Blood Pressure and Obesity Exert Independent Influences on Pulse Wave Velocity in Youth

Empar Lurbe, Isabel Torro, Consuelo García-Vicent, Julio Alvarez, José Antonio Fernández-Fornoso, Josep Redon

Abstract—The objective was to analyze pulse wave velocity (PWV) in normotensive, high-normal, and hypertensive youths by using aortic-derived parameters from peripheral recordings. The impact of obesity on vascular phenotypes was also analyzed. A total of 501 whites from 8 to 18 years of age were included. The subjects were divided according to BP criteria: 424 (85%) were normotensive, 56 (11%) high-normal, and 21 (4%) hypertensive. Obesity was present in 284 (56%) and overweight in 138 (28%). Pulse wave analysis using a SphygmoCor device was performed to determine central blood pressure (BP), augmentation index, and measurement of PWV. Among the BP groups, differences appeared in age, sex, and height but not in body mass index. Significant differences in peripheral and central systolic and diastolic BPs and pulse pressures were observed within groups. A graded increase in PWV was present across the BP strata without differences in augmentation index. Using a multiple regression analysis, age, BP groups, and obesity status were independently associated with PWV. Older and hypertensive subjects had the highest PWV, whereas, from normal weight status to obesity, PWV decreased. Likewise, PWV was positively related to peripheral or central systolic BP and negatively related to body mass index z score. For 1 SD of peripheral systolic BP, PWV increased 0.329 m/s, and for 1 SD of body mass index z score PWV decreased 0.129 m/s. In conclusion, PWV is increased in hypertensive and even in high-normal children and adolescents. Furthermore, obesity, the factor most frequently related to essential hypertension in adolescents, blunted the expected increment in PWV of hypertensive and high-normal subjects. (Hypertension. 2012;60:00.)

Key Words: hypertension ■ obesity ■ children ■ adolescents ■ augmentation index ■ pulse wave velocity

Cardiovascular damage occurring in adults finds its roots in risk factors operating early in life. Among the factors influencing cardiovascular risk, blood pressure (BP) values represent an important measurable marker of the level of potential cardiovascular risk in children and adolescents. The need to identify cardiovascular risk factors, including high BP, in youth, is acknowledged more and more frequently. Consequently, measurement of BP has become a routine part of pediatric care, and asymptomatic hypertension is now detected in pediatric care practice.

BP phenotype is determined not only by conventional risk factors but also by weight gain in childhood. The adverse effects of excessive weight gain on BP and the association of weight gain with higher incidence of BP elevation represent major issues in health care.1–5 Elevation of systolic and/or diastolic BP indicates high BP in the child. In addition, children and adolescents with mild BP elevation, in the high-normal range, are much more common than was thought in the past, ranging from 3.4% to 15.7%.6,7 Rather than having a goal of classifying children as high-normal, we should be identifying those who may be at risk for the development of hypertension in the future, in the hopes that lifestyle interventions might be instituted to prevent this development.8–10

Abnormalities in BP are accompanied by functional changes in the vascular tree, and evidence of early alterations in vascular function has been described in children and adolescents. These alterations are manifested not only in high peripheral or central BP11 but also in reflecting waves12,13 and in pulse wave velocity (PWV).14 These intermediate phenotypes, as an expression of functional or structural abnormalities in the vascular tree, can be the cause, as well as the consequence, of early vascular alterations. Vascular phenotypes of large vessels provide a novel viewpoint for studying functional abnormalities, and because it can be clinically relevant, it represents a field of growing interest.
The present research was undertaken to analyze PWV in normotensive, high-normal (before the onset of clinical hypertension), and hypertensive youths by using aortic-derived parameters from peripheral recordings. In addition, the impact of obesity on vascular phenotypes was also analyzed.

Subjects and Methods

White children and adolescents of both sexes and of European origin, ranging from 8 to 18 years of age, who attended the pediatric outpatient clinic of the general hospital of the University of Valencia for vascular phenotype assessment, including normal weight, over-weight, and obese subjects, were included. Obesity was diagnosed when body mass index (BMI; the weight in kilograms divided by the square of the height in meters) exceeded the 95th percentile for age and sex. The extent of obesity was quantified using the least mean square method of Cole et al. Subjects with a BMI ranging from the 85th to 95th percentile of the BMI distribution in a normal age-matched reference population and, therefore, defined as being overweight, were included in the study. Hypertension in children and adolescents was defined as office BP persistently over 95th percentile, specific for age, sex, and height. Children with average systolic BP (SBP) or diastolic BP at ≥90th percentile but <95th percentile are classified as having high-normal BP. Adolescents with BP ≥120/80 mmHg, even if below the 90th percentile, are also considered as having high-normal BP.

None of the subjects were taking any medication or had any clinically manifest illness. No subjects with stage II hypertension were enrolled. In all of the cases, informed consent was obtained from parents and participants before testing. The study was approved by the ethics committee of the general hospital at the University of Valencia.

Clinical Procedures

Body weight was recorded to the nearest 0.1 kg using a standard beam balance scale with the subjects wearing light indoor clothing and no shoes. Height was recorded to the nearest 0.5 cm using a standardized wall-mounted height board. BMI was calculated as weight (in kilograms) divided by height (in meters squared).

On the day of the study, trained clinic nurses measured the BP of each subject 3 times consecutively in the seated position, at 5 minute intervals, using a mercury sphygmomanometer. This was done on the nondominant arm, with a cuff and a bladder size adjusted to upper-arm girth. Office BP values were taken as the mean of 3 measurements. Office BP had to be ≥95th percentile of the BP distribution in a normal reference population on ≥3 separate occasions to be considered as indicating a hypertensive condition. Hypertension in children and adolescents was defined as office BP persistently over 95th percentile, specific for age, sex, and height. Children with average systolic BP (SBP) or diastolic BP at ≥90th percentile but <95th percentile are classified as having high-normal BP. Adolescents with BP ≥120/80 mmHg, even if below the 90th percentile, are also considered as having high-normal BP.

Pulse Wave Analysis

Pulse wave analysis using a SphygmoCor device (AtCor Medical, West Ryde, New South Wales, Australia) was performed to determine central BP, augmentation index (AI), and measurement of PWV. This device uses a tonometer applied on the artery of interest to obtain electrocardiographic gated pressure data. The AI is the pressure difference between the primary (main outgoing wave) and the reflected wave of the central arterial waveform, expressed as a percentage of the central pulse pressure. PWV is calculated as the difference in the carotid-to-femoral path length divided by the difference in the R wave from the ECG to the foot of the pressure wave taken from the superimposed ECG and pressure tracings. The distance traveled by the flow wave was measured with an external tape measure over the body surface, as the distance from the right carotid sampling site to the manubrium subtracted from the distance from the manubrium to the right femoral sampling site.

Statistical Analysis

The following parameters were calculated for each subject: (1) average for peripheral systolic BP, diastolic BP, pulse pressure (PP), and heart rate; (2) average for central systolic BP, diastolic BP, PP, and heart rate; (3) ratio of peripheral and central PP; (4) AI; and (5) PWV. Values were expressed as mean ± SD for each study group. The differences in BP mean values among the different groups were assessed through ANOVA. The difference in AI values within groups was examined using ANCOVA by height, heart rate, and office diastolic BP. Bonferroni correction was applied in the case of multiple comparisons. Multiple linear regression analyses were carried out using PWV as the dependent variable and with age, sex, obesity, and hypertension as independent variables. Two other models were calculated using BMI z score and peripheral SBP or central SBP values. The changes in PWV for 1 SD of BMI z score or peripheral and central SBP were calculated. Values of 2-sided P < 0.05 were set as the minimum level of statistical significance throughout the article.

Results

Characteristics of the Sample

A total of 501 young white subjects (mean age, 12.6 ± 2.2 years; 265 boys) were included in the study, of which 424 (85%) were normotensive, 56 (11%) high-normal, and 21 (4%) hypertensives. From the total population, obesity was present in 284 (56%) and overweight in 138 (28%).

Peripheral and Central Parameters

Subject characteristics grouped by BP are displayed in Table 1. Differences between groups in peripheral and central BPs were more prominent for SBP. Although for peripheral and central SBPs, differences were observed among the 3 groups, for diastolic BP differences were present only in normotensive subjects. Regarding PP values, differences were more marked for peripheral than they were for central BPs among the groups. The amplification phenomenon from central to peripheral vascular tree, calculated by using the radial/aortic PP ratio, tended to be lower in the normotensive group when compared with that of the other BP groups. No differences in

<table>
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<th>Table 1. Subject Characteristics Grouped by Blood Pressure</th>
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<td>Sex, male/female</td>
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<td>Height, cm</td>
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<td>BMI, kg/m²</td>
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<td>AI, %</td>
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AI indicates augmentation index; PWV, pulse wave velocity; PP, pulse pressure; HR, heart rate; DBP, diastolic blood pressure; SBP, systolic blood pressure; BP, blood pressure; BMI, body mass index.

†P < 0.05 with normotensives and high-normal groups.

P < 0.05 with normotensive group.
Impact of Obesity on PWV

Determinants of PWV

Using a multiple regression analysis, the influence of hypertension and obesity on PWV was assessed adjusting for age and sex (Table 3). Age, BP groups, and obesity status were independently associated with PWV. Older subjects and hypertensives had the highest PWV, whereas, from normal weight status to obesity, PWV decreased. When peripheral systolic BP and BMI \( z \) score were introduced into the model as continuous variables, they were both independent determinants of PWV. SBP was positively related and BMI \( z \) score inversely so. For 1 SD of peripheral systolic BP, PWV increased 0.329 m/s, and for 1 SD of BMI \( z \) score PWV decreased 0.129 m/s. Central systolic BP was also positively and significantly related to PWV, although the impact was lower than that for peripheral systolic BP; for 1 SD the increment in PWV was 0.242 m/s.

Impact of Obesity on PWV

The negative impact of obesity on PWV, demonstrated in the multiple regression analysis, is shown in the Figure. The PWV was plotted against peripheral (Figure A) and central systolic BP (Figure B) SBPs. The steepest line was present for the normal weight subjects, decreasing in slope in the overweight, and least steep in the obese. At the same peripheral or central SBPs, PWV was lower in obese compared with normal-weight subjects. The differences increased as SBP increases. This phenomenon of blunting PWV was more prominent for peripheral than for central SBP.

Discussion

The present study, carried out in normotensive, high-normal, and hypertensive children and adolescents, shows that a progressive increment in PWV values was observed across the BP groups. In contrast, obesity frequently linked to BP elevation blunted to a greater extent the progressive increment of PWV observed from normotensive to hypertensive subjects. The impact of BP condition for reflecting wave, as assessed by AI, was not different across the BP groups for weight status. These findings of the PWV may suggest that the mechanisms implicated in BP elevation have some particularities in the presence of obesity.

The PWV has been considered the most accurate noninvasive assessment of vascular stiffness and has been related not only to cardiovascular events\(^{16,17}\) but also to cardiovascular mortality.\(^{18}\) The increment in the early aging state is interesting because it is one of the first signals of abnormalities in great artery elasticity early in life, which may contribute to progressive BP elevation. Our findings confirm the graded increase in PWV from normotensive to high-normal and hypertension in the present study.

PWV at any age is linearly related to BP and is symmetrically so at any BP level, depending on the quadratic age.\(^{19}\) It seems that the increase in PWV with BP is not simply attributable to the increase in BP with age.\(^{20,21}\) The observed progressive increment of PWV with systolic BP elevation present early in life, and even in the high-normal subjects,
raised the question about the nature and significance of the increment. One possibility is that PWV reflects functional or even structural changes in the vascular wall structure as part of the evolving hypertension process and so is a harbinger of further future BP elevation. Another possibility is that the higher BP and/or stroke volume shifts the volume-pressure curve to the highest levels where the functional role of collagen is more prominent than it is for the elastic fibers. Whatever the case, it is assumed that the progressive overload of the vascular wall results in progressive BP elevation and vascular damage.

Other than the data concerning PWV in high-normal and hypertensive children and adolescents, we analyzed the impact of obesity in the PWV in normotensive and hypertensive subjects, an issue addressed previously in a few studies of children. In adults, a positive relationship between obesity and PWV has been described in cross-sectional studies, and a reduction in PWV was observed after losing weight, although these studies had not considered the impact of BP values at the same time. Controversial results exist in the childhood population that may be partially explained by differences in patient populations (age, sex, and small sample size) and heterogeneity of the techniques used. In our study, the vascular phenotype assessment was performed in a large number of nonobese and obese subjects by the same operators with homogeneous methodology in only 1 center. In agreement with the present results, previous reports concluded that obesity was associated with a decreased PWV and with high large vessel elasticity. If obesity, as observed in our study, reduces the increment in PWV and, for instance, gave spurious data for 1 of the early hypertension-induced organ damage markers, it would be a relevant clinical finding with long-lasting consequences. In fact, lower cardiovascular risk in obese subjects, as compared with lean subjects with the same BP elevation, has been described.

The role of obesity blunting early abnormalities in the great vessels was also observed in a few previous studies using a different approach. We published for the first time the effect of both low birth weight and obesity on BP values and on the AI in the natural history of functional vascular alterations. On becoming obese, low birth weight children have significantly higher office and ambulatory BPs. However, despite having the highest office and ambulatory BP values, they have a blunted AI. We hypothesized that the role of volume overload in obese subjects blunts the impact of the reflecting waves in the pulse wave contour, reducing the elevation of the systolic peak over the wave shoulder. Prospective studies may be useful in assessing the features of vascular loading beyond those obtained through BP measurements.

The potential clinical relevance of the present observation, the lower PWV in high-normal and hypertensive obese subjects as compared with nonobese, may also indicate different mechanisms in the BP elevation-obesity association. Obesity-associated BP elevation is characterized by increased vascular volume as a consequence of increased sodium reabsorption in the kidney. This volume overload can produce an increase in stroke volume and distensibility of the great vessels, which contribute to BP elevation in the absence of relevant elasticity abnormalities. The results, however, may not be representative of the entire population at risk, and they cannot be generalized to nonwhites at present.

The data of the present article also raise additional issues. The 95th percentile for pediatric hypertension is a statistical definition and may underestimate the BP risk level for
hypertension and subsequent cardiovascular disease. High-
normal BP warrants more careful attention and, when con-
firmed, is a significant risk not only for future hypertension
but also for the presence of abnormalities in the vascular tree.
The increased PWV in the presence of high-normal BP points
out that health problems may extend beyond high BP. The
evidence demonstrates that the progression from high normal
to hypertension in adolescents is not only statistically signif-
ificant, but it is also clinically relevant.10

The study needs to be analyzed for limitations and strengths.
The population studied is not a randomly selected one, because
it was collected from an outpatient clinic where children were
referred for obesity control. Still, the study was performed in a
large number of obese subjects who were not referred as a result
of BP elevation, who were seen by the same health care workers,
and who were all from the same health care center. Although
these findings are of great interest, what these measures indicate
about vascular structure and function in young children is not
entirely clear, especially in the context of childhood growth and
development. Certainly, more studies in young individuals,
especially longitudinal investigations, are needed to better assess
the role of PWV measurement and of other parameters of
vascular alterations in youth.

Clinical Perspectives

The presence of PWV increments across BP groups reflects
abnormalities of BP phenotype and vascular function that may,
therefore, be expressions of “early vascular aging” susceptibility,
because the structural and mechanical properties of the large arteries can be permanently affected by altered hemodynamic stress early in life. Moreover, these observations also raise the possibility that these vascular changes are not limited to the later phases of cardiovascular disease but may extend to an earlier phase and age as well. Obesity, the factor most frequently related to essential hyper-
tension in adolescents, blunted the expected increment in PWV of hypertensive and high-normal subjects. Whether or
not the lower impact of BP elevation in PWV of the obese subjects as compared with nonobese can be translated to
different progression of vascular damage in hypertension may be checked in prospective studies.

Sources of Funding

The study was partially funded by CIBER Fisiopatología Obesidad y Nutrición (CB06/03), Instituto de Salud Carlos III.

Disclosures

None.

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Novelty and Significance

**What Is New?**
- Graded increase in PWV from normotensive to high-normal and hypertension exists early in life.
- Obesity, the factor most frequently related to essential hypertension in adolescents, blunted the progressive increment of PWV, which exists from normotensive to hypertensive subjects.

**What Is Relevant?**
- Obesity should be taken into account when PWV is assessed in the process of risk stratification in youths.

**Summary**

PWV is increased in hypertensive and even in high-normal children and adolescents. Obesity blunted the expected increment in PWV of hypertensive and high-normal subjects.

Longitudinal follow-up is essential in determining potential effects on future vascular disease risk.
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Hypertension. published online June 25, 2012;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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