Birth Weight Relates to Salt Sensitivity of Blood Pressure in Healthy Adults

Michiel P. de Boer, Richard G. IJzerman, Renate T. de Jongh, Etto C. Eringa, Coen D.A. Stehouwer, Yvo M. Smulders, Erik H. Serné

Abstract—The association between birth weight and blood pressure is well established but at present unexplained. According to the Borst-Guyton concept, chronic hypertension can occur only with a shift in the renal pressure–natriuresis relationship resulting in increased salt sensitivity of blood pressure. We assessed salt sensitivity of blood pressure in a group of 27 healthy adults whose birth weight was available. Birth weight was ascertained from birth certificates or announcements. Salt sensitivity of blood pressure was determined as difference in mean arterial pressure (MAP) between a 1-week high-salt (≈235 mmol NaCl/d) versus low-salt diet (≈55 mmol NaCl/d). Creatinine clearance was estimated according to the formula of Cockcroft and Gault. Birth weight was negatively associated with salt sensitivity of blood pressure ($r = -0.60, P = 0.002$). The creatinine clearance was positively associated with birth weight ($r = 0.53; P = 0.008$) but did not influence the association between birth weight and salt sensitivity of blood pressure. Birth weight is associated with salt sensitivity of blood pressure, and this may play a role in the maintenance of elevated blood pressure in individuals with a low birth weight. (Hypertension. 2008;51:928-932.)

Key Words: birth weight ▪ salt sensitivity ▪ hypertension ▪ uric acid ▪ microcirculation

Epideimological studies have consistently demonstrated that low weight at birth is associated with raised blood pressure in later life.1–3 Regardless of whether the origin of this relationship is genetic or environmental, microvascular rarefaction with an increase in peripheral vascular resistance has been proposed as a possible mechanism explaining this association.4,5 However, according to the Borst-Guyton concept, chronic hypertension can occur only if renal function is abnormal with a shift in the renal pressure–natriuresis relationship.6,7 In the absence of the latter, increased peripheral resistance only temporarily raises blood pressure, to be followed by an increase in renal sodium excretion restoring blood pressure toward normal. Subtle renal microvascular disease8,9 as well as a reduced number of nephrons10–13 may reconcile the Borst-Guyton concept with the putative role of vessel rarefaction in the etiology of high blood pressure in individuals with a low birth weight. Indirect support for an association between a shift in the renal pressure–natriuresis relationship and birth weight comes from human and animal studies showing associations of low birth weight with low nephron number.14,15 Both a reduced number of nephrons and subtle microvascular injury to the kidney may induce a shift of the pressure–natriuresis relationship, resulting in increased salt sensitivity of blood pressure and eventually hypertension. It is, however, unknown whether salt sensitivity of blood pressure is associated with birth weight in humans.

We have previously shown that low birth weight was associated with a diminished microvascular function in a group of healthy adult individuals.4 We now report on the association between birth weight and salt sensitivity of blood pressure in these individuals. Because it has been suggested that uric acid might lead to a pressure–natriuresis shift via microvascular renal injury (and subsequent impaired sodium handling),16 we also investigated the role of serum uric acid levels in the association between birth weight and salt sensitivity of blood pressure.

Methods

Subjects

A group of 60 randomly selected volunteers underwent assessment of their insulin sensitivity and were subdivided into tertiles according as described previously.4 Next, 10 subjects were randomly selected from each tertile to show a substantial variation in insulin sensitivity within the study population. Data concerning the relation of birth weight with blood pressure and capillary recruitment have been published previously.4 For the present analyses, 3 subjects were excluded because of missing data on salt sensitivity of blood pressure. All subjects were white and nonsmokers. They did not use any medication, had a normal 75-g oral glucose tolerance test, were normotensive (blood pressure <140/90 mm Hg) as determined by triplicate office blood pressure measurement, and did not have proteinuria. All were born after an uncomplicated pregnancy. Six subjects had a first-degree relative with essential hypertension,
Table 1. Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (males)</td>
<td>27 (11)</td>
</tr>
<tr>
<td>Age, y</td>
<td>37.2±14.5</td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>3.44±0.45</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.84±0.09</td>
</tr>
<tr>
<td>Body mass index, kg·m⁻²</td>
<td>24.7±3.1</td>
</tr>
<tr>
<td>Uric acid, µmol/L</td>
<td>259±76</td>
</tr>
<tr>
<td>24-hour systolic blood pressure, mm Hg</td>
<td>120±7</td>
</tr>
<tr>
<td>During the day</td>
<td>125±8</td>
</tr>
<tr>
<td>During the night</td>
<td>109±7</td>
</tr>
<tr>
<td>24-hour diastolic blood pressure, mm Hg</td>
<td>73±6</td>
</tr>
<tr>
<td>During the day</td>
<td>78±7</td>
</tr>
<tr>
<td>During the night</td>
<td>62±7</td>
</tr>
<tr>
<td>24-hour heart rate, bpm</td>
<td>72±9</td>
</tr>
<tr>
<td>During the day</td>
<td>75±10</td>
</tr>
<tr>
<td>During the night</td>
<td>60±15</td>
</tr>
<tr>
<td>Systolic blood pressure dipping, mm Hg</td>
<td>16±6</td>
</tr>
<tr>
<td>Diastolic blood pressure dipping, mm Hg</td>
<td>16±5</td>
</tr>
<tr>
<td>Creatinine clearance (ml·min⁻¹)</td>
<td>115±32.4</td>
</tr>
<tr>
<td>Salt sensitivity of blood pressure, mm Hg (range)</td>
<td>1.6±1.9</td>
</tr>
<tr>
<td>Insulin sensitivity, mg·kg⁻¹·min⁻¹ per pmol · l⁻¹·s⁻¹</td>
<td>1.8±0.9</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>4.6±0.4</td>
</tr>
<tr>
<td>Fasting serum triglycerides, mmol/L</td>
<td>1.2±0.9</td>
</tr>
<tr>
<td>Fasting serum total cholesterol, mmol/L</td>
<td>4.8±1.0</td>
</tr>
<tr>
<td>Fasting HDL-cholesterol, mmol/L</td>
<td>1.4±0.4</td>
</tr>
<tr>
<td>Fasting LDL-cholesterol, mmol/L</td>
<td>2.8±0.8</td>
</tr>
</tbody>
</table>

Data are presented as mean± SD (range). Salt sensitivity of blood pressure indicates difference in mean arterial pressure between the low- and high-sodium diet. Insulin sensitivity indicates glucose infusion rate during a hyperinsulinemic, euglycemic clamp expressed per unit of plasma insulin concentration. PRH indicates peak reactive hyperemia. Creatinine clearance was determined by the Cockcroft and Gault formula.

The birth weight data concern only individuals born after a normal pregnancy duration (≥38 weeks and <42 weeks).

Birth Weight

To ascertain birth weight (in grams), the participants were asked to obtain this information from birth certificates or birth announcements. The birth weight data concern only individuals born after a normal pregnancy duration (≥38 weeks and <42 weeks).

Salt Sensitivity Testing

Salt sensitivity of blood pressure was assessed according to a standardized procedure. During 1 week, participants adhered to a high-salt diet aimed at a minimum intake of 200 mmol NaCl per day. The extra amount of salt was supplied by capsules containing approximately 8.5 mmol NaCl. The next week, participants were placed on a low-salt diet aimed at a maximum intake of 60 mmol NaCl per day. Compliance with the diet was confirmed by measurement of 24-hour urinary sodium excretion during the last 2 days of both weeks. On the seventh day of both weeks diastolic blood pressure (DBP) and systolic blood pressure (SBP) were measured in the recumbent state at 2-minute intervals for 1 hour by a semicontinuous blood pressure monitoring device (Nippon Colin BP 103 N Sphygmomanometer) with an appropriately sized cuff. Mean arterial blood pressure (MAP) was calculated as DBP plus one-third of the difference between DBP and SBP. Salt sensitivity of blood pressure was defined as the difference of MAP between the averages of 30 readings during the high and low salt periods.

Other Measurements

All of the following measurements were performed during an ad libitum salt diet. Uric acid levels were determined in plasma. The collection was done once after an overnight fast. In 5 individuals, data on uric acid levels were not available. Ambulatory blood pressure measurements (Spacelabs 90207) were performed at the nonnondominant arm with appropriately sized cuffs at 15-minute intervals from 7:00 to 22:00 hours and at 20-minute intervals from 22:00 to 7:00 hours. The readings were individually edited into daytime and nighttime periods according to participants’ activity diaries. Nailfold capillary studies and iontophoresis studies were performed as described previously. Nailfold capillaries in the dorsal skin of the third finger of the nonnondominant hand were visualized by a capillary microscope. Postocclusive reactive hyperemia after 4 minutes of arterial occlusion was used to assess functional capillary recruitment. Endothelium-(in)dependent vasodilatation of finger skin microcirculation was evaluated with laser Doppler measurements in combination with iontophoresis of acetylcholine and sodium nitroprusside, respectively. Insulin sensitivity was assessed by the hyperinsulinemic, euglycemic clamp technique as described previously. Whole body glucose uptake (M) was calculated from the glucose infusion rate during the last 60 minutes and expressed per unit of plasma insulin concentration (M/I). For convenience the M/I ratio was multiplied by 100. Creatinine clearance was estimated using the Cockcroft and Gault formula.

Statistical Analyses

Variables are presented as mean±SD. Partial correlation analyses were used to study relationships among birth weight, salt sensitivity of blood pressure, blood pressure, and uric acid. We also investigated the association between uric acid, salt sensitivity of blood pressure, and microvascular function. Subsequently, multiple regression analyses were used to investigate whether the association between birth weight and salt sensitivity of blood pressure remained when allowing for uric acid, microvascular function, and creatinine clearance. In addition, we examined whether the association of salt sensitivity of blood pressure with birth weight was affected by adjustment for blood pressure and several other variables that are related to the metabolic syndrome.

All analyses were adjusted for age, sex, waist hip ratio (WHR), and body mass index (BMI). A 2-tailed probability value of <0.05 was considered significant. All analyses were performed on a personal computer using the statistical software package SPSS version 13.0 (SPSS).

Results

Characteristics and Measurements of the Study Population

Baseline characteristics and measurements of the study population are shown in Table 1. The age of the study population averaged 37.2 years (range 20 to 65 years). Birth weight averaged 3440 g (range 2540 to 4370 g), and salt sensitivity of blood pressure averaged 1.6 mm Hg (range −1.6 to 4.6 mm Hg). The average 24-hour urinary Na-excretion was 137±20.1, 237±45.0, and 48±17.0 mmol per liter at the end of ad libitum, high- and low-salt diets, respectively.
Low Birth Weight Is Associated With Salt Sensitivity of Blood Pressure

The results of the correlation analyses are shown in Table 2. All correlation coefficients were adjusted for age, sex, and BMI.

Subjects with lower birth weights were more likely to have a salt sensitive blood pressure (Table 2; Figure). As reported earlier,4 birth weight was inversely associated with 24-hour systolic blood pressure. In addition, birth weight was inversely associated with uric acid and with estimated creatinine clearance (Table 2).

Uric acid was associated with salt sensitivity of blood pressure and 24-hour systolic blood pressure, however these associations were not statistically significant \((P=0.06\) and \(0.07\) respectively; Table 2). In addition, microvascular function (capillary recruitment and endothelium-dependent microvascular vasodilatation) was inversely associated with uric acid, however these associations were not statistically significant \((P=0.12\) and \(P=0.09\), respectively).

Multivariate Analyses of the Association Between Birth Weight and Salt Sensitivity of Blood Pressure

Subsequently, we investigated whether the association between birth weight and salt sensitivity of blood pressure could be explained by uric acid. In the individuals for whom data on uric acid levels were available, an increase in birth weight of 1 kg was associated with a decrease in salt sensitivity of blood pressure of 2.0 mm Hg \((95\%-CI: -3.6\) to \(-0.4 \) mm Hg; \(P=0.02)\). After adjustment for uric acid, the regression coefficient of the association between birth weight and salt sensitivity of blood pressure decreased by 20\% \((-1.6 \) mm Hg/kg, 95\%-CI: \(-3.5\) to \(0.4 \) mm Hg/kg; \(P=0.1)\) and was no longer statistically significant. Adjustment for the creatinine clearance did not affect the association between birth weight and salt sensitivity of blood pressure (change in the slope of the regression line: 0\%). After adjustment for capillary recruitment or endothelium-dependent vasodilatation, the regression coefficient of the association between birth weight and salt sensitivity decreased by 14\%.

Discussion

The novel finding of the present study was the inverse association between birth weight and salt sensitivity of blood pressure. In addition, we confirmed the associations of birth weight with creatinine clearance and uric acid.16,19 Microvascular rarefaction and a subsequent increase in peripheral vascular resistance has been proposed as a mechanism which might explain the association between birth weight and elevated blood pressure in later life.4,5 However, according to the Borst-Guyton concept, chronic hypertension can occur only if renal function is abnormal with a shift in the renal pressure–natriuresis relationship.6,7 Our finding of an increased salt sensitivity of blood pressure in individuals with a lower birth weight gives support to the idea that low birth weight is indeed characterized by a shift in the pressure–natriuresis curve. Several possible mechanisms may account for a shift in the renal pressure–natriuresis relationship, leading to salt sensitivity of blood pressure. Brenner et al10 proposed that low birth weight may be associated with a congenital deficit in nephron number, which would predispose to reduced renal sodium excretion and, therefore, increased susceptibility to essential hypertension, especially in...
the setting of dietary sodium excess. This hypothesis was based on the knowledge that in the setting of nephron loss, remaining glomeruli undergo compensatory hypertrophy (glomerulomegaly) and hyperfiltration (increased single nephron glomerular filtration rate) to sustain adequate renal function. This adaptation, however, is at the expense of intraglomerular hypertension, which hastens injury to functioning glomeruli and perpetuates the vicious cycle of ongoing nephron loss, eventually resulting in a shift in the pressure-natriuresis curve and a lower glomerular filtration rate in low birth weight subjects. In our study population, the creatinine clearance was negatively associated with birth weight, but it did not influence the association between birth weight and salt sensitivity of blood pressure. The latter might be attributable to a lack of power of the present study set-up and the fact that creatinine clearance is not a sensitive marker of nephron number.

Kidney development is a complex process involving tightly controlled expression of several genes and constant remodeling. It has been shown that several factors can adversely affect nephrogenesis. Recently, elevated levels of fetal uric acid have been proposed as a possible deleterious factor explaining renal microvascular injury and a lower number of nephrons with subsequent salt sensitivity of blood pressure. In the present study, adult uric acid showed an inverse association with birth weight. In addition, uric acid was positively associated with salt sensitivity of blood pressure and inversely with microvascular function, although not statistically significant. Nevertheless, these findings may be compatible with the hypothesis that elevated uric acid levels in individuals may induce microvascular dysfunction with renal injury and salt sensitivity of blood pressure. However, an increased reabsorption of uric acid in the proximal tubule coupled to impaired renal sodium handling leading to subsequent hyperuricemia could also be a reflection of the impaired renal function in individuals with salt sensitive blood pressure rather than a causative factor. Our findings therefore remain inconclusive regarding the possible role of uric acid.

We have previously demonstrated a strong association of microvascular function with birth weight and salt sensitivity of blood pressure. On the basis of these findings, it could be argued that the explanatory role for microvascular function in the association between birth weight and salt sensitivity of blood pressure is smaller than could be expected. However, the sample size of the present study is smaller and hypertensive individuals were not included. Therefore, the power of the present study is lower than that in our previous studies. Nevertheless, it may seem surprising that we found a significant association in a relatively small population. However, whereas other studies used randomly selected individuals, our study population was selected to show a substantial variation in insulin sensitivity. Because insulin sensitivity is related to birth weight and salt sensitivity of blood pressure, selection on the basis of insulin sensitivity markedly increased the statistical power of our study.

Perspectives

In conclusion, birth weight is associated with salt sensitivity of blood pressure, and this may play a role in the maintenance of elevated blood pressure in individuals with a low birth weight. Creatinine clearance (Cockcroft and Gault formula), was associated with birth weight but did not influence the association between birth weight and salt sensitivity of blood pressure. These findings improve our understanding of the pathogenesis of the association of low birth weight with elevated blood pressure.

Sources of Funding

Renate T. de Jongh was supported by a grant from The Netherlands Organization for Health Research and Development (ZonMw 940-37-025), Etto C. Eringa is supported by the Dutch Diabetes Foundation (grant 2003.00.030) and the Dutch Kidney foundation (grant C03.2046).

Disclosures

None.

References


