Decreased Arterial Elasticity Associated with Cardiovascular Disease Risk Factors in the Young

Bogalusa Heart Study

Ward A. Riley, David S. Freedman, Nancy A. Higgs, Ralph W. Barnes, Stephen A. Zinkgraf, and Gerald S. Berenson

Noninvasive ultrasonic examinations were performed in 1984 on a biracial sample of 109 10- to 17-year-old adolescents to determine whether elastic properties of the carotid arteries are associated with cardiovascular disease risk factors in the young. The subjects examined were in either the upper (high risk) or lower (low risk) race-, sex-, and age-specific tertile for both serum total cholesterol (TC) and systolic blood pressure (SBP) during a 1981–82 community survey. The pressure-strain elastic modulus (\( E_p \)), a measure of stiffness, for the carotid arteries was calculated by dividing the pulse pressure by the fractional diameter increase in the carotid artery during the cardiac cycle, as measured by ultrasonic techniques. Repeat studies on 20 randomly selected subjects demonstrated high reproducibility of the elasticity measurements (intraclass correlation coefficient = 0.84). The mean \( E_p \) in the high risk group was 5.1 kPa higher than in the low risk group, after controlling for race, sex, and age (one-sided p value = 0.03). Furthermore, a positive parental history of myocardial infarction was related to increased \( E_p \) levels (\( p < 0.05 \)), independently of race, sex, age, TC, and SBP. The results indicate that ultrasonic techniques can detect functional differences in the carotid arteries of children and adolescents that are associated with the risk of cardiovascular disease as adults. (Atherosclerosis 6:378–386, July/August 1986)

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A principal problem confronting the preventive medicine community for decades has been the identification of asymptomatic people likely to develop cardiovascular disease (CVD). In the absence of a safe and accurate noninvasive screening method for visualizing atherosclerotic lesions, a risk factor concept has evolved and been applied in several health promotion research programs.\(^1\)\(^-\)\(^4\) Since atherosclerosis begins in early life,\(^5\)\(^-\)\(^7\) many of these risk factors, such as serum total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), systolic blood pressure (SBP), and diastolic blood pressure (DBP), are currently being measured in epidemiologic surveys of children.\(^8\)\(^-\)\(^11\) Despite the fact that risk factor tracking occurs in adolescents and in children over 6 years,\(^12\) 8 years,\(^13\) and 9 years,\(^14\) a substantial proportion of children with initially elevated CVD risk factors show reduced levels at follow-up. Thus, the problem of identifying people in early life at high risk for adult CVD still persists.

Noninvasive techniques for the assessment of atherosclerosis have improved in recent years, with ultrasound demonstrating the potential for safe, reliable, and cost-
effective screening.\textsuperscript{15} Although reliable ultrasonic examination of the coronary arteries has not been achieved, examination of peripheral arteries such as the carotids and femorals is widely practiced in clinical environments.\textsuperscript{16,17} In addition, ultrasonic measurements have revealed functional changes accompanying early diet-induced atherosclerosis in male cynomolgus monkeys (\textit{M. fascicularis}) that were not detectable by conventional, clinical imaging methods.\textsuperscript{18} Standard procedures for examining the carotid arteries of children and young adults have now been developed.\textsuperscript{19}

In this study, ultrasound was used to study the elastic behavior of the carotid arteries in a biracial group of school children. The objective was to determine if ultrasonically measured, functional differences in the carotid arteries in this young population are associated with CVD risk factors and parental clinical disease.

\textbf{Methods}

\textbf{Sample Selection}

The Bogalusa Heart Study is an epidemiologic study of CVD risk factors from birth to 26 years of age in a biracial (64\% white, 36\% black) population.\textsuperscript{8} The risk factors studied include serum lipids and lipoproteins, blood pressure, and anthropometric, nutritional, and behavioral data. Between 1972 and 1983, four comprehensive surveys of 5- to 17-year-old children and adolescents were conducted in Bogalusa, Louisiana, each with a high level (over 80\%) of participation.\textsuperscript{20} In all, over 8000 different school children have been examined.

Children with 1981-82 levels of both SBP and TC in either the upper (high risk) or lower (low risk) race-, sex-, and age-specific tertiles were eligible for the current study, which was conducted in 1984. To reduce the effects of regression to the mean,\textsuperscript{21} high risk children were required to have 1978-79 SBP and TC levels above their respective medians; similarly, low risk children were required to have 1978-79 SBP and TC levels below their medians. The age range was restricted to subjects between the ages of 10 and 17 years in 1984.

A total of 227 children met these criteria. Because the ultrasonic equipment was available for only 2 months (June and July) in 1984 and we wanted to examine no more than four children per day, only 48\% (109) of these children were seen. Nonexamined children either refused or could not be scheduled within this 2-month period. Nevertheless, the anthropometric and risk factor levels of participating children were representative of all eligible children (Table 1).

\textbf{Study Protocol}

\textbf{Parental Histories}

Prior to the 1981-82 survey, histories of myocardial infarction (MI), diabetes mellitus (DM), and hypertension were obtained through questionnaires for each parent. (This information was not validated by medical records.) Paternal and maternal history categories were combined to increase the number of children with positive parental histories of MI and DM. Of the 99 subjects with ultrasonic data, 10 had a positive parental history for MI; 14, for DM; and 45, for hypertension; no parental strokes were reported. The associations between parental histories and CVD risk factors have been reported previously.\textsuperscript{22}

\begin{table}[h]
\begin{center}
\begin{tabular}{|c|c|c|c|c|c|c|c|c|c|}
\hline
\textbf{Characteristics} & \textbf{White males} & & \textbf{White females} & & \textbf{Black males} & & \textbf{Black females} & \\
\hline
& \textbf{Low risk} & \textbf{High risk} & \textbf{Low risk} & \textbf{High risk} & \textbf{Low risk} & \textbf{High risk} & \textbf{Low risk} & \textbf{High risk} \\
\hline
\textbf{Age (yrs)*} & 13.1 (n = 14) & 13.6 (n = 16) & 13.5 (n = 12) & 13.2 (n = 23) & 13.3 (n = 11) & 12.0 (n = 8) & 13.5 (n = 4) & 12.7 (n = 10) \\
\hline
\textbf{TC (mg/dl)*} & 124.0 (n = 16) & 199.4 (n = 18) & 130.0 (n = 22) & 192.3 (n = 23) & 140.8 (n = 10) & 190.0 (n = 9) & 127.8 (n = 4) & 188.1 (n = 10) \\
\hline
\textbf{SBP (mm Hg)*} & 101.7 (n = 16) & 109.3 (n = 18) & 99.2 (n = 22) & 111.7 (n = 23) & 100.9 (n = 10) & 109.4 (n = 9) & 96.3 (n = 4) & 113.8 (n = 10) \\
\hline
\textbf{Triceps skinfold (mm)*} & 11.3 (n = 16) & 14.7 (n = 18) & 13.3 (n = 22) & 19.9 (n = 23) & 10.5 (n = 10) & 13.2 (n = 9) & 11.2 (n = 4) & 21.9 (n = 10) \\
\hline
\textbf{Pulse (per min)*} & 77.9 (n = 16) & 81.6 (n = 18) & 82.4 (n = 22) & 84.9 (n = 23) & 69.8 (n = 10) & 75.5 (n = 9) & 84.5 (n = 4) & 83.6 (n = 10) \\
\hline
\textbf{Parental myocardial infarction (%)} & 0 (4/16) & 25 (4/23) & 0 (1/12) & 17 (6/23) & 0 (1/11) & 0 (1/1) & 25 (1/4) & 10 (1/10) \\
\hline
\textbf{Parental diabetes mellitus (%)} & 7 (1/14) & 13 (2/16) & 8 (1/12) & 26 (6/23) & 9 (1/11) & 0 (1/1) & 25 (1/4) & 20 (2/10) \\
\hline
\hline
\end{tabular}
\end{center}
\caption{Mean Levels of Selected Characteristics by Race, Sex, and Risk Group}
\end{table}

*Current levels. All other values are from the 1981-82 survey.

Numbers in parentheses indicate the number of individuals affected from the total sample. TC = serum total cholesterol; SBP = systolic blood pressure.
Risk Factor Data

Procedures for obtaining anthropometric and blood pressure measurements have previously been reported in detail. After identification, height was measured to the nearest 0.1 cm; weight, to the nearest 0.1 kg, and triceps skinfold thickness, to the nearest 1.0 mm. Blood pressures were obtained as right arm, sitting, relaxed levels. (The average of six measurements taken with a mercury sphygmomanometer is used in all analyses.) Replicate blood pressure measurements were obtained on a 10% sample of children at the end of each examination day to assess intra-examiner reproducibility.

Because venipuncture was not performed, fasting serum lipid and lipoprotein levels measured in the 1981-82 survey were used in all analyses. The methods and population distributions of these variables have been reported previously. The Core Lipid Laboratory has been standardized by the Centers for Disease Control and is monitored by a surveillance program. An additional blind duplicate blood sample was obtained at venipuncture on a randomly selected 10% sample to assess the reproducibility of the laboratory analyses.

Ultrasonic Determination of the Elastic Modulus

After collection of anthropometric and blood pressure data, ultrasonic measurements were obtained by a trained technician without knowledge of the subjects’ risk factor levels. Subjects were examined in the supine position with a 5 MHz prototype ultrasound system according to a detailed protocol. As previously described, a thin-walled polyethylene bag partially filled with warm tap water was suspended over the neck. The water in the bag exerted a light uniform pressure (about 4 mm Hg) over this region, comparable to ordinary fluctuations in atmospheric pressure. The ultrasonic transducer was then suspended in the water bag above the artery to be examined. Therefore, indirect pressure on the artery from the transducer, which has been suggested as a possible source of error, was eliminated. The length of examination was limited to 30 minutes.

The orientation and position of the transducer were carefully adjusted to obtain a longitudinal image of the common carotid artery, approximately 5 cm below the bifurcation, with both systolic and diastolic lumen diameters (D_s and D_d respectively) measured in this region. Care was taken to eliminate echoes from the water bag/skin interface by directing the ultrasound toward this surface at oblique incidence. The radiofrequency signals from a line near the center of the image were electronically tracked to provide an accurate estimate of the lumen diameter of the artery as a function of time during the cardiac cycle. Over 100 image frames, each consisting of 42 lines of information, were obtained each second. An important feature of this system is that any line of the image can be selected for data analysis, and the linearly amplified radiofrequency signals used to construct the image line can be readily accessed.

Systolic and diastolic blood pressures (P_s and P_d, respectively) were measured at the brachial artery using an automated device (Dinamap); these values were assumed to closely approximate pressures in the carotid arteries. The mean pressure-strain elastic modulus (E_p) for each artery was then computed by dividing the pulse pressure by the percentage of increase in the lumen diameter during the cardiac cycle:

\[ E_p = \frac{(P_s - P_d)}{[(D_s - D_d)/D_d]} \]  

As E_p increases, the stiffness of the artery increases. A high value of E_p indicates that for a given pulse pressure, the proportional change in lumen diameter would be relatively small. The E_p measurements are given in kilopascals (kPa) (1 kPa = 7.6 mm Hg), and the values of the left and right carotid arteries were averaged together. This average E_p value was highly correlated with the E_p values of both left (r = 0.88) and right (r = 0.92) carotid arteries. Repeat studies were performed on 20 randomly selected subjects, 1 to 3 weeks after their original examinations, to assess the reproducibility of the technique (Figure 1).

It was not possible to obtain E_p measurements in both carotid arteries for 10 children (seven in the high risk group and three in the low risk group), and these children were excluded from most analyses. These persons (three white boys, two white girls, two black boys, and three black girls) tended to be obese, having mean triceps skinfolds of 17.9 mm and 23.4 mm (low and high risk groups, respectively). The corresponding mean triceps skinfold measurements of children with E_p measurements were 11.7 mm for the low risk group and 17.8 for the high risk group. In addition, positive histories of MI or hypertension were reported by seven parents of these excluded children.

Statistical Methods

The reproducibility of E_p measurements was assessed using one-way analysis of variance (ANOVA) to generate the within- and between-person mean squares. The square root of within-person variability is the standard deviation of measurement error, an estimate we have extensively used in previous analyses. Two mean square estimates were then used to calculate the intraclass correlation coefficient. The reproducibility of the E_p measurements and selected characteristics measured during the 1981-82 risk factor examination were compared. The representativeness of the examined sample was assessed by comparing mean 1981-82 levels of risk factors between examined and nonexamined, but eligible, children.

Mean race- and sex-specific E_p levels were calculated and bivariate associations with the risk factor data were examined. Since E_p was associated with race, sex, and age, the comparisons of E_p levels between high and low risk children used multiple linear regression to adjust for these covariates. Because the interaction term between risk group and race was marginally significant (p = 0.11), stratified analyses (by race) were performed. Associations of parental MI, DM, and hypertension with E_p levels were assessed by using t tests and regression analyses.

The relationship between parental histories and E_p were also examined by calculating the proportion of children with positive parental histories according to E_p tertile. Since dose-response relationships were hypothesized, gradients in these proportions were assessed by using
Bartholomew’s test.29 (This statistic is more powerful than a chi-square test because it is directed against a prespecified ordering in the magnitudes of the proportions.) Multiple logistic regression was also used to assess the relationship of parental histories to $E_p$, independent of race, sex, age, TC, and SBP.30 Since it was hypothesized that high risk children would have stiffer arteries than low risk children, one-sided tests of statistical significance were used in examining associations between the risk group and $E_p$. However, all other tests of statistical significance were two-sided.

Results

Overall, 48% (109/227) of the eligible children participated in the current study; 40% (44/109) of the low risk group and 55% (65/118) of the high risk group. Table 1 gives the selected characteristics of examined and nonexamined children. No statistically significant differences were observed between the two groups for any of the measured characteristics.

The mean $E_p$ in the 99 examined subjects was 62.0 kPa ($s_d = 13.5$) with values ranging between 39.7 and 114.6 kPa. Comparisons of initial and repeat $E_p$ values (Figure 1)

Table 2. Mean Levels of Selected Characteristics by Race, Sex, and Risk Group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>White males</th>
<th></th>
<th>White females</th>
<th></th>
<th>Black males</th>
<th></th>
<th>Black females</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>High risk</td>
</tr>
<tr>
<td>Age (yrs)*</td>
<td>13.1 (n = 14)</td>
<td>13.6 (n = 16)</td>
<td>13.5 (n = 12)</td>
<td>13.2 (n = 23)</td>
<td>13.3 (n = 11)</td>
<td>12.0 (n = 9)</td>
<td>13.5 (n = 4)</td>
<td>12.7 (n = 10)</td>
</tr>
<tr>
<td>TC (mg/dl)*</td>
<td>124.0 (n = 14)</td>
<td>199.4 (n = 16)</td>
<td>130.0 (n = 12)</td>
<td>192.3 (n = 23)</td>
<td>140.8 (n = 11)</td>
<td>190.0 (n = 9)</td>
<td>127.8 (n = 4)</td>
<td>188.1 (n = 10)</td>
</tr>
<tr>
<td>SBP (mm Hg)*</td>
<td>101.7 (n = 14)</td>
<td>109.3 (n = 16)</td>
<td>99.2 (n = 12)</td>
<td>111.7 (n = 23)</td>
<td>100.9 (n = 11)</td>
<td>109.4 (n = 9)</td>
<td>96.3 (n = 4)</td>
<td>113.8 (n = 10)</td>
</tr>
<tr>
<td>Triceps skinfold (mm)*</td>
<td>11.3 (n = 14)</td>
<td>14.7 (n = 16)</td>
<td>13.3 (n = 12)</td>
<td>19.9 (n = 23)</td>
<td>10.5 (n = 11)</td>
<td>13.2 (n = 9)</td>
<td>11.2 (n = 4)</td>
<td>21.9 (n = 10)</td>
</tr>
<tr>
<td>Pulse (per min)*</td>
<td>77.9 (n = 14)</td>
<td>81.6 (n = 16)</td>
<td>82.4 (n = 12)</td>
<td>84.9 (n = 23)</td>
<td>69.8 (n = 11)</td>
<td>75.5 (n = 9)</td>
<td>84.5 (n = 4)</td>
<td>83.6 (n = 10)</td>
</tr>
<tr>
<td>Parental myocardial</td>
<td>0 (n = 14)</td>
<td>25 (n = 16)</td>
<td>0 (n = 12)</td>
<td>17 (n = 23)</td>
<td>0 (n = 11)</td>
<td>0 (n = 9)</td>
<td>25 (n = 4)</td>
<td>10 (n = 10)</td>
</tr>
<tr>
<td>Parental diabetes</td>
<td>7 (n = 14)</td>
<td>13 (n = 16)</td>
<td>8 (n = 12)</td>
<td>26 (n = 23)</td>
<td>9 (n = 11)</td>
<td>0 (n = 9)</td>
<td>25 (n = 4)</td>
<td>20 (n = 10)</td>
</tr>
<tr>
<td>mellitus (%)</td>
<td>(1/14)</td>
<td>(2/16)</td>
<td>(1/12)</td>
<td>(6/23)</td>
<td>(1/11)</td>
<td>(1/9)</td>
<td>(1/4)</td>
<td>(2/10)</td>
</tr>
<tr>
<td>Parental hypertension (%)</td>
<td>36 (n = 14)</td>
<td>38 (n = 16)</td>
<td>25 (n = 12)</td>
<td>70 (n = 23)</td>
<td>55 (n = 11)</td>
<td>44 (n = 9)</td>
<td>50 (n = 4)</td>
<td>30 (n = 10)</td>
</tr>
</tbody>
</table>

*Current levels. All other values are from the 1981–82 survey.
Numbers in parentheses indicate the number of individuals affected from the total sample. TC = serum total cholesterol; SBP = systolic blood pressure.
showed that $E_p$ measurements were reproducible, with an intraclass correlation coefficient of 0.84. However, upon reexamination, the $E_p$ levels generally were slightly lower (mean difference $= 3.3$ kPa) than the initial measurements. The standard deviation of measurement error (within-person standard deviation) was 5.2 kPa, and the ratio of the between-person-to-within-person standard deviation was 3.4.

Mean race-, sex-, and risk-specific levels of selected characteristics for the 99 children having both left and right $E_p$ measurements are shown in Table 2. Since TC and SBP levels were used in selecting the sample, large differences in the mean levels of these variables between risk groups were observed, as expected. Overall, the high risk children had elevated 1981–82 mean levels of TC ($+$62.6 mg/dl), 1984 SBP ($+$10.8 mm Hg), and 1984 triceps skinfold ($+$6.1 mm). Although triceps skinfold differences between low and high risk females were slightly larger than in males, no race or sex differences in TC or SBP levels were ever, no risk factor was related to $E_p$.

Since $E_p$ was associated with age ($r = 0.22$, $p = 0.03$) and since low risk children tended to be slightly older than high risk children, $E_p$ values were age-adjusted within each race-sex group by using analysis of covariance. (Since $E_p$ was only weakly associated with triceps skinfold ($r = 0.06$) and pulse ($r = 0.09$), further adjustment for these variables did not alter the results.) Table 3 shows both unadjusted and adjusted $E_p$ levels for each risk group. With the exception of black females, high risk children had larger percentage of high risk children had positive parental histories than did low risk children.

Multiple linear regression was then used to assess the overall $E_p$ difference between risk groups after controlling for age, sex, and age. The linear regression model statistically accounted for 14% of the variation in $E_p$; estimated differences in $E_p$ attributable to risk group, race, sex, and age are shown in Table 4. The $E_p$ levels in high risk children were 5.1 kPa greater than in low risk children ($p = 0.03$, one-sided). Mean $E_p$ levels in blacks and males were also approximately 5 kPa greater than in whites and females, respectively. In addition, $E_p$ increased by almost 2 kPa per year. Although the race by risk group interaction was not statistically significant ($p = 0.11$), an additional model allowing for different relationships of $E_p$ to risk group in each race was constructed. In this model, only high risk white children had elevated (8.1 kPa) levels of $E_p$.

For whites and blacks separately, the relationship of $E_p$ to individual risk factors were then examined, with age and sex controlled by linear regression (data not shown). TC, LDL-C, SBP, and DBP (but not HDL-C) were all significantly ($p < 0.01$) associated with $E_p$ in whites. In blacks, however, no risk factor was related to $E_p$.

Table 5 compares mean $E_p$ levels in children according to parental histories of MI, DM, and hypertension. A positive parental history of MI or DM was associated with elevated $E_p$ levels, and differences persisted after controlling for individual risk factors. $E_p$ values, following adjustment, were observed in children.

<table>
<thead>
<tr>
<th>Variable</th>
<th>$\beta$: change in $E_p$ (kPa)</th>
<th>$p$ value (two-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk: high – low</td>
<td>5.1</td>
<td>0.06</td>
</tr>
<tr>
<td>Race: black – white</td>
<td>5.2</td>
<td>0.06</td>
</tr>
<tr>
<td>Sex: male – female</td>
<td>4.8</td>
<td>0.07</td>
</tr>
<tr>
<td>Age</td>
<td>1.9</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Differences were estimated by multiple linear regression. Age differences were per year. $E_p = \text{pressure-strain elastic modulus.}$
whose parent had DM compared to other children ($p = 0.04$). (Virtually identical results were obtained in all analyses if adjustments were made for diastolic, rather than systolic, blood pressure level.) In spite of the small sample sizes resulting in nonsignificant tests of significance, increased levels of $E_p$ levels tended to be associated with parental MI and DM in both races. The results of logistic regression analyses, examining the relationships of $E_p$ to parental MI and DM, confirmed these analyses; associations existed independently of race, sex, age, TC, and blood pressure.

The proportions of children with positive parental histories were then contrasted between race-, sex-, and age-adjusted $E_p$ tertiles as shown in Figure 2. Dose-response gradients were present between elevated $E_p$ levels and parental histories; the association between $E_p$ and parental MI was statistically significant ($p = 0.01$), and the prevalence of parental DM tended to increase as $E_p$ increased ($p < 0.10$).

### Table 5. Mean $E_p$ Levels (kPa) According to Parental Histories

<table>
<thead>
<tr>
<th>Parents</th>
<th>Myocardial infarction</th>
<th>Diabetes mellitus</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 89)</td>
<td>Yes (n = 10)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>61.1†</td>
<td>70.3†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(13.3)*</td>
<td>(12.9)*</td>
<td></td>
</tr>
<tr>
<td>Adjusted for race, sex, age, TC, and SBP</td>
<td>60.9†</td>
<td>63.4†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(14.3)*</td>
<td>(12.6)*</td>
<td></td>
</tr>
<tr>
<td>Whites</td>
<td>59.7</td>
<td>65.7</td>
<td>60.5</td>
</tr>
<tr>
<td>(n = 57)</td>
<td>(n = 8)</td>
<td>(n = 10)</td>
<td>(n = 36)</td>
</tr>
<tr>
<td>Blacks</td>
<td>64.9</td>
<td>68.4</td>
<td>63.3</td>
</tr>
<tr>
<td>(n = 32)</td>
<td>(n = 2)</td>
<td>(n = 4)</td>
<td>(n = 19)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses are standard deviations.
† $p < 0.05$.
* Adjustments were made by using analysis of covariance. TC = total cholesterol; SBP = systolic blood pressure; $E_p$ = pressure-strain elastic modulus.

### Discussion

The elastic characteristics of the common carotid arteries are determined by both passive (elastin and collagen) and active factors. The absolute amounts of elastin and collagen, as well as their ratio, are important determinants of wall stiffness, and experimental studies in hypertensive animals have shown increased extracellular matrix materials. Differences in these passive components could account for a portion of the interindividual variation in stiffness. In addition, neural, hormonal, and physical stimuli can activate smooth muscle cells, leading to a reduction in lumen diameter. Care was taken during examination to avoid undue physical stretching of the artery and to maintain a uniform temperature surrounding the artery. However, neural and hormonal factors could, in part, also contribute to the observed variability in $E_p$.

Nevertheless, as shown in Figure 1, $E_p$ measurements were reproducible, with the initial measurements agreeing closely with the results obtained 1 to 3 weeks later. Table 6...
Table 6. Inter- and Intraindividual Variability for Ep and Other Selected Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of pairs</th>
<th>Mean*</th>
<th>Inter-</th>
<th>Intra-</th>
<th>Ratio (Inter-/ Intra-)</th>
<th>Intraclass correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mg/dl)</td>
<td>377</td>
<td>161.1</td>
<td>38.8</td>
<td>4.7</td>
<td>8.3</td>
<td>0.97</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>375</td>
<td>94.3</td>
<td>36.9</td>
<td>5.5</td>
<td>6.7</td>
<td>0.96</td>
</tr>
<tr>
<td>Testosterone (pg/ml)</td>
<td>73</td>
<td>3.2</td>
<td>3.7</td>
<td>0.8</td>
<td>4.6</td>
<td>0.92</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>376</td>
<td>58.6</td>
<td>26.7</td>
<td>6.4</td>
<td>4.2</td>
<td>0.89</td>
</tr>
<tr>
<td>SBP (mm Hg)†</td>
<td>321</td>
<td>102.0</td>
<td>14.9</td>
<td>3.6</td>
<td>4.1</td>
<td>0.89</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>377</td>
<td>79.7</td>
<td>9.9</td>
<td>2.7</td>
<td>3.7</td>
<td>0.86</td>
</tr>
<tr>
<td>Ep (kPa)†</td>
<td>20</td>
<td>61.0</td>
<td>17.7</td>
<td>5.2</td>
<td>3.4</td>
<td>0.84</td>
</tr>
<tr>
<td>DBP (mm Hg)†</td>
<td>321</td>
<td>62.5</td>
<td>11.8</td>
<td>3.6</td>
<td>3.3</td>
<td>0.83</td>
</tr>
<tr>
<td>Estradiol (pg/ml)</td>
<td>73</td>
<td>35.2</td>
<td>17.3</td>
<td>7.7</td>
<td>2.2</td>
<td>0.67</td>
</tr>
</tbody>
</table>

*Based on original and repeat measurements.
†Estimates of within-person variability are overestimated because effects of biologic variation over time are included in the calculation of measurement error.
See Table 1 for abbreviations.

shows (in decreasing order of reliability) the estimates of measurement error for Ep and certain characteristics measured during the 1981-82 CVD risk factor examination. Although the ratio of interindividual to intraindividual variability for Ep is less than that calculated for serum lipids and lipoproteins, the reproducibility of Ep is nearly equal to that for DBP and glucose determinations, and is greater than that for estradiol. In addition, because of the time interval between initial and repeat ultrasonic (and blood pressure) examinations, the observed measurement error for Ep and blood pressures are confounded by the inherent biologic variation. Thus, the actual error involved in the ultrasonic determination of Ep is probably less than indicated in Table 6.

In the current study, ultrasonic measurements of carotid artery stiffness were slightly elevated in adolescents having increased SBP and TC levels. The difference of 5.1 kPa was statistically significant, after correction for age, race, and sex (p = 0.03, one-sided). In addition, Ep tended to be about 5 kPa higher in both blacks (as compared to whites) and in males (as compared to females). Even within the narrow age range (10 to 17 years) of the examined subjects, Ep increased by almost 2 kPa per year. Perhaps most important, parental histories of MI and DM were related to increased Ep levels in both races, independent of race, sex, age, TC, and SBP.

These findings extend those based on our previous ultrasonic examinations conducted in North Carolina, in which mean Ep levels were 5 to 6 kPa higher in 6- to 25-year-old white males than in white females. Additional comparisons with 26- to 55-year-old adults demonstrated a striking increase in Ep levels with age: from 65 kPa to 105 kPa, an average increase of also 2 kPa per year. These age and sex differences in Ep levels, also observed in the current study, are consistent with the well-known associations of CVD incidence with both sex and age. Speculatively, since blacks have greater cerebrovascular disease mortality rates than do whites independent of blood pressure levels, the pathogenesis of cerebrovascular disease may be related to factors associated with increased arterial wall stiffness.

In the current study, Ep was not related to the risk factors in blacks, and mean Ep levels tended to be slightly greater in low risk, as compared to high risk, black females. Some possible explanations for these unexpected findings include: 1) the small sample sizes of the black subgroups, especially the low risk black female group (n = 4); and 2) the high prevalence of parental MI (¼), DM (¼) and hypertension (¼) in low risk black females.

Increases in Ep of 7 to 9 kPa, independent of race, sex, age, blood pressure, and TC, were observed in children with reported parental histories of MI and DM. These percentage increases in Ep, representing over one-half of its overall standard deviation, are greater than the previously observed increases in children and adolescents of levels of serum lipids, lipoproteins, and blood pressure associated with parental disease. Although parental history information was obtained through questionnaires, other studies have reported correlations of 0.7 to 0.8 between questionnaire data and medical record information. In any event, nonsystematic misclassification of parental histories would result in underestimations of the actual associations. Others have shown that familial clustering of risk factors cannot entirely account for the familial aggregation of clinical disease, and the results of the current study suggest that the heritability of differences in arterial wall stiffness may be important in the aggregation of CVD.

Animal studies indicate that elevated Ep levels are associated with the development of early atherosclerotic lesions in the carotid arteries. In previous work with male cynomolgus macaques (M. fasciulatus), mean Ep in animals fed a high cholesterol diet for 18 months was 109 kPa higher than in animals given standard monkey chow. The corresponding mean percentage stenoses in the carotid arteries were 30% and 0%, respectively. Similarly, other work has demonstrated increased aortic pulse-wave velocities associated with increased Ep levels in cynomolgus monkeys fed an atherogenic diet and decreased pulse-
wave velocities in rhesus monkeys undergoing regression of atherosclerosis.\textsuperscript{42} Ecologic comparisons of aortic pulse wave velocities in China showed an increased mean pulse wave velocity in a population with a high prevalence of hypertension.\textsuperscript{43} In addition, an abstract report\textsuperscript{44} on the use of M-mode ultrasound to determine aortic wall movement found increased $E_c$ values in men with both angina and a positive stress test (as compared to age-matched controls) and in cholesterolfed rabbits.

Ultrasound may be an important technique to detect early atherosclerotic lesions in epidemiologic studies and could further elucidate the role of risk factors in the development of CVD. Atherosclerosis in the carotid arteries is moderately associated ($r = 0.4$ to 0.5) with lesions in the coronary arteries.\textsuperscript{45,46} In addition, since the associations between $E_c$ and parental histories of MI and DM are independent of TC and blood pressure, the elastic modulus may be important as an additional marker for future clinical disease. The current study provides further evidence that functional changes associated with an increased risk of future CVD can be detected in early life.

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