Natural History of Aortic and Coronary Atherosclerotic Lesions in Youth
Findings From the PDAY Study

Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group

Pathology laboratories in nine cooperating centers collected arteries from 1532 persons 15 through 34 years of age who died of external causes, principally homicides, accidents, and suicides. A central laboratory stained the arteries and evaluated the atherosclerotic lesions. All of the aortas and about half of the right coronary arteries in the youngest age group (15 through 19 years) had lesions. The mean percent intimal surface involved by lesions, in 5-year age groups, increased from 15 through 34 years. Raised lesions increased with age in extent and prevalence in the aorta and the right coronary artery. Black subjects had more extensive fatty streaks than white subjects in all three arterial segments. Young women had more extensive fatty streaks in the abdominal aorta; young men had more in the thoracic aorta. Male subjects had more extensive and a higher prevalence of raised lesions than did female subjects in the right coronary artery. White and black subjects did not differ significantly in the extent of raised lesions. Among the three arterial segments, the right coronary had the least percentage of intimal surface involved with all types of lesions but had the highest proportion of raised lesions among total lesions. These results confirm the origin of atherosclerosis in childhood and show that the prevalence and extent of fatty streaks and fibrous plaques increase rapidly during the 15- through 34-year age span.

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In 1983, a group of pathologists and scientists organized a multicenter cooperative project to improve our knowledge of the natural history of atherosclerosis in childhood and young adulthood and to determine its association with the risk factors for adult coronary heart disease (CHD). The general hypotheses underlying this study are that aortic and coronary atherosclerosis begins in childhood; that it progresses during young adulthood to form the raised lesions responsible for clinically manifested atherosclerotic disease, particularly CHD, in middle age and later; that progression is associated with the risk factors for adult atherosclerotic disease; and that the cellular pathogenesis of and the risk factors associated with atherosclerosis are similar in men and women and blacks and whites. Because fibrous plaques are frequently present in the aorta and coronary arteries of 25-through 34-year-old US individuals and because these lesions are unequivocally linked to clinical disease, the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study focused on this decade and the immediately preceding decade, 15 through 24 years.

The landmark article of Enos et al published in 1953 and republished in 1986 describes the unexpected frequency of advanced coronary artery lesions in young US soldiers killed in the Korean War and focused the attention of the medical community on the presence of atherosclerosis in young persons. Subsequent reviews and the report of the National Cholesterol Education Program on blood cholesterol levels in children and adolescents continue to emphasize the importance of the development of atherosclerosis in children and youth.

The results of systematic, quantitative studies of lesions in children described the age of onset of fatty streaks and fibrous plaques in aortas and coronary arteries of autopsied subjects in New Orleans. Fatty streaks occurred in the aortas of all children after the age of 3 years and increased rapidly in extent during adolescence. Aortic fatty streaks were ubiquitous in children from many different populations, even from those that had a low prevalence of advanced atherosclerosis and CHD in adulthood. Coronary artery fatty streaks began about a decade later and increased steadily during late adolescence and young adulthood. Fibrous plaques were occasionally seen in the aortas and coronary arteries in teenaged years and increased in the third and fourth decades. These plaques and the more advanced lesions of atherosclerosis varied in extent and severity among the many human population groups studied and were consistent with CHD mortality.

In the PDAY study, medical scientists collected coronary arteries, aortas, other tissues, and selected data from persons 15 through 34 years of age examined postmortem at forensic centers in coroners' or medical examiners' laboratories and transmitted these data and materials to...
Subjects

Study subjects were persons 15 through 34 years of age who had died of external causes within 72 hours after injury and who were autopsied within 48 hours of death in one of the cooperating medical examiners' laboratories. Age, race, and cause of death were obtained from the death certificate. Data from coroners' reports, including the autopsy report, the report from emergency crews, and clinical histories, were used to determine those who did not meet study criteria. Persons of race other than black or white and those with congenital heart disease, Down's syndrome, AIDS, or hepatitis were excluded. Of the 1692 cases collected, 160 were excluded for the following reasons: death due to natural causes, 102; age less than 15 years or greater than 34 years, 23; race not white or black, 1; time between death and autopsy greater than 72 hours, 7; between event and death greater than 72 hours, 7; congenital heart defect, 4; hepatitis, 3; required information not available, 8; and incorrect tissue sampling, 5. Of the 1532 cases included in this report, thoracic aortas were obtained from 1519, abdominal aortas from 1500, and right coronary arteries from 1463. The arterial segments not collected were usually severely traumatized or were retained for medicolegal reasons.

Dissection and Preservation of Arteries

An autopsy technician removed the aorta from a point 2 cm proximal to the ligamentum arteriosum to a point 2 cm distal from the iliac bifurcation. Branching arteries were severed close to the aortic wall, and adventitial fat was removed by sharp dissection. The PDAY scientist opened the aorta along a line on the dorsal surface midway between the orifices of the intercostal and lumbar arteries, rinsed the intimal surface with Hank's modified balanced salt solution, and flattened it with the adventitial surface downward. The PDAY scientist then bisected the aorta longitudinally along a line on the ventral surface and midway between the intercostal and lumbar ostia, divided the right half for quantitative histological and micromorphometric studies as well as histochemical and chemical analyses, and placed the left half on a piece of cardboard with the adventitia downward. This latter half was covered with absorbent cotton and fixed in 10% neutral buffered formalin in a flat pan for at least 48 hours.

The PDAY scientist opened the right coronary artery, from its origin to the point at which it turned downward along the posterior interventricular sulcus, with blunt-pointed microdissecting scissors, dissected it from the heart, removed the epicardial fat, and fixed it in the same manner as the aorta. The remaining of the main branches of the coronary artery system was designated for pressure perfusion fixation and micromorphometric (circumflex branch).

The collection centers placed each aorta and coronary artery in a plastic bag and shipped them to the central laboratory each month. The central laboratory stained the arteries with Sudan IV. X-ray films of the arteries were obtained (Packer model 591, Kodak Ready Pack, RP-2, medical x-ray film at MAS, KV15, filter 2 for 20 seconds), and each artery was packaged with its identification number in a transparent plastic bag with a slight excess of 10% formalin.

Grading Arterial Specimens

Three pathologists, blinded to clinical or pathological observations and collection site, independently evaluated the stained and prepared right coronary arteries and left half of the aortas. They visually estimated the extent of intimal surface involved with fatty streaks, fibrous plaques, complicated lesions, and calcified lesions by procedures developed in the International Atherosclerosis Project (IAP). A fatty streak was a flat or slightly elevated intimal lesion stained by Sudan IV and without other underlying changes. A fibrous plaque was a firm, elevated intimal lesion, sometimes partially or completely covered by sudanophilic deposits. A complicated lesion was a plaque with hemorrhage, thrombosis, or ulceration. A calcified lesion was an area in which calcium was detectable, either visually or by palpation, without overlying hemorrhage, ulceration, or thrombus. The sum of the percentages of surface involved with fibrous plaques, complicated lesions, and calcified lesions by gross visual grading was designated "raised lesions." Visual evaluation of calcification is used in this report only for calculation of surface involved with raised lesions. Consensus grading of lesions was the average of the three independent gradings. Intraobserver variability was assessed by repeated independent gradings of coded specimens randomly interspersed among new specimens. For total percent intimal surface area involved, the intraclass correlation coefficients between pairs of pathologists ranged from \(.778 \text{ through } .945\). For the percent of surface area involved with raised lesions in the abdominal aorta and right coronary artery, the intraclass correlation coefficient ranged from \(.723 \text{ through } .925\). For involvement with raised lesions in the thoracic aorta, intraclass correlation coefficients ranged from \(.520 \text{ through } .800\).

The prevalence of cases with lesions was based on the recording by any one of the pathologists of any nonzero value of percent surface area involved for all lesion types except calcification. Prevalence of calcified lesions was based on evaluation of soft-tissue x-ray films because this measure is more accurate than gross visual grading.

The PDAY pathologists experienced in evaluating atherosclerosis regarded 5% of the intimal surface area
involved with raised lesions as biologically significant for
this age group. We applied this cut point to both total
surface area involvement and raised lesions. The preva-
lence of 5% or greater surface area involvement was
based on the consensus grading of lesions.

Statistical Analysis
The effects of sex, race, and 5-year age group on
percent surface area involved with lesions were ana-
yzed using analysis of variance. The linear model
included the effects of sex, race, 5-year age group, and
all two-factor interactions. We applied a logarithmic
transformation to the percentage of surface area in-
volved with lesions. A small constant (0.1) was added to
avoid the logarithm of zero. The transformation made
the data better able to satisfy the assumptions underly-
ing the statistical analysis. We analyzed the raised
lesions as a proportion of total lesions for those cases in
which total involvement was not zero. The prevalence of
cases having 5% or more of the intimal surface area
involved with lesions was analyzed using multiple logis-
tic regression. The linear model included the same
effects as the analysis of variance model.

Results

Cause of Death
The 1532 cases were compared by sex, race, age in
5-year age groups, and cause of death. The major cause
of death (accident, homicide, suicide, or other external
cause) differed among 5-year age groups (P<.001); amon
blacks the major cause of death was homicide, and
among whites, accidents (P<.001). The mean per-
cent intimal surface involvement with atherosclerotic
lesions did not differ significantly among the causes of
death for either total lesions or raised lesions within sex
or race groups (tables available upon request). There-
fore, all analyses were performed after pooling individ-
uals who had died of all causes.

Extent of Arterial Lesions
Table 1 shows the percent intimal surface area in-
volved with atherosclerotic lesions by sex, race, and
5-year age group for each arterial segment. Large stan-
dard deviations demonstrate the great individual vari-
ability among cases of the same age, race, and sex. There
were no significant interactions among age, race, or sex
in their effects on extent of lesions.

Mean percent area involved with total lesions in-
creased with age (P=.0001) and was greater in blacks
than in whites in all arterial segments (P<.01). Mean
total lesion area was greater in men than in women
for the thoracic aorta (P=.03), but was less in men than in
women for the abdominal aorta (P=.0001).

Mean percent area involved with raised lesions also
increased with age (P=.0001) but did not differ among
blacks and whites in any of the arterial segments. Mean
raised lesion area was greater in men than in women
in the right coronary artery (P=.0001).

Among arterial segments (Fig 1), the percent intimal
surface involved with all lesions was greatest in the
thoracic aorta and least in the right coronary artery for
every age, race, and sex group. However, the percentage
of surface involved with raised lesions was much less in
the thoracic aorta than in either the abdominal aorta or
the right coronary artery. In the oldest age group (30 through
34 years), among those whose total lesion involvement
was not zero, the proportion of lesion area made up by raised
lesions was greater in men than in women for the right
arterial segments.
Bar graphs showing percent of intimal surface involved with fatty streaks and raised lesions for the thoracic and abdominal aortas and the right coronary artery by sex, race, and 5-year age groups.

Prevalence of Arterial Lesions

Table 2 shows the prevalence of any atherosclerotic lesions and the prevalence of lesions involving more than 5% of the intimal surface. The only significant interaction (not shown in the table) was a race-by-age effect on raised lesions in the abdominal aorta (P = .0476) that was probably related to the lower prevalence of raised lesions in blacks than in whites among 15- through 19-year-old individuals.

All cases in this study had lesions in the abdominal aorta, and all except one white male had lesions in the thoracic aorta. Prevalence of lesions in the right coronary artery increased from about 50% in the youngest age group to about 75% in the 30- through 34-year-old age group (P < .001) and was greater in men than in women (P = .048).

The prevalence of lesions involving 5% or more of the arterial surface was greater in women than in men in the abdominal aorta (P = .012) and was greater in blacks than whites in the right coronary artery (P = .0018).

The prevalence of raised lesions, whether measured as any lesions or lesions involving 5% or more of the arterial surface, increased with age in all arterial segments of all sex and race groups. Prevalence of raised lesions by both measures was greater in the right coronary arteries of men than in those of women (P = .0007 and P = .0193, respectively), but there were no differences in prevalence between blacks and whites in the right coronary arteries.
We have no good explanation for these observations.

Variations Among Arteries

This report documents the lower prevalence and extent of raised lesions in the thoracic aorta in comparison with the abdominal aorta and the right coronary artery in all of the age, sex, and race groups. This report also documents the striking differences in the proportion of raised lesions to total lesions among the thoracic aorta, abdominal aorta, and the right coronary artery. We have no good explanation for these observations and are not aware of any reasonable hypotheses to explain the lesser involvement of the thoracic aorta than the abdominal aorta. We are also unaware of any documented evidence explaining the propensity of the coronary artery, although it has much less total involvement (extent) of lesions than the aorta, to have a greater proportion of raised lesions to total lesions (severity) than the aorta. The lower proportion of raised lesions to total lesions in the thoracic and abdominal aortas compared with the right coronary artery suggests that although atherosclerotic lesions begin at a later age in the coronary arteries, they may convert to clinically significant raised lesions at a more rapid rate.

Comparison With Previous Studies

The greater number of cases, particularly of women, in this study than in previous studies of young persons provides an opportunity to compare lesions by race and sex. Findings from this study, which is based on a sample of deaths drawn from several areas of the United States, are similar to many of the findings of studies based on deaths from a single area. The more extensive involvement of the aorta with fatty streaks in blacks than in whites has been reported in previous studies of New Orleans blacks.15

Table 3 shows the prevalence of lesions divided into fatty streaks, fibrous plaques, complicated lesions, and calcified lesions. Complicated and calcified lesions were rare among these cases, although all race-sex subgroups aged 30 through 34 years had some cases with calcified lesions in the abdominal aorta and the right coronary artery.

**Discussion**

**Progression of Atherosclerosis in Youth**

These results are consistent with the hypothesis that atherosclerotic lesions undergo substantial changes in extent and quality between 15 and 34 years of age. Aortic fatty streaks are universal by age 15 and increase rapidly in extent during the following decade. Raised lesions, which are principally fibrous plaques, appear in some individuals before 20 years of age, and they increase rapidly in extent and prevalence, particularly in the coronary arteries. The higher prevalence and greater extent of raised lesions in the coronary arteries of men compared with women precede the higher rate of CHD in middle-aged men compared with women.
Table 3. Prevalence of Fatty Streaks, Fibrous Plaques, Complicated Lesions, and Calcified Lesions by Sex, Race, and Age

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Race</th>
<th>Sex</th>
<th>Thoracic aorta</th>
<th>Abdominal aorta</th>
<th>Right coronary artery</th>
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<tr>
<td></td>
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<td></td>
<td>FS</td>
<td>FP</td>
<td>Comp</td>
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<tr>
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<td>Male</td>
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<tr>
<td>20-24</td>
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<td>Male</td>
<td>158</td>
<td>100</td>
<td>3.8</td>
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<tr>
<td>25-29</td>
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<td>Male</td>
<td>166</td>
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<td>10.8</td>
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<td>159</td>
<td>100</td>
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<tr>
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<td>Male</td>
<td>114</td>
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<td>Female</td>
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<td>Female</td>
<td>47</td>
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<tr>
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<td>Female</td>
<td>53</td>
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<tr>
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<td>46</td>
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<tr>
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<td>30</td>
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<tr>
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<td>Female</td>
<td>39</td>
<td>100</td>
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<tr>
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<td>Black</td>
<td>Female</td>
<td>47</td>
<td>100</td>
<td>23.4</td>
</tr>
</tbody>
</table>

FS indicates fatty streak; FP, fibrous plaque; Comp, complicated; Calc, calcified. Fatty streaks, fibrous plaques, and complicated lesions were determined by pathologists' evaluations of gross specimens. Calcified lesions were determined by evaluation of soft-tissue x-ray films.

Secular Trends

Although secular trends of atherosclerosis are beyond the scope of this report, the general pattern of development of lesions among male subjects is worthy of comment. In the IAP (1960 to 1964) and earlier studies of the natural history of atherosclerosis in New Orleans, white male subjects consistently had more extensive coronary artery raised lesions than did black male subjects. That pattern was altered in the community pathology study of atherosclerosis in New Orleans in the 1970s. In 25- through 44-year-old men, the extent of raised coronary lesions was approximately the same in black and white subjects. The results of comparisons with the IAP suggested that coronary atherosclerotic lesions had decreased in white men but had remained relatively stable in black men. While the present PDAY study subjects 15 through 34 years of age are from different geographic locations within the United States, the previously described racial differences in coronary lesions in black and white New Orleans men seen in studies in the 1950s and 1960s are not present. In fact, the white and black male PDAY subjects have similar prevalence and mean extent of raised lesions in the right coronary artery when evaluated by the grading system used in the New Orleans studies.

Determinants of Atherosclerosis

Although the exact mechanisms of atherogenesis have not yet been fully elucidated, risk factors for the development of CHD have been identified. Studies have documented the association of CHD risk factors to coronary artery and aortic atherosclerosis in adults. Until this PDAY study, however, little information was available regarding associations between serum risk factors and atherosclerosis in persons less than 25 years old except a small number of cases from the Bogalusa Heart Study. Clearly, the determinants of atherosclerosis begin to affect the coronary arteries during the third decade of life, and possibly earlier. At least some of these factors are serum lipoprotein cholesterol levels and smoking, as indicated by a preliminary report based on analysis of 390 men from this study. A subsequent report indicates that thickness of panniculus adiposus was associated with both total and raised lesions in the right coronary artery, and that glycohemoglobin was associated with total extent of lesions in the right coronary artery.

These results indicate that the topography of the lesions and the careful pathobiological studies that the PDAY program permits are likely to yield a rich harvest of additional valuable information. When the case numbers of women permit it, a detailed understanding of the effects of many of the risk factors in both sexes and the two races at the cellular and humoral arterial wall reaction level should be attainable.

Prevention of CHD

Prevention of adult CHD is likely to be most effective if control of the mutable risk factors begins in childhood or adolescence. Many of the risk factors originate in youthful behavior, with patterns of diet, physical activity, and tobacco use persisting from adolescence into adulthood; the earlier they begin, the more difficult it becomes to modify them. The results of this study clearly confirm the origin of atherosclerosis in childhood and its progression toward clinically significant lesions in young adulthood.

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Appendix: the PDAY Research Group

The investigators cooperating in the multicenter study, the Pathobiological Determinants of Atherosclerosis in Youth (PDAY), are listed below.
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