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Birth Weight Influences Blood Pressure Values and Variability in Children and Adolescents

Empar Lurbe, Isabel Torro, Concepción Rodríguez, Vicente Alvarez, Josep Redón

Abstract—The objective of the present study was to assess the relationships between birth weight and the values and variability of ambulatory blood pressure. Six hundred thirty healthy children (369 girls) age 4 to 18 years (mean, 9.9 years) born at term after a normotensive pregnancy were included. The subjects were divided into 5 groups according to birth weight. For each subject, a 24-hour ambulatory blood pressure monitoring was performed according to the protocol designed. Average and variability (estimated as the standard deviation) of ambulatory blood pressure and heart rate were calculated separately for 24-hour, daytime, and nighttime periods. When values were adjusted for gender, current age, weight, and height, children with the lowest birth weights had the highest ambulatory blood pressure values and variability, whereas no differences in heart rate were observed. Multiple regression analysis showed that although current weight was the strongest predictor for 24-hour systolic blood pressure ($P < 0.001$), there was also an independent and significant inverse relationship for birth weight ($P < 0.002$) after controlling for gender, current age, and height. Likewise, birth weight was independently and inversely correlated with 24-hour systolic blood pressure variability ($P < 0.03$). In conclusion, children who had lower birth weights tended to have not only the highest blood pressure values but also the highest blood pressure variability, independent of the increases in ambulatory blood pressure values. Knowing that high blood pressure variability is at least partially independent of blood pressure values, the importance of this variability on further blood pressure rises and/or on vascular damage later in life needs to be assessed in future studies. (*Hypertension*. 2001;38:389-393.)

Key Words: blood pressure ■ blood pressure monitoring, ambulatory ■ hypertension, essential ■ children ■ birth weight

There has recently been an increasing interest in the influence of intrauterine life as a pathogenesis in the development of chronic diseases. Evidence comes from epidemiological studies that relate birth measurements, as a proxy for fetal nutrition, with levels of cardiovascular mortality and risk factors.¹⁻³ Birth weight, a crude measure of fetal growth, includes length, fatness, and head size. An inverse relationship between birth weight and blood pressure (BP) levels has been demonstrated.⁴ Intrauterine growth retardation and relatively low birth weights, even within the normal range, are considered risk factors in the development of essential hypertension. The factors linking fetal growth to BP values later in life remain elusive. Assessment of BP characteristics may help us to better understand the mechanisms leading to hypertension.

BP fluctuates continuously over time, either spontaneously or in response to a variety of external stimuli, of which activity is a major determinant.⁵ The occurrence of continuous and often pronounced BP fluctuations not only is of pathophysiological interest but also may have clinical relevance.⁶ It has been shown that high BP variability has been

linked to the development of high BP values and/or to the presence of hypertension-related organ damage.⁷ Ambulatory BP monitoring permits the assessment of circadian and intrinsic variability and may provide the basis for easier and earlier recognition of abnormal BP values and/or behavior than is presently possible. The use of ambulatory BP monitoring, with the application of carefully standardized and specially adapted recording techniques, is feasible in a pediatric population.⁸ Under these conditions, ambulatory BP values are characterized by a reasonable reproducibility that is better than that observed for casual BP.⁹

The present research was designed to study the relationships between birth weight and the values and variability of ambulatory BP in a representative sample of children and adolescents.

Methods

Study Population

Children from 4 to 18 years of age were included in the present study. All had been selected from the Pediatric Outpatient Clinic, which the children attended for the purpose of routine health

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maintenance. Systemic and renal disease were discounted through physical examination, serum biochemistry, and urinalysis. In the present study, children included were born at term (≥ 37 weeks) after a normotensive pregnancy. Gestational age and birth weight were obtained from routine obstetrical records. The study was approved by the Committee for the Protection of Humans Subjects of the General Hospital, University of Valencia, Valencia, Spain. All parents and those children age >12 years gave their consent to participate in the study.

The subjects were divided according to birth weight: from 2.000 to 2.499 kg, from 2.500 to 2.999 kg, from 3.000 to 3.299 kg, from 3.300 to 3.599 kg, and >3.599 kg. The number of subjects per weight group was representative of that for the Comunidad Valenciana over the past 5 years, which averaged 30 982 births per year.

BP Measurements

Office and ambulatory BP measurements were performed according to a previously published protocol.^{10,11} Ambulatory BP monitoring was performed by using a Spacelabs model 90207 monitor (Spacelabs Inc) weighing 340 g. The proper cuff, placed on the nondominant arm, was selected according to the subject's upper arm length; the cuff was extended completely around the arm; and the bladder width covered at least two thirds of the upper arm.

Monitoring was performed on a regular school day with normal recreational activities. Recording began between 8:30 and 9:00 AM. The reading frequency was programmed for every 20 minutes from 6:00 AM to midnight and for every 30 minutes from midnight to 6:00 AM. During the daytime period (8:00 AM to 10:00 PM), an automatically programmed acoustic signal was triggered before the measurement to remind the child to relax the arm. The average of the total number of readings obtained at each monitoring session was 62 ± 5 .

Three different time periods were defined. The 24-hour period included all valid readings performed during the monitoring. Daytime was defined as the interval from 8:00 AM to 10:00 PM. Nighttime was defined as the interval from midnight to 6:00 AM. The following parameters were calculated for each subject: (1) total number of readings, (2) average of systolic BP (SBP), diastolic BP (DBP), and heart rate (HR) over the 24-hour, daytime, and nighttime periods; (3) circadian variability, estimated as the day/night ratio of the BP averages; and (4) variability, estimated as the standard deviation of the SBP, DBP, and HR valid measurements during 24-hour, daytime, and nighttime periods.

Statistical Analysis

The difference in BP values and variability estimates within birth weight groups were examined by ANOVA. ANCOVA by gender, current age, weight, and height was performed. Associations between 2 parameters were assessed by the Pearson correlation coefficient, controlling for the potential confounders. Multiple linear regression analyses were calculated by using ambulatory BP values and variability as dependent variables and birth weight, age, gender, current weight, and height as independent variables.

An expanded Methods section can be found in an online data supplement available at <http://www.hypertensionaha.org>.

Results

Characteristics of the Study Population

Six hundred thirty children and adolescents (261 boys and 369 girls), all white, who fulfilled the inclusion criteria were included in the analysis. The general characteristics and BP values of the study population are shown in Table 1. The birth weight of the subjects ranged from 2 to 4.8 kg. The 630 children were divided into the following birth weight groups: 35 weighed <2.500 kg (intrauterine growth retardation), 126 weighed from 2.500 to 2.999 kg, 150 weighed from 3.000 to 3.299 kg, 142 weighed from 3.300 to 3.599 kg, and 177

TABLE 1. General Characteristics of the Study Population (N=630)

Variables	Mean	SD
Age, y	9.9	3.8
Gender (male/female), n/n	261/369	...
Current weight, kg	39.7	16.4
Current height, m	1.38	0.22
Birth weight, kg	3.28	0.54
Office SBP, mm Hg	101.7	40.7
Office DBP, mm Hg	64.2	25.9
24-h SBP, mm Hg	111.0	9.4
24-h DBP, mm Hg	65.9	5.7

weighed >3.599 kg. No differences among groups in terms of gender, current age, weight, and height were observed.

BP and HR Values

The means of the SBP, DBP, and HR for office and ambulatory 24-hour, daytime, and nighttime periods for the birth weight groups adjusted by gender, current age, weight, and height are shown in Table 2. Although no differences in office SBP, DBP, or HR were observed within birth weight groups, significant differences were present for ambulatory SBP and DBP regardless of the time period (24-hour, daytime, or nighttime period). Twenty-four-hour, daytime, and nighttime BP values were significantly higher in the lowest birth weight group when they were compared with those of the other groups, as shown in Table 2. However, the differences were more prominent for SBP than for DBP. The adjusted differences and their corresponding 95% confidence intervals (CIs), relating the lowest birth weight group to the other 4 groups, are shown in Figure 1 for the 24-hour SBP and DBP. No differences among groups were observed for ambulatory HR values.

The following are the correlation coefficients between birth weight and averages of ambulatory BP, controlled for by gender and current age, weight, and height: 24-hour SBP, $r = -0.13$ ($P = 0.001$); 24-hour DBP, $r = -0.12$ ($P = 0.003$); daytime SBP, $r = -0.14$ ($P = 0.001$); daytime DBP, $r = -0.14$ ($P = 0.001$); nighttime SBP, $r = -0.07$ ($P = 0.08$); and nighttime DBP, $r = -0.06$ ($P = 0.16$). An inverse relationship between birth weight and 24-hour SBP value was also demonstrated by using multiple linear regression analysis. Although current weight at the time of monitoring was the strongest predictor for 24-hour SBP ($P < 0.001$), there was an independent significant inverse relationship between birth weight ($P < 0.002$) and 24-hour SBP after controlling for gender, current age, and height ($R^2 = 0.185$).

BP and HR Variability

No differences for either SBP or DBP within birth weight groups were found in circadian variability estimated by the day/night ratio, as shown in Table 2. The 24-hour and daytime SBP variabilities decrease significantly from the lowest to the highest birth weight group. The differences were significant between the first group, with a birth weight of

TABLE 2. Office and Ambulatory BP in the Study Population Grouped by Birth Weight

	Birth Weight Group				
	<2.500 kg	2.500–2.999 kg	3.000–3.299 kg	3.300–3.599 kg	>3.599 kg
Average weight, kg	2.217	2.712	3.115	3.405	3.932
Subjects, n	35	126	150	142	177
Office BP					
SBP, mm Hg	102.7±6.7	105.3±3.6	94.4±3.3	103.8±3.4	103.3±3.0
DBP, mm Hg	65.1±4.3	66.2±2.3	59.9±2.1	65.3±2.2	65.3±1.9
HR, bpm	79.9±5.6	80.1±2.9	74.5±2.7	78.9±2.8	82.7±2.5
Ambulatory BP					
24-h BP					
SBP, mm Hg	115.0±1.4	112.4±0.8	110.5±0.7*	109.4±0.7*	111.0±0.7*
DBP, mm Hg	68.2±1.0	66.9±0.5	65.6±0.5*	64.9±0.5*	65.7±0.4
HR, bpm	85.9±1.4	84.9±0.7	85.1±0.7	82.5±0.7	85.1±0.6
Daytime BP (8:00 AM to 10:00 PM)					
SBP, mm Hg	118.8±1.5	116.2±0.8	114.3±0.8*	112.9±0.8*	114.3±0.7*
DBP, mm Hg	72.5±1.0	70.8±0.5	69.5±0.5*	68.7±0.5*	69.1±0.5*
HR, bpm	90.9±1.6	89.6±0.8	90.1±0.8	86.8±0.8	89.3±0.7
Nighttime BP (midnight to 6:00 AM)					
SBP, mm Hg	106.5±1.5	102.8±0.8	101.1±0.7*	100.5±0.7*	102.8±0.7*
DBP, mm Hg	59.6±1.1	57.8±0.6	56.5±0.5*	56.0±0.5*	57.7±0.5
HR, bpm	76.4±1.4	75.2±0.8	74.8±0.7	73.5±0.7	76.5±0.6
Day/night ratio					
SBP	1.12±0.01	1.13±0.01	1.13±0.01	1.12±0.01	1.12±0.01
DBP	1.23±0.02	1.23±0.01	1.24±0.01	1.23±0.01	1.20±0.01

Values are mean±SD or as indicated. Average of each group was adjusted by gender and current age, weight, and height.

* $P<0.05$ vs group with lowest birth weight.

<2.500 kg, and those groups with birth weights >3.300 kg. No differences in ambulatory HR variability were observed.

The following were correlation coefficients between birth weight and BP variability, controlled by gender and current

age, weight, and height: 24-hour SBP, $r=-0.14$ ($P=0.001$); 24-hour DBP, $r=-0.13$ ($P=0.002$); daytime SBP, $r=-0.11$ ($P=0.005$); daytime DBP, $r=-0.09$ ($P=0.023$); nighttime SBP, $r=-0.04$ ($P=0.36$); and nighttime DBP, $r=-0.02$ ($P=0.58$). The relationship of birth weight to 24-hour SBP variability was also analyzed by using multiple linear regression analysis. Although 24-hour SBP values ($P<0.001$) were the strongest predictors for 24-hour BP variability, there was also an independent significant inverse relationship between birth weight ($P<0.03$) and 24-hour BP variability after controlling for potential confounders ($R^2=0.194$). Variability still decreased across the groups, even though SBP values had plateaued (see Figure 2).

Discussion

In the present study, a contribution of the intrauterine environment, as reflected by birth weight, to the ambulatory BP in a pediatric population was observed. Children who had lower birth weights tend to have not only the highest BP values but also the highest BP variability, independent of the increment in the ambulatory BP values. The characteristics of the study population and the ambulatory BP measurements provide clues as to how to better assess the influence of birth weight on BP behavior. The subjects that were included reflected the birth weight distribution of the total population born in our setting, thus avoiding a selection sample bias. Ambulatory BP

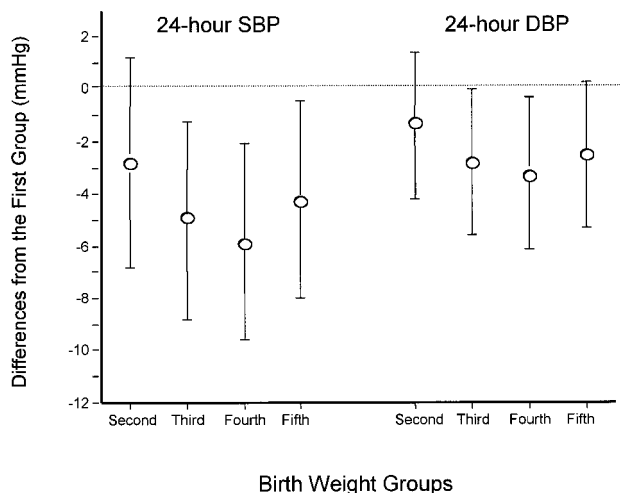


Figure 1. Adjusted differences and their corresponding 95% CIs relating the lowest birth weight group (first, <2.500 kg) to the other groups (second, from 2.500 to 2.999 kg; third, from 3.000 to 3.299 kg; fourth, from 3.300 to 3.599 kg; and fifth, >3.599 kg) for 24-hour SBP and DBP values.

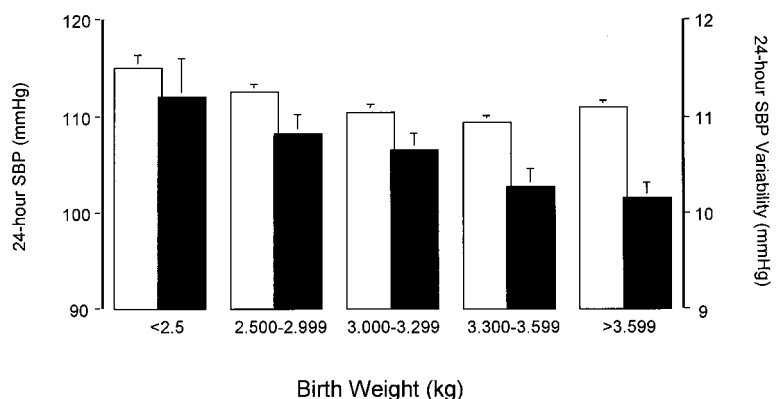


Figure 2. Average 24-hour SBP values (open bars) and variability (solid bars) and their corresponding SDs across the birth weight groups after adjustments for gender, current age, weight, and height. The variability still decreases across the groups, even though SBP values have plateaued.

monitoring with a noninvasive device offered more representative values of BP than are possible with the use of office BP assessment.⁵

The observance of a significant relationship between birth weight and ambulatory BP, not present for office BP, could be due to the characterization of each subject by a large number of measurements (≈ 60) with the use of automatic devices in regular living conditions. Thus, it is easier to show the differences in BP between groups than it is to show the differences between BP values obtained from 3 measurements in resting conditions, as is the case with office BP.¹² BP fluctuates continuously over time, either spontaneously or in response to a variety of external stimuli, of which activity is a major determinant.⁵ Because the differences in ambulatory BP were not accompanied by a similar trend in HR, the presence of differences in activity levels was ruled out as being responsible for the differences in BP among the birth weight groups.

The differences in ambulatory SBP and DBP values, across the groups, increase as the birth weight increases. Figure 1 clearly demonstrates that after removing the potential impact of other confounders, the influence of lower birth weight on BP is not limited to those subjects with intrauterine growth retardation. Although this group shows the highest BP values, subjects with birth weights between 2.500 and 3.000 kg also tend to have BP levels higher than those in the other groups with higher birth weights. These data are in agreement with previous reports summarized recently by Huxley et al,⁴ in which the inverse relationship between birth weight and BP values has been demonstrated by using office BP in a large number of subjects. The influence of birth weight is present not only in children and adolescents (as in the population analyzed in the present study) but also in 18-year-old individuals¹³ and adults.¹⁴

It is not easy to explain a "J-curve" phenomenon, which is present for ambulatory BP values but not for BP variability. Controlling for possible confounders (age, gender, and current weight and height), we avoid the possibility that the higher BP values in the highest birth weight group reflect the inclusion of the oldest, heaviest, or tallest children. Furthermore, no differences in the averages of age or of anthropometric parameters or in the gender distribution are present among the groups.

The importance of birth weight on the development of higher BP during pediatric and adult life initially was related

to the presence of intrauterine growth retardation.¹⁴⁻¹⁷ Children with lower birth weight, even in the absence of intrauterine growth retardation, also have higher BP values than do those of other birth weight groups.¹⁸ The mechanisms that promote intrauterine growth retardation and/or rising BP values later in life, such as the influence of genetic factors,^{19,20} remain to be defined.

To better understand these potential mechanisms, it may be useful to know the intermediate phenotypes of the BP in children with the lower birth weights and to compare them with those of children with higher birth weights. Retinal microvascular architecture alteration, which might reflect a persistent alteration in vascular architecture, may be a mechanistic link between birth weight and subsequently increased BP.²¹ Additionally, the influence of birth weight in the relationship between BP and natriuresis in children has previously been described. The sodium excretion rate of children with the lowest birth weights was lower than the rate observed in the group with the highest birth weight at the same level of BP.²²

A BP characteristic of subjects with low birth weight, not previously described in the literature, is a high BP variability that decreases as the birth weight increases. The different trend observed between the BP values and the BP variability indicates that the latter is at least partially independent of the former. Variability, estimated as the standard deviation from discontinuous noninvasive BP monitoring techniques, although limited, may represent important information about cardiovascular regulation. Measuring BP at interval times >10 minutes cannot provide information on rapid BP fluctuations and may offer a distorted assessment of slow BP changes.^{6,23,24} Although there may be some degree of inaccuracy in the absolute values of variability, previous studies using the same methodology have demonstrated the relationship between BP variability and the presence of early organ damage due to hypertension,^{7,25} the progression of early carotid atherosclerosis,²⁶ and the risk of developing cardiac dysfunction.²⁷ The highest variability seems to reflect a higher vascular reactivity, which could result from sympathetic overdrive, from enhancement of smooth muscle cell contractility, or from abnormal baroreflex sensitivity.

The present study did not provide information about the mechanism or mechanisms responsible for the highest BP variability, but whichever the predominant mechanism involved, it is independent of the regulatory HR mechanisms.

An increase of BP variability seems to be an early characteristic of BP in children with the lowest birth weight. The impact of higher BP values during childhood and adolescence on the BP of adulthood may be boosted by the highest variability, thus helping to explain why the differences in BP elicited by birth weight are amplified as subjects get older.

In summary, the present results disclose a relationship between birth weight and BP variability while seeking to advance the knowledge about the possible associations between birth weight and cardiovascular risk. Because high BP variability is at least partially independent of BP values, the importance of this variability on further elevations of BP and/or on vascular damage later in life needs to be assessed in future studies.

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