Effects of Coronary Heart Disease Risk Factors on Atherosclerosis of Selected Regions of the Aorta and Right Coronary Artery

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Abstract—We examined topographic distributions of atherosclerosis and their relation to risk factors for adult coronary heart disease in right coronary arteries and abdominal aortas of more than 2000 autopsied persons 15 through 34 years of age. We digitized images of Sudan IV–stained fatty streaks and of manually outlined raised lesions and computed the percent surface area involved by each lesion in each of 6 regions of each artery. In abdominal aortas of 15- to 24-year-old persons, fatty streaks involve an elongated oval area on the dorsolateral intimal surface and another oval area in the middle third of the ventral surface. Raised lesions in 25- to 34-year-old persons involve an oval area in the distal third of the dorsolateral intimal surface. In other areas of the abdominal aortas of older persons, fatty streaks occur but raised lesions are rare. In the right coronary arteries of 15- to 24-year-old persons, fatty streaks are most frequent on the myocardial aspect of the first 2 cm. Raised lesions follow a similar pattern in 25- to 34-year-old persons. High non-HDL cholesterol and low HDL cholesterol concentrations are associated with more extensive fatty streaks and raised lesions in all regions of both arteries. Smoking is associated with more extensive fatty streaks and raised lesions of the abdominal aorta, particularly in the dorsolateral region of the distal third of the abdominal aorta. Hypertension is not associated with fatty streaks in whites or blacks but is associated with more extensive raised lesions in blacks. Risk factor effects on arterial regions that are vulnerable to lesions are ≈25% greater than risk factor effects assessed over entire arterial segments. These risk factor effects on vulnerable sites emphasize the need for risk factor control during adolescence and young adulthood to prevent or delay the progression of atherosclerosis. (Arterioscler Thromb Vasc Biol. 2000;20:836-845.)

Key Words: atherosclerosis ■ aorta ■ coronary artery ■ topography ■ risk factors

Atherosclerosis follows a distinctive topographical distribution in the intimal surface of each affected artery. Hypotheses explaining the localization of atherosclerotic lesions include hemodynamic stresses related to arterial geometry1–4; anatomic, cellular, or biochemical variations in the arterial wall, particularly in endothelium5; smooth muscle cell mutations leading to monoclonal proliferation6; and infectious agents.7

Most of the established major risk factors for coronary heart disease are associated with the extent of both fatty streaks and raised lesions in the large muscular and elastic arteries of adults8 and also in arteries of adolescents and young adults.9–11 The magnitude of the effect of each risk factor varies among the arterial beds: for example, hypertension selectively augments atherosclerosis of the cerebral arteries,8 whereas smoking selectively augments atherosclerosis of the abdominal aorta and the iliac and femoral arteries.12 Although the prevailing opinion is that raised lesions (fibrous plaques and the other advanced lesions of atherosclerosis) arise from fatty streaks,13 dissimilarities in their topographical distributions are cited as evidence against that relationship.14 For example, fatty streaks are prevalent in the thoracic aortas of children and adolescents, but raised lesions rarely appear in the thoracic aortas of adults.15 These observations, together with the identification of lesion-prone and lesion-resistant intimal areas within each artery,16 suggest that the risk factors may affect regions selectively within an artery as well as between different arteries.

The multicenter cooperative study Pathobiological Determinants of Atherosclerosis in Youth (PDAY)17 collected arteries and risk factor measurements from ≈3000 young persons. The age range of these persons, 15 through 34 years,
spans the period during which fatty streaks are well established and raised lesions begin to appear. We previously have shown associations of the serum lipoprotein cholesterol concentrations, smoking, and hypertension with atherosclerosis in the abdominal aorta and right coronary artery (RCA) in these young persons.9–11 In this report, we examine the associations of the risk factors with atherosclerosis measured by computerized image analysis in regions of the abdominal aorta and the RCA.

### Methods

#### Study Design

Fifteen cooperating centers adopted a Standard Operating Protocol and Manual of Procedures to collect specimens and data and to submit them to central laboratories for analysis. A statistical coordinating center received all data pertaining to each case from the collection centers and central laboratories.

#### Subjects

Study subjects were persons 15 through 34 years of age, inclusive, who died of external causes (accidents, homicides, suicides) within 72 hours after injury and were autopsied within 48 hours after death in 1 of the cooperating medical examiners’ laboratories. Age and race were obtained from the death certificate. Persons of race other than black or white and those with congenital heart disease, Down syndrome, AIDS, or hepatitis were excluded. We collected 3210 cases from June 1, 1987, to August 31, 1994. Of these, 334 did not meet the study criteria. Of the 2876 accepted cases, we used 4 subsets in the analyses to be reported here (Table 1). Multiple subsets enabled us to match the case selection criteria used in previous PDAY reports of risk factor effects on atherosclerosis in an entire arterial segment. Subjects with elevated glycohemoglobin (≥8%) indicative of diabetes or impaired glucose tolerance were excluded in these analyses. Fifty-two percent of the PDAY cases were black, and 76% were men.

The Institutional Review Board of each participating center approved the use of tissue, blood, and data from the human subjects in this study.

#### Dissection and Preservation of Arteries

The aorta was dissected from a point 2 cm proximal to the ligamentum arteriosum to a point 2 cm distal to the iliac bifurcation. The aorta was opened along a line on the dorsal surface midway between the orifices of the intercostal and lumbar arteries, the intimal surface was rinsed with Hanks’ modified balanced salt solution (HBS), and the vessel was flattened with the adventitial surface downward. The aorta was then split longitudinally along a line on the ventral surface that bisected the celiac, superior mesenteric, and inferior mesenteric ostia; the right half was placed on cardboard with the adventitia downward. The left half was covered with absorbent cotton and fixed in 10% neutral buffered formalin for 48 hours.

The RCA was opened along the epicardial surface from its origin to the point at which it turned downward along the posterior interventricular sulcus with blunt-point microdissecting scissors. It was then dissected from the heart, the epicardial fat was removed, the intimal surface was rinsed with HBS, and the RCA was fixed in the same manner as the aorta. The left coronary artery and its branches were prepared for other studies.

Each aorta and RCA was placed in a plastic bag with 10% formalin at the collection center, and accumulated tissues were shipped to the central laboratory each month. The central laboratory stained the arteries with Sudan IV and packaged each artery with its identification number in a transparent plastic bag with a slight excess of 10% formalin.

#### Grading Atherosclerosis by Pathologists

Three pathologists independently estimated the percentage of the intimal surface area involved with fatty streaks and raised lesions in the left half of the aorta and in the entire RCA. The consensus lesion grade was the average of the grades of 3 pathologists. A fatty streak was an intimal area stained by Sudan IV without other underlying changes. A raised lesion was a firm, elevated intimal lesion, sometimes partially or completely covered by sudanophilic deposits. Raised lesions rarely included an area of hemorrhage, thrombosis, ulceration, or calcification.

#### Grading Atherosclerosis by Computerized Image Analysis

To assess the extent of fatty streaks, the morphometry laboratory scanned 35-mm color transparencies of each Sudan IV–stained RCA and each aorta at a resolution of 512×256 pixels by 8-bit gray scale through a green filter, stored the image on a DEC Microvax II computer, and displayed it at a Silicon Graphics IP1525™ processing system. The operator manually identified fiducial points by use of anatomic landmarks in the aorta and pairs of points 1 cm apart along the outer edges of the RCA. An algorithm converted each image into a standard template of the artery.

When any 1 of 3 pathologists classified an artery (either the abdominal aorta or the RCA) as positive for raised lesions, the artery was photographed and a black-and-white print was prepared. A designated pathologist, while examining the artery, outlined with a black pen on the photograph the intimal area he believed to be occupied by a raised lesion. A second designated pathologist examined the same artery and photograph; if he agreed with the marking, it was left unchanged. If he disagreed, he outlined his assessment of the raised lesions, and a third pathologist resolved the difference. Thus, the area designated as raised lesion was confirmed visually by 2 pathologists. The morphometry laboratory scanned the final marked print and converted the image into the same standard template as that used for fatty streaks.

An algorithm computed the fraction of pixels in the image of each artery (or each defined region of the artery) involved by Sudan IV staining (fatty streaks) or by pathologists’ identification of raised lesions. The fraction of involved pixels was taken to represent the percent of intimal surface involved by each type of lesion. The prevalence of lesions at each pixel location was also displayed in

### Table 1. Subsets of PDAY Cases Used in Analyses of Associations of Risk Factors and Lesions in Defined Arterial Regions

<table>
<thead>
<tr>
<th>Subset</th>
<th>Abdominal Aorta</th>
<th>RCA</th>
<th>Criteria for Inclusion</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2290</td>
<td>1852</td>
<td>Normal glycohemoglobin</td>
<td>Associations of lesions with sex, race, and age by region</td>
</tr>
<tr>
<td>2</td>
<td>1364</td>
<td>1110</td>
<td>Normal glycohemoglobin, measurement of non-HDL-C, HDL-C, thiocyanate</td>
<td>Associations of lesions with sex, race, age, non-HDL-C, HDL-C, and smoking by region</td>
</tr>
<tr>
<td>3</td>
<td>2265</td>
<td>1831</td>
<td>Normal glycohemoglobin, measurement of renal index of hypertension</td>
<td>Associations of lesions with sex, race, age, and hypertension by region</td>
</tr>
<tr>
<td>4</td>
<td>1349</td>
<td>1099</td>
<td>Normal glycohemoglobin, measurement of non-HDL-C, HDL-C, thiocyanate, renal index of hypertension</td>
<td>Associations of lesions with sex, race, age, and risk level (defined by non-HDL-C, HDL-C, thiocyanate, renal index of hypertension) by region</td>
</tr>
</tbody>
</table>
Maps by banded isopleths. Regional measurements of the abdominal aorta were computed only for cases with a complete abdominal aorta, and regional measurements of the RCA were computed only for cases with an RCA of \( \geq 6 \) cm.

**Agreement Between Pathologists’ Consensus and Results From Image Analyses**

We compared the extent of involved surface area derived from the consensus of 3 pathologists with the involved surface area computed by image analysis. Intraclass correlation coefficients describing the agreement were 0.90 for abdominal aortic fatty streaks, 0.93 for abdominal aortic raised lesions, 0.79 for RCA fatty streaks, and 0.94 for RCA raised lesions.

**Definition of Regions**

By examining color prints of composite images of arteries with fatty streaks and of composite images of the same arteries with raised lesions, we identified regions that corresponded to the distribution patterns of lesions. Figure 1 shows the outline of the left half of the abdominal aorta divided into 6 regions by 2 lines along the long axis and 3 lines perpendicular to the long axis. A narrow strip at the dorsal edge was excluded to avoid the orifices of the lumbar arteries. In preliminary studies, we ascertained that the left and right halves of the abdominal aorta were approximate mirror images of one another.

Figure 2 shows the RCA divided into 6 regions at 1-cm intervals, beginning at the origin.

**Blood**

Blood collected at autopsy from the aorta, heart, or vena cava was centrifuged. Frozen serum and cells were shipped to the central laboratory for analysis.

**Lipoprotein Cholesterol**

We measured total serum cholesterol and HDL cholesterol (HDL-C) after precipitation of other lipoproteins with heparin MnCl\(_2\) by the cholesterol oxidase method.\(^{19}\) The coefficient of variation for blind duplicate analyses of serum cholesterol was 1.3%; for HDL-C, it was 5.2%. The non-HDL-C concentration was obtained by subtraction. Triglyceride concentrations in these postmortem serum samples could not be interpreted because we could not ascertain the prandial status, and therefore, LDL was not calculated. Several studies have demonstrated that postmortem levels of serum cholesterol and lipoproteins are representative of premortem levels.\(^{20,21}\) However, because emergency medical teams often administer large quantities of intravenous fluids to some individuals immediately before death from violent causes, we excluded all serum values from the statistical analysis when serum cholesterol was \(<2.59\) mmol/L (100 mg/dL).

In the statistical analyses for effects of lipoprotein cholesterol concentrations on atherosclerosis, we used the definitions of upper
and lower thirds of non-HDL-C and of HDL-C established in the 1443 cases previously reported. Low non-HDL-C was < 2.79 mmol/L (108 mg/dL); high was > 3.88 mmol/L (150 mg/dL). Low HDL-C was < 1.11 mmol/L (43 mg/dL); high was > 1.55 mmol/L (60 mg/dL).

Thiocyanate
We measured color produced by the thiocyanate–ferric nitrate complex after treatment of trichloroacetic acid filtrates of serum with ferric nitrate.22 The coefficient of variation for blind duplicate analyses was 5.5%. A smoker was defined as having a serum thiocyanate level $\geq 90 \mu$mol/L. Forty-five percent of PDAY cases were classified as smokers.

Glycohemoglobin
We measured glycohemoglobin by affinity column chromatography.23 Values $\geq 8\%$ were defined as elevated.24 An elevated glycohemoglobin concentration $\geq 8\%$ corresponds to an average blood glucose concentration of $\approx 8.3$ mmol/L (150 mg/dL) for the previous 2 or 3 months.

Estimation of Blood Pressure
We measured the thickness of the intima of small renal arteries in histological sections of kidney. Using a method developed by Tracy et al,25 we classified each case as normotensive or hypertensive by an algorithm that predicted mean arterial pressure (MAP) from the renal measurements and age. Details of the application of this method to PDAY specimens were described in previous publications.10,26 The normotensive category included cases with a predicted MAP $< 110$ mm Hg; those with predicted MAP $\geq 110$ mm Hg were classified as hypertensive. The prevalence of hypertension was 12% among whites and 18% among blacks. The prevalence of hypertension by race, sex, and age determined in PDAY cases by this method corresponded well with prevalence reported from a survey of a living population.10

Statistical Methods
We analyzed the associations of sex, race, 5-year age group, third of non-HDL-C, third of HDL-C, smoking status, and hypertension status with the percentage of arterial intimal surface involved with lesions in the defined regions of the abdominal aorta and RCA by use of multivariate ANOVA.27 The linear model included main effects and 2-factor interactions. We applied a logit transformation to the proportion of surface area involved with lesions to better satisfy the assumptions underlying the statistical analysis.28 A small constant was added to avoid the logarithm of zero.
Results

Race Effects on Atherosclerosis by Region
Blacks have more extensive fatty streaks than whites in regions 1 and 2 of the abdominal aorta (P=0.0038) and in regions 3 through 6 of the RCA (P<0.0037) (results not shown). In regions 1 and 2 of the RCA, white and black men have similar involvement with fatty streaks, whereas black women have more extensive involvement than white women (interaction of sex and race, P<0.0184) (results not shown). Subsequent results regarding risk factor effects, except for those associated with hypertension, are adjusted for race.

Abdominal Aorta: Distribution of Fatty Streaks and Raised Lesions by Region, Age, and Sex
Figure 1 shows, by 5-year age groups and sex, maps of the prevalence of fatty streaks (left) and of raised lesions (right) in the abdominal aorta. Superimposed on the maps are outlines of the 6 regions. In younger persons (15 to 24 years of age), fatty streaks are concentrated in an elongated oval area on the dorsolateral intimal surface of the abdominal aorta, filling regions 1, 3, and 5, and in another elongated oval area on the ventrolateral intimal surface filling region 4. The prevalence of fatty streaks is less in region 5 in the 30- to 34-year age group than in the 25- to 29-year age group because this area becomes heavily involved with raised lesions. Raised lesions (right) appear to an appreciable degree in the 20- to 24-year age group and become more extensive in succeeding age groups.

The extent of fatty streaks changes with age in all regions (P=0.0001). In all regions except regions 2 and 6, the extent of fatty streaks either declines or remains unchanged in the older groups, reflecting the replacement of fatty streaks by raised lesions. The extent of raised lesions increases with age in all regions (P=0.0001). Region 5 has the most extensive raised lesions (P=0.0001); regions 3, 4, and 6 are similar in extent of raised lesions, and regions 1 and 2 have little involvement with raised lesions.

In the abdominal aorta, women have more extensive fatty streaks in all regions except region 2 (P=0.0001). Men and women have similar involvement with raised lesions in all regions, although older women have more extensive raised lesions than men in regions 1 and 4 (interaction of sex and age, P<0.0369).

RCA: Distribution of Fatty Streaks and Raised Lesions by Region, Age, and Sex
Figure 2 shows maps of the prevalence of fatty streaks (left) and of raised lesions (right) in the RCA by 5-year age group and sex. Superimposed on the maps are outlines of the 6 regions. Fatty streaks (left) in younger persons (15 to 24 years of age) form a pattern with an area of high prevalence near the origin (regions 1 and 2), another area of high prevalence at the midpoint (region 4), and a third area of high prevalence distal to region 6. These areas of more frequent involvement by fatty streaks are on the myocardial aspect of the arterial circumference. Raised lesions (right), which follow a pattern of involvement similar to that of fatty streaks, begin in the 20- to 24-year age group and become more extensive in succeeding age groups.

The extent of fatty streaks and raised lesions increases with age in all regions (P=0.0001). Men have more extensive fatty streaks in regions 3, 4, and 6 (P<0.0251) as well as in region 5, where the difference is less pronounced (P=0.0693). Men have more raised lesions than women in regions 1 through 4 (P<0.0062).

Non-HDL-C Effects by Region
In the abdominal aorta (results not shown), the extent of fatty streaks is positively associated with third of non-HDL-C in all regions except regions 3, 4, and 6 in the 15- to 24-year age groups (P<0.0487) and in all regions in the 25- to 34-year age groups (P<0.0192). The extent of raised lesions is positively associated with third of non-HDL-C in regions 3, 5, and 6 in the 25- to 34-year age groups (P<0.0139).

In the RCA, the extent of fatty streaks is positively associated with third of non-HDL-C (Figure 3; for clarity, the results for the middle third are not shown) in all regions in the 25- to 34-year age groups (P<0.0254). The extent of raised lesions is positively associated with third of non-HDL-C in regions 1, 2, 3, and 6 in the 25- to 34-year age groups (P<0.0273), whereas regions 4 and 5 show a smaller increase (P<0.0565). The effects of non-HDL-C by region follow the same pattern in men and women (no interaction of sex and non-HDL-C).
HDL-C Effects by Region

In the abdominal aorta (results not shown), the extent of fatty streaks is negatively associated with third of HDL-C in all regions after age 25 years ($P<0.0269$) and in all regions except regions 4 and 5 in the 20- to 24-year age group ($P<0.0435$), with the decrease in region 5 being slightly smaller ($P=0.0561$). The extent of raised lesions is negatively associated with third of HDL-C in regions 2, 4, and 6 in the 25- to 29- and 30- to 34-year age groups ($P<0.0367$) and in region 3 in the 25- to 29-year age group ($P=0.0686$) and the 30- to 34-year age group ($P=0.0460$).

In the RCA, the extent of fatty streaks is negatively associated with third of HDL-C (Figure 4; for clarity, the results for the middle third are not shown) in all regions after age 25 years ($P<0.0203$); in regions 1, 3, and 5 in the 20- to 24-year age group ($P<0.0245$); and to a lesser extent in region 2 ($P=0.0575$). The extent of raised lesions is negatively associated with third of HDL-C in regions 2, 3, and 4 in the 25- to 34-year age group ($P<0.0629$). The effects of HDL-C by region follow the same pattern in men and women (no interaction of sex and HDL-C).

Smoking Effects by Region

In the abdominal aorta (Figure 5), the extent of fatty streaks is greater in smokers than nonsmokers in all regions except region 5 ($P<0.0442$) and is greater in smokers to a lesser degree in region 5 ($P=0.0882$). Smokers have more extensive involvement with raised lesions than nonsmokers in all regions after age 25 years ($P<0.0001$) and in all regions in the 20- to 24-year age group ($P<0.0282$), except region 2, for which the effect of smoking is less ($P=0.0651$). The effects of smoking by region follow the same pattern in men and women (no interaction of sex and smoking).

There are no statistically significant effects of smoking on either fatty streaks or raised lesions in any regions of the RCA (results not shown).

Hypertension Effects by Region

In regions 1, 4, 5, and 6 of the abdominal aorta, the extent of fatty streaks in hypertensive women is less than that in normotensive women ($P=0.0338$) (results not shown). This difference is probably due to the replacement of fatty streaks by raised lesions in the lesion-susceptible areas. In the 20- to 24-year age group, hypertensive blacks have a slightly greater extent of raised lesions than normotensive blacks in regions 5 and 6 ($P<0.0066$). In the 25- to 29- and 30- to 34-year age groups, hypertensive blacks have more extensive raised lesions than normotensive blacks in all regions ($P<0.0570$). The effects of hypertension are similar in men and women (no interaction of sex and hypertension).
In the RCA, the extent of fatty streaks is not associated with hypertension (results not shown). In the 25- to 29- and 30- to 34-year age groups, hypertensive blacks have more extensive raised lesions than normotensive blacks in all regions \((P<0.0200)\). Hypertensive whites also have more extensive raised lesions than normotensive whites, but the difference is not statistically significant. The effect of hypertension on raised lesions is similar in men and women except in regions 1 and 4, where the effect of hypertension is smaller in women than in men (interaction of sex and hypertension, \(P<0.0322\)).

**Effects of Risk Level Based on Combinations of Risk Factors**

We identified cases in subset 4 (Table 1) as “high risk” on the basis of their having the highest third of non-HDL-C, lowest third of HDL-C, smoking, and hypertension; and as contrasting “low risk” on the basis of their having the lowest third of non-HDL-C, highest third of HDL-C, not smoking, and normotension. These risk groups define the extremes of risk profiles on the basis of the 4 mutable risk factor variables included in this analysis. The extents of involvement with lesions in the low- and high-risk groups are shown in Figure 6. For abdominal aortic fatty streaks, within 5-year age groups, the differences in extent of involvement between high- and low-risk groups are statistically similar in all regions, except that the differences are less in region 6 for 15- to 19-year-old subjects and region 2 for 25- to 29- and 30- to 34-year-old subjects. For abdominal aortic raised lesions, the differences between the low- and high-risk groups are similar for regions 1 and 2 and for regions 3, 4, and 6. After age 25 years, the differences between the low- and high-risk groups are greatest for region 5, intermediate for regions 3, 4, and 6, and least for regions 1 and 2 \((P<0.0007)\).

For RCA fatty streaks, within 5-year age groups, the differences between the low- and high-risk groups are similar in all regions. For RCA raised lesions, the differences between the low- and high-risk groups are similar in regions 1, 2, 3, and 4 and in regions 5 and 6. The differences between the low- and high-risk groups become apparent after age 25 years \((P<0.0066)\). In the 25- to 29- and 30- to 34-year age groups, the differences are greater in regions 1, 2, 3, and 4 than in regions 5 and 6 \((P<0.0445)\).

**Relation of Lesion Extent in Selected Regions and Lesion Extent in an Entire Artery**

The correlation coefficients within 5-year age groups between extent of involvement with fatty streaks in the individual regions and extent of involvement with fatty streaks in the entire arterial segment are >0.66 \((P<0.0001)\) for the abdominal aorta and >0.78 \((P<0.0001)\) for the RCA. In the 25- to 29- and 30- to 34-year age groups, the correlation coefficients between extent of raised lesions in the individual regions and the extent of raised lesions in the entire artery are >0.44 \((P<0.0001)\) for the abdominal aorta and >0.69 \((P<0.0001)\) for the RCA. In the 25- to 29- and 30- to 34-year age groups, the correlation coefficients between extent of raised lesions in region 5 of the abdominal aorta and the entire abdominal aorta are >0.83 \((P<0.0001)\). In the 25- to 29- and 30- to 34-year age groups, the correlation coefficients between extent of raised lesions in region 2 of the RCA and the entire RCA are >0.89 \((P<0.0001)\).

Table 2 shows the extent of involvement with raised lesions, in both lesion-prone regions and the entire arterial segment, in the low- and high-risk 30- to 34-year age groups. The extent of involvement in each lesion-prone region and in each entire artery is lower in the low-risk group than in the high-risk group. However, the extent of involvement in a lesion-prone region (expressed as a percentage) may be substantially greater than in an entire arterial segment, as illustrated in the RCA, for which the percentage of surface involved in region 2 is about double the percentage of surface involved in the entire RCA. The estimates of risk factor effects on atherosclerosis, that is, the ratio of extent of involvement in high-risk individuals to that in low-risk individuals, are \(\approx25\%\) greater in lesion-prone regions than the estimates of risk factor effects on atherosclerosis in entire arterial segments.

**Discussion**

**Summary of Results**

Fatty streaks develop in a characteristic pattern in the abdominal aortas of 15- to 24-year-old persons, but only fatty streaks in an area on the dorsolateral intimal surface of the distal half are replaced by raised lesions in 25- to 34-year-old persons. Fatty streaks in the proximal half of the abdominal
aorta, like those in the thoracic aorta, rarely are converted to raised lesions during young adulthood. Fatty streaks develop in a characteristic pattern in the RCA of younger persons, and the distribution of raised lesions follows the same pattern. Elevated non-HDL-C and low HDL-C augment both fatty streaks and raised lesions in both arteries, but smoking augments fatty streaks and raised lesions only in the lower half of the aorta. Hypertension augments only raised lesions in both arteries.

**Comparison With Previous Results**

These results in the RCA are consistent with the lesion prevalence for 1-cm segments of the RCA reported in 1968 by Montenegro and Eggen.\(^29\) They also reported similar patterns of lesion prevalence for the left anterior descending and circumflex coronary arteries. Our results for the abdominal aorta also are consistent with many anecdotal observations on the distribution of fatty streaks and raised lesions in that artery.

**Implications for Relationship of Raised Lesions to Fatty Streaks**

Raised lesions do not appear to any appreciable extent in segments of the abdominal aorta or RCA that are not likely to have been involved by fatty streaks at younger ages. These observations are consistent with the presumed progression of fatty streak to fibrous plaque and other more advanced lesions under certain conditions (presence of the risk factors) and in certain locations (the lesion-prone areas).

Additional evidence supporting the progression from fatty streaks to raised lesions is derived from chemical, physical, chemical, histological, and electron microscopic studies.\(^30-36\) These results show a continuous process of transition from the simple fatty streak to the typical fibrous plaque and to other more advanced lesions. Until noninvasive methods are sufficient for diagnosing lesions in young persons, these gross, microscopic, and chemical observations provide the best evidence supporting the precursor-product relationship of fatty streaks and raised lesions that we can obtain.

Fatty streaks in some well-defined intimal areas, such as regions 1 and 2 of the abdominal aorta, almost never progress to raised lesions, whereas fatty streaks in other regions, such as region 5, are likely to progress to raised lesions. This difference in propensity of fatty streaks to progress to raised lesions provides an opportunity to compare the anatomic and physiological characteristics of these areas that might be associated with their divergent tendencies.

Most studies of the effects of flow-related variables have focused on the left coronary artery, which is geometrically more complex than the RCA, because the left coronary artery branches into the circumflex and left anterior descending arteries.\(^37\) Furthermore, the proximal portion of the left anterior descending coronary artery is well known to be the most frequent site of advanced and occlusive lesions in the coronary system. However, the results from the RCA presented here show that lesions follow a consistent pattern of localization in a coronary artery with less complex geometry. Whether nonlipid intimal thickening precedes the appearance of the fatty streak in the RCA as it does in the left anterior descending coronary artery is not known, because intimal thickening of the RCA has not been extensively mapped.

**Differential Effects of Risk Factors**

An atherogenic lipoprotein profile affects both types of lesions to about the same degree in both arteries. Plausible cellular and molecular mechanisms that are now available account for intimal lipid deposition and a subsequent chronic inflammatory and reparative reaction in the presence of elevated plasma LDL concentrations. These mechanisms involve oxidized LDL, the macrophage and its scavenger receptors, and inflammatory mediators.\(^38\) Variations in intimal macrophages, endothelial transport and modification of LDL, oxidants and antioxidants, and many other processes provide possible proximate causes for localization of lesions.

In contrast, smoking selectively affects atherosclerosis in the abdominal aorta at a younger age than in the coronary arteries. This observation is consistent with the well-known predisposition of smokers to peripheral arterial disease.\(^39\) However, because we have little knowledge about the mechanism by which smoking affects atherosclerosis, no physiological explanation of this selective effect is available.
Hypertension accelerates the formation of raised lesions where fatty streaks occur but is not associated with the appearance of raised lesions at sites where fatty streaks typically do not occur in younger persons. This observation suggests that hypertension accelerates the transformation of fatty streaks to raised lesions. As with smoking, the mechanism of the effect of hypertension is not known.

Regional Measurements Compared With Total Artery Measurements
The extent of involvement with fatty streaks and the extent of involvement with raised lesions after age 25 years in the entire abdominal aorta and in the entire RCA were associated with the extent of involvement in the lesion-prone regions. These results indicate that much of the information concerning the grossly detectable lesions is contained in the measurement of the extent of involvement for an entire artery. These findings validate the conclusions from studies of atherosclerosis conducted over the last 40 years that were based on measurements of entire arteries.

Estimates of risk factor effects based on measurement of atherosclerosis in the most vulnerable regions are $\approx 25\%$ greater than estimates of risk factor effects on atherosclerosis in entire arterial segments. The extent of involvement in an entire arterial segment may be substantially lower than in a selected small region, as illustrated by the high-risk group with 5.24% intimal surface area involved with raised lesions in region 2 of the RCA compared with 2.72% for the entire RCA. Because only a small part of an artery needs to be involved to cause clinical disease, some of these young adults probably are closer to the clinical disease threshold than we might anticipate on the basis of the results for an entire artery.

Limitations of Study
Because there is within-subject biological variation in the risk factor variables measured in serum, the single measurement available for each subject in this study reflects the long-term average less precisely than multiple measurements that are possible in living subjects. Hemodilution or hemoconcentration, either of which occurs in some subjects, introduces additional variation. These sources of additional variation are expected to reduce the observed association of the risk factors measured in serum with atherosclerotic lesions. Therefore, the associations reported here probably are underestimates of the true associations. We have found no reason why these postmortem measurements of risk factors should result in spurious overestimation of the relation of risk factors to atherosclerotic lesions.

Implications for Future Studies of Atherosclerosis
The propensity to develop atherosclerosis varies widely by region within the abdominal aorta and the RCA. Some regions are resistant to atherosclerosis, whereas others are lesion-prone. The topographic distributions of fatty streaks and raised lesions are similar in the RCA, with the first 2 cm of the artery being the most frequently involved. In contrast, in the abdominal aorta, a region on the dorsalintal intimal surface of the middle third (region 3) is prone to develop fatty streaks during the 15- to 24-year age span that do not become raised lesions, but a more distal region on the dorsalintal intimal surface (region 5) is prone to develop fatty streaks that are replaced by raised lesions later in life. These differences in the propensity of fatty streaks to become raised lesions among portions of the abdominal aorta should be taken into account in studies of the pathogenesis of atherosclerosis based on aortic tissues.

Implications for Prevention
The observations reported here showing that risk factor effects are greater in vulnerable regions of the coronary arteries and aorta reinforce the previously reported effects of risk factors on atherosclerosis in young persons. Although some fatty streaks (particularly those in the thoracic aorta and upper half of the abdominal aorta) do not progress, even in the presence of the risk factors, others are susceptible to progression to clinically significant lesions in the presence of $\approx 1$ of the established risk factors for adult coronary heart disease. At least as early as 15 years of age, and probably earlier, control of dyslipoproteinemia, blood pressure, and smoking should be implemented to retard the progression of atherosclerosis at vulnerable sites in the coronary arteries and aorta.

Acknowledgments
The PDAY Research Group
The investigators cooperating in the multicenter study “The Pathobiological Determinants of Atherosclerosis in Youth” and the grants supporting their activities are listed below.

Program Director: Jack P. Strong, MD, 1996 to present; Robert W. Wissler, PhD, MD, 1985 to 1996.
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Participating Centers, Principal Investigators and Coinvestigators, and Supporting Grants from the National Heart, Lung, and Blood Institute and Other Sources
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Baylor College of Medicine, Houston, Tex: Louis C. Smith, PhD (HL-33750).
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The University of Illinois, Chicago, Ill: Abel L. Robertson, Jr, MD, PhD; Robert J. Stein, MD; Edmund R. Donoghue, MD; Robert J. Buschmann, MD; Yoshihisa Katsura, MD (HL-33758).
Louisiana State University Medical Center, New Orleans: Jack P. Strong, MD; Gray T. Malcom, PhD; William P. Newman III, MD; Margaret C. Oalmann, DrPH; Richard E. Tracy, MD, PhD; Sulochana Y. Bhandaru, MD, MPH; Cynthia S. Zsembik, BS; DeAnne G. Gibbs, BS; Dana A. Troxclair, MS (HL-33746; HL-45720).
University of Maryland, Baltimore: Wolfgang Mergner, MD, PhD; Catherine Cole, PhD; J. Smialek, MD (HL-33752, HL-45693).
Medical College of Georgia, Augusta: A. Bleakley Chandler, MD; Raghunatha N. Rao, MD; D. Greer Falls, MD; Ross G. Gerrity, PhD; Benjamin O. Spurlock, BA; Kalish B. Sharma, MD; Joel S. Sexton, MD (HL-33772).
University of Nebraska Medical Center, Omaha: Bruce M. McManus, MD, PhD; Jerry W. Jones, MD (HL-33778).

The Ohio State University, Columbus: J. Fredrick Cornhill, DPhil; William R. Adrion, MD; Patrick M. Fardel, MD; Brian Gara, MS; Edward Herderick, BS; Larry R. Tate, MD (HL-33760, HL-45694). Southwest Foundation for Biomedical Research, San Antonio, Tex: James E. Hixson, PhD (HL-39913); Henry C. McGill, Jr, MD (gift from Peter and Beth Dahlberg).

The University of Texas Health Science Center at San Antonio, San Antonio, Tex: C. Alex McMahan, PhD; Henry C. McGill, Jr, MD; Yolanda Martinez, MA; Thomas J. Prihoda, PhD (HL-33749, HL-45719).

Vanderbilt University, Nashville, Tenn: Renu Virmani, MD; James B. Atkinson, MD, PhD; Charles W. Harlan, MD (HL-33770, HL-45718).

West Virginia University Health Sciences Center, Morgantown: Singanallur N. Jagannathan, PhD; James Frost, MD (HL-33748).

References

Effects of Coronary Heart Disease Risk Factors on Atherosclerosis of Selected Regions of the Aorta and Right Coronary Artery

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for the PDAY Research Group

Arterioscler Thromb Vasc Biol. 2000;20:836-845
doi: 10.1161/01.ATV.20.3.836

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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