Low Birth Weight as a Marker of Changes in Ambulatory Blood Pressure Monitoring

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Summary
Background: Low birth weight (LBW) is associated with increased incidence of high blood pressure (BP) and cardiovascular diseases in adulthood.

Objective: To evaluate possible changes in Ambulatory Blood Pressure Monitoring (ABPM) in LBW children.

Methods: The birth weight (BW) of 1049 school children (ages 8 to 11) living in Goiânia was assessed. Children with low birth weight (BW ≤ 2.5 Kg) were compared with those of normal birth weight (BW ≥ 3.0 Kg). Information on birth weight was obtained from each child’s health card. Casual BP and ABPM were measured. Height and weight measurements were obtained to calculate the body mass index (BMI), and sexual maturity was assessed according to Tanner’s criteria (those at Tanner stage ≥ 2 were excluded).

Results: Thirty-four children had low birth weight (LBW) and 34 had normal birth weight (NBW). Both groups were similar regarding age, gender, race, body weight, height, BMI, and family history of hypertension. Low-birth-weight children had higher casual systolic blood pressure (SBP) (p = 0.007). ABPM recordings showed that these children had higher 24-hour diastolic blood pressure (DBP) (p = 0.009), daytime DBP (p = 0.002), night-time DBP and SBP (p = 0.005 and p = 0.001), and reduced nocturnal dip in SBP and DBP (p = 0.001) than those born with normal weight. Birth weight was positively correlated with nocturnal dip in SBP (p = 0.022) and negatively correlated with sleep SBP (p = 0.032).

Conclusion: Low-birth-weight children have higher BP and changes in circadian rhythm of blood pressure, with reduced nocturnal dipping. These findings may reflect increased risk of adult hypertension and cardiovascular diseases. (Arq Bras Cardiol 2009;92(2):107-115)

Key words: Infant, low birth weight; monitoring ambulatory; blood pressure.

Introduction
Hypertension is one of the leading causes of premature death worldwide. It affects approximately 25% of the adult population and its prevalence increases with age1. Epidemiological evidence indicates that low birth weight is a key determinant for the development of hypertension3, ischemic heart disease4,5, and type-2 diabetes6. This suggests that factors present in the prenatal period cause persistent metabolic changes that predispose to disease in adult life7. On the other hand, intrauterine growth retardation affects approximately 30 million newborns per year, 95% of them in poor and developing countries in various regions of the world8. There is no consensus on the correlation between low birth weight and increased blood pressure in children and adolescents. Some studies have demonstrated this association9-10, whereas others did not11,12.

Ambulatory blood pressure monitoring (ABPM) allows multiple indirect measurements of blood pressure during 24 hours or more, with a minimum amount of discomfort and is done during daily activities. A curve representing variability in blood pressure over a period of time provides a dynamic view of its behavior, rather than merely a static observation reflecting only the time at which BP was measured. ABPM is feasible in children, showing reproducible data in several consecutive studies13. With the development of lighter oscillometric devices, this method can be used in younger children, in whom accurate readings are difficult with exclusively auscultatory devices, because of their high level of activity14. Studies with hypertensive adults demonstrate that 24-hour blood pressure readings (day and night) are
more correlated with target-organ damage, either clinical or subclinical, than office readings\textsuperscript{15}. There is also evidence that ABPM values have higher predictive value for cardiovascular risk than office values\textsuperscript{16}.

This study was designed to evaluate possible changes in ambulatory blood pressure monitoring (ABPM) in prepubertal children with low birth weight.

**Method**

Study sample was drawn from the database of the CARMEN initiative, an intervention strategy aimed at reducing mortality due to non-communicable diseases – Subproject Health Promoting Schools\textsuperscript{17}. A total of 1049 children enrolled in eight schools in the city of Goiânia, Brazil, were included in the study. Ages ranged from 8 to 11, and 534 were boys. Birth weight was obtained from the child health card (a card that the family receives from the hospital containing information on labor and delivery).

The birth weight of 852 children (81.22\%) was obtained, 82 (9.62\%) of whom were considered low birth weight (≤ 2.5 Kg). These children were invited to participate in the study and compared with an age-matched group of children of the same school randomly selected among 647 of normal birth weight (≥ 3.0 Kg).

Medical examinations were scheduled for those who agreed to take part in the study (57 children, 69.5\% of the initial sample). Exclusion criteria were the following: The presence of disease (chronic or at the time of examination); history of glomerulopathy, urinary tract infection (recurrent or in the previous three months), vesicoureteral reflux, or renal scarring; and Tanner stage ≥ 2 of sexual maturity\textsuperscript{18}. Based on these criteria, 21 children were excluded (14 for being at Tanner stage 2 or above, four whose birth weight could not be confirmed, and five who met other exclusion criteria).

The study protocol was approved by the Human and Animal Experimentation Ethics Committee of Hospital das Clínicas (filed under number 122/03) and by the departments of education of the State of Goiás and of the City of Goiânia. Children were included in the study after a written informed consent was obtained from their parents or guardians.

During the medical examination the physician completed a form with patients’ identification, age, gender, race (classified as white and non-white according to their phenotypic characteristics). Data on birth weight and prematurity (gestational age < 37 weeks) were derived from each child’s health card, and the presence of family history of hypertension was investigated through interview.

Duration of breastfeeding was assessed according to the following categories and indicators proposed by the World Health Organization\textsuperscript{19}:

- **EBF** - Exclusive breastfeeding: length of time the infant was exclusively breastfed;
- **PBF** - Predominant breastfeeding: length of time the infant was breastfed, but also received water, tea, or fruit juice.

In this study, duration of breastfeeding was considered as the period the infant was in EBF and/or PBF. Height and weight were measured to calculate the body mass index (BMI)\textsuperscript{20}, and sexual maturity was assessed according to Tanner criteria. Blood pressure was measured using calibrated aneroid sphygmomanometers, with cuff size appropriate for the child’s arm circumference, according to the technique standardized by the 4\textsuperscript{th} Task Force\textsuperscript{21}.

Blood pressure was measured twice, ten minutes apart, on two different occasions, and the mean value of the four readings (casual BP) was considered.

**Ambulatory blood pressure monitoring (ABPM)**

ABPM was performed at the Hypertension Division of the Federal University of Goiás using a SPACELABS 90207 device, validated for the pediatric population\textsuperscript{22}, with a cuff of the same size as that used to measure casual BP and according to the technique described by the American Heart Association Council on High Blood Pressure Research\textsuperscript{23}. The device was programmed to obtain BP readings every 20 minutes from 7:00 AM to 10:00 PM and every 30 minutes from 10:00 PM to 7:00 AM. Recordings with at least 80\% of valid readings and at least one reading every hour were considered for the analysis.

Sleep and wake periods were defined on the basis of the actual times reported in a diary completed by the child’s parents/guardians. The following parameters were analyzed: mean 24-hour BP (systolic and diastolic), mean awake and sleep BP, plus nocturnal systolic and diastolic dipping (percent decline in BP during sleep). The latter was calculated by subtracting mean night-time BP from mean daytime BP and dividing this value by the mean daytime BP.

**Statistical analysis**

Study variables were compared between the two groups: LBW children and NBW children. The chi-square test was used to compare categorical variables, and Student’s t-test for continuous variables. Pearson’s correlation coefficient was calculated to check for a possible association between birth weight and the other variables, for every child and each group separately. Logistic regression analysis was performed to evaluate the influence of family history of hypertension and prematurity on casual BP and ABPM. Multiple linear regression analysis was performed using BP and nocturnal dip values as dependent variables and BW, age, gender and current body weight, height, and BMI as independent variables. P values ≤ 0.05 were considered statistically significant in all analyses.

SPSS 10.0 software (SPSS, Chicago, IL, USA) was used to create a database and for statistical analyses.

**Results**

**Sample characteristics**

Of the 36 children selected for the study group, two were excluded for failure to complete the necessary examinations. One of them did not tolerate ABPM and the other was unable to sleep during monitoring. Overall, ABPM was well tolerated by the children, and there were no reports of major interference with sleep on the diaries completed by the parents/guardians. Thirty-four children who completed the protocol were included.
in the study and compared with 34 NBW peers.

Table 1 summarizes the clinical and anthropometric characteristics of the participants. Distribution by gender, race, age, and anthropometric parameters was similar in both groups, and no differences were found regarding family history of hypertension. The LBW group showed a greater proportion of premature children and shorter duration of breastfeeding than the NBW group. 

There was a positive correlation between birth weight and duration of breastfeeding \( r = 0.367 \) and \( p = 0.002 \). 

**Blood pressure measurements: casual BP and ABPM**

Casual BP and ABPM readings are shown in Table 2. LBW children had higher casual systolic BP (SBP), higher mean 24-hour and daytime DBP, and higher mean night-time SBP and DBP than NBW children. In addition, they had reduced nocturnal systolic and diastolic dipping (Figures 1 and 2).

Logistic regression analysis showed that family history of hypertension was correlated with casual SBP \( p = 0.03 \), mean 24-hour SBP \( p = 0.01 \), and mean night-time SBP \( p = 0.03 \).

Offspring of hypertensive parents were excluded from the study, and a subsample of 22 LBW children and 26 NBW children was analyzed. During ABPM, NBW children showed higher daytime DBP and night-time SBP and DBP \( p = 0.025; p = 0.024 \) and \( p = 0.018 \), respectively, in addition to reduced nocturnal systolic dipping \( p = 0.002 \). No study variable was found to be significantly influenced by prematurity, as shown by the logistic regression analysis. Moreover, when premature children were excluded (leaving 24 LBW and 33 NBW children) the results were not affected (Table 3).
Correlation between birth weight and blood pressure (casual and ABPM)

Birth weight was not correlated with current anthropometric measurements (body weight, height, and BMI). However, it was negatively correlated with night-time SBP ($r = -0.244$ and $p = 0.046$) and positively correlated with nocturnal dipping in SBP and DBP (Figures 3 and 4).

In the multiple regression analysis, only birth weight was independently correlated with nocturnal SBP dipping ($p = 0.032$). Current anthropometric measurements (body weight, height, and BMI), duration of breastfeeding, and casual BP and ABPM readings were excluded from this analysis.
Table 3 - Office blood pressure and ABPM in full-term children

<table>
<thead>
<tr>
<th></th>
<th>LBW n = 24</th>
<th>NBW n = 33</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casual SBP</td>
<td>106.32±12.66</td>
<td>100.62±9.34</td>
<td>0.055</td>
</tr>
<tr>
<td>Casual DBP</td>
<td>61.77±5.24</td>
<td>61.90±8.59</td>
<td>0.940</td>
</tr>
<tr>
<td>24-hour SBP</td>
<td>115.58±15.87</td>
<td>108.81±7.18</td>
<td>0.061</td>
</tr>
<tr>
<td>24-hour DBP</td>
<td>69.95±6.07</td>
<td>65.09±4.39</td>
<td>0.001</td>
</tr>
<tr>
<td>Daytime SBP</td>
<td>117.87±14.55</td>
<td>113.08±7.18</td>
<td>0.147</td>
</tr>
<tr>
<td>Daytime DBP</td>
<td>73.65±6.57</td>
<td>69.37±5.10</td>
<td>0.011</td>
</tr>
<tr>
<td>Night-time SBP</td>
<td>111.34±18.65</td>
<td>100.60±7.79</td>
<td>0.013</td>
</tr>
<tr>
<td>Night-time DBP</td>
<td>64.03±7.40</td>
<td>57.48±4.61</td>
<td>0.001</td>
</tr>
<tr>
<td>Nocturnal SBP dip</td>
<td>6.38±5.65</td>
<td>12.79±5.60</td>
<td>0.001</td>
</tr>
<tr>
<td>Nocturnal DBP dip</td>
<td>6.04±4.89</td>
<td>11.74±5.10</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values expressed as mean ± standard deviation; Student’s t-test for two independent variables; ABPM - ambulatory blood pressure monitoring; DBP – diastolic blood pressure; SBP – systolic blood pressure.

Figure 3 - Correlation between birth weight and nocturnal systolic dip. Pearson’s correlation; r = 0.277 and p = 0.022.

No correlation was found between duration of breastfeeding and current anthropometric measurements (body weight, height, and BMI) or between duration of breastfeeding and blood pressure readings.

Discussion

In some studies, LBW has been associated with increased risk of hypertension. Our findings provide further evidence in this direction, since BP was higher in prepubertal children with LBW than in their NBW counterparts. A change in BP circadian rhythm was also found (reduced nocturnal dipping). It is worth noting that this change is related to increased risk of cardiovascular disease and mortality in adulthood.

LBW definition merits further consideration. It is known that birth weight represents a raw measurement of a dynamic process, and that it does not evaluate the effects of fetal undernutrition on body composition and development of specific tissues. In our study, LBW was defined as ≤ 2.5 Kg. This cut-off value has already been used in other studies.
examining the association between LBW and disease later in life\textsuperscript{2,23}. Children with birth weights between 2.5 and 3.0 Kg were not assessed, because this weight range might have included some who had failed to reach their intrauterine growth potential, leading to confusing results. Only school children were selected, because at this age they cooperate with ambulatory blood pressure measurement.

In this study, casual BP was higher in LBW than in NBW children. This finding was consistent with that reported in other studies, some of them involving children of the same age group\textsuperscript{2,10,23,24}. Of note, study groups were homogeneous regarding current body weight, height, and BMI, indicating that their present nutritional status was not a determinant factor for the differences observed. These findings are similar to those reported by Law et al\textsuperscript{10}, who have shown that elevated blood pressure is related to reduced body size at birth in children from China, Guatemala, and Chile, regardless of current body size. Other authors have not found raised blood pressure in LBW children, contradicting the fetal “programming” hypothesis. They suggest that postnatal factors, which come into play during childhood, have more effect on BP than intrauterine factors\textsuperscript{11,12,25}.

ABPM showed that LBW children had higher 24-hour and daytime DBP, higher night-time SBP and DBP, and reduced nocturnal dip in SBP and DBP than NBW children. We found a negative relationship between BW and night-time SBP and a positive relationship between BW and nocturnal dip in SBP and DBP, and this relationship was not influenced by BMI, age, gender, or BP readings. This is interesting data, because clinical trials using ABPM show that cardiovascular complications associated with hypertension are more common in subjects who do not experience the usual nocturnal dipping in blood pressure (non-dippers)\textsuperscript{14}. Thus, left ventricular hypertrophy, silent cardiovascular disease, microalbuminuria, and progression of renal lesion are greater in non-dippers\textsuperscript{14}.

A similar result was reported by Veening et al\textsuperscript{26} in a study with prepubertal children. These authors found higher night-time SBP in children born small for gestational age, with no difference in daytime BP. However, Lurbe et al\textsuperscript{27,28} studied children and adolescents (ages 4 to 18), also reported elevation in daytime and night-time blood pressure in 35 LBW children. Nonetheless, unlike our study, no change in BP circadian rhythm was found.

These contradictory results may be due to a number of factors, since it is known that the relationship between BW and BP strengthens with age, suggesting that this process begins in the uterus and is amplified throughout life and that it may be subject to many influences\textsuperscript{12,25,29}.

As we know, during adolescence, with the onset of puberty, several hormonal factors promote growth and accelerated, heterogeneous body changes, which may mask differences and associations under study. Therefore, unlike the studies by Lurbe et al\textsuperscript{27,28}, we assessed only prepubertal children. Onset of puberty was the most common reason for exclusion from
the study (67% of all exclusions). Of the 59 children who attended the initial visit, 14 (23.7%) had already entered puberty and were excluded. Veening et al reported similar results regarding BP circadian rhythm in a study involving only prepubertal children.

Another difference was that nocturnal dipping during ABPM was calculated using the actual awake and sleep times derived from the children’s diaries. This method is currently regarded as superior to that using a default for day-night definition, because it adds accuracy to the measurement of physiological nocturnal dipping. Such methodological difference may lead to contradictory results, particularly regarding nocturnal dipping.

Nocturnal dipping assessed by ABPM may be affected by changes in quality of sleep caused by the device itself and by intermittent BP readings, which may interfere with the results. Even though assessment of quality of sleep was not part of our study, data from ABPM recordings did not reveal major changes in the sleep pattern of these children. Furthermore, this factor would have influenced the results of both groups (study and control) and, therefore, did not account for the differences found in our study.

Some factors that could have interfered with the results of this study were analyzed separately. Among them, duration of breastfeeding, prematurity, and family history of hypertension merit discussion. A number of studies have demonstrated that breastfed infants have lower blood pressure later in life than those who were not breastfed. Our study revealed that LBW children were breastfed for shorter periods than those with NBW. In addition, there was a positive correlation between BW and duration of breastfeeding. This is worrisome, since children predisposed to future cardiovascular disease are exactly those who were breastfed for a shorter time. In our case, however, the difference in nocturnal dipping of systolic pressure between LBW and NBW children cannot be attributed to shorter duration of breastfeeding, as shown by multiple regression analysis.

Cardiovascular risk in subjects who were born small because of premature delivery is controversial. This factor was not responsible for the differences in BP found in our study, because being a full-term or pre-term child had no effect on BP, as shown by logistic regression analysis. Moreover, differences in BP, both casual and ABPM, were unaffected by exclusion of premature children.

Another factor that may have influenced BP readings was family history of hypertension. In our study, the genetic factor was ruled out as cause of differences observed. Firstly, because study groups were similar regarding family history of hypertension, and secondly because when offspring of hypertensive parents were excluded, differences in BP between LBW and NBW children remained unchanged.

A number of hypotheses have been proposed as possible causes correlating LBW to elevation in BP. Veening et al attribute this finding to reduced insulin sensitivity in LBW children, a finding that was confirmed by Yajnik et al. Another hypothesis would be a change in the pressure-natriuresis curve, as pointed by Lurbe et al. These authors found that LBW children tend to excrete less sodium during sleep than NBW children. Impaired ability to excrete sodium, therefore, may predispose to a progressive increase in BP levels throughout life.

Several authors have demonstrated the influence of socioeconomic status on the relationship between BW and later disease. In our study, all children, both LBW and NBW, were selected from within the same population (they were neighbors and attended the same schools). Therefore, although social status was not assessed individually, any significant socioeconomic difference among them can be ruled out. Socioeconomic status may have influenced the results in another manner, since these children were selected from a population experiencing an epidemiological and nutritional “transition” and that has been described as more likely to develop the adverse effects of LBW on their health later in life.

Our findings suggest that school children with low birth weight have higher blood pressure and reduced nocturnal dip than those born with normal weight. These findings may indicate increased risk for adult hypertension and cardiovascular disease.

Final remarks

Low birth weight is common in poor regions in Brazil and around the world. Our study adds further evidence that this condition has adverse effects in childhood, predisposing to early hypertension. We therefore assume that adults living in poor and developing countries are at greater risk of developing cardiovascular disease and hypertension.

One way to prevent these diseases in the future is by implementing public policies focused on maternal health during pregnancy, through good nutrition for pregnant women and adequate prenatal care, in order to promote fetal growth. This will lead to a healthier population in the future.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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References


