Effects of Systemic Hypertension, Antidiuretic Hormone, and Prostaglandins on Remnant Nephrons

Rachel Bregman, Mirian A. Boim, Oscar F.P. Santos, Oswaldo L. Ramos, and Nestor Schor

Renal function was evaluated in normal and after 30 days of % renal mass reduction (CRF) in Munich-Wistar (MW) rats, spontaneously hypertensive rats with superficial glomeruli (EPM), and in Brattleboro rats with congenital diabetes insipidus (DI). Mean arterial pressure was higher in EPM-Control and EPM-CRF rats as compared with MW and DI rats. MW and EPM rats with CRF showed increases of 120% and 196%, respectively, in single nephron glomerular filtration rate as compared with their controls. However, DI rats with CRF did not show any increase in single nephron glomerular filtration rate as compared with the control group. Therefore, the data suggest that the presence of hypertension enhances the adaptive mechanisms on remnant kidney’s function. Conversely, in the absence of antidiuretic hormone, adaptive mechanisms of remnant nephrons did not occur. In addition, it was observed that rats with CRF submitted to prostaglandin blockade with indomethacin showed for MW rats a 55% and 20% reduction in ultrafiltration coefficient and in single nephron glomerular filtration rate, respectively. Decreases of 60% and 30% in ultrafiltration coefficient and single nephron glomerular filtration rate, respectively, were observed for EPM rats. In contrast, DI rats did not show any alteration in renal function after indomethacin. It seems, therefore, that prostaglandins play a role in remnant nephron function of MW and EPM rats, but in the absence of antidiuretic hormone, prostaglandins do not affect remnant glomerular hemodynamics. (Hypertension 1990;15(suppl I):I-72–I-75)

Systemic hypertension can cause glomerular sclerosis by directly transmitting an elevated arterial pressure to the glomeruli. It has also been proposed that vasodilation and hyperfiltration of remnant nephrons are mediated by hormonal factors such as prostaglandins (PGs). Antidiuretic hormone (ADH) has been proposed to have a kidney trophic action, and homozygous Brattleboro rats (DI), which lack ADH, do not show hyperfiltration after being fed a hyperprotein diet, as is observed in other strains of rats. Thus, the objectives of the present study were to evaluate the remnant kidney’s function in hypertensive states and the role of ADH and PGs in this model by using spontaneously hypertensive rats with superficial glomeruli (EPM rats), DI rats, and indomethacin administration.

From the Nephrology Division, Escola Paulista de Medicina, São Paulo, SP, Brazil.

Address for correspondence: Nestor Schor, MD, PhD, Associate Professor of Medicine, Nephrology Division, Escola Paulista de Medicina, Rua Botucatu 740, 04023, São Paulo, SP, Brazil.

Methods

Studies were performed in Munich-Wistar (MW) rats (Simonsen Laboratories, Gilroy, California), EPM rats, and DI rats. EPM rats are the first generation of spontaneously hypertensive rats (SHR) (National Institutes of Health [NIH], Bethesda, Maryland) mated with MW rats and, thus, present spontaneous hypertension and superficial glomeruli. DI rats (NIH) have hereditary hypothalamic diabetes insipidus. All studies were performed in 3–4-month-old male rats, and they were all bred in the Animal House of Escola Paulista de Medicina. Each of the three strains of rats were divided into a control group and a group submitted to % renal mass ablation (chronic renal failure [CRF]), which was studied 30 days after. The subtotal ¾ nephrectomy was performed by ligation of two or three branches of the left renal artery and right nephrectomy at the same time. All rats were allowed free access to regular rat chow and tap water until the morning of the study. Inactin (Byk, Gulden, Konstanz, Germany) anesthetic was used, and replacement of surgical volume losses was
performed as previously described.\(^1\) In DI rats during the experimental periods, a continuous intravenous infusion of normal saline was given at a mean rate of 4 ml/100 g body wt/hr to replace surgical and urinary losses.

**Whole Kidney Function**

The glomerular filtration rate (GFR) and renal plasma flow (RPF) were estimated by means of inulin\(^6\) and para-aminohippurate (PAH) clearances.\(^7\)

**Glomerular Hemodynamics**

MW, EPM, and DI rats were prepared for micropuncture studies.\(^8\) After an equilibration period, samples of fluid were collected from surface proximal tubule convolutions of at least three nephrons for single nephron GFR (SNNGFR) determination.\(^9\) Other hemodynamic measurements were not evaluated in DI rats because they do not have superficial glomeruli. Hydraulic pressures were measured in surface glomerular capillaries (PQC), proximal tubules (PT), peritubular capillaries (PC), and efferent arterioles (PEA) using a Servo Nulling Pressure System (model 4A, IPM, San Diego, California). Blood microsamples from superficial efferent arterioles were obtained and were analyzed for total protein concentration (C\(_T\)).\(^10\) Protein concentration in femoral arterial plasma was taken as representative of preglomerular protein concentration (C\(_A\)).\(^10\) These estimations of preglomerular and postglomerular plasma protein concentration permitted calculation of single-nephron filtration fraction (SNFF) and initial glomerular capillary plasma flow rate (Q\(_A\)). SNFF and Q\(_A\), as resistance per single afferent and efferent arteriole (R\(_A\) and R\(_E\)), and the glomerular ultrafiltration coefficient (K\(_t\)) were calculated using equations given elsewhere.\(^9\)

After the first period study of clearances and micropunctures, indomethacin (Merck Sharp & Dohme, St. Louis, Missouri) was administered in a dose of 2 mg/kg body wt i.v. in bolus; and then after a new equilibration period of 45 minutes, a second period study was performed.

Data were analyzed by Student’s unpaired and paired two-tailed \(t\) test. Statistical significance was accorded for \(p\) values of less than 0.05; all data were reported as mean±SEM. **Results**

Table 1 shows values for all groups studied. Mean arterial pressure (MAP) in control groups was higher in EPM rats, and after 30 days of CRF, MAP increased in both MW and EPM rats. DI-CRF rats did not show hypertension as compared with DI-Control rats (Table 1). GFR, as well as RPF, decreased in MW-CRF and DI-CRF rats as compared with their controls. No decreases in these parameters were observed, however, for the EPM-CRF group. SNNGFR increased in MW-CRF and EPM-CRF rats as compared with their controls, whereas DI-CRF rats showed a slight increase that did not, however, reach statistical significance. In MW and EPM rats, glomerular hemodynamic studies were performed, and it was observed that Q\(_A\) increased in CRF groups. These increases occurred because of a decrease in R\(_A\) in MW rats from 2.70±0.28 to 1.82±0.31 \(10^9\) dyn-sec-cm\(^{-5}\) (\(p<0.05\)), and in EPM rats from 2.57±0.33 to 1.32±0.24 \(10^9\) dyn-sec-cm\(^{-5}\) (\(p<0.05\)). R\(_A\) did not change in MW-CRF rats, 1.23±0.22 vs. 1.72±0.14 \(10^9\) dyn-sec-cm\(^{-5}\) (\(p>0.05\)). R\(_A\) did not change in EPM-CRF rats as compared with EPM-Control rats (0.58±0.16 vs. 1.41±0.18 \(10^9\) dyn-sec-cm\(^{-5}\), \(p<0.05\)). Total arteriolar resistance (R\(_T\)) decreased in MW and EPM-CRF rats (Table 1). Mean glomerular capillary hydraulic pressure (P\(_{oc}\)) increased, comparing MW-CRF with MW-Control rats (48±3 vs. 45±1 mm Hg), but in EPM rats, a decrease in

### Table 1. Data For Munich-Wistar Rats, Spontaneously Hypertensive Rats With Superficial Glomeruli, and Diabetes Insipidus Brattleboro Rats During Control and With Chronic Renal Failure

<table>
<thead>
<tr>
<th></th>
<th>MAP (mm Hg)</th>
<th>GFR (ml/min)</th>
<th>RPF (ml/min)</th>
<th>SNNGFR (nl/min)</th>
<th>QA (nl/min)</th>
<th>P(_{oc}) (mm Hg)</th>
<th>R(_T) (10(^9) dyn-sec-cm(^{-5}))</th>
<th>K(_t) (nl/sec-mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MW-C</td>
<td>129±3</td>
<td>1.08</td>
<td>3.33</td>
<td>33.8</td>
<td>101±7</td>
<td>45±2</td>
<td>4.42±0.072</td>
<td>0.072±0.007</td>
</tr>
<tr>
<td>n=15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MW-CRF</td>
<td>146±6</td>
<td>0.66†</td>
<td>2.17†</td>
<td>73.9‡</td>
<td>200±17</td>
<td>48±3</td>
<td>3.05±0.131</td>
<td>0.131±0.030</td>
</tr>
<tr>
<td>n=7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPM-C</td>
<td>150±4</td>
<td>0.91</td>
<td>3.13</td>
<td>38.3</td>
<td>139±17</td>
<td>50±3</td>
<td>3.98±0.059</td>
<td>0.059±0.010</td>
</tr>
<tr>
<td>n=7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EPM-CRF</td>
<td>161±7</td>
<td>0.95</td>
<td>3.72</td>
<td>113.2‡</td>
<td>423‡</td>
<td>46±2</td>
<td>1.90‡±0.399‡</td>
<td>0.399±0.122</td>
</tr>
<tr>
<td>n=6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DI-C</td>
<td>133‡</td>
<td>0.81</td>
<td>2.44</td>
<td>26.6</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>n=6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DI-CRF</td>
<td>136±4</td>
<td>0.31§</td>
<td>1.33§</td>
<td>36.1</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>n=9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Values are mean±SEM. † vs. MW-C; ‡ vs. EPM-C; § vs. DI-C.

MAP, mean arterial pressure; GFR, glomerular filtration rate; RPF, renal plasma flow; SNNGFR, single nephron GFR; QA, initial glomerular capillary plasma flow rate; P\(_{oc}\), pressure measured in surface glomerular capillaries; R\(_T\), total arteriolar resistance; K\(_t\), glomerular ultrafiltration coefficient; MW, Munich-Wistar group; C, control group; CRF, group submitted to chronic renal failure; EPM, spontaneously hypertensive group with superficial glomeruli; DI, diabetes insipidus Brattleboro group; ND, not determined.
Discussion

The present study evaluated the adaptive mechanisms of remnant nephron in three different strains of rats. MW rats submitted to renal mass ablation showed basically a reduced $R_A$ that led to an increase in $Q_A$ and SNGFR, characterizing hyperfiltration of the remnant nephron due to intrarenal vasodilation. $P_{GC}$ showed a numerical increase in MW-CRF as compared with MW-Control rats. In recent years, measurements of glomerular dynamics in different experimental models of hypertension have proposed that glomerular hyperfunction is responsible for renal damage due to hypertension. EPM rats used in the present study as a model of congenital hypertension showed values for MAP and $P_{GC}$ higher than those found for MW-Control rats, thus presenting the same hemodynamic pattern found in other experimental models of hypertension, that is, increased MAP being transmitted to the glomerulus. Some workers have shown that in models of hypertension in which the number of functioning nephrons is reduced, adaptive changes in renal vascular resistance permit an increase in glomerular plasma flow and higher transmission of systemic pressure to the glomeruli due to a failure of afferent arterioles to constrict. SHR present vasoconstriction of superficial nephrons and, thus, show protection of the glomerulus from systemic hypertension. When submitted to unilateral nephrectomy, however, SHR show adaptive mechanisms that lead to glomerular hyperperfusion and hypertension (although data for glomerular hypertension were obtained through indirect measurements). In the present study, EPM hypertensive rats submitted to extensive renal mass ablation showed an exacerbated adaptive mechanism of the remnant nephron's function. An important intrarenal vasodilation was observed, which in turn led to increases in $Q_A$ and SNGFR. Thus, it seems that association of congenital hypertension with extensive reduction of renal mass implies exacerbated adaptive responses of the remnant nephrons.

This hypothesis is further supported by the finding of normal levels for GFR and RPF in EPM-CRF rats despite the $50\%$ reduction of renal mass. In general, elevation of $P_{GC}$ has been identified in hypertensive rats submitted to unilateral nephrectomy. EPM-CRF rats did not show elevation in $P_{GC}$. This finding could be because of the greater reduction of renal mass performed in these rats ($50\%$), which in turn led to important and proportional reductions in $R_A$ and $R_E$. Other workers did not find elevation in $P_{GC}$ in hypertensive rats submitted to unilateral nephrectomy. Additionally, $K_t$ increased in these rats, and this phenomenon also contributed to the increase in SNGFR. The $K_t$ is the product of the surface area available for filtration, $S$, and the hydraulic permeability of the glomerular capillary wall, $k$. It was observed that $S$ increases after nephrectomy. The exact mechanism whereby $K_t$ increased was not determined by this study; however, it is possible to suggest that because an impressive intrarenal vasodilation was shown in these rats, relaxation of mesangial cells could also have occurred.

Meyer et
all \(^1\) observed that blocking the renin-angiotensin system in rats with \(\frac{1}{3}\) renal mass reduction increased \(K_t\). Additionally, it is known that mesangial cell proliferation takes place in models of renal mass ablation,\(^3\) and thus, these two phenomena could account for the important increase in mean \(K_t\) in this strain of rats, after extensive reduction of renal mass. Data for DI-CRF rats as compared with DI-Control rats showed a decrease of renal function characterized by GFR and RPF reductions and maintenance of SNGFR. Internephron heterogeneity, a characteristic of mammalian kidneys, is absent in DI rats;\(^4\) however, reduced filtration rate for juxtamedullary nephrons and chronic infusion of ADH induces nephron heterogeneity in these rats.\(^1\) Medullary thick ascending limb of Henle's loop (mTAL) is poorly developed in DI rats and becomes hypertrophied after long-term ADH exposure.\(^1\) The reabsorption process of deep nephrons in DI rats could be inadequate, and consequently, the feedback signal could be activated and depress SNGFR.\(^1\) Thus, this atrophy of the mTAL could be at least in part responsible for the absence of an increase in SNGFR in DI-CRF rats.

Administration of indomethacin to MW-CRF and EPM-CRF rats showed a decrease in SNGFR in both groups, suggesting that PGs play a role in the vasodilation observed in the remnant nephrons of these animals and, thus, participate in the hyperfiltration mechanism as was also observed by Nath et al.\(^1\) in Sprague-Dawley rats. In contrast, DI rats with CRF did not show any alteration of the remnant kidney after indomethacin administration. It is suggested that DI rats present reduced in vivo synthesis of PGE\(_2\) and PGF\(_{2\alpha}\).\(^6\) Thus, probably the absence of hyperfiltration in remnant nephrons in DI rats was due to the lack of ADH, a diminished synthesis of PGs, or both. The present data suggest that reduction of renal mass associated with systemic hypertension enhances the adaptive mechanisms of the remnant nephron due to intrarenal vasodilation and an increase in \(K_t\) that, ultimately, causes hyperfiltration. Conversely, the absence of ADH blunts the remnant nephron hyperfiltration. Additionally, PGs play a role in the maintenance of the adaptive mechanisms that occur in remnant kidney. In the absence of ADH, however, the PGs do not exert an important role on the maintenance of remnant nephron function.

References


Key Words: indomethacin • glomerular function • chronic renal failure • Brattleboro rat • spontaneously hypertensive rats
Effects of systemic hypertension, antidiuretic hormone, and prostaglandins on remnant nephrons.
R Bregman, M A Boim, O F Santos, O L Ramos and N Schor

Hypertension. 1990;15:I72
doi: 10.1161/01.HYP.15.2_Suppl.I72
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1990 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/15/2_Suppl/I72

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/