

## ARTERIAL ABNORMALITIES IN THE OFFSPRING OF PATIENTS WITH PREMATURE MYOCARDIAL INFARCTION

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### ABSTRACT

**Background** The offspring of patients with premature coronary disease may be at increased risk for atherosclerosis. We undertook a study to determine whether changes in brachial-artery reactivity and the thickness of the carotid intima and media, two markers of early atherosclerosis, are present in adolescents and young adults with a parental history of premature myocardial infarction.

**Methods** We enrolled 40 healthy young people whose parents had had premature myocardial infarction (48 percent male; mean [ $\pm$ SD] age,  $19.0 \pm 5.2$  years) and 40 control subjects who were matched with the first group according to age and sex. All the subjects underwent high-resolution B-mode ultrasound examinations for the measurement of the brachial-artery vasodilatory response after arterial occlusion (i.e., reactive hyperemia) and the intima-media thickness of the distal common carotid arteries.

**Results** As compared with the control subjects, the offspring of patients with premature myocardial infarction had lower flow-mediated reactivity of the brachial arteries ( $5.7 \pm 5.0$  percent, vs.  $10.2 \pm 6.6$  percent in the control subjects;  $P=0.001$ ) and greater mean intima-media thickness of the common carotid artery ( $0.49 \pm 0.08$  mm, vs.  $0.44 \pm 0.07$  mm in the control subjects;  $P=0.004$ ). In the subjects with a parental history of premature myocardial infarction, an inverse association was found between brachial-artery reactivity and carotid intima-media thickness ( $r=-0.46$ ,  $P=0.003$ ). In a conditional logistic-regression analysis, both brachial-artery reactivity and carotid intima-media thickness were significantly and independently correlated with a parental history of premature myocardial infarction.

**Conclusions** Structural and functional changes are present at an early age in the arteries of persons with a parental history of premature myocardial infarction. (N Engl J Med 2000;343:840-6.)

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**A** PARENTAL history of premature coronary artery disease is an important risk factor for cardiovascular events.<sup>1-4</sup> The risk of ischemia as evidenced by electrocardiography is about 40 percent higher and the risk of death from cardiac events is 2.5 to 7 times higher in persons with a parental history of premature coronary disease than in persons without such a family history.<sup>5,6</sup> Sev-

eral reports from the Bogalusa Heart Study, an epidemiologic study in which the early natural history of atherosclerosis was evaluated, have shown higher serum concentrations of lipoproteins and homocysteine and higher blood pressure — risk factors for coronary disease — in children and young adults with a parental history of premature coronary disease than in those without such a background.<sup>7-10</sup> Furthermore, atherosclerotic lesions have been found at autopsy in the coronary arteries of infants with a family history of cardiac disease.<sup>11</sup>

Over the past decade, high-resolution B-mode ultrasonography has proved to be a valid and reliable method of detecting initial structural atherosclerotic changes in the arterial wall. Increased thickness of the intima and media of the carotid artery has been found in subjects with risk factors for cardiovascular disease and is a powerful predictor of the presence of coronary atherosclerosis and its clinical sequelae.<sup>12-14</sup> High-resolution ultrasonography has been used to evaluate endothelial function noninvasively by measuring changes in the diameter of the brachial artery due to increased blood flow induced by inflation or deflation of a pressure cuff.<sup>15</sup> Flow-mediated brachial-artery reactivity is impaired in persons with overt atherosclerosis and in asymptomatic persons with risk factors for coronary disease.<sup>16-18</sup>

We undertook the current study to investigate whether early anatomical and functional changes are present and are correlated in the arteries of children and young adults with a parental history of premature myocardial infarction.

### METHODS

#### Subjects

Forty healthy young persons (6 to 30 years of age) whose parents had premature myocardial infarction were enrolled in the study (19 male and 21 female subjects). We defined premature myocardial infarction as clinical evidence of acute myocardial infarction at or before the age of 60 years. Young persons with such a parental history were recruited among the offspring of patients

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hospitalized between January 1 and December 31, 1997, at Cardarelli Hospital in Naples, Italy, with acute myocardial infarction as defined by World Health Organization criteria (symptoms compatible with the diagnosis and either typical electrocardiographic changes or high serum cardiac-enzyme concentrations).<sup>19</sup>

We also studied 40 control subjects, matched for age and sex with the subjects described above, who had no parental history of coronary artery disease (including established or suspected infarction or angina pectoris). The control subjects were the offspring of patients who had been admitted to Cardarelli Hospital between January 1 and December 31, 1997, for a wide range of acute illnesses unrelated to coronary artery disease or diabetes.

Each subject or the subject's parents gave oral informed consent for his or her participation in the study, which was approved by the local committee on ethical practice.

#### Assessment of Risk Factors for Cardiovascular Disease

Assessments of risk factors for cardiovascular disease were made in hospital outpatient facilities according to standardized protocols. Blood pressure was measured with a standard mercury sphygmomanometer three times: two measurements one minute apart with the subject seated and a third after five minutes of rest lying down. A standard questionnaire was used to obtain information about current smoking, history with respect to diabetes and hypertension, and family history of coronary artery disease. A blood sample was drawn while the subject was fasting for the measurement of serum total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol, apolipoprotein A-I, apolipoprotein B, triglycerides, and Lp(a) lipoprotein.

#### Laboratory Methods

Serum cholesterol and triglyceride concentrations were measured with the use of an enzymatic colorimeter (BM/Hitachi 747, Boehringer Mannheim Italia, Monza, Italy). HDL and LDL cholesterol was measured by agarose-gel electrophoresis (Helena Laboratories, Assago, Italy). Serum apolipoprotein A-I, apolipoprotein B, and Lp(a) lipoprotein concentrations were determined with the use of an immunonephelometer (BNA II, Istituto Behring, Scoppito, Italy). The intraassay coefficients of variation were 2.9 percent for total cholesterol, 3.6 percent for triglycerides, 6.7 percent for HDL cholesterol, 6.9 percent for LDL cholesterol, 1 percent for apolipoprotein A-I, 1.5 percent for apolipoprotein B, and 1.8 percent for Lp(a) lipoprotein. The interassay coefficients of variation during the study were 3.1 percent for total cholesterol, 3.9 percent for triglycerides, 7.9 percent for HDL cholesterol, 8.0 percent for LDL cholesterol, 3.3 percent for apolipoprotein A-I, 4.6 percent for apolipoprotein B, and 5 percent for Lp(a) lipoprotein.

#### High-Resolution Ultrasonographic Studies

Ultrasonographic studies were performed with the use of a 7.5-MHz transducer (Sonos 2000, Hewlett-Packard, Seattle). Scans were recorded on super VHS videotape for off-line analyses. One expert reader, who was unaware of the family history of the subjects, measured brachial-artery reactivity and the thickness of the carotid-artery intima and media.

#### Evaluation of Brachial-Artery Reactivity

Subjects were asked to fast and to refrain from smoking and physical activity for two hours before the examination. They rested in a supine position for 10 minutes before the study and were kept supine during the procedure, with the left arm extended for brachial-artery imaging. In all studies, the brachial artery was scanned longitudinally; gray-scale settings were optimized to provide the clearest view of the lumen and the vessel wall, and images were then magnified. Blood pressure in the brachial artery of the right arm was recorded automatically with an ambulatory blood-pressure monitor (DynaPulse, Pulse Metric, San Diego, Calif.) at regular intervals, and the electrocardiogram was monitored continuously. The ultrasonographic protocol included an initial recording of bra-

chial-artery diameter and Doppler blood-flow velocity, after which a blood-pressure cuff was placed around the left forearm and inflated to a pressure of 300 mm Hg for 4.5 minutes and then suddenly deflated. The consequent increase in blood flow (reactive hyperemia) is a powerful stimulus for the release of endothelial nitric oxide and the resulting brachial-artery vasodilatation.<sup>20</sup>

Brachial-artery blood-flow velocity was recorded continuously for 15 seconds after deflation, and the brachial-artery diameter was measured at 45 to 60 seconds. During vessel recovery, images of brachial blood flow and diameter were recorded at 5 minutes and 10 minutes. The end-diastolic diameter of the brachial artery, defined as the distance between the near-wall and far-wall junctions of the media and adventitia, was measured over four cardiac cycles with the use of digital calipers. Flow-mediated reactivity of the brachial artery was expressed as the percentage change in the arterial diameter from base line to 45 to 60 seconds after deflation of the cuff. Brachial blood flow was determined as the product of mean velocity (estimated by means of pulsed Doppler ultrasonography at an angle of less than 60 degrees) and the arterial cross-sectional area. Hyperemic flow was calculated as the maximal flow within the first 15 seconds after deflation of the cuff divided by the flow during base-line scanning.

To assess the reproducibility of the method, scanning was repeated seven days later in a randomly selected subgroup of nine subjects; the results were analyzed by two readers. The mean ( $\pm$ SD) absolute differences in measured brachial-artery diameters between the two occasions were  $0.04 \pm 0.02$  mm (coefficient of variation, 0.9 percent) for one of the readers and  $0.07 \pm 0.06$  mm (coefficient of variation, 1.4 percent) for the other. The mean absolute difference between the readers was  $0.05 \pm 0.03$  mm (coefficient of variation, 1.0 percent). The mean differences in measured brachial-artery reactivity were  $1.1 \pm 0.7$  percent (coefficient of variation, 1.5 percent) for the first reader and  $1.8 \pm 1.0$  percent (coefficient of variation, 2.1 percent) for the second, with a variability between the readers of  $1.4 \pm 0.9$  percent (coefficient of variation, 1.8 percent).

#### Carotid-Artery Study

Longitudinal ultrasonographic scans of the carotid artery were obtained on the same day as the studies of brachial-artery reactivity and included evaluation of the far wall of the distal 1.0 cm of both common carotid arteries, immediately proximal to the origin of the bifurcation. In each examination, the sonographer used different scanning angles (anterior and lateroposterior) to identify the greatest intima-media thickness, defined as the distance between the junction of the lumen and intima and that of the media and adventitia.<sup>21</sup> Three measurements of intima-media thickness were made in the right and left carotid arteries and were averaged to determine the mean intima-media thickness for each side and for both sides combined. The mean absolute difference in intima-media thickness, as measured by one observer in 25 subjects in whom two carotid-artery examinations were performed seven days apart, was  $0.02 \pm 0.03$  mm (coefficient of variation, 2.6 percent).

#### Statistical Analysis

The results are reported as means  $\pm$ SD unless otherwise indicated. Comparisons between subjects with a parental history of premature myocardial infarction and control subjects were made with the use of paired Student's *t*-tests and chi-square analysis for continuous and categorical variables, respectively. To ensure gaussian distributions, Lp(a) lipoprotein and triglyceride concentrations were converted to logarithmic values, and comparisons were made between sets of log-transformed data. Pearson's correlation coefficients were calculated to assess the univariate association between variables relating to vascular disease. Odds ratios (with 95 percent confidence intervals) for a parental history of premature myocardial infarction were determined by conditional logistic-regression analysis. All analyses were conducted with the use of statistical software (SPSS for Windows, version 9.0, SPSS, Chicago; and SAS, version 6.12, SAS, Cary, N.C.).

## RESULTS

The clinical characteristics of the subjects with a parental history of premature coronary disease and of the subjects without such a history are shown in Table 1. There were no significant differences between the two groups with regard to body-mass index; systolic and diastolic blood pressure; the serum concentrations of cholesterol, triglycerides, and apolipoprotein A-I; and the prevalence of current smoking. However, the subjects with a parental history of premature myocardial infarction had significantly higher serum apolipoprotein B and Lp(a) lipoprotein concentrations than participants without such a history.

The results of ultrasonographic studies are shown in Table 2. As compared with the control subjects, the offspring of patients with coronary disease had less flow-mediated brachial-artery reactivity ( $5.7 \pm 5.0$  percent vs.  $10.2 \pm 6.6$  percent,  $P=0.001$ ); the two groups were similar with regard to the brachial-artery diameter at rest and the base-line and hyperemic brachial blood-flow velocity and volume. As compared with the control subjects, the subjects with a parental history of premature myocardial infarction had greater intima-media thickness of the common carotid artery (values for combined sides,  $0.49 \pm 0.08$  vs.  $0.44 \pm 0.07$  mm;  $P=0.004$ ).

A significant inverse correlation was found between

brachial-artery reactivity and intima-media thickness of the common carotid artery in the subjects with a parental history ( $r=-0.46$ ,  $P=0.003$ ) (Fig. 1) but not in the control subjects ( $r=-0.01$ ,  $P=0.93$ ) (Fig. 2).

Table 3 summarizes the results of the conditional logistic-regression analysis. The variables included in the model were only those that were significantly related to a parental history of premature myocardial infarction ( $P \leq 0.05$ ) in the univariate analysis: mean carotid intima-media thickness, brachial-artery reactivity, apolipoprotein B concentration, and log-transformed Lp(a) lipoprotein concentration. The apolipoprotein B concentration, rather than total or LDL cholesterol concentration, was chosen as a variable in the model because of the lower P value associated with it and because of the high level of collinearity between the apolipoprotein B and total cholesterol concentrations ( $r=0.71$ ) and between the apolipoprotein B and LDL cholesterol concentrations ( $r=0.74$ ). The results indicate that both brachial-artery reactivity and carotid intima-media thickness were significantly and independently associated with a parental history of premature myocardial infarction.

## DISCUSSION

A family history of premature coronary artery disease has been demonstrated to be a major risk factor

**TABLE 1.** CLINICAL CHARACTERISTICS OF THE STUDY SUBJECTS ACCORDING TO THE PRESENCE OR ABSENCE OF A PARENTAL HISTORY OF PREMATURE MYOCARDIAL INFARCTION.\*

CHARACTERISTIC†	PARENTAL HISTORY OF PREMATURE MI (N=40)	NO PARENTAL HISTORY OF PREMATURE MI (N=40)	P VALUE
Age — yr	19.0±5.2	19.2±5.3	—
Male sex — no. (%)	19 (48)	19 (48)	—
Body-mass index	22.6±2.6	23.4±2.7	0.19
Blood pressure at base line — mm Hg			
Systolic	123.4±9.6	123.0±8.5	0.85
Diastolic	63.6±6.4	62.8±4.9	0.49
Serum cholesterol — mg/dl			
Total	166.3±27.6	153.0±33.3	0.06
HDL	49.5±11.2	45.9±14.6	0.21
LDL	102.0±26.1	91.6±25.0	0.08
Serum triglycerides — mg/dl	70.6±33.7	78.3±45.0	0.49‡
Serum Lp(a) lipoprotein — mg/dl	27.5±34.9	15.8±21.9	0.03‡
Serum apolipoprotein A-I — mg/dl	143.3±23.7	143.6±24.0	0.96
Serum apolipoprotein B — mg/dl	87.5±25.5	73.0±21.1	0.003
Current smoking — no. (%)	10 (25)	7 (18)	0.41

\*Plus-minus values are means ±SD. MI denotes myocardial infarction, HDL high-density lipoprotein, and LDL low-density lipoprotein.

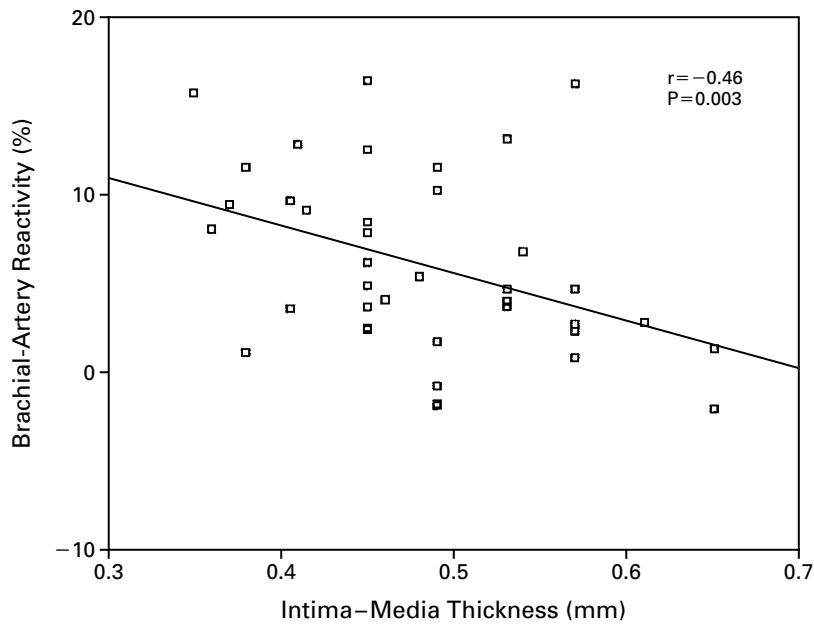
†Body-mass index is the weight in kilograms divided by the square of the height in meters. To convert values for cholesterol and triglycerides to millimoles per liter, multiply by 0.026 and 0.11, respectively.

‡The P value was calculated from the testing of log-transformed variables.

**TABLE 2.** CHARACTERISTICS OF BRACHIAL AND COMMON CAROTID ARTERIES IN SUBJECTS WITH A PARENTAL HISTORY OF PREMATURE MYOCARDIAL INFARCTION AND SUBJECTS WITHOUT SUCH A HISTORY.\*

VARIABLE	PARENTAL HISTORY OF PREMATURE MI (N=40)	NO PARENTAL HISTORY OF PREMATURE MI (N=40)	P VALUE
<b>Functional measures of the brachial artery</b>			
Base-line diameter (mm)	3.38±0.57	3.40±0.66	0.83
Base-line blood-flow velocity (cm/sec)	17.8±7.9	20.7±9.9	0.19
Base-line blood-flow volume (ml/sec)	101.9±58.9	114.6±86.2	0.58
Diameter during reactive hyperemia (mm)	3.55±0.53	3.72±0.64	0.12
Brachial-artery reactivity (%)	5.7±5.0	10.2±6.6	0.001
Blood-flow velocity during hyperemia (cm/sec)	73.0±16.4	82.1±18.7	0.29
Blood-flow volume during hyperemia (ml/sec)	441.9±287.1	540.2±459.7	0.36
<b>Structural measures of the common carotid artery</b>			
Intima-media thickness (mm)			
Right artery	0.48±0.08	0.43±0.08	0.003
Left artery	0.50±0.09	0.46±0.07	0.03
Combined arteries	0.49±0.08	0.44±0.07	0.004
Luminal diameter (mm)			
Right artery	5.43±0.51	5.51±0.58	0.51
Left artery	5.31±0.50	5.31±0.46	0.99

\*Plus-minus values are means ±SD. MI denotes myocardial infarction.

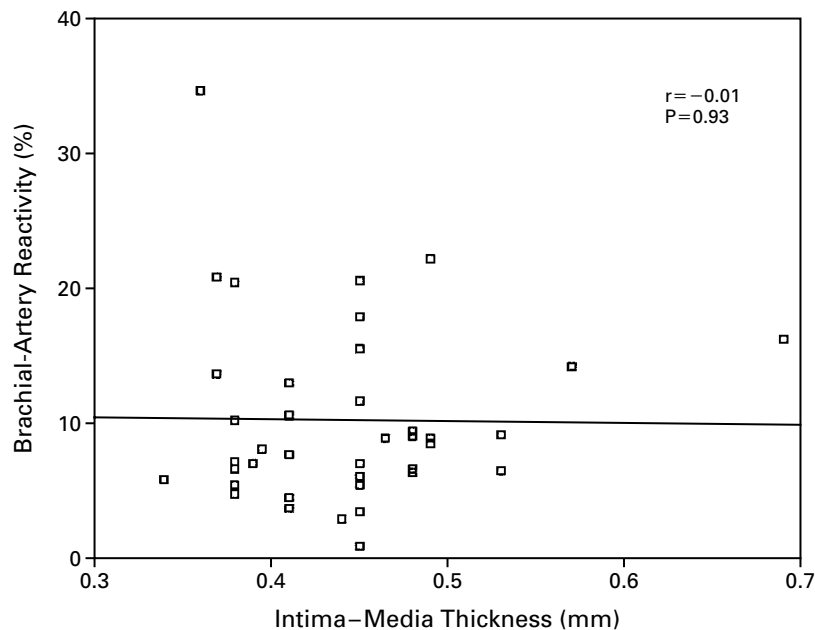


**Figure 1.** Correlation between Brachial-Artery Reactivity and Intima-Media Thickness of the Common Carotid Artery in 40 Subjects with a Parental History of Premature Myocardial Infarction.

for cardiovascular disease. It is included in clinical guidelines for the prevention of coronary heart disease and is used in pediatric cardiology as an important indication for lipid-profile screening in children.<sup>22,23</sup> Although first-degree relatives of patients with premature coronary disease have an increased prevalence of

both symptomatic and asymptomatic cardiac disease, it is still not clear when the first cardiovascular abnormalities become evident in these family members.

The availability of valid and reliable noninvasive ultrasonographic methods to detect preclinical atherosclerotic disease led us to investigate the presence and



**Figure 2.** Correlation between Brachial-Artery Reactivity and Intima-Media Thickness of the Common Carotid Artery in 40 Subjects with No Parental History of Premature Myocardial Infarction.

**TABLE 3.** ODDS RATIOS FOR A PARENTAL HISTORY OF PREMATURE MYOCARDIAL INFARCTION ACCORDING TO MULTIVARIATE CONDITIONAL LOGISTIC-REGRESSION ANALYSIS.\*

VARIABLE	ODDS RATIO (95% CI)	P VALUE
Apolipoprotein B (mg/dl)	2.13 (0.81–5.55)	0.14
Lp(a) lipoprotein (mg/dl)	2.40 (0.80–7.21)	0.10
Brachial-artery reactivity (%)	0.32 (0.13–0.80)	0.01
Carotid intima-media thickness (mm)†	4.10 (1.31–12.84)	0.01

\*The odds ratios are for each increase of 1 SD in the independent variables. The pooled standard deviations (N=80) were used and were as follows: carotid intima-media thickness, 0.076; brachial-artery reactivity, 6.268; apolipoprotein B, 24.396; and log-transformed Lp(a) lipoprotein, 0.48. Age and sex were deleted by design. Only the variables significantly related to a parental history of premature myocardial infarction in the univariate analysis ( $P \leq 0.05$ ) were entered in the model. Among total cholesterol, LDL cholesterol, and apolipoprotein B concentrations, only the apolipoprotein B concentration was chosen, because of the high collinearity among these variables and because there was a more significant difference in apolipoprotein B concentrations between the study groups in the univariate analysis. Lp(a) lipoprotein was included in the model as a log-transformed or nontransformed variable; the results with regard to statistical significance were similar. Included in the table are the values for the log-transformed variable. CI denotes confidence interval.

†The mean value for the combined sides was used.

association of early changes in arterial structure and function in a sample of young people with a parental history of premature myocardial infarction. Our findings indicate that alterations in brachial-artery reactivity and carotid intima-media thickness, two markers of early atherosclerosis, are present in young people with a parental history of premature myocardial infarction, that these vascular abnormalities are associated with each other, and that their association with a parental history is independent of several traditional risk factors for cardiovascular disease.

Few studies have examined the relation between a family history of coronary artery disease and measurements of vascular structure and function. In the Bogalusa Heart Study, children and adolescents with a parental history of myocardial infarction had an increased pressure-strain modulus of elasticity of the common carotid artery, an index of arterial stiffness.<sup>24</sup> Our data on brachial-artery reactivity are consistent with, and extend to a younger population, the observations of Clarkson et al., who found impaired flow-mediated, endothelium-dependent vasodilatation in first-degree relatives of patients with angiographic or clinical evidence of premature coronary artery disease.<sup>25</sup>

In a recent report from an epidemiologic study of vascular aging that focused on elderly persons, an association was found between a parental history of premature death from coronary heart disease and the presence of carotid atherosclerotic plaque (defined as an intima-media thickness of at least 1 mm) but not

increased intima-media thickness of the common carotid artery.<sup>26</sup> This discordance with our findings may result from the difference in the study populations (elderly subjects vs. adolescents and young adults).

Atherosclerosis is known to be a systemic process that involves several arterial beds. Therefore, morphologic and functional changes may be ubiquitous in the arterial vasculature of young persons with a parental history of premature coronary artery disease. The current study demonstrates an association between structural changes and functional changes related to early atherosclerosis in a group of young persons who are at high risk for coronary disease but have no symptoms. A relation between carotid intima-media thickness and vascular reactivity has been previously investigated in patients with symptomatic hypertension and in patients with suspected coronary artery disease.<sup>27,28</sup> The documentation of this relation provides supporting evidence that a functional impairment of the endothelium, resulting in a reduction in the availability of nitric oxide and enhanced release of vasoconstricting factors, may predispose patients to monocyte and platelet adhesion, the proliferation of smooth-muscle cells, and increased accumulation of macrophages and lipoproteins in the arterial wall. These effects promote atherosclerotic structural lesions at an early age.<sup>29</sup>

Our data confirm that young people with a parental history of premature myocardial infarction have higher concentrations of Lp(a) lipoprotein and apolipoprotein B than persons without such a history, but they also suggest that factors in addition to these classic risk factors for cardiovascular disease may mediate the effects of familial predisposition on the arterial wall. The nature of these factors requires further study. Zannad et al. have suggested that 30 percent of the variation in the thickness of the common carotid intima and media may be explained by genetic factors.<sup>30</sup> More interesting are the observations linking different mutations of the gene that codes for endothelial nitric oxide synthase either with smoking-related risk of coronary artery disease or with coronary vasospasm.<sup>31,32</sup>

The presence of asymptomatic vascular changes in adolescents and young adults and the association of these changes with a parental history of premature myocardial infarction have potential implications for clinical practice. The examination of arterial-wall structure and function in young persons with the use of noninvasive ultrasonographic methods may provide important information on early changes in the course of developing atherosclerosis, especially in persons at high risk for cardiovascular disease.

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