Detection and Quantitation of Calcific Atherosclerosis by Ultrafast Computed Tomography in Children and Young Adults With Homozygous Familial Hypercholesterolemia

Jeffrey M. Hoeg, Irwin M. Feuerstein, Eben E. Tucker

Abstract Ultrafast computed tomography (CT) is a new method for detecting calcific lesions in the coronary arteries. The ability of CT to detect and quantify coronary artery atherosclerosis in children and young adults at risk for malignant atherogenesis was evaluated. A total of 11 consecutive familial hypercholesterolemic (FH) homozygotes (3 to 37 years old) participated. Untreated total cholesterol concentrations were 488 to 1277 mg/dL (12.7 to 33.2 mmol/L). Angiography detected significant lesions in 7 of 11 patients. CT detected calcific atherosclerosis in all 9 of the patients older than 12 years of age, including all those with angina. CT was more sensitive in detecting aortic root and coronary ostial lesions, where atherosclerosis first appears in homozygous FH. The volume of calcification (in cubic millimeters) correlated with the severity and duration of the hypercholesterolemia \((r=.62, P<.05)\) as well as with the presence of angina \((P<.05)\). All patients with angina (7 of 7) had >150 mm³ of calcified volume, whereas only 1 of 4 asymptomatic patients had a volume score >150 mm³. We conclude that (1) coronary and aortic calcium phosphate deposits are common in young FH homozygotes; (2) these deposits are associated with the presence of angiographic stenoses, as has been seen in adults with coronary atherosclerosis; and (3) aortic calcific deposits are more common than calcific coronary lesions. (Arterioscler Thromb. 1994;14:1066-1074.)

Key Words • lipoproteins • familial hypercholesterolemia • atherosclerosis • computed tomography • diagnostic imaging

The inborn error in cholesterol metabolism that has provided the greatest insight into the role of low-density lipoprotein (LDL) cholesterol in human atherosclerosis is that of familial hypercholesterolemia (FH). More than 150 specific mutations in the LDL receptor gene have been identified that lead to deranged clearance of atherogenic, cholesteryl ester-rich LDL particles from the circulation.1 Patients heterozygous for this disease, in whom only one allele is affected, represent approximately 1 in 500 individuals in the population.2,2 However, the homozygous form of the disease is extremely rare. Fewer than 1 case is estimated to occur for each million births in the United States. Despite the rarity of this condition, investigation of homozygous FH has led to an array of insights into the pathophysiology of atherosclerosis, the role of LDL in cholesterol transport, the cellular process of receptor-mediated endocytosis, and treatment strategies to prevent cardiovascular disease.4

We have turned once again to patients homozygous for FH to address an emerging issue in the prevention and treatment of cardiovascular disease. Physicians are now encouraged to screen for patients likely to benefit from diet and drug therapy to prevent the development of atherosclerotic cardiovascular disease,5 most notably coronary artery disease (CAD). A variety of risk stratification recommendations have been made to attempt to effectively identify those patients most likely to benefit from treatment and to avoid needless intervention in asymptomatic individuals.5-7 The detection of coronary artery atherosclerosis by screening for calcific density with fluoroscopy was first suggested to be useful in 1927.8 Subsequent studies during the past 65 years have delineated the presence of coronary artery calcification of patients postmortem9-11 and radiographically12-19 and have correlated the severity of the coronary atherosclerosis and clinical events with the degree of calcification.9,13,14,17,19,22 Since medial calcific sclerosis does not involve the coronary arteries, calcifications in these vessels are diagnostic and pathognomonic for atherosclerosis. Using an ultrafast computed tomography (CT) scanner with a 100-millisecond acquisition time, 3-mm slice thickness, and 1-mm in-plane spatial resolution, it has been possible to quickly detect and quantitate coronary artery calcific deposits.23-26 Agaston and associates27 demonstrated that qualitative calcific plaque scoring of lesions has a specificity of 70% to 90%, a sensitivity of 71% to 74%, and a negative predictive value of 94% to 100% for symptomatic CAD in patients 30 to 69 years of age. Therefore, CT holds promise for assessing the atherosclerotic process in asymptomatic individuals.
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The children and young adults evaluated and treated for homozygous FH at the Clinical Center of the National Institutes of Health provide a population in which to compare methods to screen for atherosclerosis. We have undertaken a systematic analysis of the ability of ultrafast CT to detect and quantify atherosclerosis in children and young adults homozygous for FH.

Methods

Patients

Consecutive patients homozygous for FH (n = 11; 5 males, 6 females) participated in this study at the Clinical Center of the National Institutes of Health. These patients were diagnosed as having homozygous FH based on their plasma lipoprotein concentrations (Table 1), family history, and the presence of tuberous and tendinous xanthomata. The patients ranged in age from 3 to 37 years, with an average age of 21.8 ± 12 years. The average age at the time of diagnosis was 6.2 ± 6 years. Their fasting total and LDL cholesterol concentrations before treatment were profoundly increased. Patients >5 years of age underwent percutaneous coronary arteriography within 12 months of the CT study. Left heart catheterization and coronary arteriography were performed using standard techniques. Significant lesions were defined as those with >50% luminal diameter (or 75% luminal area) stenosis. The study was approved by the Institutional Review Board of the National Heart, Lung, and Blood Institute.

Lipoprotein Assays

The fasting total, LDL, and high-density lipoprotein (HDL) cholesterol concentrations were determined by enzymatic assays as outlined previously, and the concentration of lipoprotein(a) [Lp(a)] was determined by a sandwich enzyme-linked immunosorbent assay as previously described.

Because of the profound elevations in the concentrations of atherogenic lipoprotein particles, these patients have received a number of therapies, including a variety of hypolipidemic medications, ileal bypass, liver transplantation, LDL apheresis, and plasma exchange. The "cholesterol-years" score is an estimate of the lifelong total vascular exposure to the profound hypercholesterolemia in these patients. This cholesterol-years score was calculated as follows. The total cholesterol concentration (in milligrams per deciliter) of each patient at the time of original diagnosis was multiplied by the age of the patient at diagnosis. The total cholesterol concentration present in the patient after therapy was then multiplied by the number of years of treatment. The pretreatment and posttreatment cholesterol-years (mg-y/dL) were then added together for the total cholesterol-years score.

Ultrafast Scans

Ultrafast CT of the heart and thoracic aorta was done in all 11 patients. Scans were performed on the Imatron C-100XL CT scanner (Imatron Co). No intravenous contrast material was used. Scans were acquired using the 100-millisecond, high-resolution mode with table incrementation. Scan parameters were fixed at 130 kV and approximately 625 mA. A 26-cm reconstruction circle and 512 x 512 reconstruction matrix were used. Scans were cardiac gated, triggered at 80% of the RR interval for every other heartbeat. Each scan sequence was performed during a single breath hold of approximately 25 to 30 seconds. The upper thoracic aorta was scanned from above the arch down to the right pulmonary artery using 6-mm-thick contiguous sections. The coronary arteries, heart, and descending aorta were then scanned using 3-mm-thick contiguous sections starting at the right pulmonary artery and scanning caudally for 40 slices. Additional sections were added as needed to scan completely through the heart and descending thoracic aorta.

Calcification scoring of the coronary arteries and aorta was done at the Imatron console using standard ultrafast CT quantification schemes, with minor modifications tailored to address the calcific lesions in the aortic root. A calcification was defined as an area with at least four contiguous pixels (1 mm²) in any given slice having density values ≥ 130 Hounsfield units (HU). Detection of the appropriate pixels was facilitated by the identify function, which brightly highlights all pixels within the desired density range. Each calcified area was evaluated by two different techniques. First, a commonly used index of the relative severity of calcification, termed the calcification score, was calculated as the product of the area of calcified tissue (HU ≥ 130) multiplied by a weighting density factor (1+, 130 to 199 HU; 2+, 200 to 299 HU; 3+, 300 to 399

### Table 1. Characteristics of Children and Young Adults With Homozygous Familial Hypercholesterolemia

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y</th>
<th>Sex</th>
<th>Age at Diagnosis, y</th>
<th>Untreated Cholesterol Concentration, mg/dL</th>
<th>Cholesterol-Years, mg-y/dL</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total</td>
<td>LDL</td>
</tr>
<tr>
<td>1</td>
<td>3</td>
<td>M</td>
<td>1</td>
<td>724</td>
<td>672</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>F</td>
<td>&lt;1</td>
<td>888</td>
<td>841</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>M</td>
<td>4</td>
<td>578</td>
<td>535</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>F</td>
<td>1</td>
<td>906</td>
<td>795</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>M</td>
<td>4</td>
<td>969</td>
<td>641</td>
</tr>
<tr>
<td>6</td>
<td>18</td>
<td>M</td>
<td>2</td>
<td>1277</td>
<td>1153</td>
</tr>
<tr>
<td>7</td>
<td>27</td>
<td>F</td>
<td>3</td>
<td>612</td>
<td>572</td>
</tr>
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<td>9</td>
<td>34</td>
<td>M</td>
<td>21</td>
<td>711</td>
<td>536</td>
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<tr>
<td>10</td>
<td>35</td>
<td>F</td>
<td>9</td>
<td>740</td>
<td>534</td>
</tr>
<tr>
<td>11</td>
<td>37</td>
<td>F</td>
<td>12</td>
<td>713</td>
<td>650</td>
</tr>
</tbody>
</table>

Mean ± SD 21 ± 12 6 ± 6 782 ± 219 671 ± 198 32 ± 10 27 ± 18 52 ± 49 12 668 ± 6 349

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol; and Lp(a), lipoprotein(a).
of the altered scan parameters to detect coronary calcification, scans from 24 patients >40 years old were obtained. Consecutive patients were obtained except in the group aged 20 to 29 years, in which random, nonconsecutive patients were sought to compensate for the low number of patients obtained by chance. For each, a visual extent of lesions score was calculated for both the aorta and the coronary arteries.

For illustrative purposes, three-dimensional images were constructed and compared with angiography for selected cases. The axial Imatron scans were transferred to a Voxeloscope II three-dimensional imaging work station (Picker International). The coronary arteries and ascending aorta were separated (disarticulated) from the surrounding, overlying tissues. Rendering windows were chosen to eliminate surrounding fat. The internal coronary artery calcifications were imaged through the arterial walls using the transparency function, and the final image was photographed.

Results

Laboratory Findings

The clinical characteristics of the patients participating in this study are detailed in Table 1. The concentrations of plasma lipoproteins were strikingly altered in these patients. The average total and LDL cholesterol concentrations were more than threefold higher than the “desirable” concentrations outlined by the Adult Treatment Panel of the National Cholesterol Education Program. 5 In addition, HDL cholesterol was depressed. Therefore, the average ratio of total cholesterol to HDL cholesterol of 27 was more than fivefold higher than for average cardiovascular disease risk. The concentration of Lp(a), a lipoprotein particle proposed to be prothrombogenic, 31-33 ranged from 0 to 132 mg/dL. Two thirds of the population has concentrations of <20 mg/dL, whereas 6 of 11 of these patients exceeded this concentration. The cholesterol-years scores, which integrate the lifetime cholesterol exposure over the varying levels before and after therapy, spanned a wide range, from 2172 to 23 170 mg-y/dL (56.5 to 602.4 mmol-y/L), with a mean score of 12 668 (329.4 mmol-y/L). Since most of the total cholesterol concentrations of these patients were carried in LDL, this score largely reflects the exposure of the vasculature to this atherogenic lipoprotein particle.

Coronary Artery Assessment

All patients >5 years of age underwent cardiovascular evaluation by both cardiac catheterization and CT. One 3-year-old boy underwent CT only. The data are divided into coronary artery analysis in this section and aortic analysis in the next section. Coronary artery lesions were detected by both angiography and CT (Table 2). Of the patients catheterized, 7 of 10 were positive for significant obstructive lesions that reduced the coronary artery lumen by >50% cross-sectional diameter (or 75% luminal area). CT was positive for significant coronary calcification in 5 of 7 patients with angiographic stenosis. The 2 of 7 missed by CT were both <15 years old, and 1 was asymptomatic. One of the 3 patients with arteriograms negative for significant CAD had 71 U of calcium on CT. Since CT is more sensitive for coronary artery calcium than cardiac fluoroscopy, this is considered significant, representing preocclusive atherosclerosis.
Table 2 includes CT measures of coronary artery calcification scores. For the FH patient population the score was $65 \pm 102$, and the volume of calcification was $131 \pm 290 \text{mm}^3$. Means for control subjects were both 0 ($P<.001$, unpaired t test). The severity of the calcification lesions defined by both the calcification score and the calcified volume score was significantly higher ($P<.05$, Wilcoxon rank sum test) in those patients with angiographically evident CAD ($91 \pm 120$ and $197 \pm 355 \text{mm}^3$, respectively) than in those without lesions ($18 \pm 35$ and $20 \pm 32 \text{mm}^3$, respectively). Four of $11$ ($36\%$) of the total group and 4 of 7 ($57\%$) of the patients with angina had elevated coronary artery calcification scores. The 3 of 7 patients with angina and low CAD scores had heavy aortic root and ostial calcification, however (see below).

Although a systematic, lesion-by-lesion comparison between arteriography and CT was not performed for all coronary arterial lesions, for specific cases direct comparisons were made. For example, the three-dimensional images of the coronary artery anatomy of patient 8 by CT and by angiography have been directly compared (Fig 1). The coronary artery lesions resulting in $>50\%$ luminal diameter stenosis defined by angiography and those of CT correlate well, although the degree of stenosis can be determined only on the arteriograms.

The extent of nonocclusive atherosclerosis and marked right and left ostial plaque were clearly more evident on the CT image than on the angiographic image.

**Aortic Root Findings**

The analysis of calcific arterial lesions by CT was particularly effective for detecting and quantitating the severity of lesions in the coronary ostia and in the aorta (Fig 1A, Table 2). Quantitation of these lesions by both the calcification score and the extent of lesion score indicated that the burden of overall vascular disease was largely in the ascending aorta, particularly in the aortic root. The aortic root calcification score in FH patients was $586 \pm 732$, and the calcified volume of lesions was $499 \pm 576 \text{mm}^3$. This is compared with control CT scans from 29 age-matched (<40 years old), non-FH patients, 28 of whom had total and calcified volume scores of 0 ($P<.0001$, unpaired t test). Only one 34-year-old woman was found to have any calcific lesions using these methods, and she had an aortic lesion score of 2.

The distribution of calcifications appears to be predictable and age related in these patients. The pattern is centrifugal, in that with increasing age the burden of calcification becomes more prominent distally, moving from the aorta and coronary ostia into the coronary arteries (Fig 2). The greatest degree of calcification defined by both the calcification score and the calcified volume score was observed in the ascending aorta, particularly in the ostial and paraostial regions, and the total calcified volume is largely a reflection of aortic lesions (Table 2). Seven of the 8 patients (88%) with detectable calcium demonstrated more calcification in the aorta than the coronary arteries. The other patient was unusual in that his cholesterol levels were extremely well controlled, and in that regard he was more like the general population than a patient with FH (patient 9, Table 1). Similarly, in 7 of 8 patients with calcified lesions, at least half the calcification was in the ascending aorta and the lumen of the aorta and coronary ostia was not significantly blocked. Only one patient with FH (patient 6), had extensive calcification in the ascending aorta and the coronary ostia. The effect of age is also shown by Table 2. The youngest 6 patients had no coronary calcification, their disease clearly showing preference for the aortic root and coronary ostia. Only after age 20 do patients begin to show significant calcification and extent of lesion scores in the coronary arteries themselves.

Calcified lesions were seen by CT only in patients aged $\geq 13$ years. In those younger, CT was negative in the only patient with known CAD. The number of patients aged...
FIG 1. Identification of calcific atherosclerosis by ultrafast computed tomography (CT) (A) and by cardiac catheterization (B). Lesions were observed using both techniques. The coronary artery lesions resulting in >50% luminal diameter stenosis of the right coronary artery as defined by angiography in the left anterior oblique position are highlighted by the solid, curved white arrows (B). The three-dimensional image of the heart of this same patient in the same orientation was able to place calcification of these same stenotic lesions, again highlighted by the solid curved white arrows (A). A lesion that partially encroached on the lumen as seen by angiography was also detected by CT (straight white arrow). However, the extent of nonocclusive atherosclerosis was more fully evident in the CT image than in the anglographlc image, since ultrafast CT detected calcific lesions in both the right coronary artery and the coronary ostia (A; open arrows), which are not apparent by coronary arteriography. In the angiogram, for example, there is a hint of luminal irregularity that does not reach critical stenosis (B; short, solid arrow) but is detected by CT.

<13 years was too small to analyze, but it remains to be determined whether CT can successfully detect atherosclerosis in this younger age subpopulation.

Relation of CT Findings to Clinical Parameters

The correlation coefficients of the CT findings with atherosclerotic risk factors are illustrated in Table 3. The best correlation with CAD scores was with the age of the patient ($r=.62$, $P<.05$). Even in these profoundly hypercholesterolemic patients, the total and LDL cholesterol concentrations at the time of initial diagnosis were not highly correlated with CAD scores. Calcifications became apparent in the coronary arteries by age 13 and increased through the 20s and early 30s (Fig 3). This apparent lack of correlation was affected by the low calcification score in patient 11, the oldest patient in this study. This patient may not be entirely representative, since she had received partial ileal bypass surgery as a child and had experienced a 23% reduction in her total cholesterol concentration from this procedure.

The degree of calcific atherosclerosis in the ostia and aortic root was particularly striking in these homozygous FH patients. Since normolipidemic children and young adults have aortic calcification scores of 0, these data indicate that profound hypercholesterolemia leads to more marked lesion formation in the aortic root than in the coronary arteries. The best correlations between the severity of calcific atherosclerosis in the ostia (Fig 4) and with the total calcified volume (Fig 5) was the cholesterol-year score. This was more significant than the correlation of the other potential modifiers of the atherosclerotic process, including HDL and Lp(a). The HDL cholesterol concentration in these patients was low, with a mean concentration of $32\pm10$ mg/dL ($0.83\pm0.26$ mmol/L). But even with the range of HDL concentrations from 17 to 56 mg/dL ($0.44$ to $1.46$ mmol/L), the HDL cholesterol concentration and the ratio of total cholesterol to HDL cholesterol were not well correlated with the development of lesions. Lp(a), a lipoprotein particle that may promote intravascular clot formation, ranged in concentration from 0 to 132 mg/dL in this patient population. Despite this wide range, there did not appear to be any correlation between this particle concentration and calcific lesion formation.

The presence of aortic lesions by CT correlates well with the presence of symptomatic cardiovascular disease. The aortic calcification score for the patients with symptoms ($1201\pm1040$) was much higher than in asymptomatic patients ($129\pm154; P<.05$). In contrast, the degree of coronary calcification does not correlate as
TABLE 3. Correlations of Computed Tomographic Findings With Atherosclerotic Cardiovascular Disease Risk Factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>CAD</th>
<th>Ostia</th>
<th>Aortic Root</th>
<th>Total</th>
<th>CAD</th>
<th>Ostia</th>
<th>Aortic Root</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
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<td>.41</td>
<td>.36</td>
<td>.29</td>
<td>.39</td>
<td>.51</td>
<td>.40</td>
<td>.45</td>
</tr>
<tr>
<td>TC</td>
<td>-.47</td>
<td>.09</td>
<td>.29</td>
<td>.63*</td>
<td>-.49</td>
<td>.02</td>
<td>.26</td>
<td>.38</td>
</tr>
<tr>
<td>LDL</td>
<td>-.54</td>
<td>-.23</td>
<td>.01</td>
<td>.46</td>
<td>-.46</td>
<td>-.26</td>
<td>-.02</td>
<td>.20</td>
</tr>
<tr>
<td>HDL</td>
<td>.12</td>
<td>.23</td>
<td>.18</td>
<td>-.16</td>
<td>-.01</td>
<td>.17</td>
<td>.17</td>
<td>-.11</td>
</tr>
<tr>
<td>TC/HDL</td>
<td>-.32</td>
<td>-.24</td>
<td>-.05</td>
<td>.48</td>
<td>-.27</td>
<td>-.22</td>
<td>-.06</td>
<td>.28</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>-.23</td>
<td>.07</td>
<td>.11</td>
<td>-.12</td>
<td>-.14</td>
<td>.08</td>
<td>.10</td>
<td>.09</td>
</tr>
<tr>
<td>Cholesterol-years</td>
<td>.45</td>
<td>.54</td>
<td>.55</td>
<td>.59</td>
<td>.17</td>
<td>.62*</td>
<td>.56</td>
<td>.62*</td>
</tr>
</tbody>
</table>

Regression analysis $r$ values are given for total (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol concentrations, TC/HDL ratio, and lipoprotein(a) [Lp(a)] levels vs coronary artery (CAD), ostial, aortic, and total calcific atherosclerosis defined by computed tomography (CT).

*Significant correlation ($P<.05$) by linear regression analysis.

Discussion

The most profoundly elevated concentrations of LDL are present in individuals totally lacking functional LDL receptor genes. These patients homozygous for FH have been noted to have angina pectoris, aortic stenosis, supravalvular aortic stenosis, aortic insufficiency, and sudden cardiac death as children and young adults. The most aggressive forms of therapy, including plasma exchange, LDL apheresis, and liver transplantation, have been successfully applied to patients experiencing the most aggressive form of this disease. Therefore, early detection of aggressive atherosclerosis in these patients would permit the application of experimental therapy before the signs and symptoms of atherosclerosis develop. The use of a noninvasive technique would permit the detection and sequential evaluation of these patients prone to early cardiovascular disability and death.

One means of screening for accelerated atherosclerosis is to detect lesions that have become calcified. Although patients could be categorized as being either positive or negative for coronary calcification by fluoroscopy, digital subtraction fluoroscopy, fluoroscopy plus cineangiography, and conventional CT, the ability to accurately detect and quantitate lesions became available only with the use of ultrafast CT in 1989. Subsequently, a number of reports have demonstrated that ultrafast CT, which acquires images in 100 milliseconds gated to the electrocardiogram, is a sensitive technique for detecting coronary artery calcification as well as for quantitating the degree of lesion calcification. The major focus of these efforts was to compare CT-defined lesions with those seen at coronary angiography, with the implicit assumption that a noninvasive coronary angiogram could be developed. Agatston et al reported that for 110 healthy individu-
been determined. Further investigation is required to determine the evaluable age range for CT efficacy has not yet been established.

Lesions in children and young adults begin with lipid deposition in children and young adults. The lower limit of the age range for CT efficacy has not yet been established. This technique only detects a portion of advanced, mature lesions. Our young-age cohort who manifested CAD had substantially higher scores than the asymptomatic patients. Therefore, coronary calcified lesion scoring is indeed a discriminator for the presence of angina. An additional hypothesis is that, at some point, calcification should be predictive for development of angina in those FH patients who have not yet developed symptoms. On the other hand, the correlation between density of calcification and degree of occlusion for a specific lesion is weaker, and CT cannot replace angiography to evaluate the degree of luminal obstruction. Furthermore, the calcified lesions may not reflect lesions prone to rupture. Therefore, CT should be considered complementary in the detection of atherosclerotic plaque. This is clinically relevant because the formation of these calcified lesions appears to presage the development of symptomatic coronary artery disease in FH patients (Fig 6). These findings then shift the emphasis and goals of noninvasive imaging strategy in FH patients. Previously, asymptomatic patients were evaluated using magnetic resonance imaging and ultrafast CT as surrogates for arteriography. Instead, these findings suggest that CT is a complementary technique to detect the atherosclerotic process during its "silent," presymptomatic stage.

Some limitations inherent in the present study limit the generalizability of these findings. First, the striking aortic atherosclerosis that these patients manifest may not be representative of more common forms of atherosclerosis. However, the limited number of calcific lesions detected in the control group suggests that this is not commonly detected. Only additional investigation with this technique will reveal the utility of aortic root screening in more common clinical contexts. Another limitation is that only calcific lesions are detected with this technique. Atherosclerosis begins with lipid deposition in children and young adults in the general population, and only later are calcific changes seen. Therefore, this technique only detects a subpopulation of advanced, mature lesions. Our youngest patient with angiographically defined obstructive CAD had no calcifications at CT, presumably due to an immature, noncalcified, "soft" plaque. The lower limit of the age range for CT efficacy has not yet been determined. Further investigation is required to prospectively evaluate the prognostic and clinical utility that detection of advanced lesions signifies for the prevention of cardiovascular disease sequelae.

Our findings in young patients homozygous for FH have a number of both theoretical and practical ramifications. We have observed that the earliest indication of accelerated atherosclerosis is in the aortic root and at the coronary ostia, evidenced by localized predominance in the younger subset of patients. This focuses enhanced attention on the aorta, which contrasts with most previous work that has concentrated on the coronary artery lesions. Although aortic calcification has long been known to occur, these are the first data to suggest that screening patients for a diathesis toward malignant atherosclerosis is best directed toward identifying and quantitating calcific aortic atherosclerotic plaque. This is clinically relevant because the formation of these calcified lesions appears to presage the development of symptomatic coronary artery disease in FH patients (Fig 6). These findings then shift the emphasis and goals of noninvasive imaging strategy in FH patients. Previously, asymptomatic patients were evaluated using magnetic resonance imaging and ultrafast CT as surrogates for arteriography. Instead, these findings suggest that CT is a complementary technique to detect the atherosclerotic process during its "silent," presymptomatic stage.

A second practical issue relates to the therapeutic decisions that must be made in these homozygous FH patients. Previous novel treatment attempts for this disease were restricted to patients with severe end-stage cardiovascular disease. Liver transplantation, for example, was attempted only in homozygous FH patients who were close to death. Therefore, the use of a CT-derived score could facilitate the identification of patients likely to develop the sequelae of hypercholesterolemia before myocardial infarction. In addition, the CT lesion score will facilitate the treatment of FH patients with more conventional methods. Since plasma exchange and LDL apheresis are the current treatments...
of choice for this disease, the timing related to insti-
tuting these costly and time-consuming procedures may
be facilitated using the CT results. Ultrafast CT pro-
vides an independent means by which the calcium in
nonocclusive lesions could be quantitated, providing
additional information about the overall burden of
atherosclerosis not available by fluoroscopy or angiog-
raphy. Once the calcified volume exceeds 150 mm³ (Fig
6), the probability of developing angina markedly in-
creases, and efforts at aggressive treatment would be of
benefit. Assessment of other treatment modalities in
these patients, such as liver transplantation, porto-
caval shunting, and gene therapy, could also benefit
from the use of CT. The calcification score could not
only help to select patients for treatment protocols but
might also be a means of assessing the impact of therapy
on the rate of progression (changing the slope of the
regression lines in Figs 4 and 5) or the regression of
atherosclerotic lesions.

One of the most interesting theoretical developments
that emerged from this study is the utility of cholesterol-
year risk. The most significant predictor of the severity
of the coronary artery calcification score was age; the
total plasma cholesterol concentration did not signif-
ically correlate with calcific lesion formation (Table 3).
However, by combining these two variables into a single
formula, one integrates the lifelong endothelial ex-
posure to atherogenic lipoproteins, which not only im-
proves the statistical correlation (Figs 4 and 5) but also
has biologic plausibility. Using this concept, calcific
atherosclerosis does not appear below an apparent
threshold of <7000 cholesterol-years (182.0 mmol·y/L).
Of course, atheromatous plaque formation most likely
occurs long before sufficient calcium has been deposited
to be detectable by CT. However, it may become useful
to extend the concept of cholesterol-year as well as the
technique of ultrafast CT beyond homozgyous FH.

References
1. Hobbs HH, Brown MS, Goldstein JL. Molecular genetics of the
LDL receptor gene in familial hypercholesterolemia. Hum
2. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky
AG. Genetics of hyperlipidemia in coronary heart disease. Trans
3. Hazzard WR, Goldstein JL, Schrott HG, Bierman EL. Hyperlipidemia in coronary heart disease. III: evaluation of
lipoprotein phenotypes of 156 genetically defined survivors of myo-
Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The Metabolic Basis
Co; 1989:1215-1250.
5. Report of the National Cholesterol Education Program Expert
Panel on detection, evaluation, and treatment of high blood cho-
7. Assmann G. At what levels of total low- or high-density lipoprotein
cholesterol should diet/drug therapy be initiated? European guide-
lines: West Germany. Am J Cardiol. 1990;65:11F-15F.
8. Lenk T. Rontgendiagnose der koronarsklerose in vivo. Fortschr
1961;7:41-49.
11. Frink RJ, Achor RWP, Brown AL, Kincaid OW, Brandenburg
RO. Significance of calcification of the coronary arteries. Am J
12. Warburton RK, Tampas JP, Soule AB, Taylor HC III. Coronary
artery calcification: its relationship to coronary artery stenosis
13. Hambly RI, Tabrah F, Wisoff BG, Hartstein ML. Coronary artery
calcification: clinical implications and angiographic correlates.
Am Heart J. 1974;87:556-560.
14. Bartel AG, Chen JT, Peter RH, Behar VS, Kong Y, Lester RG.
The significance of coronary calcification detected by fluoroscopy.
15. Aldrich RF, Brenske JF, Battaglini JW, Richardson JM, Loh IK,
Stone NJ, Passamani ER, Ackerstein H, Senginen R, Borer JS,
Ley RI, Epstein SE. Coronary calcifications in the detection of
coronary artery disease and comparison with electrocardiographic
Bourassa MG. Noninvasive diagnostic test choice for the eval-
uation of coronary artery disease in women: a multivariate com-
parison of cardiac fluoroscopy, exercise testing, thallium myocardial perfusion scintigraphy. J Am Coll Cardiol. 1984;4:8-16.
17. Langou RA, Huang EK, Kelley MJ, Cohen LS. Predictive accuracy
of coronary artery calcification and abnormal exercise test for
62:1196-1203.
18. Dettano R, Markovic D, Simplendorfer C, Franco I, Holland J,
Grigera F, Stewart W, Ratcliff N, Salcedo EE, Leatherman J.
Digital subtraction fluoroscopy: a new method of detecting
coronary calcification with improved sensitivity for the prediction
19. Dettano R, Salcedo EE, Hobbs RE, Viannis L. Cardiac cine
fluoroscopy as an inexpensive aid in the diagnosis of coronary
20. Beadendkopf WG, Daoud AS, Love BM. Correlation of the coronary arteries by ultrafast computed tomography and its
21. Rifkin RD, Parisi AF, Folland E. Coronary calcification in the
diagnosis of coronary artery disease. Am J Cardiol. 1979;44:
141-147.
22. Margolis JR, Chen JTT, Kong Y, Peter H, Behar VS, Kisao JA.
The diagnostic and prognostic significance of coronary artery cal-
23. Reinmuller R, Lipton MJ. Detection of coronary artery calcifi-
cation by computed tomography. Dyn Cardiovasc Imaging. 1987;1:
139-145.
24. Tunenbaum SR, Dondos GT, Veselik KE, Prendergast MR,
Brundage BH, Chomka EV. Detection of calcific deposits in
coronary arteries by ultrafast computed tomography and corre-
25. Lipton MJ, Rumberger JA. Exercise ultrastart computed
tomography for the detection of coronary artery disease. J Am Coll
quantitative evaluation of calcified coronary artery plaque by
ultrafast computed tomography in persons with and without
27. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte J
JR, Dettano R. Quantification of coronary artery calcium using
29. Hoeg JM, Maher MB, Bou E, Zech LA, Bailey KR, Gregg RE,
Sprecher DL, Susser JK, Pikus AM, Brewer HB Jr. Normalization
of plasma lipoprotein concentrations in patients with type II hyper-
lipoproteinemia by combined use of neomycin and niacin.
Circulation. 1984;70:1004-1011.
30. Rader DJ, Cain W, Zech LA, Usher D, Brewer HB Jr. Variation
in lipoprotein(a) concentrations among individuals with the same
apo(a) isoform is determined by the rate of lipopro-
31. Eaton DL, Fless GM, Kohr WJ, McLean JW, Xu QT, Miller CG,
Beaudet AL, Scriver CR, Wilson JS, Malloy RM, et al. Lipoprotein(a)
shows that it is homologous to plasminogen. J Biol Chem.
32. Scanu AM, Lawn RM, Berg K. Lipoprotein(a) and atherosclerosis.
33. Lawn RM. Lipoprotein(a) in heart disease. Sc Am. 1992;266:54-60.


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