Elastic Properties of the Ascending Aorta in Healthy Children and Adolescents

– Age-Related Reference Values for Aortic Wall Stiffness and Distensibility Obtained on M-mode Echocardiography –

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Background: Compliance of the aorta is important in maintaining normal cardiovascular physiology. Pathological conditions can induce changes in elastic properties, having profound effects on their prognosis. The aim of this study was to establish age-related reference values for distensibility and wall stiffness index of the ascending aorta.

Methods and Results: A total of 165 normal subjects (mean age, 11.92 ± 4.0 years) were investigated on transthoracic echocardiography. Ascending aortic diameter was recorded in M-mode above the sinotubular junction. Blood pressure was measured simultaneously at the right arm. Aortic pulse pressure, distensibility and aortic wall stiffness index were calculated offline. Distensibility decreased significantly with age ($r = -0.462$, $P < 0.001$); the regression line indicated an average decrease of $5.1 \cdot 10^{-3} \text{ kPa}^{-1}$ (95% confidence interval [CI]: $3.9\text{--}6.8 \cdot 10^{-3} \text{ kPa}^{-1}$) per year. Significant correlations could be found between distensibility and weight, height, body surface area (BSA) and body mass index (BMI) ($P < 0.001$). Stiffness index increased significantly with age ($r = 0.399$, $P < 0.001$); the regression line indicated an average increase of 0.066 (95% CI: $0.047\text{--}0.085$) per year; significant correlations could be found between wall stiffness index and weight, height, BSA and BMI ($P < 0.001$). The 2.5th and 97.5th percentiles of the distribution of distensibility and stiffness index related to age, weight, height, BSA and BMI were calculated.

Conclusions: Normal values of arterial elastic properties throughout childhood and adolescence have been provided, and might serve as a reference for individuals with cardiovascular and metabolic disease. (*Circ J* 2013; **77**: 3007–3014)

Key Words: Aorta; Echocardiography; Elasticity

Arterial compliance and stiffness of the ascending aorta are important components of the elastic nature of the arterial system. Because of the pulsatile blood flow generated by the contraction of the heart, these elastic properties play an important role in maintaining normal cardiovascular physiology.¹

Decreased aortic compliance and increased wall stiffness alter myocardial blood flow by a decrease in diastolic perfusion pressure,^{2,3} and cardiac performance may be reduced by an increase in ventricular workload.^{4,5}

A number of pathological conditions in childhood can potentially induce changes in arterial properties, having profound effects on prognosis, as could be demonstrated in patients with arterial hypertension,^{6–8} vasculitis and vasculopathies,⁹ in pa-

tients with aortic coarctation,¹⁰ with congenital heart disease,¹¹ in diabetes mellitus type I,¹² in patients after anthracycline chemotherapy¹³ and in obese children.¹⁴ Aortic wall elasticity may also be of importance in the follow-up of patients with fibrillinopathies such as Marfan and Williams syndromes^{15,16} and in individuals with bicuspid aortic valve,^{17,18} prone to develop aortic aneurysm.

It is necessary to measure physiologic age-related changes in arterial elastic properties in healthy individuals in order to provide a reference for early detection of abnormalities in patients at risk of developing vascular disease.

The objective of the present study was to establish age-related reference values and percentiles for distensibility and wall stiffness of the proximal aorta in normal healthy children

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Table 1. Subject Clinical Characteristics				
	n (%)	Mean±SD	Range	Median
Male	80 (48.5)			
Female	85 (51.5)			
Age (years)	165	11.9±4.0	2.0–18.0	12.8
Height (cm)	165	153±23	86–199	159
Weight (kg)	165	44.7±17.1	12.0–84.0	46.0
BSA _{Haycock} (m ²)	165	1.4±0.4	0.5–2.1	1.4
BMI	165	18.3±2.9	10.2–24.9	17.9
RR _{syst} (mmHg)	165	109±15	76–178	107
RR _{diast} (mmHg)	165	59±9	35–85	58
HR (beats/min)	165	78±16	49–132	75
RPP	165	8,359±1,978	4,928–16,896	8,196

BMI, body mass index; BSA, body surface area; HR, heart rate; RPP, rate-pressure product; RR, Riva-Rocci blood pressure.

and adolescents.

Methods

Subjects

Subjects were 165 healthy children and adolescents (male, n=80, 48.5%; female, n=85, 51.5%), who were considered to have normal systemic vascular beds. Mean age was 11.92±4.0 years (range, 1.992–17.891 years), with a median of 12.761 years. Weight, height, body surface area (BSA), body mass index (BMI) and systolic blood pressure (SBP) and diastolic blood pressure (DBP) were within the normal range; none of the normal subjects was overweight; BMI was defined as normal below 25. None of the children had structural abnormalities of the heart or the great vessels; there was no history of fibrillinopathy or vasculopathy; all children presented with a tricuspid aortic valve, the ascending aorta had normal dimensions, ejection fraction (EF), fractional shortening (FS) and ventricular dimensions were within the normal range; no medication was used for any of the individuals. The clinical characteristics are listed in Table 1.

Figure 2. Automatic recognition of the endovascular and aortic wall borders of the aorta throughout the heart cycle.

Study Protocol

The children underwent physical examination, blood pressure monitoring and 12-channel electrocardiogram (ECG). Length and weight were recorded for each subject. All subjects underwent complete transthoracic echocardiography with a General Electric Vingmed Vivid 7 Dimension echo machine with 5S and M4S MHz multi-frequency probes (General Electric, Horten, Norway). Two-dimensional guided M-mode measurements of the left ventricle were performed according to the recommendations of the American Society of Echocardiography¹⁹ to determine FS, EF and left ventricular end-diastolic and end-systolic di-

ameters.

Anatomy and function of the heart were assessed on 2-D echocardiography, color flow mapping, pulsed-wave and continuous-wave Doppler recordings. Morphology of the aortic arch was evaluated on 2-D echocardiography and color-flow Doppler. Systolic peak flow velocities in the descending aorta were determined on continuous-wave Doppler from a suprasternal or high right parasternal axis view. M-mode tracings of the ascending aortic wall motion were recorded simultaneously with an ECG recording 5 mm superior to the sinotubular junction (Figure 1).

Attention was paid to setting the cursor line exactly perpendicular to the long axis of the aorta in views showing the largest aortic diameters. Sharp endothelial lines were used as additional indicators for the cursor line to cut the central line of the aorta. All images were digitally stored as raw data using EchoPAC PC version BT 08 (General Electric).

Three experienced echocardiographers examined the children and did the image acquisition. The offline measurements were performed by 2 of them.

Throughout echocardiography, supine SBP and DBP were measured 3 times in the right arm using an automatic oscillometric device (Dinamap PRO 300; Critikon) according to the recommendations of the American Heart Association.²⁰ For further calculations, the mean of the 3 measurements was taken. The difference between SBP and DBP was taken as an estimation of the aortic pulse pressure. Accuracy and reproducibility of this method have been demonstrated previously.²¹

The study was approved by the ethics committee of the Technical University Munich. All parents and guardians gave written consent for the participation in the study and all data

Table 2. Distensibility and Wall Stiffness Index of the Ascending Aorta

	Mean $\pm$ SD	Range	Median
Distensibility (10^{-3} kPa^{-1})	97.1 $\pm$ 47.6	22.6–368.5	85.7
Distensibility/BSA (10^{-3} kPa^{-1})	84.5 $\pm$ 63.6	12.9–324.5	62.8
Stiffness index	1.18 $\pm$ 0.57	0.24–3.69	1.05
Stiffness index/BSA (m^2)	0.89 $\pm$ 0.37	0.18–2.22	0.84

Abbreviation as in Table 1.

were handled according to the 1975 Declaration of Helsinki.

Determination of Aortic Elastic Properties

The evaluation of the aortic elastic properties was performed using a new software application (Curefab, Munich, Germany). This technique allows for automatic detection of the maximum systolic and minimal diastolic aortic dimension from the stored M-mode trace.

The digitally stored Dicom images were loaded into the application. Numeric data (SBP, DBP, height and weight) were entered.

After loading the Dicom file the user has to set markers in the center of the aorta. When the evaluation process is started, the application moves parts of the picture in such a way that it straightens the waveform-like M-mode pattern of the aortic wall in order to achieve a straight edge of the aortic internal wall surface, eliminating all moving artifacts. This step is done for the anterior and posterior aortic wall separately (Figure 2). With a second line the aortic intima-media thickness was de-

Figure 3. Distensibility vs. age, height, weight, body mass index (BMI) and body surface area (BSA). Median, solid line; 2.5th and 97.5th percentiles, dashed lines.

Table 3. Reference Intervals for Distensibility and Stiffness Index in Healthy Children

Age (years)	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Distensibility (10 ⁻³ kPa ⁻¹)																	
2.5th	84.4	80.4	76.4	72.5	68.5	64.5	60.6	56.6	52.6	48.7	44.7	40.7	36.7	32.8	28.8	24.9	20.9
97.5th	241.6	234.1	226.5	219.1	211.5	203.9	196.4	188.9	181.4	173.9	166.3	158.8	151.2	143.7	136.2	128.6	121.1
Stiffness																	
2.5th	0.33	0.39	0.41	0.43	0.45	0.47	0.49	0.51	0.53	0.55	0.57	0.59	0.61	0.63	0.65	0.67	0.69
97.5th	1.04	1.15	1.25	1.36	1.46	1.56	1.67	1.78	1.88	1.98	2.09	2.19	2.30	2.40	2.51	2.61	2.71
Height (cm)	85	95	105	115	125	135	145	155	165	175	185	195					
Distensibility (10 ⁻³ kPa ⁻¹)																	
2.5th	86.3	80.3	74.2	68.1	61.9	55.9	49.8	43.7	37.6	31.5	25.4	19.3					
97.5th	239.7	228.4	216.9	205.6	194.3	182.9	171.6	160.2	148.8	137.5	126.1	114.8					
Stiffness																	
2.5th	0.39	0.42	0.45	0.48	0.51	0.54	0.57	0.60	0.63	0.66	0.68	0.71					
97.5th	1.00	1.16	1.31	1.47	1.63	1.78	1.94	2.09	2.25	2.40	2.56	2.71					
Weight (kg)	15	25	35	45	55	65	75	85									
Distensibility (10 ⁻³ kPa ⁻¹)																	
2.5th	74.1	64.6	55.0	45.5	35.9	26.5	16.9	7.4									
97.5th	213.3	194.4	175.4	156.4	137.4	118.5	99.5	80.5									
Stiffness																	
2.5th	0.42	0.48	0.54	0.60	0.66	0.73	0.79	0.85									
97.5th	1.25	1.53	1.82	2.11	2.40	2.69	2.97	3.26									
BMI	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	
Distensibility (10 ⁻³ kPa ⁻¹)																	
2.5th	80.7	76.9	73.2	69.4	65.6	61.9	58.1	54.3	50.6	46.8	43.0	39.3	35.5	31.8	27.9	24.2	
97.5th	272.8	259.7	246.7	233.7	220.7	207.6	194.6	181.6	168.6	155.5	142.5	129.5	116.5	103.4	90.4	77.4	
Stiffness																	
2.5th	0.30	0.34	0.37	0.40	0.43	0.46	0.49	0.52	0.55	0.58	0.62	0.65	0.68	0.71	0.74	0.77	
97.5th	0.71	0.89	1.06	1.23	1.41	1.58	1.75	1.92	2.10	2.27	2.45	2.61	2.79	2.97	3.13	3.31	
BSA (m ²)	0.5	0.75	1	1.25	1.5	1.75	2										
Distensibility (10 ⁻³ kPa ⁻¹)																	
2.5th	85.6	73.8	61.8	49.7	37.7	25.7	13.6										
97.5th	243.1	218.4	193.8	169.1	144.4	119.8	95.1										
Stiffness																	
2.5th	0.35	0.42	0.49	0.56	0.63	0.70	0.76										
97.5th	0.95	1.30	1.64	1.98	2.32	2.67	3.01										

Abbreviations as in Table 1.

terminated. The cross-section dimension was determined using the leading edge rule.²²

Offline processing and verification of the detected diameters of the aorta were done by 2 trained investigators. To allow comparison of the subsequently recorded data sets in every patient, the progression of the aortic diameter of the investigated heart cycles is demonstrated by the curves below the original M-mode (Figure 2). In cases of improper border detection, these data were excluded.

Three heart cycles per patient were taken at minimum for averaging and calculation of elastic parameters.

The time-diameter curves of all included heart cycles were averaged. By using the median, minimum and maximum aortic diameter, aortic elastic properties (cross-sectional distensibility, wall stiffness index) were computed with the blood pressure entered previously. The formulas for calculating distensibility and wall stiffness index are as follows:

$$\text{distensibility} = (A_s - A_d) / [A_d \cdot (P_s - P_d) \cdot 1333] \cdot 10^7 \text{ (10}^{-3} \text{ kPa}^{-1}\text{)},$$

and

$$\text{stiffness index} = [\ln(P_s/P_d)] / [(D_s - D_d)/D_d] \text{ (dimensionless)},$$

where A_s is systolic area, A_d is end-diastolic area, P_s is SBP, and P_d is DBP (both in mmHg). Area A was determined as $A = (D/2)^2 \times \pi$. All results were digitally stored for statistical evaluation.

Statistical Analysis

Categorical variables are presented as frequencies and percentages, and continuous variables as mean $\pm$ SD and median (range). The association of distensibility/stiffness index with patient characteristics was evaluated with the use of Pearson correlation coefficients. Differences in distensibility/stiffness index regarding gender were evaluated using independent sample t-test.

To obtain reference intervals for healthy children, the quantile regression was used to estimate the 2.5th and 97.5th percentiles of the distribution of distensibility and stiffness index as a function of age, height, weight, BMI and BSA.

Additionally, a model was calculated adjusted for the rate-pressure product (RPP), to evaluate the influence of RPP on the association between age and distensibility and stiffness index.

Inter- and intraobserver variability was assessed using

Bland-Altman plots and calculating 95% limits of agreement. In Bland-Altman analysis, the percentage difference (bias) between the 2 raters (or the 2 ratings of the same rater) was plotted against the mean of the 2 measurements. Percentage difference was defined as the difference of the 2 measurements, divided by the mean of the 2 measurements, multiplied by 100.

All statistical tests were 2-sided, with a significance level of 0.05 and have not been adjusted for multiple testing. All analyses were performed with R version 2.13.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical and hemodynamic subject characteristics are listed in [Table 1](#). Cross-sectional distensibility and wall stiffness index of the ascending aorta are listed in [Table 2](#). There was no statistically significant difference between men and woman with regard to distensibility (men, $91.4 \pm 42.4 \times 10^{-3} \text{ kPa}^{-1}$; women, $102.4 \pm 51.6 \times 10^{-3} \text{ kPa}^{-1}$) or wall stiffness index (men, 1.26 ± 0.64 ; women, 1.10 ± 0.48).

Distensibility

There was a significant association between distensibility and age ($r = -0.462$, $P < 0.001$). Distensibility decreased significantly with age ([Figure 3](#)). On average the median of distensibility decreased by $5.1 \times 10^{-3} \text{ kPa}^{-1}$ (95% confidence interval [CI]: 3.9 – $6.8 \times 10^{-3} \text{ kPa}^{-1}$) per year of age.

Statistically significant associations additionally could be found between distensibility and weight ($r = -0.501$), height ($r = -0.443$), BSA ($r = -0.495$) and BMI ($r = -0.469$) (all $P < 0.001$).

An increase in weight, height, BSA and BMI was associated with a decrease of distensibility of the ascending aorta ([Figure 3](#)). The 2.5th and 97.5th percentiles for distensibility for specific parameters are given in [Table 3](#).

Aortic Wall Stiffness Index

A significant correlation was found for stiffness index and age ($r = 0.399$, $P < 0.001$; [Figure 4](#)). An increase in age of 1 year was on average associated with an increase of median stiffness index of 0.049 (95% CI: 0.031 – 0.058). There were also a statistical significant correlation between stiffness index and weight ($r = 0.462$), height ($r = 0.389$), BSA ($r = 0.448$) and BMI ($r = 0.436$; all $P < 0.001$).

An increase in weight, height, BSA and BMI was associated with an increase of stiffness index of the ascending aorta. The 2.5th and 97.5th percentiles for stiffness index for specific parameters are given in [Table 3](#).

Because the age-related decrease of distensibility and increase of wall stiffness index may be influenced by RPP as an index of cardiac work, multiple regression analysis was done to adjust for RPP-induced effects. It was found that distensibility significantly decreased and wall stiffness index significantly increased with age, weight, height, BSA and BMI, despite adjustment for the corresponding RPP.

Inter- and Intraobserver Variability

There was a slight bias between the 2 raters. Bland-Altman analysis for the interobserver variability resulted in a mean percentage difference (bias) between the 2 raters of 14% and limits of agreement of -15% to 43% for distensibility as well as for the stiffness index.

The intraobserver differences were small. There was no systematic difference between the 2 ratings of the same rater for distensibility and stiffness index. On Bland-Altman analysis, the bias was 0%. The limits of agreement were -16% to 16%.

Discussion

In adult patients, impairment of the elastic properties of the aorta as a marker and risk factor for cardiovascular morbidity and mortality is gaining importance.²³⁻²⁵

The list of childhood factors and conditions found to be associated with arterial stiffening has expanded rapidly. Cardiovascular risk factors such as hypercholesterolemia and diabetes mellitus type I, prenatal growth retardation and prematurity, vasculopathy and fibrillinopathy associated with various syndromes, congenital heart disease and several systemic diseases should also be noted.⁷

Elastic properties of the aortic wall have been measured by means of transthoracic,²⁶ transoesophageal²⁷ and intravascular echocardiography.²⁸

In the present series we used transthoracic M-mode tracings of the ascending aorta, together with non-invasive oscillometric blood pressure measurement, to calculate wall stiffness index and distensibility. The advantage of this method is that it can be performed easily at any age, at low cost, using a standard echo machine and a routine echo modality. The complete offline calculation is reasonably quick and takes approximately 10 min.

Pediatric reference values for aortic stiffness and distensibility thus are necessary for adequate interpretation. Reference values describe a population sample expected to be representative with respect to the parameter evaluated; reference values may also provide limits for risk factors; the usually accepted upper limit is the 97.5th percentile in a given population.

The present data represent a normal population of children and adolescents, showing that elastic properties of the proximal aorta are age dependent with a significant decrease in older individuals. Vice versa, wall stiffness increases with increasing age.

An age-associated decrease in arterial distensibility in a pediatric population has also been reported by Avolio et al.²⁹ They showed that aortic pulse wave velocity, an index of arterial stiffness, increased linearly with age in individuals younger than 20 years of age.

Aging effects on elastic properties were also assumed by O'Rourke and Hashimoto, showing that mechanical stress causes fatigue and fracture of elastin lamellae of central arteries, causing them to stiffen.³⁰

Besides aging, elastic properties of the ascending aorta are negatively influenced by parameters such as weight, height, BSA and BMI, as was shown in studies of obese children.³¹

Compliance and elasticity of the major arteries play a key role in cardiac function, serving as a pressure reservoir by means of the elastic properties of the walls. Driving systemic blood flow via the storage of elastic tensile energy in the aorta, pulsatile flow is converted to steady blood flow. The ascending aorta functions as a surge-chamber immediately downstream from the left ventricle.²³ In the case of impairment of elastic properties of the aorta, ventricular afterload is increased. Concomitantly the left ventricle has to generate a higher end-systolic pressure at the expense of greater myocardial oxygen consumption. Additionally, alteration of the phasic coronary blood flow pattern with a reduction of diastolic coronary perfusion pressure leads to structural adaption^{32,33} of the left ventricle with myocardial hypertrophy, subendocardial ischemia

and interstitial fibrosis, which can impair myocardial relaxation and reduce ventricular compliance with a negative influence on diastolic function.^{34,35}

Stiffness of the ascending aorta is primarily determined by structural components of the arterial wall, vascular smooth muscle tone, and transmural distending pressure.³⁶ Increasing evidence suggests a role of the endothelium in the regulation of arterial stiffness through the release of vasoactive mediators that affect smooth muscle tone.¹⁰

Age-related reductions in arterial compliance are well known independently of confounding factors such as atherosclerosis and hypertension, leading to an increase in SBP in the aorta, a major risk factor for the development of heart failure and neurological complications.

During childhood the arterial structure has a progressive increase in intima-media thickness beginning at birth.³⁷ The growth of the tunica media of the ascending aorta is in part different from that of the aortic isthmus and descending aorta, given that the 3 parts are different in embryological origin. At birth the tunica media of these 3 parts of the aorta are similar in histological structure. During growth the tunica media of these parts grow differently. Only the ascending aorta has a marked increase of the thickness of its tunica media as well as the packing density of its elastic fibers, resulting in an increase in rigidity of the arterial wall.³⁸

Phenotypic changes of human smooth muscle cells occur, given that mature aortic smooth muscle cells contain high amounts of α -SM-actin, a major contractile protein, metavinculin, a cytoskeletal protein and 150-kDa caldesmon, which is involved in the regulation of smooth muscle cell contraction; a similar pattern of proteins is found in patients with atherosclerosis.³⁹

In addition to age-dependent chemical and biochemical mechanisms, the extreme mechanical demands made on tissue such as the aorta may promote the mechanical failure of elastic fibers. With age-related cyclical mechanical stress, fragmentation of the elastin fibers and transfer of stress to the much stiffer collagen fibers inevitably result in a progressive increase in vascular stiffness.⁴⁰

The fundamental role of elastin fiber components in maintaining arterial function is underlined by the severe clinical consequences of both fibrillin and tropoelastin mutations. Mutations in fibrillin-1, for example, cause Marfan syndrome, a heritable connective tissue disorder associated with ocular, skeletal, pulmonary and vascular defects. Increased aortic stiffness is well documented in patients with Marfan syndrome, as shown by the decreased distensibility and increased stiffness index.⁴¹⁻⁴⁴

Importantly, aortic stiffness has been shown to be an independent predictor of progressive aortic dilation and aortic dissection.⁴⁵ Beta-blockade therapy⁴⁶ and angiotensin-converting enzyme inhibition appear to reduce aortic stiffness, which may in turn slow aortic dilation and aortic root replacement.⁴⁷

In both children and adults, isolated bicuspid aortic valve may be associated with progressive dilation of the ascending aorta and increased aortic stiffness.⁴⁸

This may be due to a common developmental defect, which is hypothesized to be responsible for the coexistence of bicuspid aortic valve and aortic root enlargement.¹⁶

In several congenital heart defects abnormalities of the tunica media with elastic fiber fragmentation have been histologically identified.¹⁰ Cono-truncal malformations such as tetralogy of Fallot, common arterial trunk, complete transposition of the great arteries, double outlet ventricles, univentricular hearts and aortic coarctation should be noted.¹⁰ In tetralogy of

Fallot, elastic properties of the ascending aorta are reduced, with an increase in aortic stiffness, which is related to dilatation of the proximal aorta. In transposition of the great arteries patients show impaired distensibility of the neo-aorta,⁴⁸ and it is suggested that impaired elastogenesis may be an intrinsic component of this congenital anomaly. In patients with coarctation of the aorta elastic properties are primarily impaired and remain unchanged even years after successful operation;^{11,49} recent studies on adults with coarctation repair have shown that age and bicuspid aortic valve are the main risk factors for wall complications in the long-term follow up period.⁵⁰

Conclusions

The present study provides quantification of in vivo age-associated changes in arterial elastic properties in children and adolescents, and is potentially useful as a reference for patients with disease that involves the vascular system.

Age-related percentiles should help in the identification of abnormal elastic properties of the ascending aorta. Pathologic changes in distensibility and aortic wall stiffness index influence prognostic outcome in several groups of pediatric patients, and early detection may be of benefit in those at risk of impairment of elastic properties. Medical treatment, as recommended in patients with fibrillinopathy, and timing of surgical intervention in patients with aortic dilatation could be monitored more precisely.

Study Limitations

Given that attenuation of arterial elastic properties is an ongoing process, influenced by several age-dependent factors, the reference values for distensibility and aortic stiffness provided here could be utilized only for children and adolescents under the age of 20 years; for older individuals age-related references must be used.

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