Effects of some vasodilator drugs on transcapillary fluid exchange in renal cortex

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Baylis, Christine, William M. Deen, Bryan D. Myers, and Barry M. Brenner. Effects of some vasodilator drugs on transcapillary fluid exchange in renal cortex. Am. J. Physiol. 230(4): 1148-1158. 1976. - In 23 Munich-Wistar rats with surface glomeruli, the determinants of glomerular ultrafiltration and peritubular capillary uptake of proximal reabsorbate were studied before and during intra-arterial infusions of mildly vasodepressor doses of prostaglandin E₁, acetylcholine, and bradykinin. For each drug single-nephron glomerular filtration rate remained unchanged from normal hydropenic values while glomerular plasma flow rate increased, resulting in declines in single-nephron filtration fraction (SNFF). Mean glomerular transcapillary hydraulic pressure difference (ΔP) increased or remained unchanged on average. Declines in SNFF were accompanied by reductions in efferent arteriolar oncotic pressure (Δπ). Filtration pressure equilibrium, equality between ΔP and Δπ, obtained before but not during drug infusions. In the latter situation values for the glomerular capillary ultrafiltration coefficient were calculated and found to be significantly reduced from published control values. Despite marked falls in Δπ during drug infusion, absolute proximal reabsorption was not reduced significantly, due, it is suggested, to the opposing effects of increases in efferent arteriolar plasma flow and interstitial hydraulic pressure.

METHODS

Glossary of Symbols

ACh Acetylcholine
AP Mean femoral arterial pressure, mmHg
APR Absolute rate of fluid reabsorption to the end of accessible proximal tubule, nl/min
BK Bradykinin
C Protein concentration, g/100 ml
EABF Efferent arteriolar blood flow, nl/min
GBF Glomerular blood flow, nl/min
GFR Glomerular filtration rate (whole kidney)
Hct Blood hematocrit in femoral artery or afferent arteriole
Kᵣ Glomerular ultrafiltration coefficient, nl/(s·mmHg)
Kᵣ Reabsorption coefficient, nl/(s·mmHg)
P Hydraulic pressure, mmHg
PGF₁₉ Prostaglandin E₁
ΔP Transmembrane hydraulic pressure difference, Pₜ - Pᵣ, mmHg
π Colloid osmotic pressure, mmHg
Δπ Transmembrane oncotic pressure difference, πᵣ - πₜ, mmHg
Q Plasma volume flow rate, nl/min
R Resistance to blood flow, dyn·s·cm⁻²
Rₜθ Total arteriolar resistance, Rₜ + Rₜ, dyn·s·cm⁻²
SNFF Single-nephron filtration fraction
SNGFR Single-nephron glomerular filtration rate, nl/min

Many investigators have shown that infusions of potent vasodilators such as acetylcholine, prostaglandin E₁, and bradykinin have little effect on whole-kidney or single-nephron glomerular filtration rate (GFR), despite large measured increases in renal blood flow (1, 26, 38, 40, 43). A number of hypothetical explanations have been offered to account for this failure of GFR to increase in association with increases in renal blood flow, but these explanations have of necessity been speculative and untestable in the absence of measurements of the various forces and flows that govern GFR. For this reason, inferences regarding the precise mode of action of vasodilator drugs based on estimates of GFR, filtration fraction, and renal blood flow but in the absence of direct measurements of the determinants of GFR may not be correct.

Since the Munich-Wistar rat has been shown to possess accessible surface glomeruli, it is now possible to make direct measurements of preglomerular, glomerular, and postglomerular pressures as well as initial glomerular plasma flow rate (8, 10, 13, 14, 18, 29, 33, 35). These measurements have enabled us to characterize the determinants of single-nephron GFR prior to and during the infusion of three commonly studied vasodilators, prostaglandin E₁, acetylcholine, and bradykinin. Additionally, this study permits an assessment of the effects of vasodilators on absolute proximal reabsorption and on the determinants of peritubular capillary uptake of isotonic reabsorbate.
EFFECTS OF VASODILATORS ON RENAL MICROCIRCULATION

(TF/P)\textsubscript{in} Tubule fluid-to-plasma inulin concentration ratio
V_{TF} Tubule fluid flow rate

Subscripts
A Afferent arteriole
C Peritubular capillary
E Efferent arteriole
GC Glomerular capillary
I Interstitial fluid
T Proximal tubule

General

Studies were performed in 23 adult Munich-Wistar rats weighing 203–307 g, allowed free access to a rat pellet diet and water. Animals were anesthetized by intraperitoneal injection of Inactin (100 mg/kg) and placed on a temperature-regulated micro puncture table; a tracheotomy then was performed. Polyethylene catheters were inserted into the right and left jugular veins for infusion of inulin and injection of lissamine green, respectively, and into the left femoral artery for periodic blood sampling and estimation of AP. The vasodilators were infused via a 27 gauge needle placed into the abdominal aorta just above the origin of the left renal artery. Mean arterial pressure was monitored by means of an electronic transducer (model P23Db, Statham Instruments, Oxnard, Calif.) connected to a direct-writing recorder (model 7702B, Hewlett-Packard Co., Palo Alto, Calif.). The left kidney was prepared for micropuncture in the manner described previously (33).

Sixty minutes before micropuncture rats received an intravenous infusion of isotonic NaCl at the rate of 0.02 ml/min. Inulin was present in a concentration of 10%, thereby resulting in final plasma concentrations of about 100 mg/100 ml. After this 60-min equilibration period, exactly timed (1–2 min) samples of fluid were collected from late surface proximal convolutions from each of two to three nephrons for determination of flow rate and inulin concentration and calculation of SNGFR. These late convolutions were identified by intravenous injection of 0.05 ml of 5% lissamine green. The rate of fluid collection was adjusted to maintain a column of polymer oil (Kel F polymer oil, 3M Co., Medical Products Div., St. Paul, Minn.), three to four tubule diameters in length, in a relatively constant position just distal to the site of puncture. With the collection technique of controlled suction validated for this laboratory (5), minimal changes in tubule diameter or the position of the distal oil block were produced. Coincident with these tubule fluid collections, femoral arterial and efferent arteriolar blood plasma were measured as described previously (6); \( C_\text{A} \) is taken as a measure of protein concentration in the afferent arteriole. Colloid osmotic pressures were calculated from these measured values of \( C \) with the equation:

\[
\pi = 1.63C + 0.294C^2
\]

Equation 1 assumes an albumin/globulin (A/G) ratio of unity, the value found in normal hydropenic rats in this laboratory. In support of this assumption, electrophoresis of plasma obtained from rats before and during administration of the vasodilators studied showed no significant change in the A/G ratio, giving a control mean of 1.158 ± 0.077 (SE) versus a mean of 1.116 ± 0.091 during infusion of the drugs. These estimates of pre- and postglomerular protein concentration permit calculation of SNFF and \( Q_\text{in} \) (see equations 4 and 5). From direct measurements of the decline in hydraulic pressure along single afferent and efferent arterioles, and from estimates of blood flow through these vessels, vascular resistances to blood flow through these individual vessels were calculated (see equations 8–10).

Effects of Infusion of Vasodilator Substances

Group I: prostaglandin infusion. After the above-described measurements in normal hydropenia, prostaglandin E\(_2\) (Upjohn Company, Kalamazoo, Mich.) was infused into eight rats at a rate of 0.4–0.8 \( \mu \)g/kg per min in order to produce a sustained depressor response. After a 15-min equilibration period, collections of tubule fluid (recollections), efferent arteriolar and femoral arterial blood samples, and measurements of AP, \( P_{\text{in}} \), \( P_{\text{T}} \), \( P_{E} \), and \( P_s \) were repeated in each rat.

Group II: acetylcholine infusion. After measurements in normal hydropenia in seven other rats, acetylcholine chloride (Sigma, St. Louis, Mo.) was infused at a rate of 2–3 \( \mu \)g/min. After a 15-min equilibration period measurements carried out in the normal hydropenic period were repeated as in group I.

Group III: bradykinin infusion. As in groups I and II, repeat measurements were made in eight other rats during infusion of bradykinin triacetate (Sigma) at a rate of 1 \( \mu \)g/kg per min, after a 15-min equilibration period.

Analytical

The volume of tubule fluid collected from individual nephrons was estimated from the length of the fluid column in a constant bore capillary tube of known internal diameter. The concentration of inulin in tubule fluid was measured, usually in duplicate, by the microfluorescence method of Vurek and Pegram (41). Inulin response, and stability features of this servo system have been reported previously (9). Direct measurements of hydraulic pressure in single glomerular capillaries, proximal tubules, efferent arterioles, and third-order peritubular capillaries were recorded in each rat.

To obtain estimates of colloid osmotic pressure of plasma entering and leaving glomerular capillaries, protein concentrations in femoral arterial and efferent arteriolar blood plasma were measured as described previously (6); \( C_\text{A} \) is taken as a measure of protein concentration in the afferent arteriole. Colloid osmotic pressures were calculated from these measured values of \( C \) with the equation:
Calculations

Single-nephron glomerular filtration rate:

$$\text{SNGFR} = \frac{(\text{TF}/\text{P})_{\text{in}} \cdot \text{V}_{\text{TF}}}{(\text{TF}/\text{P})_{\text{in}} \cdot \text{V}_{\text{TF}}}$$

(2)

Absolute proximal fluid reabsorption:

$$\text{APR} = \text{SNGFR} - \text{V}_{\text{TF}}$$

(3)

Single-nephron filtration fraction:

$$\text{SNFF} = 1 - \frac{C_{\text{A}}}{C_{\text{E}}}$$

(4)

Initial glomerular plasma flow rate:

$$\text{Q}_{\text{A}} = \frac{\text{SNGFR}}{\text{SNFF}}$$

(5)

Blood flow rate per single afferent arteriole or glomerulus:

$$\text{GBF} = \frac{\text{Q}_{\text{A}}}{1 - \text{Hct}_{\text{A}}}$$

(6)

where \(\text{Hct}_{\text{A}}\), the hematocrit of afferent arteriolar blood, is taken to be equal to femoral arterial hematocrit.

Efferent arteriolar blood flow rate:

$$\text{EABF} = \text{GBF} - \text{SNGFR}$$

(7)

Resistance per single afferent arteriole:

$$R_{\text{A}} = \frac{\text{AP} - \text{P}_{\text{GC}}}{\text{GBF}} \times (7.962 \times 10^9)$$

(8)

where the factor \(7.962 \times 10^9\) is used to give resistance in dyn \(\cdot\) s/cm \(^2\) when \(\text{AP}\) and \(\text{P}_{\text{GC}}\) are expressed in millimeters of Hg and GBF in nanoliters per minute.

Resistance per single efferent arteriole:

$$R_{\text{E}} = \frac{\text{P}_{\text{GC}} - \text{P}_{\text{T}}}{\text{EABF}} \times (7.962 \times 10^9)$$

(9)

Total arteriolar resistance for a single pre- to post-glomerular vascular unit:

$$R_{\text{TA}} = R_{\text{A}} + R_{\text{E}}$$

(10)

Mean glomerular transcapillary hydraulic pressure difference:

$$\Delta \text{P} = \text{P}_{\text{GC}} - \text{P}_{\text{T}}$$

(11)

The ultrafiltration coefficient is calculated with a differential equation that gives the rate of change of protein concentration with distance along an idealized glomerular capillary. This equation, together with its derivation and the method for its solution, is given in detail elsewhere (18).

RESULTS

Measurements Made During Hydropenia

Mean data for hydropenic rats studied before infusion of PGE\(_1\), ACh, or BK are summarized in Tables 1-3. Systemic hematocrit values were similar in all three groups, averaging 52.5 ± 0.7 (SE), 53.0 ± 1.2, and 52.8 ± 0.8 vol%, respectively; \(\Delta \text{P}\) averaged 115 ± 2, 110 ± 2, and 117 ± 3 mmHg, and \(\text{P}_{\text{GC}}\) was 47, 45, and 48 mmHg, respectively (Tables 1-3). Thus the drop in hydraulic pressure along afferent arterioles (\(\Delta \text{P} - \text{P}_{\text{GC}}\)) averaged 68 ± 2, 65 ± 2, and 69 ± 2 mmHg, or about twice the corresponding drop along efferent arterioles (\(\text{P}_{\text{GC}} - \text{P}_{\text{T}}\)), which averaged 38 ± 1, 36 ± 1, and 39 ± 1 mmHg. Mean values for \(\text{P}_{\text{T}}\) were 11, 11, and 12 mmHg. Therefore, the mean glomerular transcapillary hydraulic pressure difference was 36.4 ± 0.6, 33.6 ± 0.8, and 36.0 ± 1.2 mmHg. These mean values are similar to those previously reported from this laboratory for the normal Munich-Wistar rat (8, 10, 13, 14, 18, 29, 33, 35). Mean values for \(\pi_{\text{A}}\) ranged from 15 to 17 mmHg in the three groups (Tables 1-3), and mean values for \(\pi_{\text{E}}\) ranged from 32 to 37 mmHg. In all three groups of hydropenic rats the net afferent driving force for ultrafiltration (\(\Delta \text{P} - \pi_{\text{A}}\)) was about 20 mmHg and by the efferent end of the glomerular capillary \(\Delta \text{P}\) was essentially equal to \(\pi_{\text{E}}\) (Tables 1-3), indicating the existence of filtration pressure equilibrium. Mean values for SNGFR for the three groups ranged from 30 to 32 nl/min. Single nephron filtration fraction, calculated from the measurements of afferent and efferent arteriolar plasma protein concentrations, averaged approximately 0.4 for all three groups. Mean values for \(\text{Q}_{\text{A}}\) and \(\text{Q}_{\text{E}}\) were similar in all three groups of hydropenic rats, as shown in Tables 1-3. Mean values for proximal (\(\text{TF}/\text{P}\)\(_{\text{in}}\)) and APR were also similar in the three groups, as shown in Tables 1-3. Resistances to blood flow in single afferent and efferent arterioles were likewise similar among groups. On average, \(R_{\text{A}}/R_{\text{TA}}\) was approximately 0.6 in each group, indicating that most of the resistance to blood flow in normal hydropenia is located in the afferent arterioles.

Infusion of Vasodilators

Group 1: prostaglandin infusion. Infusion of PGE\(_1\) was associated with a fall in \(\text{AP}\) from a mean of 115 ± 2 to 104 ± 3 mmHg (\(P < 0.001\)). Nevertheless, as shown in Table 1 and Fig. 1, there was little change in either \(\text{P}_{\text{GC}}\) or \(\Delta \text{P}\). Thus, the afferent arteriolar hydraulic pressure drop (\(\Delta \text{P} - \text{P}_{\text{GC}}\)) fell on average by 12 ± 2 mmHg (\(P < 0.001\)), but the mean efferent arteriolar hydraulic pressure drop (\(\text{P}_{\text{GC}} - \text{P}_{\text{T}}\)) did not change. Afferent and efferent arteriolar blood flow rates increased significantly, from 166 ± 8 to 215 ± 16 nl/min (\(P < 0.025\)) and 134 ± 7 to 179 ± 15 nl/min (\(P < 0.01\)), respectively. On average, \(R_{\text{A}}\) fell significantly with PGE\(_1\) infusion, both because of the large increase in efferent arteriolar blood flow rates increased significantly, from 166 ± 8 to 215 ± 16 nl/min (\(P < 0.025\)) and 134 ± 7 to 179 ± 15 nl/min (\(P < 0.01\)), respectively. On average, \(R_{\text{A}}\) fell significantly with PGE\(_1\) infusion, both because of the large increase in efferent arteriolar blood flow; \(R_{\text{E}}\) also fell significantly, on average, because of the large increase in efferent arteriolar blood flow. As shown in Fig. 1, the fall in \(R_{\text{E}}\) was proportionately less than the fall in \(R_{\text{A}}\). This is also indicated by the fall in \(R_{\text{A}}/R_{\text{TA}}\) (Table 1). In many but
### Table 1. Summary of single nephron and microvascular measurements before and during prostaglandin E, infusion

<table>
<thead>
<tr>
<th>Rat.</th>
<th>Normal Hydropenia</th>
<th>Prostaglandin E,</th>
<th>P value</th>
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<td></td>
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<td>$T_F$, $P_0$, $SNGFR$, $APR$, $SNFF$, $Q_0$, $Q_1$, $R_0$, $R_1$,</td>
<td>$\Delta T_F$, $P_0$, $C_0$, $C_1$, $x$, $t$,</td>
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<td>11 min</td>
<td>11 min</td>
<td>$\Delta T_F$, $P_0$, $C_0$, $C_1$, $x$, $t$,</td>
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<td>mmHg</td>
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<td>8.5</td>
<td>1.50</td>
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<td>10</td>
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<td>1.50</td>
<td>42.5</td>
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* Mean paired change in proximal fractional reabsorption = 100.
TABLE 2. Summary of single-nephron and microvascular measurements before and during acetylcholine infusion

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<td>p&lt;sub&gt;1&lt;/sub&gt;, P&lt;sub&gt;2&lt;/sub&gt;, C&lt;sub&gt;1&lt;/sub&gt;, C&lt;sub&gt;2&lt;/sub&gt;, n</td>
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* Mean paired change in proximal fractional reabsorption × 100.
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<td>Mean ±SE</td>
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<td>9.1 ± 0.05</td>
<td>1.1 ± 0.003</td>
<td>2.0 ± 0.04</td>
<td>5.6 ± 0.03</td>
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* Mean paired change in proximal fractional reabsorption × 100.
not all tubules SNGFR increased slightly, the mean increase for the group to 35 nl/min not being significant statistically (Table 1).

Systemic plasma protein concentration \(C_A\) remained essentially constant during PGE\(_{1}\) infusion. By contrast, the fall in \(C_E\), the efferent arteriolar protein concentration, was substantial (Table 1) and was associated with a highly significant decline in SNFF, from 0.41 to 0.34 \((P < 0.001)\). Systemic hematocrit did not change significantly with PGE\(_{1}\) infusion (mean = 51.5 ± 0.7 vol%). On average, \(Q_s\) increased from 78.4 to 104.1 nl/min \((P < 0.01)\), and \(Q_x\) increased from an average of 46.6 to 69.1 nl/min \((P < 0.01)\). With infusion of PGE\(_{1}\), filtration pressure equilibrium no longer obtained, the ratio \(\pi_E/\Delta P\) falling in each rat, on average to 0.84 ± 0.05 \((P < 0.001)\). Since equilibrium was not achieved, it was possible to calculate a unique value for the glomerular capillary ultrafiltration coefficient in each of the eight rats \(K_f\) averaged 0.045 ± 0.002 nl/(s·mmHg) (Fig. 2), a value considerably lower than the mean values obtained in control Munich-Wistar rats in this laboratory. As shown in Table 1, values for proximal \((TF/P)_{in}\) and APR were not significantly altered by infusion of PGE\(_{1}\).

**Group II: acetylcholine infusion.** Infusion of ACh in seven rats resulted, on average, in a fall in \(\Delta P\) from 110 ± 2 to 96 ± 1 mmHg \((P < 0.001)\), an increase in \(P_{in}\) from 45 to 53 mmHg \((P < 0.005)\, Table 2), as well as in \(P_r\), \(P_e\), and \(\Delta P\). In this group of animals, therefore, the mean afferent arteriolar hydraulic pressure drop fell significantly, on average from 65 ± 2 to 43 ± 2 mmHg \((P < 0.001)\), but the efferent arteriolar pressure drop failed to change significantly (from 36 ± 1 to 39 ± 1, \(P > 0.1\)). With ACh infusion, afferent and efferent arteriolar blood flow rates increased, on average from 165 ± 19 nl/min and 135 ± 17 before to 221 ± 18 and 187 ± 16 during ACh infusion, respectively. Hence, there were large falls in the calculated resistances to blood flow along single afferent and efferent arterioles, with \(R_a\) falling proportionately more than \(R_e\) (Fig. 3). As was the case
during PGE\textsubscript{1} infusion, ACh resulted in a small but statistically insignificant mean increase in SNGFR, to 34.3 nl/min (Table 2). During ACh infusion C\textsubscript{A} also fell slightly though the decline in C\textsubscript{e} was more pronounced, falling on average from 8.1 g/100 ml to 7.0 (P < 0.001). Accordingly, SNFF fell from 0.40 to 0.32 (P < 0.001). Systemic hematocrit fell slightly, from a mean of 53.0 \pm 1.2 to 51.7 \pm 1.4 vol\%, during ACh. As noted in Table 2, Q\textsubscript{A} and Q\textsubscript{e} increased significantly. As with PGE\textsubscript{1}, ACh infusion led to a decline in \( \pi_r/\Delta P \) in each rat, on average from 0.96 to 0.65 (P < 0.001). Whereas the mean ratio in normal hydropenia was not significantly different from unity (P > 0.2), the marked fall in this ratio during ACh denotes failure to achieve filtration pressure equilibrium. The calculated individual values for K\textsubscript{f} during ACh infusion are shown in Fig. 2, the mean value being 0.038 nl/(smmHg) \pm 0.002, with individual values as 34.3 nll/min (Table 2). During ACh infusion C\textsubscript{A} also fell to falls in R\textsubscript{a} and R\textsubscript{e}, the fall in R\textsubscript{a} being proportionately greater. Although the mode of action of these vasodilators is unknown, it has been suggested that prostaglandins inhibit the vasoconstrictor effects of norepinephrine and angiotensin II (31, 32). Presumably all three vasodilator drugs studied exert their action by somehow diminishing the vasoconstrictor tone of the renal arterioles.

In spite of the marked rises in Q\textsubscript{A} with all three drugs studied, SNGFR did not rise significantly (Figs. 1, 3, and 4). Many other workers have found that whole-kidney GFR and SNGFR failed to increase in the dog during vasodilation with these drugs (1, 12, 26, 40, 43); the present study demonstrates that the renal response to vasodilation with these drugs is similar in the rat. Given the observed increases in QA and P\textsubscript{f}, in several measures of surface nephron and microvascular function.

**DISCUSSION**

The present study provides the first direct assessment of the effects of PGE\textsubscript{1}, ACh, and BK on preglomerular, glomerular, and postglomerular pressures and flows. As shown in Figs. 1, 3, and 4, mildly vasodepressor doses of these drugs resulted in significant increases in Q\textsubscript{A}, due to falls in R\textsubscript{a} and R\textsubscript{e}, the fall in R\textsubscript{a} being proportionately
sure disequilibrium is obtained by increasing \( Q_\text{v} \), either by plasma volume expansion or isovolemic reduction of hematocrit. Figure 2 illustrates the range of values for \( K_f \) obtained under these control conditions. As shown, the mean value for \( K_f \) in the Munich-Wistar rat is 0.078 n/(s/mmHg) during plasma volume expansion and 0.070 n/(s-mmHg) during acute, isovolemic hematocrit reduction (18, 33). Since filtration pressure equilibrium failed to obtain during administration of all three vasodilators, it was possible to calculate unique values for \( K_f \). Individual and mean values obtained with each drug are shown in Fig. 2. All three vasodilators investigated are shown to produce values of \( K_f \) substantially lower than those found previously in control rats. In addition, using a mathematical model of glomerular ultrafiltration described previously (15), we have found that the mean value of \( K_f \) obtained during infusion of PGE\(_1\), ACh, and BK are not sufficiently large to have yielded filtration pressure equilibrium in the corresponding hypodraenic periods. With these values of \( K_f \), and the mean values of \( Q_\text{v} \), \( \Delta P \), and \( C_\text{f} \) observed during hypodraenia (Tables 1-3), the calculated values of \( n_f/\Delta P \) are 0.92, 0.77, and 0.88, substantially less than the observed values of 1.03, 0.96, and 0.98 for the PGE\(_1\), ACh, and BK control periods, respectively. These calculations confirm that infusions of these vasodilator substances was indeed accompanied by marked reductions in \( K_f \).

Previous evidence also suggests that certain vasoactive drugs may have an effect on \( K_f \). Using the vasodilator papaverine in the plasma-loaded Munich-Wistar rat, we found relatively low values of \( K_f \) as shown in Fig. 2 (17). Blantz (4) recently reported a similar fall in \( K_f \) during infusion of the vasoconstrictor drug angiotensin II (AII). Since the ultrafiltration coefficient \( K_f \) is the product of surface area of the glomerular capillary and its hydraulic permeability, a reduction in either or both of these terms could account for the observed fall in \( K_f \). At least in the case of AII, it has been suggested that the glomerular capillary may constrict, possibly by a contractile action of the mesangial cells, leading to a reduction in surface area (25, 37). In order for the fall in \( K_f \) during vasodilator administration to be caused by a fall in surface area, however, it would seem necessary to postulate, not a reduction in the number of patent capillaries, but rather a shunting of blood fromafferent to efferent arterioles, thus bypassing at least a part of the glomerular capillary bed. Because of the observed fall in \( K_f \) during administration of these vasodilators, any blood shunted past the glomerular capillary bed would have to reenter the efferent arteriole proximal to our sampling site, i.e., the star vessel. Indeed, there are several histological studies in which such an intraglomerular shunt has been observed (2, 19, 23, 27), thereby lending credence to this possibility. We have no information at present regarding the alternative possibility, i.e., that vasodilators produce a fall in hydraulic permeability by some common action apart from their vasoactive effect. Of interest, however, are the observations in isolated perfused cortical collecting tubules and toad bladder that demonstrate that PGE\(_1\) substantially diminishes the hydraulic permeability of these tissues (22, 30) by an action thought to involve adenyly cyclase (34).

It has repeatedly been shown that the vasodilators produce large increases in urinary Na excretion (1, 12, 24, 26, 38-40, 43). In the dog there is some evidence that the natriuresis may be due to inhibition of absolute proximal reabsorption during administration of ACh or PGE\(_1\), (39, 40). Using vasodepressor doses in the same range as those employed in these other studies, we were unable to produce any significant effect on APR in the rat with PGE\(_1\), ACh, or BK. Similar findings were reported by Stein et al. (38) for BK in the dog. However, ACh in the dog produced a large inhibition of APR (39), perhaps due to the very large decline in filtration fraction in those studies. The results of numerous investigations suggest that APR is controlled to a large extent by the forces governing peritubular capillary uptake of reabsorbate (e.g., 7, 11, 36, 44). As shown in Tables 1-3, infusion of each substance resulted in marked falls in \( \pi_f \); with ACh and BK, \( P_f \) also rose significantly. Opposing these changes in \( \pi_f \) and \( P_f \), which would be expected to lower APR, were increases in \( Q_\text{v} \) (statistically significant for PGE\(_1\) and ACh). The extent to which these opposing changes in \( \pi_f \), \( P_f \) and \( Q_\text{v} \) would be expected to affect APR therefore was calculated by an approach described previously (16). For each group of rats, with the use of measured mean values of APR, \( Q_\text{v} \), \( \pi_f \), and \( P_f \), we calculated \( K_f \). The extent to which \( K_f \) would be expected to affect APR therefore was calculated by an approach described previously (16). For each group of rats, with the use of measured mean values of APR, \( Q_\text{v} \), \( \pi_f \), and \( P_f \), we calculated the observed changes in \( \pi_f \), \( P_f \) and \( Q_\text{v} \), which were unchanged by infusion of vasodilators, the value of APR for the experimental period for each group was calculated with the observed changes in \( Q_\text{v} \), \( \pi_f \), and \( P_f \). As shown in Table 4, values of APR calculated in this way fall below the observed values. Thus, in the absence of any change in the interstitial pressures, APR would be expected to decrease. Note, however, that agreement of the calculated and observed values of APR is obtained when \( \pi_f - P_f \) is assumed to decrease by the amounts shown in the right-hand column of Table 4. In support of such a change in \( \pi_f , P_f \), and \( Q_\text{v} \), Strandhoy et al. (40), using the chronically implanted porous-capsule technique, observed that during PGE\(_1\) and PGE\(_2\) infusion, PCl increased by \(-10 \text{ mmHg}, \) without appreciable changes in \( \pi_f \). Simpler conclusions were reached by Bell (3) for dogs studied with ACh. Thus it seems likely that the failure for APR to decline in the present study was the consequence of the similar increases in \( P_f \), a quantity that cannot yet be measured directly in the rat.

TABLE 4. Comparison of calculated and observed absolute proximal reabsorption during infusion of prostaglandin \( E_1 \), acetylcholine, and Bradykinin

<table>
<thead>
<tr>
<th>Group</th>
<th>Observed APR, n/min</th>
<th>Calculated APR*, n/min</th>
<th>Estimated Change* in ( \pi_f - P_f ), mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGE(_1)</td>
<td>15.1 ± 1.0 SE</td>
<td>11.5</td>
<td>-5</td>
</tr>
<tr>
<td>ACh</td>
<td>10.3 ± 1.4</td>
<td>6.0</td>
<td>-5</td>
</tr>
<tr>
<td>BK</td>
<td>13.4 ± 0.8</td>
<td>11.2</td>
<td>-3</td>
</tr>
</tbody>
</table>

*Calculated assuming \( \pi_f - P_f = 4 \text{ mmHg} \) in both control and experimental periods. **Indicates change in \( \pi_f - P_f \) required to give exact agreement between calculated and observed values of APR during vasodilator infusions.
EFFECTS OF VASODILATORS ON RENAL MICROCIRCULATION

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REFERENCES


