Elevated Plasma Catecholamines in Hypertensives with Primary Glomerular Diseases

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SUMMARY Supine plasma concentration of norepinephrine (PNE), epinephrine (PE), and aldosterone (PA), plasma renin activity (PRA), and blood volume (BV) were measured in 25 normotensive and 11 hypertensive patients with biopsy-proven glomerulonephritis who had serum creatinine concentrations of less than 1.6 mg/dl, and in 20 normotensive control subjects. PNE and PE were measured according to the trihydroxyindol method using high pressure liquid chromatography. Renal clearances of p-aminohippurate (CPAH) and endogenous creatinine (Ccr) were also determined. Age, BV, and 24-hour urinary excretion of sodium were not significantly different in the three groups. Although all the measured variables were comparable between the control subjects and the normotensive nephritic patients, blood pressure, PNE, PE, PRA, and PA were significantly higher and CPAH and Ccr were significantly lower in the hypertensive nephritic patients than in the normotensive nephritic patients or the control subjects. In the pooled nephritic patients, mean blood pressure was significantly correlated with PNE (r = 0.76, p < 0.001), PE (r = 0.34, p < 0.05), PRA (r = 0.33, p < 0.05), PA (r = 0.40, p < 0.05) and CPAH (r = -0.51, p < 0.01). Highly significant positive correlation was also observed between PNE and systolic pressure (r = 0.63, p < 0.001) or diastolic blood pressure (r = 0.78, p < 0.001). The results suggest that deterioration of renal function is an important factor in the development of hypertension even in non-azotemic patients with glomerulonephritis, and that increased activities of the sympathetic nervous system and the renin-aldosterone system participate, in part, in elevating blood pressure in the hypertensive nephritic patients. Mechanisms involved in the elevation of plasma concentrations of catecholamines and renal effects on the plasma catecholamines remain to be elucidated. (Hypertension 5: 545-551, 1983)

Key Words • plasma renin activity • plasma aldosterone • hypertension • glomerulonephritis

Hypertension associated with primary glomerular disease is the most common form of secondary hypertension. For example, it has been suggested that there is relative suppression of the renin-angiotensin-aldosterone system in patients with diabetic glomerulosclerosis and that the prevalence of hypertension is higher in the latter than the former group. Also, it has been reported that plasma renin activity (PRA) is reduced in hypertensive patients with diabetic glomerulosclerosis. Thus, it is desirable to study the hypertension associated with renal parenchymal diseases in a homogenous population. For example, it has been suggested that there is relative suppression of the renin-angiotensin-aldosterone system in patients with tubular or interstitial disorders as compared to those with primary glomerular disease, and that the prevalence of hypertension is higher in the latter than the former group. Also, it has been reported that plasma renin activity (PRA) is reduced in hypertensive patients with diabetic glomerulosclerosis. Thus, it is desirable to study the hypertension associated with renal parenchymal diseases in a homogenous population. Studies of the mechanisms of hypertension in the early stages of chronic renal parenchymal diseases have mostly been focused on the roles of renin or body fluid volume and on the relationship between body fluid volume and renin system. Only a few studies have been reported in regard to changes in plasma concentration of catecholamines in the early stages of primary glomerular diseases.
We undertook the present study to delineate the characteristics and mechanisms of hypertension associated with early stages of primary glomerular diseases. Plasma concentrations of catecholamines, aldosterone, and PRA were measured in patients with biopsy-proven glomerulonephritis, and the relationship of these variables to blood pressure and renal function was examined.

Subjects and Methods

We studied 36 hospitalized patients with biopsy-proven primary glomerular diseases, who represented all the patients, ranging in age from 25 to 51 years, who underwent evaluation by renin-aldosterone profiles, plasma catecholamines, and renal biopsy at our institution during the period from January, 1980, to March, 1982, and whose serum creatinine concentration was less than 1.6 mg/dl. Patients whose blood pressure before admission was consistently higher than 160 mm Hg systolic and/or 90 mm Hg diastolic without any antihypertensive agents were classified as hypertensive, and the others as normotensive. Eleven of the 36 patients were hypertensive and the other 25 were normotensive. Only one patient in the hypertensive group had eye ground changes of KW III. No patient had signs or symptoms of encephalopathy or congestive heart failure. Diagnosis was based on a histological examination of the renal biopsy specimen, but laboratory examinations including endocrine, immunological, and radiological studies were performed to exclude renal lesions due to systemic diseases. Family history of hypertension was also examined. If one or both parents were hypertensive, the family history was defined as positive for hypertension.

The normotensive control subjects were selected from patients who had been hospitalized because of a chance hematuria and diagnosed as having idiopathic recurrent hematuria on the basis of renal histological studies, and patients who had been hospitalized for health checks. No abnormalities in laboratory examinations including renal function and endocrine studies were found in any of the control subjects. Informed consent was obtained from all subjects.

All subjects were put on a diet containing 6 to 8 g of salt per day after hospitalization. The examinations were performed either on untreated patients or at least 2 weeks after withdrawal of any antihypertensive agents. On the day of examination, the subjects, who had fasted for 14 hours, were kept supine for 1 to 2 hours after awakening. Following measurements of blood pressure with a sphygmomanometer and of pulse rate, blood specimens were obtained from the cubital vein for determination of plasma concentrations of norepinephrine (PNE), epinephrine (PE), and aldosterone (PA). PRA, and serum concentrations of sodium, potassium, and creatinine. The blood specimens for PNE, PE, PRA, and PA were placed into tubes containing EDTA-Na2 (2 mg/ml), and immediately centrifuged at 3000 rpm for 20 minutes (4°C). The plasma samples were stored at -70°C until assay.

Following this, plasma volume was determined by the isotope dilution technique using radioiodinated (131I) human serum albumin (RISA). The plasma volume was obtained by dividing the total radioactivity by the plasma concentration of 131I at time zero which was attained by extrapolation of the concentrations 10, 20, and 30 minutes after injection of the RISA. Blood volume was calculated from plasma volume and hematocrit according to the following formula:

\[
\text{blood volume} = \frac{\text{plasma volume} \times 100}{100 - 0.91 \times \text{hematocrit}}
\]

Since blood volume per body weight (ml/kg) demonstrates a linear relationship with leanness index, which is a ratio of the cube of body height to body weight (m/ kg), blood volume was expressed in terms of percentage of the normal value obtained by comparing blood volume per body weight (ml/kg) with the expected normal value (ml/kg), which was assessed with the normogram of blood volume (ml/kg) against leanness index (m³/kg) in the normotensive control subjects pooled in our laboratory. Urine was collected for a prior 24-hour period to determine sodium excretion.

For several days thereafter, glomerular filtration rate and effective renal plasma flow were measured in 31 of the 36 patients with glomerulonephritis and 17 of the 20 control subjects under the same conditions as described above. Glomerular filtration rate was determined by measuring the renal clearance rate of endogenous creatinine (Ccr), and effective plasma flow by the clearance rate of p-aminohippurate (PAH) which was infused intravenously with a constant infusion pump. After a 30-minute run-in period, two 30-minute urine collections were performed. Plasma samples for PAH and creatinine concentrations were obtained midway through the collection period. Creatinine and PAH in plasma and urine were measured by Jaffe's reaction and Marchall's reaction, respectively. Renal blood flow (RBF) was calculated from C_PAH and hematocrit as follows:

\[
\text{RBF} = \frac{\text{C}_{\text{PAH}} \times 100}{100 - \text{hematocrit}}
\]

RBF, C_PAH, and Ccr were expressed in terms of milliliters per minute per body surface area (ml/min·m²).

PNE and PE were determined according to the modified method of Anton and Sayre,17 using high-pressure liquid chromatography. Briefly, 3 ml of plasma was added 0.2 ml of 0.4 N perchloric acid, and plasma protein was removed; then, plasma catecholamines were adsorbed on alumina. The adsorbed catecholamines were washed with 2 M tris-acetate buffer (pH 8.8) containing 2% of EDTA-NA2 and 1% of Na2SO3, and then with distilled water, after which they were eluted with about 4 ml of methanol. After being dried under vacuum, the eluted catecholamines were dissolved in 0.14 ml of 0.25 N acetic acid solution, and then applied to a high-pressure liquid chromatograph (Shimadzu LC-1) using a column of Zipax and 0.125 N NaH2PO4 solution as carrier. Reagents...
applied to the chromatograph to form and detect fluorescent trihydroxyindole derivatives were 0.5 M phosphate buffer solution containing 0.1% K$_3$Fe(CN)$_6$ and 0.1% citrate (pH 6.5), a solution containing 0.05% 1-ascorbic acid and 0.05% Na$_2$S$_2$O$_5$ (pH 3.5) and 5 N NaOH solution. The sensitivity for detection was 10 pg for norepinephrine and 12 pg for epinephrine. Coefficients of variation for norepinephrine were 5.0% for intraassay variation and 8.7% for interassay variation. Coefficients of variation for epinephrine were 6.0% for intraassay variation and 15.6% for interassay variation.

PRA was measured by the radioimmunoassay method of Sealey et al. after plasma samples, which had been processed according to the method of Kaneko et al., were incubated at 37°C for 6 hours. PA was determined with a nonchromatographic radioimmunoassay method. Serum sodium and potassium and urinary sodium were analyzed with an Instrument Laboratory flame photometer, and serum creatinine was determined with an automatic analyzer.

Within 1 week of the above studies, percutaneous needle biopsy was performed in all the patients with primary glomerular diseases and those with idiopathic recurrent hematuria. Renal tissue obtained by biopsy was processed for light microscopic, electronmicroscopic, and immunofluorescence studies. Histological diagnoses were classified according to the classification of Churg and Sobin.

Measured variables were expressed in mean ± SE. Group differences were assessed by Student’s $t$ test or $\chi^2$ method.

### Results

Table 1 shows the morphological forms of glomerulonephritis in the normotensive and the hypertensive nephritic patients. Many patients had mild morphological changes of the glomeruli. Mesangial deposition of immunoglobulin A was observed in 13 of the 20 normotensive patients and nine of the 11 hypertensive patients who had focal and segmental lesion or diffuse glomerulonephritis.

Table 2 shows the main clinical findings in all subjects. The blood pressure, heart rate, and serum con-
centrations of sodium, potassium, and creatinine are the values determined at the same time as the measurements of PNE, PE, PRA, and PA. There were no significant differences in age, body weight, body height, serum concentrations of creatinine, sodium, and potassium, blood volume, and 24-hour urinary excretion of sodium among the three groups. Although systolic, diastolic, and mean blood pressures, PRA, PA, PNE, and PE were comparable in the control subjects and the normotensive nephritic patients, these values were significantly higher in the hypertensive nephritic patients than in the other two groups. The mean heart rate of the hypertensive nephritic patients was significantly higher than that of the control subjects, but not different from that of the normotensive nephritic patients.

Family history of hypertension was positive in 10 (40%) of the 25 normotensive nephritic patients and in five (45%) of the 11 hypertensive nephritic patients (table 2). This was not significantly different ($\chi^2 = 0.038$).

RBF, $C_{PAH}$, Ccr, and filtration fraction were similar in the control subjects and the normotensive nephritic patients (table 3). RBF, $C_{PAH}$, and Ccr were lower by 27%, 30%, and 21%, respectively, in the hypertensive nephritic patients than in the normotensive patients (table 3). The differences of these variables between the hypertensive nephritic patients and the normotensive nephritic patients or the control subjects were significant (table 3).

When relationship between mean blood pressure and various parameters was examined in the pooled nephritic patients, there was a highly significant positive correlation between mean blood pressure and PNE (fig. 1, table 4). The same relationship still held between PNE and systolic blood pressure or diastolic blood pressure (table 5). Furthermore, mean blood pressure was significantly positively correlated with PRA, PA, PE, and filtration fraction, and significantly negatively correlated with $C_{PAH}$ (table 4). There was a significant positive correlation between PRA and PA ($r = 0.57, p < 0.001$). There was no definite relationship between mean blood pressure and age, Ccr, or blood volume (table 4).

Relationship between PNE or PE and various parameters was also examined in the nephritic patients. There was a significant negative correlation between PNE and $C_{PAH}$ (table 5). No significant relationship was observed between PNE and age, pulse pressure, heart rate, PRA, Ccr, filtration fraction, and blood volume (table 5). PE was correlated with PNE (table 5). There was rough, but significant, positive correlation between PE and systolic blood pressure or pulse pressure (table 5). PE had no definite relationship with age, diastolic blood pressure, heart rate, PRA, $C_{PAH}$, Ccr, or blood volume (table 5).

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**Table 3. Renal Function in Control Subjects, Normotensive, and Hypertensive Nephritic Patients**

<table>
<thead>
<tr>
<th></th>
<th>Control subjects (n = 16)</th>
<th>Normotensive patients (n = 21)</th>
<th>Hypertensive patients (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal blood flow (ml/min/m²)</td>
<td>483.9 ± 33.8</td>
<td>478.4 ± 30.9</td>
<td>349.0 ± 29.8*</td>
</tr>
<tr>
<td>CPAH (ml/min/m²)</td>
<td>286.4 ± 18.1</td>
<td>282.8 ± 15.1</td>
<td>198.2 ± 14.7*</td>
</tr>
<tr>
<td>Ccr (ml/min/m²)</td>
<td>74.6 ± 4.8</td>
<td>68.9 ± 4.1</td>
<td>54.1 ± 4.2†</td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>0.260 ± 0.040</td>
<td>0.247 ± 0.010</td>
<td>0.274 ± 0.010</td>
</tr>
</tbody>
</table>

*$p < 0.01$ and $t p < 0.05$ vs the control subjects and the normotensive nephritic patients.

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**Table 4. Correlation Coefficients Between Mean Blood Pressure and Various Parameters in the Pooled Nephritic Patients**

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>t value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.15</td>
<td>0.702</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>0.33</td>
<td>2.046†</td>
</tr>
<tr>
<td>Plasma aldosterone concentration</td>
<td>0.40</td>
<td>2.319†</td>
</tr>
<tr>
<td>Plasma norepinephrine</td>
<td>0.76</td>
<td>6.898*</td>
</tr>
<tr>
<td>Plasma epinephrine</td>
<td>0.34</td>
<td>2.047†</td>
</tr>
<tr>
<td>CPAH</td>
<td>-0.51</td>
<td>-3.279†</td>
</tr>
<tr>
<td>Ccr</td>
<td>-0.27</td>
<td>-1.540</td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>0.39</td>
<td>2.309‡</td>
</tr>
<tr>
<td>Blood volume§</td>
<td>-0.16</td>
<td>-0.685‡</td>
</tr>
</tbody>
</table>

* $p < 0.001$, † $p < 0.01$, and ‡ $p < 0.05$.

§ Blood volume is expressed in terms of percentage of normal value.

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**Table 5. Correlation Coefficients between Plasma Concentration of Norepinephrine or Epinephrine and Various Parameters in the Pooled Nephritic Patients**

<table>
<thead>
<tr>
<th></th>
<th>Norepinephrine</th>
<th>Epinephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>t</td>
</tr>
<tr>
<td>Age</td>
<td>0.03</td>
<td>0.191</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.63</td>
<td>4.774*</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.78</td>
<td>7.311*</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>-0.06</td>
<td>-0.332</td>
</tr>
<tr>
<td>Heart rate</td>
<td>0.29</td>
<td>1.698</td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>0.19</td>
<td>1.119</td>
</tr>
<tr>
<td>Plasma epinephrine</td>
<td>0.34</td>
<td>2.047†</td>
</tr>
<tr>
<td>CPAH</td>
<td>-0.36</td>
<td>-2.095†</td>
</tr>
<tr>
<td>Ccr</td>
<td>-0.18</td>
<td>-0.978</td>
</tr>
<tr>
<td>Blood volume</td>
<td>-0.12</td>
<td>-0.496</td>
</tr>
</tbody>
</table>

* $p < 0.001$ and $t p < 0.05$. 

---
These patients with mild-to-moderate renal impair-
tions of creatinine, sodium, and potassium, and blood
tion, even mild or moderate, is an important factor in
comparable in the normotensive nephritic patients and
patients, and the normotensive control subjects with a
three groups, while blood pressure, PRA, PA, PNE,
clinical findings were compared among the normo-
tensive nephritic patients, and the hypertensive nephritic
patients, and the normotensive control subjects with a
similar intake of salt. All the measured variables were
comparable in the normotensive nephritic patients and
the control subjects. Age, body size, serum concentra-
tions of creatinine, sodium, and potassium, and blood
volume were not significantly different among the
three groups, while blood pressure, PRA, PA, PNE,
and PE were elevated in the hypertensive nephritic
patients as compared with the normotensive nephritic
patients and the control subjects. RBF, C_{PAH}, and Ccr
were significantly lower in the hypertensive nephritic
patients than in the patients of the other groups. These
results suggest, first, that deterioration of renal func-
tion, even mild or moderate, is an important factor in
the development of hypertension in patients with glo-
erulonephritis; second that increased activity of the
renin-aldosterone system is related to the hyperten-
sion. Also, it seems possible that increased activity of
the sympathetic nervous activity is another factor in-
volved in the elevation of blood pressure.
In the present study, PRA showed a significant posi-
tive correlation with mean blood pressure in the pooled
nephritic patients. Blood volume was slightly, but not
significantly, greater in the hypertensive nephritic pa-
tients than in the normotensive nephritic patients. Our
results as to the renin system seem to be consistent with
the hypothesis that a deranged relationship between
body sodium or volume state and PRA is important in
the development of hypertension even in patients with
early-stage renal parenchymal diseases.\textsuperscript{4,5,11} PA was
also increased in the hypertensive nephritic patients as
compared to the patients in the other groups, and was
significantly correlated with PRA and mean blood
pressure. Thus, it is suggested that the elevated PA is
also related to the hypertension, and that the interplay
between renin and aldosterone functions normally in
patients with early stage glomerulonephritis.

One of the most prominent findings in the present
study is that PNE and PE are definitely elevated in
hypertensive nephritic patients as compared to normo-
tensive nephritic patients and control subjects, and that
PNE has a highly significant positive correlation with
systolic, diastolic, and mean blood pressures. This is
similar to the findings reported by De Champlain et
al.\textsuperscript{23} and Louis et al.\textsuperscript{24} who have demonstrated that
PNE correlates with blood pressure in essential hyper-
tension. PE, which could be an indicator of sympathet-
ic nervous activity, also had a significant positive cor-
relation with systolic, mean, and pulse pressures. Unlike
PNE, subtle changes in PE lead to some cardio-
vascular manifestations.\textsuperscript{35} The significant correlation
observed between PE and pulse pressure supports the
accuracy of our measurement of PE. The hypertensive
nephritic patients demonstrated an increase in PRA as
well as in PNE and PE. Increased release of renin into
the circulation could be an indicator of an increase in
sympathetic activity.\textsuperscript{36} Thus, it seems likely that the
elevation of PNE and PE observed in the hypertensive
nephritic patients reflects an increase in sympatho-
adrenal activity. The increase in sympathoadrenal ac-
tivity seems to have been responsible, in part, for the
decrease in renal blood flow, since there was a signifi-
cant correlation between C_{PAH} and PNE.
There are only a few reports available that have
related plasma concentrations of catecholamines to
blood pressure in the early stage of chronic renal pa-
renchymal diseases.\textsuperscript{13,14} Skrabal et al.\textsuperscript{13} reported that
mean PNE and PE were not statistically different in
primary and secondary hypertension, being compar-
able to levels in normotensive controls. The reasons for
the differences between their results and ours, although
not clear, may be related to the differences in underly-
ing renal diseases and in degree of renal impairment.

The mechanisms involved in the presumed enhance-
ment of activity of the sympathetic nervous system in
hypertensive nephritic patients remain unclear. In the
present study, all the subjects were on mildly sodium-
restricted diets after hospitalization. The higher PNE
and PE in the hypertensive nephritic patients may have

\textbf{Discussion}

It is well known that hypertension has an important
prognostic implication in chronic renal parenchymal
diseases.\textsuperscript{3,5} Since it was considered desirable to study
hypertension associated with chronic renal parenchym-
al diseases in a homogenous population,\textsuperscript{4} patients
with biopsy-proven primary glomerular diseases
whose serum concentrations of creatinine were less
than 1.6 mg/dl were selected for the present study.
These patients with mild-to-moderate renal impair-
ment seem to be suitable subjects to examine the role
of sympathoadrenal function in the development of
hypertension in patients with primary glomerular dis-
eases, because these patients are generally not exposed
to metabolic influences resulting from terminal renal
failure.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Relationship between plasma concentration of
norepinephrine and mean blood pressure in the pooled nephrit-
ic patients. There is a highly significant positive correlation
between the two parameters.}
\end{figure}
simply reflected poor sodium conservation in these patients. However, this mechanism seems to be unlikely, because the degree of renal insufficiency in the hypertensive nephritic patients was minimal and the salt restriction was mild. In addition, blood volume was slightly, but not significantly, increased in the hypertensive nephritic patients. Alternatively, it is conceivable that sodium retention which results from impaired renal function induced activation of the sympathetic nervous system in a similar way to those which occur in DOCA-salt hypertensive rats or salt-sensitive hypertensive people. Nicholls et al. have reported that mild salt loading could increase PNE and urinary excretion of norepinephrine in normotensive people. Although other mechanisms for enhancement of sympathetic nervous activity related to deterioration of renal function may be clarified in further studies, the results of the present study indicate that some overactivity of the sympathetic nervous system may account for the blood pressure elevation in hypertensive nephritic patients.

Furthermore, there is a possibility that the elevation of plasma catecholamines is due to an impairment of the ability of the kidney to excrete, extract, and metabolize circulating catecholamines. Recent experimental studies have demonstrated that: 1) norepinephrine and epinephrine are excreted by filtration and tubular secretion; 2) norepinephrine and epinephrine are metabolized with O-methylation as the major metabolic route; 3) the kidney secretes both dopamine and norepinephrine into the circulation; and 4) epinephrine is preferentially excreted and metabolized. Mechanisms for catecholamines excretion, extraction, and metabolism in the human kidney are still poorly understood.

Some previous studies have demonstrated that plasma concentrations of catecholamines are elevated in renal failure, whereas other studies have reported that elevation of plasma catecholamines are not always observed in patients with renal failure and dialysis patients, and that PNE is significantly lower in anephric patients than in non-nephrectomized patients with terminal renal failure. Masuyama et al. have reported that, when patients with essential hypertension and those with secondary hypertension are examined, renal clearance of norepinephrine was significantly decreased and PNE was definitely elevated only when Ccr was reduced to less than 35 ml/1.48 min (24 ml/min-m²). The average Ccr in the hypertensive nephritic patients in the present study was far above 24 ml/min-m². Accordingly, the elevated PNE and PE seen in the hypertensive nephritic patients cannot be attributed solely to the impairment of renal function. The changes in PNE and PE observed in the hypertensive nephritic patients could, however, be explained by the coexistence of impairment of renal function and an increase in sympathetic nervous activity. Further studies are needed regarding the modulation of plasma levels of catecholamines by the human kidney.

One cannot, however, exclude the possibility that the hypertensive nephritic patients in the present study might share the same etiological factors as those with essential hypertension. The familial occurrence of hypertension was not significantly different between the hypertensive and the normotensive nephritic patients, and although we must be careful to exclude genetic factors in the hypertensive nephritic patients, the familial tendency for hypertension does not appear to have been a factor in the results.

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References
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