ORIGINAL ARTICLE

Aortic Pulse Wave Velocity in Healthy Children and Adolescents: Reference Values for the Vicorder Device and Modifying Factors

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BACKGROUND
Aortic pulse wave velocity (PWV), an indicator of arterial stiffness, independently predicts cardiovascular mortality risk in adults. Arterial stiffening advances with age and seems accelerated in children with certain disease conditions such as chronic kidney disease or diabetes. The Vicorder, an oscillometric device to measure PWV, has been validated in children, but reference values in a large pediatric cohort, association to carotid stiffness and influence of individual and family risk factors have not been determined.

METHODS
Pulse waves were captured in 1,003 healthy children (aged 6–18 years) in 6 centers and gender-specific reference data normalized to age/height were constructed. In 589 children carotid distensibility and intima media thickness were measured. Gestational and family history was reported.

RESULTS
PWV correlated with age ($r = 0.57$, $P < 0.0001$) with significant gender-related differences starting at age 9. Further significant correlations were seen for height, weight, body mass index, blood pressure, pulse pressure, and heart rate. Independent predictors for PWV in a multivariate regression analysis were gender, age, height, weight, mean arterial pressure, and heart rate. Risk factors for higher PWV included small for gestational age at birth, secondhand smoking, parental hypertension, and obesity. PWV showed weak correlations with 2 of the carotid distensibility measures, but not with intima media thickness.

CONCLUSION
This study defines reference values for PWV captured by the Vicorder device in children and adolescents and reveals associations with potential cardiovascular risk factors in a healthy population. Gender-specific percentiles for age/height will allow for the assessment of pediatric cohorts using this oscillometric method.

Keywords: arterial stiffness; blood pressure; cardiovascular; hypertension; pediatrics; pulse wave velocity; risk factors.

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Identification of subjects with cardiovascular risk and possible subclinical cardiovascular disease is increasingly explored in childhood and adolescence, especially in populations that are likely to develop vascular complications later in life.[1–3] One of the most prominent age-associated changes of the cardiovascular system is large artery stiffening.[4] This process results in reduced arterial distensibility and leads to elevated brachial pulse pressure, elevated pulse wave velocity (PWV) and consecutively to a higher left ventricular afterload, higher systolic blood pressure (BP), and reduced coronary perfusion.[5] In adults, carotid to femoral PWV has become an established measure for arterial stiffness predicting the risk for cardiovascular events.[6–13] Even though significant age-associated stiffening of the large arteries seems to occur mostly after the 5th decade in healthy individuals,[14,15] several studies found signs of advanced arterial stiffening in children with cardiovascular disease associated conditions such as diabetes and chronic kidney disease.[16–18]

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However, most of these studies are limited by small patient numbers, use of different detection methods, and lack of standardization of measurements based on appropriate control populations.

We have previously reported the use of a relatively new oscillometric device for PWV detection that allows simultaneous recordings of the carotid and femoral pulse waves.[19] The best agreement with a well-established tonometry device was obtained with the path length that most accurately describes the aortic tree. We found excellent intra- and interobserver repeatability and thereby confirmed comparability to PWV values obtained by tonometry. Other investigators have satisfactorily used the same device in a cohort of healthy children,[20] but the study population was too small to provide valid percentiles for gender, age, and height.

The present study investigates aortic PWV in healthy children and adolescents aged 6–18 years and provides reference values generated by a validated oscillometric device. In addition, we evaluated the association between anthropometric and hemodynamic factors and PWV. In a subgroup of individuals, we also analyzed the relationship to parameters of carotid distensibility and carotid intima media thickness (cIMT) as well as to environmental, prenatal, and family risk factors potentially influencing PWV in the offspring.

METHODS

Study population

A total of 1,003 healthy Caucasian children and adolescents aged between 6 and 18 years (mean age: 11.6 ± 3.0 years) participated in 6 cooperating centers. The number of children recruited per center was as follows: Adana 99, Ankara 55, Hannover 429, Heidelberg 184, Istanbul 96, and Izmir 140. Individuals included in the study had no history of acute or known chronic disease (such as diabetes, chronic kidney disease, cardiac valve malformations), any chronic medications, or of acute intercurrent infection. The characteristics of the subjects are given in Table 1.

The study was approved by the institutional review committees and all parents and children gave informed consent or assent as appropriate. The study has been performed in accordance with the principles of the Helsinki Declaration.

Table 1. Characteristics of the 1,003 participants within the 4 age groups (total cohort)

		Age (years)			
Parameters	**Gender**	**6–8.99**	**9–11.99**	**12–14.99**	**15–18**
Subjects (*n*)	M	115	154	110	83
	F	89	210	150	92
Height (cm)	M	128.0 ± 6.6	142.6 ± 9.4	161.1 ± 9.5	172.3 ± 9.0
	F	126.3 ± 6.1	144.2 ± 10.0	158.9 ± 6.8	165.3 ± 6.7
Height SDS	M	0.67 ± 0.96	0.26 ± 1.11	0.35 ± 1.10	−0.11 ± 1.11
	F	0.47 ± 0.95	0.35 ± 1.11	0.37 ± 0.82	0.43 ± 1.03
BMI (kg/m^2)	M	16.7 ± 2.5	18.2 ± 3.0	20.8 ± 3.5	21.4 ± 3.0
	F	16.2 ± 2.1	17.9 ± 2.8	20.0 ± 2.9	21.5 ± 2.6
BMI SDS	M	0.23 ± 0.86	0.26 ± 1.05	0.41 ± 1.00	0.27 ± 0.91
	F	0.07 ± 0.94	0.02 ± 1.23	0.14 ± 0.98	0.30 ± 0.93
SBP (mm Hg)	M	106 ± 11	109 ± 10	118 ± 12	122 ± 9
	F	106 ± 10	109 ± 11	112 ± 11	119 ± 10
DBP (mm Hg)	M	61 ± 7	63 ± 7	65 ± 7	65 ± 7
	F	63 ± 7	63 ± 7	65 ± 7	67 ± 6
MAP (mm Hg)	M	79 ± 1	85 ± 2	91 ± 3	88 ± 3
	F	82 ± 1	85 ± 2	86 ± 2	92 ± 3
Heart rate (bpm)	M	91 ± 1	87 ± 2	86 ± 3	81 ± 3
	F	92 ± 1	91 ± 2	85 ± 2	86 ± 3
% SGA		12.8	11.4	10.1	14.2
% Premature birth		9.4	8.8	11.5	11.6
% CV disease[a]	Parents	2.6	1.7	1.5	7.9
	Grandparents	13.9	32.3	30.6	23.4

Abbreviations: BMI, body mass index; CV, cardiovascular; DBP, diastolic blood pressure; f, female; m, male; MAP, mean arterial pressure; SBP, systolic blood pressure; SDS, standard deviation score; SGA, small for gestational age.

[a]CV disease was defined as either a history of a cardiovascular event, cardiovascular disease, or the presence of multiple cardiovascular risk factors.

Measurement of blood pressure (BP), aortic pulse wave velocity (PWV), carotid intima media thickness (cIMT), and carotid distensibility.

Settings and measurement conditions were according to the recommendations of the Task Force III on clinical applications of arterial stiffness.[21] Measurements were performed using the oscillometric Vicorder system (Skidmore Medical, Bristol, UK; Software Version 4.0) by 8 jointly trained physicians (D.K., B.M.W.S., A.D., B.S., A.B., A.D., E.W., and S.C.) as previously reported.[19]

Briefly, measurements were performed in a quiet and temperated room after a resting time of at least 5 minutes in supine position with a 30° elevated head and shoulder part to prevent venous artefacts. Two cuffs were placed to capture the pulse waves of carotid and femoral artery. The neck cuff (width: 30 mm, in smaller children width 20 mm) containing a small inflatable cushion was placed above the right common carotid artery. The femoral cuff (width: 100 mm) was placed around the upper right thigh as close to the groin as possible. After inflating both cuffs to the automatically set value, carotid and femoral pulse waves were recorded synchronously, in real time over at least 10 heartbeats. The measurement was stopped by the operator when the waves on the display had a clear and steep ascending part and were of similar size and shape. The Vicorder software automatically marks the pulse wave's steepest ascending part (maximum systolic upstroke) and uses a defined timeframe to detect the wave's nadir to calculate transit time. The shift in time between the marked areas on the carotid and femoral pulse waves, which is the transit time, is detected by cross-correlation. All measurements were done in triplicates. Mean values were used for further analysis. The carotid to femoral path length representing the distance traveled by the pulse wave was determined with a measuring tape. We used a path length that more accurately follows the real path of the arterial tree by measuring (suprasternal notch (SSN) to umbilicus (Umb)) + (Umb to femoral recording site) − (SSN to carotid recording site). PWV was calculated as path length (L) along the skin between the recording sites divided by the transit time (Δt) of the arterial pulse wave along the analyzed segment (PWV = $L/\Delta t$ and m/sec). We reported excellent intra- and interobserver repeatability with this method.[19]

High-resolution B-mode and M-mode ultrasound images of both common carotid arteries were obtained with a linear array transducer according to the Mannheim consensus.[22] Subjects were placed in a supine position with the head rotated 45° to the left or right, respectively. The jugular vein and carotid artery were located in the transverse view. The transducer was then rotated to obtain a longitudinal image. All examinations were recorded digitally. Recordings were done on the far wall of the common carotid artery. The length of the assessed carotid region was at least 10 mm. Five averaged measurements were obtained on each side and values from left and right carotid artery were averaged. Measurements included cIMT, distensibility coefficient (DC), incremental modulus of elasticity (Einc), and stiffness index beta (beta) as described previously.[23]

Along with each investigation, BP measurements were performed oscillometrically (Dinamap, Criticon, Tampa, FL). The measurement procedures were based on recommendations from the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents (NHBPEP).[24]

Those participants, whose oscillometric BP levels were elevated, underwent additional verification by the auscultatory method according to the NHBPEP recommendations.[24] Casual hypertension was defined by systolic and/or diastolic oscillometric BP above the 95th height-, age-, and sex-adjusted percentile derived from the NHBPEP reference tables.[24]

Cardiovascular risk factors and family history of cardiovascular disease

Birth weight and length of the children were documented. Moreover, parents were asked to complete a structured questionnaire about disorders during pregnancy (pregnancy associated diabetes or hypertension), tobacco smoking during pregnancy, mother's and father's current weight and height, age, and individual and familial cardiovascular risk factors (arterial hypertension, diabetes, or tobacco smoking). All data gathered were recorded in a pseudonymized manner; 77.3% of the families returned a completed questionnaire, revealing prematurity in 11.2% and low birth weight (small for gestational age, SGA) in 12.2% of the children. A history of hypertension was reported in 14.6% of fathers and in 9.2% of mothers. Paternal obesity was present in 14.8% and maternal obesity in 14.6%; 37.4% of fathers and 25.4% of mothers (with 15.0% admitting that they had smoked during pregnancy) stated to smoke regularly. In 20.5% of all grandparents and in 2.9% of parents a history of either a cardiovascular event, cardiovascular disease, or multiple cardiovascular risk factors were reported.

Statistical analysis

The statistical analysis was performed using SAS 9.2 software (SAS Institute, Cary, NC). Correlation of variables was tested with Spearman rank order correlation, and variables were tested for their independent predictive influence by multivariate stepwise linear regression. A cutoff of 0.15 was used for entry or removal of variables. All multivariate models controlled for the influence of gender.

The LMS method[25] was applied as published previously. This method is widely used for the description of pediatric anthropometric data and allows calculating percentiles and accurately normalized standard deviation scores (SDS) accounting for nonlinearity and skewed distributions of the reference data set. The reference tables in the Supplement display the mean (M), the coefficient of variation (S), and a measure for the skewness (L). The SDS for each individual can be calculated by the equation $\mathrm{SDS} = [(Y/M(t))^{L(t)} - 1]/[L(t) \times S(t)]$, where Y is the individual measurement and L, M, and S originate from the specific reference values for each age (t) or height (t).

Comparability of age and height normalization for PWV was tested by paired t-tests for extreme height SDS groups (<10th and >90th percentile). The difference between PWV

SDS measures for age and height (ΔPWV SDS) was plotted against height percentile groups, and linear regression analysis was performed for ΔPWV SDS vs. height SDS in order to search for systematic divergences.

Standardized height and body mass index were calculated from the WHO growth charts (http://www.who.int/childgrowth/standards/en). BP values were standardized according to the 4th report of diagnosis, evaluation, and treatment of high BP in children.[24]

RESULTS

Mean values for PWV increased from 4.3 ± 0.4 m/s in the lowest age group (6–8.99 years) to 5.3 ± 0.5 m/s in the highest age group (15–18 years) in this healthy reference population. Gender differences were present starting from the age of 9 years and revealed significantly higher PWV values in boys than in girls (Supplementary Table S1). The gender-specific *L*, *M*, and *S* values for height and age are given in Supplementary Table S2A–C (also see Supplement for glossary of abbreviations). The respective percentile curves are shown in Figure 1A, B. At the age of 18 years, the 50th (10th, 90th) percentile of PWV was 5.57 (4.80, 6.66) m/s for males and 5.36 (4.29, 6.33) m/s for females. These values appear to merge with reference values previously obtained in adults with optimal BP levels[15] (Figure 2B).

PWV increased significantly with age, height, weight, body mass index, and body surface area. Further positive correlations were found for systolic and diastolic BP, mean arterial pressure (MAP), brachial pulse pressure, and heart rate (Table 2).

A stepwise multivariate analysis was performed using either PWV or PWV SDS according to age or height as dependent variable (Tables 3 and 4) . Male gender, older age as well as greater height, weight, and heart rate were independently associated with higher PWV, explaining 35.4% of the variability seen for PWV (Table 3). Systolic and diastolic BP SDS as well as standardized height was independently associated with PWV corrected for gender and age, while body mass index SDS, BP SDS, and age-predicted PWV standardized for gender and height (Table 4). These models explain 12.6 or 12.2%, respectively, of the variability seen for PWV.

To assess a potential impact of normalization either to age or height, the difference of age- vs. height-normalized PWV (ΔPWV SDS) was calculated. There was a systematic difference between height and age normalization, showing higher height-adjusted SDS values for PWV in children with lower height percentile and vice versa (Supplementary Figure S1).

Paternal hypertension, maternal obesity, and secondhand smoking turned out to be additional, independent risk factors for higher PWV, whereas a positive family history of cardiovascular disease had no significant impact. Children born SGA showed higher PWV SDS (according to height) values, prematurity *per se* had no effect (Table 5).

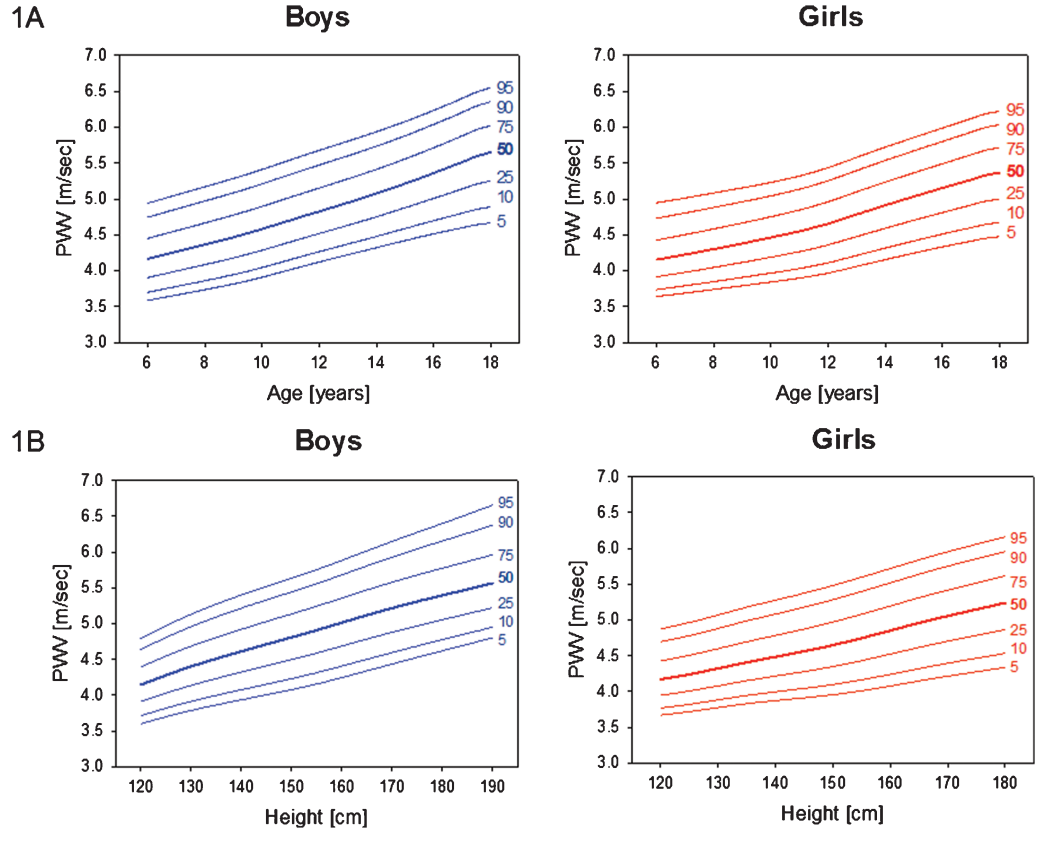

Figure 1. Gender-specific percentile curves for PWV for (**A**) age and (**B**) height.

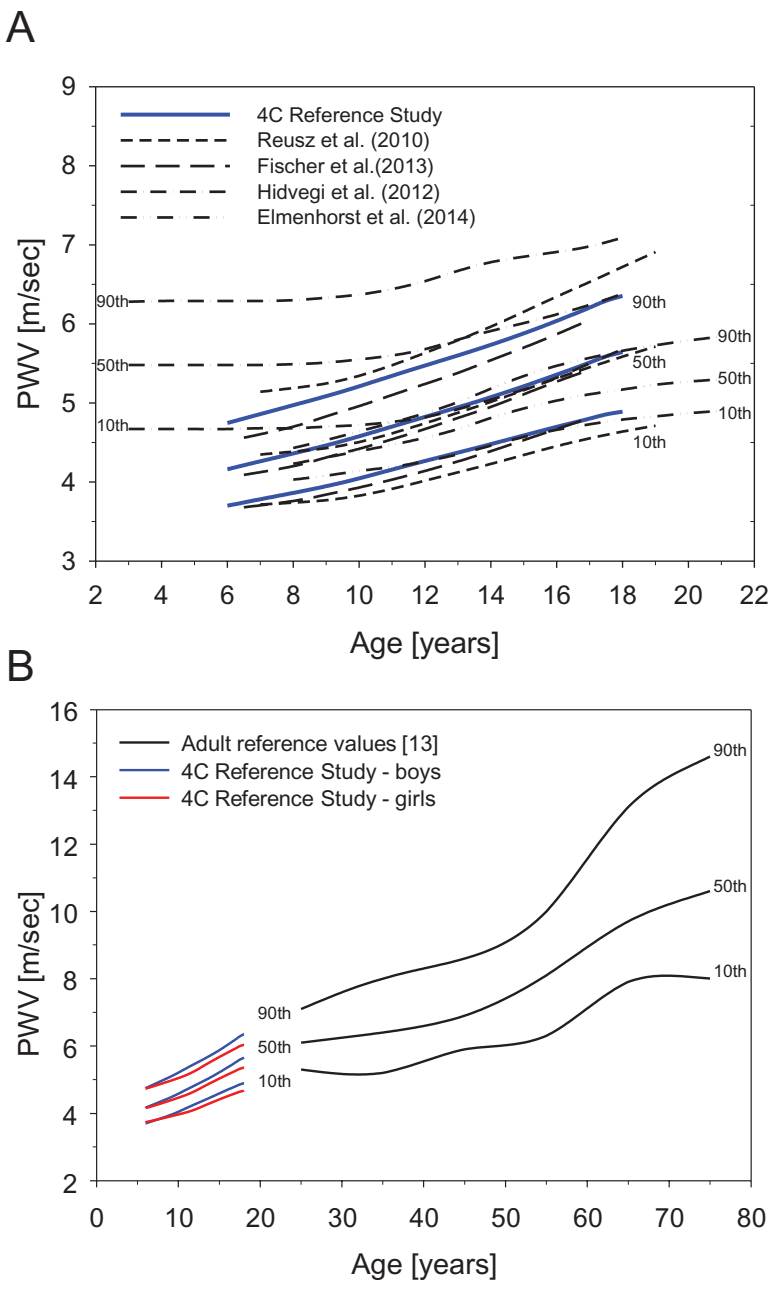

Figure 2. Synopsis of recently published pediatric (**A**) and adult (**B**) normative data for PWV according to age. (**A**) The median, 10th and 90th percentiles for PWV in boys from 3 different pediatric studies[20,26,27] were compared with the normative data from the 4C Reference Study. (**B**) The median, 10th and 90th percentiles for adults with optimal blood pressure[15] were compared with the normative PWV data for boys and girls from the 4C Reference Study.

Correlation of PWV with parameters of carotid distensibility and cIMT

For a subgroup of 589 individuals, additional standardized data on DC, Einc, beta, and cIMT were available for further analysis. PWV SDS correlated slightly but significantly with DC SDS ($r = -0.11$) and Einc SDS ($r = 0.12$), but not with beta SDS or cIMT SDS (Supplementary Table S3). In a stepwise multivariate regression analysis, PWV according to age was independently associated with DC, beta, and height, and PWV according to height was independently associated with DC, beta, and age. These models explain 14% of the variability seen for PWV.

DISCUSSION

This study in a large cohort of healthy Caucasian children elucidated the role of gender and body dimensions as well as personal and family cardiovascular risk factors for PWV and provides gender-, age-, and height-specific reference values for the use of an oscillometric device. Analysis of almost

Table 2. Univariate correlation matrix of PWV with anthropometric and hemodynamic parameters

Parameters	PWV	PWV SDS for age	PWV SDS for height
Age	0.572 (*<0.0001*)	−0.003 (*0.99*)	0.071 (*0.026*)
Height	0.572 (*<0.0001*)	0.064 (*0.044*)	0.001 (*0.966*)
Height SDS	0.113 (*0.0003*)	0.160 (*<0.0001*)	−0.115 (*0.0003*)
BMI	0.427 (*<0.0001*)	0.110 (*0.0005*)	0.101 (*0.0015*)
BMI SDS	0.084 (*0.008*)	0.115 (*0.0003*)	0.047 (*0.14*)
BSA	0.583 (*<0.0001*)	0.095 (*0.0027*)	0.047 (*0.14*)
SBP	0.498 (*<0.0001*)	0.241 (*<0.0001*)	0.231 (*<0.0001*)
SBP SDS	0.246 (*<0.0001*)	0.257 (*<0.0001*)	0.265 (*<0.0001*)
DBP	0.311 (*<0.0001*)	0.247 (*<0.0001*)	0.280 (*<0.0001*)
DBP SDS	0.084 (*0.008*)	0.206 (*<0.0001*)	0.259 (*<0.0001*)
PP	0.344 (*<0.0001*)	0.102 (*0.0012*)	0.073 (*0.022*)
MAP	0.315 (*<0.0001*)	0.235 (*<0.0001*)	0.229 (*<0.0001*)
Heart rate	−0.075 (*0.018*)	0.160 (*<0.0001*)	0.151 (*<0.0001*)

Correlations are given for absolute and standardized values.

Abbreviations: BMI, body mass index; BSA, body surface area; DBP, diastolic blood pressure, MAP, mean arterial pressure; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure; SDS, standard deviation score.

Table 3. Stepwise multivariate regression analysis for PWV

	PWV		
	β	SE	*P-value*
Age	0.065	0.0112	<0.0001
Weight	0.003	0.002	<0.0001
Gender	−0.143	0.031	<0.0001
Height	0.007	0.003	0.15
Heart rate	0.0008	0.0006	0.17
Model R^2	0.354		

Abbreviations: β, parameter estimate; PWV, pulse wave velocity; R^2, *R* square.

600 individuals with additional data on carotid distensibility allowed for the description of a moderate association between aortic and carotid stiffness.

Our study confirms other studies in showing an age-related increase in arterial stiffness[26–28] (Figure 2), but extends these findings by providing evidence that cardiovascular risk factors (male gender, higher BP, born SGA, presence of risk factors within the family) have a significant influence even in healthy children and at a young age. It is noteworthy that children exposed to secondhand smoking had a significantly higher PWV compared to unexposed children, adding further evidence for the potent adverse effect of tobacco smoke on cardiovascular health. In addition, parental obesity and hypertension were associated with the child's PWV, suggesting a major role of family/genetic determinants of childhood cardiovascular status. To date the natural history of arterial stiffening in the general population is largely unknown. It is likely that during lifetime additional risk factors will contribute to increased aortic stiffness, a hallmark of the aging process, but longitudinal studies are lacking. Therefore, the differences in PWV seen in our study likely reflect the cumulative load of genetic and acquired cardiovascular risk factors of each individual even at a very young age.

The increase in PWV with age observed in the present study is continuous and starts already at 6 years of age. This is similar to 3 other studies in pediatric cohorts: the study by Reusz *et al.* in 1008 healthy individuals (aged 6–20 years) using Pulse Pen applanation tonometry (DiaTecne s.r.l., Milan, Italy),[26] the data of Fischer *et al.* in 303 individuals (aged 5–19 years) also using the oscillometric Vicorder device,[20] and the study by Elmenhorst *et al.* including 1,445 healthy subjects (aged 8–22 years) using the Mobil-O-Graf (IEM GmbH, Stolberg, Germany)[28] but different from one large study by Hidvegi *et al.* in 3374 individuals (aged 3–18 years) using the oscillometric Arteriograph device (Arteriomed, Grevenbroich, Germany).[27] The latter study starts off with a plateau phase, during which PWV does not change; increases in PWV are only seen from 8 to 9 years of age (Figure 2A).

Although all studies, except for the study from Hidvegi, resulted in comparable median PWV curves over age, the range of the 10th and 90th percentile curves differed considerably between studies. This most likely reflects device-specific differences and reinforces the need for device- and setting-specific reference values.[29,30] But it also raises the question which method reflects real differences in cardiovascular health or the predisposition for cardiovascular disease. As outlined above, to further elucidate this question, longitudinal assessments of PWV performed with different devices would need to be linked to known risk factors or cardiovascular endpoints. For now, the ability to reveal increases in PWV before the age of 9 years and the early demonstration of gender differences may be seen as the results of a higher sensitivity of the oscillometric device in detecting subtle changes in PWV.

Table 4. Stepwise multivariate regression analysis for PWV according to age or height

	PWV SDS for age			PWV SDS for height		
	β	SE	*P-value*	β	SE	*P-value*
Age	—	—	—	0.049	0.012	<0.0001
Height SDS	0.191	0.029	<0.0001	—	—	—
BMI SDS	0.055	0.030	0.06	0.069	0.031	0.03
SBP SDS	0.124	0.044	<0.0001	0.181	0.047	0.0001
DBP SDS	0.338	0.061	<0.0001	0.324	0.062	<0.0001
PP	0.003	0.003	0.36	−0.005	0.004	0.19
Model R^2	0.126			0.122		

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; PP, pulse pressure; PWV, pulse wave velocity; SDS, standard deviation score; SBP, systolic blood pressure.

Table 5. Effect of gestational, parental, and environmental risk factors on PWV

		PWV SDS for height			PWV SDS for age		
		Mean ± SD	Delta	*P*	Mean ± SD	Delta	*P*
Parental risk factors	Obese	0.171 ± 1.03	0.199	0.002	0.233 ± 0.989	0.275	0.001
	Non-obese	−0.027 ± 1.03			−0.042 ± 1.02		
	Hypertensive	0.247 ± 0.946	0.320	0.0002	0.304 ± 1.05	0.354	<0.0001
	Normotensive	−0.044 ± 1.01			−0.049 ± 1.01		
	Smoking	0.113 ± 1.06	0.161	0.02	0.139 ± 1.03	0.201	0.003
	Non-smoking	−0.047 ± 1.01			−0.062 ± 1.01		
Gestational risk factors	SGA	0.317 ± 0.936	0.286	0.021	0.203 ± 0.943	0.116	0.34
	Non-SGA	0.031 ± 1.05			0.086 ± 1.04		
	Born preterm	−0.084 ± 1.04	−0.174	0.17	−0.066 ± 1.04	−0.188	0.13
	Born at term	0.088 ± 1.04			0.106 ± 0.989		
	Gestational smoking: yes	0.087 ± 0.928	−0.027	0.81	0.051 ± 0.901	0.040	0.71
	No	0.060 ± 0.964			0.091 ± 0.956		

Abbreviations: PWV, pulse wave velocity; SDS, standard deviation score; SGA, small for gestational age.

The significant but rather weak correlation between PWV and carotid distensibility measures and the complete absence of a correlation to cIMT might point out that these measurements reflect 2 different locations in the cardiovascular system with different aging patterns and susceptibility to cardiovascular risk factors.[6] Future studies should assess these parameters in parallel with the ultimate goal to allow for the prediction of different disease patterns based on the changes seen in these cardiovascular measures.

In was not possible to assess all endogenous and environmental risk factors influencing PWV within the frame of this study on healthy school children. Our study is especially limited with regard to laboratory data, thus no additional conclusions on the impact of potential risk factors as lipid status, glucose metabolism, markers of subclinical inflammation, sex steroids, or gene polymorphisms on PWV in healthy children can be drawn.

However these analyses have been partially performed in a substudy of Reusz *et al.*,[26] with no correlations of blood glucose levels or lipid values to PWV. Our data could also not be presented relative to the pubertal status of the children, since we had no ethics permission to assess pubertal stages. However, gender differences in biomechanical properties of the arterial walls pre- and postpuberty have been reported and described earlier and are likely to have an influence on PWV.[31,32]

PWV is regarded the most widely accepted method for the assessment of vascular stiffness in children and young adults as stated by *American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee of the Council on Cardiovascular Disease in the Young*.[33] Our study defines normal values for PWV in children and young adults using the validated noninvasive oscillometric Vicorder method and highlights the need of device- and setting-specific reference values in pediatric cohorts. The definition of such reference values will further improve our ability to identify individuals at high risk, especially in light of our own findings showing a significant early influence of cardiovascular risk factors in healthy children.

SUPPLEMENTARY MATERIALS

Supplementary materials are available at *American Journal of Hypertension* (http://ajh.oxfordjournals.org).

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DISCLOSURE

The authors declared no conflict of interest.

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