Noninvasive Definition of Anatomic Coronary Artery Disease by Ultrafast Computed Tomographic Scanning: A Quantitative Pathologic Comparison Study

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Objectives. The aim of this study was to determine the relation between coronary artery calcification detected by ultrafast computed tomographic scanning and histopathologic coronary artery disease.

Background. Recent studies suggest that discrete coronary artery calcification as visualized by ultrafast computed tomographic scanning may facilitate the noninvasive detection or estimation, or both, of the in situ extent of coronary disease. Such quantitative relations have not been established.

Methods. Thirteen consecutive perfusion-fixed autopsy hearts (from eight male and five female patients aged 17 to 83 years) were scanned by ultrafast computed tomographic scanning in contiguous 3-mm tomographic sections. The major epicardial arteries were dissected free, positioned longitudinally and scanned again in cross section. Coronary artery calcification in a coronary segment was defined as the presence of one or more voxels with a computed tomographic density >130 Hounsfield units. Each epicardial artery was sectioned longitudinally, stained and measured with a planimeter for quantification of cross-sectional and atherosclerotic plaque areas at 3-mm intervals, corresponding to the computed tomographic scans. A total of 522 paired coronary computed tomographic and histologic sections were studied.

Results. Direct relations were found between ultrafast computed tomographic scanning coronary artery calcium burden and atherosclerotic plaque area and percent lumen area stenosis. However, the range for plaque area or percent lumen stenosis, or both, associated with a given calcium burden was broad. Three hundred thirty-one coronary segments showed no calcification by computed tomography. Although atherosclerotic disease was found in several corresponding pathologic specimens, >97% of these noncalcified segments were associated with nonobstructive disease (<75% area stenosis); if no calcification was determined in an entire coronary vessel, all corresponding coronary disease was found to be nonobstructive. To determine the relation between arterial calcification and any atheromatous disease, computed tomographic calcium burden for each segment was paired with the histologic absence or presence of disease. Ultrafast computed tomographic scanning had a sensitivity and specificity of 59% and 90% and a negative and positive predictive value of 65% and 87%, respectively. A direct correlation was found (r = 0.99) between total calcium burden calculated from tomographic scans of the heart as a whole and scans of the arteries obtained in cross section.

Conclusions. The detection of coronary calcification by ultrafast computed tomographic scanning is highly predictive of the presence of histopathologic coronary disease, but the use of this technique to define the extent of coronary disease may be limited. However, the absence of coronary calcification at any site is highly specific for the absence of obstructive disease.

detect lesions that are flow limiting and thus lead to cardiac

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Coronary artery disease is a leading cause of mortality and morbidity in industrialized nations. Current methods to screen for its absence or presence, such as routine treadmill exercise testing or radionuclide exercise testing, or both,

ischemia during stress. However, acute myocardial infarction or sudden death, or both, is often the first clinical presentation of coronary artery disease (1). Evaluation of flow-limiting lesions may also not be useful in predicting those patients who later have a myocardial infarction. The seminal study by Little et al. (2) showed that only 34% of patients who had a myocardial infarction after undergoing baseline coronary angiography had the infarction at a site associated with the artery that previously demonstrated the most severe stenosis. Thus, a method is needed that will detect atherosclerotic plaque before it is large enough to limit flow.

Coronary artery calcification is both a sensitive and a

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specific marker for the presence of coronary artery atherosclerosis (3-5). Fluoroscopy and conventional computed tomographic scanning (6,7) can detect calcification, but Agatston et al. (8) recently demonstrated that ultrafast computed tomography is more sensitive and specific than fluoroscopy for quantifying the presence of coronary artery calcification. Ultrafast computed tomography has advantages over conventional computed tomography because of its rapid scan acquisition times (50 or 100 ms/image), which, facilitated by excellent spatial resolution (≤ 1 mm), are applicable to quantification of in vivo cardiac anatomy and function. Thus, this method has been suggested as a convenient method of screening for coronary artery disease, particularly in asymptomatic, high risk subgroups of the general population. The examination to identify coronary artery calcification is noninvasive and easily performed and does not require use of intravenous contrast medium. However, a direct relation between coronary artery calcification detected by ultrafast computed tomographic scanning and the extent of histopathologic atheromatous disease at the same anatomic site has not been previously established.

The purpose of the current investigation was threefold: to determine in situ the nature of the relation between coronary artery calcification detected by ultrafast computed tomographic scanning and the *quantitative extent* of coronary artery disease; to determine the relation between the extent of coronary artery disease and the *absence* of calcification identified by this technique, and to define the sensitivity and specificity of this technique for detecting *any* atherosclerotic plaque in segments of human coronary arteries.

Methods

Ultrafast computed tomographic scanner. The ultrafast computed tomographic scanner (Imatron C-100) is a unique electron beam device with no moving parts (other than the scanning gantry) that has previously been shown (9-13) to provide quantitative assessment of cardiac size, shape and function. This device can be operated in two modes: 1) a high temporal resolution mode allowing electrocardiographic (ECG) triggering of images from multiple cardiac planes at a rate of 17 frames/s, for use in standard cardiac functional assessment, and 2) a high spatial resolution, 100-ms singlelevel mode used for radiologic applications (that is, routine chest and abdominal computed tomography). In the latter mode, the device is capable of performing ECG-triggered or manually triggered 3-, 6- or 10-mm thick contiguous tomograms per level at a clinical rate of up to 40 images in 70 s. For the present study, 100-ms, 3-mm thick tomograms were acquired by manual trigger with use of a 22-cm field of view and a matrix size of 512×512 . The individual voxel size was nominally $0.58 \times 0.58 \times 3.0$ mm.

Coronary artery specimens. Thirteen consecutive autopsy hearts were obtained from 13 patients, 8 men and 5 women ranging in age from 17 to 83 years (mean 43.5). The

causes of death varied; only two patients had an antemortem diagnosis of coronary atherosclerosis, and both died after a myocardial infarction. Of the remaining 11 patients, 6 died of trauma, 3 of metastatic carcinoma, 1 of suicide and 1 of a gun shot wound.

Each heart was pressure perfusion fixed with formalin at 70 mm Hg to maintain coronary anatomic integrity. The hearts were scanned by ultrafast computed tomography during two separate sessions. In the first scan the heart was imaged as a whole to mimic acquisition that could be accomplished in the clinical situation. For this portion of the study, each heart was imaged in the standard transaxial position; each was scanned serially from base to apex in 3-mm contiguous tomographic sections with use of the high resolution mode and 100-ms scan time.

For the second imaging sequence, the three major epicardial coronary arteries were carefully dissected and separated from the underlying myocardium, straightened and pinned to a backboard. A second set of 3-mm contiguous scans was acquired perpendicular to the longitudinal direction at each cross section. The most proximate image was obtained at the anatomic origin of each coronary artery. The left main coronary artery was included as part of the left anterior descending coronary vessel.

After the second scan, cross-sectional histologic sections were prepared every 3 mm for each coronary artery to correspond to each 3-mm computed tomographic image. Representative 5- μ m thick hematoxylin-eosin, and elastic van Gieson stains were made at each 3-mm section. Histologic sectioning continued up to approximately 9 cm for each artery or until the arterial diameter was too small to sample properly. From this total of 39 coronary arteries (13 \times 3 epicardial vessels/heart), 522 histologic sections were prepared. Each histologic section was examined both qualitatively and quantitatively. One of us (W.D.E.), an experienced cardiac pathologist, carefully reviewed each histologic specimen and assigned to each a qualitative numeric score of 0 (no atherosclerotic disease), 1 (25% area obstruction), 2 (25% to 50% stenosis), 3 (50% to 75% stenosis) or 4 (>75% stenosis). Each coronary segment that demonstrated qualitatively the presence of coronary disease was also *quantified* by light microscopy for the extent of atherosclerosis by determining the cross-sectional, lumen and atherosclerotic plaque areas with quantitative planimetry. For each histologic section, a percent lumen area stenosis of 0% (no histologic disease) and 100% (total obstruction by atherosclerotic disease) was calculated. The histologic sections were analyzed in random fashion with the reviewers unaware of the results of the computed tomographic examinations.

Each ultrafast computed tomographic scanning image for both image sets was analyzed with use of conventional imaging software supplied by the manufacturer. From each scan, the examiner is able to identify and visually inscribe a region of interest that contains the tomographic coronary section. The image-processing software then automatically

TACC Vol. 20, No. 5

November 1, 1992:1118-26

1120 SIMONS ET AL. ULTRAFAST COMPUTED TOMOGRAPHY IN CORONARY DISEASE





Figure 1. A, Ultrafast computed tomographic (CT) scan acquired at the base of an intact human heart that was perfusion fixed at the time of postmortem examination. This image was acquired in the 100-ms single-slice mode with a tomographic thickness of 3 mm. This scan images proximal portions of the left anterior descending and circumfiex coronary arteries. The prominent high computed tomographic densities in the region of the left anterior descending artery are absent from the adjacent circumflex vessel. The peak computed tomographic densities in the circumscribed regions of interest and the number of voxels with a computed tomographic density >130 Hounsfield units (HU) (representing areas of discrete coronary artery calcification) are indicated in the margins. B, Ultrafast computed tomographic scan from the same heart but at the mid-heart level, now showing a proximal section of the right coronary artery in the anterior atrioventricular groove. LA = left atrial cavity; RA = right atrial cavity; RV = right ventricular cavity.

searches the inscribed region of interest and determines the computed tomographic density of the individual voxels within the region. The presence of coronary artery calcification was defined as any voxel within the region of interest with a computed tomographic density >130 Hounsfield units (H) in a fashion similar to that employed by Agatston et al. (8). The scan data of each intact heart usually consisted of 40 3-mm thick contiguous images. For each 3-mm thick tomogram, the right, left anterior descending (including the left main) and left circumflex coronary arteries were identified (Fig. 1). For each individual coronary segment in each tomographic section, the number of voxels with a computed tomographic density >130 H was determined and termed the "calcium burden" for that coronary segment. When the analysis was completed, the total calcium burden for coronary artery segments individually, or summed for a vessel or the heart as a whole, could be calculated directly.

The scan data for each *dissected* coronary artery usually consisted of 30 3-mm thick images/artery. With use of the same procedures as described, each 3-mm thick computed tomographic image was analyzed, and for each coronary artery segment, the number of voxels >130 H in each 3-mm slice quantified (Fig. 2).

To complete the analysis, the dissected coronary artery ultrafast computed tomographic scanning data and the corresponding representative histologic data for each coronary artery were paired and entered into a relational data base. Because care was taken to match each 3-mm slice in the dissected artery scans with the representative histologic section for the corresponding 3-mm slice, a direct comparison for each vascular segment could then be performed. For each segment, data on the calcium burden (obtained from computed tomographic scan analysis) and the corresponding atherosclerotic plaque area, cross-sectional lumen narrowFigure 2. Same patient as in Figure 1. Ultrafast computed tomographic (CT) scans through three cross sections of the major epicardial coronary arteries. Discrete high density calcification is present in the left anterior descending and right coronary arteries but absent (at this level) in the left circumflex vessel. Software analysis required the operator to define the coronary artery region of interest as shown. The number of voxels with a density >130 Hounsfield units (HU) and the peak computed tomographic density within that region were then displayed and recorded for each sample. These cross sections do not necessarily correspond to the tomographic sections in Figure 1.



ing and histologic stenosis grade (obtained from histologic data) could be compared directly.

Statistics. Results are presented for coronary artery calcium content (or calcium "burden") as discrete values (for the number of voxels with a computed tomographic density \geq 130 H). Atherosclerotic plaque area and lumen crosssectional stenoses are presented as discrete values or as minimal, maximal and mean for each histologic segment. Linear and polynomial (nonlinear) regression modeling was performed with standardized methods. The level of significance was determined as p < 0.05 with use of a two-tailed *t* test and standardized look-up tables for the analysis of continuous variables. Sensitivity, specificity and predictive accuracy were calculated by using standard 2 × 2 contingency methods. Statistical significance for analyses of discrete variables was performed by using a chi-square analysis with significance set at p < 0.05.

Results

Coronary artery calcification of intact heart versus dissected coronary artery specimens. Although the major intent of the current study was to investigate the relation between in situ coronary artery calcification and the extent of atherosclerotic disease, it is also important to determine whether "ideal" scanning of the dissected specimens in a fashion perpendicular to the vessel's long axis is approximated by scanning of the heart as a whole. To make this comparison, the total sum of coronary artery calcifications found in each of the three epicardial coronary arteries was determined for each of the 13 hearts by analysis of both image sets. For each heart, the two data points were plotted and the results correlated. There was a direct and highly significant correlation between the calcification detected in the coronary tree for the hearts scanned as a whole (Fig. 3, r =0.99, y = 0.98x, p < 0.001). Thus ultrafast computed tomographic coronary artery scans of the heart as a whole to define coronary calcium burden yields, at least under the optimal scanning conditions of the current study, results nearly identical to coronary calcium burden determined from tomographic imaging perpendicular to the vessel cross sections.

In situ coronary artery calcification and quantifiable extent of atherosclerotic disease. The paired data of calcium burden by ultrafast computed tomographic scanning and the quantitative histologic extent of coronary atheromatous disease were examined in two ways, first as continuous variables and then as discrete variables. For each histologic coronary artery section, the atherosclerotic plaque area was quantified

Figure 3. Linear sum of the number of voxels within a given heart that displayed coronary artery ultrafast computed tomographic (CT) sections with densities >130 Hounsfield units (HU) (that is, total "calcium burden" per heart) for all 13 postmortem hearts examined. Data compare calculations made with the heart intact and imaged in a conventional fashion (abscissa) and calculations made from "ideal" cross-sectional imaging of the coronary artery sections individually (ordinate). The correlations are excellent.







Figure 4. Calcium burden as defined by ultrafast computed tomographic (CT) scanning (see text for details) versus atherosclerotic plaque area per histologic specimen for the left anterior descending (A), right (B) and left circumflex (C) coronary arteries. Data are presented as mean values. Individual error bars represent the maximal and minimal plaque areas determined from analysis of all specimens within the epicardial arteries displaying a given value for the calcium burden. The linear correlation in each panel represents analysis of the data from all segments of a given coronary artery. There is a direct and linear correlation between increasing calcium burden as defined by computed tomography and quantification of individual plaque area/segment. See text for discussion. \blacksquare = mean lumen stenosis; * = maximal lumen stenosis; + = minimal lumen stenosis.

and compared with the corresponding calcium burden found in that section from the dissected coronary artery computed tomographic scan data. Each of the major epicardial coronary arteries—the left anterior descending, right and circumflex coronary arteries—was analyzed separately (Fig. 4, A to C). Overall, there was a direct linear relation between atherosclerotic plaque area in any coronary artery section and the computed tomographic calcium burden for that



Figure 5. Coronary artery calcium burden (number of coronary artery voxels on ultrafast computed tomographic scanning with a density >130 Hounsfield units (HU) for all specimens (n = 522) versus percent lumen area stenosis determined in paired histologic samples. There is a direct correlation between calcium burden and lumen area stenosis, but the spread of the data limits the application on a sample by sample basis.

vascular segment (0.57 \leq r \leq 0.76, p \leq 0.001). However, at any particular value for calcium burden, the associated atherosclerotic plaque area varied considerably as seen by the variable range of the maximal and minimal atheromatous involvement noted at each measurement point. However, segments with greater calcification tended to have a larger burden of atherosclerotic plaque, and segments with less calcification tended to have less atherosclerotic plaque.

Although it was our hypothesis that coronary artery calcium burden defined by ultrafast computed tomographic scanning was a direct result of the presence of coronary artery atherosclerotic plaque, it is of potential clinical interest to compare coronary calcium burden with individual percent coronary lumen area stenoses. The relation between the percent area stenosis found for each coronary segment and the corresponding amount of coronary artery calcification was determined. For all 522 coronary artery sections, the coronary calcium burden at any point in the artery was quantified and plotted against the corresponding percent area stenosis found on histologic examination of the same coronary segment. Figure 5 shows the percent area stenosis versus the corresponding number of voxels with a computed tomographic number >130 representing coronary artery calcification. Here a quadratic curve fit for all coronary segments was determined as suggested by review of the data. Similar to the results found when plotting coronary calcification versus plaque area, a direct and positive relation was found between the amount of calcification detected by computed tomography and the percent area lumen obstruction by atherosclerotic plaque. Highly calcified segments have a high likelihood of total or near total coronary occlusion, although there is considerable spread within the data. However, segments with no obvious tomographic calcification (that is, calcium burden = 0) displayed a wide range of atherosclerotic narrowing.

SIMONS ET AL. ULTRAFAST COMPUTED TOMOGRAPHY IN CORONARY DISEASE



Figure 6. A, Frequency distribution of noncalcified segments by ultrafast computed tomographic examination and the associated percent lumen area stenoses by decade. The most frequently occurring coronary lesion is approximately 20% to 30% lumen *area* stenosis. B, Cumulative frequency distribution of noncalcified segments by ultrafast computed tomographic examination and the associated percent lumen area stenoses for those segments displaying <75% and \geq 75% stenosis. Nearly 98% of all coronary segments that failed to display detectable calcification by computed tomography were associated with nonobstructive disease.

To further analyze the relation between *no* coronary artery calcification as detected by ultrafast computed tomographic scanning with the corresponding atherosclerotic lumen area obstruction, data were analyzed on a segment by segment and vessel by vessel basis. In total, of the 522 paired computed tomographic and histologic sections, 331 (63%) were found to have no detectable coronary artery calcification from the tomographic analysis. For this set of scans, performed under "ideal" scanning circumstances, corresponding histologic lumen cross-sectional stenoses ranged from 0% to 99% (Fig. 5). Thus the absence of coronary calcium by computed tomography at a single anatomic site did *not* imply the absence of corresponding histologic coronary artery disease. Figure 6A shows the frequency distribution of lumen area stenoses in the noncalcified coronary PERCENT LUMEN AREA STENOSIS



Figure 7. Analysis of the corresponding percent lumen area stenosis within any section of a given coronary artery when the vessel as a whole failed to demonstrate coronary calcification on ultrafast computed tomographic scanning. Data are presented as the maximal and mean coronary stenoses of all segments within the respective coronary vessels. LAD = left anterior descending, LCX = left circumflex and RCA = right coronary artery.

artery segments. The mode of this distribution suggests that the most frequently observed percent lumen area stenosis was between 20% and 30% for these noncalcified segments, a value that would correspond to minimal disease (*diameter* stenosis <20%) on routine coronary angiography.

The majority of clinical investigations consider that stenoses of \leq 50% diameter narrowing are nonobstructive (that is, not "hemodynamically" significant). Assuming a circular cross section, this level of stenosis corresponds roughly to an *area* stenosis of \leq 75%. Figure 6B shows the frequency distribution for these noncalcified coronary artery segments expressed as representing histologic measurements of <75% or \geq 75% area stenosis. In this case, 322 (97.5%) of the segments found by ultrafast computed tomographic scanning corresponded to segments with no histologic evidence of obstructive coronary artery stenosis. Only eight segments (2.5%) had disease representing \geq 75% area stenosis.

Analysis of noncalcified coronary segments was extended to include whole coronary vessels that failed to show any calcification by ultrafast computed tomographic scanning. A total of 15 (38%) of the coronary vessels fit this criteria (4 left anterior descending, 7 left circumflex and 4 right coronary arteries; Fig. 7). Here, if no detectable coronary calcification was found by computed tomographic scanning of an entire coronary vessel, no obstructive coronary disease could be found at histologic sectioning. Coronary disease, if present, was minimal.

The previous results and graphs presented the evaluation of coronary artery calcification and atherosclerotic plaque burden as continuous variables. To further elucidate the relation between the presence of coronary artery calcification by ultrafast computed tomographic scanning and the presence or absence of *any* coronary artery disease, further analysis was performed. The histologic sections with an assigned stenosis score of 0 (that is, no obvious coronary atherosclerosis) were paired with the corresponding com-

1123

puted tomographic scans to determine the number of "true negative" results (calcium burden = 0) and "false negatives" (calcium burden > 0). Two hundred forty-two of the 522 total samples were assigned histologic grade 0 disease and 280 histologic grade ≥ 1 disease (41 = grade 1, 121 = grade 2, 73 = grade 3, 45 = grade 4). Thus the overall prevalence of histopathologic coronary artery disease in the group examined was 54%.

Table 1 shows the 2 \times 2 contingency table for the presence of *any* histopathologic coronary artery disease as defined by the absence or presence of coronary artery calcification detected by ultrafast computed tomographic scanning (n = 522). The sensitivity and specificity were 59% and 90%, respectively; the negative predictive value was 65% and the positive predictive value was 87%.

Discussion

Relation between ultrafast computed tomographic imaging results and histologically defined coronary artery disease. The objective of our study was to investigate the relation between coronary artery calcification as detected by ultrafast computed tomographic scanning and histopathologic coronary artery disease. The results from this human pathologic study can be used to conclude the following regarding the definition of coronary artery calcification by ultrafast computed tomographic imaging and the corresponding extent of histologically defined coronary artery disease.

1. The coronary artery calcium burden defined by ultrafast computed tomographic scanning and the quantitative extent of coronary artery atheromatous plaque are directly correlated. In general, the more extensive the calcium burden, the more extensive the atheromatous involvement of the coronary artery segment. However, the distribution of corresponding plaque areas at a given measured calcium burden was substantial, making tenuous the applicability of this measurement on a segment by segment basis.

2. For the major epicardial coronary vessels, the correlation of calcium burden measured by ultrafast computed tomographic scanning with percent lumen area stenosis is highly significant; however, by analogy to plaque burden, the results are not readily applicable on a segment by segment basis.

3. The total absence of any coronary artery calcification

 Table 1. Contingency Table Comparing Histologic Detection of

 Any Coronary Artery Disease in a Section with Ultrafast

 Computed Tomographic Detection of Coronary Artery

 Calcification in That Section

Coronary Calcification by Ultrafast Computed Tomography	Histopathologic Coronary Artery Disease	
	Present	Absent
Present	167	24
Absent	114	217

Chi-square = 135, p < 0.0001. See text for details.

within a given coronary artery segment by ultrafast computed tomographic scanning does not confirm the absence of corresponding coronary artery atheromatous plaque, but the mode of the distribution suggests that the most frequently observed atherosclerotic involvement corresponds to minimal coronary artery disease. However, the tomographic *absence* of detectable coronary artery calcification is highly predictive of the *absence* of obstructive coronary artery disease (that is, no area stenosis \geq 75%) on a segment by segment (negative predictive value 97.5%) and a vessel by vessel (negative predictive value 100%) basis.

4. When predicting the *presence* of any definable coronary artery calcification by ultrafast computed tomographic scanning with the presence of any atherosclerotic plaque within any given segment of the coronary arteries, the overall sensitivity and specificity were 59% and 90%, respectively. The positive predictive value of tomographic coronary calcification and *any* coronary artery disease in the present study was 87%, whereas the negative predictive value was 65%.

Finally, definition of the total cardiac as well as the individual coronary artery calcium burden is virtually identical whether ultrafast computed tomographic scanning is performed under "ideal" (transaxial) conditions or under conditions consistent with clinical image acquisition (that is, imaging of the heart as a whole).

Application of ultrafast computed tomography to definition of coronary artery disease. Atherosclerotic coronary artery disease is one, if not the leading, cause of morbidity and mortality in industrialized nations. Early detection may benefit the population in general but may be especially useful in subgroups of patients at high epidemiologic risk for myocardial infarction or sudden death who are asymptomatic at the time of initial evaluation. Detrano and Froelicher (14) summarized current methods of screening for coronary artery disease. The rest ECG is readily available and inexpensive but is useful primarily to detect intercurrent ischemia or infarction, or both. ST segment abnormalities are only slightly more sensitive than are Q waves, but their presence is not sufficiently specific for effective screening. Treadmill exercise testing has an average sensitivity of 65% with a specificity of 85% in detecting flow-limiting coronary artery disease. The average sensitivity for thallium stress testing for any vessel disease is 84% with a specificity of 87% (15), but these results are highly dependent on the incidence of disease in the patient group examined. Exercise testing is most helpful in symptomatic men over the age of 55 to 60 years and is least helpful in young women with atypical angina. However, current methods of screening for coronary artery disease can only detect atherosclerotic plaque when a sufficient amount is present to impede coronary artery flow or flow reserve. Nonobstructive coronary lesions are generally undetected by traditional treadmill or pharmacologic stress testing.

Three postmortem studies (3–5) have shown that coronary artery calcific deposits are both sensitive and specific for predicting the presence of coronary atherosclerosis. For clinical applications, fluoroscopy was first used to detect coronary artery calcification; although it is highly specific, it lacks sensitivity because of overlapping structures and low resolution (14). Agatston et al. (8) recently used ultrafast computed tomographic scanning to detect and quantify coronary artery calcium burden in patients with and without coronary artery disease. They concluded that in patients with disease (a history of myocardial infarction or documented angiographic lesions of >50% lumen diameter stenosis), this tomographic technique had a high sensitivity of detecting coronary artery calcification, which was significantly better than that of fluoroscopy (90% vs. 52%, respectively); additionally, the negative predictive value of a calcification score of 0 and no coronary artery disease was high.

The absence of coronary artery calcification detected by ultrafast computed tomographic scanning may allow identification of a subset of patients who have an underlying *low* risk of developing subsequent cardiac events. Conversely, the presence of such calcification and its relation to atherosclerotic plaque may allow for a noninvasive means to follow the progression or regression of anatomic coronary artery disease. Lipid-lowering therapy or other risk factor modifications could then be directed toward a group of patients who may be at higher risk and benefit more from this intervention than would the general population. In the current study, only 2 (15%) of the 13 patients had an antemortem diagnosis of coronary artery disease despite the >50% prevalence of histologic coronary artery atherosclerosis in the population studied.

Studies such as those of Agatston and colleagues (8) provided important data on the potential clinical applicability of ultrafast computed tomographic screening for coronary artery disease and on the epidemiology of coronary artery calcification. Our study indicates the direct relation of coronary calcification to disease and helps to define the absolute limits of any clinical application of the ultrafast computed tomographic methodology. Our results show that coronary calcification as detected by this technique is highly predictive of the presence of histopathologic coronary artery disease, but the amount of calcification present has limited application in determining the in situ degree of atherosclerotic involvement. Conversely, the absence of any coronary calcification on a segment by segment and vessel by vessel basis is highly predictive of the absence of anatomically significant coronary artery disease.

Ultrafast computed tomographic screening may eventually prove to be a most effective noninvasive method to detect anatomic coronary artery disease or to rule out the presence of critical disease in humans. However, although the present results are encouraging, long-term clinical studies are needed before the significance of coronary artery calcification detected by ultrafast computed tomographic scanning and its natural history are known. Screening for coronary artery disease with this tomographic technique should not be widely employed until such studies are completed. Major questions need to be answered regarding the appropriateness of general screening for coronary artery disease because the total absence or the presence of a small amount of coronary calcification does not necessarily imply the absence of disease or the presence of "significant" disease, respectively. Only carefully performed epidemiologic investigations will establish the applicability of this methodology to identification of clinical coronary disease.

Limitations of the study. There are several limitations of the current study. First, a single $5-\mu m$ histologic sample to quantify the extent of coronary artery disease in a 3-mm thick tomographic section can be questioned. Limitations of the imaging method at present do not allow for thinner direct tomographic sectioning, although a 1-mm helical scanning protocol is under development. Nevertheless, it is assumed that direct comparisons can be determined because the presence of coronary calcification implies coronary plaque somewhere within that coronary segment. Some sampling errors are to be expected, but efforts to be consistent were made throughout the study.

The actual in situ extent of coronary artery calcification and the amount detected by ultrafast computed tomographic scanning may not be identical. Direct comparisons between histologic coronary artery calcium content and tomographic calcium burden need to be performed. In the current study, all coronary specimens were decalcified before histologic preparation, as is standard in most pathology laboratories, to allow for ease of microtome sectioning. Methods are underway in our laboratory to allow for proper sectioning of specimens that are not decalcified by using techniques developed in bone histomorphometry.

The choice of 130 H for a threshold was intended to mimic the value used in the prior clinical study by Agatston et al. (8). Noncontrast-enhanced myocardial tissue density by computed tomography is approximately 35 to 55 H. A higher value for the threshold for coronary calcification as any discrete density above the 130 H used in the current study might have increased specificity but probably would have reduced sensitivity; the converse would be true if a lower threshold value were used. When viewed on the display screen, the areas of coronary artery calcification are almost always quite obvious within the tomogram (Fig. 1 and 2). For the present, the threshold of 130 H is considered to be a reasonable value, being at least two to three times greater than the maximal density of noncontrast-enhanced myocardial tissue. Additional statistical analysis using receiver operating characteristic curves are required to examine the effect of variable threshold on sensitivity and specificity. However, this type of analysis is not possible with the available image processing software. Additionally, variable patient body habitus may alter the computed tomographic attenuation such that a proper threshold in clinical practice may be greater or less than the single value of 130 H used in the current investigation. More clinical work is necessary to determine the threshold or thresholds that provide the greatest clinical utility.

Comparisons between histologic findings and computed

tomographic results were made only during the final data analysis; thus the results of the histologic analysis were obtained without knowledge of the results of the computed tomographic analysis. The software employed required placing an operator-defined region of interest around the vessel and defining the number of voxels with a computed tomographic density \geq 130 H. For each section examined, the results were exactly reproducible; thus there was no inter- or intraobserver variability for the computed tomographic analysis. The relation between paired computed tomographic and histologic samples may have been confounded in that experimental error could have allowed a slight discordance between the 3-mm computed tomographic scan and the amount of calcification and the corresponding histologic plaque. Areas that were deemed to be noncalcified might have had less disease if this had occurred. Also, because coronary calcification may not be homogeneously distributed within a plaque, a long lesion that is calcified at one point but not at another could be misclassified as a noncalcified lesion associated with significant atherosclerosis.

Finally, the histologic sampling was performed at another site and time from the tomographic sectioning by ultrafast computed tomography. Minor errors of misregistration could occur with improper assignment of one computed tomographic section with an incorrect histologic section. Again, the histologic sectioning was performed in a consistent manner by the same investigators (D.B.S., W.D.E.) for each heart and vessel; thus, considering the large number of samples, minor errors may be present but should not change the overall outcome.

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