Low Birth Weight Predicts Higher Blood Pressure But Not Dermal Capillary Density in Two Populations

R. John Irving, Angela C. Shore, Neville R. Belton, Robert A. Elton, David J. Webb, Brian R. Walker

Abstract—The association between low birth weight and high blood pressure is well established, but underlying mechanisms remain undefined. Vascular rarefaction, which may elevate peripheral vascular resistance, has been observed in capillaries of young men at risk for hypertension and men who had low birth weight. We looked for evidence that capillary rarefaction explains the association of low birth weight with high blood pressure in two cohorts. Participants in study 1 included 107 healthy boys aged 6 to 16 years recruited at random from a single school. Study 2 included 61 members of a cohort recruited at birth and studied at age 24 years. Measurements included indices of current size, blood pressure by automated sphygmomanometer, and dermal capillary density by video capillaroscopy of dorsal index finger skin after 10 minutes of venous occlusion. Lower birth weight predicted higher systolic blood pressure in both studies: in study 1, 3.57 mm Hg/kg birth weight (after adjustment for current height, 95% confidence interval 0.38 to 6.75, P<0.05); in study 2, 122±12 mm Hg in low birth weight (<2 kg) versus 115±9 in controls (P<0.05). Dermal capillary density was not associated in either group with birth weight or systolic blood pressure. We have found no evidence in these 2 cohorts that reduced capillary density explains the associations between lower birth weight and higher blood pressure. (Hypertension. 2004;43:610-613.)

Key Words: blood pressure ■ capillaries ■ children ■ vascular disease

Associations between low birth weight and high blood pressure in later life have been reported in many populations, but there is no consensus as to the mechanisms that underpin these observations. It has been suggested that cardiovascular and metabolic processes are “programmed” during an adverse intrauterine development, eg, because of impaired maternal nutrition. Animal studies suggest that there may be crucial windows during development when plasticity of structure and function is sensitive to external influences, and the exposed individual will subsequently display a permanently altered phenotype. A putative target for programming that could mediate subsequent hypertension and insulin resistance is alteration in microvascular structure. High blood pressure is characterized by increased peripheral resistance and normal cardiac output. Although the exact site of true resistance vessels in humans is unknown, in animal studies it is likely that the microcirculation, comprising vessels <100 μm in internal diameter, makes a significant contribution to peripheral resistance. Reduced microvascular density (ie, “rarefaction,” which predicts increased peripheral resistance) has been identified at early stages in the development of high blood pressure. It has been suggested by Tooke and Hattersley that diminished somatic and capillary growth as a result of insulin resistance could link the associations between birth weight and blood pressure. In support of this, there are reports that individuals born with low birth weight have rarefaction of capillaries in retinal and, after ischemia, in finger nailfold circulations. Rarefaction in established hypertension may be a cause or consequence of higher blood pressure. To test the hypothesis that capillary density is reduced throughout life as a result of the processes that result in low birth weight, we measured capillary density in children and young adults with known birth characteristics.

Methods

Study 1
We studied boys attending George Watson's College, a private, fee-paying school in Edinburgh. Participants were chosen randomly from each year group from ages 5 to 16 years. Parents of 110 boys were sent a questionnaire requesting parental size, offspring birth weight, and informed consent. Only 3 declined to allow their sons to participate. Maternal recall of birth weight has been shown previously to be accurate in adults. We studied boys attending George Watson's College, a private, fee-paying school in Edinburgh. Participants were chosen randomly from each year group from ages 5 to 16 years. Parents of 110 boys were sent a questionnaire requesting parental size, offspring birth weight, and informed consent. Only 3 declined to allow their sons to participate. Maternal recall of birth weight has been shown previously to be accurate in adults.12–14

Study 2
We have previously published an analysis of associations between birth weight and adult cardiovascular risk factors in this prospectively recruited cohort. Briefly, in the Simpson Memorial Maternity Pavilion in Edinburgh between November 1973 and February 1975, mothers of 72 low-birth-weight (<2000 g) babies agreed to participate. As controls, mothers of 54 normal birth weight (>2000 g) were included.

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g) babies born on the same day and matched for sex, birth order, and father’s social status were also recruited. Gestational age was estimated from the mother’s last menstrual period and by developmental assessment by a pediatrician. Low-birth-weight babies were classified as either having appropriate weight for gestational age (n=30) or having intrauterine growth retardation (IUGR) (n=42) by means of a cut-off of the 10th percentile on Gardner-Pearson growth charts. From 1998 to 1999, we contacted 81 of the original 126 babies, and 61 consented to a further study. Local research ethics committee approval and informed consent were obtained for both studies.

Clinical Measurements

Height, weight, and waist/hip ratio were recorded before the subject reclined on a couch. After 1 minute, blood pressure was recorded in the left arm using an automated sphygmomanometer (Omron HEM 705CP).

The index finger of the right hand was then positioned on the stage of a videomicroscope and secured gently in place with Blu-tak (Bostik Inc). Dermal capillary density was recorded on the dorsum of the middle phalanx of the right index finger by intravital videomicroscopy. The skin was prepared with a coating of clear nail varnish. Dermal capillaries were visualized using a microscope (Leitz; Leica UK) under illumination with a mercury filament lamp (Leitz). To maximize the number of perfused capillaries, venous occlusion was achieved by inflating a cuff (Peni-cuff; Hokanson) to 40 mm Hg around the base of the finger. After 10 minutes, 6 adjacent fields of 0.25 mm² were recorded via a television camera (Phillips LDH0703; KRP Power Source) onto videotape for 30 seconds. Calibration was checked periodically with a graticule (Gricules Ltd). Capillary counting was performed at a later date by an investigator who was blind to the blood pressure and birth weight data. In the adult participants in study 2, we also recorded 6 fields before inflation of the venous occlusion cuff to measure basal capillary number as well as maximal capillary number; this step was omitted in the children to improve compliance. In our hands, the intrasubject coefficient of variation for measurement of capillary density before venous occlusion was 8%, and after venous occlusion it was 7%.

Statistics

In study 1, data were normally distributed and comparisons were made by linear regression. In study 2, comparisons between groups were by unpaired Student t tests. Power calculations show that the sample size in study 1 gives 89% power to detect a difference of 4 capillaries/mm² at P<0.05, which is the magnitude of difference previously observed between adults with and without a familial predisposition to high blood pressure.

Results

Study 1

Characteristics of participants in study 1 are recorded in Table 1. Systolic blood pressure increased with older age (slope=2.02 mm Hg per year, r=0.50, P<0.0001), height (slope=0.32 mm Hg per cm, r=0.53, P<0.0001), and weight (slope=0.47 mm Hg per kg, r=0.66, P<0.0001).

Birth weights were normally distributed in the population (mean: 3.41 kg; range: 1.35 to 5.06 kg; Shapiro Wilks w test: not significant). Lower birth weight predicted lower childhood height after adjustment for age (2.90 cm/kg birth weight; 95% confidence intervals 0.59 to 5.21; P=0.01) but did not predict age-adjusted weight (1.37 kg/kg birth weight; −1.62 to 4.35; P=0.36) or body mass index (BMI) (−0.10 kg/m² per kg birth weight; −1.03 to 0.82; P=0.82). In simple regression analyses, birth weight did not predict systolic blood pressure (r=−0.14, P=0.15) or diastolic blood pressure (r=0.05, P=0.61). In multiple regression, after adjusting for the effects of age, height, and weight on blood pressure, lower birth weight predicted higher systolic blood pressure (Table 2). Diastolic blood pressure was not significantly predicted by birth weight in similar analyses (data not shown).

Capillary density was not recordable in 9 subjects. Data were rejected from another 4 subjects in whom fewer than 5 fields were countable. Technical failures occurred because of poor skin preparation or excessive movement. Younger age correlated with fewer countable fields (r=−0.30, P=0.002). In simple regression, capillary density was not significantly associated with birth weight (r=−0.01, P=0.91), systolic blood pressure (r=−0.03, P=0.77), or diastolic blood pressure (r=0.01, P=0.96). In multiple regression, capillary density did not confound...
TABLE 2. Multiple Regression Models to Predict Systolic Blood Pressure in Study 1

<table>
<thead>
<tr>
<th>Models</th>
<th>Adjusted B Coefficient with Systolic BP</th>
<th>95% Confidence Limits of B</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1 (R²=0.32)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight</td>
<td>−3.57</td>
<td>−6.75 to −0.38</td>
<td>0.03</td>
</tr>
<tr>
<td>Age</td>
<td>−0.40</td>
<td>−2.23 to 1.42</td>
<td>0.66</td>
</tr>
<tr>
<td>Height</td>
<td>0.39</td>
<td>0.11 to 0.67</td>
<td>0.01</td>
</tr>
<tr>
<td>Model 2 (R²=0.48)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight</td>
<td>−3.22</td>
<td>−5.95 to −0.50</td>
<td>0.02</td>
</tr>
<tr>
<td>Age</td>
<td>−0.74</td>
<td>−1.76 to 0.28</td>
<td>0.15</td>
</tr>
<tr>
<td>Weight</td>
<td>0.58</td>
<td>0.40 to 0.76</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Model 3 (R²=0.48)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight</td>
<td>−3.36</td>
<td>−6.27 to −0.46</td>
<td>0.02</td>
</tr>
<tr>
<td>Age</td>
<td>−0.67</td>
<td>−1.76 to 0.43</td>
<td>0.23</td>
</tr>
<tr>
<td>Weight</td>
<td>0.58</td>
<td>0.39 to 0.77</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Capillary density</td>
<td>0.23</td>
<td>−0.29 to 0.76</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Alternative models that predict systolic blood pressure in subjects in study 1. Omitting age from the analyses did not alter the association with birth weight and current size. B indicates beta coefficient.

associations between birth weight, current height or weight, and systolic blood pressure (Table 2).

Study 2
In study 2, the characteristics of the groups were published previously. As shown in Table 3, subjects in the low-birth-weight group had higher adult blood pressure, irrespective of whether they were in the premature group who were appropriate size for gestational age or in the group with IUGR. The IUGR group remained shorter and lighter as adults. In these adults, we counted capillary density before and after venous occlusion. Neither index of capillary density was different between the groups with differing birth weight and intrauterine growth (Table 3).

TABLE 3. Characteristics of Participants in Study 2

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Controls</th>
<th>All Low Birth Weight</th>
<th>Low Birth Weight Appropriate for Gestational Age</th>
<th>Low Birth Weight Intrauterine Growth Retardation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of males/females/females using oral contraceptive</td>
<td>11/16/4</td>
<td>13/21/4</td>
<td>9/10/2</td>
<td>4/11/2</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
<td>3.13±0.45</td>
<td>1.68±0.22†</td>
<td>1.66±0.22</td>
<td>1.70±0.22</td>
</tr>
<tr>
<td>Gestational age at birth (weeks)</td>
<td>39.3±1.9</td>
<td>33.4±2.3‡</td>
<td>31.9±1.5</td>
<td>35.2±1.7‡</td>
</tr>
<tr>
<td>Age when studied (years)</td>
<td>24.0±0.7</td>
<td>24.3±0.5</td>
<td>24.4±0.4</td>
<td>24.3±0.6</td>
</tr>
<tr>
<td>Adult height (m)</td>
<td>1.68±0.10</td>
<td>1.67±0.09</td>
<td>1.70±0.08</td>
<td>1.63±0.09*</td>
</tr>
<tr>
<td>Adult weight (kg)</td>
<td>64.9±11.1</td>
<td>66.9±12.7</td>
<td>71.7±13.4</td>
<td>60.8±8.7†</td>
</tr>
<tr>
<td>Adult systolic blood pressure (mm Hg)</td>
<td>115±9</td>
<td>122±12*</td>
<td>123±9</td>
<td>120±14</td>
</tr>
<tr>
<td>Adult diastolic blood pressure (mm Hg)</td>
<td>73±7</td>
<td>78±7*</td>
<td>80±7</td>
<td>77±6</td>
</tr>
<tr>
<td>Dermal capillary density before venous occlusion (per 0.25 mm²)</td>
<td>27.0±4.2</td>
<td>28.3±5.0</td>
<td>28.1±5.8</td>
<td>28.5±4.0</td>
</tr>
<tr>
<td>Dermal capillary density during venous occlusion (per 0.25 mm²)</td>
<td>29.0±4.3</td>
<td>30.7±5.6</td>
<td>30.1±6.5</td>
<td>31.3±4.7</td>
</tr>
</tbody>
</table>

Data are mean±SD. Comparisons were made between controls and all low-birth-weight subjects, and between AGA and IUGR, by unpaired Student t test.

*P<0.02. †P<0.001.

Discussion
These studies examined relationships between birth weight and blood pressure, dermal capillary density, height, and weight during childhood and in young adults. In both studies, lower birth weight predicted higher subsequent blood pressure. In the adults, as previously reported, this relationship occurred irrespective of whether the low birth weight was caused by IUGR or prematurity. In the children, we did not obtain data on gestational age at birth. However, in neither group did we find evidence that diminished dermal capillary density is a programmed mechanism that mediates the association between birth weight and blood pressure.

The current studies had similar power to detect capillary rarefaction as a previous study of 104 young adults, which demonstrated dermal capillary rarefaction in men with an inherited predisposition to high blood pressure but not in men with higher blood pressure whose parents had low blood pressure. In this previously studied cohort, we also provided evidence that the inheritance of high blood pressure cosegregates with low birth weight, leading us to propose that capillary rarefaction would be demonstrable in individuals of low birth weight throughout life. Although small effects cannot be excluded, we conclude from the current studies that the factors influencing birth weight and blood pressure, in a cohort of socio-economically advantaged boys and also in a highly selected cohort of premature and term babies, do not strongly influence dermal capillary density. This is in keeping with similar observations of resting capillary number in the skin in infants, prepubertal children, and adults. These studies explored the relationship between birth weight and capillary density in groups that were not preselected for hypertension risk. It may be true that if we had selected individuals with contrasting familial predisposition to hypertension, then we would have obtained different results.

These studies do not exclude the possibility that capillary density in other vascular beds may be influenced by birth weight, or that functional changes in the microcirculation are programmed by events in early life. Indeed, a previous study...
of middle-aged men did show a relationship between low birth weight and altered microvascular structure in the retinal circulation. Stehouwer’s group have reported microvascular abnormalities in the nailfolds of children and adults with low birth weight. The recruitment of capillaries to perfusion after ischemia was increased even though basal capillary numbers were not different. The mechanisms for these changes remain to be elucidated, but they appear to reflect functional rather than structural changes in blood vessels.

Other studies of microvascular function have shown that endothelium-dependent dermal vasodilatation was lower in 9-year-old children with low birth weight than in controls. This group also showed a correlation between carotid artery stiffness and low birth weight. Similar findings were demonstrated in a study of infants aged 3 months; however, impaired endothelial function in this study was found only in babies with low birth weight at term and not in premature and/or IUGR babies. Further, another study suggests that endothelial dysfunction is not the only mediator of altered vasodilator responses in low birth weight babies, because it showed diminished hyperaemic skin response to heating in low-birth-weight infants without any change in endothelium-dependent vasodilatation.

Perspectives
An attractive and topical explanation for links between low birth weight and adult disease is that intrauterine growth retardation prevents normal peripheral vascular development. We have found no evidence of programming of capillary density by birth weight in two cohorts in which lower birth weight predicted higher blood pressure. The decrease in dermal capillary density observed in adult men with a familial predisposition to hypertension appears not to be explained by permanent “programming” of vascular structure by events in early life. However, further studies on capillary and arteriolar structure in beds that make a greater contribution to peripheral vascular resistance remain of interest.

Acknowledgments
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References
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