Aortic Elastic Properties in Preschool Children Born Preterm

Irena Odri Komazec, Anna Posod, Martin Schwienbacher, Maria Resch, Ulrike Pupp Peglow, Stefan Kiechl, Daniela Baumgartner, Ursula Kiechl-Kohlendorfer

Objective—Preterm birth predisposes children to the development of cardiovascular diseases in adulthood. The aim of this study was to characterize elastic properties of the aorta at preschool age and test the hypothesis that prematurity is associated with decreased aortic distensibility and increased stiffness, both of which are predictors of increased cardiovascular risk.

Approach and Results—In an observational study of 76 five- to seven-year-old children born at a gestational age <32 weeks and 79 term-born controls, elastic parameters of the ascending and descending abdominal aorta were determined noninvasively by means of M mode echocardiographic tracings and calculated using computerized wall contour analysis. Compared with children born at term, the preterm group showed significantly reduced distensibility and increased stiffness of the descending abdominal aorta. These results remained significant under multivariable adjustment for birth weight z score, maternal smoking in pregnancy, maternal education, family history of cardiovascular disease, breastfeeding, childhood nutrition, and current body mass index z score (multivariable odds ratios and 95% confidence intervals 5.1, 1.7–15.9; \( P = 0.005 \) and 2.8, 1.0–7.9; \( P = 0.046 \), respectively). Further adjustment for intravenous lipid therapy attenuated the strength of association. Elastic properties of the ascending aorta did not differ between the 2 study groups.

Conclusions—Children born preterm are characterized by decreased elastic properties of the descending abdominal aorta potentially attributable to impaired viscoelastic properties of and lipid damage to the aorta. Clinical follow-up of preterm infants with a focus on aortic elastic properties may be useful for tailoring early prevention programs and counteracting cardiovascular risk in adulthood. (Arterioscler Thromb Vasc Biol. 2016;36:2268-2274. DOI: 10.1161/ATVBHA.116.308144.)

Key Words: aorta ■ cardiovascular disease ■ elasticity ■ follow-up studies ■ pediatrics

Previous studies have shown that preterm birth is associated with increased cardiovascular risk and mortality because of cardiovascular disorders in adult life.\(^1\)\(^-\)\(^3\) Over the last years, the number of preterm deliveries and the number of survivors have steadily increased, and adverse health impact is of relevance to the growing cohort of a preterm-borne population entering adulthood.\(^4\) Development of cardiovascular disease (CVD) in adulthood was initially attributed to the programming effect of low birth weight resulting from impaired fetal growth because of undernutrition or placental dysfunction.\(^5\) However, the mechanisms are still not clear and may also involve other factors, such as early impairment of arterial wall properties related to prematurity.\(^6\) Arterial stiffness may put individuals at risk for hypertension, left-ventricular hypertrophy, and CVD.\(^7\)\(^-\)\(^9\)

Most of the studies investigating vascular function in preterm-born children included adolescents or young adults in whom conventional risk factors for CVD might already be present and do not permit straightforward attribution of vascular abnormality to prematurity.\(^10\)\(^-\)\(^21\) Studies in young children would be best suitable, but are limited to 3 evaluations with small sample size.\(^22\)\(^-\)\(^24\)

Our study aims at investigating arterial wall properties in a comparatively large cohort of children at preschool age by means of a standardized, semiautomated, and noninvasive method.\(^25\)\(^-\)\(^27\)

Materials and Methods

Materials and Methods are available in the online-only Data Supplement.

Briefly, we investigated a group of children born preterm between January 2007 and July 2009 with a gestational age of <32 weeks (n=76), who were invited for a routine preschool visit at our preterm follow-up clinic, and a control group of children born at term who were mainly recruited through local kindergartens (n=79). Aortic elastic properties were calculated from transthoracic M mode echocardiographic tracings using a standardized ultrasound protocol and a software tool for computerized wall contour analysis (Figures 1 and 2).\(^25\)\(^,\)\(^26\) This method was validated and tested for its reproducibility in our cardiological ultrasound laboratory.

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Arterioscler Thromb Vasc Biol is available at http://atvb.ahajournals.org

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Results

Study Population
During the study period, 90 children born at term and 182 children born preterm were assessed for eligibility. Eighty-nine children born at term and 93 children born preterm were included in the study. Complete data regarding aortic properties were available in 79 children born at term and 76 children born preterm (for further details, see Figure 3 and detailed methods in the online-only Data Supplement).

The final group of children born at term did not differ significantly from the general Tyrolean birth cohort with regards to gestational age, birth weight, and sex distribution, but maternal educational status was significantly higher. In line, preterm-born children in our study did not differ significantly in gestational age, birth weight, and sex distribution from all preterm infants in the survey area. Maternal educational status again was higher in the study group.

Population Characteristics
Characteristics of all children included in the current study are given in Table 1. Children born preterm had significantly lower body mass indices and body mass index z scores at preschool age than did term controls (P<0.001). Interestingly, they also had a smaller percentage of favorable childhood nutrition profiles, and the mothers of children born preterm reported smoking during pregnancy more frequently. Preterm-born children had a significantly higher mean systolic (P<0.001) and diastolic blood pressure (P<0.05) than term controls. None of the children were taking medication that might influence aortic properties.

Aortic Distensibility and Stiffness Index
Preschool children born preterm had a significantly increased risk for low distensibility (bottom quintile group, cutoff 26 kPa<sup>-1</sup>·10<sup>-3</sup>) and increased stiffness (top quintile group, cutoff 3.6) of the descending abdominal aorta in comparison to children born at term (Table 2; Model 1: age- and sex-adjusted odds ratio (OR) and 95% confidence interval (CI) 5.5, 2.0–15.5; P=0.001 and 3.0, 1.2–7.5; P=0.024, respectively). These results remained significant in the multivariable model adjusted for birth weight z score, maternal smoking in pregnancy, maternal education, family history of CVD, breastfeeding and childhood nutrition, and current body mass index z score (Table 2; Model 2: OR and 95% CI 5.1, 1.7–15.9; P=0.005 and 2.8, 1.0–7.9; P=0.046, respectively) and on adding adjustment for body length, heart rate, and distending pressure (Table 2; Model 3).

Intravenous lipid therapy emerged as a significant predictor of low descending abdominal aortic distensibility and high stiffness in children born preterm (age- and sex-adjusted OR and 95% CI 3.8, 1.3–11.8; P=0.018 and 3.2, 1.0–10.0; P=0.051). Once added to the multivariate model, the associations between prematurity and descending abdominal aortic distensibility and stiffness decreased in strength (Table 2; Model 4).

There was no association between prematurity and distensibility and stiffness of the ascending aorta.

Gestational age on a continuous scale was also related to low distensibility and high stiffness of the descending abdominal aorta (multivariable OR and 95% CI for an increment of one week 0.88, 0.80–0.97; P=0.01 and 0.92, 0.84–1.01; P=0.082, respectively). Birth weight emerged as a significant predictor of low descending abdominal aortic distensibility and high stiffness as well (multivariable OR and 95% CI per 100 g increase in birth weight 0.93, 0.88–0.98; P=0.006 and

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**Nonstandard Abbreviations and Acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
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<tr>
<td>OR</td>
<td>odds ratio</td>
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**Figure 1.** M mode tracing of the descending aortic wall motions proximal to the branching of the coeliac trunk (level 2).
Of note, the associations between prematurity and low distensibility and high stiffness remained similar when children small for gestational age at birth (n=17) were excluded from the analysis (multivariable OR 5.6, 95% CI 1.7–19.0; \( P = 0.005 \) and multivariable OR 2.5, 95% CI 0.9–7.3; \( P = 0.009 \)).

**Discussion**

In this study of preschool children, prematurity was related to a decrease in elastic properties of the descending abdominal aorta. Early impairment of arterial wall properties may permanently alter cardiovascular physiology and, thus, be considered a risk factor for CVD in later life—where lifestyle risk factors such as active smoking and also large differences in physical activity do not exist. Previous comparable studies were smaller in size.\(^{22,23} \) The study by Cheung et al\(^ {22} \) reported an increased brachioradial pulse wave velocity among 8-year-old children born preterm, with intrauterine growth retardation, but interpretation is complicated by the fact that pulse wave velocity has not been validated for preschool children.\(^ {35} \) In the study by Morsing et al,\(^ {24} \) the highest aortic stiffness and the lowest distensibility was seen in adequately grown preterm-born children.\(^ {23} \) Tauzin et al\(^ {23} \) reported impaired arterial viscoelastic properties of the abdominal aorta of healthy preterm infants, which persisted until the seventh week of life. However, it remained unclear whether arterial stiffness improved after the critical neonatal period based on adaptive phenomena or not.\(^ {36} \)

Additional studies have demonstrated a decrease in aortic distensibility among infants small for gestational age.\(^ {37,38} \) Others reported on the relation between arterial stiffness and low birth weight in term-born children and adults, but findings were not entirely consistent.\(^ {39–41} \) Class et al\(^ {42} \) showed a clear relation between low birth weight and an increased risk of cardiovascular morbidity and mortality independent of gestational age in a large population-based sibling comparison study. In our study, descending abdominal aorta distensibility remained significantly lower in the group of children born preterm when small–for-gestational-age children were excluded from analysis, indicating that prematurity is related to impaired elastic properties independent of growth retardation. As a common readout of our and the previous studies, intrauterine growth retardation and low birth weight as well as prematurity may contribute to early aortic stiffening. Potentially underlying mechanisms may partly be shared and partly diverse.

First, permanent alterations of viscoelastic properties of the aortic wall may arise from a decrease in elastin synthesis and maturation and a parallel increase in collagen content. In healthy subjects, elastin’s share of the aortic dry weight is as high as 50% and 45% in the ascending and descending abdominal aorta, respectively.\(^ {5} \) In the context of intrauterine growth retardation and low birth weight, impaired elastogenesis was attributed to a variety of pathological events, including placental hypoxia, leading to fragmentation of the elastic

![Figure 2. A. Descending aorta diameter–time curve over 4 heart cycles. B. Averaged diameter–time curve of the descending aorta.](http://atvb.ahajournals.org/)

0.96, 0.92–1.00; \( P = 0.074 \), but this did not extend to birth weight z score, that is, deviation of birth weight from gestational age–specific normative values.

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lamellae, diminished insulin-like-growth factor-1 plasma levels, as well as maternal and placental malnutrition featured by aberrant micro-RNA expression profiles. All these mechanisms may also be of relevance to prematurity. On top of that, hyperoxic stress caused by transient neonatal high-oxygen exposure in rats (a model of preterm birth–related complications) was shown to accelerate elastin precursor degradation and unfavorably affect matrix composition. Finally, premature birth disrupts elastin synthesis, usually peaking in a narrow time window at the end of gestation. After birth, elastogenesis pursues but decreases rapidly when the transitional rise in blood pressure stabilizes. Although abdominal aortic compliance of preterm infants partially improves over several weeks, postnatal elastin synthesis cannot entirely compensate for in utero deficiency. It merits attention that in a sheep model, preadaptive elastin formation in utero and in the first postnatal days (until closure of the ductus arteriosus) was substantially higher for the abdominal (+66%) than for the thoracic aorta (+41%), and postnatal elastogenesis suspends within 3 weeks at the abdominal level (because of reduced blood flow), but not in the thoracic segment. Accordingly, the abdominal aorta may be more susceptible to preterm birth effects, consistent with the findings in our study.

Second, aortic lipid accumulation and toxicity because of intravenous lipid exposure in preterm infants entails aortic stiffness in early adulthood. Exogenous lipids supplied for more than a week results in a doubling of cholesterol levels, which downregulates elastin maturation (by inhibiting lysyl-oxidase activity required for cross-linking) and induces early vascular lipid damage in a critical developmental period of the still immature vessels. Of particular note, these effects are most prominent in the abdominal aorta prone to lipid accumulation, which is an appealing explanation for prematurity’s preferential effects on the abdominal aortic section in our study. Actually, exposure to exogenous lipids was related to descending abdominal aortic distensibility at preschool age, and adjustment for intralipid use attenuated the strength of association between prematurity and aortic distensibility in the multivariable analysis (OR 5.5–3.2) and stiffness (OR 3.0–2.0).

Third, arterial stiffness in preterm infants may also arise from early vascular ageing and telomere shortening because of extensive cell proliferation after preterm birth and oxidative stress in the critical newborn period (respiratory distress, infections, etc.). Benetos et al showed that for a given chronological age, subjects with shorter telomere length are at increased risk for higher pulse wave velocity values.

**Limitations**

Only 93 out of 182 preterm-born children assessed for eligibility were included in the current study. However, both the...
preterm and control groups were representative of all children born preterm and term in the survey area with regards to sex distribution, gestational age, and birth weight. Only maternal educational level was higher for children enrolled, reflecting the well-known fact that highly educated parents are more likely to participate in research projects.

Our study, although the largest in this age range, is not a large study in absolute terms. Limitations inherently linked to observational research like unmeasured confounding also apply to our study. To minimize recall error, we used the Mutter–Kind Pass records containing prospectively collected and validated (by obstetricians and pediatricians) information on pregnancy (eg, smoking) and childhood ≤6 years of age.

Calculations of aortic distensibility and stiffness have been made on the basis of brachial pulse pressure. This could produce non-negligible errors because of pulse pressure amplification. However, measuring aortic pulse pressure takes longer and is less convenient, especially, for children at preschool age, thus, causing more stress and potentially affecting the blood pressure. Moreover, we are referring to differences between groups and not to absolute values.

Unexpectedly, our study yielded a higher distensibility for the descending abdominal aorta compared with the ascending aorta.\(^53\) However, segment-specific distensibility and stiffness indices were logarithmically transformed. BMI indicates body mass index; CVD, cardiovascular disease; and SD, standard deviation.

\(*P<0.001, \text{term vs preterm group.}
\)
\(†P<0.05, \text{term vs preterm group (yes/no).}
\)
\(‡P<0.05, \text{term vs preterm group (neutral/favorable).}
\)

### Conclusion

In preschool children born preterm, elastic properties of the descending abdominal aorta are decreased, which may predispose to CVD in adulthood. Early identification of high-risk individuals is a prerequisite for tailored prevention programs.
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Disclosures
None.

References
Our findings support the hypothesis that prematurity impairs arterial wall properties and composition. Inadequate elastin synthesis because of preterm birth may cause a permanent increase in arterial stiffness. The current study shows that children born preterm have decreased elastic properties of the descending abdominal aorta at a preschool age.


Smith GD. Birth size and arterial compliance in young adults.


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Study Population

The study survey area was Tyrol, a state in Western Austria with 680,000 inhabitants and about 7000 live births per year. We investigated a group of children born preterm between January 2007 and July 2009 with a gestational age of <32 weeks, who were invited for a routine preschool visit at our preterm follow-up clinic, and a control group of children born at term from the same geographical region who were recruited through local kindergartens and to a minor extent (n=14) from the pediatric outpatient departments of Innsbruck Medical University Hospital (mainly children who had routine preoperative evaluation for common surgical procedures like adenotomy or tonsillotomy). None of cases and controls had congenital malformations or chromosomal abnormalities.

Prior to enrollment in the study, all children orally consented to participation, and written parental/legal guardians’ informed consent was obtained. This study was conducted at the Department of Pediatrics, Innsbruck Medical University Hospital, Austria, from May 2012 to March 2015. Approval by the local ethics committee was obtained in advance.

Perinatal Characteristics

Perinatal data (gestational age, birth weight, perinatal morbidity, maternal morbidity, etc.) for children born preterm were prospectively collected and derived from the routine preterm follow-up database at our institution and the Mutter-Kind Pass records, the official Austrian pregnancy and early childhood medical record book. In children born at term, basic perinatal data were also collected from the “Mutter-Kind Pass” records, and at the study visit. Birth weight z scores were calculated for every subject using the Fenton 2013 Growth Calculator for Preterm Infants (available from http://www.peditools.org/fenton2013) to account for gender- and gestational age-specific differences.1 Small for gestational age was defined as a birth weight lower than the 10th percentile for sex and gestational age. Information about smoking during pregnancy (classified as “yes” or “no”) and maternal educational status (classified as “less than 12 years” or “12 years and more”) was based on self-reporting by mothers. Infant feeding in the first month of life was categorized as “mainly breastfed”, if the proportion of human milk exceeded 50%.

Study visit

All examinations were performed either at Innsbruck Medical University Hospital or at the participating kindergartens between 8 a.m. and 10 a.m. Specifically trained professionals performed a routine clinical examination, current height was determined with a Harpenden stadiometer and current weight was measured with a calibrated medical precision scale. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. To account for gender- and age-specific differences, BMI z scores were calculated with a reference data set.2
Blood pressure was measured three times on the right upper arm after a five-minute resting period using an appropriate cuff size and an automated oscillometric device (Blood Pressure Monitor BP-8800C, Manufactured by Colin Corporation, Hayashi, Japan, or Sure Signs VM6, PHILIPS MEDICAL SYSTEMS, USA). Children’s eating habits at preschool age were assessed using a standardized food frequency questionnaire (“What do you eat?”, kindly provided by the Robert Koch Institute, Berlin, Germany). Childhood nutrition habits were categorized as unfavorable, neutral or favorable. Family history of cardiovascular disease (CVD) was assessed with a questionnaire that all parents were asked to fill out (available from https://www.bhf.org.uk/heart-health/risk-factors/family-history).

**Echocardiographic evaluation**

Study participants underwent a complete transthoracic echocardiographic examination, performed by experienced staff, according to the recommendations of the American Society of Echocardiography, using the ACUSON SC2000 ultrasound system (8V3 transducer, Siemens Medical Solutions, USA Inc.). In addition to the standard examination, M mode tracings of the ascending and descending aorta were obtained in the left supine position according to the published criteria by using 2-dimensional guidance at two different levels: level 1, proximal ascending aorta 10 to 20 mm distal to the sinotubular junction (parasternal long-axis view) and level 2, descending abdominal aorta just proximal to the branching of the celiac trunk (abdominal paramedian long-axis view) (Figure 1). Aortic distensibility and stiffness index calculation was not possible in 27 out of 182 subjects (10 born at term, 17 born preterm). In most of the cases (25/27) either echocardiography (16/27) or blood pressure measurement (9/27) could not be done for the following reasons not related to ultrasound quality (anxious children, not willing to remain quiet or parental lack of time). Only in two further cases, quality of ultrasound M-mode was insufficient. Temporal and spatial resolutions were approximately 10 ms and 0.07 mm. The spatial resolution seems adequate given an average aortic diameter change per hear cycle of 2.8 mm (interquartile range 2.3-3.4) and 1.9 (interquartile range 1.5-2.1) in the ascending and descending abdominal aorta.

**Calculation of the elastic properties of the aorta**

Using a software tool for computerized wall contour analysis aortic elastic properties were calculated from transthoracic M mode echocardiographic tracings established by our Pediatric Cardiology Study Group and described elsewhere. This method was validated and tested for its reproducibility and has already been shown to be useful in the early detection of aortic abnormalities in patients with Marfan syndrome. Briefly, aortic diameters at the two described levels were continuously measured. Time-diameter curves of at least three heart cycles were generated, averaged, and slightly smoothed to eliminate digitalization noise (Figures 2A and 2B). From these curves maximal systolic and minimal diastolic aortic diameters were measured and aortic elastic parameters such as cross-sectional distensibility and wall stiffness index were then automatically calculated using the well-known equations:

\[
\text{Distensibility} = \frac{(A_s - A_d)}{(A_d \times (P_s - P_d)) \times 1333} \times 10^7 \text{ (kPa}^{-1} \times 10^{-3})
\]
Stiffness index=$[\ln(Ps/Pd)]/[(Ds−Dd)/Dd]$ (dimensionless).\(^7,^8\)

In these equations, \(A_s\) is systolic, \(A_d\) is end-diastolic area, \(P_s\) is systolic and \(P_d\) is diastolic blood pressure (both in mm Hg). Area \(A\) was determined as \((D/2)^2\pi\). \(D_s\) is systolic (maximum) and \(D_d\) is end-diastolic (minimum) aortic diameter.

**Statistical Analysis**

All calculations were performed using the SPSS 22.0 software package (SPSS Inc., Chicago, Illinois, USA). Differences in characteristics at study visit between term and preterm study groups were determined by means of Pearson’s Chi-Square, Fisher’s exact, Mann-Whitney U or Student’s T test, depending on type and distribution of the variable analyzed. To account for non-normal distribution of the dependent variable distensibility and stiffness indices were logarithmically transformed. With regard to covariates and potential confounders, a step-wise approach was used. Model 1 was adjusted for age at examination and sex, Model 2 for all parameters of Model 1 plus birth weight \(z\) score, maternal smoking during pregnancy, maternal education, family history of CVD, breastfeeding and childhood nutrition, and current BMI \(z\) score and Model 3 also included body length, heart rate and distending pressure. Odds ratios (OR) and respective 95% confidence intervals (95% CI) were calculated for low distensibility (lowest quintile) and high stiffness (highest quintile). Sensitivity analyses used gestational age on a continuous scale, focused on birth weight, or excluded subjects small for gestational age. A previous study proposed that intravenous lipid therapy contributes to the association between prematurity and aortic distensibility\(^9\) by amplifying cholesterol synthesis and plasma levels within one week of therapy. To test this hypothesis multivariate analysis was additionally adjusted for intralipid use. All reported \(p\) values are two-sided.

**References**


Elastic Properties of Descending Abdominal Aorta

SGA & low birth weight
- Placental and maternal malnutrition, low IGF-1, hypoxia, hyperoxic stress, disrupted elastogenesis
- Excessive cell proliferation after birth, infections, etc.
- Lipid parenteral nutrition, cholesterol synthesis and hypercholesterolemia

Prematurity

Inadequate elastin synthesis and maturation
- Oxidative stress and telomere shortening
- Lipid toxicity and accumulation

Distensibility ↓
Stiffness index β↑

Aorta

Hypertension
Vascular ageing
Cardiac remodelling
Cardiovascular disease

Early screening
Prevention

Neonatal period
Preschool age
Adolescence
Adulthood