Effects of Norepinephrine and Angiotensin II on the Determinants of Glomerular Ultrafiltration and Proximal Tubule Fluid Reabsorption in the Rat

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ABSTRACT

In 26 Wistar rats with surface glomeruli, the determinants of glomerular ultrafiltration and peritubular capillary uptake of proximal reabsorbate were studied before and during intravenous infusions of norepinephrine or angiotensin II. Regardless of whether renal perfusion pressure \( AP \) was permitted to increase, both hormones produced elevations in single nephron filtration fraction due to declines in glomerular plasma flow with little change in neophron glomerular filtration rate. The resulting large increases in the efferent arteriolar onotic pressure, \( \pi_E \), were accompanied by equivalent increases in the mean glomerular transcapillary hydraulic pressure difference, \( \Delta P \). Equality of \( \pi_E \) and \( \Delta P \), denoting filtration pressure equilibrium, obtained before and during infusion of either hormone. For both hormones, when elevations in \( \Delta P \) were allowed, marked and roughly proportional increases in the resistance to blood flow through single afferent and efferent arterioles occurred, whereas when increases in \( \Delta P \) were prevented by partial aortic constriction increases in resistance were confined primarily to the efferent arteriole. Despite the marked increases in \( \pi_E \), absolute rates of proximal tubule fluid reabsorption, on the average, were unchanged by these hormones due to the opposing effects of marked decreases in efferent arteriolar plasma flow rate and, to a lesser extent, increases in peritubular capillary hydraulic pressure.

It has long been appreciated that the hydraulic pressure of the blood flowing through the mammalian kidney declines from a maximum value of approximately 120 mm Hg in the renal artery to roughly 10 mm Hg by the time the blood enters the peritubular capillary bed. Some two-thirds of this axial pressure drop occurs prior to the division of the afferent arterioles into the tufts of capillaries that compose single glomeruli (1-9). Since the afferent arteriolar blood flow rate is not very much greater than that in the efferent arterioles, the greater axial pressure drop along the afferent arteriole clearly indicates a resistance to blood flow along this vessel larger than that along the efferent arteriole.

Prior to the availability of methods and animal species permitting direct measurements of these hydraulic pressure profiles, numerous investigators (10–21) used a variety of vasoactive substances in an effort to identify the relative contributions of these pre- and postglomerular vascular resistances to the overall regulation of renal blood flow and glomerular filtration rate. The generally accepted interpretation of results of such studies is that the filtration fraction and the glomerular filtration rate are primarily dependent on the mean transcapillary hydraulic pressure difference, \( \Delta P \), which is thought to be altered by changes in either afferent or efferent arteriolar tone. For example, if a vasoactive substance causes constriction of the afferent arteriole, thereby increasing afferent arteriolar resistance, \( R_A \), renal blood flow will be reduced with a consequent fall in \( \Delta P \). As a result of this fall in \( \Delta P \), the filtration fraction and the glomerular filtration rate will also decline. Alternatively, if efferent arteriolar resistance, \( R_E \), is selectively increased, \( \Delta P \) will rise, even though renal blood flow declines, thereby increasing the filtration fraction, with little, if any, decline in glomerular filtration rate. Selective decreases in \( R_A \) and \( R_E \) are thought to have effects opposite to those just described.

In view of recent evidence indicating that \( \Delta P \) is considerably lower than previously believed (1–8) and that glomerular filtration rate is highly plasma-flow dependent, the possible hemodynamic responses to changes in \( R_A \) and \( R_E \) become difficult to anticipate. For example, the situation for a selective increase in \( R_E \) is complicated in that,
given the expected decline in renal blood flow, glomerular filtration rate can conceivably decrease, increase, or remain unchanged depending on the extent to which \( \Delta P \) and, hence, the filtration fraction increase. Similarly, an increase in \( R_A \) can elicit several combinations of responses. Whether renal blood flow remains unchanged or declines moderately or markedly cannot be predicted from simple hydrodynamic considerations. Similar uncertainty exists with regard to the magnitude and the direction of changes in \( \Delta P \) and the filtration fraction, despite the likelihood that the glomerular filtration rate will decrease when \( R_A \) is increased.

Thus, despite numerous studies employing vasoactive substances, inferences regarding their differential effects on \( R_A \) and \( R_E \) based on estimates of glomerular filtration rate, filtration fraction, and renal blood flow may not be entirely accurate in the absence of direct measurements of \( \Delta P \). Accordingly, to examine these resistances directly, preglomerular, glomerular, and postglomerular pressures and flows were determined in Munich Wistar rats with accessible surface glomeruli prior to and during infusion of two commonly studied vasoconstrictors, norepinephrine and angiotensin II. In addition, the present study permitted an assessment of the effects of these vasoconstrictors on proximal tubule fluid reabsorption and on the determinants of peritubular capillary uptake of this reabsorbate.

### Methods

**Symbols**

- \( AP \) = Mean femoral arterial blood pressure (mm Hg).
- \( APR \) = Absolute rate of fluid reabsorption to the end of the accessible proximal tubule (nliters/min).
- \( C \) = Protein concentration (g/100 ml).
- \( EABF \) = Efferent arteriolar blood flow (nliters/min).
- \( GBF \) = Glomerular blood flow (nliters/min).
- \( GFR \) = Whole kidney glomerular filtration rate (ml/min).
- \( Hct_a \) = Blood hematocrit in the femoral artery or the afferent arteriole (vol %).
- \( K_r \) = Reabsorption coefficient (nliters/[min-mm Hg]).
- \( P \) = Hydraulic pressure (mm Hg).
- \( P_r \) = Net reabsorptive pressure (mm Hg).
- \( \Delta P \) = Transmembrane hydraulic pressure difference, \( P_{GC} - P_r \) (mm Hg).
- \( Q \) = Plasma volume flow rate (nliters/min).
- \( R \) = Resistance to blood flow (dyne·sec/cm²).
- \( R_{TA} \) = Total arteriolar resistance, \( R_A + R_E \) (dyne·sec/cm²).
- \( SNFF \) = Single nephron filtration fraction.
- \( SNGFR \) = Single nephron glomerular filtration rate (nliters/min).

\[(TF/P)_{IN} = \text{Tubule fluid/plasma inulin concentration ratio.}\]
\[V_{TF} = \text{Tubule fluid flow rate (nliters/min).}\]
\[\pi = \text{Colloid osmotic pressure (mm Hg).}\]
\[\Delta \pi = \text{Transmembrane oncotic pressure difference, } \pi_{GC} - \pi_r \text{ (mm Hg).}\]

**Superscripts**

An overbar indicates a mean value.

**Subscripts**

- \( A \) = Afferent arteriole.
- \( C \) = Peritubular capillary.
- \( E \) = Efferent arteriole.
- \( GC \) = Glomerular capillary.
- \( I \) = Interstitial fluid.
- \( T \) = Proximal tubule.

### General Procedures

Studies were performed on 26 adult Wistar rats weighing 216-315 g; the animals were allowed free access to a rat pellet diet and water. Rats were anesthetized with Inactin (100 mg/kg, ip), placed on a temperature-regulated microcircuit, and subjected to a tracheotomy. Polyethylene catheters were inserted in the right and left jugular veins for infusion of inulin and vasoconstrictor drugs, respectively, and in the left femoral artery for periodic blood sampling and estimation of mean arterial blood pressure (\( AP \)). \( AP \) was monitored with an electronic transducer, (Statham model P23Db) connected to a direct-writing recorder (Hewlett Packard model 7702B). The left kidney was prepared for micropuncture in the manner described previously (8).

Sixty minutes before micropuncture, the rats received an intravenous infusion of isotonic NaCl at 0.02 ml/min. Inulin was present in a concentration of 10%, thereby resulting in a final plasma concentration of about 100 mg/100 ml. After this 60-minute equilibration period, exactly timed 1-2-minute samples of fluid were collected from late surface proximal convolutions from each of two or three nephrons for determination of flow rate and inulin concentration and calculation of single nephron glomerular filtration rate (SNFGR). The rate of fluid collection was adjusted to maintain a column of polymer oil (Kel F polymer oil, 3M Co.), three to four tubule diameters in length in a relatively constant position just distal to the site of puncture. Using the collection technique of controlled suction validated for this laboratory (22), minimum changes in tubule diameter or the position of the distal oil block were produced. Coincident with these tubule fluid collections, femoral arterial blood samples, 100 nliters in volume, were obtained for determination of hematocrit and plasma inulin concentration.

Hydraulic pressures were measured in single capillaries within surface glomeruli using a continuously recording, servonull micropipette-transducer system (9, 23, 24). Micropipettes with outer tip diameters of 2-3 \( \mu \)m and containing 2.0M NaCl were used. Hydraulic output from the servosystem was channeled via an electronic transducer (Statham model P23Db) to a second channel of the recorder. The accuracy, frequency response, and stability features of this servosystem have been reported previously (9). Direct measurements of hydraulic pres-
sure in single glomerular capillaries ($P_{oc}$), proximal tubules ($P_{p}$), efferent arterioles ($P_{e}$), and third-order peritubular capillaries ($P_{c}$) were recorded in each rat.

To obtain estimates of colloid osmotic pressure ($\pi$) of plasma entering and leaving glomerular capillaries, protein concentrations ($C$) in femoral arterial ($C_{f}$) and efferent arteriolar ($C_{e}$) blood plasma were measured as described previously (25). $C_{w}$ was taken as a measure of protein concentration in the afferent arteriole. Colloid osmotic pressures were calculated from these measured values of $C$ using the equation:

$$\pi = 1.63C + 0.294C^2. \quad (1)$$

This equation has been shown (26) to agree to within 1% with the empirical equation derived by Landis and Pappenheimer (27). Eq. 1 assumes an albumin-globulin ratio of unity, the value found in normal hydropenic rats in this laboratory. These estimates of pre- and postglomerular protein concentration permitted calculation of the single nephron filtration fraction (SNFF) and $Q_{a}$ (see Eqs. 4 and 5). From direct measurements of the decline in hydraulic pressure along single afferent and efferent arterioles and estimates of blood flow through these vessels, vascular resistances to blood flow through these individual vessels were calculated (see Eqs. 8-10).

**EFFECT OF INFUSION OF VASOCONSTRICTOR SUBSTANCES**

**Group 1: Norepinephrine Infusion.**—Following the aforementioned measurements in normal hydropenia, l-norepinephrine (Levarterenol, Winthrop Laboratories) was infused intravenously in seven rats at a rate of 2.0-4.0 $\mu$g/min kg$^{-1}$ to produce a sustained pressor response. Following a 15-minute equilibration period, collections of tubule fluid (recollections) and efferent arteriolar and femoral arterial blood samples and measurements of $AP$, $P_{oc}$, $P_{p}$, $P_{e}$, and $P_{c}$ were repeated in each rat.

**Group 2: Norepinephrine Infusion with Aortic Constriction.**—After measurements in normal hydropenia, norepinephrine (2.0-4.0 $\mu$g/min kg$^{-1}$) was infused in six other rats, while renal perfusion pressure was restored to values similar to those present prior to norepinephrine infusion by partially constricting the abdominal aorta. This procedure has been described in detail elsewhere (3). From direct measurements of the decline in hydraulic pressure along single afferent and efferent arterioles and estimates of blood flow through these vessels, vascular resistances to blood flow through these individual vessels were calculated (see Eqs. 8-10).

**Group 3: Angiotensin II Infusion.**—After measurements in normal hydropenia, angiotensin II amide (Hyptensin, Ciba) was infused intravenously at a rate of 0.2-0.6 $\mu$g/min kg$^{-1}$ in seven other rats. Following a 15-minute equilibration period, measurements carried out in the normal hydropenic period were repeated as in group 1.

**Group 4: Angiotensin II Infusion with Aortic Constriction.**—As in group 2, repeat measurements were made in six other rats during angiotensin II infusion (in a dose identical to that employed in group 3) after partial abdominal aortic constriction had restored renal perfusion pressure to preinfusion levels.

**ANALYTICAL PROCEDURES**

The volume of tube 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 the tubule fluid was measured, usually in duplicate, by the microfluorescence method of Vurek and Pegram (28). Inulin concentration in plasma was determined by the macroanthrone method of Führ et al. (29). Protein concentrations in efferent arteriolar and femoral arterial blood plasma were determined, usually in duplicate, with an ultramicrocolorimeter using a microadaptation (25) of the method of Lowry et al. (30).

**CALCULATIONS**

Single nephron glomerular filtration rate was calculated as

$$SNFF = \frac{(TF/P)_{IN} - V_{TF}}{Q_{a}}. \quad (2)$$

where $Q_{a}$ represents the tubule fluid/plasma inulin concentration ratio and the tubule fluid flow rate, respectively.

Absolute proximal fluid reabsorption was determined from the equation

$$APR = SNFF - V_{TF}. \quad (3)$$

Single nephron filtration fraction was derived from the equation

$$SNFF = 1 - \frac{(C_{a}/C_{e})}{V_{TF}}. \quad (4)$$

where $C_{a}$ and $C_{e}$ denote afferent and efferent arteriolar protein concentrations, respectively.

Initial glomerular plasma flow rate was calculated as

$$Q_{a} = SNFF/SNFF. \quad (5)$$

Blood flow rate per single afferent arteriole or glomerulus was determined from the equation

$$GBF = Q_{a}/(1 - Hct_{a}), \quad (6)$$

where $Hct_{a}$, the hematocrit of afferent arteriolar blood, was considered to be equal to the femoral arterial hematocrit.

Efferent arteriolar blood flow rate was derived from the equation

$$EABF = GBF - SNFF. \quad (7)$$

Resistance per single afferent arteriole was calculated as

$$R_{a} = \frac{(\Delta P - P_{oc})/GBF}{(7.962 \times 10^{10})}, \quad (8)$$

where the factor $7.962 \times 10^{10}$ was used to give resistance in units of dyne·sec/cm$^5$ when $\Delta P$ and $P_{oc}$ were expressed in mm Hg and GBF in nliters/min.

Resistance per single efferent arteriole was determined from the equation

$$R_{e} = \frac{(P_{oc} - P_{c})/EABF}{(7.962 \times 10^{10})}. \quad (9)$$
Summary of Measured Determinants of Glomerular Ultrafiltration and Proximal Tubule Fluid Reabsorption

Values are expressed as means ± 1 SE.

<table>
<thead>
<tr>
<th>Group</th>
<th>AP (mm Hg)</th>
<th>PGc (mm Hg)</th>
<th>Pr (mm Hg)</th>
<th>ΔP (mm Hg)</th>
<th>Prc (mm Hg)</th>
<th>Hct (vol %)</th>
<th>Csa (g/100 ml)</th>
<th>Ces (g/100 ml)</th>
<th>τs (mm Hg)</th>
<th>τt (mm Hg)</th>
<th>τs/ΔP</th>
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<tbody>
<tr>
<td>Group 1</td>
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<tr>
<td>Normal hydropenia (n = 7)*</td>
<td>116 ± 5</td>
<td>44.7 ± 1.3</td>
<td>11.9 ± 0.7</td>
<td>33.7 ± 1.5</td>
<td>7.9 ± 0.5</td>
<td>51.8 ± 1.3</td>
<td>5.4 ± 0.1</td>
<td>8.3 ± 0.3</td>
<td>17.5 ± 0.3</td>
<td>33.9 ± 1.7</td>
<td>1.01 ± 0.02</td>
</tr>
<tr>
<td>Norepinephrine (n = 7)*</td>
<td>140 ± 4</td>
<td>58.4 ± 1.6</td>
<td>11.9 ± 0.5</td>
<td>46.6 ± 1.9</td>
<td>12.6 ± 0.6</td>
<td>53.6 ± 1.0</td>
<td>5.4 ± 0.1</td>
<td>10.1 ± 0.4</td>
<td>17.5 ± 0.6</td>
<td>48.3 ± 2.8</td>
<td>1.00 ± 0.03</td>
</tr>
<tr>
<td>Angiotensin II (n = 6)*</td>
<td>120 ± 3</td>
<td>58.3 ± 1.7</td>
<td>12.8 ± 0.5</td>
<td>45.5 ± 1.9</td>
<td>12.5 ± 1.4</td>
<td>53.3 ± 0.6</td>
<td>5.1 ± 0.1</td>
<td>10.2 ± 0.2</td>
<td>15.9 ± 0.4</td>
<td>47.7 ± 1.9</td>
<td>1.05 ± 0.03</td>
</tr>
<tr>
<td>Normal hydropenia (n = 6)*</td>
<td>120 ± 3</td>
<td>45.3 ± 0.8</td>
<td>11.2 ± 0.5</td>
<td>34.2 ± 0.9</td>
<td>9.2 ± 0.8</td>
<td>52.2 ± 0.4</td>
<td>5.0 ± 0.1</td>
<td>8.4 ± 0.1</td>
<td>15.6 ± 0.2</td>
<td>34.3 ± 0.9</td>
<td>1.01 ± 0.03</td>
</tr>
<tr>
<td>Norepinephrine with aortic constriction (n = 6)*</td>
<td>120 ± 3</td>
<td>58.3 ± 1.7</td>
<td>12.8 ± 0.5</td>
<td>45.5 ± 1.9</td>
<td>12.5 ± 1.4</td>
<td>53.3 ± 0.6</td>
<td>5.1 ± 0.1</td>
<td>10.2 ± 0.2</td>
<td>15.9 ± 0.4</td>
<td>47.7 ± 1.9</td>
<td>1.05 ± 0.03</td>
</tr>
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</table>

Values are expressed as means ± 1 SE.

† N = number of tubules.

‡ Calculated from paired data using Student’s t-test.

Results

Measurements Prior to Infusion of Vasoconstrictor Substances.—Individual and mean values for AP and a number of pertinent measures of single nephron function in 26 normal hydropenic rats studied before norepinephrine or angiotensin II infusion are summarized in Table 1 and in Figures 1 and 2. Mean values for (TF/P)n ratios and SNGFR were similar among the four groups of rats, as were mean values for SNFF, QA, and APR. Mean values for PGc in groups 1–4 ranged from 44 to 48 mm Hg. Pressures measured at random sites along surface proximal convoluted tubules (Pr) averaged about 11 mm Hg in each group, yielding mean values for the glomerular transcapillary hydraulic pressure difference, ΔP, ranging from about 34 to 37 mm Hg. Values for PC likewise were similar among the groups, as were mean values for efferent arteriolar hydraulic pressure, Pr, which ranged from 12.3 to 14.5 mm Hg. Mean values for the pressure drop along single afferent arterioles (ΔP – PGc) averaged 71, 80, 72, and 75 mm Hg for groups 1–4, respectively, values essentially twice as large as the pressure drops measured along corresponding efferent arterioles (PGc – PC), which averaged 37, 36, 35, and 38 mm Hg, respectively.

Mean values for RA and RE are also summarized in Figures 1 and 2 and in Table 1. On the average, afferent arterioles contributed nearly two-thirds of the total resistance to blood flow to the level of the smallest peritubular capillaries, a finding in close quantitative accord with that reported by us previously (2, 3, 5, 8).

Measurements of total protein concentration in afferent (Csa) and efferent (Ces) arteriolar plasma permitted calculation of πs and πt, respectively; these values are given in Table 1. It is possible from measurements of PGc and Pr and the estimates of πs and πt to determine the magnitude of the net transcapillary pressure difference favoring ultrafiltration across afferent- and efferentmost points along the glomerular capillary network in each rat. ΔP exceeded the opposing oncotic pressure (πt) at afferent ends of the glomerular capillaries by 16–18 mm Hg, on the average. This net pressure favoring filtration essentially disappeared by the efferent ends, however, where the ratio πt/ΔP did not differ significantly from unity in any of the four groups of rats. This finding indicates that filtration pressure equilibrium was achieved under these conditions of normal hydropenia. All values for single nephron and microvascular function are in close accord with values for similarly hydropenic Wistar rats reported from this laboratory previously (1–5, 7–9).

Group 1: Norepinephrine Infusion.—As shown in Table 1, infusion of norepinephrine resulted in a uniform increase in AP, on the average, from 116 to...
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149 mm Hg ($P < 0.001$). Despite this increase in $\Delta P$, SNGFR failed to change; the mean increase of $1.2 \pm 2.2$ liters/min was not statistically significant. Values for $(TF/P)_{in}$ tended to decline in nearly every tubule from an average of $2.03 \pm 0.12$ (n = 15 tubules) in control experiments to $1.76 \pm 0.10$ (n = 14 tubules) during norepinephrine infusion ($P < 0.005$). $A_P$, on the average, fell slightly but not significantly, averaging $12.1 \pm 1.0$ liters/min before and $10.8 \pm 1.1$ liters/min during norepinephrine infusion ($P > 0.2$). SNFF increased in each rat, on the average, by $0.11 \pm 0.02$ ($P < 0.001$). This rise in SNFF was associated with uniform decreases in $Q_{A}$ and $Q_{E}$ (Table 1). Failure of SNGFR to rise occurred despite a significant increase in $\Delta P$, on the average, from $33.7 \pm 1.5$ mm Hg to $46.6 \pm 1.9$ mm Hg. During norepinephrine infusion, the hydraulic pressure drop along single afferent arterioles ($A_P - P_{GC}$) increased in each rat to a mean of 91 mm Hg ($P < 0.001$). The magnitude of the pressure drop along efferent arterioles ($P_{GC} - P_{E}$) also increased, on the average, to 45 mm Hg ($P < 0.001$). Rates of blood flow through single afferent (GBF) and efferent (EABF) arterioles decreased uniformly from average values of $158 \pm 15$ liters/min and $132 \pm 13$ liters/min before norepinephrine infusion to $126 \pm 3$ liters/min and $99 \pm 3$ liters/min during norepinephrine infusion, respectively (both $P < 0.05$). It follows from Eq. 8 that, since this decrease in GBF occurred despite a substantial increase in $A_P - P_{GC}$, $R_A$ increased significantly (Table 1 and Fig. 1). A similar increment in $R_E$ is demonstrated by the simultaneous decline in EABF and rise in $P_{GC}$ – $P_C$. Thus, the rise in total arteriolar resistance, $R_{T}A$, during norepinephrine infusion was the result of proportional increases in $R_A$ and $R_E$ (Table 1 and Fig. 1). Hence, the fraction of the total arteriolar resistance contributed by $R_A$ and $R_E$ was the same during, as well as before, norepinephrine infusion (Table 1). During norepinephrine infusion, $C_{ir}$, on the average, remained unchanged from preinfusion values (Table 1), whereas $C_G$ increased in each rat (range $+0.8$ to $+2.6$ g/100 ml), on the average, to $10.1 \pm 0.4$ g/100 ml ($P < 0.001$). Corresponding values for $\pi_A$ and $\pi_E$ are given in Table 1 and Figure 1. As shown, equality of $\Delta P$ and $\pi_A$ was observed during norepinephrine infusion, denoting persistence of filtration pressure equilibrium despite marked increases in $\Delta P$.

Group 2: Norepinephrine Infusion with Aortic Constriction.—In six rats, during norepinephrine infusion $\bar{A}_P$ was restored to a value not significantly different from preinfusion levels by partial aortic constriction (Table 1). Measures of single nephron and microvascular function studied before and during norepinephrine infusion with aortic constriction are also summarized in Table 1 and Figure 1. Despite the absence of a rise in $\bar{A}_P$, mean values for SNGFR, $Q_{A}$, $Q_{E}$, SNFF, and $\Delta P$ were similar in magnitude and direction to values observed in rats in group 1 for which the pressor response was not prevented. Similarly, mean values for $\pi_A$ and $\pi_E$ were comparable to those in group 1 rats, and filtration pressure equilibrium again persisted. With constant renal perfusion pressure,
Summary of the effects of an intravenous infusion of norepinephrine on several measures of surface nephron and microvascular function. The section on the left represents results obtained when renal perfusion pressure (AP) was allowed to increase; results obtained during prevention of this increase in AP are summarized on the right.

In spite of this pressor effect, SNGFR failed to change significantly, notwithstanding a significant rise in \( \Delta P \) of 14.4 ± 1.3 mm Hg. A uniform rise in SNFF, on the average, by 0.14 ± 0.02 (\( P < 0.001 \)) was associated with significant declines in \( Q_A \) and \( Q_E \). Values for \( (TF/P)_{IN} \) increased during angiotensin II infusion in nearly every tubule studied from an average of 1.93 ± 0.01 to 2.34 ± 0.14 (\( P < 0.001 \), Table 1). In contrast, \( APR \) failed to change significantly, averaging 11.8 ± 1.0 nliters/min and 12.3 ± 1.1 nliters/min prior to and during angiotensin II infusion, respectively (\( P > 0.5 \)). \( C_A \) and hence \( \pi_A \) did not change during angiotensin II infusion, and the increases in \( C_E \) and \( \pi_E \) were similar to those seen during norepinephrine infusion. As with norepinephrine infusion, filtration pressure equilibrium persisted during angiotensin II infusion; \( \pi_E/\Delta P \) did not differ significantly from unity. The magnitude of the hydraulic pressure drop increased along both afferent and efferent arterioles in each rat (Table 1). \( GFB \) and \( EABF \) decreased uniformly from average values of 133 ± 11 nliters/min and 108 ± 9 nliters/min before angiotensin II infusion to 91 ± 11 nliters/min and 68 ± 9 nliters/min during

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In this study, the effects of an intravenous infusion of norepinephrine on renal function were investigated. The study focused on the changes in renal perfusion pressure (AP), with results obtained when AP was allowed to increase and during prevention of this increase. The study also examined the effects of angiotensin II infusion on renal function, including changes in systemic and renal hemodynamics, filtration rates, and hydraulic pressures along afferent and efferent arterioles.

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**Key Points**

1. **Norepinephrine Infusion**
   - **Renal Hemodynamics**: The drop in hydraulic pressure along single afferent arterioles declined from a mean of 81 mm Hg before to 62 mm Hg during norepinephrine infusion (\( P < 0.001 \)).
   - **Pressure Drop**: Axial pressure drop along single efferent arterioles increased appreciably, on the average, from 36 mm Hg to 46 mm Hg (\( P < 0.001 \)).
   - **GBF Decline**: GFR declined substantially from a mean value of 176 nliters/min to 139 nliters/min (\( P < 0.005 \), Table 1), but, since this decline was proportional to the decline in \( \Delta P \), \( R_A \) remained essentially unchanged from control values (Table 1 and Fig. 1).
   - **APR Increase**: APR failed to change significantly, averaging 11.8 ± 1.0 nliters/min and 12.3 ± 1.1 nliters/min prior to and during angiotensin II infusion, respectively (\( P > 0.5 \)).

2. **Angiotensin II Infusion**
   - **SNFF Increase**: A uniform rise in SNFF, on the average, by 0.14 ± 0.02 (\( P < 0.001 \)) was associated with significant declines in \( Q_A \) and \( Q_E \).
   - **TF/P IN Increase**: Values for \( (TF/P)_{IN} \) increased during angiotensin II infusion in nearly every tubule studied from an average of 1.93 ± 0.01 to 2.34 ± 0.14 (\( P < 0.001 \), Table 1). In contrast, \( APR \) failed to change significantly, averaging 11.8 ± 1.0 nliters/min and 12.3 ± 1.1 nliters/min prior to and during angiotensin II infusion, respectively (\( P > 0.5 \)).
   - **Filtration Pressure**: As with norepinephrine infusion, filtration pressure equilibrium persisted during angiotensin II infusion; \( \pi_E/\Delta P \) did not differ significantly from unity.

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**Conclusion**

The study provides insights into the hemodynamic and filtration changes induced by intravenous infusions of norepinephrine and angiotensin II, highlighting the importance of renal perfusion pressure on renal function and the role of filtration pressure in maintaining filtration equilibrium.
angiotensin II infusion, respectively. Hence, $R_A$ and $R_E$ rose significantly, and $R_{TA}$ increased, on the average, from $7.3 \pm 0.9$ dyne·sec/cm$^4 \times 10^{10}$ to $14.5 \pm 2.3$ dyne·sec/cm$^4 \times 10^{10}$ ($P < 0.025$) (Table 1 and Fig. 2).

Group 4: Angiotensin II Infusion with Aortic Constriction.—$\Delta P$ was restored to a value not significantly different from preinfusion levels by partial aortic constriction in six rats receiving an angiotensin II infusion (Table 1). Mean values for $(TP/P)_{IN}$, SNGFR, APR, SNFF, $Q_A$, $Q_E$, $\Delta P$, $\pi_A$, and $\pi_E$ were similar to those seen during angiotensin II infusion in group 3 rats in which the pressor effect was not abolished. As in group 2, constancy of $\Delta P$ did not prevent the rise in $\Delta P$ nor the achievement of equality between $\pi_E$ and $\Delta P$. In this group, $\Delta P - P_{GC}$ declined significantly, on the average, by $18$ mm Hg; $P_{GC} - P_c$ increased, on the average, by $10$ mm Hg. As with group 3 rats, $GBF$ and $EABF$ fell during angiotensin II infusion (Table 1). Thus, while $R_A$ rose slightly, albeit significantly, there was a proportionately greater rise in $R_E$, which now contributed more than half of the total arteriolar resistance, $R_{TA}$ (Table 1 and Fig. 2).

**Discussion**

The present study provides the first direct assessment of the effects of norepinephrine and angiotensin II on preglomerular, glomerular, and postglomerular pressures and flows. As shown in Figure 1 (left), a pressor dose of norepinephrine resulted in highly significant and proportional increases in $R_A$ and $R_E$. Whereas $\pi_A$ remained unchanged, norepinephrine infusion resulted in large and equivalent increases in $\Delta P$ and $\pi_E$. The rise in $\Delta P$ resulted entirely from increases in glomerular capillary hydraulic pressure; tubule hydraulic pressure remained essentially unchanged. Equality of $\pi_E$ and $\Delta P$, denoting the existence of filtration pressure equilibrium, obtained both before and during norepinephrine infusion. Hence, the marked increase in the net driving pressure for ultrafiltration at the afferent end of the capillary, $\Delta P - \pi_A$, did not prevent attainment of filtration equilibrium. The highly significant increase in $SNFF$ noted in the top section of Figure 1 (left) was a result of the marked increase in $\Delta P$. This rise in filtration fraction corresponded to a

---

**FIGURE 2**

Summary of the effects of an intravenous infusion of angiotensin II on several measures of surface nephron and microvascular function with (left) and without (right) increases in renal perfusion pressure.
reduction in \( Q_A \) (open circles), in the absence of a significant change in \( SNGFR \) (solid circles). Given filtration pressure equilibrium, \( SNGFR \) is determined by just three quantities, namely, \( Q_A, \Delta P \), and \( \pi_A \) (26, 31). Thus, since \( \pi_A \) remained unchanged, constancy of \( SNGFR \) was maintained, despite the increase in \( \Delta P \) because of the opposing effect of a reduction in \( Q_A \).

Figure 2 (left) summarizes the results of similar experiments carried out before and during infusion of angiotensin II. The results in response to a pressor dose of angiotensin II were essentially the same as those observed with norepinephrine in that \( R_A \) and \( R_E \) both increased, as did \( \Delta P \) and \( \pi_E \). Once again, the increase in \( \Delta P \) was responsible for a large increase in \( SNGFR \), representing a highly significant fall in \( Q_A \) in the absence of a significant change in \( SNGFR \).

Of interest was the extent to which the rise in \( \Delta P \) observed with norepinephrine and angiotensin II was dependent on the simultaneous rise in mean aortic blood pressure, since filtration fraction has been shown to rise in the absence of an increase in renal perfusion pressure (19, 32). To examine this question, experiments with identical doses of norepinephrine and angiotensin II were repeated in separate groups of rats in which constriction of an aortic snare prevented the rise in renal perfusion pressure. The results are summarized in Figures 1 and 2 (right). It can be seen for both hormones that when the rise in renal perfusion pressure was prevented, the effects on \( SNGFR, Q_A, \Delta P, \pi_A, \) and \( \pi_E \) were essentially identical to those found when the rise in renal perfusion pressure was allowed. In contrast, however, when renal perfusion pressure was held constant, \( R_A \) no longer increased following norepinephrine infusion, whereas the change in \( R_E \) was identical to that seen when the rise in \( \Delta P \) was permitted (Fig. 1, left). This finding suggests that the increase in \( R_A \) seen when pressure is not controlled is not the result of a pharmacological effect of norepinephrine per se but is secondary to the rise in renal perfusion pressure, perhaps the consequence of a myogenic reflex. In other words, the direct action of norepinephrine appears to be confined to the efferent arteriole, a site of action suggested by Richards and Plant (10) for the related hormone, epinephrine, more than a half-century ago. This finding raises the intriguing possibility that alpha receptors are localized to this vessel. An alternative explanation can be advanced to account for the failure of \( R_A \) to increase when renal perfusion pressure is held constant. Since constriction of the aortic snare would not prevent the increase in pressure in baroreceptors (such as in the carotid sinuses and aortic arch), reduced sympathetic activity to the kidneys might be expected. Constancy of \( R_A \) in this setting could occur as a result of a pharmacological effect of norepinephrine to counteract any fall in afferent arteriolar tone due to baroreceptor stimulation.

When the rise in \( \Delta P \) was prevented during angiotensin II infusion (Fig. 2, right), the increase in \( R_A \) was not entirely abolished, in contrast to the case for norepinephrine. Nevertheless, \( R_A \) increased considerably less than did \( R_E \), suggesting that angiotensin II also acts preferentially on the efferent arteriole. Future studies utilizing specific angiotensin II antagonists are needed to determine whether the small but significant rise in \( R_A \) (Fig. 2, right) represents a true pharmacological effect of angiotensin II on the afferent arteriole.

The design of the present study also permitted an assessment of the effects of norepinephrine and angiotensin II on the absolute rate of proximal tubule fluid reabsorption (APR) and on the determinants of peritubular capillary uptake of this isotonic reabsorbate. Irrespective of whether \( \Delta P \) was controlled, neither norepinephrine nor angiotensin II significantly altered APR relative to preinfusion normal hydropenic control values. Similar findings have been reported by others (33–35). Given the large and uniform increases in \( \pi_E \) with each hormone, this constancy of APR is seemingly at variance with the concept of peritubular control of APR, based largely on the extensive body of evidence that indicates a parallel relationship between \( \pi_E \) and APR (see refs. 36 and 37 for comprehensive bibliographies). This apparent discrepancy disappears when changes in the other determinants of peritubular capillary fluid uptake in addition to \( \pi_E \) are taken into account, namely, \( Q_E, P_c, \) and the interstitial oncotic and hydraulic pressures, \( \pi_I \) and \( P_I \). In particular, the marked reductions in \( Q_E \) and, to a lesser degree, the elevations in \( P_c \) induced by norepinephrine and angiotensin II would be expected from theoretical considerations (38, 39) to oppose the effects on APR of increases in \( \pi_E \). As discussed in detail previously (38), APR is relatively insensitive to changes in \( Q_E \) for values of \( Q_E \) greater than those found in the normal hydropenic rat. In contrast, however, reductions in \( Q_E \) to values below normal, as was found during infusions of norepinephrine and angiotensin II, would be expected to have more profound effects on APR. Therefore, the extent to which the observed marked decreases in \( Q_E \) and lesser increases in \( P_c \) opposed the effects on APR of APR.
EFFECTS OF VASOCONSTRICTORS ON RENAL FUNCTION

TABLE 2
Comparison of Calculated and Observed Values of Absolute Proximal Reabsorption during Infusion of Norepinephrine or Angiotensin II

<table>
<thead>
<tr>
<th>Group</th>
<th>Observed APR (nliters/min)</th>
<th>Calculated APR (nliters/min)</th>
<th>Estimated change in $\pi_e - P_i$ (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.8 ± 1.1</td>
<td>12.8</td>
<td>+2.8</td>
</tr>
<tr>
<td>2</td>
<td>14.6 ± 0.4</td>
<td>15.6</td>
<td>+1.0</td>
</tr>
<tr>
<td>3</td>
<td>12.3 ± 1.1</td>
<td>13.5</td>
<td>+1.4</td>
</tr>
<tr>
<td>4</td>
<td>12.5 ± 0.8</td>
<td>12.9</td>
<td>+0.5</td>
</tr>
</tbody>
</table>

Values for observed and calculated APR are means ± se.

Increases in $\pi_e$ was calculated using an approach described previously (38). For each group of rats, using the measured mean values of APR, $Q_E$, $\pi_e$, and $P_C$ (Table 1), and assuming $\pi_e - P_i = 4$ mm Hg (38), $K_e$ the coefficient of reabsorption, was computed for the control periods. Assuming also that $\pi_e - P_i$ and $K_e$ were unchanged by norepinephrine or angiotensin II infusion, the value of APR for the experimental period for each group was calculated using the observed changes in $Q_E$, $\pi_e$, and $P_C$. As shown in Table 2, the close agreement between calculated and observed values of APR indicates that the effect on APR of increases in $\pi_e$ would be expected to be offset almost exactly by the measured changes in $Q_E$ and $P_C$. Perfect agreement between calculated and observed values of APR is found when $\pi_e - P_i$ is assumed to increase by the small amounts shown in the right column of Table 2. Thus, failure of APR to change in parallel with changes in $\pi_e$ cannot be taken as evidence against peritubular control of APR. Rather, the present analysis emphasizes the need to consider, in addition to $\pi_e$, the simultaneous changes in $Q_E$ as well as $P_C$, $P_i$, and $\pi_e$. It is clear that when all of the determinants of peritubular capillary fluid uptake are considered the results are entirely in keeping with the concept of peritubular capillary control of APR and eliminate the need to postulate a direct effect of norepinephrine or angiotensin II on proximal tubule epithelium.

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References


Effects of norepinephrine and angiotensin II on the determinants of glomerular ultrafiltration and proximal tubule fluid reabsorption in the rat.

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