Glomerular Hyperfiltration, High Renin, and Low-Extracellular Volume in High Blood Pressure


Abstract—Abnormal renovascular resistance and glomerular filtration rate are characteristic of established hypertension and may also be involved in its pathogenesis. To determine renal and body fluid correlates of the predisposition to high blood pressure, we examined 100 healthy young adults with high or low blood pressure. Within each group, half had parents with high blood pressures, and half had parents with low blood pressures. Renal function and hemodynamics, body fluid volumes, and relevant hormones and genotypes were measured. Subjects with high personal and parental blood pressures had the highest levels of glomerular filtration rate (P<0.02) and plasma active renin concentration and low levels of exchangeable sodium and plasma volume (P<0.02). High glomerular filtration rate was not associated with differences in urinary kallikrein or prostaglandins. Polymorphisms of the renin, angiotensin-converting enzyme, and angiotensinogen genes were not associated with differences in glomerular filtration rate or renin. Subjects with high personal, but low parental, blood pressures had low exchangeable sodium and plasma volumes (P<0.02) but normal glomerular filtration rates. In this population, extracellular volume depletion and high renin are correlates of high blood pressure in early adulthood, and glomerular hyperfiltration is a feature of those who also have familial predisposition to high blood pressure. (Hypertension. 2000;35:952-957.)

Key Words: electrolytes ■ family history ■ genetics ■ renal function ■ renin

Established hypertension is associated with increased renal vascular resistance (RVR) and a decline in glomerular filtration rate (GFR) and renal blood flow (RBF). Such abnormalities may also exist at an early stage in the development of hypertension, and it has been proposed that a primary abnormality in renal function leads to expansion of the extracellular volume, to which the body responds by increasing blood pressure (BP) to reduce sodium and fluid volumes. Although impaired renal function and normal or reduced extracellular fluid volumes in hypertensive subjects are consistent with this hypothesis, there is no consensus on the nature of early renal changes that characterize predisposition to high BP.

In humans, borderline hypertension or a family history of hypertension has been associated with high or normal GFR and low or normal RBF. Few data exist in relation to extracellular fluids, but 1 study has suggested that exchangeable sodium is reduced in young hypertensive subjects. Animal models of genetic hypertension show renal phenotypic abnormalities during the development of hypertension, but their exact nature depends on the specific strain. In young spontaneously hypertensive rats, low GFR and RBF are seen during the development of hypertension. In contrast, young Milan hypertensive rats and fawn-hooded rats exhibit increased GFR compared with control rats.

The aim of the present study was to examine renal function and hemodynamics, extracellular sodium and fluid volumes, and plasma active renin in healthy young adults with contrasting predispositions to high BP.

Methods

Subject Selection

The selection and recruitment of families in the present study has been described previously. The research design uses BP measurements from both parents and children. In brief, BPs were measured in 864 young adults, aged 16 to 24 years, from 603 families. Their parents had undergone BP measurement 8 years before as part of the screening phase of the Medical Research Council (MRC) Mild Hypertension Trial. BP values were standardized for the effects of age, gender, and the use of oral contraception. Subjects being treated for hypertension were accorded standardized values equivalent to the top 5% of the distribution. Maternal and paternal BPs were combined to provide a single parental BP.

Offspring personal BPs were plotted against their combined parental pressures in a scatter diagram. For the purposes of this

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analysis and consistent with our previous methods, high BPs were considered to be those in approximately the top 30% of age- and gender-specific parental and offspring BP distributions. Low pressures were those in the bottom 30% of the distributions. The different combinations of high and low personal and parental BPs in each corner of the scatter diagram resulted in 4 parent and offspring combinations constituting offspring with high personal and low parental BPs, high personal and high parental BPs, low personal and low parental BPs, and low personal and high parental BPs. In the original selection of 864 offspring, these groups were composed of 122, 118, 163, and 68 individuals, respectively. The definition of high BP used in the present study meant that the group with high personal and high parental BP was representative of ~14% of the general population. When considered according to personal and parental BPs, this group constituted approximately one third of the young adults with high BP and about one half of the offspring with high parental BPs. For the present study, a contact list was compiled of 200 offspring, composed of 50 subjects chosen at random from the 4 original groups. This list did not reveal group allocations. One investigator (S.B.H.) recruited 100 offspring from this list. After the clinical experiments, it was revealed that there were ~25 offspring from each group.

Clinical Protocol

Subjects were admitted to the hospital overnight on their normal diet. To minimize potential bias or perturbation of physiological traits, the BP categorization of the parents and the offspring was not revealed to either the participants or the clinical investigators. To minimize variation related to the menstrual cycle, all females were asked to attend within 10 days of their last menstrual period. Informed consent was obtained from all subjects, and the studies were approved by the Western Infirmary Ethics Committee. On admission, the height and weight of participants were measured. Measurements of subcutaneous fat were used to calculate total body fat and lean body mass. All subjects were given a solution containing Na and H for body sodium and water estimation. To measure isotope and electrolyte excretion, urine was collected from the time of isotope administration until the time of blood sampling 20 hours later. Other than water, all subjects were fasted from 9 PM on the first day.

The following morning, subjects were prepared for investigation, and intravenous cannulas were inserted into the right and left cubital veins. A BP cuff was attached to the right arm, and BP and pulse rate were measured automatically by a Copal UA251 Auto-Inflation Digital Sphygmomanometer (Takeda Medical Corp) while subjects remained semiprone in bed. Three readings were taken every half hour and were averaged to calculate the systolic and diastolic BPs and pulse rate. Mean arterial pressure was calculated as diastolic BP plus one third of the difference between systolic and diastolic BPs.

Electrolytes and Renal Function

These methods have been described in detail elsewhere. Total exchangeable sodium and body water were estimated from dilution of Na and H given earlier. Plasma volume was estimated from the dilution of an injected bolus of I-labeled albumin. GFR and renal plasma flow were measured by using constant infusions of inulin (50 g/50 mL, Laevosan-Gesellschaft MBH) and p-aminohippurate (PAH, 2 g/10 mL, MSD), respectively. A loading dose of inulin (30 g/70 kg) and PAH (0.8 g/70 kg) was given, half as a rapid bolus injection and the rest over 10 minutes, and a constant infusion of inulin (0.96 g/h) and PAH (0.48 g/h) was begun. To ensure stable levels, clearance measurements were not begun until 2 hours later. Each subject was given 5 mL/kg of water to drink at the time of the loading bolus, followed by 1 mL/kg every half hour. Four consecutive half-hour estimates of GFR and effective renal plasma flow (ERPF) were made. RBF was calculated from ERPF and the hematocrit, and RVR was calculated from the RBF and mean arterial pressure. The concentration of urinary albumin was measured in a sample of urine collected during the first 2 hours of inulin and PAH infusion.

Biochemical Phenoypes

Just before the initiation of renal function studies, blood samples were taken for plasma active renin and aldosterone concentrations, which were measured according to previously published methods. These samples were also used for determination of total body water and exchangeable sodium and plasma volume. At the time of discharge, all participants were given a container and asked to complete a 24-hour urine collection for measurement of electrolytes, creatinine, prostaglandins, and total kallikrein.

Genotypes

DNA was extracted from whole blood and purified as described previously, and polymorphic variants of relevant genes were determined for each person to test for associations between genotypes and GFR and plasma active renin. The following polymorphisms were determined: renin gene (HindIII and BflI restriction fragment length polymorphisms), angiotensin-converting enzyme (ACE) gene (insertion/deletion polymorphism), and angiotensinogen gene (M23ST polymorphism).

Statistical Analysis

Data are summarized as means with 95% CIs except where stated. Urinary kallikrein and prostaglandin data underwent logarithmic transformations before parametric analyses. The effects of categorization according to high or low parental and personal BPs were analyzed by using a 2 × 2 factorial ANOVA design. Regression analysis was used to examine relations between variables in the combined group of 100 subjects. To control for any gender-related differences in ANOVA and regression analyses, gender was also entered as a dummy variable (female 0, male 1). The χ² test was used to compare gender distribution and the use of the oral contraception between groups. The effects of genotype were assessed by 1-way ANOVA. In view of the number of comparisons, statistical significance was accepted as P < 0.02.

Results

The average age of the subjects was 22 years, and there was no significant difference between the 4 groups. The gender balance (Table 1; χ² 2.31, df 3, P = 0.51) and use of the oral contraceptive pill (χ² 6.35, df 3, P = 0.10) did not differ between groups. The mean systolic and diastolic BPs of the 4 groups (Table 1) were consistent with the original categorization that had been defined by BP measurements 3 years before the present study. This consistency demonstrates the continued robustness of the original sampling criteria. High BP in offspring was associated with significantly higher body weight and body fat (Table 1). Body mass index showed a similar pattern (data not shown).

Exchangeable Sodium, Body Fluid Volumes, and Plasma Active Renin

Exchangeable sodium and plasma volume were significantly lower in offspring with high BP (Table 2). There were no significant differences in total body water (data not shown).

Plasma active renin was significantly higher in offspring with high BP (Table 2). The highest average plasma active renin was seen in offspring with high personal and parental pressures. Plasma active renin correlated significantly (r = −0.26, P < 0.006) with plasma volume. No significant differences in plasma aldosterone or the daily urinary excretion of sodium or potassium were detected between the groups (data not shown).

Average values for 24-hour urinary excretion of kallikrein were not different between the groups (Table 2). The daily
excretion of 6-ketoprostaglandin F$_{1\alpha}$ and prostaglandin E$_2$ did not differ according to either parental or personal BP groupings (data not shown).

**Renal Function and Hemodynamics**

The highest average GFR was observed in offspring from families in which both parents had high BP (Table 2; $P=0.02$, 1-way ANOVA). With use of a factorial analysis, a significant effect of parental pressure on GFR was found (Table 2, $P=0.02$). However, this effect was most striking for subjects with high personal BP, in whom the difference associated with high parental BP was 19 mL/min per 1.73 m$^2$, compared with only a 3 mL/min per 1.73 m$^2$ difference in subjects with low personal BP (Table 2).

Urinary albumin concentrations were below detectable limits (<5 mg/L) in 89 of the 100 subjects. Average levels of GFR were not different in subjects with (125.5±22.2 mL/min per 1.73 m$^2$) or without (125.6±24.7 mL/min per 1.73 m$^2$) detectable urinary albumin (5 to 22 mg/L). Detectable albumin was not associated with high parental or personal BPs.

No significant differences in ERPF (Table 2) or RBF (data not shown) were observed between the groups. The RVR was significantly higher in offspring with high BP ($P=0.02$), irrespective of parental BP (Table 2). We observed a significant inverse correlation between plasma active renin and both GFR ($r=0.22$, $P=0.02$) and filtration fraction ($r=0.20$, $P=0.02$).

A significant inverse correlation also existed between GFR and exchangeable sodium ($r=-0.26$, $P=0.01$).

**Genotypes**

The summary data of phenotypes in relation to genotypes are shown in Table 3. No significant differences were observed in plasma active renin or GFR for genotypes of the renin, ACE, or angiotensinogen genes.
TABLE 3. Genotypes and Phenotypes

<table>
<thead>
<tr>
<th></th>
<th>PRC, mU/mL</th>
<th>GFR, mL/min per 1.73 m²</th>
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<tbody>
<tr>
<td><strong>Hind III</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aa (n=5)</td>
<td>36.2 (29.8–42.6)</td>
<td>111 (71–150)</td>
</tr>
<tr>
<td>aA (n=49)</td>
<td>36.5 (31.7–41.3)</td>
<td>129 (123–135)</td>
</tr>
<tr>
<td>AA (n=44)</td>
<td>41.6 (36.5–46.6)</td>
<td>124 (116–131)</td>
</tr>
<tr>
<td><strong>Bgl I</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aa (n=11)</td>
<td>43.0 (28.3–57.6)</td>
<td>132 (110–154)</td>
</tr>
<tr>
<td>aA (n=37)</td>
<td>35.7 (30.4–40.9)</td>
<td>122 (114–129)</td>
</tr>
<tr>
<td>AA (n=35)</td>
<td>38.3 (33.4–43.3)</td>
<td>121 (114–129)</td>
</tr>
<tr>
<td><strong>Angiotensinogen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MM (n=38)</td>
<td>40.6 (35.5–45.6)</td>
<td>125 (118–132)</td>
</tr>
<tr>
<td>MT (n=41)</td>
<td>37.7 (32.7–42.7)</td>
<td>122 (115–130)</td>
</tr>
<tr>
<td>TT (n=8)</td>
<td>41.6 (26.6–56.7)</td>
<td>125 (106–144)</td>
</tr>
<tr>
<td><strong>ACE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II (n=31)</td>
<td>39.9 (33.9–45.9)</td>
<td>126 (117–135)</td>
</tr>
<tr>
<td>ID (n=49)</td>
<td>37.5 (32.7–48.2)</td>
<td>125 (118–132)</td>
</tr>
<tr>
<td>DD (n=12)</td>
<td>38.6 (29.0–48.2)</td>
<td>127 (109–144)</td>
</tr>
</tbody>
</table>

Values are mean, with 95% CI for the mean in parentheses. PRC indicates plasma active renin concentration. The following renin restriction fragment length polymorphism allele sizes pertain: for BglI, a 5.0 kb and A 9.0 kb; for Hind III, a 6.2 kb and A 9.0 kb. M and T represent angiotensinogen gene alleles coding for methionine and threonine, respectively, at position 235; I and D represent the insertion and deletion alleles, respectively, of the ACE gene.

Discussion

In the present study, we found that glomerular hyperfiltration correlates with high plasma renin and is observed in healthy young adults with high BP who also have parents with high BP. The importance of this observation is that renal abnormalities in association with high BP are present in this subgroup, which is representative of 14% of the general population. The present study has also revealed that irrespective of parental BP, high BP in young adults is associated with low exchangeable sodium and plasma volume and increased plasma renin.

Two special features of the research design deserve comment. First, the definition of high and low BP equates to pressures in the upper and lower thirds of the age and gender distributions, respectively. Therefore, our findings are relevant and explain why large numbers of people have BPs above and below the population mean rather than why a few people have pressures in the upper tail of the distribution. The epidemiological significance is that most of the cardiovascular events that are attributable to raised BP occur in the large numbers of people at moderate risk rather than the small number of people at high risk.28,29

Second, predisposition to hypertension was defined in terms of personal and parental pressures.19,20 As a consequence of tracking, high personal pressures in youth predispose one to high pressures throughout adulthood. High parental pressure predisposes offspring as a result of familial aggregation. The 4 combinations of high and low personal and parental pressures afford special opportunities to examine familial and nonfamilial correlates of high BP. The approach provides information that might be diluted in studies that use either personal pressure (eg, “borderline” hypertension) or parental (eg, “family history” of hypertension) pressure alone to define BP predisposition.

Despite the broad definitions of high BP in the present study, the findings are consistent with observations in established clinical hypertension. In particular, the reduced plasma volume and exchangeable sodium observed in young adults with high BP mirrors findings in hypertensive subjects.4,6,30,31 The confluence between high pressure and low fluid extracellular volumes suggests that volume depletion is a consequence of high BP, even from the earliest phases, when BP differences are relatively small.

In the present study and also in studies of hypertensive subjects, lower exchangeable sodium and extracellular fluid volumes might reflect the differences in body composition associated with high BP. Young adults with high BP in the present study were, on average, 7 kg heavier than those with low BP. About half of this difference was attributable to differences in body fat, which is relatively free of extracellular fluid. Therefore, some (but not all) of the findings of low exchangeable sodium and extracellular fluid volume are attributable to increased fat mass.

We observed a qualitatively different relation between plasma renin and BP in subjects in the present study compared with subjects with essential hypertension. In hypertension, as in the normal population, higher BP is associated with lower plasma renin.32 However, high BP in young adults in the present study was associated with significantly higher plasma active renin. High renin in young people predisposed to hypertension has been reported in many10,33–38 but not all8,11,39,40 published studies.

Our findings suggest that the normal baroreceptor-mediated suppression of renin by high BP41 is perturbed in the early development of high BP. Sympathetic renal nerve activity may be an important stimulus to renin release in high BP.42–44 We have demonstrated previously evidence of increased activity of the sympathetic nervous system associated with high BP in our population.45 As hypertension develops, renin levels become suppressed, partly because of higher arterial pressures but also as a result of increased central blood volume.46

We observed glomerular hyperfiltration in young people with high personal and parental BPs. High GFR is not a feature of established hypertension, nor is it a feature of high BP per se in the present study, being absent in young people with high BPs who have parents with low BPs. Our observations are consistent with 2 previous studies of normotensive subjects with a family history of hypertension.7,12 These findings contrast with other studies reporting normal GFR in subjects predisposed to hypertension.5,11,47–49 The reasons for the discrepancies are not immediately obvious, but the studies differ substantially in the populations examined, the definition of predisposition, the age of subjects, and the methods of measuring GFR. The inulin clearance method used in the present study is one of the most reliable available.

The observed correlation between plasma renin with GFR and filtration fraction suggests a link between the 2 phenotypes. This may result from angiotensin-dependent preferen-
tial vasoconstriction of the postglomerular arterioles and increase in glomerular hydrostatic pressure. Although other vasoactive systems may be relevant, we could find no association between GFR and the urinary excretion of the vasodilators kallikrein and prostaglandin E2 or the vasopressor prostaglandin F1α.

The renal phenotypes found in the present study resemble those observed in the fawn-hooded rat model of hypertension and renal failure. Before the development of hypertension, these animals show glomerular hyperfiltration. Despite the fact that these animals appear to have low plasma renin activity, ACE inhibition or angiotensin receptor blockade restores renal function and BP to normal.

Functional polymorphisms of the ACE and angiotensinogen genes have been associated with renal abnormalities. However, we could find no association of GFR and plasma active renin with these ACE and angiotensinogen polymorphisms or those of the renin gene. Our results do not exclude small phenotypic effects of these polymorphisms or the involvement of other polymorphisms of these or other genes.

In summary, the present study reveals extracellular sodium and volume depletion in young adults with high BP. We hypothesize that volume depletion augments sympathetic nerve activation and renin release, which, in combination with familial factors, contribute to glomerular hyperfiltration.

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