Intimal Thickening of the Coronary Arteries in Infants in Relation to Family History of Coronary Artery Disease

Jaakko Kaprio, MD; Reijo Norio, MD; Erkki Pesonen, MD; and Seppo Sarna, PhD

Background. Intimal thickenings of the coronary arteries of newborn children are composed mainly of smooth muscle cell proliferations. To investigate whether thickening of the intima in infants is associated with a family history of coronary artery disease (CAD), we studied the relation of coronary death of grandparents to intimal thickening of 136 infants.

Methods and Results. The length of internal elastic lamina of the artery and the areas of arterial layers in cross section were measured, and the arteries were transformed to idealized round circles. Intimal thickening was assessed as the degree of luminal narrowing (ratio of intimal area to the area on the luminal side of the arterial media). Among 136 infants, luminal narrowing varied between 0% and 58%. CAD deaths accounted for 108 of the total 281 deaths among the grandparents of the infants. Family history of CAD (defined as at least one CAD death among the four grandparents) was positive for 77 infants. Family history of CAD was significantly more common in the infants with luminal narrowing of both the left and right coronary arteries compared with the infants with no narrowing in at least one artery (odds ratio adjusted for sex, infection status, and age of infant, 5.69; 95% confidence interval, 1.46–22.2). After adjustment for sex and age, infants with both a positive family history and presence of infection had an increased degree of luminal narrowing compared with infants with a negative family history and no infection.

Conclusions. The association of coronary artery intimal thickening in infancy with family history of CAD suggests that intimal thickening is a morphological manifestation of predisposition to CAD. (Circulation 1993;87:1960–1968)

KEY WORDS • morphogenesis • arteriosclerosis • genetics

Clinical manifestations of coronary artery disease (CAD) first present in middle age, and the incidence of disease increases with age. However, the anatomic basis of atherosclerosis may already be present in childhood or possibly infancy. Even in newborn children, massive intimal thickenings of the coronary arteries are observed. Since these intimal thickenings apparently regress to some degree during childhood, it is not known whether the thickenings of the arteries seen in infants are precursors and predictors of adult atherosclerosis and whether they are genetically determined.

The intimal thickening of the coronary arteries in newborns is related to known risk factors for CAD. Male children have thicker inner vascular layers and a greater degree of luminal narrowing. Also, infants and children whose grandparents originate from ethnic areas with a high incidence of CAD have greater thickenings of the coronary arteries than children whose grandparents are from areas with low incidence. In this article, we investigate whether coronary artery thickenings in infants are associated with family history of CAD as assessed by the CAD mortality of their grandparents.

Methods

Samples of coronary arteries were obtained at 141 autopsies performed on infants who had died at <1 year of age from different causes at the Children's Hospital and Women's Hospital, University Central Hospital of Helsinki. These tertiary care hospitals treat patients from southern Finland, and almost all children who die in the hospital are autopsied. The only selection made, besides the age of the patient, was that the autopsy was made in 1970–1972 by one of the authors (E.P.) within 48 hours after death. Five infants were excluded from the present analyses because at least one parent was not born in Finland and thus, the death certificates of the grandparents were not available. Sixty-two infants had signs of infection at death. Infections were mainly bacterial, but four had viral infections (two herpetic infections, one hepatitis, and one mononucleosis). The mean±SD gestational age was 34.9±5.3 weeks, and the mean age at death was 31.1±63.2 days.

Both coronary arteries were sectioned semiserially at intervals of 200 μm. The section from each coronary artery with the greatest intimal thickenings, i.e., the
greatest area of the musculoelastic layer and intima, was 
chosen for morphometric studies. However, the samples 
taken close to the bifurcation were not accepted for 
morphometry. In the bifurcation, the arterial radius 
lengthens and the arterial layers cannot be cut trans-
versely. In this material, no sample was taken closer 
than 0.6 mm to the bifurcation. The outer radius of the 
arteries varied from 0.19 to 1.1 mm (mean, 0.56 mm)  
(Figure 1). The radii of the right and left coronary 
arteries and the thicknesses of the intima and media 
were measured. The total technical error of the method 
can be calculated to be about 5%.3 The methods of 
preparing the specimen and making the measurements 
have been described elsewhere.3,6 In brief, the areas of 
the arterial layers were measured with a coordinate 
digitizer. The circumference of the internal elastic lam-
ina at the boundary of the intima and media was 
measured and its radius computed. The collapsed artery 
was transformed mathematically into a dilated “physi-
ological” state, and the theoretical cross-sectional area 
of the artery on the luminal side of the media was com-
puted. The degree of narrowing of the artery was 
defined as the area of the intima on the luminal side of 
the arterial media divided by the computed luminal area 
of the artery (Figure 2).6

Previous analyses of data on coronary artery narrow-
ing in infants and children from Finland indicated that 
increased narrowing was found among boys.6 The pres-
ence of infection also was associated with an increased 
intimal thickening.7 Therefore, these variables were 
considered relevant concomitants of luminal narrowing 
to include in the analyses. Because most infants had 

FIGURE 1. Scatterplot shows distribution of left coronary artery radius (in millimeters) by age (gestational plus postnatal age) of the infant (individual points). Continuous line represents the linear regression equation of radius on age with 95% confidence limits for mean predicted values (dotted lines).

FIGURE 2. Schematic of idealized arterial cross section to 
demonstrate computation of luminal narrowing (ratio of 
intimal area to the original luminal area [π×radius²]). IEL, internal elastic lamina.
Table 1. Distribution of Families by Number of Grandparents Traced and Deaths From All Causes or From CAD

<table>
<thead>
<tr>
<th>No. of grandparents traced</th>
<th>No. of families</th>
<th>No. with at least one deceased grandparent</th>
<th>No. with at least one death from CAD</th>
<th>No. of CAD deaths among grandparents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Four</td>
<td>115</td>
<td>107</td>
<td>70</td>
<td>One: 47, Two: 17, Three: 5, Four: 1</td>
</tr>
<tr>
<td>Three</td>
<td>10</td>
<td>10</td>
<td>5</td>
<td>One: 4, Two: 1, Three: 0, Four: 0</td>
</tr>
<tr>
<td>Two</td>
<td>11</td>
<td>6</td>
<td>2</td>
<td>One: 2, Two: 0, Three: 0, Four: 0</td>
</tr>
<tr>
<td>Total</td>
<td>136</td>
<td>123</td>
<td>77</td>
<td>One: 53, Two: 18, Three: 5, Four: 1</td>
</tr>
</tbody>
</table>

died soon after birth, the total age of the infants (gestational plus postnatal age; mean±SD, 271.5±74 days; range, 140–568 days) was used in analyses.

As described earlier, the parents and grandparents of the infants had been identified. The vital status of the grandparents was determined from population registers. If the infant or one of his or her parents was born out of wedlock, one or more of the grandparents could not be traced. Mortality follow-up was complete up to November 1990. For those who had died, copies of death certificates were obtained from the Cause-of-Death Bureau of the Central Statistical Office. The death certificates were reviewed to check for information on CAD. A total of 281 grandparents had died. There were 108 subjects with coronary disease, of whom 39 (36%) had been autopsied. In 53 CAD deaths (49%), there was either a documented history of earlier hospitalization for myocardial infarction or an indication that clinical diagnosis of CAD was confirmed by ECGs and blood chemistry investigations or both. In the remaining 16 people, the diagnosis of CAD was based only on clinical examination before death in ambulatory care or on history only. For three deceased persons, no death certificate was obtained, and for one of them, follow-up time could not be computed because the date of death was unknown.

A family history of CAD was considered positive when at least one grandparent had died of CAD. If none of the deceased grandparents had died of CAD, the family history was considered negative. The mean±SD age of the grandparents at the end of follow-up was 69.4±11.3 years (range, 25.8–92.9 years). For those alive at the end of follow-up, it was 72.8±6.8 years (range, 56.4–87.4 years); the mean age of death for subjects with CAD was 69.4±11.6 years (range, 34.4–90.4 years), and the mean age of death for subjects without CAD was 64.8±14.1 years (range, 25.8–92.9 years).

The families were also classified by the birthplace of the grandparents to determine whether the family originated from an area with high or low CAD mortality rates. The subjects were called western or eastern if at least three of the grandparents were born in the western (low CAD mortality) or eastern (high CAD mortality) area of Finland.

Differences in luminal narrowing between the family history and positive family history infants were tested by ANOVA and ANCOVA to include concomitants associated with luminal narrowing. To examine whether infants with the greatest amount of narrowing had a positive family history of CAD more often than infants with the smallest luminal narrowing, the distribution of narrowing percentages was divided into tertiles with equal numbers of subjects. The odds ratio of positive family history of CAD in these tertiles was assessed by logistic regression analysis, which permitted modeling of concomitants (sex, age, and infection status). The statistical significance of the association between tertile of coronary narrowing and family history was assessed by comparing models without and with coronary narrowing; the change in model fit is χ² distributed. Data analysis was done with the SAS® and EGRET® software packages.

**Results**

**Family History of CAD**

A total of 136 infants and their grandparents were ascertained. Of the total potential 544 grandparents, 512 were traced (Table 1). At least two grandparents were traced from all families. In 115 families, all four grandparents could be traced; in 10 families, three grandparents were traced; and for 11 families, only two grandparents were traceable. In 77 families, at least one grandparent had died of CAD, and these families were considered positive for a family history of CAD. In 59 families, none of the grandparents had died of CAD, and these families were considered negative for family history of CAD. Table 1 also gives the number of CAD deaths per family by the total number of grandparents in the family. In one family, all four grandparents and in five families, three grandparents had died of CAD.

**Mean Luminal Coronary Artery Narrowing by Family History**

The left coronary artery had a mean luminal narrowing of 16.9% (range, 0–56.2%) (Figure 3). The mean luminal narrowing in the left coronary artery was 13.9% in infants with no family history of CAD compared with 19.3% in infants with a positive family history of CAD, a 1.4-fold statistically significant difference (p=0.014) (Table 2). Right coronary artery narrowing had a mean value of 11.9% (range, 0–58.3%) (Figure 4). For the right coronary artery, the infants with a positive family history did not have a significantly greater degree of arterial narrowing compared with infants with a negative family history (Table 2). Also, when the maximal luminal narrowing found in either artery was computed, no significant differences were found between positive family history and negative family history infants (Table 2). Luminal narrowing did not increase with the number of deaths from CAD in the families. There was no association of luminal narrowing in either artery with age at death from CAD of the grandparent (Pearson's correlation coefficient, r=0.004 [left artery] and r=0.04 [right artery]).
Kaprio et al  Coronary Thickenings in Infancy and Family History of CAD  1963

FIGURE 3. Scatterplot shows distribution of luminal narrowing of the left coronary artery in infants by age (gestational plus postnatal age). Open circles represent infants without a family history of CAD (no cases of CAD among the grandparents); stars represent infants with a positive family history (at least one grandparent who died of CAD).

Effect of Concomitants of Arterial Narrowing in Infants on Mean Luminal Narrowing
The correlation of total age (gestational age plus postnatal age) with arterial narrowing was 0.46 (p<0.01) for the right and 0.38 (p<0.02) for the left coronary artery (Figures 3 and 4). The sex difference was not statistically significant in this series. The presence of infection at the time of death was associated

Table 2. Mean Degree of Coronary Artery Narrowing of Infants by Family History of CAD in the Grandparents Before and After Adjustment for Age, Sex, and Infection Status

<table>
<thead>
<tr>
<th></th>
<th>Percent narrowing (mean±SEM) by family history of CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative history (n=59)</td>
</tr>
<tr>
<td>Left coronary artery</td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>13.9±1.6</td>
</tr>
<tr>
<td>Age</td>
<td>14.6±1.5</td>
</tr>
<tr>
<td>Age, infection status, and sex</td>
<td>15.1±1.5</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>10.5±1.8</td>
</tr>
<tr>
<td>Age</td>
<td>11.5±1.5</td>
</tr>
<tr>
<td>Age, infection status, and sex</td>
<td>11.6±1.5</td>
</tr>
<tr>
<td>Maximum value of right and left coronary arteries</td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>17.3±1.9</td>
</tr>
<tr>
<td>Age</td>
<td>18.2±1.6</td>
</tr>
<tr>
<td>Age, infection status, and sex</td>
<td>18.7±1.6</td>
</tr>
</tbody>
</table>

*Adjustment for concomitants by ANCOVA using PROC GLM in SAS. Tests for heterogeneity of variance between groups were nonsignificant.
FIGURE 4. Scatterplot shows distribution of luminal narrowing of the right coronary artery in infants by age (gestational plus postnatal age). Open circles represent infants without a family history of CAD (no cases of CAD among the grandparents); stars represent infants with a positive family history (at least one grandparent who died of CAD).

with a greater luminal narrowing of the coronary arteries. The mean age-adjusted luminal narrowing in the left coronary artery was 14.4% in infants with no infection compared with 19.5% in infants with infection ($p=0.0137$). The mean age-adjusted luminal narrowing in the right coronary artery was 10.6% in infants with no infection compared with 13.7% in infants with infection ($p=0.135$).

After adjustment by ANCOVA for sex, age, and infection status, the differences in mean arterial narrowing between infants with a positive family history and infants with no family history of CAD decreased (Table 2) and were statistically nonsignificant. When adjusted for sex and age, positive family history and presence of infection both increased the mean luminal narrowing in both arteries (Table 3). In a group with positive family history and infection, the mean left coronary narrowing was 20.9%, and in a group without infection and with a negative family history, the mean was 12.7%. In the right coronary artery, an effect of family history was evident only when no infection was present. However, the interaction term of infection status and family was not statistically significant.

The outer diameter of the arteries was not related to luminal narrowing. Variation in the outer diameter after adjustment for age did not correlate significantly with variation in luminal narrowing (left coronary artery partial correlation squared, 0.011; right coronary artery partial correlation squared, 0.031).

Family History of CAD by Presence or Absence of Coronary Artery Narrowing

Family history of CAD was significantly associated with the presence of coronary artery narrowing in the infant (Table 4). There were no infants without any luminal narrowing of the left coronary artery if they had a family history of CAD, whereas five of 59 infants

<table>
<thead>
<tr>
<th>Family history</th>
<th>Infection status</th>
<th>Left coronary artery narrowing (%)</th>
<th>Right coronary artery narrowing (%)</th>
<th>No. of infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>No</td>
<td>12.7†</td>
<td>8.7</td>
<td>36</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>16.0</td>
<td>12.0</td>
<td>38</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>17.5</td>
<td>15.5</td>
<td>23</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>20.9</td>
<td>12.1</td>
<td>39</td>
</tr>
</tbody>
</table>

*Adjustment for sex and age by ANCOVA using PROC GLM in SAS. Interaction terms of infection status and family history were statistically nonsignificant.

†$p=0.038$ no family history and no infection vs. family history and infection.
without a family history of CAD had no left coronary artery narrowing (odds ratio [OR], ∞; 95% confidence interval [CI], 1.24–∞). A significant change in the fit ($\Delta \chi^2$, 6.56; df, 1; $p<0.05$) of the logistic regression model was found when the luminal narrowing variable was added to a model with age, sex, and infection status. However, adjusted ORs for the left coronary artery could not be computed because of the sparse data with a structural zero cell. Three infants of 77 had no luminal narrowing of the right coronary artery but had a family history of CAD, whereas nine of 59 infants without a family history of CAD had no right coronary artery narrowing (OR, 4.39; 95% CI, 1.03–26.5). After adjustment for sex and infection status in a logistic regression model, a statistically significant association for the right coronary artery remained (OR, 4.16; 95% CI, 1.07–16.2), but further adjustment for age reduced the magnitude and statistical significance of the association (OR, 3.51; 95% CI, 0.87–14.2). A statistically significant odds ratio of similar magnitude was found when the left and right coronary arteries were considered together; presence of intimal thickening was defined as presence of luminal narrowing in both arteries, and absence was considered to be absence of narrowing in at least one artery (unadjusted OR, 6.87; 95% CI, 1.76–39.6). Adjustment for sex and infection status (adjusted OR, 6.39; 95% CI, 1.71–23.9) and for sex, infection status, and age (adjusted OR, 5.69; 95% CI, 1.46–22.2) only slightly weakened the observed association between coronary artery thickening and family history of CAD. The odds ratios for the combined-arteries measure were similar in both sexes and by infection status (tests for common odds ratios nonsignificant). The age of the grandparents at the end of follow-up was similar for infants with absence of luminal narrowing (mean, 71.0 years) and for infants with presence of luminal narrowing in both arteries (mean, 69.2, $p=0.18$).

**Family History of CAD by Tertiles of Coronary Artery Narrowing**

We next considered whether the association of coronary narrowing in the infant with family history of CAD is a result of only its presence or absence as analyzed above. Thus, we investigated whether the luminal narrowing in infants with any narrowing is also related to family history of CAD. In 81 infants (67.5%), the luminal narrowing was greater in the left coronary artery than in the right coronary artery, whereas in 37 infants (30.8%), the converse was true (two infants had equal amounts of narrowing in both arteries). The ORs of positive family history of CAD by tertiles of coronary narrowing are given in Table 5 for the sample after exclusion of subjects with no luminal narrowing. For the left coronary artery, the ORs increased by tertile nonsignificantly ($p=0.35$). For the right coronary artery, the change in model fit after coronary narrowing was included was statistically almost significant ($p=0.05$); the ORs in the middle and upper tertiles were 3.07 and 1.49, respectively, compared with the lowest tertile.

The ORs of positive family history of CAD by tertiles of coronary narrowing were also analyzed without exclusion of subjects with no luminal narrowing. For the left coronary artery, the ORs increased by tertile nonsignificantly ($p=0.06$) as assessed by the change in model fit after coronary narrowing was included: the ORs in the middle and upper tertiles were 1.88 (95% CI, 0.81–4.34) and 2.69 (95% CI, 1.15–6.28), respectively, compared with the lowest tertile. For the right coronary artery, the change in model fit after coronary narrowing was included was statistically significant ($p=0.01$); the ORs in

### Table 4. Family History of Coronary Heart Disease According to Presence or Absence of Luminal Narrowing of the Coronary Arteries in Infants

<table>
<thead>
<tr>
<th>Artery</th>
<th>Family history of CAD</th>
<th></th>
<th>Unadjusted odds ratio (95% confidence interval)</th>
<th>Odds ratio adjusted for age, sex, and infection status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Luminal narrowing</td>
<td>Luminal narrowing</td>
<td>Luminal narrowing</td>
<td>Luminal narrowing</td>
</tr>
<tr>
<td></td>
<td>absent</td>
<td>present</td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td>Left coronary</td>
<td>5</td>
<td>54</td>
<td>0</td>
<td>77</td>
</tr>
<tr>
<td>Right coronary</td>
<td>9</td>
<td>50</td>
<td>3</td>
<td>74</td>
</tr>
<tr>
<td>Both†</td>
<td>13</td>
<td>46</td>
<td>3</td>
<td>74</td>
</tr>
<tr>
<td>Boys</td>
<td>7</td>
<td>26</td>
<td>2</td>
<td>45</td>
</tr>
<tr>
<td>Girls</td>
<td>6</td>
<td>20</td>
<td>1</td>
<td>29</td>
</tr>
<tr>
<td>No infection</td>
<td>10</td>
<td>26</td>
<td>2</td>
<td>36</td>
</tr>
<tr>
<td>Infection</td>
<td>3</td>
<td>20</td>
<td>1</td>
<td>38</td>
</tr>
</tbody>
</table>

NA, not applicable.

* Adjusted odds ratio could not be computed because of a structural zero cell.

† Presence of luminal narrowing is defined as presence in both arteries; absence as no luminal narrowing in at least one artery. (There was only one subject with intimal thickenings absent from both arteries; family history of CAD was negative.)
Table 5. Odds Ratios for Family History of CAD by Tertile of Coronary Artery Measures

<table>
<thead>
<tr>
<th>Tertiles of narrowing</th>
<th>Cutoff points, %</th>
<th>No. of subjects*</th>
<th>Family history negative</th>
<th>Family history positive</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>Change in model fit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left coronary artery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.4-10.47</td>
<td>21</td>
<td>22</td>
<td>1.00</td>
<td>(\chi^2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10.5-19.8</td>
<td>19</td>
<td>26</td>
<td>1.32</td>
<td>0.56-3.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>20.1-56.2</td>
<td>14</td>
<td>29</td>
<td>1.90</td>
<td>0.79-4.73</td>
<td>2.13;</td>
<td></td>
</tr>
<tr>
<td>Right coronary artery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.6-3.6</td>
<td>22</td>
<td>19</td>
<td>1.00</td>
<td>(\chi^2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3.8-15.8</td>
<td>11</td>
<td>31</td>
<td>3.07</td>
<td>1.21-7.82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>16.1-58.3</td>
<td>17</td>
<td>24</td>
<td>1.49</td>
<td>0.61-3.65</td>
<td>5.93;</td>
<td></td>
</tr>
</tbody>
</table>

Change in model fit and odds ratio computed after adding measure variable to model including sex and infection status. Odds ratios, confidence intervals, and estimates of model fit using logistic regression analysis in EGRET.

*Subjects with no luminal narrowing in specified artery excluded from the analysis.

the middle and upper tertiles were 3.59 (95% CI, 1.49–8.85) and 2.52 (95% CI, 1.09–5.77), respectively, compared with the lowest tertile.

Geographical Origin and Family History of CAD

Ninety-two families could be classified by predominant area of birth of the grandparents, i.e., at least three of the grandparents having been born in either the eastern or western part of Finland (Table 6). Further division of the families by extremes of CAD mortality rates in the provinces of origin increased the regional differences in the prevalence of positive family history, although differences were not statistically significant. The distribution of the number of CAD deaths was not significantly different by geographic origin. Adjustment for geographic origin did not change the relation between family history of CAD and coronary artery luminal narrowing.

Discussion

Coronary artery disease clusters in families\(^{11-13}\) but does not segregate in a Mendelian fashion.\(^{14}\) Our results suggest that within families, thickening of the intima of the coronary arteries in infants is associated with CAD risk factors in the grandparents. The intimal thickenings are composed mainly of smooth muscle cell proliferations, which are a major component of the atherosclerotic plaque.\(^{15}\) Intimal thickness has been suggested to have an important role in the genesis of atherosclerosis.\(^{16-20}\) Significant thickening of the intima of coronary arteries starts in infancy\(^{1,2,5,21}\) and continues in young adulthood.\(^{30}\) The degree of thickening in children increases with age and is somewhat greater in boys than in girls.\(^{1,4,5,21}\) The degree of thickening in infants and children is also greater on average in families originating from eastern Finland, which has higher CAD mortality rates, than in those from western Finland.\(^{3,6}\) However, it has not been shown that family history of CAD is related to intimal thickening in infants.

Coronary heart disease in the grandparents was assessed on the basis of death certificate data. Of the CAD diagnoses on the death certificates, 15% were based on unreliable or undocumented diagnostic decisions. This proportion is comparable to that found in earlier mortality studies in Finland.\(^{3,6}\) There is no reason to believe that misclassification of coronary deaths would be associated with characteristics of the grandchild. Thus, the relative insensitivity and possible misclassification bias from using death certificate data would weaken a true association between the presence of CAD in the family and coronary intimal thickening in the infant. This source of bias is mitigated in part by using data from all grandparents to form the family history of CAD. Although only 55% of the grandparents had died by the end of follow-up, CAD was the most common cause of death (38% of all deaths). This proportion is close to the 30.5% of deaths attributed to CAD in Finland in 1984. Further mortality follow-up or clinical studies of the parents and grandparents would yield additional information for a more detailed classification of family history of CAD; however, very few of the parents would now have clinical manifestations of CAD.

The relation of intimal thickening with family history of CAD was analyzed by different statistical approaches. First, the mean intimal thickening of the arteries was greater in positive family history subjects. Second, the distribution of intimal thickening was investigated in relation to family history: a positive family history of CAD was significantly associated with any presence of
intimal thickening. This association remained statistically significant even after adjustment for concomitants of luminal narrowing. This was complemented by analyses by tertile of the distribution of intimal thickening, which indicated that even after the infants with no thickenings were excluded, higher ORs of family history of CAD were associated with a higher degree of thickening. The increased intimal thickening in families with CAD was greater for the left coronary than the right coronary artery, as is CAD.

The mean degree of luminal narrowing was adjusted for age, sex, and the presence of infection at the time of death. After adjustment, the observed associations between arterial intimal thickening and family history of CAD mostly weakened. If these concomitants were also to be intermediates in the process linking intimal thickening in infancy and CAD, adjustment for them could diminish the magnitude of a true association. Adjustment for developmental age (gestational age plus postnatal age) took into account variation in the development history of intimal structure. Although the outer diameter of the coronary arteries increases with age in infancy, arterial diameter did not correlate with age-adjusted degree of thickening in either the left or right coronary arteries.

Sex-related factors may be involved in the pathogenesis of atherosclerosis. In these infants, boys did not have more intimal thickening than girls on average, although this association has been reported.1,4,5,21 We have also observed a sex difference in coronary artery thickening in larger series6 in which older children are also included. This relates to the fact that Finnish men have high mortality rates from CAD,32 whereas rates among Finnish women are on a level found in Europe on the average.

A distinguishing feature of CAD epidemiology in Finland has been the increased incidence and mortality in eastern Finland compared with western Finland. This difference might be caused by both genetic and environmental differences. There are also east–west differences in the distribution of the major risk factors for CAD.32 Genetic origin is suggested by the findings that children from families originating in eastern Finland had higher total and low density lipoprotein (LDL) cholesterol levels than children of families from western Finland independently of current place of residence and type of diet.33

The dualistic immigration theory proposes that eastern and western Finns have somewhat different origins.34 According to this theory, the eastern immigrants come westward through the Lake Ladoga area, whereas the western part of Finland was settled by peoples coming north across the Gulf of Finland. Different archaeological and linguistic findings,34 anthropological characteristics,35 and dialects36 support the dualistic theory. Thus, the populations of eastern and western Finland might differ in genetic characteristics and tendency to develop CAD. In the present study, families of eastern Finnish origin tended to be CAD positive more often than families of predominantly western origin, but statistically significant differences were not found. Geographic origin of the grandparents did not modify the relation between family history and intimal thickening, which is well explained by small sample size. On the other hand, family history may be independent of geographic origin and the effect may operate equally in areas with both high and moderate CAD mortality.

Infections associate with intimal thickening.7 In the present analysis, in the subgroup of infants without infections, those with positive family histories had greater intimal thickening for both right and left coronary arteries. In the presence of infection, the relation of family history to intimal thickening was less clear. Although it could have been speculated that there is also genetic variation in how tissues react to injury, which thus contributes to the familial aggregation of CAD, the present results do not permit us to demonstrate this. The mechanism by which familial CAD is associated with the level of intimal thickening is not clear.

Investigations of the genetic basis of CAD have focused on the genetics of the major risk indicators for CAD, namely, on disturbances of lipid metabolism and hemostasis and on elevated blood pressure.14 Many genes involved in the underlying metabolic processes have been identified, and about 50% can be expected to be polymorphic.14 The apolipoprotein (apo) genes have been much studied in relation to quantitative risk factors for CAD, such as plasma LDL and high density lipoprotein cholesterol. Hixson37 demonstrated that among autopsied young (15–34-year-old) Caucasian men, apo E polymorphisms account for about 1% of the variability of all atherosclerotic lesions and about 3% of raised lesions (fibrous plaques, complicated lesions, and calcified lesions) of the right coronary artery. The amount of variance resulting from apo E structural variation did not decrease after adjustment for smoking or cholesterol levels.37 This suggests that apo E may affect the extent of atherosclerosis in young adults independently of its known effects on cholesterol levels, which may be explained by apo E's role in immunoregulation and modulation of cell growth and differentiation.38 There has been very little study of the genetic architecture of determinants of blood vessel structure. Some genes may code for proteins that are structural components of the affected tissues, such as the arterial intima, whereas others code for genes involved in determining response to injury. The present study suggests that there is variation in the structure of the coronary arteries already in infancy that appears to be related to familial risk of CAD.

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Intimal thickening of the coronary arteries in infants in relation to family history of coronary artery disease.

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