Pressure-Diuresis in Volume-Expanded Rats
Cortical and Medullary Hemodynamics
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SUMMARY This study evaluated whether pressure-diuretic and pressure-natriuretic responses are associated with alterations in vasa recta hemodynamics. Autoregulation of cortical and papillary blood flow was studied using a laser-Doppler flowmeter in volume-expanded and hydropenic rats. Superficial cortical flow and whole kidney renal blood flow were autoregulated in volume-expanded rats and decreased by less than 10% after renal perfusion pressure was lowered from 150 to 100 mm Hg. In contrast, papillary blood flow was not autoregulated and fell by 24 ± 2%. The failure of papillary blood flow to autoregulate was due to changes in the number of perfused vessels as well as to alterations in blood flow in individual ascending and descending vasa recta. Pressure in vasa recta capillaries increased from 6.8 ± 0.8 to 13.8 ± 1.2 mm Hg after renal perfusion pressure was elevated from 100 to 150 mm Hg, and renal interstitial pressure rose from 7.4 ± 0.8 to 12.3 ± 1.4 mm Hg. In hydropenic rats, papillary blood flow was autoregulated to a significant extent, but it still decreased by 19% after renal perfusion pressure was lowered from 150 to 100 mm Hg. The pressure-diuretic and pressure-natriuretic responses in hydropenic rats were blunted in comparison to those observed in volume-expanded rats. These findings indicate that the pressure-diuretic and pressure-natriuretic responses are associated with changes in vasa recta hemodynamics and renal interstitial pressure. (Hypertension 12: 168–176, 1988)

KEY WORDS • hypertension • kidney • vasa recta • urine concentration and dilution • kidney papilla • rats

ALTHOUGH changes in renal perfusion pressure (RPP) are known to alter tubular reabsorption of water and electrolytes, the mechanism of pressure-diuresis is unresolved. This response has been attributed to changes in glomerular filtration rate (GFR) and to inhibition of tubular reabsorption in the proximal tubule, the loop of Henle, and the collecting duct. It has been suggested that pressure-diuresis and natriuresis may be caused by an increase in renal interstitial pressure that inhibits tubular reabsorption in the proximal tubule of superficial or deep nephrons (or both). However, pressure-diuresis can occur in the absence of measurable changes in the oncotic or hydrostatic pressures in the peritubular capillaries. Thus, the factors responsible for causing a sustained increase in renal interstitial pressure have not been identified. Recently, Chou and colleagues suggested that RPP may influence proximal tubular reabsorption by altering the release of an autacoid. Others have suggested that elevations in RPP inhibit reabsorption in the loop of Henle and the collecting duct by increasing medullary blood flow and dissipating the medullary solute gradient.

Part of the problem in determining the mechanism of pressure-natriuresis is that it is difficult to manipulate RPP without changing neural tone and the levels of hormones that regulate renal function. Previous studies have examined the effects of reducing RPP after pressure was first increased by bilateral carotid occlusion. Others have studied the effects of elevating RPP by infusion of catecholamines or by ligation of the carotid arteries. However, activation of the renal nerves and release of vasoactive hormones blunt the pressure-natriuretic response under these conditions.

We recently characterized a model for the study of pressure-natriuresis in volume-expanded rats with a fixed neural and hormonal background to the
kidney. This model was used in the present investigation to determine whether pressure-natriuresis is associated with changes in vasa recta hemodynamics or renal interstitial pressure (or both). Autoregulation of cortical and papillary blood flow was studied using laser-Doppler flowmetry. Changes in papillary blood flow were confirmed by measuring the velocity of red blood cells (RBCs) in vasa recta capillaries. Peritubular and vasa recta capillary pressures were measured using a servomull micropressure device. Changes in renal interstitial pressure were evaluated using the implanted capsule method.

Materials and Methods

Experimental Groups

Experiments were performed on 172 male Sprague-Dawley rats (weight, 225–325 g) purchased from Harlan Industries (Madison, WI, USA). Food and water were allowed ad libitum before the study.

Two groups of rats were studied. Group 1 consisted of volume-expanded rats in which the neural and hormonal influences on the kidney were controlled. The right kidney and adrenal gland of these rats were removed before the study. On the day of the experiment, the remaining adrenal gland was removed and the left kidney was denervated. Aldosterone (66 ng/kg/min), cortisol (33 ng/kg/min), vasopressin (0.17 ng/kg/min), and norepinephrine (333 ng/kg/min) were dissolved in a 0.9% sodium chloride solution with 1% bovine serum albumin and infused intravenously at 33 μl/min/100 g body weight. [3H]Inulin (1 μCi/ml) was included in the infusion solution for measurement of GFR.

These rats were studied in all eight protocols outlined in the following sections.

Group 2 consisted of hydropenic rats that were infused with 0.9% sodium chloride solution at 20 μl/min throughout the experiment. Neural and hormonal influences on the kidney were not fixed in this group. The rats were not adrenalectomized or uninephrectomized, and the renal innervation was left intact. These animals were studied in Protocols 1 and 8.

Surgical Preparation for the Clearance Experiments

The rats were prepared for study of the pressure-natriuretic response as described previously. They were anesthetized with Inactin, 100 mg/kg and maintained at 37 °C. The carotid and femoral arteries were cannulated for measurement of RPP. Cannulas were placed in the jugular vein for infusions and in the ureter for collection of urine. A 2-mm flow probe was placed around the renal artery for measurement of renal blood flow (RBF) using an electromagnetic flowmeter (Model 501, Carolina Instruments, King, NC, USA). Adjustable clamps were placed around the abdominal aorta above and below the kidney, and ligatures were placed around the celiac and mesenteric arteries so that RPP could be varied by adjusting peripheral vascular resistance. A 60-minute equilibration period was allowed after the operation before measurements were obtained.

Exposure of the Papilla for Studies of the Vasa Recta

One week before an experiment, the rats were anesthetized with ketamine (100 mg/kg) and acepromazine (1 mg/kg). A small amount of renal cortical tissue on the dorsal surface of the left kidney was removed for exposure of the renal papilla. On the day of the experiment, the animal was prepared for a clearance experiment as already described. The left kidney was immobilized in a holder. The papilla was exposed by excising the ureter and was bathed in paraffin oil during the experiment.

Protocol 1: Autoregulation of Cortical and Papillary Blood Flow

The relationships between cortical and papillary blood flow and RPP were characterized in 30 volume-expanded rats (Group 1) and in 12 hydropenic rats (Group 2). Cortical and papillary blood flows were measured using a laser-Doppler flowmeter (Model Pfdl, Perimed KB, Stockholm, Sweden). RPP was first increased approximately 25 mm Hg by occluding the celiac and mesenteric arteries. In half the animals, papillary flow was measured as RPP was lowered from 150 to 50 mm Hg in steps of 15 mm Hg. RPP was then returned to 150 mm Hg, and the protocol was repeated while cortical blood flow was measured. The order of study was reversed in the remaining animals. Cortical and papillary blood flow autoregulatory indices (AI) were calculated using the following formula:

\[ AI = \frac{\text{Flow}_1 - \text{Flow}_2}{\text{Flow}_1} \times \frac{\text{RPP}_1 - \text{RPP}_2}{\text{RPP}_1} \]

According to this analysis, an index of 0 indicates perfect autoregulation of blood flow while an index of 1 indicates a system with a fixed resistance.

To study the influence of hydration state on the autoregulation of cortical and papillary blood flow, seven of the hydropenic rats received an i.v. bolus of 0.9% sodium chloride solution equal to 2% of body weight followed by a maintenance infusion (6 ml/hr). One hour later, the relationships between cortical and papillary blood flow and RPP were redetermined.

Protocol 2: Autoregulation of Renal Blood Flow

Autoregulation of RBF in the range of RPP from 150 to 50 mm Hg was studied in 25 volume-expanded rats (Group 1) prepared for clearance experiments.

Protocol 3: Relationships Between Cortical and Vasa Recta Capillary Pressures and Renal Perfusion Pressure

Seventeen volume-expanded rats (Group 1) were prepared with an exposed papilla. RPP was lowered
to 100 mm Hg during a 20-minute control period. Pressure was then increased in steps of approximately 20 mm Hg, during three successive 20-minute periods. In 10 rats, pressures were measured in six to eight vasa recta capillaries during each period using a servonull micropressure system (Model 900, World Precision Instruments, New Haven, CT, USA). Equal numbers of ascending and descending vasa recta capillaries were punctured during each period. Since all of the capillaries were close to the tip of the papilla, ascending and descending vasa recta capillary pressures were similar and the values were pooled. In seven rats, the relationship between peritubular capillary pressure and RPP was determined using this same protocol.

Protocol 4: Vasa Recta Hematocrit

Seven volume-expanded rats (Group 1) were prepared with an exposed papilla. RPP was lowered to 100 mm Hg, and samples of blood (100–300 nl) were collected from three descending vasa recta capillaries near the tip of the papilla using siliconized, glass micropipettes (outside diameter, 12–15 μm). RPP was increased to 125 and to 150 mm Hg during two 20-minute periods while blood samples were collected from capillaries that had not been previously punctured.

Blood samples were expelled into 1-μl capillary tubes that were sealed at one end with cyanoacrylate adhesive (Permabond, Englewood, NJ, USA). These tubes were placed in microhematocrit tubes that were sealed at one end and centrifuged for 15 minutes. The hematocrits of the samples were determined using a microscope eyepiece micrometer. In preliminary experiments, the ratio of hematocrits of arterial blood samples measured using this micro-method and values measured using 100-μl capillary tubes was 0.99 ± 0.03 (n = 28).

Protocol 5: Effect of Changes in Renal Perfusion Pressure on the Number of Perfused Vasa Recta Capillaries

Experiments were performed on 16 volume-expanded rats (Group 1). During the equilibration period, 20 mg of fluorescein isothiocyanate (FITC)-labeled gamma globulin was injected intravenously. The papilla was illuminated with a 100-W mercury vapor epipillimator and viewed with an Olympus Model BHS microscope (Lake Success, NY, USA). The incident light was filtered using an infrared and a 50% neutral density filter to minimize heating of the papilla. A 25 × (0.35 numerical aperture) long-working distance objective (Leitz Wetzlar, West Germany) and a 2.5 × eyepiece were employed in the system. Areas of the papilla were excited using 490-nm light, and the emitted light (>520 nm) was observed using an intensified, Newvicon television camera (Model WV-1900, Panasonic, Rockleigh, NJ, USA). The images were displayed on a monitor (Model TC1112, RCA, Lancaster, PA, USA) and videorecorded (Model SL450, Sony Corporation of America, Park Ridge, NJ, USA). Precamera magnification was 62.5×; total magnification was 1000×. Depth of focus was 20 μm, and the field of view was 200 × 200 μm².

The microcirculation in different areas of the papilla was videorecorded at an RPP of either 100 or 150 mm Hg in random order. In each area, the ascending and descending vasa recta capillaries in which RBCs were moving were counted at low and high RPP. The results were tabulated as the number of perfused vessels per 0.04 mm² of papillary surface area.

The FITC-labeled gamma globulin was prepared by dissolving 60 mg of bovine gamma globulin (Sigma Chemical, St. Louis, MO, USA) in 5 ml of 0.9% sodium chloride solution. The pH was adjusted to 9.9 using sodium carbonate. Forty milligrams of FITC adsorbed on infusorial earth particles (Celite, F1628, Sigma) was added to the solution. After 2 hours, the unreacted FITC was removed by centrifugation and dialysis.

Protocol 6: RBC Velocity and Vessel Diameter in Vasa Recta Capillaries

Studies were performed on 12 volume-expanded rats (Group 1) with an exposed papilla. RPP was adjusted to 100, 125, or 150 mm Hg, and blood flow in vasa recta capillaries was videorecorded. Each area was studied for 5 minutes at three levels of RPP. The order in which the pressures were studied was randomized. Capillary diameters were measured using the x, y window position controls of a videophotometric analyzer (Model 204, Instruments for Physiology and Medicine, San Diego, CA, USA). The resolution of the system was ± 1 μm.

The velocity of RBCs in vasa recta capillaries was measured from the videorecordings using the dual slit cross-correlation technique. The video photometric analyzer was used to align two electronic windows, 25 μm apart, over a vessel. The filtered voltages from the photoanalyzer (2–25 Hz) were analyzed using a velocity tracking device (Model 102B, Instrumentation for Physiology and Medicine). This instrument produced a signal (0–1 V full scale) proportional to the velocity of the cells moving between the windows. A measurement was accepted if a stable reading was obtained for 1 minute.

The velocity tracking system was calibrated using a smear of RBCs on a rotating wheel in the range from 0.3 to 2 mm/sec. The slope of the calibration was 38.9 ± 0.3 U/μm/sec (r = 0.998), and the y intercept was 4.7 ± 0.3 U/μm/sec.

Protocol 7: Measurement of Renal Interstitial Pressure

The relationship between renal interstitial pressure and RPP was studied in seven volume-expanded rats (Group 1). Urine flow, sodium excretion, and renal interstitial pressure were measured...
at an RPP of 100, 125, and 150 mm Hg during six successive 15-minute periods. Deep cortical interstitial pressure was measured using a modification of the implanted capsule technique.\textsuperscript{26} The capsule was constructed by inserting a 0.5 × 2 mm piece of polyethylene matrix material (35 μm pore size, Bel-Art Associates, Pequannock, NJ, USA) into a catheter (outside diameter, 0.89 mm, SV 31, Dural Plastics, New South Wales, Australia). The matrix material was secured in the catheter using a 6-0 suture.

A small hole, 1 mm in diameter and 3 mm deep, was created in the renal cortex using an electrocautery needle. After the bleeding was stopped, the capsule was inserted into the hole. Cyanoacrylate adhesive was placed on the surface of the kidney to prevent leaks. The catheter was flushed with 20 μl of saline, and the pressure in the capsule was recorded using a transducer (P23, Gould Statham Instruments, Cleveland, OH, USA) and a Grass polygraph (Quincy, MA, USA) calibrated between 0 and 20 mm Hg. The response of the system was tested by partially occluding the renal vein. The capsule had to record a 20 mm Hg increase in pressure within 5 seconds to be included in these experiments.

Protocol 8: Characterization of the Pressure-Natriuretic Response

These experiments were performed in 38 volume-expanded (Group 1) and eight hydropenic (Group 2) rats. RPP was lowered by 20 mm Hg, and urine flow, sodium excretion, GFR, and RBF were measured during two 30-minute periods. Then, RPP was returned to control and urine and plasma samples were collected during two 15-minute periods. RPP was then increased to 150 mm Hg by occluding the mesenteric and celiac arteries and the aorta below the kidney. Urine and plasma samples were again collected during two 15-minute periods.

Urine flow was determined gravimetrically. \[^{[3]H}\]Inulin concentration of the samples was determined using a liquid scintillation spectrophotometer (Model 2450, Packard Instrument, Downers Grove, IL, USA). Sodium and potassium concentrations of all samples were determined using a flame photometer (Model 143, Instrumentation Laboratories, Lexington, MA, USA). GFR was calculated as the urine to plasma inulin concentration ratio times urine flow. GFR, RBF, urine flow, and electrolyte excretions were factored per gram of kidney weight.

Statistical Methods

Data are presented as mean values ± 1 SE. The significance of differences in values measured at different levels of RPP was evaluated using an analysis of variance for repeated measures.\textsuperscript{24} The significance of differences in measured values between groups of animals was evaluated using analysis of variance and a Duncan multiple range or an unpaired t test.\textsuperscript{25} The curves relating blood flow and RPP were determined using a third-order fitting procedure. A probability level of p below 0.05 (two-tailed test) was considered significant.

Results

Autoregulation of Renal, Superficial, Cortical, and Papillary Blood Flow

The results in the volume-expanded rats (Group 1) are presented in Figures 1 and 2. Control mean arterial pressure averaged 118 ± 2 mm Hg, and RBF was 5.3 ± 0.4 ml/min/g kidney weight. RBF was autoregulated in the range of pressures from 95 to 150 mm Hg. The RBF autoregulatory index averaged 0.36 ± 0.06 over this range.

The control cortical and papillary blood flow signals averaged 53 ± 3 units (1.76 V) and 52 ± 3 units (1.73 V), respectively, at an RPP of 119 ± 2 mm Hg. Cortical blood flow was autoregulated and declined by only 9 ± 2% when pressure was lowered from 157 to 102 mm Hg (see Figure 2). The cortical blood flow autoregulatory index was 0.29 ± 0.05 and was not different from the corresponding RBF index.

Papillary blood flow was not autoregulated as efficiently as RBF or cortical blood flow in the range of pressures from 100 to 150 mm Hg. Papillary blood flow fell significantly (to 93 ± 1% of control) when RPP was lowered to 105 ± 2 mm Hg, and it averaged 135 ± 5% of control at an RPP of 159 ± 3 mm Hg. The papillary blood flow autoregulatory index over this range of pressures averaged 0.85 ± 0.07, which was significantly greater than the corresponding cortical or RBF indices.

Vasa Recta and Peritubular Capillary Pressures

Vasa recta capillary pressure was directly related to the level of RPP in volume-expanded rats (Figure 3). It averaged 9.1 ± 1.0 mm Hg at a control RPP of 123 ± 2 mm Hg. Vasa recta capillary pressure increased by 103% when RPP was elevated from 99 ± 2 to 152 ± 3 mm Hg. In contrast, peritubular capillary pressure increased by only 16% when RPP...
was varied over this range. The rise in vasa recta capillary pressure (7 ± 1 mm Hg) in response to an elevation in RPP from 100 to 150 mm Hg was significantly greater than the increase in peritubular capillary pressure (2 ± 1 mm Hg).

Vasa Recta Hematocrit

The hematocrit of vasa recta blood (26 ± 2%) measured at the control RPP of 134 mm Hg was significantly lower than that of arterial blood (48 ± 2%). The hematocrit of the blood perfusing the vasa recta was not altered by changes in RPP and averaged 24 ± 2% at perfusion pressures of 104 and 172 mm Hg.

Number of Perfused Vasa Recta Capillaries

Increasing RPP produced a significant increase in the number of perfused ascending and descending vasa recta capillaries (Figure 4). This increase was due to the initiation of the flow of RBCs through capillaries that had been filled with plasma.

RBC Velocities and Vessel Diameters in Vasa Recta Capillaries

The control diameters of ascending and descending vasa recta capillaries (Figure 5) averaged 19.1 ± 0.8 and 16.7 ± 1.1 μm, respectively. The diameters of ascending and descending vasa recta capillaries did not change significantly when RPP was varied.

The velocity of RBCs in the ascending vasa recta capillaries averaged 0.56 ± 0.09 mm/sec at a control RPP of 125 mm Hg (see Figure 5). It fell to 0.37 ± 0.07 mm/sec when RPP was lowered, and it increased significantly to 0.75 ± 0.10 mm/sec when RPP was elevated. The control velocity of the RBCs in descending vasa recta was 0.80 ± 0.11 mm/sec (see Figure 5). It fell significantly to 0.49 ± 0.09 mm/sec after RPP was reduced. The velocity of RBCs in the descending vasa recta capillaries at an RPP of 145 mm Hg was not significantly different from control, but it was greater than the velocity measured at a RPP of 103 mm Hg.

Renal Interstitial Pressure

Cortical interstitial pressure (Figure 6) averaged 9.3 ± 1.0 mm Hg at a control RPP of 122 ± 1 mm Hg and fell by 20% after RPP was lowered to 104 ± 1 mm Hg. Increasing RPP to 144 ± 4 mm Hg increased interstitial pressure by 32%. Urine flow increased in these rats from 7 ± 1 to 64 ± 5 ml/min/g kidney weight in response to the elevation in RPP, and sodium excretion increased from 1.3 ± 0.2 to 12.4 ± 1.0 µEq/min/g kidney weight. RBF and GFR were not significantly altered by changes in RPP.

Autoregulation of Cortical and Papillary Blood Flow in Hydropenic Rats

Hydropenic rats (Group 2) exhibited several differences from the volume-expanded rats (Group 1). Hematocrit was significantly higher (50.4 ± 0.9%) in the hydropenic rats than in the volume-expanded animals (43.5 ± 1.0%). The control cortical (45 ± 3

![Figure 2](image1.png)

**Figure 2.** Relationships between cortical and papillary blood flow and renal perfusion pressure in volume-expanded rats. Blood flows are expressed as percentages of the flow signals measured at the control level of arterial pressure (○, ○).

![Figure 3](image2.png)

**Figure 3.** Relationships between peritubular and vasa recta capillary pressures and renal perfusion pressure (RPP). In each rat, five to seven capillaries were punctured at each level of RPP. Numbers in parentheses indicate the number of rats studied.

![Figure 4](image3.png)

**Figure 4.** Effect of renal perfusion pressure (RPP) on the number of perfused ascending and descending vasa recta capillaries per unit area of the papilla.
FIGURE 5. Effect of renal perfusion pressure on vessel diameter and the velocity of RBCs in ascending and descending vasa recta capillaries. N = number of vessels studied in 12 rats.

units; 1.49 V) and papillary blood flow signals (43 ± 3 units; 1.43 V) in the hydropenic rats were 15 and 23% lower than the corresponding values measured in the volume-expanded animals.

Cortical blood flow was well autoregulated down to an RPP of 80 mm Hg in the hydropenic rats (Figure 7). The cortical blood flow autoregulatory index in the pressure range of 100 to 150 mm Hg averaged 0.14 ± 0.16 and was not different from that measured in the volume-expanded rats (0.29 ± 0.05).

Papillary blood flow was autoregulated to some extent in the hydropenic rats over the pressure range of 100 to 150 mm Hg (see Figure 7). The papillary blood flow autoregulatory index observed in the volume-expanded rats (Group 1), which averaged 0.85 ± 0.07. After the hydropenic rats were subjected to acute volume expansion, cortical blood flow was well autoregulated with an index of −0.04 ± 0.015. However, papillary blood flow no longer exhibited significant autoregulation, and the autoregulatory index rose to 0.86 ± 0.15.

Comparison of the Pressure-Natriuretic Responses in Volume-Expanded and Hydropenic Rats

In hydropenic rats, urine flow and sodium excretion increased significantly after RPP was elevated from 100 to 150 mm Hg (Figure 8). In the volume-expanded rats, the increases in urine flow and sodium excretion were significantly greater than those observed in the hydropenic animals. Control GFR was similar in both groups, and averaged 1.3 ml/min/g kidney weight. GFR fell after RPP was lowered to 100 mm Hg in both groups, but it was autoregulated when RPP was elevated to 150 mm Hg. Control RBF was 20% lower in the hydropenic rats than in the volume-expanded animals. In both groups, RBF was well autoregulated over the range of RPP studied.

Discussion

Interest in the mechanism of pressure-natriuresis stems from the analysis of Guyton et al.26 indicating that this mechanism allows the kidney to perfectly regulate blood volume and arterial pressure (infinite gain hypothesis). For the kidney to function in this manner, pressure-natriuresis must be regulated by an intrarenal signal that is proportional to RPP and the response cannot be completely overridden by other regulatory systems. These requirements suggest that pressure-natriuresis may be mediated by a hemodynamic action (i.e., an increase in GFR)4, 5 or by inhibition of tubular reabsorption secondary to changes in the pressures in the capillaries8 or the interstitium of the kidney (or both).11, 12 However, pressure-diuresis can occur in the absence of measurable changes in GFR, RBF, or oncotic and hydrostatic pressures in the peritubular capillaries.6, 10-15 Thus, the intrarenal signal for the response has yet to be identified.

Selkurt et al.2 suggested that elevations in RPP might inhibit tubular reabsorption by altering medullary blood flow and the medullary solute gradient. Studies of Thurau,27 indicating that medullary blood flow is not autoregulated, supported this hypothe-
The results of a recent study, however, cast doubt on this proposal. The purpose of the present investigation was to determine if pressure-natriuresis is associated with changes in medullary hemodynamics or renal interstitial pressure (or both).

The results of our experiments indicate that papillary blood flow is not autoregulated as well as RBF or cortical blood flow in volume-expanded rats (see Figures 1 and 2). In the range of RPP from 100 to 150 mm Hg, the papillary blood flow autoregulatory index was significantly greater than the corresponding cortical and RBF indices. The papillary blood flow autoregulatory index was also not significantly different from 1, indicating that medullary vascular resistance remained constant in response to changes in RPP.

Cohen et al. reported that the velocity of RBCs in the vasa recta was unaltered after RPP was lowered from 115 to 85 mm Hg and concluded that pressure-natriuresis could not be related to changes in papillary blood flow. In the present study, alterations in RPP significantly altered papillary blood flow (see Figures 2 and 7) and vasa recta capillary pressure (see Figure 3). RBF, GFR, cortical blood flow, and peritubular capillary pressure remained relatively constant when RPP was varied between 100 and 150 mm Hg. These results indicate that changes in medullary hemodynamics are associated with the pressure-natriuretic response at least over the range of RPP from 110 to 150 mm Hg. In the lower range of RPP (80–120 mm Hg), cortical and papillary blood flow decreased significantly by about the same amount in response to a reduction in RPP (see Figure 2). Therefore, in this range of pressures we cannot exclude the possibility that alterations in cortical hemodynamics also contribute to pressure-mediated changes in sodium excretion.

Laser-Doppler flowmeters respond to changes in the local tissue hematocrit as well as the mean RBC velocity in the area of interest. Therefore, one explanation for the lack of agreement between the present study and that of Cohen et al. is that RPP may influence papillary blood flow by altering intravascular hematocrit or the number of perfused vessels. The results of our hematocrit studies confirmed previous reports that the hematocrit of blood in the vasa recta is less than that of arterial blood. However, changes in hematocrit did not contribute to the rise in papillary blood flow in our study because it remained constant as RPP was varied.

The videomicroscopy studies indicated that the number of perfused vasa recta capillaries (see Figure 4) and the velocity of RBCs in these vessels increased significantly after RPP was elevated (see Figure 5). The rise in papillary blood flow was caused by an increase in blood flow through perfused capillaries as well as the recruitment of flow in nonperfused capillaries. These findings confirm, using another method, that papillary blood flow is not autoregulated in volume-expanded rats.

Recent studies have indicated that papillary blood flow is influenced by humoral factors and renal sympathetic tone. Plasma levels of vasopressin, angiotensin, atrial natriuretic factor, and renal nerve activity are all affected by changes in blood volume. To determine whether the efficiency of papillary blood flow autoregulation is altered by changes in the level of hydration, experiments were performed in hydropenic rats. Papillary blood flow was autoregulated to a significant extent in hydropenic rats (see Figure 7). Acute volume expansion eliminated the papillary blood flow autoregulatory response in these animals. Thus, differences in the neural and humoral background to the kidney and the volume status of the rats probably explain the discrepancy between our results and those reported by Cohen et al.

Even though papillary blood flow was autoregulated to some extent in the hydropenic rats, it decreased significantly when RPP was lowered from 150 to 100 mm Hg (see Figure 7). Thus, changes in pressure and flow in the vasa recta circulation could still serve as an intrarenal signal for the pressure-natriuretic response. In volume-expanded rats, the rise in papillary blood flow (see Figure 2) was greater than that seen in the hydropenic animals and the magnitude of the pressure-natriuretic response...
was much greater (see Figure 8). These observations suggest that the magnitude of the pressure-natriuretic effect may be influenced by the efficiency of papillary blood flow autoregulation.

The rise in papillary blood flow at elevated perfusion pressures could have been due to a failure of juxtamedullary glomeruli to autoregulate single nephron GFR and blood flow. However, we and others have reported that single nephron GFR measured at the tip of the loop of Henle of deep nephrons is well autoregulated. The mechanism by which papillary blood flow can increase if single nephron GFR in deep nephrons is autoregulated is unknown. It could be related to the anatomy of the efferent arterioles of juxtamedullary nephrons that supply parallel flow beds (i.e., peritubular capillaries and the capillary beds in the inner and outer medulla). Papillary blood flow could increase in face of a constant deep nephron glomerular blood flow if the vascular resistance of the descending vasa recta decreases after RPP is elevated. The present finding that the pressures in the vasa recta became equivalent when RPP was elevated supports this possibility.

Renal interstitial pressure is a determinant of the natriuretic response to volume expansion and renal vasodilators. Changes in renal interstitial pressure may mediate pressure-natriuresis by altering tubular reabsorption in the proximal tubule of cortical or deep nephrons (or both). The present results indicate that the pressure-natriuretic response in volume-expanded rats is associated with a significant elevation in renal interstitial pressure (see Figure 6). The rise in renal interstitial pressure was similar to the increase in pressure in the vasa recta capillaries. The rise in vasa recta pressure likely increased medullary interstitial pressure by transiently reducing the uptake of fluid from medullary nephron segments. Since the kidney is encapsulated, the rise in medullary interstitial pressure may also account for the observed increase in cortical interstitial pressure. Recent preliminary studies in which cortical and medullary interstitial pressures were simultaneously measured support this hypothesis. Changes in cortical interstitial pressure may participate in the pressure-natriuretic response by inhibiting tubular transport of sodium and water in the thin descending limb of the loop of Henle.

In summary, elevations of RPP increased pressure and flow in the vasa recta circulation. These findings indicate that changes in medullary hemo-
dynamics or renal interstitial pressure (or both) may serve as the intrarenal signal for the pressure-diuretic and pressure-natriuretic responses.

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References

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