatt model. Two cases of renovascular hypertension are presented. These, I believe, illustrate many of the points made in the discussion in relation to the features of the development and maintenance of this syndrome. Also, they are examples of how we may learn more about the pathophysiology of disease from the results of therapeutic interventions.

In an attempt to simplify my work, I have divided the syndrome that the Goldblatt model represents into various phases. Clearly, no attempt is made to absolutely encase these in time frames or to dogmatically insist on their sharp delineation. In fact, a consistent, systematic approach to define the phases of Goldblatt hypertension is curiously missing despite the long history of the paradigm.

Case Presentations

Case 1
A 61-year-old white man was admitted to the Nashville Department of Veterans Affairs (DVA) Medical Center because of severe uncontrolled hypertension. The diagnosis had been established 6 months before admission, but despite treatment with diuretics and calcium antagonists, the response had been poor. On admission, blood pressure was 220/130 mm Hg, pulse was 86 beats/min, and temperature was 98°F. A family history of hypertension could not be elicited. He was a chronic, frequent smoker. He complained of frequent headaches and a chronic cough. Fundoscopic examination only revealed mild arteriovenous nicking. Examination of the chest disclosed diffuse bilateral rhonchi and diminished
breath sounds. No rales or wheezes were heard. The rest of the examination was unremarkable.

Chest x-ray was normal. Electrocardiogram demonstrated normal sinus rhythm with nonspecific ST-T wave changes but no criteria for cardiomegaly. The blood urea nitrogen (BUN) was 37 mg/dl, and creatinine was 3.1 mg/dl; all other values, including the complete blood count, were within normal limits. Plain film of the abdomen showed bilateral renal shadows. The length of the kidneys was 10.2 cm for the left and 8.9 cm for the right kidney. Sonography confirmed the approximate measures. Digital subtraction angiography revealed severe obstruction of the right renal artery with modest constriction of the left renal artery. The ratio of renin concentration of the right over the left renal venous blood was 2.4; however, left renal renin concentration was clearly higher than normal.

Bilateral renal arterial bypass was performed. Blood pressure fell to 170/90 mm Hg almost immediately and remained at that level during the first postoperative week without medication. Plasma renin activity became normal. BUN and creatinine fell to 17 mg/dl and 1.6 mg/dl, respectively. Administration of β-blockers and furosemide further reduced pressure to 154/84 mm Hg.

Four years after surgery, blood pressure was 170/90 mm Hg despite β-blockers and low doses (25 mg twice a day) of captopril. BUN and creatinine have risen to 22 mg/dl and 2.1 mg/dl, respectively. Revision of the bypass is planned.

Case 2

A 38-year-old black man was admitted to the Nashville DVA Medical Center 5 years ago for accelerated hypertension. A diagnosis of high blood pressure had been made 11 years before, but treatment had been unsuccessful partly because of lack of compliance. His mother was hypertensive and he had smoked a pack of cigarettes a day for many years.

Except for a blood pressure of 180/120 mm Hg and mild arteriogenous nicking in the fundoscopic examination, physical examination was unremarkable. Laboratory studies were within normal limits. Creatinine clearance was 110 ml/min. Blood pressure was controlled with clonidine, hydralazine, furosemide, and low salt diet. Over the next 2 years, the hypertension was difficult to control and required increasing doses of medication and addition of captopril to the regimen. Hydralazine was discontinued and minoxidil begun.

Three years ago he was readmitted with accelerated hypertension and symptoms of congestive heart failure. Blood pressure was 180/110 mm Hg, and the physical examination was unchanged from the previous occasion except for an S4 gallop and trace pedal edema. Laboratory results were within normal limits except BUN (46 mg/dl) and creatinine (3.0 mg/dl). Nifedipine was added to the treatment, furosemide and minoxidil doses were increased, and captopril was continued.

The blood pressure continued to rise and required intravenous nitroprusside. Over the next 5 days, BUN and creatinine increased to 77 mg/dl and 6.6 mg/dl, respectively. Decreased bilateral perfusion was shown by radioisotopic techniques. Intra-arterial digital subtraction angiography demonstrated bilateral, almost complete renal artery stenosis.

Bilateral renal endarterectomy was performed 2 years ago. At that time therapy, which included hemodialysis, had resulted in a fall in BUN (59 mg/dl) and creatinine (4.6 mg/dl); after surgery these fell progressively to 10 mg/dl and 1.2 mg/dl, respectively. Blood pressure is presently controlled (less than 90 mm Hg diastolic) on minoxidil, clonidine, atenolol, and diltiazem.

Various Phases of Goldblatt Hypertension

Phase I or Renin-Angiotensin–Dependent Phase

Renin-angiotensin system. It is well accepted that development of hypertension after reducing flow to one kidney (Figure 1), in the presence of an intact contralateral kidney, is mediated by the renin-angiotensin system (RAS). The same is partly also true for the hypertension that follows removal of one kidney with clipping of the artery to the remaining kidney. Immediately on reducing blood flow to one kidney, there is a rise in renin secretory rate, plasma renin activity (PRA), and systemic blood pressure. It is also evident that systemic angiotensin II (Ang II) is elevated and that this peptide is completely (or almost completely) accountable for the rise in blood pressure. Administration of inhibitors of the enzyme that converts angiotensin I to Ang II or of competitors for the angiotensin receptor promptly lowers blood pressure. Furthermore, removal of the clip or ligature is attended by a prompt return of blood pressure to normal that is paralleled by a reduction in PRA and circulating Ang II. In addition, active or passive immunization to Ang II or the administration of renin inhibitors can lower blood pressure in 2K1C chronic severe hypertension. The renin inhibitor CGP-29287 caused declines in blood pressure that could be correlated with basal PRA in one study. Nevertheless, a clear-cut relation between the blood pressure response and baseline PRA for a minimum effective dose of the renin inhibitor is yet to be shown.

Although the role of salt and water retention is not particularly prominent in the first stage of Goldblatt hypertension, in addition to the RAS it plays a fundamental part in the 1K1C model in the development of high blood pressure. It has been repeatedly shown that total exchangeable sodium and plasma volume are elevated in 1K1C hypertension. Despite this, PRA is high or normal, certainly an anomalous situation under these circumstances. In fact, this aberrant interrelation between extracellular volume and renin release can be gleaned from the response of the blood pressure to therapeutic manipulations. Administration of converting enzyme inhib-
Arbitrary time is in the abscissa; phase I is approximately 4 weeks; phase II, 5–8 weeks; phase III, 9 weeks or more. Ordinate is mortality was increased by the concomitant administration of indomethacin. Moreover, the antihypertensive effect of hydralazine, which prevented mortality during the duration of the experiment, was blunted during the duration of the experiment, was blunted.

The severity of the hypertension was worsened and an increased circulating angiotensin II (Ang II) concentration. ACE inhibition or clip removal within 7–10 days causes a fast reduction of blood pressure to normal (phase I). During phase II or salt-retention phase, blood pressure may remain stable or continue to rise (solid horizontal and inclined lines) despite a fall in PRA. Infusion of exogenous Ang II shows an increased sensitivity (less Ang II needed for a rise in blood pressure), indicating downregulation of Ang II receptors. Increased plasma volume and total exchangeable sodium are found in this stage. Removal of clip or treatment with ACE inhibitors reduces blood pressure to normal, but a longer time is required to achieve a normal blood pressure. In phase III, whether blood pressure has remained as high or higher (parallel solid lines) than in phase I, PRA and plasma Ang II fall, but clip removal and administration of doses of converting enzyme inhibitor (CEI), equal to those used in phase I and II, do not return blood pressure to normal. Higher doses of CEI, however, and other antihypertensive medication will reduce blood pressure, sometimes to normal. Ang II, angiotensin II.

Prostaglandins. The primacy of the RAS in Goldblatt hypertension does not preclude other systems or hormones from participation in the generation, maintenance, and severity of the syndrome. In our laboratory, we have examined the role of prostaglandins in phase I. We studied four groups of animals treated with the nonspecific vasodilator hydralazine. Severe hypertension developed in the control group over a period of 7 days. The severity of the hypertension was worsened and mortality was increased by the concomitant administration of indomethacin. Moreover, the antihypertensive effect of hydralazine, which prevented mortality during the duration of the experiment, was blunted by cotreatment with indomethacin. During the period that preceded ligation of the renal artery, therapy induced changes in PRA that were not accompanied by alterations in blood pressure. Thus, indomethacin alone led to a modest reduction in PRA, as did the combination of indomethacin and hydralazine. During the initial phase of the hypertension, there was a rise in PRA in all groups, but the changes in PRA were not statistically significant until 6–7 days after ligation. In view of this, it is safe to infer that prostaglandin inhibition in the presence of even slight increases in renin production may lead to hypertension and that these autacoids play a major role in the counterbalance of the hypertension induced by Ang II in the Goldblatt model. Finally, it is clear that prostaglandin synthesis modifies the mortality and morbidity of hypertension in Goldblatt hypertension.

Worsening of renal function or systemic blood pressure has been observed by others when cyclooxygenase inhibitors were administered to Goldblatt animals (rats and rabbits). Stahl et al. showed a borderline fall in 6-ketoprostaglandin (6-keto-PGF₁α) in isolated glomeruli of unclipped kidneys, an observation not corroborated by others. Inhibition of the synthesis of prostaglandins in the presence of elevated Ang II production is almost
always accompanied by reductions in renal blood flow and glomerular filtration rate (GFR).

**Thromboxane.** Altered arachidonic acid metabolism has been demonstrated in the clipped kidney of Goldblatt hypertension.\(^{29}\) As already discussed, this partly contributes to the initiation and maintenance of hypertension. Perfusion of isolated rabbit kidneys 7 days after supraportal aortic constriction revealed these to be exquisitely sensitive to the vascular effects of Ang II as compared with a sham group.\(^{31}\) In addition, Ang II caused the release of Ang II, and blood pressure regulation seems to be enhanced by this vasocostrictor eicosanoid by arterial constriction. Release of thromboxane was not enhanced by either vasopressin or arachidonic acid. By the same token, the isolated perfused contralateral kidney of 2K1C rats has been shown to produce exaggerated amounts of thromboxane but not prostacyclin 4 weeks after induction of hypertension.\(^{30}\) Increased thromboxane production was inversely proportional to the reduced GFR in the nonclipped kidney. Treatment with thromboxane synthase inhibitors or thromboxane receptor antagonist increased GFR in the unclipped kidney and lowered systemic blood pressure. This indicates that enhanced thromboxane synthesis may have both intrarenal and systemic actions that contribute to the development and maintenance of hypertension.

**Renal medullary vasodepressor system.** Muirhead and his collaborators\(^ {32-34} \) have advanced evidence that the interstitial cells of the renal medulla are a source of important nonprostanoid vasodilator lipids in normal dogs as well as in dogs with renovascular hypertension. Chemical medullectomy worsens 2K1C hypertension and partially prevents the fall in blood pressure that follows unclipping.\(^ {35} \) The alterations in blood pressure after deconstriction are a function of the degree of medullary damage. Neither indomethacin nor aprotinin interfere with the fall in blood pressure after clip removal.\(^ {36} \) This suggests that although both prostaglandin and medullary vasodepressor systems may counteract 2K1C, Ang II-induced hypertension, the latter but not the former plays a role in after-clipping recovery. In fact, infusion of CV 3988 (a competitive inhibitor of the polar lipid acetyl-glyceryl-ether-phosphorylcholine, one of the putative medullary vasodilator lipids) does not further increase blood pressure in Goldblatt hypertension but significantly inhibits the fall that follows deconstriction.\(^ {37,38} \)

A relation among the medullary vasodepressor system, Ang II, and blood pressure regulation seems to exist under normal as well as abnormal circumstances. Normal rats that undergo chemical medullectomy exhibit a rise in blood pressure that appears to be mediated by increased peripheral resistance.\(^ {39} \) A peripheral \(\alpha\)-adrenergic antagonist as well as a central action have been proposed as the mediator of the change, but this remains controversial. Moreover, 2K1C rats that underwent chemical medullectomy did not become normotensive on unclipping.\(^ {39} \) Furthermore, the degree of medullary damage correlates closely with the inhibition of blood pressure fall after renal artery deconstriction.\(^ {39} \) Although the stimulus for the release of medullary lipids is unknown, it is of interest that removal of the clipped kidney is as effective as removal of the clip in lowering peripheral resistance, suggesting that the contralateral kidney secretes the lipids.\(^ {40} \) The signal could be, at least partially, the fall in circulating Ang II. Infusion of Ang II to maintain elevated blood pressure after unclipping is followed, on discontinuation, by a sharp fall in blood pressure. The time course mimics that observed on removal of the clip and is not reproducible by other pressor agents (e.g., norepinephrine).\(^ {41} \) Further, inhibition of Ang II receptor with saralasin in 2K1C rats for 15 hours before unclipping or nephrectomy does not reduce peripheral resistance, but the pattern of blood pressure fall after the surgical procedure is identical to control animals not receiving saralasin. It is therefore conceivable that a feedback system may exist between Ang II and medullary vasodepressor lipid release.

Although a role of vasodepressor medullary lipids is perhaps most dramatic in the period after clipping, the possibility remains that they may be critical in determining the degree of hypertension in the early stages.

**Sympathetic system.** A role for changes in sympathetic tone in 2K1C hypertension has been suggested. Faber and Brody\(^ {42} \) reported sympathetic tone to be inappropriately increased, and renal denervation has been reported to ameliorate hypertension in Goldblatt animals.\(^ {43} \) Plasma norepinephrine levels, however, are not elevated\(^ {44} \) or affected by surgical correction of the hypertension.\(^ {45} \) In addition, administration of the opioid antagonist naloxone in doses that block the hemodynamic effects of morphine is without effect on the pattern of blood pressure fall after unclipping in 2K1C hypertension.\(^ {46} \) Nevertheless (Figure 2), McElroy and Zimmerman\(^ {47} \) have shown that in Goldblatt rabbits, affinity of the \(\alpha_1\) receptor for \(\text{[H]}\text{prazosin binding was elevated in the stenotic but not the contralateral kidney 2 weeks after clipping. Furthermore, at 6 weeks, the receptor affinity of both kidneys was enhanced compared with the control normotensive animals. By 12 weeks, no changes in \(\alpha_1\) affinity were detected, and no differences in affinity for the \(\alpha_2\) antagonist rauwolscine could be demonstrated between normotensive and hypertensive rabbits at any time. Maximal binding for each ligand was unaltered at any of the week intervals for either normotensive or hypertensive animals. These results indicate that early stage modification of adrenergic receptor affinity may participate in the development and perpetuation of abnormal vascular responses in Goldblatt hypertension.

**Renal nerves.** Primary essential hypertension has been attributed by some to an abnormal function of the renal nerves through their effects on renal vascu-
Efferent renal sympathetic nerve activity has been found to be increased in humans with essential hypertension and in a series of experimental animal models, including 2K1C rats.49 In this model, thoracolumbar dorsal rhizotomy to produce afferent renal denervation attenuated the severity of hypertension.50 Selective afferent renal nerve denervation is mediated by a central feedback mechanism that decreases hypothalamic norepinephrine stores, which results in a decrease in peripheral sympathetic nervous system activity and reduces blood pressure.

Evidence of a contribution of the sympathetic system and the renal nerves can also be marshalled from experiments by Kopp and Buckley-Bleiler.51 These investigators denervated the nonclipped kidney of 2K1C hypertensive rats, and the rats responded as normal rats do with an excitatory renorenal reflex (Figure 3), which is characterized by increased ipsilateral urine sodium excretion and decreased contralateral urine sodium excretion. Denervation of the clipped kidney, however, increased both ipsilateral and contralateral sodium excretion, suggesting that lack of inhibitory renorenal reflexes from the clipped kidney may enhance efferent sympathetic nervous activity, which may contribute to the hypertension in this model.

Further evidence for a role of the sympathetic system in Goldblatt hypertension is the fact that the vasoconstrictor response to exogenously infused norepinephrine is greater in experimental than in control rats, despite no evidence of increased sympathetic nerve ending release of norepinephrine.52 Enhanced local sensitivity, therefore, may be critical in view of normal or, actually, reduced circulating norepinephrine levels. It is of interest in this context

![Figure 2](image_url)

**Figure 2.** Bar graph showing measurement of dissociation constants (Kd) of [3H]prazosin in a smooth muscle plasma membrane enriched microsomal fraction prepared from rabbit intrarenal arterial vasculature. Age-matched, sham-operated normotensive rabbits are compared with two-kidney, one clip hypertensive rabbits. LK, left kidney; RK, right kidney; S, sham; C, clipped. *p<0.002. Redrawn from Figure 3 in McElroy and Zimmerman.47

![Figure 3](image_url)

**Figure 3.** Schematic drawing showing renorenal reflex in Goldblatt hypertension. Panel A: Under normal circumstances, stimulation of mechanoreceptors (Uo, ureteral obstruction) or chemoreceptors (pelvic perfusion with 0.9 M NaCl) results in an inhibitory renorenal reflex characterized by contralateral natriuresis (↑ UrineV, urinary sodium excretion). Panel B: In rats with 4-week (phase I) Goldblatt hypertension, renal mechanisms and chemoreceptor stimulation of either the clipped or unclipped kidneys failed to affect contralateral efferent renal nerve activity, contralateral urine flow rate, and UrineV. Ipsilateral afferent renal nerve activity was also unaffected. Panel C: Renal denervation of the nonclipped kidney (indicated by 1) increased ipsilateral UrineV and decreased contralateral diminution in UrineV. Denervation of the clipped kidney (indicated by 2) increased UrineV bilaterally. These suggest that lack of inhibitory renorenal reflexes from clipped kidney may enhance efferent sympathetic nervous activity and contribute to hypertension in Goldblatt hypertension. Adapted from Kopp and Buckley-Bleiler.48
that aortas isolated from Goldblatt animals have a higher content and concentration of cyclic AMP than their normotensive controls despite normal circulating norepinephrine levels.\textsuperscript{53} Nevertheless, a similar situation was found in deoxycorticosterone acetate hypertensive rats, a model that differs considerably from the Goldblatt model. Whether cyclic AMP accumulation is an expression of enhanced β agonism remains to be elucidated.

\textit{Vasopressin.} Mohring and his collaborators used an antibody against arginine vasopressin (AVP) and demonstrated a fall in blood pressure in Goldblatt rats.\textsuperscript{54} Conversely, Rabito et al\textsuperscript{55} found little effect of competitive vasopressin inhibitors in this model. Both Mohring and Rabito studied their animals in the malignant hypertension phase of the Goldblatt model. Using a synthetic AVP antagonist, Ichikawa and his collaborators\textsuperscript{56} demonstrated a systemic vasodilatory effect, but no renal vasodilatation, in rats 4 weeks after renal artery clipping. Because of the fall in systemic blood pressure in the absence of renal vasodilatation, there was a fall in glomerular capillary hydraulic pressure, plasma flow rates, and single nephron GFR in the nonclipped kidney. This is in keeping with the impaired autoregulatory control of nonclipped kidneys shown by Ploth et al.\textsuperscript{57} This suggests that AVP is at least partly responsible for maintenance of high glomerular pressures and flow rates in the nonclipped kidney of Goldblatt animals. Despite this strong evidence, the role of AVP in the regulation of systemic blood pressure in Goldblatt animals remains controversial. Woods and Johnston\textsuperscript{58} demonstrated that the level of blood pressure in the Goldblatt model in Brattleboro rats, which lack antidiuretic hormone (ADH), was of the same magnitude as that in the heterozygous controls, the Long-Evans rat. Possibly, ADH is unnecessary for the development of renal hypertension but when present may contribute to some of the systemic hemodynamic changes in the syndrome.

\textit{Atrial natriuretic factor.} Atrial natriuretic factor (ANF) is known to antagonize the vasoconstrictor effects of the renin-angiotensin system. It relaxes vascular smooth muscle previously constricted with angiotensin,\textsuperscript{59} but it also inhibits the secretion of renin and may reduce PRA.\textsuperscript{60} Yet the basal levels of immunoreactive ANF in Goldblatt hypertensive rats is elevated when compared with sham normotensive rats\textsuperscript{61,62} (Figure 4). Moreover, chronic infusion (24–28 hours) of ANF to conscious Goldblatt rats led to blood pressure reduction mediated by a fall in cardiac index rather than reduced peripheral resistance. By 3–5 days of infusion, however, the fall in blood pressure was maintained by a fall in total peripheral resistance.\textsuperscript{62} This change could be attributed in part to a fall in PRA as well as to some inhibition of the vasoconstrictor actions of angiotensin II.\textsuperscript{63}

These studies suggest that ANF may partially prevent large rises in pressure in the early stages. Also, they suggest that changes in its secretion as hypertension progresses may modify the two major components of blood pressure regulation, peripheral resistance and cardiac output.

That ANF may participate importantly in modulation of blood pressure level in Goldblatt hypertension is also suggested by the studies of Gauquelin et al.\textsuperscript{64} These investigators have shown that, in addition to the early stages (this study arbitrarily sets the early stage at 3 weeks, middle stage at 5 weeks, and late stage at 7 weeks), plasma ANF is elevated in all stages of 2K1C hypertension in the rat as compared with controls. Furthermore, ANF receptor density is reduced in the clipped kidney at all stages and in the contralateral kidney in the middle (5 weeks) and late (7 weeks) stages. Receptor density was elevated in the nonclipped kidney at 3 weeks. In another study,\textsuperscript{65} in vitro autoradiography with \textsuperscript{125}I-ANF demonstrated that after 4 weeks of clipping, binding sites were increased in the aorta, but the increase in the glomeruli of the clipped as compared with the nonclipped kidney did not achieve statistical significance. Perhaps the difference of 1 week between this and the Gauquelin study is responsible for the variant results. Nevertheless, it is clear that the changes conform to physiological regulation of the ANF receptor and provide evidence, however indirect, of a possible interaction between ANF and the RAS in Goldblatt hypertension.

In this context, it has been shown that bolus administrations of graded doses (2.5–10 μg/kg) of ANF produce dose-dependent reductions in systemic blood pressure but that renal functional changes predominate in the unclipped kidney.\textsuperscript{66} Thus, significant increases in GFR, urine flow, and absolute and fractional sodium and potassium excretion were observed in the unclipped kidney. While these pharmacological experiments give some insight as to what the effect of endogenous ANF might be in the regulation of salt and water balance by the unclipped kidney, a certain role for ANF as modifier of blood pressure regulation in Goldblatt hypertension may require the development of an antagonist to the
peptide. Only this may allow adequate dissection of its contribution to cardiac and renal excretory functions and in the regulation of peripheral resistance.

**Kallikrein-bradykinin system.** Kallikrein is increased in Goldblatt animals. Because the kallikrein-kinin system is a vasodilator, diuretic system, it has been postulated that its function is to offer homeostatic defense against the antidiuretic, vasoconstrictor action of the RAS. Early in the development of renovascular hypertension the kallikrein system is called on to oppose the action of the RAS, but later on, urine kallikrein excretion and its renal synthesis are reduced. Conceivably, this also contributes to the hypertension.

In summary, the initial phase of Goldblatt hypertension is clearly principally dependent on the RAS. Yet, numerous other systemic or local hormonal systems may participate in the counterregulation of the hemodynamic actions of the RAS. Although the acute phase of the Goldblatt model starts almost immediately, many studies have been conducted at 3–4 weeks after clipping. As a consequence, it is not clear whether this period of time is exclusive of some of the intrarenal effects of the RAS on salt and water retention. Conversely, studies in the rat and other experimental animals 3–4 weeks beyond the induction of Goldblatt hypertension may be closer to the temporal situation in most humans when they present clinically.

**Phase II or Salt Retention Phase: Underlying Influence of Phase I (see Figure 1)**

**Whole kidney effects of renal artery clipping (see Table I).** In conscious dogs and anesthetized rats, there is an immediate fall in renal plasma flow (RPF) and GFR in the clipped kidney. The unclipped kidney also undergoes changes in an attempt to protect its microenvironment. Vascular resistance rises as a result of an increase in both afferent and efferent arteriolar vasoconstriction, but in contrast to the clipped kidney, where the ratio of afferent to efferent arteriolar vasoconstriction, but in contrast to the clipped kidney, where the ratio of afferent to efferent resistance falls, the ratio remains constant in the unclipped kidney. As a result of the heightened systemic pressure, therefore, RPF and GFR may rise or remain unchanged. In mildly hypertensive conscious dogs, the rise in GFR of the unclipped kidney usually takes 2–3 weeks. In this species, the rise in RPF never achieves statistical significance. Nevertheless, RPF and GFR tend to normalize in both kidneys by 3–4 weeks, although at 4 weeks in anesthetized rats, reduced GFR results from a fall in the clipped kidney and no rise in the unclipped kidney. A fall in RPF and GFR has also been described in the clipped kidney of anesthetized, severely hypertensive rats after 3–4 weeks. At this time interval, in mild-to-moderate hypertensive anesthetized rats, unclipped kidney GFR and RPF may be slightly elevated.

It seems clear that variations in renal hemodynamic response in either kidney of Goldblatt animals is dependent on the conditions under which the animals are studied, their species, the severity, and the duration of the hypertension. An important factor is the state of salt and water retention at the time of study. It should be pointed out that atrophy of the clipped and hypertrophy of the unclipped kidney occurs. As a result, total renal mass and total RPF are often similar in Goldblatt as compared with normal animals.

As discussed above, the unclipped kidney of Goldblatt rats and rabbits has been shown not to autoregulate normally. Thus, stepwise reduction in renal perfusion pressure reduces whole kidney blood flow proportionately. This may explain in part the hemodynamic dependency of the unclipped kidney on the level of the hypertension.

**Single nephron effects of renal artery clipping.** Microscopic studies have not shown any changes in the single nephron GFR (SNGFR) or glomerular plasma flow (Q_A) of mildly hypertensive Goldblatt animals. Both functions were elevated in the contralateral kidney of severely hypertensive rats. The increase occurs in both superficial and deep nephrons, but it is more pronounced in cortical than in juxtamedullary nephrons. In superficial nephrons, the increase in SNGFR and Q_A are proportional, so filtration fraction does not change.

Some studies have not demonstrated a rise in SNGFR or Q_A. Capillary hydraulic pressure is increased in rats with severe as well as mild hypertension, which should increase SNGFR. The offsetting factor, however, has been found to be a fall in the ultrafiltration coefficient (K_f) in the unclipped but not the clipped kidney. The fall in K_f was accompanied by an increase in glomerular diameter, which tends to rule out a reduction in surface area as a cause and points to reductions in basement membrane hydraulic permeability as the culprit. These results indicate that the rate of SNGFR in the unclipped kidney is determined by the increase in glomerular capillary pressure and the reduction in K_f. Furthermore, the nephron hypertrophy and increased number of functioning glomeruli in the unclipped kidney will influence and help set the RPF-dependent SNGFR.

It is apparent that GFR and SNGFR are generally elevated in the unclipped kidney of moderate-to-severe hypertensive Goldblatt animals. This occurs despite a reduction in K_f and seems to be the consequence of increased hydraulic pressure and Q_A. Afferent arteriolar resistance rises and effluent resistance falls, but overall kidney resistance is elevated as compared with the clipped kidney. Yet overall GFR and RPF in Goldblatt animals are frequently not different from controls.

**Salt and water retention.** However transient, the increase in contralateral kidney RPF and GFR plays an important role in the attempt to maintain sodium and volume balance. Salt and water retention by the clipped kidney is initially balanced by the pressure diuresis induced by the elevated systemic blood pressure. As contralateral GFR falls to or below normal, circulating and local hormones influence salt and water reabsorption and lead to serious systemic...
hemodynamic and volume changes. The systemic and local effects may be triggered by the overproduction of Ang II.79

Role of angiotensin II and catecholamines (Figure 5). Ang II can lead to renal sodium and water retention in a variety of ways. Because it is a major stimulus for the production of aldosterone by the zona glomerulosa of the adrenal glands, it may lead to salt retention through the effects of the mineralocorticoid.80 Nevertheless, it has not been possible to prove that excess aldosterone production is a prominent mechanism by which salt retention occurs in renovascular hypertension, since levels of the hormone are frequently depressed or not as high as expected for the level of plasma renin.81 Also, Ang II is capable of central stimulation of thirst and the secretion of ADH, which will enhance water ingestion, retention, and volume expansion.82 Ang II can increase release of norepinephrine from the adrenals and terminal nerve endings. Adrenergic receptor stimulation has been shown to cause increased sodium reabsorption in the renal proximal tubule,83 a site that is also a target for the sodium-retentive effects of Ang II.84 Moreover, Ang II has been shown to increase loop of Henle sodium reabsorption, perhaps through its capacity to reduce medullary blood flow.85,86 Renal nerve stimulation is also known to enhance sodium reabsorption, and it is possible that Ang II may also exert a local effect by afferent neural stimulation.87 As systemic blood pressure rises and afferent arteriolar constriction of the unclipped kidney is maximal, changes in the intrarenal regulation of salt and water will ensue.

Ang II has a major vasoconstrictive action in the efferent arteriole of the glomerulus.88 It is also capable of constricting the afferent arteriole, although this effect may be mediated by another substance.89 Increases in efferent arteriolar resistance will enhance reabsorption by reducing hydraulic pressure and increasing oncotic pressure across the wall of the proximal tubule. Thus, while the ratio of the resistances of the afferent to the efferent arterioles may remain constant in the unclipped kidney, sodium and water retention will be favored in the clipped kidney the ratio is low and reabsorption intense.

A discussion of the mechanism by which Ang II can directly increase tubular sodium reabsorption is beyond the scope of this essay, but activation of the Na⁺-H⁺ antiporter is in part responsible.90 Suffice it to say that converting enzyme inhibition to reduce Ang II production is accompanied by a return of blood pressure to control, and diuresis and natriuresis may occur in Goldblatt hypertension.91,92 Converting enzyme activity in the proximal tubule is prominent,93 and its strategic location may be related to a local regulatory function of Ang II in sodium balance as well as in acid-base homeostasis,94 a subject that has been little studied in 2K1C hypertension. Also, through its capacity to mediate tubular hypertrophy in the clipped and in the unclipped kidney, Ang II may forestall atrophy and loss of function.95

Possible role of angiotensin as a trophic hormone (see Table 2). Indirect evidence for the possible role of Ang II in preventing atrophy of the clipped kidney has been obtained by Jackson et al.96 These investigators demonstrated that chronic enalapril treatment (blood pressure at the end of 12 months was 129±3 mm Hg) of Goldblatt rats was associated with atrophy (GFR=0) of the clipped kidney. In minoxidil-treated animals (12-month blood pressure was 181±6 mm Hg), GFR was one third that of untreated rats (12-month blood pressure was 20†±8 mm Hg), and kidney weight was not different in either group (1.2 g minoxidil; 1.14 g untreated), but kidney weight was less than 50% of this in the enalapril-treated group (0.46 g). On the other hand, survival in the enalapril-treated rats was almost twice that of the minoxidil group and five times that of the untreated animals. Clearly, removal of the systemic effects of
Ang II diminished blood pressure and its mortality but also led to pharmacological nephrectomy of the clipped kidney. Although these studies may be more pertinent to the third phase of Goldblatt hypertension, they serve to illustrate the critical role of locally produced hormones and the possible pitfalls in pharmacological treatment of the condition.

Clinical relevance. Case 1, I believe, strong evidence that other factors besides the RAS are critical in the maintenance of hypertension in renovascular disease. Despite presumably complete revascularization (as evidenced by the restoration of renal function toward normal and normalization of PRA), reduction in sympathetic tone by the use of β-blockers and volume contraction with furosemide were needed for optimal blood pressure control. This patient seems to represent an almost idealized version of phase II as defined in Figure 1.

In summary, a vicious circle of further elevations of blood pressure and structural damage of the kidneys and other organs will characterize the untreated second and third phases of Goldblatt hypertension. Countercoupling forces such as putative polar medullary lipids, ANF, and prostaglandins are not sufficiently protective. The elevation of ANF does not bring sodium balance back to normal, while prostaglandins are diminished or normal when they should be vigorously produced. It is unlikely that other systems, such as bradykinin, play a major role in the salt retention since their inhibition does not ameliorate the worsened blood pressure.

This phase of the hypertension has not been as well studied as the initial phase, but it seems clear that elevated renin-angiotensin activity is not solely responsible for the sustained hypertension. Although the role of volume expansion has been inferred, further study will be necessary to elucidate and harmonize some of the conflicting data in the literature in this regard.

Phase III or the Systemic Renin-Angiotensin Independent Phase

Possible role of local renin-angiotensin systems. In the dog, chronic Goldblatt hypertension is eventually accompanied by a fall in PRA. By contrast, PRA usually rises in the chronic model in the rat (more than 12 weeks). Although PRA may be normal in humans with long-standing, predominantly unilateral renovascular hypertension, its level is never low nor does it closely correlate with the degree of blood pressure elevation. Yet hypertension will respond to converting enzyme inhibition in this stage. The possibility must be considered that local renin-angiotensin action, rather than the circulating concentrations of these substances, is what determines the level of blood pressure and organ damage.

Evidence has accumulated that local vascular Ang II production may have an impact in the control of sympathetic neurotransmission and in smooth muscle hyperplasia. Uptake of renin by cells mars the interpretation of high tissue renin levels detected by conventional methods. Fortunately, recent studies have shown the presence of renin messenger RNA (mRNA) in the arterial wall, liver, adrenal gland, heart, and brain. This extrarenal gene expression system does not appear to be under control of feedback regulation by either salt balance or the circulating renin-angiotensin levels. The importance of the independence of this extrarenal system can be appreciated when the effects of the systemic RAS on gene expression and its consequences are considered.

In a recent study, Goldblatt hypertension of 4 weeks' duration in rats resulted in a sixfold rise in renin mRNA levels in the clipped as compared with the control kidney. This was accompanied by an eightfold reduction in the unclipped kidney. By the end of 20 weeks, the right kidney renin mRNA had fallen 16-fold as compared with age-matched, sham-operated control rats; the clipped kidney was only fourfold higher than the control. This suggests that the negative feedback that Ang II can exert on renin secretion was also linked to suppression of renal renin gene expression in both kidneys of the acute and chronic Goldblatt model.

Despite a fall in the output of renin indicated by a fall in PRA and in gene expression in both kidneys, intrarenal angiotensin formation undoubtedly remains elevated in the clipped kidney, as evidenced in other studies by the increased concentration of Ang II in the venous effluent as compared with the aorta. Moreover, local levels of Ang II in the brain, heart, vascular tissue, and adrenal glands might remain unchanged (elevated) despite altered levels of circulating Ang II or volume expansion. This speculation of the role of an extrarenal RAS must be tested experimentally.

In summary, the compartmentalized RAS may be responsible for persistent renal and perhaps peripheral vasoconstriction, increased sympathetic tone, and perhaps alterations in cardiac muscle leading to hypertrophy. It may also help explain some of the phenomena observed on removal of the clip in chronic animals. For example, rapid turnover of the vasoconstrictor elements of the RAS in smooth muscle leading to vasodilation might mediate the fall in blood pressure and the incapacity of extracellular (exogenously administered) converting enzyme to modify the fall in blood pressure. Conversely, fall of intrarenal concentration of Ang II may allow increased local synthesis of vasodilation, salt-retaining factors, or increased sensitivity to circulating levels of substances such as ANF and prostaglandins.

Treatment With Converting Enzyme Inhibitors As Proof of Tenets of Goldblatt Paradigm

The development of converting enzyme inhibitors has dramatically improved the diagnosis and medical treatment of renovascular hypertension. In fact, the single dose captopril test may be the best screening test for the identification of renovascular hypertension. Not only is PRA dramatically increased in renovascular hypertensive as compared with essential
hypertensive individuals, but sampling of renal vein renin usually corroborates the unilateral predominance of the disease.

The response to converting enzyme inhibitors is equally dramatic. Several mechanisms have been proposed for the descent in pressure, but it seems clear that inhibition of Ang II formation is the predominant effect: the acute blood pressure response is proportional to the baseline PRA. In addition, the fall in blood pressure is almost universally greater in renovascular patients than in essential hypertensive patients.

Blood pressure may transiently increase toward pretreatment levels despite continuation of therapy, but it promptly has a further fall. The long-term response of this triphasic action of converting enzyme inhibitors has been used as a good predictor of surgical success on revascularization.112,113

Patients with unilateral stenosis of a solitary kidney or those with bilateral stenosis may experience a reduction in RPF and GFR accompanied by elevation of serum creatinine and BUN.114 This is most likely the result of inhibition of intrarenal Ang II production leading to renal vasodilatation, which when accompanied by a fall in systemic pressure will reduce renal perfusion and function.115

The remarkable sequence of events in case 2 suggests that inhibition of intrarenal Ang II formation under some circumstances may lead to severe renal insufficiency that need not be irreversible. This case is also indicative of the difficulty in treating late phase II or III individuals. (This man’s hypertension was present for over 11 years.) Although revascularization led to improved renal function, numerous other medications were required for adequate blood pressure control. Taken together with the symptomatology of heart failure, it is evident that organ damage was contributory to the hypertension (Figure 5).

I have already alluded to the potentially noxious effects of chronic converting enzyme inhibitor therapy in experimental renovascular disease. Some evidence has also accumulated in humans, but as cogently discussed in a recent editorial, the significance of these findings and their relevance in humans must be analyzed carefully.116

In essence, however, the response to converting enzyme inhibitor resembles that of clip removal at various stages in the experimental animal and is further evidence of the importance of the RAS system in this model.

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