Renal Hemodynamic Effects of Calcium Antagonists in Rats With Reduced Renal Mass

Sharon Anderson

The intrarenal hemodynamic effects of antihypertensive agents vary considerably, and these microcirculatory effects may contribute to long-term structural sequelae in the setting of chronic renal disease. To investigate the consequences of blood pressure reduction with calcium antagonists, 5/6 nephrectomized Munich-Wistar rats underwent baseline determinations of mean arterial pressure, whole kidney function, and single nephron glomerular filtration rate, after which intravenous infusions of verapamil or diltiazem were given in doses that acutely normalized blood pressure; control rats received saline vehicle. During the baseline period, all rats exhibited comparably elevated values for mean arterial pressure and single nephron glomerular filtration rate. During the experimental infusion, control rats exhibited continued single nephron hyperfiltration (84±8 nl/min) as a result of elevations in both glomerular capillary plasma flow rate (330±36 nl/min) and glomerular capillary hydraulic pressure (68±3 mm Hg), whereas the glomerular capillary ultrafiltration coefficient was low [0.050±0.009 nl/(sec*mm Hg)]. Both verapamil (148±6 to 103±3 mm Hg, p<0.05) and diltiazem (154±6 to 102±2 mm Hg, p<0.05) normalized arterial pressure, which did not change in control rats (150±7 to 142±8 mm Hg). Single nephron hyperfiltration and hyperperfusion were comparable among groups during the experimental period; compared with baseline values, diltiazem (97±8 to 71±7 nl/min, p<0.05) but not verapamil (90±7 to 83±6 nl/min, p=NS) modestly lowered the single nephron glomerular filtration rate. Compared with vehicle rats, glomerular capillary pressure was reduced in rats receiving verapamil (52±2 mm Hg) and diltiazem (50±2 mm Hg), whereas both agents increased the ultrafiltration coefficient [0.102±0.012 and 0.123±0.018 nl/(sec*mm Hg), respectively]. Thus, calcium antagonists acutely control glomerular hypertension and improve the ultrafiltration coefficient in remnant kidney rats. (Hypertension 1991;17:288–295)

Calcium antagonists are being used increasingly for the treatment of hypertension because of their antihypertensive efficacy, ability to maintain renal function, and relative absence of troubling metabolic side effects. In addition to potential cardioprotective effects, it has been suggested that these agents may afford structural protection to the kidney in patients with hypertension and progressive glomerular injury.1-3 Systemic hypertension is an important risk factor for the progression of renal disease,4 and control of hypertension may slow the development of renal injury. However, recent evidence suggests that the ability of antihypertensive therapy to protect the kidney relates in large part to the glomerular hemodynamic consequences of therapy and that the intrarenal responses to antihypertensive agents vary considerably. In this experimental model, both severe systemic hypertension and impaired autoregulatory capacity render the glomerular capillary network susceptible to transmission of high systemic perfusion pressures. Thus, the intraglomerular hemodynamic consequences of antihypertensive agents depend not only on changes in systemic arterial pressure but also on potential influences on arteriolar resistances and autoregulatory capacity. Studies in a variety of experimental models of renal disease suggest that antihypertensive agents that normalize the glomerular capillary hydraulic pres-

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sure ($\bar{P}_{GC}$) are most likely to slow the progression of renal disease, whereas drugs that control systemic but not glomerular hypertension do not necessarily afford protection.5-10

Most widely studied have been the angiotensin I converting enzyme inhibitors, which lower efferent arteriolar resistance ($R_e$) and thereby $\bar{P}_{GC}$ in experimental animals5,7-10 and generally preserve or even increase renal plasma flow and glomerular filtration rate (GFR) in patients with essential hypertension or renal disease.9 Similar renal hemodynamic effects have been reported with calcium antagonists in clinical studies.3,11 However, relatively little information regarding the glomerular hemodynamic and morphological consequences of these agents in experimental renal disease has been reported, and the available evidence is somewhat conflicting. Accordingly, the present study was undertaken to determine the intrarenal hemodynamic consequences of normalization of blood pressure with several clinically available, structurally dissimilar calcium antagonists in a rat model of hypertensive renal disease.

Methods

The present study was conducted in adult male Munich-Wistar rats with body weights of 230–270 g and performed in accordance with the guidelines established by the Harvard Medical Area Animal Care and Use Committee. Rats were allowed ad libitum access to standard rat chow (Rodent Laboratory Chow 5001, Ralston Purina Co., Richmond, Ind.) and tap water throughout the studies. All rats were anesthetized with Breval (50 mg/kg i.p.) and subjected to 5/6 nephrectomy by right uninephrectomy and ligation of two or three branches of the left renal artery. Verification of renal mass reduction was confirmed by documentation of elevated systemic blood pressure, increased values for 24-hour urinary protein excretion ($U_{prot}$), and visual inspection of the remnant kidney at the time of micropuncture.

At 4 weeks after ablation, functional studies were carried out as follows. Rats were anesthetized with Inactin (100 mg/kg i.p.) and placed on a temperature-regulated table. Left femoral artery catheterization was followed by blood collection for baseline measurements of hematocrit, inulin and para-aminohippurate (PAH) "blanks," and plasma sodium and potassium levels. This arterial catheter was used for subsequent periodic blood sampling and measurement of mean arterial pressure (AP) via an electronic transducer connected to a direct-writing recorder. After tracheostomy, venous catheters were inserted for infusions of plasma, inulin and PAH, and test drug or vehicle. Intravenous infusions of isoncotic rat plasma and 4% inulin and 0.4% PAH were started at rates of 6.0 and 1.2 ml/hr, respectively. The left ureter was catheterized for urine collection, and the remnant kidney was exposed for micropuncture. To avoid the 20% reduction in plasma volume that results from this surgical preparation,12 euvolemia was maintained by infusing isoncotic rat plasma at a rate of 6 ml/hr with a total amount equal to 1% of body weight, followed by a reduction in infusion rate to 1.6 ml/kg/hr to maintain a constant hematocrit.

During period 1 (baseline control period), no additional fluids were infused. Exactly timed (45–60 seconds) samples of tubule fluid were collected from at least three tubules for determination of flow rate and inulin concentration, enabling calculation of the single nephron GFR. Arterial blood was obtained for measurement of hematocrit and plasma concentrations of inulin, PAH, and protein, and 10–20-minute urine collections were obtained for determination of flow rate and sodium, potassium, inulin, and PAH concentrations. These measurements permitted calculation of GFR (inulin clearance) and renal plasma flow rate (RPF) (PAH clearance) as well as urinary sodium ($U_{Na}$) and potassium ($U_{K}$) excretion rates.

During period 2 (experimental period), rats were randomized to receive infusions of either saline vehicle at a rate of 0.008 ml/min, verapamil (Sigma Chemical Co., St. Louis), or diltiazem (Marion Laboratories, Kansas City, Mo.). All experiments with calcium antagonists were performed in blinded fashion, without knowledge of the compounds infused. Experiments with saline could not be effectively blinded because AP did not change. All infusions were provided in syringes and tubing that were protected from light and begun at a rate of 0.008 ml/min; thereafter, doses of experimental drugs were individually adjusted to decrease AP to the range of 100–110 mm Hg. The doses required to achieve this blood pressure averaged 21 $\mu$g/kg/min (range, 10–37 $\mu$g/kg/min) for verapamil and 84 $\mu$g/kg/min (range, 17–241 $\mu$g/kg/min) for diltiazem. On achieving a stable AP in the desired range, a 30-minute period was allowed for equilibration before experimental measurements were performed.

During period 2, repeat measurements of AP, hematocrit, GFR, RPF, $U_{Na}$, $U_{K}$, and single nephron GFR (at least three tubules) were performed. In addition, two or three samples of arterial and four to eight samples of efferent arteriolar blood were obtained for determination of protein concentration. Time-averaged hydraulic pressures were measured in one to five (usually at least two) surface glomerular capillaries, four to 11 proximal tubules, and three to seven effert arterioles with a sernonull micropipette transducer system (Instrumentation for Physiology and Medicine, San Diego, Calif). Colloid osmotic pressure of plasma entering and leaving glomerular capillaries was estimated from femoral arterial and efferent arteriolar plasma, thus permitting calculation of the single nephron filtration fraction, the glomerular capillary ultrafiltration coefficient ($K_{f}$), and afferent and efferent arteriolar blood flow rates and resistances, using equations previously detailed.13* Because all animals were in filtra-

*It has been suggested that internephron heterogeneity in the remnant kidney rat at 4 weeks is sufficient to invalidate use of standard equations to calculate $K_{f}$. However, study of remnant kidney rats at earlier time points (1–2 weeks) is problematic.
TABLE 1. General Parameters

<table>
<thead>
<tr>
<th>Group</th>
<th>Body weight (g)</th>
<th>U_{prot}V (mg/day)</th>
<th>Sodium (meq/l)</th>
<th>Potassium (meq/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline (n=6)</td>
<td>254±6</td>
<td>35±7</td>
<td>145±3</td>
<td>5.4±0.3</td>
</tr>
<tr>
<td>Verapamil (n=9)</td>
<td>256±6</td>
<td>55±15</td>
<td>141±2</td>
<td>5.1±0.3</td>
</tr>
<tr>
<td>Diltiazem (n=8)</td>
<td>257±3</td>
<td>47±5</td>
<td>144±5</td>
<td>4.7±0.3</td>
</tr>
</tbody>
</table>

Values are given as mean±SEM. U_{prot}V, 24-hour urinary protein excretion. There were no significant differences among groups in any parameter.

TABLE 2. Systemic and Renal Parameters Before and During Infusion

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>GFR (ml/min)</th>
<th>RPF (ml/min)</th>
<th>WKFF (μl/min)</th>
<th>UV (mg/day)</th>
<th>U_{nit}V (μeq/min)</th>
<th>U_{pot}V (μeq/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline (n=6)</td>
<td>6</td>
<td>0.70±0.15</td>
<td>2.28±0.47</td>
<td>0.30±0.02</td>
<td>18.2±3.7</td>
<td>1.65±0.52</td>
<td>2.87±0.05</td>
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<td></td>
<td>During</td>
<td>0.61±0.15</td>
<td>2.07±0.57</td>
<td>0.29±0.02</td>
<td>23.4±5.9</td>
<td>2.38±0.76</td>
<td>2.83±0.72</td>
</tr>
<tr>
<td>Verapamil (n=9)</td>
<td>9</td>
<td>0.43±0.04</td>
<td>1.54±0.22</td>
<td>0.29±0.01</td>
<td>18.8±5.6</td>
<td>1.50±0.73</td>
<td>1.64±0.18</td>
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<tr>
<td></td>
<td>During</td>
<td>0.41±0.06</td>
<td>1.39±0.20</td>
<td>0.31±0.03</td>
<td>23.5±3.6</td>
<td>2.00±0.49</td>
<td>1.85±0.18</td>
</tr>
<tr>
<td>Diltiazem (n=8)</td>
<td>8</td>
<td>0.47±0.06</td>
<td>1.66±0.06</td>
<td>0.29±0.02</td>
<td>17.2±3.0</td>
<td>1.00±0.31</td>
<td>1.85±0.22</td>
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<tr>
<td></td>
<td>During</td>
<td>0.35±0.07*</td>
<td>1.27±0.21*</td>
<td>0.28±0.02</td>
<td>15.2±2.1</td>
<td>1.10±0.19</td>
<td>1.43±0.30</td>
</tr>
</tbody>
</table>

Values are given as mean±SEM. There were no significant differences among groups during either period. GFR, glomerular filtration rate; RPF, renal plasma flow rate; WKFF, whole kidney filtration fraction; UV, urine volume; U_{nit}V, urinary sodium excretion; U_{pot}V, urinary potassium excretion.

*p<0.05 versus before.

Results

General Parameters

Values for body weight, U_{prot}V, and plasma sodium and potassium levels in the three groups of rats are given in Table 1. Values for body weight were comparable among all groups. All groups exhibited values for awake systolic pressure (not shown) and U_{prot}V that were typical of those in rats with 5/6 nephrectomy{sup}5 and markedly elevated compared with those measured in normal rats from our laboratory.{sup}8,10 There were no significant differences in any of these parameters among the groups.

Systemic and Whole Kidney Parameters

Values for whole kidney function during the baseline and experimental periods are summarized in Table 2, and individual values for AP and single nephron are depicted in Figures 1 and 2. All groups exhibited severe systemic hypertension in the baseline period. Values for AP remained elevated in the vehicle-infused time control animals but by design were equally reduced to the normal range by both verapamil and diltiazem (Figure 1). As in previous studies in this experimental model{sup}5 all groups exhibited elevation of the single nephron GFR, reduced...
values for the whole kidney GFR and RPF, increased urinary flow rates, and enhanced \( U_{\text{Na}} V \) and \( U_{\text{K}} V \) during the baseline period compared with values in normal rats.8,10

During the experimental period, infusion of saline vehicle had no significant effect on any parameter measured. Acute normalization of AP with verapamil did not significantly affect the single nephron GFR or any whole kidney parameter; as depicted in Figure 2, effects on single nephron GFR were somewhat variable, but overall single nephron GFR changes were not statistically significant. Comparable AP reduction with diltiazem, however, resulted in significant reductions in the single nephron GFR, which decreased in all except two animals, and in the whole remnant kidney GFR and RPF compared with values in the same animals before the drug infusion. Proportional reductions in GFR and RPF led to relative constancy of the whole kidney filtration fraction. Although reduced compared with baseline values in the same animals, values obtained during the diltiazem infu-
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**Microcirculatory Parameters in Experimental Period**

Mean values for single nephron GFR and the pressures, flows, and resistances governing glomerular ultrafiltration in the three groups during the experimental period are summarized in Table 3 and Figure 3. All groups demonstrated equal single nephron hyperfiltration and hyperperfusion and equal values for the single nephron filtration fraction. In the rats receiving saline vehicle, single nephron hyperfiltration resulted from both glomerular capillary hyperperfusion and glomerular capillary hypertension, with values for both \( P_{GC} \) and \( \Delta P \) far exceeding the normal ranges. \(^8,10\) Reductions in both \( R_A \) and afferent arteriolar resistance (\( R_e \)) contributed to the increase in the glomerular capillary plasma flow rate (\( Q_A \)); a proportionately greater decrement in \( R_A \), together with the elevated values for \( \Delta P \), allowed the development of glomerular capillary hypertension. These animals also exhibited values for \( K_f \) that were somewhat lower than those observed in normal animals. \(^8,10\)

Despite the substantial reduction in \( \Delta P \) with verapamil and diltiazem, both single nephron GFR and \( Q_A \) were maintained at supranormal levels. Of note, control of systemic hypertension was associated with control of glomerular capillary hypertension, so values for \( P_{GC} \) and \( \Delta P \) were reduced to the normal ranges by each calcium antagonist. There were no apparent differences in values for \( R_A \) or \( R_e \) among the three groups, suggesting that the reduction in \( P_{GC} \) resulted primarily from the reduction in \( \Delta P \). Values for hematocrit, proximal tubular and efferent arteriolar pressures, and plasma and efferent arteriolar protein concentrations and colloid osmotic pressures did not differ among the groups. In concert with the normalization of \( P_{GC} \) values for \( K_f \), in animals receiving calcium antagonists were maintained in the normal range and significantly exceeded those in the untreated hypertensive rats. In no parameter did measurements significantly differ between verapamil and diltiazem.

**Discussion**

Systemic hypertension was readily controlled by acute intravenous calcium antagonist infusion in this model. Normalization of \( \Delta P \) with verapamil was achieved with doses lower than those previously used\(^{20,21} \) and was also demonstrated with diltiazem. The clinical efficacy of chronic calcium antagonist administration in reducing blood pressure has been amply demonstrated,\(^3,11\) but their efficacy is less clear in rat models of hypertensive renal disease, with blood pressure control achieved in some studies\(^{21-27} \) but not in others.\(^{28,29}\) Whether these inconsistent findings relate, at least in part, to differences in dosage, route of administration, experimental model, or potency of the various calcium antagonists cannot be determined from current literature.

A substantial renal effect of calcium antagonists might not have been anticipated in this model characterized by renal vasodilation because the renal hemodynamic consequences of these agents are highly dependent on basal vascular tone and are most readily demonstrated in states of renal vasoconstriction.\(^1,20\) In a series of studies in the isolated perfused kidney, Louzenthiser and Epstein\(^1,30\) noted minimal effects of calcium antagonists in the baseline vasodilated state but a potent ability to attenuate or reverse the increase in vascular resistance induced by various vasoconstrictor stimuli. In normal rats, infusion of verapamil in a nonhypotensive dose does not appreciably influence glomerular hemodynamics,\(^31\) and a modestly hypotensive verapamil dose minimally increases single nephron GFR, proportionately slightly reduces \( R_A \) and \( R_e \), and does not affect \( P_{GC} \).\(^32\) However, the vasodilatory actions of verapamil in vivo are dramati-
cally unmasked when the kidney is preconstricted with renal nerve stimulation31 or angiotensin II (Ang II).32 In this setting, an enhanced hypertensive response to verapamil is associated with reversal of the Ang II–induced glomerular hypertension and hypoperfusion; arteriolar resistances again decrease proportionately but more profoundly.32 Results of the present study add to the recently emerging evidence that calcium antagonists may exert important effects on glomerular hemodynamics in the vasodilated kidney in vivo and may confirm the observation that renal responsiveness to these agents is enhanced in the presence of systemic hypertension.30 In the present acute study, calcium antagonists did not markedly influence the reduced arteriolar resistances but, through a large decrease in blood pressure, were able to normalize $P_{\text{OC}}$. Renal filtration and perfusion were not compromised by verapamil despite the large decrease in AP, although single nephron GFR decreased slightly with diltiazem.

Few studies of the glomerular hemodynamic effects of calcium antagonists in experimental hypertensive renal disease are available. In the partially nephrectomized rat, the present study confirms the findings of Yoshioka et al30 regarding verapamil, whereas both of these studies are at odds with results of the preliminary report by Brunner et al31 using the same model. In the former study,20 infusion of relatively high doses of verapamil resulted in normalization of AP and $P_{\text{OC}}$ and a reduction in proteinuria, with little change in single nephron GFR or $Q_{\text{A}}$; arteriolar resistances were fairly proportionately reduced. In contrast, Brunner and co-workers,21 using intermediate verapamil doses, found a significant although lesser decrease in AP, which was associated with a decrease in GFR and an increase in $P_{\text{OC}}$ and proteinuria. These inconsistencies are not readily explained. Calcium antagonists may acutely normalize $P_{\text{OC}}$ when AP is fully controlled to the normal range yet yield intermediate or poor control of glomerular hypertension when given in doses that do not completely control blood pressure. Failure to limit $P_{\text{OC}}$ might also be more apparent in the absence of a reduction in $R_{\text{E}}$, as discussed below. In addition to confirming one previous report with verapamil,20 the present study provides novel evidence of an equal reduction in $P_{\text{OC}}$ and increase in $K_{f}$ with diltiazem.

Even less information is available regarding the glomerular hemodynamic consequences of chronic calcium antagonist administration. In the partially nephrectomized rat, chronic administration of verapamil in nonhypotensive doses resulted in relatively unchanged values for single nephron GFR, $Q_{\text{A}}$, and $P_{\text{OC}}$; arteriolar resistances were only minimally affected, with $R_{\text{E}}$ lowered slightly more than $R_{\text{A}}$33. Again, these observations might suggest that the ability to normalize $P_{\text{OC}}$ is more readily obtainable when blood pressure is decreased to the normal level.

Although some antihypertensive regimens appear to induce consistent hemodynamic changes in diverse experimental models, other antihypertensive regimens are more variable. For example, converting enzyme inhibitors almost always reduce AP and $P_{\text{OC}}$.57–10,34 In contrast, the combination of reserpine, hydralazine, and hydrochlorothiazide normalizes AP in numerous models, but concurrent reduction in $P_{\text{OC}}$ does not always ensue.5–9 Calcium antagonists may prove equally variable because normalization of AP with chronic nifedipine administration normalizes $P_{\text{OC}}$ in uninephrectomized spontaneously hypertensive rats24 but fails to do so in rats with mineralocorticoid-salt hypertension.22

The capacity for renal autoregulation is clearly impaired in this model,35–37 and this defect certainly contributes to the intraglomerular hemodynamic consequences of antihypertensive therapy. The failure of calcium antagonists to acutely reduce $R_{\text{A}}$, despite a large decrease in AP, may relate more to this impairment of autoregulation than to any specific action of these drugs because a similar failure of $R_{\text{A}}$ to decrease with acute converting enzyme inhibitor administration has been reported in this model.34 In normal rats, the autoregulatory response to a decrease in renal perfusion pressure also involves an increase in $R_{\text{E}}$, although only at the lowest perfusion pressures. Failure of $R_{\text{E}}$ to change in the present study could also reflect impaired autoregulation or concomitant interference with endogenous efferent arteriolar vasoconstrictors such as Ang II.

It is interesting that despite the conflicting evidence regarding calcium antagonists and $P_{\text{OC}}$, a point of commonality is the virtually uniform finding that calcium antagonists increase values for $K_{f}$, as shown in References 20, 32, and 33 and the present study. An increase in $K_{f}$ would preserve or increase single nephron GFR, thereby partially offsetting the reduction in $P_{\text{OC}}$. The mechanism by which calcium antagonists increase $K_{f}$ are unknown, although interference with Ang II action and/or interaction with a mesangial site are possibilities.

Given the excellent ability of many antihypertensive agents to control blood pressure, investigative attention has focused in recent years on potential specific actions to prevent target organ damage. Experimental and preliminary clinical studies suggest that not all antihypertensive regimens may afford equal renal protection and that agents that control glomerular hypertension may provide maximal protection to the kidney at risk for progressive glomerular injury. The reported long-term renal morphological sequelae of calcium antagonist administration are no more common than are the hemodynamic studies. It has been reported that verapamil in nonhypotensive doses affords protection,38 whereas others have found hypertensive doses ineffective in reducing proteinuria and glomerular injury.25,29 Nifedipine and other dihydropyridine derivatives have been more successful in affording structural protection,22–24,27 although not consistently,25 and diltiazem and its analogues have not proven to be particularly effective.28,39

Variability in dosage, route of administration, degree of blood pressure reduction, and pathophysiology of the various disease models may all contribute to these...
disparate findings. In addition, both hemodynamic and nonhemodynamic mechanisms may operate differentially in various models. Reduction of $P_{GC}$ is one mechanism by which protection is generally afforded. However, calcium antagonists have been postulated to afford protection by nonhemodynamic mechanisms as well, including diminution of calcium deposition in the kidney, decreased oxygen consumption and presumably decreased oxygen radical generation, and limitation of glomerular hypertension and glomerular capillary wall tension. Failure to afford protection may relate to inability to normalize glomerular capillary hypertension or lack of contribution of these other deleterious pathogenetic mechanisms. Further studies are needed to clarify the mechanisms by which these agents might afford protection and to determine their efficacy in slowing the progression of clinical renal disease.

In summary, in hypertensive partially nephrectomized rats, acute normalization of $AP$ with either verapamil or diltiazem resulted in normalization of $P_{GC}$ and an increase in $K_t$. In this vasodilated model, the reduction in $P_{GC}$ appeared to result primarily from the reduction in perfusion pressure because arteriolar resistances were not disproportionately affected. Whether these acute changes will be consistently maintained with chronic therapy and whether these agents will prove effective in preventing experimental and clinical renal disease await further study.

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References


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