Sequential Renal Hemodynamics in Experimental Benign and Malignant Hypertension

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SUMMARY To examine the sequential renal hemodynamic changes in experimental renovascular hypertension, the uninephrectomized dog was studied immediately after renal artery constriction, throughout chronic benign hypertension, and during malignant hypertension. Intrarenal resistance fell immediately after renal artery constriction, but rose above control within hours. Intrarenal infusion of teprotide resulted in vasodilatation during the first 3 days but failed to do so during the chronic phase of benign hypertension. During the transition from benign to malignant hypertension, angiotensin II-dependent renal vasoconstriction developed associated with natriuresis, plasma volume contraction and a vicious cycle of hyperreninemia and severe vascular damage. (Hypertension 3 (supp I): I-63-I-68, 1981)

KEY WORDS • renal hemodynamics • renin-angiotensin system

GOLDBLATT et al.1 first produced experimental benign hypertension by moderate constriction of the renal artery in the uninephrectomized dog, or of both renal arteries in the intact dog. Many investigators have confirmed his observations and have also reported that hypertension could be produced without significant renal ischemia.1,2 On the other hand, "severe" ischemia of the kidney leads to the development of malignant hypertension.1 The more recent study of Ferrario and McCubbin3 showed that severe renal artery stenosis with an acute reduction in renal blood flow of 35% to 40% will induce accelerated hypertension in the dog; with less severe constriction, benign hypertension ordinarily ensues with prompt restoration of blood pressure following release of constriction.3 Although the changes in renal blood flow in response to acute renal artery constriction and during the development of experimental hypertension have been examined by several investigators,4,5 a more detailed, sequential analysis in benign and malignant hypertension and during the transition from the benign to malignant phase is warranted. We studied the changes in renal hemodynamics immediately after renal artery constriction, throughout benign hypertension, and during malignant hypertension, and evaluated the role of the renin-angiotensin system in the control of renal blood flow during these three conditions.

Material and Methods

Mongrel dogs were placed on a fixed diet containing 80 mEq sodium and 60 mEq potassium per day. Each day, 24-hour urinary output, sodium and potassium excretions were measured and the animals weighed.

Surgical procedures were performed with sterile conditions under pentobarbital anesthesia. The renal artery, abdominal aorta, and inferior vena cava (IVC) were exposed retroperitoneally through a flank incision and catheterized with polyvinyl tubing by the method of Herd and Barger.6 An inflatable Silastic cuff (Hazen Everett, Mahwah, New Jersey), filled with 10% dextran in 1.3% saline and connected to a fluid-filled polyvinyl catheter, was secured around the renal artery proximal to the renal artery catheter. An electromagnetic flowprobe (Zepeda Instruments) was placed around the renal artery at the origin, and proximal to the renal artery cuff; minimal dissection was done to maintain intact innervation. The proximal end of each catheter and the flowprobe wires were exteriorized, tied to a plastic loop in the skin, and protected by a cotton jacket. The contralateral kidney was then removed. A recovery period of 10 to 14 days was allowed before experiments were started.

Extensive experience with this renal artery occluder cuff in our laboratory4,7 demonstrated that it is
Reliable and does not leak. Routinely, these cuffs are fully inflated with solution for 24 to 48 hours prior to implantation, to check for leakage. At the end of experiment, total recovery of the volume of fluid injected into the cuff has been invariably observed with cuff deflation. Careful comparison of metallic snare and this occluder cuff has been performed by Anderson et al., who also found no leakage and demonstrated that both devices were comparable.

Systemic blood pressure and renal arterial pressure distal to the cuff were monitored with P23 Statham pressure transducers and the outputs recorded on a Grass polygraph. Both mean and pulsatile pressures were recorded simultaneously. Renal blood flow was measured by the krypton washout method in some animals. However, to study minute-to-minute changes in flow, the electromagnetic flowmeter was used in an additional group of dogs; a close correlation was observed in the results obtained by the two methods. The flowprobes were calibrated before implantation by perfusing blood at known rates through a 3-4 cm segment of renal artery. In two dogs, a second constricting cuff was placed around the renal artery distal to the renal artery catheter, to determine the zero flow during the experiments. Since occlusive zero corresponded closely to the electronic zero, in the remaining dogs, electronic zeroing alone was used. Frequent monitoring showed little zero drift. The intrarenal resistance was calculated from the pressure gradient across the renal vascular bed divided by renal blood flow and expressed as arbitrary units; renal venous pressure was assumed to be 10 mm Hg.

Plasma renin activity (PRA) was determined by the radioimmunoassay method of Haber et al. and expressed as ng/ml/hr of angiotensin I (A1) generated at pH 7.4. Plasma volume was measured with Evans blue. Serum and urinary sodium and potassium were determined by flame photometry.

Experimental Protocols

Acute Renal Artery Constriction Experiments

Renal artery stenosis was produced by inflation of the occluder cuff, producing an aortorenal gradient. Reduction of renal perfusion pressure in a stepwise fashion in 5 to 20 mm Hg increments from control (100 mm Hg) to 30 mm Hg was performed (n = 21). Each decrement was maintained for 20 minutes. Systemic and renal hemodynamics were monitored continuously, and PRA was determined at the end of each period.

Benign Renal Hypertension

Renal perfusion pressure was rapidly reduced in a single stage to a predetermined level (50-80 mm Hg) by renal artery constriction according to the method of Tagawa et al. (n = 6). Renal artery hypotension was maintained for 10 days by cuff adjustment. Systemic and renal pressures, renal blood flow and PRA were measured daily.

Experimental Malignant Hypertension

Mild progressive renal artery constriction by daily incremental cuff inflation over 10 days was performed in 11 dogs (fig. 1). To induce hypertension, sufficient fluid was injected to inflate the cuff and to lower perfusion pressure by 5 mm Hg on the first experimental day. However, as mean aortic pressure rose, renal perfusion pressure returned toward control level within minutes despite the maintenance of cuff inflation. On the following morning, more dextrose solution was added to the cuff to lower the renal perfusion pressure 5 mm Hg below that observed on the second day. For example, at the first constriction, renal arterial pressure was lowered from 100 to 95 mm Hg; by the next morning, if the perfusion pressure was 98 mm Hg, it was then lowered to 93 mm Hg. Daily inflation in this fashion was performed for 10 days. As seen in figure 1, renal perfusion pressure rose above control by the seventh day and continued to rise throughout the rest of the experiment, paralleling the mean aortic pressure, despite continued inflation of the cuff. At the end of this period, the cuff was deflated and the animal observed until the experiment was terminated. The PRA was measured every morning. Systemic blood pressure and renal arterial pressure were monitored during those periods, and renal blood flow was measured simultaneously in the dogs with flowprobes.

Intrarenal Blockade of the Renin-Angiotensin System

To assess the contribution of the renin-angiotensin system to the changes in renal hemodynamics, the nonapeptide AI converting enzyme inhibitor (tensidine, or SQ 20,881) or the AlI antagonist (Sar1 Ala8

**Figure 1.** Representative illustration of protocol used for mild daily progressive renal artery constriction. • represents renal perfusion pressure each morning before constriction; ○ represents renal pressures at 1, 3, and 9 hours after constriction on each day. A 5 mm Hg reduction in renal pressure induced by cuff inflation is designated by †.
AII) was infused into the renal artery at increasing rates (starting at 0.5 μg/kg/min) until a barely detectable drop in systemic pressure was observed. The doses of both agents were similar and ranged from 0.5 to 4 μg/kg/min. There was minimal systemic spill-over of the blocking agents during the intrarenal infusions as evidenced by the lack of inhibition of blood pressure response to systemically administered test doses (2 to 4 μg) of AII or AII during the highest infusion of the inhibitors. These doses of AII or AII invariably resulted in greater than 15-20 mm Hg rise in systemic blood pressure. Intrarenal infusion of inhibitors in the usual doses resulted in no more than 5% increase in renal blood flow in the sodium replete control dogs (fig. 2). Results are expressed as mean ± standard error of the mean. Statistical significance was determined by the Student's t test. A detailed pathological examination was performed on all dogs.

Results

Intrarenal Hemodynamic Changes Immediately After Renal Artery Constriction

When renal perfusion pressure was lowered from 100 to 70 mm Hg, renal blood flow remained unchanged as autoregulatory renal vasodilatation occurred. Intrarenal resistance decreased from 0.96 ± 0.03 to 0.66 ± 0.09 units. Further reduction of perfusion pressure resulted in a decline of renal flow in a linear fashion (fig. 2). At 55 mm Hg, vasodilatation reached its maximum as intrarenal resistance decreased to 50% ± 8% of control. The PRA increased inversely with the perfusion pressure from a control of 1 ± 0.02 to 7.8 ± 0.8 AI ng/ml/hr at a renal perfusion pressure of 20 mm Hg. Intrarenal infusion of teprotide or saralasin resulted in further renal vasodilation at renal perfusion pressures below 75 mm Hg. The intrarenal resistance fell from 0.66 ± 0.3 to 0.52 ± 0.2 units (p < 0.001) at a renal pressure of 70 mm Hg; from 0.59 ± 0.06 to 0.44 ± 0.06 units (p < 0.005) at 50 mm Hg, and from 0.71 ± 0.08 to 0.41 ± 0.06 units (p < 0.005) at 40 mm Hg (fig. 2).

Benign One-Kidney One Clip Renovascular Hypertension

Benign hypertension was produced by rapid inflation of the constricting cuff, reducing renal pressure to 50-80 mm Hg. The systemic and renal hemodynamic responses were similar for this range of renal pressure. Renal vasodilatation occurred immediately after the renal artery constriction. The intrarenal resistance decreased from 0.9 ± 0.01 units to a nadir of 0.65 ± 0.09 units (fig. 3). By 30 minutes to several hours after constriction, the renal arterial pressure rose toward control level as intrarenal resistance increased slightly above control (1.14 ± 0.2 units). These parameters remained relatively constant throughout the chronic hypertension. The PRA rose from 0.5 ± 0.1 to 2.4 ± 0.2 AI ng/ml/hr after artery constriction and returned to normal in 2 to 3 days. Sodium and water retention resulted in plasma volume expansion from 2010 ± 130 ml to 2650 ± 140 ml within 3 days (fig. 4). Intrarenal infusions of teprotide (SQ 20,881) resulted in a fall in intrarenal resistance from 1.18 to 0.82 units on Day 1 and 1.15 to 0.9 units on Day 3, but failed to decrease during the later, chronic phase of hypertension (fig. 5). In benign hypertension, deflation of the constricting cuff resulted in immediate diuresis and natriuresis with restoration of blood pressure to normal in 2–3 days.
Malignant Hypertension

During the first 3 to 5 experimental days, the response to mild progressive renal artery constriction was similar to that of single stage constriction (fig. 4). Moderate increases in systemic blood pressure, PRA, and renal vascular resistance were observed in both models during this period. Renal artery pressure remained near control levels despite repeated constriction (fig. 1). An initial increase in plasma volume from 2018 ± 145 to 2285 ± 19 ml (p < 0.01) was also seen here by Day 5. However, further constriction resulted in progressive increases in PRA, systemic and renal blood pressure, and intrarenal resistance. On Day 10, the PRA was 8.8 ± 4 ng/ml/hr, the systemic blood pressure was 149 ± 5 mm Hg, renal perfusion pressure was 112 ± 10 mm Hg, while renal blood flow fell to 12% ± 4% of control. A progressive increase in intrarenal resistance was noted, starting on Day 3. The initial vasodilatation after each mild constriction was followed by vasoconstriction within hours. Intrarenal resistance was 15-fold greater than control on Day 10 and was associated with natriuresis (urinary sodium excretion was 140 mEq on Day 10), diuresis, and plasma volume contraction (1869 ± 147 ml on Day 10, p < 0.02). Clinical signs of malignant hypertension were evident. Despite removal of the gradient, natriuresis and diuresis increased, resulting in further volume contraction (1769 ± 105 ml on the day of sacrifice, p < 0.02), a greater than 30-fold rise in PRA as well as a 40-fold increase in renal resistance (fig. 4).

To determine whether the rise in intrarenal resistance was the result of the AI-induced vasoconstriction, teprotide or saralasin was infused intrarenally. A small decrease in renal resistance was observed on Days 3 and 5, whereas marked reduction occurred on Day 7 (fig. 5) as renal blood flow rose from 25% ± 3% to 56% ± 7% of control (p < 0.05) and on Day 10 as renal flow increased from 8% ± 0.8% to 25% ± 2% of control (p < 0.005). The response was similar with both inhibitors.

At postmortem examination, fibrinoid necrosis of blood vessels associated with parenchymal damage was observed in all organs. There was no evidence of embolic changes in the kidney in relation to the renal artery catheter or cuff.

Discussion

The sequential renal hemodynamic changes during experimental benign and malignant renal hypertension are elucidated in this study. Immediately
following renal hypotension, renal vasodilation occurs. The renin-angiotensin system is also activated but its constrictor effect is initially opposed by endogenous vasodilators. Within hours, however, intrarenal vascular resistance returns to control and, in fact, rises above control. The vasoconstrictor response is AII-dependent and is reversible with the intrarenal blockade of the renin-angiotensin system. After 3 to 5 days, intrarenal administration of teprotide no longer reduces renal vascular resistance; in addition, systemic hypertension is no longer renin-dependent but is volume-dependent.2-11 Similar changes in intrarenal resistance have also been observed by Harris and Ayers4 and Anderson et al.4 Ayers et al.14 further demonstrated that sodium depletion at this chronic non-renin-dependent stage once more makes the renal vasoconstriction AII-dependent. These data suggest that renin-AII-volume interdependent mechanisms control renal vascular resistance. Since the changes in renal hemodynamics are moderate in benign hypertension, and appear to be purely functional, release of cuff constriction resulted in restoration of normal renal function and reversal of hypertension.

We utilized the method of mild progressive renal artery constriction for the study of the development of malignant hypertension. Since the transition from benign to malignant hypertension is gradual in this model, we were able to perform a detailed sequential analysis of hemodynamic, fluid, electrolyte, and hormonal changes. The response to mild progressive renal artery constriction during the benign phase was similar to that of the single stage constriction. During the transition from benign to malignant hypertension, two factors appear to be important: 1) increasing renal vasoconstriction, and 2) the development of natriuresis and diuresis resulting in plasma volume contraction. Angiotensin II appears to be, in large part, responsible for the increasing intrarenal resistance. During the transition phase, PRA activity is markedly increased. Intrarenal blockade of the renin-angiotensin system resulted in a significant increase in renal blood flow, although it is not restored to control levels, suggesting participation of other mechanisms or pathological changes in renal vasculature. When renal tubular dysfunction occurs as a result of marked decrease in renal blood flow, increasing AII and prostaglandins lead to natriuresis. The volume depletion further stimulates renin release. Thus a vicious cycle of volume contraction, renin secretion, and vasoconstriction develops in malignant hypertension.18,14 When the vicious cycle is established and vascular damage has occurred, renal ischemia and malignant hypertension are irreversible despite cuff deflation.

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Figure 5. Response of intrarenal vascular resistance to intrarenal blockade of the renin angiotensin system in benign and malignant hypertension.
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