Cholesterol and Arterial Distensibility in the First Decade of Life
A Population-Based Study
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Background—Blood cholesterol levels are a key determinant of coronary heart disease risk in adults, but the importance of lipid levels in the general population during childhood is less clear. We related arterial distensibility, a marker of structural changes in atherosclerosis, to the lipid profile of a population-based sample of children aged 9 to 11 years.

Methods and Results—A noninvasive ultrasound technique was used to measure arterial distension during the cardiac cycle in the brachial arteries of 361 children from 4 towns in the United Kingdom. This measure was related to their pulse pressure to assess arterial distensibility. All the children had previously had a comprehensive assessment of cardiovascular risk including a full lipid profile, cotinine-assessed smoke exposure, serum glucose, and questionnaire data on socioeconomic and dietary factors. Mean total cholesterol in the population was 4.72 [SD 0.75] mmol/L. There was a significant, inverse relation between cholesterol and distension of the artery across this range (linear regression coefficient \(-11.8 \mu m \cdot mmol^{-1} \cdot L^{-1}, P=0.003\)). Similar relationships were demonstrated with LDL and apolipoprotein B \((-12.9 \mu m \cdot mmol^{-1} \cdot L^{-1}, P=0.005\) and \(-36.9 \mu m/mmol/L, P=0.01\)). HDL and triglyceride levels showed no consistent association with distensibility.

Conclusions—LDL cholesterol levels had an impact on arterial distensibility in the first decade of life. Furthermore, the functional differences in the arterial wall were demonstrated within the lipid range found in normal children, a finding that raises the possibility that cholesterol levels in the general population during childhood may already be relevant to the development of vascular disease. (Circulation. 2000;101:1533-1538.)

Key Words: cholesterol ■ physiology ■ atherosclerosis

Hypercholesterolemia is a key factor initiating early structural changes in atherosclerosis. There is a direct relationship between serum cholesterol level in adult life and the risk of cardiovascular morbidity and mortality. In animal experiments, the reduction of blood cholesterol levels leads to regression of atherosclerosis, and in humans, it has been shown to be beneficial for both primary and secondary prevention of heart disease. Cholesterol can therefore be considered an important modifiable risk factor that affects the natural history of atherosclerosis.

The relevance of cholesterol during childhood is more difficult to evaluate. Cholesterol levels in young men have been linked to eventual morbidity and mortality. However, the long period between these measurements in early life and the late clinical end points makes it difficult to establish causal relations, especially when studies are extended to include younger children. Autopsy investigations indicate pathological changes can be identified in large arteries as early as fetal life, and by the first decade, the majority of children are affected. Importantly, LDL cholesterol level appears to relate to the anatomic extent of atherosclerosis in these preclinical studies.

Noninvasive assessment of disturbed arterial physiology, relevant to the atherosclerotic process, represents a novel means of studying the evolution of arterial disease during these key early years. We have previously demonstrated that young subjects with familial hypercholesterolemia have vascular endothelial dysfunction. However, there was no relationship between cholesterol level and endothelial response in a population-based study of normal 9- to 11-year-old children. It therefore remains unclear what effect cholesterol, at levels found in the general population, has on the vessel wall early in life.

Arterial distensibility, a measure of vascular elastic behavior, is altered during early arterial cholesterol accumulation in
animal models, before other vessel wall changes, and in adults, loss of distensibility is related to risk factors for clinical vascular disease. In the present study, we investigated the pathophysiology behind changes in distensibility and examined the influence of childhood lipid profiles on this measure. We show for the first time a relationship between lipid levels and conduit artery function, within the range of cholesterol found in the normal United Kingdom childhood population, as early as the first decade of life.

Methods
The study was performed as part of a larger, mixed longitudinal investigation of cardiovascular risk factors in 10 British towns. Within each town, the study was based on a stratified random sample of 10 local authority primary schools; in each school, 50 children aged 9 to 11 years were invited for measurement (overall response rate 75%). The present study was performed in the last 4 towns, 2 with high adult cardiovascular mortality rates (Rochdale and Rhondda) and 2 with very low adult cardiovascular mortality rates (Bath and Tunbridge Wells). Thirty-three of 40 schools in the original study could provide suitable accommodation for the vascular studies and were included. In each school, the oldest 15 of the 37 pupils who had participated in the previous study were invited to take part.

Vascular Study Measurements
Brachial artery distension during the cardiac cycle was measured for each child at rest. The subject lay supine on a couch, and room temperature was recorded. After 10 minutes’ rest, the right brachial artery was imaged in longitudinal section at 10 to 15 cm above the antecubital fossa with a 7-MHz linear array transducer and Acuson 128XP/10. To measure arterial distension, the M-mode cursor was positioned at right angles to the arterial lumen over the clearest defined section of the artery on the B-mode image. A 5-second segment of the radiofrequency signal was recorded by a separate commercially available Wall Tracking System (Ingenious Medical Systems) at a rate of 800 Hz (1 frame/ms). The initial frame (amplitude waveform) is displayed, and the operator selects 2 sample volumes coinciding with the arterial wall-lumen interfaces. The relative position of the walls within these volumes is measured every 25 ms (~20% of the expected time for an upstroke) by use of a displacement detection algorithm based on the cross-correlation model for corresponding segments of the radiofrequency lines (Figure 2). Arterial distension is measured as the mean diameter change between diastole and systole over the 5-second period. Coefficients of variation for diameter and distension measurements with this technique are reported as 2% to 3%. Pulse pressure was measured in the left brachial artery with a Dinamap 1846SX oscillometric blood pressure recorder (Critikon Inc) at the same time that distensibility was measured in the right arm. This method has been shown to provide a representative measure of the pulse pressure in the right brachial artery during data collection.

Scan quality analysis was performed by independent observers as described previously. To assess within-subject reproducibility of the technique, the third subject each day was invited back in the afternoon for repeat measurements, with the ultrasonographer blinded to the earlier results. Height and weight were measured with a portable stadiometer (CMS Ltd) and digital weighing scale (Soehnle Ltd). Ethnic group was recorded as Caucasian, Asian, or other. A saliva sample was collected for cotinine analysis.

Cardiovascular Risk Factor Measurements
The risk factor profile of each subject had been established 8 months earlier. This included total cholesterol, LDL, HDL, ApoB, and plasma glucose measurements. Half of the subjects had a venipuncture while in the fasted state and the remainder 30 minutes after a standard glucose load (1.75 g/kg). Samples were separated and frozen for storage within 6 hours. Total serum cholesterol was measured with the Technicon Dax system, HDL cholesterol with the dextran-sulfate-magnesium precipitation method, and ApoB by the Beckman rate nephelometric method. LDL cholesterol was calculated from the Friedewald method. Fasting and nonfasting lipid levels were similar and were therefore combined for analysis. A self-completion questionnaire was forwarded to parents that provided information on head-of-household occupation for socioeconomic coding and data on diet, exercise, and medical and birth history of the child.

Study Determining the Contribution of Endothelium-Derived NO to Arterial Distensibility
To investigate the pathophysiology behind changes in arterial distensibility, we related measures of arterial distension in the cohort to data on endothelium-dependent flow-mediated dilatation collected for each subject. We then performed a new laboratory-based study in a smaller group of older subjects using an intra-arterial infusion of the specific NO synthesis inhibitor L-NMMA to determine the relationship between distensibility and endothelium-dependent NO release. In 6 healthy normocholesterolemic adults (mean age 34 years; range 30 to 40), radial artery distensibility during infusion of L-NMMA (4 μmol/min) was compared with normal saline and a nonspecific endothelium-independent constrictor, NE (240 pmol/min). The saline and drugs were infused at a constant rate (0.5 mL/min) via a 27-gauge needle introduced under local anesthetic into the proximal brachial artery. Measures of arterial distensibility were based on the mean of 3 separate measurements of arterial distension during an infusion in relation to the pulse pressure.

Statistical Analysis
Arterial distensibility is usually represented as the DC, calculated as the change in cross-sectional area between diastole and systole relative to the area at diastole, divided by the pulse pressure. DC was used to analyze data from the smaller groups involved in studying ultrasound measurement repeatability and investigating endothelium dependence of distensibility. Ultrasound repeatability is presented as the correlation of repeat measurements and as the mean of the differences with the SD. The effect of L-NMMA and NE on DC was compared by repeated-measures ANOVA.

For analysis of the complete cohort, relations between explanatory variables and arterial distensibility were assessed with a linear regression model, with absolute arterial distension as the dependent variable and pulse pressure as an independent variable. This method is justified, because distension is normally distributed, and over the blood pressure range in our cohort, distension was linearly related to pulse pressure (regression coefficient 0.91 μm/mm Hg, 95% CI 0.33 to 0.49, \( P = 0.002 \)). The main model examined the effect of each variable on absolute distension of the vessel wall, with pulse pressure, age, sex, and town included as independent variables. Additional models adjusted for body size and other risk factors. Linearity of associations was examined visually and by fitting quadratic and cubic terms in the model.

Results
Five hundred and fourteen children with blood sample data were invited to participate in the study; 390 took part, and 361 had both satisfactory ultrasound measurements and a complete lipid profile available (181 girls and 180 boys; 70% of children invited). Characteristics of the participants are listed in Table 1. Age, sex, or body build had no influence on whether a full set of data was obtained. Twenty-nine subjects had repeat vascular measurements (mean difference in the distensibility coefficient [DC] between the first and second reading 0.01 [SD 0.06] mm Hg⁻¹; correlation between measurements 0.84).
TABLE 1. Main Variables in 361 Study Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>11</td>
<td>0.36</td>
</tr>
<tr>
<td>Height, cm</td>
<td>146</td>
<td>7</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>39.8</td>
<td>9.4</td>
</tr>
<tr>
<td>Ponderal index, kg/m³ × 10⁶</td>
<td>12.7</td>
<td>2.2</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>114</td>
<td>12</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>67</td>
<td>7</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.72</td>
<td>0.75</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>2.86</td>
<td>0.66</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.40</td>
<td>0.28</td>
</tr>
<tr>
<td>ApoB cholesterol, mmol/L</td>
<td>0.90</td>
<td>0.21</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.02</td>
<td>0.47</td>
</tr>
<tr>
<td>Arterial distension, mm</td>
<td>0.13</td>
<td>0.06</td>
</tr>
<tr>
<td>Distensibility coefficient, 1/mm Hg</td>
<td>0.19</td>
<td>0.09</td>
</tr>
</tbody>
</table>

There was no significant difference in distensibility between children from the 4 towns in which this study was conducted, and there was no relation with room temperature or the time of day. Distensibility was similar in girls and boys and was not affected by age. Salivary cotinine concentration (to assess passive smoke exposure), social class, ethnicity, and preload and postload glucose showed no significant relationship with distensibility (data not presented). Height was related to distensibility, but relations with ponderal index and resting vessel size were not significant. Diastolic but not systolic blood pressure was related to distensibility. Regression coefficients are presented in Table 2.

**Blood Lipids and Arterial Distensibility**

Arterial distensibility declined with increasing cholesterol levels. With this cohort size, the precise nature of the relationship could not be determined. A linear model provided the closest fit and is therefore used in describing the relations; however, cubic, quadratic, and logarithmic models were also significant, and a threshold cholesterol level within the population range beyond which arterial distensibility was significantly affected could not be excluded (Figure 1A). Similar associations were found with LDL (Figure 1B) and apolipoprotein B (ApoB). Relations between HDL or triglycerides and distensibility were inconsistent and not statistically significant. The association was similar in girls and boys.

Cholesterol was independently correlated to height (r = −0.13, P = 0.01) and body size, assessed by ponderal index (r = 0.16, P = 0.002). However, the association between cholesterol and distensibility remained significant after these factors were included in the model (Table 3). Adjustment for diastolic and systolic blood pressures in the model did not significantly alter the relation between cholesterol and distensibility (regression coefficient after adjustment −9.41 μm · mmol⁻¹ · L⁻¹, P = 0.02).

**Study Determining the Contribution of Endothelium-Derived Nitric Oxide to Distensibility**

Neither absolute distension nor DC was correlated to endothelium-dependent flow-mediated dilatation in the children (correlation of DC on flow-mediated dilatation, r = −0.04, P = 0.52).

In the 6 adults studied, intra-arterial infusion of L-5-monomethyl-l-arginine (L-NMMA) had no significant effect on DC, which indicates that this measure is not importantly influenced by endothelium-derived nitric oxide (NO) (change in DC after infusion of L-NMMA, −0.01 mm Hg⁻¹; 95% CI −0.05 to 0.03, P = 0.53; after norepinephrine [NE] −0.01 mm Hg⁻¹, 95% CI −0.04 to 0.03, P = 0.49). There was no significant change in systemic blood pressure after local forearm infusion of L-NMMA and NE. Mean vessel size was 2.83 [SD 0.75] mm; both vessel size and levels of flow were similar after infusion of L-NMMA and NE.

**Discussion**

This study shows an association between arterial distensibility and cholesterol in a population of apparently healthy 9- to 11-year-olds. In children with higher serum cholesterol levels, the brachial artery was less distensible. The association

**TABLE 2. Relations Between Main Variables and Arterial Distension**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression Coefficient</th>
<th>95% CI</th>
<th>P</th>
<th>Standardized Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>−11.8</td>
<td>−19.7 to −4.00</td>
<td>0.003</td>
<td>−8.9</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>−12.9</td>
<td>−21.9 to −3.98</td>
<td>0.005</td>
<td>−8.5</td>
</tr>
<tr>
<td>ApoB cholesterol, mmol/L</td>
<td>−36.9</td>
<td>−66.0 to −7.75</td>
<td>0.01</td>
<td>−7.7</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>−17.0</td>
<td>−38.6 to 4.65</td>
<td>0.12</td>
<td>−4.8</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.81</td>
<td>−12.2 to 13.8</td>
<td>0.90</td>
<td>0.4</td>
</tr>
<tr>
<td>Height, cm</td>
<td>1.45</td>
<td>0.57 to 2.34</td>
<td>0.001</td>
<td>10</td>
</tr>
<tr>
<td>Ponderal index, kg/m³ × 10⁶</td>
<td>−1.20</td>
<td>−4.00 to 1.60</td>
<td>0.40</td>
<td>−2.6</td>
</tr>
<tr>
<td>Resting vessel size, mm</td>
<td>1.47</td>
<td>−20.1 to 23.1</td>
<td>0.89</td>
<td>0.5</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>−1.77</td>
<td>−2.57 to −0.96</td>
<td>&lt;0.001</td>
<td>−12</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>−0.04</td>
<td>−0.59 to 0.50</td>
<td>0.88</td>
<td>−0.5</td>
</tr>
</tbody>
</table>

The second column contains the linear regression coefficient (with 95% CIs and P values in columns 3 and 4) for the association between the variable and arterial distension (with pulse pressure, age, sex, and town included in the model). Units are micrometer per unit change in the explanatory variable. The standardized coefficient is the linear regression coefficient multiplied by the SD of the variable to allow comparison between strengths of association.
with arterial distensibility in our young population was found within the range of LDL and ApoB levels of the general population, which suggests that these lipid subfractions may be relevant to arterial disease from a point very early in life.

The data are consistent with accumulating experimental and clinical evidence that cholesterol is integral to the early pathophysiology of atherosclerosis. Elevated LDL levels result in accumulation of lipoproteins in the vessel wall, which when oxidized are rapidly taken up by macrophages to form foam cells. This process starts remarkably early in life. LDL accumulation has been shown in fetal aortas even before monocyte migration into the vessel wall, with the degree of vascular change depending on fetal and maternal lipid levels. The role of HDL early in disease is less clear. In adult population studies and in coronary disease cohorts, HDL levels have an inverse association with adverse events. In the present study, there was no relation between HDL and distensibility, and studies of HDL in children with high familial risk do not always show anticipated associations. The importance of HDL may therefore differ between stages of atherogenesis.

The precise characteristic of the vessel wall underlying changes in distensibility and its relation to disease pathogenesis require further study. Previous work in animals and humans indicates distensibility is related to the structural arrangement of the artery and that subjects with risk factors for clinical coronary disease have reduced distensibility resulting from changes in wall architecture. Animal studies show arterial elasticity is reduced even during early fatty streak formation, before other pathophysiological changes. Our results in the present study suggest that differences in distensibility found in young children are not likely to represent impaired endothelial NO synthesis, because distensibility was not significantly blocked by L-NMMA in healthy adults. We and others have demonstrated that endothelium-dependent flow-mediated dilatation is abnormal in young subjects with risk factors for vascular disease. However, it was not related to cholesterol level or arterial distensibility in this normal cohort. Distensibility

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** A, Inverse relation between arterial distensibility and total cholesterol across normal lipid range in population-based sample of 9- to 11-year-olds. B, Relation between arterial distensibility and LDL cholesterol. Mean and SD of arterial distension (adjusted for pulse pressure, age, sex, and town) for each fifth of the cholesterol distribution are plotted at mean lipid level for that division. + represents adjustment for height and ponderal index.

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Example of wall tracking output, showing movement of anterior and posterior walls and (below) change in arterial diameter (distension) during 4 cardiac cycles. If distension is related to pulse pressure, by use of a coefficient or in a regression model, the change in diameter for a unit change in pressure can be assessed. The “stiffer” the artery, the smaller this change will be.
greater vessel size. Biochemical variables including glucose

relation in our group was only partly explained by the

tween diastolic blood pressure and arterial distensibility in

tinuous and genetic influences.

Interestingly, we have also shown a graded relation be-

between diastolic blood pressure and arterial distensibility in

this group of normotensive children. A similar relation has

been reported in adults at various ages and over larger blood

pressure ranges, including hypertensive patients.35,36 How-

ever, the demonstration of an association between distensi-

bility and blood pressure in children in the general population

is new. This finding supports the idea of an intrinsic relation-

ship between blood pressure and distensibility and indicates

that the impact of blood pressure on the vessel wall may start

very early in life.

The mean cholesterol levels are high compared with those

in American children; however, they are similar to results in

the whole study population21 and findings in other British

children.37 This may reflect higher fat intake of British

children,38 which is paralleled by higher cholesterol levels in

adults.39 Our sampling procedure has been shown to produce

a socially representative population of children in whom the

prevalence of private education is low. Because neither blood

lipids nor distensibility was related to social class, socioeco-

nomic and educational differences are unlikely to have

influenced the findings. The cohort has a narrow age range,

and the effects of age on arterial distensibility are therefore

minimal; however, our observations in 9- to 11-year-olds

cannot provide information about the development of the

relation between risk and the arterial wall over time. In these

prepubertal children, the association of cholesterol to disten-

sibility did not differ between sexes. Risk factor levels also do

not normally vary between sexes at this age,40 which suggests

that the determinants of the variation in vascular disease risk

between sexes later in life are not yet operating. Height was

related to distensibility, but the reason is not immediately

apparent. Short adult stature is known to be an independent

risk factor for cardiovascular morbidity and mortality.41 The

relation in our group was only partly explained by the

association of increased height with lower cholesterol and

greater vessel size. Biochemical variables including glucose

and insulin did not appear to influence the association of
distensibility with cholesterol levels.

This study has established for the first time that changes in

the arterial wall relevant to the atherosclerotic process can be

identified in a population-based sample of children who have

a normal range of cholesterol levels. Our findings suggest that

the emergence of arterial disease at this early stage may not

be confined to high-risk groups, but that early arterial changes

are already present within the general population. We were

unable to establish the precise shape of the association

between LDL cholesterol and arterial distensibility and there-

fore cannot determine whether there is a linear relation or

threshold effect for cholesterol. This may have potentially

important management implications in terms of cholesterol-

level recommendations and reduction targets in a population.

Whether these vascular differences can be modified to pre-

vent the development of arterial disease is presently unknown

but will be of considerable interest. In adults, a reduction in

cholesterol of 1% reduces the risk of coronary heart disease

by 2% to 3%.4,5 The potential benefit, however, may be

greater if intervention is started earlier in the atherogenic

process. Additional longitudinal and interventional studies

using noninvasive vascular measures will be able to assess

disease development during these key years.

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