Renal functional reserve, microalbuminuria, and plasma atrial natriuretic factor were measured in 21 offspring (9.5±0.5 years of age, mean±SEM) of hypertensive parents and in eight children (10±0.5 years of age) with no family history of hypertension who were used as a control group. Renal functional reserve was evaluated by measurement of the changes in creatinine clearance after an oral protein load of 45 g/m². Atrial natriuretic factor levels were determined before and 60 minutes after the protein load, and microalbuminuria in fractional urine before and 120 minutes after the same stimulus as well as in a 24-hour urine collection. All children in the control group significantly increased their creatinine clearance after the protein load (preload, 122±12; 60 minutes, 144±9; 120 minutes, 154±11; 180 minutes, 144±9 ml/min/1.73 m²; all values were significant vs. preload, p<0.005). In contrast, only 13 of 21 offspring of hypertensive parents increased their creatinine clearance to values within 2 SD of the increase shown by the control group (preload, 144±11; 60 minutes, 153±7; 120 minutes, 202±13 ml/min/1.73 m²; p<0.001 vs. preload; 180 minutes, 214±19 ml/min/1.73 m²; p<0.001 vs. preload). The remaining eight offspring of hypertensive parents showed no detectable changes (nonresponders) (preload, 189±18; 60 minutes, 146±11; 120 minutes, 170±14; 180 minutes, 168±13 ml/min/1.73 m²; all values p=NS). No changes in atrial natriuretic factor after the protein load were observed in any group. Offspring of hypertensive parents presented higher microalbuminuria levels in 24-hour urine specimens (3.1 μg/min, tolerance factor [TF]2.2) than controls (2.1 μg/ml, TF 1.5) (p<0.05). Although microalbuminuria increased significantly after the water load in the control group (p<0.05) and in the offspring of hypertensive parents (p<0.01), it returned to baseline at 120 minutes in the former but not in the latter (p<0.05 vs. baseline). The lack of renal functional reserve in nonresponders was significantly related (p<0.05) to the presence of higher levels of microalbuminuria. We conclude that the absence of renal functional reserve and increased microalbuminuria in some normotensive children who are offspring of essential hypertensive parents can indicate that subtle alterations in renal function may precede the onset of clinical hypertension. (Hypertension 1990;15:257-261)

Several lines of evidence suggest that a genetic factor is involved in the pathogenesis of essential hypertension in some patients. A number of past observations supports the hypothesis that inherited abnormalities in kidney function may participate in the pathogenesis of essential hypertension.

We have reported decreased active and inactive urinary kallikrein excretion after a diuretic stimulus in a subgroup of normotensive offspring of essential hypertensive parents as well as in normotensive children with a single kidney. As urinary kallikrein has been proposed as an indicator of distal tubular mass or function, our findings could be interpreted as an expression of a diminished functional renal mass in the normotensive offspring of hypertensive parents.

To gather additional information on their renal function, we evaluated the renal functional reserve (as indicated by the increase in the creatinine clearance after an oral protein load) and the microalbuminurin excretion in a group of normotensive children who are offspring of essential hypertensive parents. Oral protein load has been shown to increase glomer-
TABLE 1. Basal Blood Pressure at the Beginning of the Study

<table>
<thead>
<tr>
<th>N-EH</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient no.</td>
<td>Sex</td>
</tr>
<tr>
<td>1.</td>
<td>F</td>
</tr>
<tr>
<td>4.</td>
<td>F</td>
</tr>
<tr>
<td>5.</td>
<td>M</td>
</tr>
<tr>
<td>6.</td>
<td>M</td>
</tr>
<tr>
<td>7.</td>
<td>M</td>
</tr>
<tr>
<td>8.</td>
<td>F</td>
</tr>
<tr>
<td>9.</td>
<td>M</td>
</tr>
<tr>
<td>10.</td>
<td>F</td>
</tr>
<tr>
<td>11.</td>
<td>M</td>
</tr>
<tr>
<td>15.</td>
<td>F</td>
</tr>
<tr>
<td>17.</td>
<td>M</td>
</tr>
<tr>
<td>19.</td>
<td>F</td>
</tr>
<tr>
<td>21.</td>
<td>F</td>
</tr>
<tr>
<td>SEM</td>
<td>2/1</td>
</tr>
</tbody>
</table>

N-EH, normotensive children with a single hypertensive parent; BP, blood pressure.

determination from an intravenous butterfly needle introduced into a peripheral arm vein. Baseline Ccr was calculated from the mean value obtained at the two 30-minute periods. The children were then fed an oral protein load (OPL) (lean, cooked hamburger meat) of 45 g/m² body surface area ingested during a 20–30-minute period. After the meal was completed, three 60-minute urine samples were collected and blood again drawn at the midpoint of each period for Ccr. At the end of each urine collection, an amount of water equivalent to the volume voided was ingested by each child. Blood pressure was taken hourly from the preload period through the third hour of the post–protein load period with a mercury sphygmomanometer.

Plasma and urinary creatinine were measured by a standard method by means of an automatic analyzer (Abbott VP Bichromatic Analyzer, Abbott Labs., Dallas, Texas), and Ccr was corrected for body surface and expressed per 1.73 m². Urinary sodium was measured in the 24-hour urine collection by flame spectrophotometry.

Microalbuminuria was measured in three different urine samples: 1) 24-hour urine specimen collected the day before the OPL study; 2) in the second 30-minute urine collection after the water load administered before the protein meal; 3) in the second 60-minute urine collection after the protein load. Urinary urea was also measured in the last two
samples. Microalbuminuria was measured by radioimmunoassay with the method of Miles et al, as modified in our laboratory. The first antibody was purchased from Serotec (Oxfordshire, UK). Standards for iodination and standard curves were from Calbiochem (Calbiochem Corp., La Jolla, California) catalogue No. 126658 and 126654, respectively. Interassay variation coefficient was 15% and 13%, respectively, and the sensitivity was 7.8 ng.

ANF was measured by radioimmunoassay in three different plasma samples: 1) in basal conditions before the water load, 2) 1 hour after the water load and before the protein meal, and 3) 1 hour after the protein load. Plasma levels of ANF were measured with the method of Gutkowska et al. The antibody against ANF-(99-126) was kindly supplied by Y. Gutkowska, who also helped us set up the assay in our laboratory. All the other reactions were obtained from Peninsula Labs., Inc., Belmont, California.

Parental consent for the present study was obtained after giving appropriate information in all cases.

**Statistical Methods**

Statistical analysis of the results was done by nonparametric methods because changes in Ccr after the protein load, as well as microalbuminuria, may not follow a normal distribution, as stated by other authors. The Wilcoxon signed rank test was used to evaluate changes in Ccr after the protein load within each group. The median test was applied to study the differences among the groups. Fisher's exact test on two-by-two contingency tables were used to determine a possible relation between the response to the protein load and microalbuminuria. Results are expressed as mean±SEM, except for microalbuminuria; which is expressed antilogged with a geometric mean (GM) equivalent to the arithmetic mean of the logged data, and a tolerance factor (TF) equivalent to the standard deviation of the logged data, except that the GM is multiplied or divided by the TF. Results were considered statistically significant when p<0.05.

**Results**

Creatinine clearance values obtained after the oral protein load are shown in Table 2. Although the Ccr in the children in the control group increased significantly after the protein load (p<0.005), no significant changes in the mean Ccr were recorded in the N-EH group children. However, when the results obtained in the latter group were analyzed in a more discriminative manner, two subsets of children could be identified: 13 of 21 children in the N-EH group (62%) did in fact increase their Ccr significantly (p<0.001) (responders) to values within 2 SD of the increase shown by the control group, whereas 8 of 21 children in the N-EH group (38%) did not (nonresponders) (Figure 1).

No significant changes in blood pressure were recorded throughout the study.

Basal urinary urea excretion was similar in N-EH responders and nonresponders, and it increased significantly after the protein load (responders: basal 13.4±9 g and post-protein load 16.3±1.2 g, p<0.01; nonresponders: basal 10.7±1.7 g and post-protein load 18.2±2.5 g, p<0.01).

Urinary sodium excretion was similar in the N-EH responder and nonresponder groups, and it was not different from the control groups (responders, 98 ±17 meq/24 hr; nonresponders, 94 ±20 meq/24 hr; and C, 110±23 meq/24 hr).

Basal plasma ANF levels were similar in control and N-EH children, and they showed no significant changes either after the water load or after the protein load (C: basal 107±10 pg/ml, after water load 98±18 pg/ml, and after protein load 94±5 pg/ml; N-EH: basal 111±47 pg/ml, after water load 118±46 pg/ml, and after protein load 124±67 pg/ml).

Microalbuminuria in the 24-hour urine collection was higher in a total population of 33 N-EH than in

**Table 2. Creatinine Clearance Values After an Oral Protein Load**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Basal</th>
<th>Preload</th>
<th>1 hour</th>
<th>2 hours</th>
<th>3 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>8</td>
<td>143±22</td>
<td>122±12</td>
<td>144±9 *</td>
<td>154±11 †</td>
<td>144±9 †</td>
</tr>
<tr>
<td>N-EH</td>
<td>21</td>
<td>135±8</td>
<td>161±11</td>
<td>151±6</td>
<td>156±18</td>
<td>169±21</td>
</tr>
<tr>
<td>Responders</td>
<td>13</td>
<td>134±11</td>
<td>144±11</td>
<td>153±7</td>
<td>202±13 ‡</td>
<td>214±19 ‡</td>
</tr>
<tr>
<td>Nonresponders</td>
<td>8</td>
<td>136±14</td>
<td>189±18</td>
<td>146±11</td>
<td>170±14</td>
<td>168±13</td>
</tr>
</tbody>
</table>

Values are mean±SEM (ml/min/1.73 m²). N-EH, normotensive offspring of hypertensive parents; basal, values obtained from 24-hour urine collected the day before the study.

* p<0.05; † p<0.01; ‡ p<0.005; § p<0.001 when compared with respective preload values. ¶ p<0.01 when compared with N-EH responders.

**Figure 1. Graph showing creatinine clearance response to an oral protein load. N-EH, normotensive offspring of hypertensive parents; full lines, responders; dotted lines, nonresponders.**
Discussion

Our results indicate that the creatinine clearance response to an oral protein load was significantly altered in 38% of a cohort of N-EH children, suggesting that some of these children may have an abnormal renal functional reserve in spite of having shown normal renal function by standard diagnostic tests. In addition, N-EH children presented significantly increased mean microalbumin excretion when compared with control subjects without a family history of essential hypertension. Furthermore, a significant relation between the lack of renal functional reserve and increased microalbuminuria was also found in these children.

We used the endogenous creatinine clearance as an estimation of the glomerular filtration rate, as other authors have previously shown that creatinine clearance and inulin clearance rendered similar results in this test. Although it has long been known that both clearances may be discordant because of tubular secretion of creatinine, this discrepancy becomes important only when the glomerular filtration rate is decreased. Differences between both clearances have previously been reported to be less than 10% in subjects with normal renal function.

The observation that bilaterally nephrectomized spontaneously hypertensive rats will become normotensive when transplanted with a kidney donated from a normotensive rat lends support for the theory on the primacy of the kidney in the pathogenesis of essential hypertension. A dramatic reversal of hypertension has also been reported in some patients with end-stage renal disease after successful renal transplantation. Thus, a number of past observations support the contention that something in the kidney may be primarily at fault, in at least a subset of essential hypertensive patients.

Healthy subjects have been shown to increase their glomerular filtration rate after a meat meal, and this increase has been considered a measure of the renal functional reserve. Patients with renal disease have a lack of renal functional reserve, and the presence of glomerular hyperfiltration in the remnant nephrons has been postulated as the underlying mechanism. Further support for the latter comes from experimental data demonstrating an increase in single nephron glomerular filtration rate of the remnant nephrons after renal ablation.

Our present finding of a lack of renal functional reserve in a subset of normotensive offspring of essential hypertensive patients, together with our past observation of a decreased urinary kallikrein excretion in both the N-EH and normotensive single kidney children, lend additional support to our hypothesis that a diminished functional renal mass is present in a subset of normotensive children who are offspring of essential hypertensive parents.

A primary defect in glomerular development leading to a reduction in single nephron filtration rate (probably due to a lower glomerular hydraulic conductivity or surface area) was described in Milan hypertensive strain rats, an animal model for essential hypertension. Based on these data, it may be speculated that hypofiltration rather than hyperfiltration could have led to the lack of renal functional reserve found in some of our patients.

Vascular structural changes before the development of hypertension have been reported in spontaneously hypertensive rats. An inappropriate vascular constrictory state has recently been postulated to be present in offspring of essential hypertensive parents. Therefore, structural or functional vascular alterations, or both, may be mediators of the lack of response to the meat meal.

Differences in dietary protein intake or in the absorption of the meat meal could be ruled out as responsible for our findings as 24-hour urinary urea was similar in all children studied and urea excretion after the protein load increased comparably in both responder and nonresponder N-EH groups.

A restricted sodium diet cannot be related to the lack of creatinine clearance either, as the urinary sodium excretion was again similar in both N-EH subgroups.

Our findings do not support a role for ANF in mediating the creatinine clearance response to an oral protein load. The increased microalbuminuria found in N-EH children could have been the result of
early alterations in the glomerular capillary permeability secondary to glomerular hemodynamic abnormalities, as previously suggested. The above speculation is furthered by our observation of a significant relation between the absence of renal functional reserve and microalbumin excretion in the N-EH group.

In synthesis, the absence of renal functional reserve and increased microalbuminuria in some normotensive children who are offspring of essential hypertensive parents, indicate that subtle alterations in renal function may precede the onset of clinical hypertension. Long-term follow-up of these children may contribute to the understanding of the pathophysiological meaning of the findings here reported and presumably establish their possible usefulness for the identification of children at risk for developing essential hypertension.

References


KEY WORDS • microalbuminuria • atrial natriuretic factor • family history • renal function
Renal functional reserve and microalbuminuria in offspring of hypertensive parents.
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