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# Pressor and Vascular Responsiveness in Renal Prehypertensive Rabbits with a Nonfiltering Kidney (42138)

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*Abstract.* This study examined the possibility that the renal tubules are the site of the sensors that respond to renal artery stenosis (RAS) and which initiate the events leading to pressor hyperresponsiveness. A nonfiltering kidney (NFK) was produced in 32 rabbits by 2 hr of total renal ischemia plus permanent ligation of the ureter; the opposite kidney remained undisturbed. Sixteen of these rabbits also received RAS of the NFK. An additional 16 rabbits received RAS without production of a NFK, and 16 more rabbits were sham-operated controls. In acute experiments 3 days later in conscious rabbits, infusions of norepinephrine at several doses resulted in greater increases in mean arterial pressure in the RAS rabbits, with filtering kidneys (2-K, 1-clip) and with NFKs (2-K, 1-clip with NFK), than in the NFK rabbits without RAS (2-K control with NFK) or in the control rabbits (2-K control). Measurements of cardiac output revealed greater increases in total peripheral resistance as well as in mean arterial pressure in response to norepinephrine in the RAS rabbits both without and with a NFK. Because production of a NFK in rabbits did not prevent the development of pressor and vascular hyperresponsiveness 3 days after RAS, these studies indicated that the renal sensors that detect changes in the kidney following RAS and which initiate the series of events leading to pressor and vascular hyperresponsiveness, probably are not located in the renal tubules.

It is well established that patients with hypertension, as well as animals with experimental hypertension, have exaggerated increases in arterial pressure in response to vasoconstrictor agents (1–4). The mechanisms responsible for this pressor hyperresponsiveness in hypertension are not understood completely. In previous studies (5–8) we have shown that pressor hyperresponsiveness occurs in rabbits 3 days after renal artery stenosis (RAS), with the opposite kidney either removed (1-K, 1-clip) or intact (2-K, 1-clip). The renal perturbations which occur in the kidney during RAS and which result in pressor hyperresponsiveness probably are perceived by sensors or receptors of some type in the kidney. These most likely are baroreceptors located in the arterial system of the kidney or chemoreceptors located in the renal tubules or renal vascular system. The present study was designed to provide information on the location of these receptors. To test the hypothesis that these receptors are located solely or mainly in the renal tubules, this study used rabbits with a nonfiltering kidney (NFK).

**Methods.** A total of 64 male New Zealand white rabbits, 2.8 to 3.2 kg in body wt, were used in these studies. The rabbits were caged singly in a constant environmental temperature of 27°C. Room lights were controlled by an automatic time switch that provided illumination from 7:00 AM to 7:00 PM daily. All rabbits received an excess of a commercial rabbit diet (Purina Lab Rabbit Chow

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HF5326), which provided 0.167 meq of $Na^+$ and 0.467 meq of $K^+$ per gram of feed. Water was available *ad libitum.*

Four different animal preparations were used. Sixteen rabbits were sham-operated (2-K controls). An additional 16 rabbits had only a unilateral RAS (2-K, 1-clip). A unilateral NFK was produced in 16 other rabbits (2-K control with a NFK), and 16 more rabbits had a unilateral NFK plus RAS of the same kidney (2-K, 1-clip with a NFK).

*Surgical procedures.* The production of RAS was by the method of Brooks and Muirhead (9). Rabbits were anesthetized with halothane (2–5%) in nitrous oxide and oxygen, as described by Sartick *et al.* (10). The left kidney was exposed by a midventral laparotomy, with sterile surgical procedures. A silver clip, with a gap size of 0.6 mm, was placed around the left renal artery to produce a reduction in renal blood flow; the clip was secured in place by a ligature across the open end of the clip. The right kidney was not disturbed. Each rabbit then was closed and was returned to its cage.

A unilateral NFK was produced in rabbits by the method described for dogs by Blaine *et al.* (11). Rabbits were anesthetized with halothane plus nitrous oxide and were opened by a midventral incision. The left ureter was ligated permanently with 2-O silk suture. A serrefine clamp was placed on the left renal artery to produce total occlusion of the vessel. Each rabbit was then closed, with the renal artery occluded, and was allowed to recover from the anesthesia. Two hours later, each rabbit was again anesthetized as before, reopened, and the serrefine clamp was removed from the left renal artery to reestablish blood flow to the kidney. The right kidney remained intact. In rabbits designated to receive both RAS and a NFK, the clip was placed around the left renal artery at this time. Each rabbit again was closed and was returned to its cage.

Rabbits selected as sham-operated controls were anesthetized with halothane plus nitrous oxide. They were subjected to a midventral laparotomy, and the left kidney was exposed. These rabbits then were closed and were returned to their cages without either kidney being disturbed.

Three days after these initial operations, each rabbit again was anesthetized as before, and polyvinyl catheters (Fr 5 infant feeding tubes) were placed in the lower aorta and inferior vena cava via the femoral artery and vein. These catheters were filled with a heparin solution (1000 units/ml), and the free ends of the catheters were sutured to the backs of the animals. Thirty-two rabbits in which cardiac output was to be determined (experiment 2) also had a similar catheter placed in the jugular vein so that the catheter tip would lie near the right atrium; this catheter also was filled with a heparin solution and was coiled and sutured to the back of the neck. Each rabbit was allowed to recover from the anesthesia, was weighed, and was placed in a rectangular box to limit its movements. The acute experiments were performed 6 hr later in conscious rabbits. During the acute experiments the rabbits were not restrained in any way except by the limitations of the size of the box.

Two separate experiments were performed. Each experiment used eight 2-K control rabbits; eight 2-K, 1-clip rabbits; eight 2-K control rabbits with a NFK; and eight 2-K, 1-clip rabbits with a NFK.

*Experiment 1: Pressor responses to norepinephrine.* At the start of the acute experiment an arterial blood sample (2 ml) was obtained from the arterial catheter and was placed in a chilled tube containing ethylenediaminetetraacetate (EDTA); this blood sample was used for the determination of plasma renin activity (PRA). Mean arterial pressure was measured through the arterial catheter with a pressure transducer (Statham, Model P23Db) and was recorded on an oscillographic recorder (Hewlett-Packard, Model 7754A). Heart rate was obtained by recording pulsatile arterial pressure at a fast paper speed (10 mm/sec). The gain of the recorder amplifier then was increased so that a 1-mm pen deflection represented a change in mean arterial pressure of 1 mm Hg, and the pen position was adjusted on the recorder channel by the use of a zero-suppression control on the amplifier. This allowed the recording of small changes in mean arterial pressure. Norepinephrine solutions were prepared by diluting a fresh ampule of a commercial solu-

tion (Levophed, Breon Laboratories) in 5% dextrose in water. While mean arterial pressure was being recorded continuously, norepinephrine was infused iv at doses of 25, 50, 100, 200, 400, 800, and 1200 ng/min/kg of body wt, with a syringe infusion pump. Norepinephrine solutions were infused at flow rates of 0.3 or 0.6 ml/min. Each norepinephrine solution was infused for 5 min, and 5 min were allowed between infusions for the mean arterial pressure to return to the preinfusion level and to stabilize. The mean arterial pressure during the 1-min period prior to each norepinephrine infusion was taken as the control pressure, and the increase in mean arterial pressure that occurred during the fifth minute of norepinephrine infusion was accepted as the pressor response.

At the end of the experiment, each rabbit was sacrificed with 3 ml of a strong barbiturate solution (Sleepaway, Fort Dodge Laboratories). Each NFK was examined grossly, and the decapsulated kidney was examined under a dissecting microscope. Tissue samples were obtained from each NFK; these were placed in neutral Formalin and were processed for histologic examination.

*Experiment 2: Vascular responses to norepinephrine.* An arterial blood sample (2 ml) for PRA was obtained at the start of the acute experiment. Each rabbit then was given 1000 units of heparin iv. Control measurements were obtained for mean arterial pressure, heart rate, and cardiac output. Cardiac output was determined by dye dilution, as has been described previously (12). Blood was pumped from the arterial catheter through a densitometer cuvette (model DC-410, Waters Instruments) at a rate of 10.0 ml/min by a roller pump; the blood was returned to the rabbit through the femoral catheter. A volume of 0.15 ml of indocyanine green dye (Cardio-Green; Hynson, Westcott, and Dunning, Inc.), with a dye concentration of 2.5 mg/ml, was placed in the jugular catheter and was flushed into the circulation with 0.8 ml of isotonic saline. The densitometer cuvette was interfaced with a densitometer (Model TD-1; Waters Instruments), and the dye concentration curves were recorded on the oscillographic recorder. All cardiac output determinations were performed in triplicate, and the average of the three determinations was accepted as the cardiac output value.

Following these control measurements, a solution of norepinephrine, prepared as described in experiment 1, was infused iv at a dose rate of 800 ng/min/kg of body wt, for 5 min, and the pressor response was recorded. During the final minute of norepinephrine infusion, heart rate and cardiac output again were determined. Each rabbit was then sacrificed as before, and tissue samples were obtained from each NFK for histologic examination.

Cardiac output values were expressed in ml/min/kg of body wt. Values for total peripheral resistance (TPR) were expressed in the arbitrary units that result from dividing the mean arterial pressure in mm Hg, by the cardiac output in ml/min/kg of body wt. Stroke volume was calculated as ml/kg of body wt.

*Analytical procedures.* Blood samples for PRA were spun in a refrigerated centrifuge, and the plasma was stored frozen at −14° C. At a later time the plasma samples were thawed, and PRA was determined by radioimmunoassay of generated angiotensin I, by a modification of the method of Cohen *et al.* (13); these procedures, as used in our laboratory, have been described previously in detail (12). Values for PRA were expressed as nanogram of generated angiotensin I per milliliter of plasma, per hour of incubation.

*Statistics.* In experiment 1, the values for mean arterial pressure, heart rate, PRA, and the pressor response to each dose of norepinephrine were compared among the four groups of rabbits by analysis of variance (14). In experiment 2, the values for mean arterial pressure, heart rate, PRA, cardiac output, TPR, and stroke volume in the initial part of the experiment were compared among the four groups of rabbits by analysis of variance. In both experiments, when significant values were obtained, the data were analyzed further by Duncan's new multiple range test (14). In experiment 2, values for mean arterial pressure, heart rate, cardiac output, TPR, and stroke volume during norepinephrine infusion were compared to the values prior to norepinephrine infusion by the $u$ test (14), to

TABLE I. INITIAL VALUES FOR RABBITS IN EXPERIMENT 1

| | Mean arterial pressure (mm Hg) | Heart rate (per min) | PRA |
|---|---|---|---|
| 2-K control rabbits | 94 ± 2 | 272 ± 14 | 5.9 ± 0.8 |
| 2-K, 1-clip rabbits | 95 ± 3 | 260 ± 13 | 5.0 ± 0.6 |
| 2-K control rabbits with a NFK | 97 ± 3 | 263 ± 11 | 6.1 ± 1.3 |
| 2-K, 1-clip rabbits with a NFK | 102 ± 3 | 250 ± 11 | 5.1 ± 0.8 |

*Note.* Values are means ± SEM for eight rabbits per group. PRA = plasma renin activity. 2-K, 1-clip = 2-kidney rabbits with unilateral 3-day renal artery stenosis. NFK = nonfiltering kidney. There were no significant differences among the four groups of rabbits for any of these measurements.

determine if a change occurred during the infusion of norepinephrine. For those measurements in which a change occurred with norepinephrine, the values for the changes were analyzed among the four groups of rabbits by analysis of variance plus Duncan's new multiple range test.

**Results.** The initial values for mean arterial pressure, heart rate, and PRA for the rabbits in all four groups in experiment 1 are given in Table I. There were no significant differences among the groups of rabbits for any of these values. The pressor responses to norepinephrine in these four groups of rabbits are illustrated in Fig. 1, which is a plot of the various doses of norepinephrine infused, on a logarithmic scale, vs the increase in mean arterial pressure produced by these doses. It was found that these dose–response relationships could be described adequately by the equation $y = a(\log x)^n$, where $y$ is the increase in mean arterial pressure, $x$ is the dose of norepinephrine, and $a$ and $n$ are constants. The curves in this figure are the least-squares fit of this equation to the values obtained for each group of rabbits. The increases in mean arterial pressure in response to norepinephrine were significantly greater in the 2-K, 1-clip rabbits with a filtering kidney than in either group of rabbits without RAS, for all doses of norepinephrine. Pressor responses to norepinephrine in the 2-K, 1-clip rabbits with a NFK were significantly greater than in the 2-K control rabbits with a NFK for all norepinephrine doses except 25 and 100 ng/min/kg. The 2-K, 1-clip rabbits without a NFK had pressor responses that were generally greater than those of the 2-K, 1-clip rabbits with a NFK, but these differences were significant only for norepinephrine doses of 100 and 200 ng/min/kg. There were no significant differences in the pressor responses to any of the doses of norepinephrine between the 2-K controls and the 2-K controls with a NFK.

Table II presents the initial values for mean arterial pressure, heart rate, PRA, cardiac output, TPR, and stroke volume for all

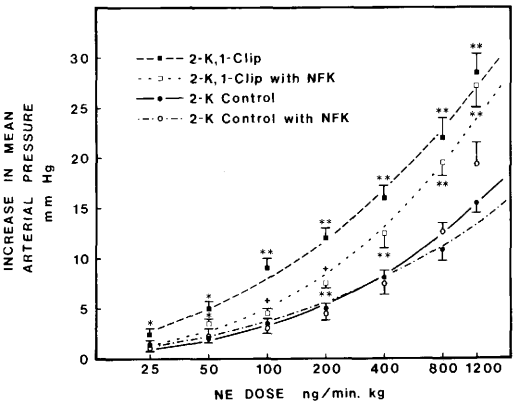


FIG. 1. Increases in mean arterial pressure (mm Hg) in response to infusions of norepinephrine (ng/min/kg body wt; log scale) in four groups of rabbits in experiment 1. 2-K, 1-Clip = 2-kidney rabbits with 3-day unilateral renal artery stenosis. NFK = nonfiltering kidney. Values are means ± SEM for eight rabbits per group. Lines represent best fit of the data to the equation: $y = a(\log x)^n$. * = $P < 0.05$ and ** = $P < 0.01$ that the value is greater than the corresponding value for the 2-K control group and the 2-K control group with a NFK. $^+$ = $P < 0.05$ that the value for the 2-K, 1-Clip with a NFK is less than the corresponding value for the 2-K, 1-Clip group.

TABLE II. INITIAL VALUES FOR RABBITS IN EXPERIMENT 2

| | Mean arterial pressure (mm Hg) | Heart rate (per min) | PRA | Cardiac output (ml/min kg) | TPR | Stroke volume (ml/kg) |
|---|---|---|---|---|---|---|
| 2-K control rabbits | 93 ± 2 | 263 ± 13 | 5.5 ± 0.9 | 260 ± 13 | 0.36 ± 0.02 | 1.00 ± 0.06 |
| 2-K, 1-clip rabbits | 94 ± 3 | 275 ± 14 | 4.9 ± 1.0 | 249 ± 10 | 0.38 ± 0.01 | 0.92 ± 0.05 |
| 2-K control rabbits with a NFK | 95 ± 3 | 243 ± 11 | 5.2 ± 0.9 | 263 ± 13 | 0.37 ± 0.02 | 1.10 ± 0.07 |
| 2-K, 1-clip rabbits with a NFK | 97 ± 5 | 255 ± 10 | 5.8 ± 0.8 | 279 ± 8 | 0.35 ± 0.02 | 1.10 ± 0.05 |

*Note.* Values are means ± SEM for 8 rabbits per group. PRA = plasma renin activity. TPR = total peripheral resistance. 2-K, 1-clip, = 2-kidney rabbits with unilateral 3-day renal artery stenosis. NFK = nonfiltering kidney. There were no significant differences among the four groups of rabbits for any of these measurements.

four groups of rabbits in experiment 2. There were no significant differences among these groups for any of these factors. The changes in mean arterial pressure, heart rate, cardiac output, TPR, and stroke volume that occurred during the infusion of norepinephrine at 800 ng/min/kg are summarized in Table III. Norepinephrine infusion resulted in significant increases in mean arterial pressure, TPR, and stroke volume in all groups of rabbits, while heart rate decreased significantly; cardiac output decreased slightly but significantly only in the 2-K, 1-clip rabbits without a NFK. Comparing the magnitudes of these changes among these four groups of rabbits revealed that the increases in mean arterial pressure and TPR were significantly larger in the 2-K, 1-clip rabbits and in the 2-K, 1-clip rabbits with a NFK than they were in the 2-K control rabbits or in the 2-K control rabbits with a NFK. The changes in heart rate and stroke volume were not different among the four groups of rabbits.

Gross examination of each NFK revealed a mild hydronephrosis. Visualization of the decapsulated surface with a dissecting microscope showed an extensive network of short, white lines, which were the necrotic surface tubules; examination of the cut surface of these kidneys revealed that these extended

TABLE III. CHANGES DURING NOREPINEPHRINE INFUSION FOR RABBITS IN EXPERIMENT 2

| | Mean arterial pressure (mm Hg) | Heart rate (per min) | Cardiac output (ml/min kg) | TPR | Stroke volume (ml/kg) |
|---|---|---|---|---|---|
| 2-K control rabbits | +13 ± 1[a] | −51 ± 8[a] | −5 ± 6 | +0.06 ± 0.01[a] | +0.23 ± 0.08[a] |
| 2-K, 1-clip rabbits | +25 ± 2[a,b] | −43 ± 6[a] | −14 ± 5[a] | +0.13 ± 0.01[a,b] | +0.12 ± 0.04[a] |
| 2-K control rabbits with a NFK | +12 ± 1[a] | −36 ± 4[a] | −6 ± 8 | +0.06 ± 0.01[a] | +0.19 ± 0.07[a] |
| 2-K, 1-clip rabbits with a NFK | +19 ± 1[a,b,c] | −55 ± 8[a] | −16 ± 16 | +0.10 ± 0.02[a,b] | +0.24 ± 0.09[a] |

*Note.* Values are means ± SEM for eight rabbits per group. TPR = total peripheral resistance. 2-K, 1-clip = 2-kidney rabbits with unilateral 3-day renal artery stenosis. NFK = nonfiltering kidney.

[a] $P < 0.05$ that a change occurred during infusion of norepinephrine.

[b] $P < 0.05$ that the increase in mean arterial pressure and TPR were greater than in the 2-K control rabbits or in the 2-K control rabbits with a NFK.

[c] $P < 0.05$ that the increase in mean arterial pressure was less than in the 2-K, 1-clip rabbits.

throughout the renal cortex. Figure 2 is a photomicrograph of a histologic section from the cortex of a rabbit NFK. Histologic examination revealed extensive tubular necrosis with casts filling the tubular lumina, but with normal glomerular tufts.

**Discussion.** The production of RAS in rabbits initiates an unknown series of events that lead to pressor and vascular hyperresponsiveness to vasoconstrictor substances. Although elevated angiotensin II concentrations will result in pressor hyperresponsiveness in rabbits (5), and increased activity of the renin–angiotensin system occurs acutely after RAS in rabbits (12), by 3 days after RAS the plasma angiotensin II levels (8) and PRA (5–7) are normal. Normal PRA values were observed in the 3-day RAS rabbits in the present study. Thus, increased plasma angiotensin II probably was not responsible

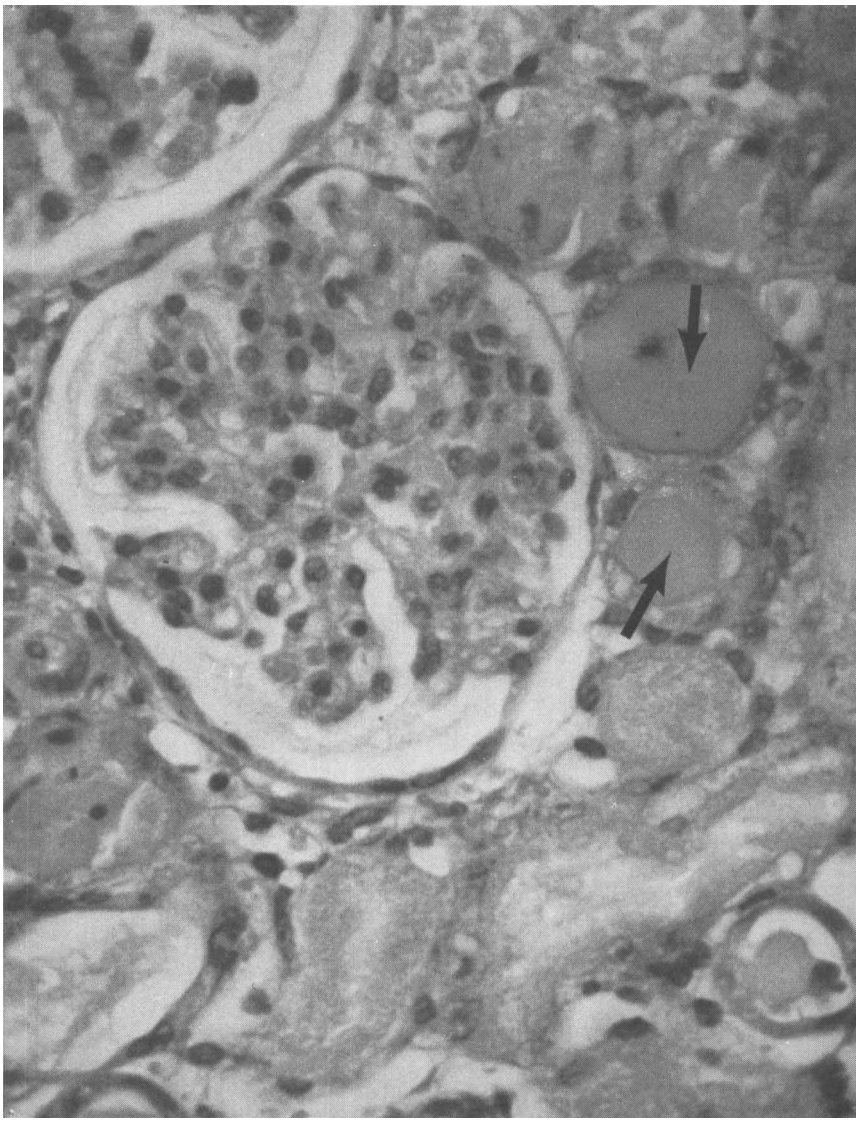

FIG. 2. Photomicrograph of a nonfiltering kidney preparation from a rabbit. Note the tubular necrosis with casts in the tubular lumina (arrows). The glomerular tufts appear normal.

for the pressor and vascular hyperresponsiveness in these 3-day RAS rabbits.

Folkow *et al.* (15) proposed that pressor hyperresponsiveness in hypertension may be due to structural changes in the arterioles resulting from the elevated arterial pressure. As seen in the present study and in previous studies from this laboratory (5–8), rabbits with RAS of 3-days duration were normotensive, but nevertheless these rabbits had enhanced pressor responses to norepinephrine to the same extent as rabbits with chronic hypertension due to RAS (5, 7). Thus, it seems unlikely that the structural alterations in the arterioles contributed to the pressor hyperresponsiveness in these 3-day RAS rabbits.

Expansion of body fluid volumes will result in pressor hyperresponsiveness, as shown by recent experiments (16) in which the iv infusion of isotonic saline at 1.5 to 1.8 ml/min for 24 hr in rabbits resulted in pressor and vascular hyperresponsiveness to norepinephrine. Three-day 2-K, 1-clip rabbits, however, have been shown to have normal values for plasma volume, extracellular fluid volume, and total body water (7). Therefore, the RAS rabbits in the present study probably were not volume expanded, and the pressor and vascular hyperresponsiveness observed in these rabbits probably were not due to increases in body fluid volumes.

Following RAS there is decreased pressure in the arterial system of the kidney and decreased glomerular filtration rate, which decreases the amount of the filterable components of the plasma reaching the renal tubular system. It is likely that in animals with RAS these disturbances act on baroreceptors in the renal vascular system or on chemoreceptors in the renal tubular system or in the renal vascular system to trigger mechanisms which ultimately result in pressor and vascular hyperresponsiveness. The possibility exists that, like the control of renin release (17), both vascular and tubular receptors may be involved in promoting hyperresponsiveness following RAS.

The NFK model has been used to study the mechanisms controlling renin release in dogs (11, 18) and in rats (19). That glomerular filtration is lacking in this model has been demonstrated by the failure of lissamine green, a dye that is filtered by the glomerulus, to appear in the surface tubules of dogs and rats following its injection into the circulatory system; also, after reopening the ureter in dogs with a NFK, the glomerular filtration rate remained extremely low (20). In the present study, the histologic appearance of the NFKs from rabbits (Fig. 2) was similar to that seen in NFKs from rats (19). The gross and histologic appearance of the NFK preparations in this study suggested that these kidneys did, indeed, lack filtration.

In this study, the 3-day 2-K, 1-clip rabbits had pressor hyperresponsiveness to norepinephrine when compared to controls, as was seen in an earlier study (7). Also, the 3-day 2-K, 1-clip rabbits with a NFK had greater pressor responses to norepinephrine than did the 2-K control rabbits or the 2-K rabbits without RAS. The results of experiment 2 revealed that the exaggerated increases in mean arterial pressure in response to norepinephrine in the 3-day 2-K, 1-clip rabbits with and without a NFK were accompanied by more pronounced increases in TPR than occurred during norepinephrine infusion in the 2-K control rabbits or in the 2-K rabbits with a NFK without RAS. These pronounced increases in TPR in response to norepinephrine presumably were due to more pronounced contractions of arteriolar smooth muscle cells. Thus, these 3-day 2-K, 1-clip rabbits, both with and without a NFK, exhibited vascular hyperresponsiveness as well as pressor hyperresponsiveness to norepinephrine.

The 2-K rabbits with a NFK but without RAS did not show pressor and vascular hyperresponsiveness. However, the 2-K, 1-clip rabbits with a NFK did exhibit pressor and vascular hyperresponsiveness to norepinephrine. Because hyperresponsiveness occurred in these rabbits with RAS of a kidney that lacked filtration, it seems improbable that the renal tubules are the site of the receptors that sense the changes in the kidney following RAS and that initiate the events leading to pressor and vascular hyperresponsiveness. This suggests that the renal vasculature is the most likely location for these sensors.

Studies from this laboratory (21) have

shown that a bloodborne substance is involved in mediating pressor hyperresponsiveness in 3-day 1-K, 1-clip rabbits, as the cross-circulation of blood between these rabbits and normal rabbits resulted in the transfer of pressor hyperresponsiveness to the normal rabbits. We speculate that RAS produces changes in the kidney, and that these changes are detected by sensors in the kidney, bringing about the release of a hormonal factor that then acts to promote increased responsiveness of the arteriolar smooth muscle cells to pressor agents. Because the kidney is the organ perturbed directly by RAS, it is suspected that the kidney may be the source of this circulating humoral hyperresponsiveness factor; however, it is also possible that the changes in the kidney following RAS might alter afferent neuronal signals from the kidney (22) that could bring about release of the hormonal hyperresponsiveness factor from some other organ.

It is of interest that although the 2-K, 1-clip rabbits with a NFK had greater pressor and vascular responses to norepinephrine than did either the 2-K control group or the 2-K group with a NFK but without RAS, these 2-K, 1-clip rabbits with a NFK had pressor and vascular responses that were less than the 2-K, 1-clip rabbits with RAS of a filtering kidney. This difference in the pressor responsiveness was significant at two dose levels of norepinephrine. In the NFK preparation there was less total functional renal tissue in the NFK, due to the period of ischemia. If the hormonal hyperresponsiveness factor originates from the kidney, this observation could be explained by there being less of the hormonal factor being produced and available for release in response to RAS in the NFK rabbits than in the rabbits with filtering kidneys.

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1. Doyle AE, Black H. Reactivity to pressor agents in hypertension. Circulation **12**:974–980, 1955.
2. Finch L, Haeusler G. Vascular resistance and reactivity in hypertensive rats. Blood Vessels **11**:145–158, 1974.
3. Goldenberg M, Pines KL, Baldwin EF, Greene DG, Roh CE. The hemodynamic response of man to norepinephrine and epinephrine and its relation to the problem of hypertension. Amer J Med **5**:792–806, 1948.
4. Kaplan NM, Silah JG. The effect of angiotensin II on blood pressure in humans with hypertensive disease. J Clin Invest **43**:659–669, 1964.
5. Ichikawa S, Johnson JA, Fowler WL Jr, Payne CG, Kurz K, Keitzer WF. Pressor responses to norepinephrine in rabbits with 3-day and 30-day renal artery stenosis. The role of angiotensin II. Circ Res **43**:437–446, 1978.
6. Johnson JA, Ichikawa S, Kurz KD, Fowler WL Jr, Payne CG. Pressor responses to vasopressin in rabbits with 3-day renal artery stenosis. Amer J Physiol **240**: H862–H867, 1981.
7. Johnson JA, Kurz KD, Siripaisarnpipat S, Zeigler DW, Payne CG. Fluid volumes and pressor responsiveness in two-kidney rabbits with renal artery stenosis. Amer J Physiol **243**:H779–H787, 1982.
8. Koivunen DG, Johnson JA, Nichols WK, Zeigler DW, Siripaisarnpipat S, Payne CG. Pressor responses to norepinephrine during captopril in renal prehypertensive rabbits. Hypertension **5**:159–165, 1983.
9. Brooks B, Muirhead EE. Rigid clip for standardized hypertension in the rabbit. J Appl Physiol **31**:307–308, 1971.
10. Sartick M, Eldridge ML, Johnson JA, Kurz KD, Fowler WL Jr, Payne CG. Recovery rate of the cardiovascular system in rabbits following short-term halothane anesthesia. Lab Anim Sci **29**:186–190, 1979.
11. Blaine EH, Davis JO, Witty RT. Renin release after hemorrhage and after suprarenal aortic constriction in dogs without sodium delivery to the macula densa. Circ Res **27**:1081–1089, 1970.
12. Siripaisarnpipat S, Johnson JA, Kurz KD, Fowler WL Jr, Payne CG. Cardiovascular changes within 24 h after renal artery stenosis in rabbits. Amer J Physiol **240**:H2–H8, 1981.
13. Cohen EL, Grim CE, Blough WM Jr, Guyer RB, Kem DC, Lucas CP. Accurate and rapid measurement of plasma renin activity by radioimmunoassay. Results in normal and hypertensive people. J Lab Clin Med **77**:1025–1038, 1971.
14. Li JCR. Statistical Inference. Ann Arbor, Edwards Brothers, 1964.
15. Folkow B, Hallback M, Lundgren Y, Sivertsson R, Weiss L. Importance of adaptive changes in vascular design for establishment of primary hypertension studied in man and in spontaneously hypertensive rats. Circ Res (Suppl I) **32, 33**:2–13, 1973.

16. Sakamaki T, Johnson JA, Zeigler DW, Koivunen DG, Siripaisarnpipat S, Fowler WL Jr, Payne CG. Pressor hyperresponsiveness in saline infused rabbits. Hypertension **6**:503–510, 1984.
17. Davis JO. What signals the kidney to release renin? Circ Res **28**:301–306, 1971.
18. Witty RT, Davis JO, Johnson JA, Prewitt RL. Effects of papaverine and hemorrhage on renin secretion in the nonfiltering kidney. Amer J Physiol **221**:1666–1671, 1971.
19. Villarreal D, Davis JO, Freeman RH, Dietz JR, Lugar AM. A deneravated nonfiltering kidney preparation in the rat: A model for study of renin release. Proc Soc Exp Biol Med **173**:140–147, 1983.
20. Johnson JA, Davis JO, Shade RE, Witty RT. Effects of reopening the ureter in the nonfiltering kidney model. Proc Soc Exp Biol Med **139**:997–1001, 1972.
21. Johnson JA, Kurz KD, Siripaisarnpipat S, Koivunen DG, Zeigler DW, Sakamaki T, Payne CG. Humoral factor in pressor hyperresponsiveness in renal prehypertensive rabbits. Hypertension **5**:453–459, 1983.
22. Niijima A. Afferent discharges from arterial mechanoreceptors in the kidney of the rabbit. J Physiol (London) **219**:477–485, 1971.

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