Renal Functional Reserve and Microalbuminurin in Offspring of Hypertensive Parents

Beatriz Grunfeld, Eduardo Perelstein, Rosa Simsolo, María Gimenez, and Juan C. Romero

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/min, 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.1,2 A number of past observations supports the hypothesis that inherited abnormalities in kidney function may participate in the pathogenesis of essential hypertension.3-5

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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.6 As urinary kallikrein has been proposed as an indicator of distal tubular mass or function,7 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 microalbumin excretion in a group of normotensive children who are offspring of essential hypertensive parents. Oral protein load has been shown to increase glomer-
**Methods**

**Patient Population**

Twenty-one normotensive children (N-EH) with a single essential hypertensive parent (11 boys, mean age 9.5±0.5 years) and eight normotensive children without a family history of essential hypertension (C) (five boys, mean age 10±0.5 years) who were attending the Outpatients Clinic at Children’s Hospital were included in the study. Children were considered normotensive according to the criteria of the Second Task Force on Blood Pressure Control in Children (Table 1). Creatinine clearances (Ccr) were within the normal range in all propositi and none had proteinuria. All subjects were free of medication at the time of the study. All studies were carried out on an outpatient basis.

**Oral Protein Load**

Studies were started at 8:00 AM after an overnight fast. After emptying their bladders, the children were given an oral water load of 20 ml/kg body wt, after which two timed 30-minute urine samples were collected by spontaneous voiding; at a midpoint of each 30-minute period, blood was drawn for the creatinine 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
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>Postload</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>8</td>
<td>143±22</td>
<td>122±12</td>
<td>144±9*</td>
</tr>
<tr>
<td>N-EH Responders</td>
<td>13</td>
<td>134±11</td>
<td>144±11</td>
<td>146±11</td>
</tr>
<tr>
<td>N-EH Nonresponders</td>
<td>8</td>
<td>136±14</td>
<td>189±18</td>
<td>168±13</td>
</tr>
<tr>
<td>N-EH</td>
<td>21</td>
<td>135±8</td>
<td>161±11</td>
<td>151±6</td>
</tr>
<tr>
<td>Responders</td>
<td></td>
<td></td>
<td></td>
<td>153±7</td>
</tr>
<tr>
<td>Nonresponders</td>
<td></td>
<td></td>
<td></td>
<td>202±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.

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 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).
The observation that bilaterally nephrectomized spontaneously hypertensive rats will become normotensive when transplanted with a kidney donated from normotensive rats lent 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.\textsuperscript{19} 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


\textbf{KEY WORDS} • microalbuminuria • atrial natriuretic factor • family history • renal function
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