Renal autoregulation, filtration rate,
and electrolyte excretion during vasodilatation

PHILIP G. BAER, L. GABRIEL NAVAR, AND ARTHUR C. GUYTON

Department of Physiology and Biophysics, University of Mississippi School of Medicine, Jackson, Mississippi 39216

BAER, PHILIP G., L. GABRIEL NAVAR, AND ARTHUR C. GUYTON. Renal autoregulation filtration rate and electrolyte excretion during vasodilatation. Am. J. Physiol. 219(3): 619-625. 1970.—The responses of the kidney to changes in renal arterial pressure were observed before and during renal vasodilatation induced by infusion of acetylcholine or papaverine directly into the renal artery. Partial abrogation of blood flow autoregulation was produced. Glomerular filtration rate, however, continued to be autoregulated at arterial pressures between 90 and 150 mm Hg. This was true for both drugs, despite reduction of absolute filtration rate levels to 60% of control levels during papaverine infusion. Filtration rate during acetylcholine infusion was essentially unchanged from control. The marked increases in urine flow rate and electrolyte excretion accompanying vasodilatation were decreased linearly by decreases in renal arterial pressure, despite relatively constant glomerular filtration rate. It is suggested that a noncontractile method of blood flow-filtration rate regulation, operating by feedback at the juxtaglomerular cells, continues to function during vasodilatation. It is further suggested that tubular reabsorption of water and electrolytes is affected by variations in perfusion pressure of the renal vascular bed, in particular, the peritubular capillaries.

Vasodilatation of the renal vasculature, caused by infusion of either acetylcholine or papaverine, has been described by various investigators to cause three primary effects: 1) marked increase in renal blood flow (3, 4, 7, 11, 12, 14, 15, 19, 21), 2) marked increase in output of essentially all urinary constituents (3, 4, 11, 15, 21), and 3) loss of renal autoregulation (2, 12, 14, 19). Based on these results, we postulated that glomerular filtration rate, during vasodilatation, could probably be varied at will by altering renal perfusion pressure. We hoped to use such a preparation to quantitate the effect of changes in glomerular filtration rate on urinary electrolyte and water excretion.

However, in preliminary experiments we observed four responses indicating that the effects of renal vasodilatation are much more complex than previously indicated. These responses were: a) partial, rather than complete, loss of blood flow autoregulation when maximal urinary responses to acetylcholine and papaverine were obtained, b) autoregulation of glomerular filtration rate that was equally good during infusion of both acetylcholine and papaverine as during control observations, despite the fact that these drugs did reduce the effectiveness of blood flow autoregulation, c) markedly different effects of acetylcholine and papaverine on the absolute glomerular filtration rate, and d) urine flow and electrolyte excretion responses to papaverine that were almost the same as those caused by acetylcholine, despite differences in glomerular filtration rate.

Because of these observations, we performed additional experiments to document the differences in renal responses to these two vasodilator agents and to characterize more fully the effects of changes in renal perfusion pressure on renal hemodynamics and excretory rates during vasodilatation caused by either of the two agents.

METHODS

Experimental Preparation

The basic experimental technique has been previously described (13) and was slightly modified for these experiments. Dogs of both sexes, weighing 17-23 kg, were anesthetized with 30 mg/kg sodium pentobarbital. Catheters for infusion and withdrawal were inserted into the left jugular vein and right femoral artery. A tracheotomy was performed, and the carotid arteries were isolated and exposed. As illustrated in Fig. 1, the left kidney was exposed through a flank incision, and the ureter and renal artery were isolated. A square-wave electromagnetic flow transducer (Carolina Medical Electronics) was placed around the renal artery adjacent to the aorta, and a plastic, adjustable occluder was placed distal to the flow transducer. Following determination of control renal blood flow, a 20-gauge Teflon catheter, connected to a Statham pressure transducer and to a Harvard syringe pump, was inserted into the renal artery distal to the clamp. Renal blood flow was not altered by this procedure in any of the experiments reported. To ensure patency, isotonic saline was infused through this catheter at a rate of 0.2 ml/min throughout the control measurements. This did not affect either renal blood flow or the measured value of renal perfusion pressure. Perfusion pressure could be set at any level below or equal to aortic pressure by adjustment of the occluder. Aortic pressure was elevated by partially constricting the carotid arteries in about one-half of the experiments, with no effect on renal blood flow, indicating that an increase in basal renal resistance had occurred in these experiments. The ureter was catheterized, and urine was collected using an LKB fraction collector.

To determine glomerular filtration rate, inulin (Arnar-Stone Laboratories) was given in a priming dose followed by continuous infusion to establish stable blood concentrations. Following a 30-min equilibration period, samples were collected.
Experimental Protocol

Control measurements. Renal function was studied over a perfusion pressure range of 48–153 mm Hg. In all experiments pressure was decreased from the highest pressure in four to six steps. At each pressure level, following a 10-min stabilization period, two to four urine samples and one or two blood samples, collected from the femoral artery at the midpoint of urine sampling periods, were taken. Following completion of sampling, the occluder was released, and perfusion pressure returned to the level of aortic pressure; the experiment was continued only after renal blood flow returned to between 90 and 110% of the original control level.

Measurements during vasodilatation. The infusion of isotonic saline into the renal artery was interrupted momentarily and replaced by either acetylcholine chloride (Matheson Coleman and Bell) or papaverine hydrochloride (Eli Lilly and Co.), both in isotonic saline solution. Acetylcholine was infused at 0.25 mg/min in a volume of 0.1 ml/min. This rate of infusion caused the greatest vasodilation which could be achieved with this drug; at higher dosages renal blood flow decreased progressively to very low values, apparently due to a direct vasoconstrictor effect, which has also been observed by Aström (1). This dosage produced a slight decrease in systemic blood pressure in about one-half of the experiments. Papaverine was infused at 6 mg/min in a volume of 0.5 ml/min. This produced a lesser degree of vasodilatation, but was the largest dosage which could be continuously infused without causing drastic lowering of systemic arterial pressure.

During infusion of the vasodilator drugs, renal perfusion pressure was lowered by compressing the renal artery, and urine and blood samples were collected in the same manner as described for control measurements.

Analytical procedures. Analyses of sodium and potassium in the plasma and urine samples were by flame photometry, using an Instrumentation Laboratories instrument, and osmolality was determined by the freezing-point depression method using an Advanced Instruments instrument. Inulin analyses were made by an automated anthrone method, slightly modified from that suggested by Wright and Gann (22), using the Technicon AutoAnalyzer.

RESULTS

Renal Blood Flow

Autoregulation of renal blood flow (RBF) was observed in all experiments during the control period, as shown by the control curve in Fig. 2. The control RBF at 100 mm Hg renal arterial pressure (RAP), designated RBFc, averaged 4.18 ± 0.91 SD ml/min per g kidney wt. All values in Fig. 2 are expressed as percent of RBFc. Although the composite control curve shifts from the linear portion to the plateau in a gradual fashion, individual curves broke much more sharply. This occurred between 55 and 70 mm Hg RAP in all kidneys studied.

Infusion of acetylcholine and papaverine caused increased mean RBF at all perfusion pressures. Renal blood flow was significantly higher than control at all renal arterial pressures above 50 mm Hg during acetylcholine infusion and at all pressures above 70 mm Hg during papaverine infusion. Also, the increase due to acetylcholine was significantly greater than that caused by papaverine. Although autoregulatory capacity was greatly diminished by both vasodilators, neither caused a truly passive pressure-flow relationship over the entire perfusion pressure range. Evaluation of the three curves in Fig. 2 for efficiency of autoregulation was performed using the Semple-de Wardener index (17). This is calculated by the following formula:

\[
\text{index} = \frac{\text{flow}_2 - \text{flow}_1}{\text{pressure}_2 - \text{pressure}_1}
\]

An index value of 1 or greater indicates no autoregulation of blood flow, whereas an index of 0 indicates maximal autoregulation.

Between 20 and 70 mm Hg arterial pressure, index values for the control, acetylcholine, and papaverine curves were 1.49, 1.58, and 1.65, respectively, indicating a passive pres-
flow rate during papaverine infusion was significantly increased \((P < 0.05)\) from control flows at every perfusion pressure. During acetylcholine infusion, urine flows were significantly increased from control at renal arterial pressures above 70 mm Hg \((P < 0.05)\). At 70 mm Hg the urine flow rate caused by papaverine was significantly higher \((P < 0.05)\) than that caused by acetylcholine infusion. It should be noted again that at 70 mm Hg, GFR was markedly lower during acetylcholine infusion than during control measurements.

**Electrolyte Excretion Rate**

**Sodium.** Control sodium excretion rate at 100 mm Hg renal arterial pressure designated \(\text{Na}_c\), averaged 1.04 ± 0.08 \(\mu\)Eq/min per g kidney wt, and all values in Fig. 5 are expressed as percent of \(\text{Na}_c\). During control measurements, sodium excretion increased from 25 \% \(\text{Na}_c\) at 70 mm Hg to 300 \% \(\text{Na}_c\) at 150 mm Hg.

Infusion of acetylcholine and papaverine caused increases in sodium excretion rates which were not significantly different from each other at any arterial pressure, but were significantly different from the control values at all pressures above 70 mm Hg. At 150 mm Hg the excretion of sodium during vasodilator infusion was increased to an average of 1,950 \% \(\text{Na}_c\). This represents a 4.1-fold increase over control excretion rate at that pressure, slightly less than the 5.6-fold increase seen in urine flow rate.

**Potassium.** Control potassium excretion rate at 100 mm Hg renal arterial pressure, designated \(\text{K}_c\), averaged 0.55 ± 0.32 \(\mu\)Eq/min per g kidney wt and increased from 40 \% \(\text{K}_c\) at 70 mm Hg to 150 \% \(\text{K}_c\) at 150 mm Hg. As shown in Fig. 6, the response of potassium excretion rate to vasodilatation was less dramatic than that of either urine flow rate or

---

**Glomerular Filtration Rate**

As shown in Fig. 3, control measurements demonstrated autoregulation of glomerular filtration rate (GFR) at renal arterial pressures between 90 and 150 mm Hg. The GFR in the control series, at 100 mm Hg RAP, is designated GFR\(_c\) and had a mean value of 0.81 ± 0.22 \(\text{ml/min per g kidney wt}\). All values in Fig. 3 are expressed as percent of GFR\(_c\).

Infusion of acetylcholine caused no significant alteration from control values at renal arterial pressures between 90 and 130 mm Hg. At 70 mm Hg, GFR was significantly lower than control.

Infusion of papaverine caused marked decrease in glomerular filtration rate at all pressures, as shown in Fig. 3. The values were significantly different from control at all renal arterial pressures levels above 70 mm Hg, averaging 50–70 \% of GFR\(_c\).

It should be noted that autoregulation of GFR was maintained during infusion of each of the drugs. Although the absolute rate was decreased by papaverine, a definite plateau appears in the renal arterial pressure-filtration rate relationship.

**Urine Flow Rate**

As shown in Fig. 4, urine flow during control measurements averaged 0.0079 ± 0.0068 \(\text{ml/min per g kidney wt}\) at a renal arterial pressure of 100 mm Hg, this value designated UF\(_c\). The urine flow rate increased during control measurements from 50 \% UF\(_c\) at 70 mm Hg to 200 \% UF\(_c\) at 150 mm Hg.

The onset of diuresis following vasodilator infusion was rapid, with maximum flows attained in 30 sec or less. Urine
sodium excretion rate. Excretion was significantly higher than control at renal arterial pressures above 110 mm Hg, and no difference could be seen in the response to the two drugs. The maximum increase in potassium excretion, occurring at 150 mm Hg, was slightly less than twice the control excretion rate at that pressure.

FIG. 5. Sodium excretion rate responses to changes in renal arterial pressure during control measurements and during intra-arterial infusion of acetylcholine or papaverine. SEM demarcated.

FIG. 6. Response of potassium excretion rate to changes in renal arterial pressure during control measurements and during intra-arterial infusion of acetylcholine or papaverine. SEM demarcated.

FIG. 7. Osmolar excretion rate response to changes in renal arterial pressure during control measurements and during intra-arterial infusion of papaverine or acetylcholine. SEM demarcated.

**Total Osmolar Excretion**

Total osmolar excretion rate at 100 mm Hg renal arterial pressure was 5.15 ± 2.95 μOs/min per g kidney wt, designated Ox, and increased from 40% Ox at 70 mm Hg to 180% Ox at 150 mm Hg. As shown in Fig. 7, infusion of acetylcholine and papaverine produced increases in osmolar excretion rates which were not significantly different from each other at any arterial pressure, but were significantly higher than control at all pressures above 70 mm Hg. At 150 mm Hg the osmolar excretion rate during vasodilation averaged 450% Ox, or slightly more than a twofold increase over control osmolar excretion rates at that pressure.

**DISCUSSION**

From these studies came two findings that could be of significance in advancing our understanding of intrarenal control of electrolyte and water excretion and the autoregulatory mechanism. These were the following: 1) When acetylcholine and papaverine were infused intra-arterially into the renal arteries at dosage levels that gave maximum increase in urinary output, partial autoregulation of renal blood flow still occurred, and autoregulation of glomerular filtration rate was equally as effective as in the control animals. 2) Glomerular filtration rate was essentially the same in kidneys perfused with acetylcholine as in control kidneys but was reduced to approximately 60% of control in animals perfused with papaverine. This difference occurred despite the fact that both acetylcholine and papaverine greatly increased renal blood flow, and both also greatly increased urinary output of fluid and electrolytes.

**Autoregulation in the Vasodilated Kidneys**

Other investigators have reported that renal blood flow autoregulation is partially (14) or completely abolished by infusion of acetylcholine (2, 12) or papaverine (14, 19) into the renal artery. Results from the present experiments, using autoperfused kidneys with control renal blood flows...
in the normal range, indicated that the reduction in autoregulatory efficiency was partial rather than complete. The dosage of acetylcholine used in this work was identical to that shown by Harvey to exceed the minimum effective dose (7) and was equal to that used in other studies (2), but only one-half to one-fourth that used by Nahmod and Lanari (12). Furthermore, attempts to reduce autoregulation further by doubling the infusion rate of acetylcholine resulted in a paradoxical effect of renal vasoconstriction and eventual cessation of blood flow rather than further vasodilatation, a similar effect has been observed previously by Aström (1), using bolus injections. Further investigation will be required to determine whether this response is due to a direct renal vasoconstrictor effect of large acetylcholine dosages, or to sympathetic discharge accompanying the systemic blood pressure decrease caused by this dosage, or to extrarenal catecholamine release. The infusion rate of papaverine was also at the highest level that could be given without causing severe decreases in systemic arterial pressure. Furthermore, maximal urinary output response was achieved at the dosage level of papaverine that was infused.

But even more important than the autoregulation of blood flow was the failure of the two vasodilator drugs to diminish the effectiveness of autoregulation of glomerular filtration rate even the slightest amount. Other investigators have found that glomerular filtration rate is unchanged (2, 3, 7, 15, 21), slightly increased (10), greatly increased (19), or decreased (4, 11) by vasodilator infusion. However, the response observed in these studies, namely, normal autoregulation of glomerular filtration rate over a normal pressure range, despite partial abrogation of renal blood flow autoregulation, has not been demonstrated previously. Again it should be pointed out that this autoregulation of glomerular filtration rate occurred despite the fact that renal blood flow was greatly increased under the influence of both acetylcholine and papaverine, urine output of fluid and electrolytes was greatly increased with both of these drugs, and glomerular filtration rate was decreased to 60% of normal by papaverine (though not by acetylcholine).

Most theories for renal autoregulation assume that afferent arteriolar constriction, or a combination of afferent and efferent arteriolar constriction, occurs in response to increased arterial pressure, and most theories have assumed that the increase in resistance in these segments of the renal vasculature results from smooth muscle contraction. If autoregulation continues to occur in the presence of what appeared to be maximal or nearly maximal dosages of acetylcholine and papaverine, both of which should paralyze or nearly paralyze the vascular smooth muscle, the question must be asked: How can the resistance be increased? There are several possible answers to this, one of which is based on the type of autoregulation that Hinshaw has described (8) in isolated perfused kidneys that seem to have reduced vascular responsiveness. That is, an increase in arterial pressure increases vascular pressures throughout the kidney, and fluid leaks rapidly into the interstitial spaces. This in turn increases the intrarenal pressure and compresses the intrarenal veins. As a result, intrarenal resistance increases. Though a similar type of response could have occurred in the present experiments, there are several reasons to believe that this was not the case. First, the glomerular filtration rate was depressed markedly after administration of papaverine, though it was not depressed after administration of acetylcholine, indicating a basic difference in the mechanics of glomerular filtration control between kidneys affected by these two respective drugs. If the Hinshaw type of autoregulation were operating, one would expect the results to be the same with both of these drugs. Second, one would expect autoregulation of glomerular filtration rate to be diminished to some degree if tissue pressure were determining intrarenal resistance, rather than remaining completely effective, although this objection may not be valid in light of observation of continued glomerular filtration rate autoregulation, despite loss of blood flow autoregulation, at renal perfusion pressures above 200 mm Hg (18). It should also be pointed out that the resistance of the collecting ducts to urine outflow during severe diuresis may cause elevation of proximal tubular and capsular pressures (5, 20). If this occurred in the present study, alterations in filtration pressure accompanying arterial pressure changes might have been balanced by proportional capsular pressure changes such that effective filtration pressure and glomerular filtration rate would have been autoregulated to a greater degree than renal blood flow.

However, there is another type of autoregulation which could also explain these results: This is the possibility that feedback occurs at the juxtaglomerular apparatus operating from the macula densa in the distal tubules to the afferent arterioles. Such feedback has been postulated on many occasions (6), but in essentially all instances it has been assumed that the final pathway for the feedback is contraction of the smooth muscle in the wall of the afferent arterioles. However, in the original studies of Ruyter (16), he postulated that swelling of the juxtaglomerular cells could regulate the size of the afferent arteriolar lumen and control glomerular blood flow. If this should be the case a juxtaglomerular feedback mechanism could operate entirely independently of smooth muscle contraction. Or it is also possible that a secretory substance from the macula densa cells could act on the juxtaglomerular cells to cause contraction of the actomyosin complexes of these cells, despite the presence of vasodilator substances such as acetylcholine or papaverine. At any rate, the results of the present experiments could theoretically fit with a juxtaglomerular feedback mechanism. The most important support for this concept was the almost complete autoregulation of glomerular filtration rate that was still present even after marked effect of acetylcholine and papaverine. This is what would be expected if the factor being autoregulated were some constituent in the tubular fluid at the macula densa level, so that any slight change in its concentration would cause immediate readjustment of glomerular filtration rate back to its previous level. In this way autoregulation of glomerular filtration rate would continue to be preserved, despite marked alterations in vascular tone in parts of the renal vasculature other than the juxtaglomerular cells.

**Difference in Response to Acetylcholine and Papaverine**

Although evidence to the contrary has been presented, the possibility remains that observed differences in the re-
response to the two drugs, especially that of glomerular filtration rate, were simply dose differences. Proportionate changes in afferent and efferent contractility have been postulated by other investigators (7, 21) to be responsible for unchanged glomerular filtration rate during acetylcholine infusion. Possibly, papaverine produced greater dilatation at the efferent arteriole than at the afferent, thus reducing effective filtration pressure and filtration rate. Such a disproportionate response could be due either to dosage or to some difference in sensitivity of the afferent and efferent arterioles to acetylcholine and papaverine. It is also conceivable that the observed autoregulation of glomerular filtration rate was mediated through proximal tubule pressure changes, but that the two drugs caused unequal changes. Martino (10) has demonstrated substantial elevations in deep venous pressure following acetylcholine infusion. It has also been shown that proximal tubular and peritubular capillary pressures, although remaining nearly constant in the normal kidney at perfusion pressures in the autoregulatory range, vary in a roughly linear fashion with perfusion pressure during papaverine infusion (20). Reductions in renal perfusion pressure, during vasodilatation, would cause decreases in both glomerular capillary and proximal tubular pressure, resulting in relative constancy of effective filtration pressure and allowing glomerular filtration rate to remain constant.

Urine Flow and Electrolyte Excretion

The increases in urine flow and electrolyte excretion accompanying vasodilatation were due to decreased tubular reabsorption, since glomerular filtration rate was not elevated and plasma electrolyte levels did not show consistent change. The marked decrease in urine flow rate and electrolyte excretion, caused by reduction in perfusion pressure, despite autoregulation of glomerular filtration rate, indicates a direct effect of pressure or renal blood flow, or both, on reabsorption rate. The importance of peritubular pressure as a determinant of electrolyte reabsorption was suggested by Earley (4), who reported that infusion of pressor agents, after establishment of vasodilatation, caused additional natriuresis despite reductions in renal blood flow. It has also been suggested that the volume of the "basal labyrinth," determined by the balance between peritubular capillary pressure and colloid osmotic pressure, may affect reabsorption rate through altered intrarenal dimensions (9). In addition, Daugherty (3) has recently demonstrated that the diuretic-natriuretic response to vasodilatation is reversed by infusion of hyperoncotic solutions, presumably by increasing the reabsorptive capacity at the peritubular capillaries. In our study, renal arterial pressure reduction from 150 to 90 mm Hg during vasodilatation caused the filtration fraction to increase progressively while blood flow fell markedly and glomerular filtration rate remained nearly constant. Such an increase would result in relative elevation of peritubular colloid oncotic pressure. This effect, in addition to decreased hydrostatic pressure in this segment, could result in lowered urine flow and electrolyte excretion rates by allowing increased peritubular reabsorption (9).

This work was supported by Public Health Service Grant HE 11420-03.

P. G. Baer was a Predoctoral Fellow of the National Institutes of Health.

L. G. Navar was a Postdoctoral Fellow of the National Institute of Arthritis and Metabolic Diseases.

Received for publication 24 November 1969.


