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<td><strong>Author(s)</strong></td>
<td>Cheung, YF; Wong, KY; Barbara C C; Lam, BCC; Tsoi, NS</td>
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Relation of arterial stiffness with gestational age and birth weight

Y F Cheung, K Y Wong, Barbara C C Lam and N S Tsoi

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Relation of arterial stiffness with gestational age and birth weight

Y F Cheung, K Y Wong, Barbara C C Lam, N S Tsoi

Background: The cardiovascular risk of individuals who are born small as a result of prematurity remains controversial. Given the previous findings of stiffer peripheral conduit arteries in growth restricted donor twins in twin–twin transfusion syndrome regardless of gestational age, we hypothesised that among children born preterm, only those with intrauterine growth retardation are predisposed to an increase in cardiovascular risks.

Aim: To compare brachioradial arterial stiffness and systemic blood pressure (BP) among children born preterm and small for gestational age (group 1, n = 15), those born preterm but having birth weight appropriate for gestational age (group 2, n = 36), and those born at term with birth weight appropriate for gestational age (group 3, n = 35).

Methods: Systemic BP was measured by an automated device (Dinamap), while stiffness of the brachioradial arterial segment was assessed by measuring pulse wave velocity (PWV). The birth weight z score was adjusted for gestational age and expressed as a z score for analysis.

Results: The 86 children were studied at a mean (SD) age of 8.2 (1.7) years. Subjects from group 1, who were born at 32.3 (2.0) weeks’ gestation had a significantly lower z score of birth weight (−2.29 (0.63), p < 0.001), compared with those from groups 2 and 3. They had a significantly higher mean blood pressure (p < 0.001) and their diastolic blood pressure also tended to be higher (p = 0.07). Likewise, their brachioradial PWV, and hence arterial stiffness, was the highest of the three groups (p < 0.001). While subjects from group 2 were similarly born preterm, their PWV was not significantly different from that of group 3 subjects (p = 1.00) and likewise their z score of birth weight did not differ (−0.01 (0.71) v −0.04 (1.1), p = 1.00). Brachioradial PWV correlated significantly with systolic (r = 0.31, p = 0.004), diastolic (r = 0.38, p < 0.001), and mean (0.47, p < 0.001) BP, and with z score of birth weight (r = −0.43, p < 0.001). Multiple linear regression identified mean BP and z score of birth weight as significant determinants of PWV.

Conclusion: The findings of the present study support the hypothesis that among children born preterm, only those with intrauterine growth retardation are disadvantaged as a result of increase in systemic arterial stiffness and mean blood pressure.

It has been more than a decade since the first report of associations between low birth weight and increased risk of cardiovascular disease.1 These findings, having been replicated in a number of studies,2−4 have led to the "fetal origins hypothesis",5 which states that cardiovascular disease originates through adaptation to an adverse environment in utero. These adaptations may permanently alter the cardiovascular structure and physiology through the process of programming. However, the mechanisms that underlie the link between reduced fetal growth and increased cardiovascular risk remain speculative. There is accumulating evidence that vascular dysfunction occurs in individuals who are born small. Arterial endothelial dysfunction has been demonstrated in term infants,6 children,7 and young adults8 with low birth weight. Impaired synthesis of elastin in the arterial wall leading to an increase in arterial stiffness and accentuation of systolic afterload of the left heart has also been proposed as a possible mechanism.9 Indeed, impairment of fetal growth has been shown to associate with decreased compliance in the conduit arteries of the trunk and legs.10

In many of the previous studies, however, either the gestational age of the subjects has not been mentioned, or those subjects born preterm were excluded. Hence, the cardiovascular risk for individuals who are born small as a result of prematurity remains controversial.11 12 While Irving et al reported an increase in systolic blood pressure and fasting glucose in young adults born prematurely, whether or not they have intrauterine growth retardation,13 a more recent study failed to confirm their findings;12 flow mediated dilation in adolescents born preterm was shown not to differ from that of controls born at term,14 suggesting that low birth weight as a result of preterm birth is not associated with endothelial dysfunction.

We have previously demonstrated that growth restricted donor twins in twin–twin transfusion syndrome have stiffer peripheral conduit arteries than the recipients, regardless of the gestational age.15 It is perhaps reasonable to speculate that prematurity alone may not constitute a cardiovascular risk later in life. Rather, it is the discordance between birth weight and gestational age that may predispose to cardiovascular risks as adults. We hypothesised that among children born preterm, only those with intrauterine growth retardation are predisposed to an increase in cardiovascular risks. To test this hypothesis, we compared the peripheral conduit artery stiffness and systemic blood pressure among
children born preterm and small for gestational age (SGA), those born preterm but having birth weight appropriate for gestational age, and those born at term with birth weight appropriate for gestational age.

**PATIENTS AND METHODS**

**Subjects**

Children born between 1990 and 1996 were recruited. The birth weight was traced from the medical records, while the gestational age was estimated from the mother’s last menstrual period. Invitation letters were sent to addresses as retrieved from the records. To maximise the inclusion rate, stamped addressed envelopes were sent and flexible appointment times arranged. A total of 650 invitation letters were sent, and responses were obtained from 110 families. The parents of 86 children (78%) agreed to participate in the study.

Subjects were classified as being born SGA when the birth weight is below the 10th percentile on the growth chart derived from 15,815 Hong Kong Chinese live births.14 Prematurity is defined by a gestation age of less than 37 weeks. Based on gestational age and birth weight, the cohort was categorised into three groups: group 1 comprised 15 patients who were born preterm and SGA, group 2 comprised 36 children who were born preterm but with birth weight appropriate for gestation, and group 3 comprised 35 patients who were born at term with birth weight appropriate for gestation; group 3 therefore acted as controls. Furthermore, based on normal population data,14 the birth weight was converted to z score, adjusted for gestational age, for subsequent analysis. The institutional ethics committee approved the study and all parents of the subjects gave written informed consent.

All subjects were well at the time of the study and none had any chronic disease or disability. The body weight and height were measured and body mass index was calculated accordingly. All subjects rested for at least 15 minutes before blood pressure and cardiovascular assessments, and remained supine throughout. Blood pressure in the right arm was measured twice using an automated oscillometric device (Dinamap, Critikon), and the average of two readings was used for analysis. The cuff size was selected in accordance with the recommendations of 1987 Report of the Second Task Force on Blood Pressure Control in Children.15

**Principle and measurement of pulse wave velocity**

The peripheral conduit arterial stiffness was estimated by measuring the pulse wave velocity (PWV) across the brachioradial arterial segment. PWV is related to the mechanical properties of an arterial segment. The mathematical model is represented by the Moens-Korteweg equation16:

\[
PWV = \sqrt{\frac{Eh}{2pR}},
\]

where \(E\) is the elastic modulus of the arterial wall, \(h\) is wall thickness, \(R\) is arterial radius, and \(p\) is blood density. The PWV depends, therefore, on arterial stiffness, as represented by the elastic modulus. Arterial stiffness is important as it is related to the impedance of the arterial tree, which constitutes the pulsatile component of vascular resistance, and in turn contributes to the pulsatile afterload that is presented to the left ventricle.17

The PWV in the brachioradial arterial segment was measured by a non-invasive photoplethysmographic technique.18 Two photoprobe pairs were placed over the right brachial and right radial arteries and secured without compression. The infrared beam is scattered by the skin and other soft tissue and strongly absorbed by the blood as it passes along the blood vessel. The signals generated from the varying fraction of reflected beam, due to pulsatile changes of the arterial diameter, are converted into waveforms. The transit time was determined from the time delay between the foot of the corresponding brachial and radial pulse waves, as this point is relatively free of wave reflection.19 The foot was determined by an algorithm that identified the point at which the smoothed second derivative of the diameter waveform was maximum.20 The PWV was then derived by dividing the measured distance, to the nearest millimetre, between the two probes by the transit time. The intraobserver variability for measurement of PWV, as determined from the mean and standard deviation of differences in two consecutive results from 20 studies, was 0.08 (0.82) m/s. The interobserver variability was 0.18 (1.1) m/s. The measurements of distance and transit time were repeated when assessing the intra- and inter-observer variability.

**Statistical analysis**

All data are presented as mean (SD) unless otherwise stated. Demographic and haemodynamic parameters among the three groups were compared using analysis of variance, with post hoc comparison by the Bonferroni test. The Pearson correlation coefficient was calculated for assessment of possible associations between PWV and other variables. Multiple linear regression was performed to identify significant determinants of PWV and systemic blood pressure. A p value of <0.05 was considered statistically significant. All analyses were performed using SPSS (version 10.0; SPSS, Chicago, IL, USA).

**RESULTS**

**Subjects**

A total of 86 subjects were studied at an age of 8.2 (1.7) years (range 5.7 to 12.6). The demographic and anthropometric data are summarised in table 1. Group 1 comprised 15 subjects who born preterm at 32.3 (2.0) weeks of gestation with a gestational age adjusted z score of birth weight of −2.29 (0.63). Group 2 comprised 36 subjects who, although born similarly preterm at 29.4 (2.9) weeks of gestation, had a significantly greater z score of birth weight (−0.01 (0.71), p<0.001). Group 3 comprised 35 subjects who were born at term with an z score of birth weight of −0.04 (1.1). There was no significant difference in the gestational age-adjusted birth weight between group 2 and 3 subjects (p = 1.00). At the time of the study, there were no significant differences between body weight, height, and body mass index among the three groups.

**Systemic blood pressure**

Subjects in group 1 had a significantly higher mean blood pressure (one way analysis of variance, p = 0.01), compared with those in groups 2 (p = 0.04) and 3 (p = 0.01) (table 2). Their diastolic blood pressure also tended to be higher (one way analysis of variance, p = 0.07). Furthermore, although the difference in systolic blood pressure among the three groups did not reach statistical significance, there was a trend towards higher blood pressure in group 1 subjects (p = 0.11).

For assessment of significant determinants of mean blood pressure of the entire cohort, the following dependent variables were included: age, sex, body mass index, and PWV. Significant determinants were age (β = 1.14, p = 0.006) and PWV (β = 1.74, p<0.001; model \(r^2 = 0.29\)). Even after covariance adjustment for age and PWV, the mean blood pressure of group 1 subjects remained significantly higher (one way analysis of variance, p = 0.029) (table 2).
**Pulse wave velocity**

The PWV was significantly greater in subjects in group 1 (9.45 (1.79) m/s) compared with those in groups 2 (7.29 (1.85) m/s, \( p < 0.001 \)) and 3 (7.09 (1.20) m/s, \( p < 0.001 \)) (fig 1). There was, however, no significant difference in PWV between subjects in group 2 compared with those in group 3 (\( p = 1.00 \)). Hence, while these two groups differed significantly in their gestational age (\( p < 0.001 \)), their peripheral conduit arterial stiffness remained similar.

**Determinants of arterial stiffness**

The results of univariate analysis to detect associations between PWV and other variables are summarised in table 3. Brachioradial arterial stiffness correlated significantly with systolic (\( p = 0.004 \)), diastolic (\( p < 0.001 \)), and mean blood pressure (\( p < 0.001 \)). While no significant correlation existed between gestational age and PWV (\( p = 0.81 \)) and between birth weight and PWV (\( p = 0.28 \)), a significant negative correlation existed between gestational age adjusted \( z \) score of birth weight and PWV (\( r = -0.43, p < 0.001 \)) (fig 2). When the significant variables were entered into a multivariate model (\( R^2 = 0.39 \)), only the \( z \) score of birth weight (\( \beta = -0.61, p < 0.001 \)) and mean blood pressure (\( \beta = 0.11, p < 0.001 \)) remained significant determinants of PWV and hence arterial stiffness.

**DISCUSSION**

This study demonstrates that peripheral conduit arterial stiffness and mean systemic blood pressure are increased in children who are born preterm and small for gestational age. Additionally, our findings suggest that children whose birth weight is appropriate for gestation are not predisposed to such cardiovascular risk factors, regardless of the gestational age. Indeed, the birth weight standardised for gestational age is negatively correlated with and is a significant determinant of arterial stiffness.

The cardiovascular risk for individuals who are born small as a result of prematurity has been controversial. In a cohort of 34 young adults born prematurely, Irving et al reported an increase in systolic blood pressure and fasting glucose, regardless of whether or not the individuals had intrauterine growth retardation. However, their conclusion has been questioned as the two groups were not totally comparable.

Recently, Singhal et al concluded, based on findings in a large cohort of 216 subjects born preterm, that low birth weight as a result of prematurity is not associated with endothelial dysfunction as assessed by brachial arterial flow mediated dilation. However, in their secondary analysis, individuals who had been preterm babies with intrauterine growth retardation did have a significantly lower

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**Table 1** Demographic and anthropometric data of the children in the three groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 (n = 15)</th>
<th>Group 2 (n = 36)</th>
<th>Group 3 (n = 35)</th>
<th>( p^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>7.4 (1.4)</td>
<td>8.3 (1.8)</td>
<td>8.4 (1.6)</td>
<td>0.14</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>10/5</td>
<td>14/22</td>
<td>15/20</td>
<td>0.18</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>24.1 (10.1)</td>
<td>27.2 (10.0)</td>
<td>27.8 (7.9)</td>
<td>0.42</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.22 (0.13)</td>
<td>1.26 (1.35)</td>
<td>1.30 (0.11)</td>
<td>0.10</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>15.4 (3.0)</td>
<td>16.6 (2.7)</td>
<td>16.1 (2.5)</td>
<td>0.34</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>32.3 (2.0)</td>
<td>29.4 (2.9)</td>
<td>39.5 (2.1)</td>
<td></td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1245 (242)</td>
<td>1381 (433)</td>
<td>3253 (396)</td>
<td></td>
</tr>
<tr>
<td>( z ) score of birth weight</td>
<td>-2.29 (0.63)</td>
<td>-0.01 (0.71)</td>
<td>-0.04 (1.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*One way analysis of variance

BMI, body mass index

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**Table 2** Systemic blood pressure of children in the three groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 (n = 15)</th>
<th>Group 2 (n = 36)</th>
<th>Group 3 (n = 35)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td>105 (9)</td>
<td>103 (9)</td>
<td>102 (8)</td>
<td>0.5</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>56 (7)</td>
<td>53 (6)</td>
<td>51 (6)</td>
<td>0.07</td>
</tr>
<tr>
<td>Mean BP</td>
<td>75 (8)</td>
<td>72 (7)</td>
<td>68 (6)</td>
<td>0.01</td>
</tr>
<tr>
<td>*Adjusted mean BP</td>
<td>73 (4)</td>
<td>70 (4)</td>
<td>70 (3)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

*Adjusted for age and pulse wave velocity

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**Table 3** Determinants of pulse wave velocity

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
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<tr>
<td></td>
<td>( R )</td>
<td>( p )</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.11</td>
<td>0.33</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.19</td>
<td>0.14</td>
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<tr>
<td>Height (m)</td>
<td>0.12</td>
<td>0.29</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.14</td>
<td>0.19</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>-0.12</td>
<td>0.28</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>0.03</td>
<td>0.81</td>
</tr>
<tr>
<td>( z ) score of birth weight</td>
<td>-0.43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.31</td>
<td>0.004</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.38</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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**Figure 1** Box plots of pulse wave velocity of subjects in the three groups. Bold lines represent the medians in each group. *\( p < 0.001 \) v group 1.
flow mediated dilation. Our findings similarly suggest that it is this group of subjects who are predisposed to the cardiovascular risks of increased systemic arterial stiffness and blood pressure in the present study.

The mechanism whereby discordance between birth weight and gestational age leads to an increase in arterial stiffness in children born preterm remains unclear. However, given the critical role of the endothelium in the control of vascular tone, the reported impairment of endothelial function in individuals born preterm and SGA suggests that functional alteration of arterial tone may contribute to an increase in systemic arterial stiffness. In children born at term, leanness at birth, as defined by a lower weight for length at birth, has been reported to correlate with the lowest endothelium dependent microvascular responses and the highest carotid stiffness indices. Interestingly, in this study, those who had been proportionately small at birth had vascular function that did not differ significantly from those in the controls. The altered haemodynamics in intrauterine growth retardation that result in preferential perfusion of upper part of body may affect the mechanical properties of the large arteries concerned. Thus, selective atherosclerotic degeneration of the carotid arteries in elderly people has been demonstrated to be more severe in those with the lowest birth weight. Structural alteration of the brachioradial arteries as a result of antenatal disturbance of haemodynamics may hence operate in a similar fashion in our cohort, and accounts for the increased arterial stiffness of the upper limb arteries.

Additionally, accelerated rates of postnatal growth in early childhood in babies with low birth weight may exert influence on the systemic blood pressure later in life. Increased weight gain in later childhood or adolescence has been reported to be associated with higher cardiovascular risk in adult life. Law et al have further shown that lower birth weight and greater weight gain between 1 and 5 years of age are associated with higher systolic blood pressure in young adult life. The risk is partly mediated through predilection of arterial fatness. In the present study, however, we did not have adequate postnatal growth data to address on this issue. Nevertheless, the fact that subjects in group 1 have growth parameters similar to those in groups 2 and 3 would suggest the presence of catch up growth, and hence its associated implications. Whether postnatal catch up growth impacts on arterial stiffness, however, remains unknown.

A reduction in arterial compliance increases the impedance of the arterial tree, thus increasing the pulsatile component of the afterload that is presented to the left ventricle. Furthermore, increased arterial stiffness may contribute to the pathogenesis of hypertension. The relation between systemic blood pressure and birth weight becomes progressively stronger with increasing age. It is hypothesised that the initiating process occurs in utero and amplifies throughout life. Interactions between increased arterial stiffness, increased pulse pressure, stretching of vascular smooth muscles, and synthesis of collagen may contribute to this amplification phenomenon through establishment of a feedback loop.

The relatively small number of subjects has undoubtedly diminished the power of the study. Nevertheless, the highly statistically significant results suggest that the positive findings obtained are genuine rather than being due to chance. Blood samples for fasting cholesterol and glucose levels were not obtained from our subjects, as previous studies did not detect significant differences in these parameters between children born preterm and those born at term.

In summary, the findings of the present study support the hypothesis that among children born preterm, only those with intrauterine growth retardation are more disadvantaged as a result of increased systemic arterial stiffness and mean blood pressure. In contrast, children born preterm, but with birth weight appropriate for gestational age, are not predisposed to such cardiovascular risks.

ACKNOWLEDGEMENT
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Authors’ affiliations
Y F Cheung, Division of Paediatric Cardiology, Department of Paediatrics and Adolescent Medicine, Grantham Hospital, Hong Kong, China
Y Y Wong, Barbara C C Lam, N S Tsoi, Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong, China

REFERENCES
Sternal fractures

There have been few reports of isolated fracture of the sternum in children. It is widely believed that such fractures are caused by a powerful blow to the chest, with a high likelihood of intrathoracic injury, such as may occur in a car crash. Experience at the children’s hospital in Edinburgh, however, suggests that sternal fracture may be a result of less dramatic trauma (L.P. Ferguson and colleagues. *Emergency Medicine Journal* 2003;20:518–20).

Children with possible sternal injury, including all children who had plain radiography of the sternum and all who had CT of the chest after trauma, were identified from the hospital’s radiology database for July 1998 to October 2001. There were 33 children in all, 12 of whom had sternal fracture on plain films. These twelve were 8 girls and 4 boys aged 5 to 12 years. Seven children had had a direct blow to the anterior chest wall, 4 on falling from a bicycle, and the other three after falling in the street, in the bath, and from a trampoline. Five children had sternal fractures caused by hyperflexion of the thoracic spine after falling on their backs. Three of these fell while bouncing (two on a trampoline, one on a bouncy castle) and two fell from five or six feet (one from a tree, one from a gymnasium bar). None of the children had been involved in a car crash.

Eleven children had an undisplaced fracture of the anterior cortex of the first or second sternebra of the body of the sternum. One girl had a displaced fracture through the manubriosternal joint after falling at high speed from a bicycle onto a wall. Her fracture reduced spontaneously but redislocated after 4 days and needed internal fixation. No child had serious spinal or intrathoracic injury and all children with isolated anterior cortical fracture were discharged from the emergency department and came to no harm, though they often needed analgesia for pain on deep inspiration for several weeks.

Children may have sternal fractures after relatively minor trauma. Rib fractures, common in adults with sternal injuries, did not occur in these children. The sternum may be fractured after either a direct blow to the anterior chest wall or a fall on the upper back causing flexion-compression injury.