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Birth Weight Impacts on Wave Reflections in Children and Adolescents

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Abstract—The objective of the present study was to assess central aortic pressure and wave reflection in children and adolescents at different birth weights. Two hundred nineteen healthy children (126 girls), from 7 to 18 years of age (mean, 11.3 years) and born at term after a normotensive pregnancy, were included. The subjects were divided according to birth weight: <2.5 kg, from 2.5 to 2.999 kg, from 3.0 to 3.5 kg, and >3.5 kg. Pressure waveforms were recorded from the radial artery of the wrist, and the waveform data were then processed by the SphygmoCor radial/aortic transform software module to produce the estimated aortic pressure waveform. Augmentation index, an estimate of the pulse wave reflection, was significantly higher in children with the lowest birth weights compared with the other birth weight groups. In a multiple regression analysis, short stature, low heart rate, female gender, and lower birth weight had independent significant inverse correlations to the augmentation index when adjusted for diastolic blood pressure ($R^2=0.21$). In summary, the results showed a relatively aged phenotype of large-vessel function in the children with the lowest birth weights. These early alterations may be amplified throughout life and may contribute to the increased cardiovascular risk associated with low birth weight. (*Hypertension*. 2003;41[part 2]:646-650.)

Key Words: birth weight ■ augmentation index ■ children ■ pulse pressure

During the past decade, epidemiologists have focused on the influence of events that occurred during fetal life on the cardiovascular risk later in life.[1] Most of the studies have reported a negative association between birth weight and systolic blood pressure (BP),[2–4] as well as an increase in the risk of developing hypertension among subjects with the lowest birth weights.[5] Studies that have reported results for both systolic and diastolic BP found either an inverse relation with birth weight for systolic but not diastolic BP, or an inverse relation with birth weight that was greater for systolic than for diastolic BP.[2–4] The results of a recent study found a relationship between birth weight and pulse pressure (PP) measured in the arm over 24 hours, a surrogate measure of arterial stiffness.[6] Whether or not this increased peripheral PP has a corresponding increment in the central aortic pressure and/or modifications in the waveform has not been assessed until now.

Central aortic pressure and waveform convey important information about cardiovascular status and risk.[7–9] Noninvasive assessment of aortic hemodynamic parameters can be obtained from peripheral recordings by using applanation tonometry, which uses an externally applied micromanometer-tipped probe to continuously record peripheral pulse waveforms.[10–12] From carotid or radial tonometry, it should be possible to estimate the central aortic pressure wave with the use of mathematical transformation.[13,14]

The present research was designed to study central aortic pressure and wave reflection in children at different birth weights to assess early functional changes in large-vessel properties. If changes are present, they may indicate an aged vascular phenotype in an otherwise young and healthy population.

Methods

Study Population

Subjects from 7 to 18 years of age, selected from a study that is part of a larger project in which reference values and determinants of ambulatory BP had been assessed, were included in the present study. All were selected from the Pediatric Outpatient Clinic of the General Hospital of the University of Valencia, Spain. Systemic and renal diseases were discounted through physical examination, serum biochemistry, and urinalysis. In the present study, subjects included were born at term (≥37 weeks) after a normotensive pregnancy. Gestational age and birth weight were obtained from routine obstetrical records. Parents gave their consent for their children to participate in the study. The subjects were divided according to birth weight: <2.5 kg, from 2.5 to 2.999 kg, from 3.0 to 3.5 kg, and >3.5 kg. The study was approved by the Committee for the Protection of Human Subjects of the General Hospital, University of Valencia, Spain.

BP Measurements

Nurses measured the BP of the subjects 3 times consecutively with a mercury sphygmomanometer, in the sitting position and after a rest of ≥5 minutes. Korotkoff phase I was used to measure systolic BP.

TABLE 1.   General Characteristics of the Study Population Grouped by Birth Weight

	Birth Weight Groups			
Characteristic	<2.500 kg (n=17)	2.500–2.999 kg (n=50)	3.000–3.500 kg (n=61)	>3.500 kg (n=91)
Age, y	11.5±3.6	11.0±3.0	11.0±3.6	11.5±3.1
Gender, M/F	4/13	19/31	25/36	45/46
Birth weight, kg	2.14±0.3	2.74±0.1	3.20±0.2	3.90±0.4
Weight, kg	48.0±14.3	47.4±11.2	48.4±13.1	50.8±14.2
Height, cm	146±13.2	146±13.8	149±16.1	152±16.2
Office measurements				
SBP, mm Hg	107.8±10.1	105.9±12.4	102.3±10.79	104.4±12.69
DBP, mm Hg	63.8±9.2	57.8±9.9	56.52±10.27	58.27±9.73
PP, mm Hg	44.06±9.3	47.1±9.7	45.82±8.75	46.10±10.65
HR, bpm	81.4±15.5	81.5±16.3	80.48±14.61	80.26±11.91

Values are mean±SD. SBP indicates systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; and HR, heart rate.

Diastolic BP was measured using phase IV in children ≤13 years of age and phase V in those >13 years.[15] The mean of the 3 measurements was taken as the office BP. PP was calculated as the difference between systolic BP and diastolic BP.

Aortic-Derived Parameters

Pressure waveforms were recorded from the radial artery of the wrist of the dominant hand with a high-fidelity micromanometer (SPC-301; Millar Instruments), and the waveform data were then processed by the SphygmoCor radial/aortic transform software module (PWV Medical) to produce the estimated aortic pressure waveform.[13,14] The series of estimated aortic waveforms, together with the series of radial waveforms from which these were derived, were each ensemble-averaged over a 8-second period into a single calibrated waveform.

Statistical Analysis

The difference in office and aortic-derived parameters values within birth weight groups were examined by ANOVA. Associations between the 2 parameters were assessed by partial correlation coefficient, controlling for the potential confounders of age and gender. Multiple linear regression analyses were calculated using augmentation index as a dependent variable, whereas birth weight, gender, current height, heart rate, and diastolic BP were the independent ones.

Results

General Characteristics of the Study Population

Two hundred nineteen subjects (126 girls), all white, who fulfilled the inclusion criteria were included in the analysis. The general characteristics, BP, and heart rate values of the study population are shown in Table 1. When the study population was divided into groups of birth weight, no differences were observed in terms of gender, current age, weight, and height. Despite BP values being slightly higher in the lowest birth weight group, there were no significant differences among groups.

Aortic-Derived Parameters

The aortic-derived parameters are shown in Table 2. The derived aortic systolic and diastolic values tend to be higher in the lowest birth weight group compared with the other birth weight groups. Augmentation index, the parameter used to estimate the pulse wave reflection expressed in mm Hg or by the percentage of aortic PP, was significantly higher in the 2 lowest birth weight groups compared with the other 2 birth weight groups (Table 2). These differences among birth

TABLE 2.   Aortic-Derived Parameters of the Study Population Grouped by Birth Weight

	Birth Weight Groups			
Parameters	<2.500 kg (n=17)	2.500–2.999 kg (n=50)	3.000–3.500 kg (n=61)	>3.500 kg (n=91)
Aortic BP, mm Hg				
SBP	93.3±2.5	90.7±1.5	86.1±1.2	88.2±1.1
DBP	65.6±2.0	59.9±1.3	58.1±1.3	60.1±1.0
PP	27.6±1.8	30.8±1.1	28.0±0.7	28.1±0.7
AI	3.9±1.3	3.7±0.8	0.9±0.6*	0.7±0.5†
AI/PP, %	11.1±3.5	11.7±2.5	3.4±2.1*	2.5±1.6†
Radial/aortic PP	1.61±0.4	1.59±0.3	1.65±0.2	1.65±0.2

Values are mean±SE. AI indicates augmentation index.
*$P<0.05$, †$P<0.01$ vs the second birth weight group.
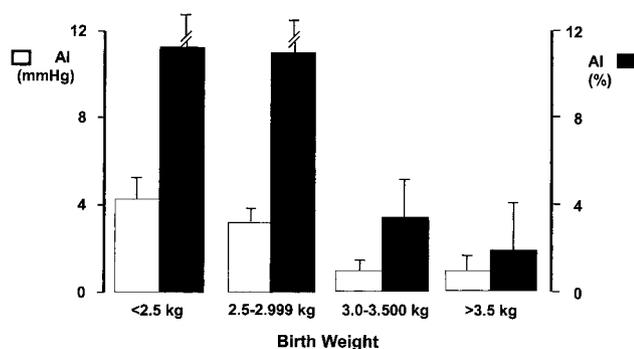
Figure 1. The augmentation index, expressed in mm Hg (open bars) or by the percentage of aortic PP (closed bars) and their corresponding standard error, in the birth weight groups. Values are adjusted for heart rate and diastolic BP. Significant differences were present across the birth weight groups (augmentation index in mm Hg, $P=0.007$; augmentation index as a percentage, $P=0.039$)

weight groups remained significant after controlling for heart rate and diastolic BP (Figure 1). The amplification phenomenon from central to peripheral vascular tree was calculated by using the radial-to-aortic PP ratio. Although this ratio was lower in the first 2 groups, indicating a trend of less central to peripheral amplification, it did not achieve statistical significance (Table 2).

Birth Weight and Aortic-Derived Parameters

The relationship between birth weight and anthropometric and BP parameters was analyzed by partial correlation coefficients covariate of age and gender. A significant positive relationship between birth weight with current height ($r=0.25$, $P<0.001$) was observed, as well as a significant negative relationship with aortic systolic BP ($r=-0.17$, $P=0.015$) and augmentation index ($r=-0.19$, $P=0.006$). Likewise, the relationship between the augmentation index and the anthropometric and BP parameters was analyzed by partial correlation coefficients covariate for age and gender. A significant positive relationship between augmentation index with aortic systolic BP ($r=0.20$, $P=0.004$) was observed, as well as a significant negative relationship with current height ($r=-0.34$, $P<0.001$) and heart rate ($r=-0.30$, $P<0.001$).

Considering the potential interactions among the parameters, a multiple regression analysis was performed. Augmentation index was independently related to heart rate, current height, birth weight, and gender (Table 3). Short stature, low heart rate, female gender, and lower birth weight were

TABLE 3.   Factors Related to Augmentation Index Estimated by Multiple Regression Analysis

Variable	β	SD	P
Birth weight, kg	−1.123	0.495	0.024
Current height, cm	−0.123	0.024	0.000
Gender, female vs male	1.303	0.642	0.044
Heart rate, bpm	−0.148	0.026	0.000
Diastolic BP, mm Hg	−0.030	0.034	0.364
			R^2 0.21
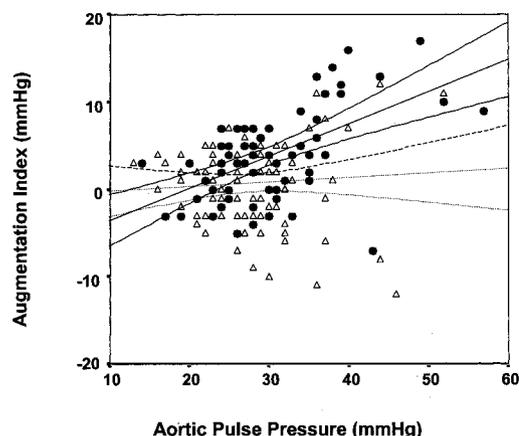
Figure 2. Relationship between augmentation index and aortic PP. The figure represents regression slopes and their corresponding 95% confidence interval, showing augmentation index and central aortic PP in children with birth weight >3.5 kg (△ and dotted lines) and in children with birth weight <3.0 kg (● and continuous lines). Although across the aortic PP range the augmentation index did not increase in children with birth weight >3.5 kg, a progressive increment of augmentation index was present in children with birth weight <3.0 kg.

inversely correlated to the augmentation index. The model explained 21% of the augmentation index variability.

The contribution of the augmentation index to the aortic PP was explored separately in the birth weight groups (Figure 2.). Although across the aortic PP range, the augmentation index did not increase in children with birth weight >3.5 kg, a progressive increment of augmentation index was present in children with birth weight <3.0 kg. Thus, the PP depends on the increase in augmentation index in those children who had the lowest birth weights but not in the other children.

Finally, the radial/aortic amplification was independently related to heart rate ($P<0.001$), current height ($P<0.001$), and gender ($P=0.017$), but not to birth weight ($P=0.648$). The model explained 19% of the radial/aortic amplification variability.

Discussion

Aortic-derived parameters, obtained from radial peripheral recordings with SphygmoCor software, were analyzed in children and adolescents at different birth weights. An inverse relationship between birth weight and augmentation index was observed, independent of other strong determinants of wave reflection such as short stature and low heart rate. Augmentation index seems to contribute to the increment in aortic PP in children with the lowest birth weight compared with the other birth weight groups. The higher augmentation index suggests a relatively aged arterial phenotype in these children and adolescents.

The subjects included reflected the birth weight distribution of the total population born in our setting, avoiding a selection sample bias. The influence of lower birth weight on augmentation index is limited not only to those subjects with intrauterine growth retardation, 8% of the study population, but also to those children in absence of intrauterine growth retardation, birth weight between 2.5 kg to 3.0 kg.

The importance of birth weight in the development of higher BP during pediatric and adult life initially was related to the presence of intrauterine growth retardation,[1,2] but other studies have demonstrated that it is also present in lower-birth-weight subjects, even in the absence of intrauterine growth retardation.[4] In these children, the identification of subtle abnormalities in BP characteristics, which may indicate a high risk of developing hypertension later in life, would indicate an early intervention to reduce future risk. Despite the potential interest in knowing these early BP abnormalities, the number of studies is scarce, because this requires the use of techniques not regularly applied to children and adolescents. Using ambulatory BP monitoring with an automatic device, we observed a high BP variability, estimated as the SD of the BP measured during 24 hours, in children with the lowest birth weights. The BP variability decreases as birth weight increases.[16] Furthermore, a restricted ability for sodium excretion in children has been demonstrated during nighttime, when both sodium excretion and BP were measured simultaneously.[17]

Another technique used infrequently in children is to record pulse wave contour by using applanation tonometry in peripheral arteries and then to calculate the aortic pressures and waveforms.[10–12] This technique, introduced by O'Rourke several years ago, is highly reproducible when compared with direct central aortic measurements.[18,19] Although the method has not been validated specifically for children, there is data available that supports the validity of the technique in children and adolescents. Vascular properties of the upper-limb vessels vary little with age, in contrast to the changes observed in trunk and lower-limb vessels.[20] This allows constructs of central aortic pressures derived from the radial waveform, whatever the age, when good quality peripheral pulse tracings are obtained. In the present study, the peripheral pulse wave was recorded from the radial artery at wrist. In contrast to the carotid artery, the radial artery is very accessible and well supported by bony tissue, making optimal applanation far easier to achieve. The disadvantage of using the radial pulse is that the pressure contour changes appreciably as it travels from the aorta to more peripheral sites.[21]

The present study offers further insight into the mechanisms involved in the association between birth weight and increased systolic BP and PP, but not diastolic BP. The major finding was the increase in the augmentation index, a quantitative measure of the contribution of wave reflection to the central pressure waveform, which is affected by the timing and magnitude of reflecting wave.[22] The time of appearance of the reflection depended on the pulse wave velocity, which was in turn directly related to the elastic properties of large vessels and less to the peripheral resistance.[23] Apart from and independent of other determinants of the augmentation index, such as height, heart rate, and gender, subjects with the lowest birth weights had higher augmentation index values. This indicated an early wave return and, consequently, suggested an early reduction in the elastic properties of arteries[24,25] in children with the lowest birth weights. This is in concordance with a previous report in adults that described an inverse relationship between birth weight and pulse wave velocity, a

marker of aortic elasticity and one of the main determinants of reflecting waves.[26]

The contribution of the augmentation index to the aortic PP at different birth weights was also analyzed. From the data in Figure 2, it seems that the contribution of the augmentation index to the aortic PP, and consequently to systolic aortic pressure, was larger in the lowest-birth-weight children than it is in the highest-birth-weight ones. Thus, early reflecting waves became prominent in these low-birth-weight children and may contribute to the progressive BP increase later in life.

The functional age phenotype observed seems to be according with the fetal origin hypothesis of cardiovascular risk that suggests intrauterine growth retardation results in a forward resetting of arterial age during extrauterine life.[27] The present data also exposes that the same phenomenon can be present in children with the lowest birth weights, even in the absence of intrauterine growth retardation, and points to the large arteries as the potential origin of a high risk to develop hypertension later in life.

Perspectives

The most important clinical implications that can be derived from this study are that, in children and adolescents with the lowest birth weights, (1) there is a higher contribution of the reflecting waves on central PP; (2) this suggests an early abnormality of aortic elasticity that can perpetuate a vicious cycle of accelerated increase in BP levels; and (3) a high augmentation index is an early subtle abnormality in BP components. Whether or not the early detection of this subtle abnormality in BP components permits a successful intervention to reduce cardiovascular risk is an intriguing question that only future studies can answer.

References

1. Barker D, Osmond C, Golding G, Kuh D, Wadsworth M. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ*. 1989;298:564–567.
2. Law CM, Shiell AW. Is blood pressure inversely related to birth weight? The strength of evidence from a systematic review of the literature. *J Hypertens*. 1996;14:935–942.
3. Huxley RR, Shiell AW, Law CM. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systemic review of the literature. *J Hypertens*. 2000;18:815–831.
4. Lurbe E, Redon J, Alvarez V, Durazo R, Gomez A, Tacons J, Cooper RS. Relationship between birth weight and awake blood pressure in children and adolescents in absence of intrauterine growth retardation. *Am J Hypertens*. 1996;9:787–794.
5. Law CM, de Swiet M, Osmond C, Fayers PM, Barker DJP, Crudas AM, Fall CHD. Initiation of hypertension in utero and its amplification throughout life. *BMJ*. 1993;306:24–28.
6. Lurbe E, Rodríguez C, Torró I, Cremades B, Alvarez V, Redon J. Inverse relationship between birth weight and pulse pressure in adolescents. *Hypertension*. 2001;38:483. Abstract.
7. Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation*. 2001;103:987–992.
8. Franklin SS, Khan SA, Wong ND, Larson MG, Levy D. Is pulse pressure useful in predicting risk for coronary heart disease? The Framingham Heart Study. *Circulation*. 1999;100:354–360.
9. Safar ME, Blacher J, Pannier B, Guerin AP, Marchais SJ, Guyonvarc'h PM, London GM. Central pulse pressure and mortality in end-stage renal disease. *Hypertension*. 2002;39:735–738.
10. O'Rourke MF, Safar ME, Dzau V, eds. *Arterial Vasodilation: Mechanisms and Therapy*. Philadelphia: Lea and Febiger; 1993.

11. Karamanoglu M, O'Rourke MF, Avolio AP, Kelly RP. An analysis of the relationship between central aortic and peripheral upper limb pressure waves in man. *Eur Heart J*. 1993;14:160–167.

12. Pauca AL, O'Rourke MF, Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. *Hypertension*. 2001;38:923–937.

13. Takazawa K, O'Rourke M, Fujita M, Tanaka N, Takeda K, Kurosu F, Ibukiyama C. Estimation of ascending aortic pressure from radial arterial pressure using a generalized transfer function. *Z Kardiol*. 1996;85(suppl 3):137–139.

14. Karamanoglu M, Gallagher DE, Avolio AP, O'Rourke MF. Pressure wave propagation in a multibranched model of the human upper-limb. *Am J Physiol*. 1995;269(pt 2):H1363–H1369.

15. Report of the Second Task Force on Blood Pressure Control in Children. *Pediatrics*. 1987;79:1–25.

16. Lurbe E, Torró I, Rodríguez C, Alvarez V, Redon J. Birth weight influences blood pressure values and variability in children and adolescents. *Hypertension*. 2001;38:389–393.

17. Lurbe E, Redon J, Tacons J, I Torró, Alvarez V. Current and birth weights exert independent influences on nocturnal pressure-natriuresis relationships in normotensive children. *Hypertension*. 1998;31(pt 2):546–551.

18. Chen CH, Nevo E, Fetics B, Pak PH, Yin FCP, Maughan WL, Kass DA. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure: validation of generalized transfer function. *Circulation*. 1997;95:1827–1836.

19. Fectis B, Nevo E, Chen CH, Kass DA. Parametric model derivation of transfer function for non-invasive estimation of pressure by radial tonometry. *Trans Biomed*. 1999;46:698–706.

20. Avolio AP, Chen SG, Wang RP, Zhang CL, Li MF, O'Rourke MF. Effects of aging on changing arterial compliance and left ventricular load in a northern Chinese urban community. *Circulation*. 1983;68:50–58.

21. Franklin SS, Gustin W, Wong ND, Larson MG, Weber MA, Kannel WB, Levy D. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation*. 1997;96:308–315.

22. Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE, Webb DJ. The influence of heart rate on augmentation index and central arterial pressure in humans. *J Physiol*. 2000;525:263–270.

23. Wilkinson IB, Fuchs SA, Jansen IM, Spratt JC, Murray GD, Cockcroft JR, Webb DJ. The reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. *J Hypertens*. 1998;16:2079–2084.

24. Wilkinson IB, Franklin SS, Hall IR, Tyrrell S, Cockcroft JR. Pressure amplification explains why pulse pressure is unrelated to risk in young subjects. *Hypertension*. 2001;38:1461–1466.

25. Segers P, Qasem A, DeBacker T, Carlie S, Verdonk P, Avolio A. Peripheral "oscillatory" compliance is associated with aortic augmentation index. *Hypertension*. 2001;37:1434–1439.

26. Martyn CN, Barker DJP, Jespersen S, Greenwald S, Osmond C, Berry C. Growth in utero, adult blood pressure and arterial compliance. *Br Heart J*. 1995;73:116–121.

27. Aviv A. Pulse pressure and human longevity. *Hypertension*. 2001;37:1060–1066.