Carotid Artery Intima-Media Thickness and Distensibility in Children and Adolescents

Reference Values and Role of Body Dimensions

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Abstract—Carotid intima-media thickness (cIMT) and carotid artery distensibility are reliable screening methods for vascular alterations and the assessment of cardiovascular risk in adult and pediatric cohorts. We sought to establish an international reference data set for the childhood and adolescence period and explore the impact of developmental changes in body dimensions and blood pressure (BP) on carotid wall thickness and elasticity. cIMT, the distensibility coefficient, the incremental modulus of elasticity, and the stiffness index β were assessed in 1155 children aged 6 to 18 years and sex-specific reference charts normalized to age or height were constructed from 1051 nonobese and nonhypertensive children. The role of body dimensions, BP, and family history, as well as the association between cIMT and distensibility, was investigated. cIMT increased and distensibility decreased with age, height, body mass index, and BP. A significant sex difference was apparent from the age of 15 years. Age- and height-normalized cIMT and distensibility values differed in children who are short or tall for their age. By stepwise multivariate analysis, standardized systolic BP and body mass index were independently positively associated with cIMT SD scores (SDS). Systolic BP SDS independently predicted all distensibility measures. Distensibility coefficient SDS was negatively and β SDS positively associated with cIMT SDS, whereas incremental modulus of elasticity was independent of cIMT. Morphological and functional aspects of the common carotid artery are particularly influenced by age, body dimensions, and BP. The reference charts established in this study allow to accurately compare vascular phenotypes of children with chronic conditions with those of healthy children. **(*Hypertension*. 2013;62:550-556.)** • **Online Data Supplement**

Key Words: carotid ■ child ■ intima-media thickness ■ vascular stiffness

The assessment of cardiovascular risk in pediatric cohorts is challenging. Cardiovascular events or even death rarely occur in children. However, alterations of the cardiovascular system can be identified at an early age in pediatric populations,.[1–3] High-resolution vascular ultrasound is a reliable screening method and in this regard, carotid intima-media thickness (cIMT) has been shown to be increased in children with traditional cardiovascular risk factors, such as obesity, hypertension, and chronic kidney disease.[4,5] In adults, increased cIMT has been demonstrated to allow risk stratification for the occurrence of cardiovascular disease[6] and has, therefore, recently been considered as a valid intermediate outcome variable for cardiovascular risk.[7]

Although cIMT reflects morphological alterations of the vascular tree, functional changes might occur at an even earlier stage of cardiovascular disease. Arterial distensibility is considered a very sensitive indicator for functional changes. The distensibility of the carotid artery, expressed by the distensibility coefficient (DC), the stiffness index β, and the incremental elastic modulus (Einc) is most suitable to determine local arterial stiffness. Decreased carotid distensibility has been observed in adults with hypertension and

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Received February 25, 2013; first decision March 18, 2013; revision accepted June 6, 2013.

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The online-only Data Supplement is available with this article at http://hyper.ahajournals.org/lookup/suppl/doi:10.1161/HYPERTENSIONAHA.113.01297/-/DC1.

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Hypertension **is available at http://hyper.ahajournals.org** **DOI: 10.1161/HYPERTENSIONAHA.113.01297**

hyperglycemia,[8,9] and in children with familial hypercholesterinemia and severe obesity.[10,11]

In children, cIMT and arterial distensibility change with growth and development. Therefore, large studies with cIMT and carotid distensibility as intermediate end points, like the Cardiovascular Comorbidity in Children with Chronic Kidney Disease (4C) Study,[12] require valid reference data. A previous study of 247 healthy children between 10 and 20 years has provisionally defined normative values for cIMT and carotid distensibility for the adolescent age group.[13] Here, we provide reference ranges for subjects aged 6 to 18 years on the basis of measurements in 1155 healthy controls, thereby improving the validity of the normal range definition and expanding the defined reference age range to younger children.

Methods

Subjects and Study Design

The cIMT reference study was conducted to create reference values for cIMT and distensibility. CIMT was measured in 1155 children and adolescents aged 6 to 18 years with no history of chronic disease, chronic medication, or signs of acute infection. Of these, cIMT and distensibility reference values were calculated from 1051 nonobese and nonhypertensive participants,[14,15] hereafter referred to as the reference population. Measurements were performed by 7 jointly trained observers in Adana (n=84), Ankara (n=34), Hannover (n=404), Heidelberg (n=169), Huddinge (n=14), Izmir (n=140), and Warsaw (n=310). The study protocol was approved by all local ethical committees. Written informed consent was obtained from parents and adolescents and assent from younger children.

Sonographic and Blood Pressure Measurements

Images of the carotid artery were obtained according to the Mannheim cIMT consensus.[16] cIMT was obtained either by 5 averaged measurements on each side or semiautomatically using a digital image evaluation software (Syngo US Workplace; Siemens Medical Solutions, USA Inc), depending on the availability of the software package. Systolic and diastolic internal diameters of the common carotid artery were obtained from M-mode recordings of 5 consecutive heart cycles. Brachial blood pressure (BP) was measured simultaneously on the side of the M-mode recording. A detailed description of the sonographic measurements has been published previously.[13] Reproducibility and agreement of both methods were demonstrated by measuring 74 samples both with the semiautomatic and with the manual method. The mean paired difference between methods was 0.004±0.018 mm (n.s.). Accordance of both methods was excellent with an intraclass correlation coefficient of 0.83 and a coefficient of variation of 9.9%. Interobserver variation was tested for 2 observers independently measuring 55 data sets, showing an intraclass correlation coefficient of 0.42 and an interobserver coefficient of variation of 7.3%. BP measurements were performed oscillometrically (Dinamap; Criticon Inc, Tampa, FL), elevated BP levels were verified by auscultation.

Data Analysis

Data were tested for normal distribution by the Shapiro–Wilk test. 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 were controlled for the influence of sex. Percentile and least mean squares (LMS) reference values were calculated exclusively from the reference population, sex differences were also analyzed from this group. All regression models and the comparison of height versus age normalization included the complete study population.

The LMS method was applied as published previously.[17] This method is widely used for the description of pediatric anthropometric data, for example, for the Centers for Disease Control and Prevention growth charts[18] and allows to calculate percentiles and accurately normalized SD scores (SDS) accounting for nonlinearity and skewed distributions of the reference data set. The reference tables (see the online-only Data 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, $SDS = \left\{\left[Y / M(t)\right]^{L(t)} - 1\right\} \Big/ \left[L(t) \times S(t)\right]$, 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 cIMT and distensibility was tested by paired *t* tests of cIMT and distensibility, respectively, for extreme height SDS groups (<10th and >90th percentile). The difference between cIMT SDS or distensibility SDS measures for age and height (ΔcIMT SDS, ΔDC SDS, ΔEinc SDS, and Δβ SDS) was plotted against height percentile groups, and linear regression analysis was performed for ΔcIMT SDS and Δdistensibility SDS versus height SDS to search for systematic divergences.

Standardized height and body mass index (BMI) were calculated from the World Health Organization growth charts (http://www.who.int/growthref/en). BP values were standardized according to the summary of the Fourth Report on Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.[15] cIMT and distensibility differences between sexes were analyzed by *t* test and multiple linear regression correcting for the influence of BP and BMI differences between both groups.

Results

Subject Characteristics

Subject characteristics of the reference group are given in Table 1. For subject characteristics of the complete study population, see the online-only Data Supplement.

Maternal obesity was present in 14% and paternal obesity in 18%. A history of hypertension was present in 16% of fathers and in 9% of the mothers. Twenty-seven percent of the mothers and 39% of the fathers stated to smoke regularly. In 3.6% of parents and 14.7% of all grandparents a history of a cardiovascular event, cardiovascular disease, or multiple cardiovascular risk factors was reported.

Table 1. Subject Characteristics

	Age, y			
Parameters	6–8.99	9–11.99	12–14.99	15–18
No. of subjects				
M	95	120	124	153
F	86	178	163	132
Height, cm				
M	127.0±6.3	142.5±9.5	161.8±11.0	176.5±9.3
F	126.2±7.3	143.7±9.5	157.8±6.5	165.2±5.9
BMI, kg/m²				
M	16.1±1.45	17.3±1.97	20.0±2.6	21.7±2.7
F	16.3±1.6	17.6±2.4	20.2±2.6	21.4±2.5
Systolic BP, mm Hg				
M	102.8±9.6	104.0±8.7	110.2±9.7	120.8±9.7
F	103.7±8.2	103.9±9.9	108.1±9.3	112.9±8.4
Diastolic BP, mm Hg				
M	59.0±7.1	57.6±6.1	57.9±6.4	60.3±6.3
F	59.2±7.4	58.5±6.8	60.1±7.0	62.8±5.9

Reference population; n=1051. BMI indicates body mass index; BP, blood pressure; F, female; and M, male.

Intima-Media Thickness

Carotid wall thickness in this healthy study cohort largely followed a Gaussian distribution in both sexes. There was no significant sex difference from 6 to 14.9 years, but starting at the age of 15 years boys had significantly higher cIMT values than girls ($P<0.0004$). The difference remained significant when correcting for height, BP, and BMI differences by multivariate analysis ($P<0.02$). Thus, sex-specific *L*, *M*, and *S* values were calculated for height at 5-cm intervals and for age at 6-month intervals and respective percentile curves were created (Figure 1).

cIMT increased significantly with body dimensions, BP, and pulse pressure (Table 2). In a stepwise multivariate model, systolic BP SDS and BMI SDS were significant independent positive predictors of cIMT SDS (Table 3). The 50th percentile of cIMT increases from 0.37 for both sexes at age 6 years to 0.39 for girls and 0.41 for boys at age 18 years. These values are associated closely with reference values previously obtained in healthy young adults[19,20] (Figure 2). cIMT SDS was significantly higher in subjects with high BP or elevated BMI (Figure 3). Family history of cardiovascular risk factors or manifest disease did not show any significant associations with cIMT.

Distensibility

As for cIMT, measurements of distensibility showed age- and sex-specific differences starting from the age of 15 years. Therefore, LMS tables and percentile curves for height and age were constructed for both sexes (Figure 1). Height-specific normal ranges were calculated for boys ranging from 120 to 190 cm and for girls between 120 and 180 cm.

The associations of the distensibility measures with anthropometric and hemodynamic parameters are given in Tables 2 and 3. Systolic BP SDS was the major independent predictor of age-adjusted arterial elasticity as calculated by DC SDS, Einc SDS, and β SDS, whereas cIMT SDS explained only a small portion of variability in the models. Height SDS was not associated to any distensibility measure. Einc and β SDS were significantly higher ($P<0.0001$ and <0.002) and DC SDS was

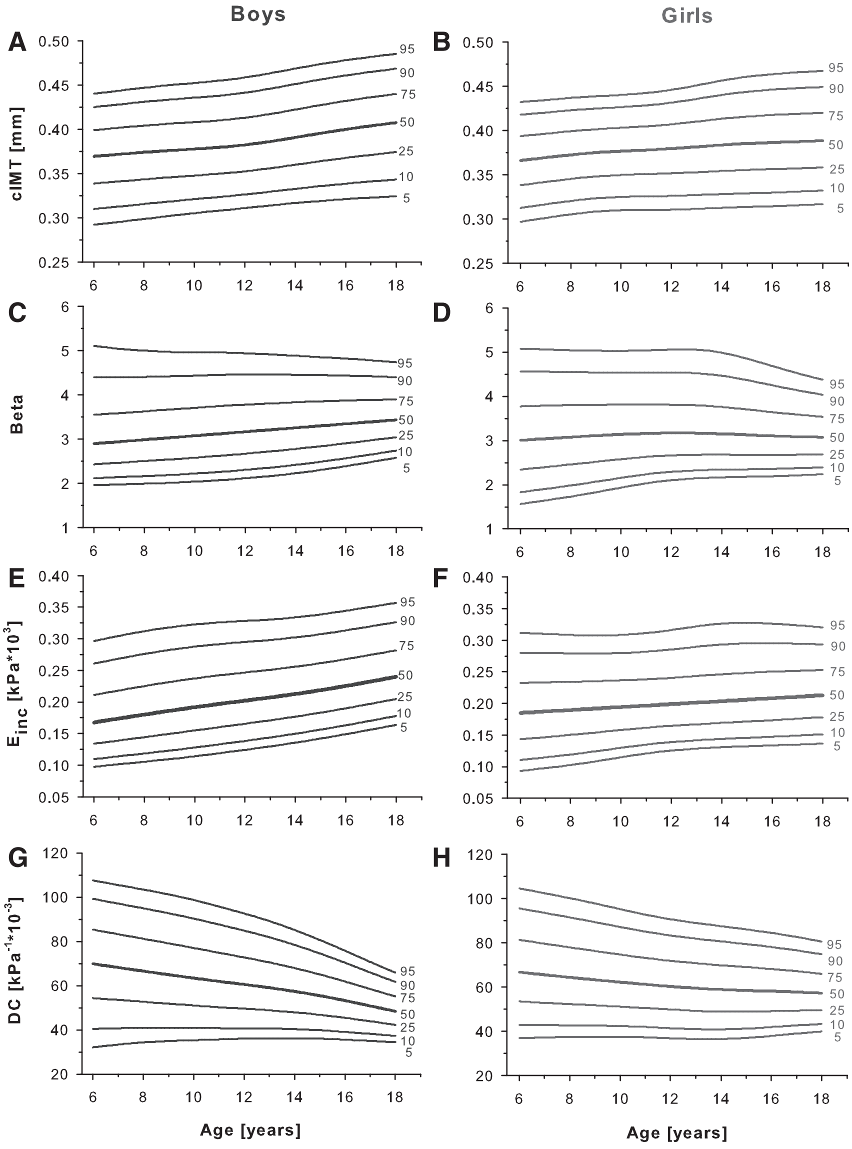

Figure 1. Sex-specific percentile curves for carotid intima-media thickness (cIMT, mm; **A** and **B**), β (**C** and **D**), incremental modulus of elasticity (Einc, kPa×10^3; **E** and **F**), and distensibility coefficient (DC, kPa^{-1}×10^{-3}; **G** and **H**) according to age.

Table 2. Univariate Correlation Matrix of cIMT and Distensibility With Anthropometric and Hemodynamic Parameters

	Age	Height	Height SDS	BMI	BMI SDS	Syst BP	Syst BP SDS	Diast BP	Diast BP SDS	Pulse Pressure	Heart Rate
cIMT	0.15‡	0.17‡	…	0.13‡	0.13‡	0.27‡	0.16‡	0.14‡	...	0.20‡	...
cIMT SDS	…	…	…	0.11‡	0.13†	0.18‡	0.18‡	0.13‡	0.11†	0.09†	0.11‡
β	0.1†	0.08†	…	0.10‡	...	0.24‡	0.20‡	−0.06*	−0.10†	0.31‡	...
β SDS	…	…	…	...	0.17†	0.17‡	0.22‡	−0.07*	−0.07†	0.24‡	0.08*
DC	−0.24‡	−0.21‡	…	−0.22‡	−0.08†	−0.5‡	−0.42‡	−0.18‡	−0.08†	−0.44‡	−0.14‡
DC SDS	…	…	…	−0.10‡	−0.13‡	−0.37‡	−0.45‡	−0.16‡	−0.15‡	−0.31‡	−0.20‡
Einc	0.21‡	0.19‡	…	0.21‡	0.09†	0.42‡	0.34‡	0.16‡	0.07*	0.37‡	0.11†
Einc SDS	…	…	…	0.10†	0.14‡	0.29‡	0.35‡	0.14‡	0.13‡	0.23‡	0.16‡

Correlations are given both for absolute and normalized height, BMI, and BP. BMI indicates body mass index; BP, blood pressure; cIMT, carotid intima media thickness; diast BP, diastolic BP; DC, distensibility coefficient; Einc, incremental modulus of elasticity; SDS, SD score; and syst BP, systolic BP.

*$P<0.05$.

†$P<0.001$.

‡$P<0.0001$.

lower ($P<0.0001$) in subjects with high BP values but not in those with elevated BMI (Figure 3).

All stiffness parameters were intercorrelated. β SDS and Einc SDS showed strong positive associations to each other ($r=0.89$; $P<0.0001$) and both were negatively correlated to DC SDS ($r=-0.94$ and -0.92; $P<0.0001$).

Standardized DC was inversely ($r=-0.28$; $P<0.0001$) and β ($r=0.22$; $P<0.0001$) was positively correlated with cIMT, whereas Einc was independent of cIMT by univariate analysis.

Normalization to Age or Body Height

LMS tables were calculated referencing cIMT and distensibility measures to either age or height (see the online-only Data Supplement).

To assess a potential impact of normalization either to height or to age in short and tall subjects, the difference of height versus age normalized IMT, DC, Einc, and β (ΔcIMT SDS, ΔEinc SDS, and Δβ SDS) was calculated (Figure S8 in the online-only Data Supplement). Normalization to height yielded higher cIMT and lower distensibility scores in small subjects than normalization to age.

LMS and percentile tables for age and height are given in the online-only Data Supplement.

Discussion

This study in a large cohort of healthy children and adolescents provides extensive novel information about the morphological and functional properties of the carotid arterial wall in the pediatric age range. A previous study described the dependence of cIMT and distensibility of age, body dimensions, and BP in adolescents.[13] Our study confirmed these findings with greater statistical reliability. In addition, our analysis of a larger population with a more extended age range revealed a significant sex difference and allowed the calculation of age-, height-, and sex-specific normal values.

Biologically, evidence from large adult cohorts suggests that cIMT and arterial stiffness increase throughout life.[19–23] Physiological aging is, therefore, a main determinant of cIMT. The pediatric reference ranges established in this study, including the slight increase of cIMT observed with age, fit in nicely with the gradual increase in cIMT during adult life observed in the mentioned previous studies (Figure 2).[19,20] Hence, it is possible that the changes of cIMT and arterial elasticity with age noted in this study reflect the precedents of vascular ageing. An alternative or additional mechanism underlying the observed changes at childhood age might be adaptive remodeling of the vessel walls in response to physiological developmental changes in body dimensions and BP.

Whereas our data cannot conclusively answer the question whether vascular aging or changing body dimensions are more relevant for the vascular changes in childhood, the comparison of the age- and height-related SDS values according to relative body height (Figure S8) emphasize that growth abnormalities need to be considered in the assessment of cIMT and arterial distensibility. Children who are very short or tall for age might be assessed more accurately by height-normalized reference values.

cIMT increased not only with age and height but also there was a significant independent association with BMI. This

Table 3. Stepwise Multivariate Regression Analysis for cIMT, Distensibility, and Anthropometry

	cIMT SDS			β SDS			DC SDS			Einc SDS		
	β±SE	r^2	P	β±SE	r^2	P	β±SE	r^2	P	β±SE	r^2	P
BMI SDS	0.14±0.03	0.02	<0.0001	…	…	n.s.	...	…	n.s.	…	…	n.s.
Syst BP SDS	0.17±0.03	0.03	<0.0001	0.24±0.04	0.05	<0.0001	−0.48±0.03	0.21	<0.0001	0.44±0.03	0.13	<0.0001
IMT SDS	…	…	…	0.15±0.03	0.02	<0.0001	−0.16±0.03	0.02	<0.0001	−0.1±0.03	0.009	0.001
Model R^2	…	0.05	…	...	0.07	...	...	0.23	...	...	0.14	...

BMI indicates body mass index; cIMT, carotid intima media thickness; DC, distensibility coefficient; Einc, incremental modulus of elasticity; SDS, SD score; and syst BP, systolic BP.

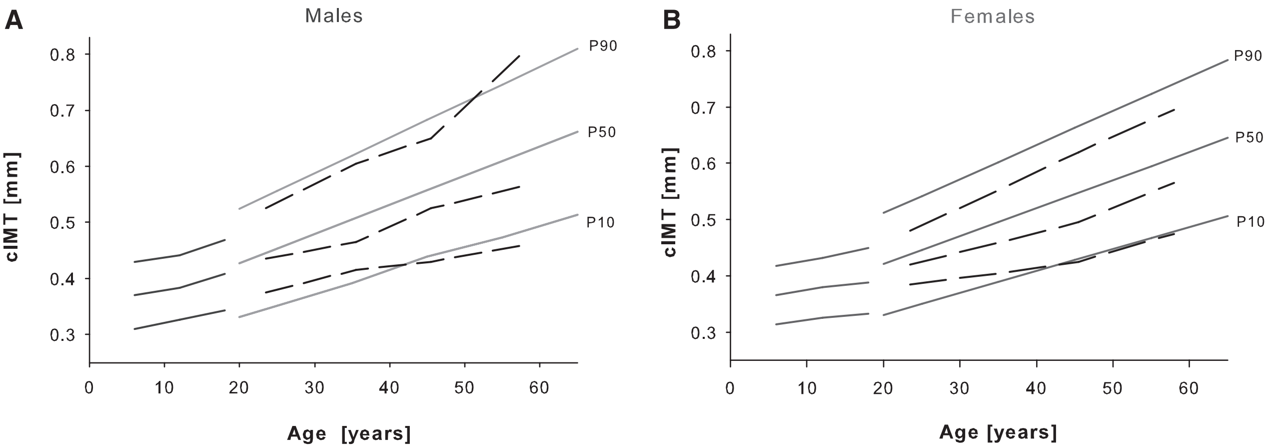

Figure 2. Synopsis of carotid intima-media thickness (cIMT) percentiles (10th, 50th, and 90th) in children and adolescents (6–18 years, this study) and adults (dotted lines, 17–65 years; Denarié et al[19] and solid lines, 20–85 years; Engelen et al[20]); cIMT in males (**A**) and cIMT in females (**B**).

finding confirms earlier observations and supports the assumption of obesity as a relevant risk factor for vascular alterations starting from very early age.[11,20,24,25]

An important finding of our study is that both absolute and standardized systolic BP, as well as pulse pressure, are related to cIMT. This indicates that cIMT increases as a physiological reaction of the vessel to adapt to the age-dependent rise in BP. The observed sex differences, with higher values and a steeper increase of cIMT in boys starting around age 15 years, might reflect the more marked increase in BP coinciding with the distinct growth spurt in pubertal boys.[26,27] Furthermore, the consistent association even of standardized systolic BP and cIMT values in these children and adolescents points to an intrinsic link between vascular remodeling and the presence of physical stress on the cardiovascular system already very early in life. Indeed, previous studies demonstrated increased cIMT in children with primary hypertension[28,29] and a strong correlation to systolic BP or pulse pressure,[13,30,31] suggesting that the peak force exerted on the vessel might be a major determinant of arterial remodeling.

Carotid artery distensibility measures can help to assess determinants of local arterial function.[32] Our study revealed sex-specific differences. Also, there were significant changes with age and body dimensions; the tissue-specific distensibility tended to decrease and arterial stiffness to increase with age, height, and relative body weight.

DC describes the relative diameter change for a defined pressure impact.[33] Inversely, Einc expresses the pressure force needed to result in a defined vessel deformation. Hence, DC and Einc are closely inversely correlated and substantially affected by systolic BP. Even when expressed as age- and height-adjusted SDS, systolic BP explained 14% to 23% of the variability of DC and Einc. The remaining variability of DC and Einc is independent of fundamental anthropometric variables, such as height and BMI, and may represent intrinsic and environmentally induced biological variation. The stiffness index β was proposed as a largely BP-independent measure. It is defined as the association between the logarithmic relationship of systolic and diastolic BP and vessel strain (relative diameter change), resulting in a dimensionless constant describing the intrinsic rigidity of a vessel.[34] In our analysis, systolic BP, when adjusted for age- and height-dependent changes, still explained ≈5% of variation, suggesting that BP can cause immanent changes of vessel characteristics.

Furthermore, the observed correlations of cIMT and the distensibility measures DC and β indicate a close link between functional and morphological variation.

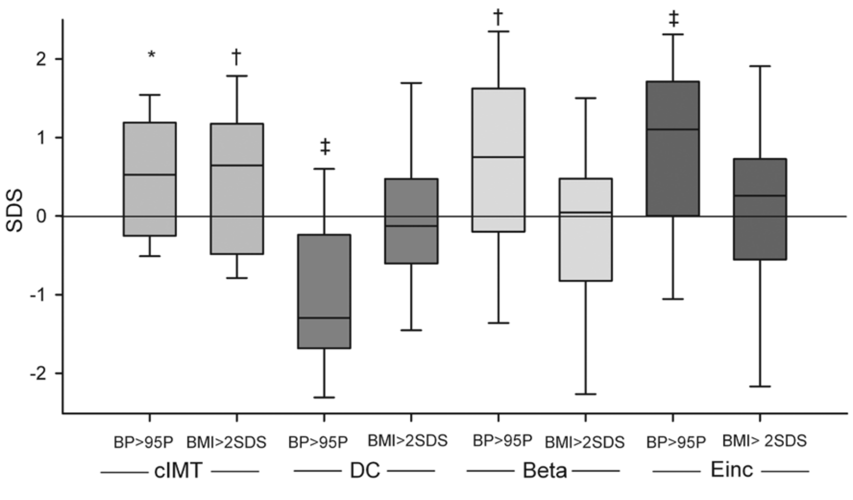

Figure 3. Carotid intima-media thickness (cIMT), distensibility coefficient (DC), β, and incremental modulus of elasticity (Einc) for subjects with blood pressure (BP)>95th percentile or body mass index (BMI)>2 SD scores (SDS). **P*<0.0002, †*P*<0.002, ‡*P*<0.0001.

Limitations

Despite our efforts to minimize interobserver variation by repeated intense joint training sessions, the use of several observers may have limited the precision and accuracy of data capture in this study. Furthermore, although our study included >1000 healthy children, the subject number per age and sex group might still be considered limited. Finally, our analysis was limited to cIMT and distensibility measures of the common carotid artery. Future studies will be required to assess the pediatric normal range of novel vascular indices, such as the longitudinal displacement of the CCA and adventitial thickness.[35,36] Moreover, reference measurements on the carotid bulb and internal carotid artery as the potentially earliest sites of vascular alteration are desirable.

Conclusions

cIMT has become a standard surrogate marker of early vascular changes. It has been widely used in adults and also in several pediatric cohorts.[3,5,29,37–40] The characterization of this cohort helped to identify fundamental factors affecting vessel morphology and function in childhood and our findings emphasize the variability of vascular phenotypes depending on physical constitution.

Perspectives

The reference values for cIMT and distensibility provided by this study allow an accurate evaluation of the vascular status in healthy children and in those with cardiovascular risk factors. Given the emerging focus on treatment strategies to modify the vascular phenotype,[41] there is a need for longitudinal studies in pediatric populations considered at increased long-term cardiovascular risk. The normative values provided here for cIMT and carotid artery stiffness will provide a framework of reference to such studies.

Acknowledgments

We thank all children and adolescents for their participation in the study and the participating schools for their active support of the project, in particular the school of Bilge Kagan Ilkogretim Okulu, Adana and the Integrierte Gesamtschule Roderbruch, Hannover. We gratefully acknowlegde the support of our colleagues and friends Sajoscha Sorrentino, Christoph Jacobi, Meike Hömme, Birgit Berkenkamp, Margit Überheide, Carolin Schildhorn, Sabrina Baig, Julian Lünig, Ulrike Dringenberg, and Susanne Schaefer.

Sources of Funding

The study has been made possible by grants of the KfH Foundation for Preventive Medicine, the European Renal Association—European Dialysis and Transplant Association (www.era-edta.org) and the German Federal Ministry of Education and Research (reference number: 01EO0802).

Disclosures

None.

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Novelty and Significance

What Is New?

- This study established for the first time pediatric reference values for carotid intima-media thickness and distensibility in >1000 healthy European children.
- This revealed a high impact of sex, age, body dimensions, and blood pressure to both carotid intima-media thickness and distensibilty.

What Is Relevant?

- The findings emphasize the variability of vascular phenotypes depending on physical constitution and blood pressure even in children.
- Changing body dimensions require age- or height-adjusted reference values, which are provided as LMS tables and sex-specific percentile curves.

Summary

The characterization of this healthy cohort helped to identify fundamental factors affecting vessel morphology and function in childhood. The provided reference values for carotid intima-media thickness and distensibility allow an accurate, quantitative assessment of the vascular status in healthy and in children with cardiovascular risk factors.