PrevaHealth
WELLNESS DIAGNOSTIC CENTER

John A. Rumberger, PhD, MD, FACC
Medical Director

Emerald Professional Building
5747 Perimeter Drive, Suite 105
Dublin, OH 43017
www.prevahealth.com

Clinical Use of Coronary Calcium Scanning With Computed Tomography

Synopsis

This review focuses on non-contrast quantitation of coronary artery calcium (CAC) using x-ray computed tomography (CT). It begins by examining the pathologic basis of CAC as a surrogate to atherosclerotic plaque burden. The discussion continues with the clinical development of CT based imaging for this purpose, examining both electron beam CT (EBT) and multidetector CT (MDCT). The commentary ends with the subsequent patient applications, and uses of coronary calcium for assessment of cardiovascular risk and clinical-decision making in asymptomatic adult individuals.

Introduction

X-ray computed tomography (CT) provides exquisite, rapid, high resolution imaging of the body and in particular the heart (and vascular system in general). Tomographic imaging by CT has shown significant advances in the past 20 years as it relates to both temporal and spatial resolution to facilitate non-invasive cardiac imaging. In particular both electron beam tomography (EBT) and multi-detector CT (MDCT) have shown applicability, under certain defined circumstances, for coronary artery imaging and atherosclerotic plaque identification.

Coronary lumen imaging of the major epicardial coronary arteries using EBT/MDCT during intravenous contrast administration is not only feasible, but is in routine use in some clinical settings. Coronary artery imaging by CT without contrast administration has focused on identification of mural coronary calcification. This review will focus on non-contrast CT quantitation of coronary artery calcium by examining the pathologic basis of this as a surrogate to atherosclerotic plaque burden, clinical development of CT based imaging for this purpose and subsequent applications, and uses of coronary calcium for assessment of cardiovascular risk and clinical-decision making in asymptomatic adult individuals.

Coronary Calcium and Atherosclerotic Plaque

Recent studies have confirmed that arterial mural calcification is intimately associated with vascular injury and atherosclerotic plaque evolution and is largely controlled by common cellular and sub-cellular mechanisms. [1,2,3,4]

The incidence of coronary artery calcium by CT as a function of age has been shown to mimic the incidence of cardiovascular atherosclerotic disease in men and women. The data [5] show the following: a) the incidence of coronary artery calcium increases from only a few percent in the second decade of life to nearly 100% by the 8th decade in men and women; b) the general incidence of coronary artery calcium in women is similar to that in men who are a decade younger; and c) this separation in prevalence with age is eliminated by approximately age 65-70, when the incidence of coronary calcium in women is similar to that of men of the same age.

Although there is an increasing incidence of coronary calcification in patients as one grows older this simply parallels the increased incidence of coronary atherosclerosis with advancing age. Coronary artery calcium score as a measure of the extent of coronary disease also increases with age, but the magnitude of the estimated atherosclerotic plaque burden is quite different in men versus women. [6]

Atherosclerosis is the only disease known to be associated with coronary calcification. [7-9] Recent studies have shown that calcium can be seen in all degrees of atherosclerotic involvement and is an active process. [10-13]

Coronary calcification is common in patients with known coronary heart disease [14,15], and is strongly related to age, increasing dramatically after age 50.[16-19] Since Faber[20] in 1912 noted that Mönckeberg's calcific medial sclerosis does not occur in the coronary arteries, atherosclerosis is the only vascular disease known to be associated with coronary calcification.

However, coronary plaque and its associated coronary calcification may have only a poor correlation with the extent of histopathologic stenosis.[21] This fundamental finding has been shown to largely be accounted for as a result of individual variations in coronary artery remodeling[22], while in-situ coronary calcium, on the other hand, is associated with plaque size.(23)

A fundamental requirement for the use of coronary calcium quantification by CT to define coronary artery plaque is to establish how these two measures relate to each other. Rumberger and colleagues at the Mayo Clinic initially examined random autopsy hearts and compared measures of coronary calcium using EBT as compared with direct histologic plaque areas, and percent luminal stenosis.[23-25] These studies determined that the total area of coronary artery calcification quantified by EBT is linearly correlated ($r = 0.90$) with the total area of histologic coronary artery plaque per vessel. Here, although the total atherosclerotic plaque burden was tracked by the total calcium burden, not all plaques were calcified and the total calcium area was around 20% of the total atherosclerotic plaque area. This suggests that there may be a size of coronary plaque that is most commonly associated with coronary calcium but, in the smaller plaques, the calcium is either not present or is undetectable. A study by Baumgart et al [26] compared direct intracoronary ultrasound measures during angiography with EBT calcium scanning and confirmed a direct association of coronary calcium score with localization and extent of atherosclerotic plaques, in vivo.

Coronary Calcium Identification by CT

EBT Methods

Electron beam tomography [EBT] is a mature body-imaging device developed over 20 years ago and is the only CT device specifically designed from inception for cardiac imaging. Although the technique can quantify ventricular anatomy and global and regional function[27] as well as myocardial perfusion[28], it is currently best known for defining and measuring coronary artery calcified plaque and for performing non-invasive coronary and vascular angiography. To date, and specifically over the past decade, there have been over 600 articles published regarding the validation of EBT for coronary artery plaque and lumen imaging.

EBT [General Electric Medical Systems, Milwaukee, WI] employs unique technology enabling ultrafast scan acquisition times of 33 msec, 50 msec, 100 msec, and multiples of 100 msec [up to 1.5 seconds] per slice. There have been 3 iterations for EBT since it was introduced clinically in the early 1980's. The overall imaging methods have remained unchanged, but there have been improvements in data storage, data manipulation and management, data display, and spatial resolution. The original C-100 scanner was replaced in 1993 by the C-150, which was replaced by the C-300 in 2000. The current EBT scanner, the "e-speed©" (GE/Imatron) was introduced in 2003. The "e-speed" is a multi-slice scanner and currently performs a heart or body scan in one-half the total exam time required by the C-150 and C-300 scanners. The "e-speed", in addition to the standard 50 msec and 100 msec scan modes common to all EBT scanners, is capable of imaging speeds as low as 33 msec, but as of this writing, no validation studies on the applicability of calcium scoring in this mode are available. Thus, the current discussion of EBT will focus on the established methods of the C-150 and C-300 imaging systems.

EBT employs a stationary multi-source/split-detector combination coupled to a rotating electron beam and produces serial, contiguous, thin section tomographic scans in synchrony with the heart cycle. EBT is distinguished by its use of a scanning electron beam rather than a traditional x-ray tube and mechanical rotating device used in current "spiral" single and multiple detector scanners. The electron beam [cathode] is steered by an electromagnetic deflection system that sweeps the beam across the distant anode, a series of 4 fixed tungsten "target" rings. A stationary, currently dual level, detector lies in apposition to the tungsten target rings. Thus, as opposed to physically moving the x-ray tube in a circle about the patient, as is done by the mechanical CT (spiral) scanners, only the electron beam is moved in EBT.

Standardized methods for imaging, identification and quantification of coronary artery calcium using EBT have been established.[9] The scanner is operated in the high resolution, single slice mode with continuous, non-overlapping slices of 3 mm thickness, a reconstruction field of view (FOV) of 26 cm, and an acquisition time of 100 msec per tomogram. Patients are positioned supine and, after localization of the main pulmonary artery, a sufficient number of tomographic slices are obtained to cover the complete heart through the left ventricular apex (usually 36 to 40 slices). For the C-150/C-300 scanners this takes about 30-35 seconds; for the "e-speed" it would be about 15-20 seconds. Electrocardiographic triggering is done at a time determined from the continuous ECG tracing recorded during scanning. Current clinical protocols for EBT perform triggering during the cardiac cycle as varied depending on the patient's resting heart rate. This is intended to minimize coronary motion artifacts since the ballistics of cardiac motion are highly dependent on resting heart rate. Nominally, this is currently done for most studies at a time corresponding to 40%-60% of the total RR interval, or near the end of electro-mechanical systole.

The presence of coronary calcium is sequentially evaluated in all levels. Coronary calcium is defined as a hyperattenuating lesion above a threshold of 130 "Hounsfield Units" with an area of 3 or more adjacent pixels [at least 1 mm2.]. CT Hounsfield Unit (HU) densities range from -1000 [air], through 0 [water], and up to +1000 [dense cortical bone]. The "calcium score" developed by Agatston[29] and predicated on a 3 mm slice thickness is a product of the area of calcification per coronary cross-section and a factor rated 1 through 4 dictated by the maximum calcium CT density within that cross-section. A calcium score is reported for a given coronary segment/artery and for the entire coronary system; however, most research studies have reported data related to the summed or total “score” for the entire epicardial coronary system.

Quantification of coronary artery calcium using EBT scanning has been proven as a valid surrogate for atherosclerotic plaque burden and as a measure of the severity of coronary disease in direct pathologic comparison studies[25] regardless of age or gender[24], and in clinical studies using coronary angiography[30] and intravascular ultrasound[26] as reference standards.

MDCT Methods

The current generation of multi-detector computed tomography (MDCT) systems are capable of acquiring 2, 4, 8 or 16 (and potentially soon 32) levels of the heart simultaneously with ECG gating in either a prospective or retrospective mode. Multi-level images are also possible of any part of the body without the use or need for ECG information. MDCT differs from single slice (helical or spiral) CT systems principally by the design of the detectors and data acquisition systems that allow the detector arrays to be configured electronically to acquire multiple levels at variable slice thickness simultaneously. Thus in the current state of the art 16 channel MDCT systems 16 slices can be acquired at nominally 1.25 mm slice widths for cardiac imaging. As of 2003, 4-slice MDCT systems are the most widely deployed with an estimated installed base in the U.S. of over 2,000 (compared to roughly 200 EBT systems), but with natural attrition and replacement of CT scanners on the average of every 2 to 5 years in most medical centers, they are being replaced with 8-slice and 16-slice systems. Thus the term “MDCT” refers to a variety of systems from the newest to systems approaching 5-7 years in age. Each system, manufactured by various vendors, may have unique properties that are not found in competitors systems.

In MDCT systems, like the preceding generation of single slice spiral scanners, the X-ray photons are generated within a specialized X-ray tube mounted on a rotating gantry. The patient is centered within the bore of the gantry such that the array of detectors is positioned to record incident photons after traversing the patient. Within the X-ray tube a tungsten filament allows the tube current to be increased (milliampere - mA) which proportionately increases the number of X-ray photons for producing an image. This is a design difference with current generation EBT systems, which use a fixed mA. The attenuation data (after passing from the source, through the body, and incident on the detector array) are recorded and transformed through a filtered back-projection into the CT image. This final step is common to both EBT and MDCT. Spiral and MDCT systems have two principal modes of scanning which are dependent upon whether the patient on the CT couch is stationary (axial mode) or moved at a fixed speed relative to the gantry rotation (spiral mode). The axial mode utilizes prospective ECG gating at predetermined offset from the ECG detected R wave analogous to EBT (but at a physically slower speed per image than EBT) and is the current mode for measuring coronary calcium at most centers using MDCT. This mode is preferred mainly due to issues of keeping the radiation dose similar to that of EBT (see below).

The temporal resolution of a spiral or MDCT system is determined by the gantry speed, which determines the number of views possible per second. To reconstruct each slice 180 degrees plus the angle of the fan beam is required, typically a total of 220 degrees of rotation. For a 16-channel system with 0.4 sec rotation the temporal resolution is 0.244 seconds or 244 msec for a 50 cm display FOV. Reducing the display FOV to the 20 cm to encompass the heart the number of views can be reduced, theoretically, to further improve temporal resolution for a 16-channel scanner to approximately 200 msec. The majority of MDCT systems in 2003 have gantry speeds of 500 to 750 msec and temporal resolution of 320-500 msec per image when used for measuring coronary calcium, as compared to 100 msec or less for EBT.

The rapid evolution of MDCT while potentially of great value for coronary artery calcium (CAC) quantitation because of the generally greater availability than EBT makes current application of guidelines for MDCT uses more confusing and not universal since, as noted, all installed MDCT systems are not the same. All comparisons between MDCT and EBT data show good group correlation values but with each improvement in MDCT speed and slice profile the correlation with EBT is found to be better despite the strong claims of comparability declared by same vendors of preceding generation scanners. Another issue relates to the image "slice thickness" used for imaging, which varies between manufacturers. The issue of slice thickness and the effects on calcium scoring are discussed below.

Studies Comparing EBT and MDCT for Calcium Scoring

Becker et al studied 100 patients comparing MDCT with EBT and reported a high correlation between the 2 modalities.(31) In this study however, the percent variability between individuals was 32% for CAC scores. There were relatively few patients with scores < 100, and the high correlation may have been driven by those individuals with high scores. Moreover, the level of individual precision was limited and the scores < 100 appeared to have the most deviation by MDCT as compared to EBT. Although a high correlation indicates that these two measures have a linear relationship to one another, the spread about the line can still be significant and can limit use in individuals.

Knez et al studied the diagnostic accuracy of MDCT compared to EBT in 99 symptomatic male patients (60±10 years).(32) For quantification of CAC, the volumetric calcium score was determined. The results indicated excellent correlation between the two modalities (r= 0.99). The mean variability between the MDCT and EBT derived scores was 17%. Importantly, the study population had 26 patients with score ranging from 0-100, and the mean variability between the test was 7±8 (20%), which was not significantly different from very high scores.

The above studies were performed in older male symptomatic adults with a mean age above 60 years and a high range of calcium score values. The findings of extensive calcification and a good correlation over a large range of values, however does not fully address the need to measure CAC scores accurately and reproducibly in a given individual. In addition, these high correlations may not apply as well to a younger 'asymptomatic' population with generally much lower scores. The studies by Budoff(33), Carr(34) and Goldin(35), each comparing EBT and spiral CT, indicated a range of poor to fair and fair to excellent agreement at a series of clinical cut-points as proposed by Rumberger(36) using the Agatston score. However, Carr, et. al.(34) indicated that agreement could be improved by calibration of the Agatston score to an external standard.

It should be emphasized that the clinical value for CAC determination is to facilitate individual risk assessment and thus scoring for a given patient should be a accurate as possible. However, for epidemiologic studies and investigations of coronary calcium in broad population groups, measures by MDCT and EBT may provide similar insight into the atherosclerotic process.

Radiation Exposure

One drawback of MDCT as compared to EBT is the higher radiation exposure to the patient.(35,37-46) Radiation exposure from prospectively gated studies is much less than from retrospectively gated studies. The x-ray photon flux expressed by the product of x-ray tube current and exposure time (mAs) is generally higher with MDCT. For example, 400 mA with 0.5 sec exposure time yields 200 mAs in MDCT versus 614 mA (fixed tube current) with 0.1 sec exposure time yields 61.4 mAs in EBT. The increase in radiation dose with MDCT compared to EBT has been estimated to range from 3-10 times higher, depending on the protocol employed and whether prospective or retrospective gating is employed.(38,40,41) The most modern MDCT devices used in the retrospective imaging mode probably expose the patient to about 30-40 mGy (3-4 rad), equivalent to a conventional angiographic study, and up to 10-fold higher than the doses delivered during EBT of 3-4 mGy (0.3-0.4 rad).(42,43)

The radiation dose estimation has a wide margin of error and depends significantly on the method of estimation. Furthermore, the distributions of radiation dose are different for MDCT and EBT. In EBT the maximum dose is delivered at the entrance surface to the patient's anatomy lying closest to the target ring (usually the posterior elements) due to the configuration of target rings, while in MDCT, the dose is uniform around the patient and decreases towards the center. This results in a decreased dose distribution in EBT to organs lying anteriorly such as breasts. Thus, with MDCT the effective dose in women is 25% higher than in males raising the mean dose from 30 mGy (3 rad) per study in men to 40 mGy (4 rad) per study in women.(42) In MDCT, using prospective gating, the radiation dose is lower than that of retrospective gated studies. However, results from a recent study showed that ECG-controlled tube current modulation allows significant dose reduction of 48% and 45% in males and females respectively, while performing retrospectively ECG-gated MDCT of the heart.(46)

CT Coronary Calcification and Clinical Outcomes

Calcification of the coronary arteries occurs in rough proportion to the severity and extent of coronary atherosclerosis. (47) In a landmark study of atherosclerosis, persons dying of coronary disease were found to have two to five times as much coronary calcification as age matched controls that died accidentally or of other natural causes.(48) In a five-year study of 800 consecutive patients undergoing cardiac catheterization, fluoroscopically evident coronary calcification was associated with higher mortality, even after adjustment for ejection fraction and the number of diseased vessels.(49)

Seven studies have examined the prognostic accuracy of EBT scanning of the coronary arteries. The first and longest study of EBT scanning of the coronary arteries, the South Bay Heart Watch(50,51), began in 1990 as a prospective study of the prognostic accuracy of cardiac-fluoroscopy in 1461 asymptomatic, high risk subjects. Beginning in 1992, 1289 study participants, mean age 66 + 8 years, underwent EBT scanning. Although early analysis showed no advantage of EBT scanning over conventional risk factor assessment(50), long-term (6.4 years) follow-up has demonstrated that the CAC score predicts events independently of standard coronary risk factors. (51) Thus, the study required longer follow-up to demonstrate the independence of the CAC score in predicting coronary events. The initial South Bay Heart Watch study also employed six millimeter EBT slices (twice the slice thickness used in all other studies) which has subsequently been shown to have lower discriminatory power for detecting any calcification (zero score) as well as yielding total scores that are less than one half those using the 3 mm standard slice method(52,53), and thus not comparable with published EBT databases.(6)

In a retrospective analysis of 632 asymptomatic persons (mean age 52 + 9 years) followed for a mean of 2.7 years, investigators from Nashville, Tennessee reported that the rate of non-fatal myocardial infarction and coronary death increased from 0.045% per year in the lowest quartile of EBT calcium scores to 2.7% among subjects in the highest quartile of calcium scores (a 59-fold increase). (54) In contrast, the rate of non-fatal myocardial infarction and coronary death was 0.09% per year in the quartile of patients at lowest risk by standard coronary risk factors compared to 1.05% per year in patients in the highest quartile of risk, as defined by standard risk factors (a 12-fold difference). This difference in relative risks (highest quartile versus lowest quartile) occurred because EBT better stratified groups of patients into lower and higher risk groups than did standard coronary risk factors alone; i.e., EBT defined subsequent coronary disease risk more accurately than risk factors. These investigators demonstrated that EBT added incremental benefit to standard coronary risk factors for risk stratification.(55)

Investigators from St. Francis Hospital in New York have conducted two studies of EBT scanning for the prediction of atherosclerotic cardiovascular disease events in asymptomatic persons. In the first study, a retrospective analysis of 1172 persons (mean age 53 + 11 years) followed for 3.6 years, a calcium score >160 predicted non-fatal myocardial infarction and coronary death with sensitivity of 0.86, specificity of 0.80, and an odds ratio of 23.3 (95% confidence interval 5.7 – 105.2).(56) Although cholesterol values were not directly measured, the calcium score predicted events independently of and more accurately than self-reported risk factors.

Wong et al reported 3.3 years of follow-up on 926 asymptomatic persons, mean age 54 + 10 years. The calcium score predicted events independently of age, gender, and other cardiovascular risk factors, such as diabetes. Relative risks for scores above versus below the mean and median calcium scores were 4.5 and 4.6, respectively, increasing to 8.8 for scores in the top quartile.(57)

In another retrospective study, Kondos et al reported 37 month follow-up on 5,635 initially asymptomatic low to intermediate risk adults.(58) In men, events (n=192) were associated with the presence of CAC (RR=10.5, P<0.001), diabetes (RR=1.98, P=0.008), and smoking (RR=1.4, P=0.025) whereas in women events (n=32) were linked to the presence of CAC (RR=2.6, P=0.037) and not risk factors. While follow-up was only obtained in 64% of patients, patients with scores >170 had a relative risk for developing of hard cardiac events of 7.24 (95% CI, 2.01–26.15), after multivariable analysis was performed with adjustment for age and other coronary heart disease risk factors. The presence of CAC provided incremental prognostic information over age and other risk factors (see Figure 1).

The largest prospective study reported to date also supports the use of CAC in the intermediate population. In the St. Francis Heart Study, a prospective study of 5585 subjects aged 59 + 5 years, a calcium score >100 predicted all atherosclerotic cardiovascular disease events, all coronary events, and the sum of non-fatal myocardial infarction and coronary death events with relative risks of 9.5 to 10.7 at 4.3 years.(59) The calcium score also predicted events independently of and more accurately than measured risk factors. The area under the receiver operating characteristic curve for event prediction with risk factors alone in this study was 0.71, increasing to 0.81 with EBT testing ($p<0.001$).

A recent study by Pohle looked at first MI in a group of patients under the age of 59 (average age 41+10 years).(60) One hundred two patients along with 102 age, gender, and risk factor matched individuals without MI were examined by EBT. The patients with MI had significantly higher EBT calcium scores and 95% of them had detectable coronary calcium as compared to xx percent of control subjects. Importantly, 87% and 61% of the MI patients had calcium scores above the established 50th and 90th percentiles, respectively (see Figure xx). These data underscore that patients with MI have more extensive coronary calcium than those of their matched peers.

In summary, all published studies, with mean age of subjects ranging from 41 to 66 years, have reported that the EBT derived coronary calcium score predicts coronary disease events independently of and more accurately than standard risk factors. No prognostic data related to MDCT is yet available. However, the Multi-Ethnic Study of Atherosclerosis (MESA) was initiated in July 2000 to investigate the prevalence, correlates, and progression of subclinical cardiovascular disease (CVD) in a population-based sample of 6,500 men and women aged 45-84 years. Measurement of CAC will be obtained with EBT or MDCT (3 sites will use EBT, three sites will use MDCT from one of two vendors) together with risk factors and repeated during the study for progression assessment over 7 years. Participants will be followed through 2008 for identification and characterization of cardiac and vascular events, including acute myocardial infarction and other coronary heart disease, stroke, peripheral vascular disease, and congestive heart failure; therapeutic interventions, and mortality.(61) This National Institutes of Health study will help establish the clinical utility of MDCT as compared with EBT, and determine what scores are clinically useful to the clinician. While MDCT does not correlate well with EBT at lower scores, this may prove to be less important if only high scores are found to be more useful in risk prediction.

Use of CAC in the Asymptomatic Patient

The absence of CAC on EBT identifies a group of patients at very low risk of events with a very high sensitivity and negative predictive value for obstructive disease (>99%).(62) A score of 0 (no coronary calcium) with EBT can virtually exclude those patients with obstructive coronary heart disease. Raggi et al(55) demonstrated an annual event rate of only 0.11% for patients with scores of zero by EBT. Both the American College of Cardiology/American Heart Association writing group(63) and the Prevention V Conference agreed that the negative predictive value of EBT is very high for short term events.(64) This was reinforced by the St. Francis Heart Study, where a score of zero had a negative predictive value for cardiac events of 99.5%.(56) It remains to be determined if a zero score derived from MDCT devices has the same prognostic and diagnostic significance in ruling out obstructive coronary heart disease. Only one study has looked at the predictive power of zero scores by MDCT and suggested a negative predictive value for obstructive coronary disease of approximately 60%.

The most powerful and important data for CT scanning for coronary calcium relates to its ability to predict future coronary events in asymptomatic persons. Risk factors have been demonstrated to be suboptimal predictors of future events, failing to predict one-third of future deaths due to coronary heart disease. (65) At least half of all first coronary events occur in asymptomatic individuals who are unaware that they have developed silent coronary heart disease. A sub-group of the Prevention V authorship(66) supported the use of EBT for risk stratification of intermediate risk patients.

The new NCEP Adult Treatment Panel III guidelines(67) support the conclusions of the Prevention Conference V and the ACC/AHA report that high coronary calcium scores confirm increased risk for future cardiac events, stating: "Therefore, measurement of coronary calcium is an option for advanced risk assessment in appropriately selected persons. In persons with multiple risk factors, high coronary calcium scores (e.g., >75th percentile for age and sex) denote advanced coronary atherosclerosis and provide a rationale for intensified LDL-lowering therapy. Moreover, measurement of coronary calcium is promising for older persons in whom the traditional risk factors lose some of their predictive power." Thus, a high CAC score may make a clinician more likely to institute secondary prevention measures sooner (e.g. aspirin, aim for a lower blood pressure [<130/80 versus <140/90, an LDL-C less than < 100 mg/dl as opposed to < 130 or triglycerides <150 mg/dl versus <200 mg/dl). Table I suggests an overall application of CAC scoring with respect to defining overall individual cardiac risk and suggested target goals for LDL (based upon current NCEP guidelines).

Thus current recommendations are to use CAC to measure plaque burden in physician-referred, intermediate risk patients, irrespective of age, in whom the use of lifestyle and/or pharmacologic therapies can be more vigorously applied in a cost-effective manner. Use of EBT or MDCT in very low risk cohorts has not demonstrated to have clinical utility, and focus on intermediate and high-risk cohorts is better substantiated. Generally, the data show that invasive procedures should be reserved for symptomatic patients with inducible ischemia since there is limited information showing benefit in terms of prolongation or quality of life in asymptomatic patients.(68,69,70) To avoid inappropriate or unnecessary follow-up testing or invasive therapeutic procedures in patients who undergo EBT or MDCT, the clinician should determine a priori that the goal of such noninvasive testing is to refine prognostic assessment and then employ, or not, well-proven preventive interventions based on test outcome.

Heart Age and Calculation of Long Term Risk Using CAC

The current NCEP ATP III guidelines(67) strongly encourage use of conventional risk factor analysis and calculation of annual risk in those without established coronary heart disease or known equivalents such as diabetes or pre-existing peripheral vascular disease. Although the goals of this exercise are to determine acceptably levels for LDL cholesterol targeting, they serve useful purposes in defining an estimation of risk for all adults. The general ranges for risk, generally expresses as a risk per decade are as follows: <10% per decade – low risk; >10% but <20% per decade, intermediate or moderate risk; and, >20% per decade as high risk (or coronary disease risk equivalency).

Calculation of risk incorporates data from the Framingham heart study that emphasized the values of combining risk factors into a single calculation.(71) Knowing the total cholesterol, the HDL cholesterol, blood pressure and information on history of hypertension, gender, smoking history, and chronological age this calculation is affected by summing "points" assigned to various ranges for these values. However, it is well known that after the age of 50, age becomes the dominant factor here in defining risk.

The incidence of symptomatic coronary heart disease increases with age and this is the major factor that has provided the evidence for chronological age as a dominant risk factor. The extent or severity of coronary disease increases with age, as has been noted earlier. However, there are numerous additional potential risks for a given individual that are not easily modeling. These include patterns of heredity, general lifestyle and habits, and environmental and social influences. As noted earlier, the coronary artery calcium score is a valid method to estimate coronary "plaque burden". Furthermore, there are data showing how these scores compare between individuals as a function of age and gender.

Grundy(72) was the first to suggest that coronary calcium scores could be used to calculate "heart age" based upon chronological age and ranking of these scores in peer groups. For example, a man at age 50 who has a coronary artery calcium score at the median (50th percentile) for men at this age would have no adjustment in his heart age. However, were he to have a score that was either below the 25th percentile or above the 75th percentile, then his "heart age" would be adjusted downwards by 10 years or upwards by 10 years, respectively. Grundy then suggested that the point scoring system used in the Framingham calculation could be reassigned based upon coronary calcium scores defined by EBT (table 2).

The EBT calcium score, as most experts suggest, should not be viewed in isolation for defining coronary risk, but must be examined in the context of current and important risk factors. Although the calcium score is valuable, it gives no clue as to the reasons for these findings. This "clinical approach" or case management approach makes the most sense. By combining conventional risk factors analysis with "heart age", an estimation of absolute cardiac risk can be defined further risk stratifying the patient for implementation of appropriate risk factors modification goals.

Conclusions

EBT has undergone rigorous testing for reliability and validity and has proven to be useful in identifying individuals with, or at risk for, coronary heart disease. Although MDCT is a promising tool for coronary calcium scoring, more studies are needed comparing EBT and MDCT scans in the same patients, especially with calcium scores < 100. Further radiation dose reduction with MDCT is currently being evaluated. MDCT studies evaluating progression, reproducibility and outcomes studies are needed to fully evaluate its potential to measure and track atherosclerosis. Testing the benefit of serial coronary calcium scores to non-invasively assess for progression or regression of coronary calcium is currently underway.

EBT is a method that can be used to estimate the overall coronary atherosclerotic plaque burden. It can be used to diagnose its presence and determine its extent; furthermore, the information from the calcium score can be used to assess the likelihood of advanced obstructive disease and to provide prognostic information. Finally, it has the potential to determine the consequences of therapeutic interventions regarding progression, stabilization, or regression of coronary atherosclerotic disease.(73)

References Cited:

1. Bostrom K, Watson KE, Horn S, Wortham HC, Herman IM, Demer LL: Bone Morphogenetic Protein Expression in Human Atherosclerotic Lesions. J Clin Invest 1993;91:1800-1809
2. Ideda T, Shirasawa T, Esaki Y, Yoshiki S, Hirokawa K. Osteopontin mRNA is Expressed by Smooth Muscle-derived Foam Cells in Human Atherosclerotic Lesions of the Aorta. J Clin Invest 1993;92:2814-2820
3. Hirota S, Imakita M, Kohri K, Ito A, Morii E, Adachi S, Kim HM, Kitamura Y, Yutani C, Nomura S. Expression of osteopontin messenger RNA by macrophages in atherosclerotic plaques. A possible association with calcification. Am J Pathol 1993;143:1003-8
4. Shanahan CM, Cary NR, Metcalfe JC, Weissberg PL. High expression of genes for calcification-regulating proteins in human atherosclerotic plaque. J Clin Invest 1994;93:2393-402
5. Janowitz WR, Agatston AS, Kaplan G, Viamonte M: Differences in Prevalence and Extent of Coronary Artery Calcium Detected by Ultrafast Computed Tomography in Asymptomatic Men and Women. Am J Cardiol 1993;72:247-254
6. Hoff JA, Chomka EV, Krainik AJ, Daviglus M, Rich S, Kondos GT. Age and Gender Distributions of Coronary Artery Calcium Detected by Electron Beam Tomography in 35,246 Adults. Am J Cardiol 2001;87:1335-1339
7. Blankenhorn DH, Stern D: Calcification of the coronary arteries. Am J Roentgen 1959;81:772-777
8. Frink RJ, Achor RWP, Brown AL, Kincaid JW, Brandenburg RO. Significance of calcification of the coronary arteries. Am J Cardiol 1970;26:241-247.
9. Wexler L, Brundage B, Crouse J, Detrano R. Fuster V, Maddahi J, Rumberger JA, Stanford W, White R: Coronary Artery Calcification: Pathophysiology, Epidemiology, Image Methods and Clinical Implications - A Scientific Statement from the American Heart Association. Circulation 1996;94:1175-1192
10. Bostrom K, Watson KE, Horn S, Wortham HC, Herman IM, Demer LL: Bone Morphogenetic Protein Expression in Human Atherosclerotic Lesions. J Clin Invest 1993;91:1800-1809
11. Ideda T, Shirasawa T, Esaki Y, Yoshiki S, Hirokawa K. Osteopontin mRNA is Expressed by Smooth Muscle-derived Foam Cells in Human Atherosclerotic Lesions of the Aorta. J Clin Invest 1993;92:2814-2820
12. Hirota S, Imakita M, Kohri K, Ito A, Morii E, Adachi S, Kim HM, Kitamura Y, Yutani C, Nomura S. Expression of osteopontin messenger RNA by macrophages in atherosclerotic plaques. A possible association with calcification. Am J Pathol 1993;143:1003-8
13. Shanahan CM, Cary NR, Metcalfe JC, Weissberg PL. High expression of genes for calcification-regulating proteins in human atherosclerotic plaque. J Clin Invest 1994;93:2393-402
14. McCarthy JH, Palmer FJ. Incidence and significance of coronary artery calcification. Brit Heart J 1974; 36:499-506.
15. Lieber A, Jorgens J. Cinefluorography of coronary artery calcification. Am J Radiol 1961; 86:1063.
16. McGuire J, Schneider HJ, Chou T. Clinical significance of coronary artery calcification seen fluoroscopically with the image intensifier. Circulation 1968; 37:82-87.
17. Lieber A, Jorgens J. Cinefluorography of coronary artery calcification. Am J Radiol 1961; 86:1063.
18. McGuire J, Schneider HJ, Chou T. Clinical significance of coronary artery calcification seen fluoroscopically with the image intensifier. Circulation 1968; 37:82-87.
19. Uretsky B, Rifkin R, Sharma S, Reddy P. Value of Fluoroscopy in the detection of coronary stenosis: influence of age, sex, and number of vessels calcified on diagnostic efficacy. Am Heart J 1988;115(2):323-33.
20. Faber A: Die Arteriosklerose, from Pathologische Anatomie, from Pathogenese Und Actiologie. G. Fischer, 1912
21. Clarkson TB, Prichard RW, Morgan TM, Petrick GS, Klein KP. Remodeling of Coronary Arteries in Human and Nonhuman Primates. JAMA 1994;271:289-294
22. Sangiorgi G, Srivatsa SS, Rumberger JA, Severson A, Edwards WD, Gregoire J, Fitzpatrick LA, Schwartz RS. Arterial Calcification and Not Lumen Stenosis is Highly Correlated with Atherosclerotic Plaque Burden in Humans: A Histologic Study of 723 Coronary Artery Segments using Nondecalcifying Methodology. J Am Coll Cardiol 1998;31:126-33
23. Simons DB, Schwartz RS, Edwards WD, Sheedy PF, Breen JF, Rumberger JA: Non-Invasive Definition of Anatomic Coronary Artery Disease by Ultrafast CT: A Quantitative Pathologic Study. J Am Coll Cardiol 1992; 20: 1118-26
24. Rumberger JA, Schwartz RS, Simons DB, Sheedy PF, Edwards WD, Fitzpatrick LA: Relations of Coronary Calcium Determined by Electron Beam Computed Tomography and Lumen Narrowing Determined at Autopsy. Am J Cardiol 1994;73:1169-1173

25. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS: Coronary Artery Calcium Areas by Electron Beam Computed Tomography and Coronary Atherosclerotic Plaque Area: A Histopathologic Correlative Study. Circulation 1995;92:2157-2162

26. Baumgart D, Schmermund A, Goerge G, Haude M, Ge J, Adamzik M, Sehnert C, Altmaier K, Groenemeyer D, Seibel R, Erbel R; Comparison of Electron Beam Computed Tomography with Intracoronary Ultrasound and Coronary Angiography for Detection of Coronary Atherosclerosis. J Am Coll Cardiol 1997; 30:57-64

27. Rumberger JA, Sheedy PF, Breen JF: Use of ultrafast (cine) x-ray computed tomography in cardiac and cardiovascular imaging. IN - Mayo Clinic Practice of Cardiology; Eds: ER Giuliani, BJ Gersh, MD McGoon, DL Hayes, HF Schaff (3rd Edition), Mosby, St. Louis, 1996, Chapter 8, pp. 303-324

28. Bell RM, Lerman L, Rumberger JA: Validation of Minimally Invasive Measurement of Myocardial Perfusion using Electron Beam Computed Tomography and Application in Human Volunteers. Heart 1999;81:628-635

29. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R: Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990:15:827-832

30. Schmermund A, Denktas AE, Rumberger JA, Christian TF, Sheedy PF, Bailey KR, Schwartz RS: Independent and Incremental Value of Coronary Artery Calcium for Predicting the Extent of Angiographic Coronary Artery Disease: Comparison with Cardiac Risk Factors and Radionuclide Perfusion Imaging. J Am Coll Cardiol 1999;34:777-86

31. Becker CR, Kleffel T, Crispin A, Knez A. Coronary artery calcium measurement: agreement of multirow detector and electron beam CT. Am J Roentgenol 2001;176:1295-298.

32. Knez A, Becker CR, Becker A. Determination of coronary calcium with multi-slice spiral computed tomography: a comparative study with electron-beam CT. Int J Cardiovasc Imaging 2002;18:295-303

33. Budoff MJ, Songshou M, Zalace CP, Bakhsheshi H, Oudiz RJ. Comparison of spiral and electron beam tomography in the evaluation of coronary calcification in asymptomatic persons. International Journal of Cardiology 2001;77:181-188

34. Carr JJ, Crouse JR, D'Agostino RB, Peterson NP, Burke GL: Evaluation of a Subsecond Gated Helical CT for Quantification of Coronary Artery Calcium and Comparison with Electron Beam CT. Am J Roentgenol 2000;174:15-21

35. Goldin, J. G., Yoon, H. C. Spiral versus electron-beam CT for coronary artery calcium scoring. Radiology 2001;221(1): 213-21.

36. Rumberger JA, Brundage BH, Rader DJ, Kondos G: Electron Beam CT Coronary Calcium Scanning: A Review and Guidelines for use in Asymptomatic Individuals. Mayo Clinic Proceedings 1999; 74:243-252

37. Kopp AF, Ohnesorge B, Becker CR. Reproducibility and Accuracy of Coronary Calcium Measurements with Multi-Detector Row versus Electron-Beam CT. Radiology 2002 ;225:113-9

38. Horiguchi J, Nakanishi T, Ito K. Quantification of coronary artery calcium using multidetector CT and a retrospective ECG-gating reconstruction algorithm. Am J Roentenol. 2001; 177:1429-435.

39. Ohnesorge B, Flohr T, Fischbach R, et al. Reproducibility of coronary calcium quantification in repeat examinations with retrospectively ECG-gated multisection spiral CT. Eur Radiol 2002 ;12:1532-1540

40. Hidajat N, Wolf M, Rademaker J, et al. Radiation dose in CT of the heart for coronary artery disease and CT of lung for pulmonary embolism: comparison between single-slice detector CT, multislice detector CT and EBT. Radiology 2000;217:74.

41. Cohen M, Poll L, Pittmann C, et al. Radiation exposure in multi-slice CT of the heart. Fortschr Rontgenstr 2001;178:295-99

42. Ohnesorge B, Flohr T, Becker CR, et al. Dose evaluation and dose reduction strategies for ECG-gated multislice spiral CT of the heart. Radiology. 2000;217:487.

43. Jerijan K, Brant-Zawadzki MN. Radiation dose in coronary calcium: comparison of multi-slice and electron beam CT scanners. Radiology. 2001;221:365

44. Schmidt B, Ulzheimer S, kalender WA. Dose in multislice cardiac CT. Assessment of organ and effective dose values with Monte Carlo methods. Radiology. 2001;221:414

45. Hunold P, Vogt FM, Schmermund A, et al. Radiation exposure during noninvasive coronary artery imaging: comparison of multislice CT and electron-beam CT. Radiology. 2001;221:540

46. Jakobs TF, Becker CR, Ohnensorge B, et al. Multislice helical CT of the heart with retrospective ECG gating: reduction of reduction of radiation exposure by ECG-controlled tube current modulation. Eur Radiol 2002;12:1081-86

47. Rifkin RD, Parisi AF, Folland E: Coronary calcification in the diagnosis of coronary artery disease. Am J Cardiol 1979, 44:141-147.

48. Eggen DA, Strong JP, McGill HC: Coronary calcification: Relationship to clinically significant coronary lesions and race, sex and topographic distribution. Circulation 1965, 32:948-955.

49. Margolis JR, Chen JTT, Kong Y, et al.: The diagnostic and prognostic significance of coronary artery calcification. Radiology 1980, 137:609-616.

50. Detrano RC, Wong ND, Doherty TM, et al.: Coronary calcium does not accurately predict term coronary events in high-risk adults. Circulation 1999, 99:2633-8.

51. Park, R, Detrano R, Xiang M, et al.: Combined use of computed tomography coronary calcium scores and C-reactive protein levels in predicting cardiovascular events in non-diabetic individuals. Circulation 2002, 106:2073-7.

52. Callister TQ, Janowitz W, Raggi P. Comparison of the sensitivity of two electron beam computed tomography imaging protocols for the detection and quantification of coronary artery calcium. Am J Roentgenol 2000;175:1743-6.

53. Mao S, Child J, Carson S, et al. Sensitivity to detect small coronary artery calcium lesions with varying slice thickness using electron beam tomography. Invest Radiol 2003;38(3):183-7

54. Raggi P, Callister TQ, Cooil B, et al.: Identification of patients at increased risk of first unheralded acute myocardial infarction by electron beam computed tomography. Circulation 2000, 101:850-5.

55. Raggi P, Cooil B, Callister TQ. Use of electron beam tomography data to develop models for prediction of hard coronary events. Am Heart J 2001;141:375-82.

56. Arad Y, Spadaro L, Goodman K, et al.: Prediction of coronary events with electron beam computed tomography. J Am Coll Cardiol 2000, 36:1253-60.

57. Wong ND, Hsu JC, Detrano RC, et al: Coronary artery calcium evaluation by electron beam computed tomography and its relation to new cardiovascular events. Am J Cardiol 2000, 86:495-498.

58. Kondos GT, Hoff JA, Sevrukov A, et al. Coronary Artery Calcium and Cardiac Events Electron-Beam Tomography Coronary Artery Calcium and Cardiac Events: A 37-Month Follow- Up of 5,635 Initially Asymptomatic Low to Intermediate Risk Adults. Circulation 2003;107:2571-2576.

Arad Y, Roth M, Newstein D, et al: Coronary calcification, coronary risk factors, and atherosclerotic cardiovascular disease events. The St. Francis Heart Study. J Am Coll Cardiol 2003;41:6.

Pohle K, Ropers D, Maffert R, Gentner P, Moshage W, Regenfus W, Kusus M, et al. Coronary calcification in young patients with first, unheralded myocardial infarction: a risk factor matched analysis using electron beam tomography. Heart 2003;89:625-628

Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol 2002;156(9):871-81.

62. Haberl R, Becker A, Leber A, et al. Correlation of coronary calcification and angiographically documented stenoses in patients with suspected coronary artery disease: results of 1,764 patients. J Am Coll Cardiol 2001;37:451-7.

O'Rourke RA, Brundatge BH, Froelicher VF, et al.: American College of Cardiology/American Heart Association expert consensus document on electron beam computed tomography for the diagnosis and prognosis of coronary artery disease. Circulation 2000, 102:126-40.

64. Smith SC, Greenland P, Grundy SM. Prevention Conference V: beyond secondary prevention: identifying the high-risk patient for primary prevention. Executive summary. Circulation 2000;101:111-6.

65. Grover SA, Coupal L, Hu XP. Identifying adults at increased risk of coronary disease: how well do the current cholesterol guidelines work? JAMA 1995;274:801-806

Greenland P, Smith Jr SC, Grundy SM. Improving coronary heart disease risk assessment in asymptomatic people: role of traditional risk factors and noninvasive cardiovascular tests. Circulation 2001;104(15):1863-7

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Circulation 2002;105:3157-3373

68. Gibbons RJ, Balady GJ, Bricker JT, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Circulation 2002 Oct 1;106(14):1883-92.

69. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA guidelines for coronary artery bypass graft surgery: executive summary and recommendations: a report of the American College of Cardiology/American Heart

Association Task Force on Practice Guidelines (Committee to Revise the 1991 Guidelines for Coronary Artery Bypass Graft Surgery). Circulation. 1999;100:1464-1480.

70. Forrester JS, Shah PK. Lipid lowering versus revascularization. An idea whose time (for testing) has come. Current Perspectives. Circulation 1997;96:1360-2.

71. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998;97:1837-1847

Grundy SM. Coronary plaque as a replacement for age as a risk factor in global risk assessment. Am J Cardiol 2001;88 (supplement):8E-11E

73. Budoff MJ, Raggi P. Coronary artery disease progression assessed by electron beam computed tomography. Am J Cardiol 2001;88(suppl):46E-50E

Table 1: Clinical interpretation of coronary artery calcium (CAC) scores in asymptomatic individuals (no known history of cardiac disease) and suggested LDL goals for treatment.

Clinical Situation	Range of Cardiovascular Risk (Framingham Risk)	LDL goal (mg/dl)
CAC score <10 and score <75th percentile for age/gender	Low (<10% per decade)	<160
CAC score 10-100 and score <75th percentile for age/gender	Intermediate (10-20 % per decade)	<130
CAC score >100 or score >75th percentile for age/gender	High (>20 % per decade) Coronary disease risk equivalency	<100

Table 2: Estimation of "heart age" by CAC score percentile. Note that this scheme adds 10 years to the current chronological age if the score is above the 75th percentile and subtracts 10 years from current chronological age if the score is <25th percentile. If the score is in the median range for a given age, then there is no adjustment in the traditional Framingham risk points. Adapted from data presented in reference 72. See text for details.

	Men				Women			
		CAC Score Rank				CAC Score Rank		
Age (years)	Framingham Age Points	<25th percentile	25th-75th percentile	>75th percentile	Framingham Age Points	<25th percentile	25th-75th percentile	>75th percentile
20-34	-9	-12	-9	0	-7	-11	-7	0
35-39	-4	-9	-4	3	-3	-9	-3	3
40-44	0	-6	0	6	0	-6	0	6
45-49	3	-4	3	8	3	-3	3	8
50-54	6	0	6	10	6	0	6	10
55-59	8	3	8	11	8	3	8	12
60-64	10	6	10	12	10	6	10	14
65-69	11	8	11	13	12	8	12	16
70-74	12	10	12	14	14	10	14	18
75-79	13	11	13	15	16	12	16	20

Figure 1: Relative risk (RR) for a cardiac event using conventional risk factors and CAC score (EBT database). Results for 37+12 month follow up on 5635 initially asymptomatic individuals of low to intermediate pre-test likelihood. Cardiac events included initial survival of an acute myocardial infarction, documented sudden cardiac death, or coronary/peripheral revascularization procedure. The age range for men (75%) and women (25%) was 30-76 years with an average age of 51+9 years. Adapted from data presented in Reference 58. See text for details. TC = total cholesterol; HTN = history of hypertension; DM = known diabetes.

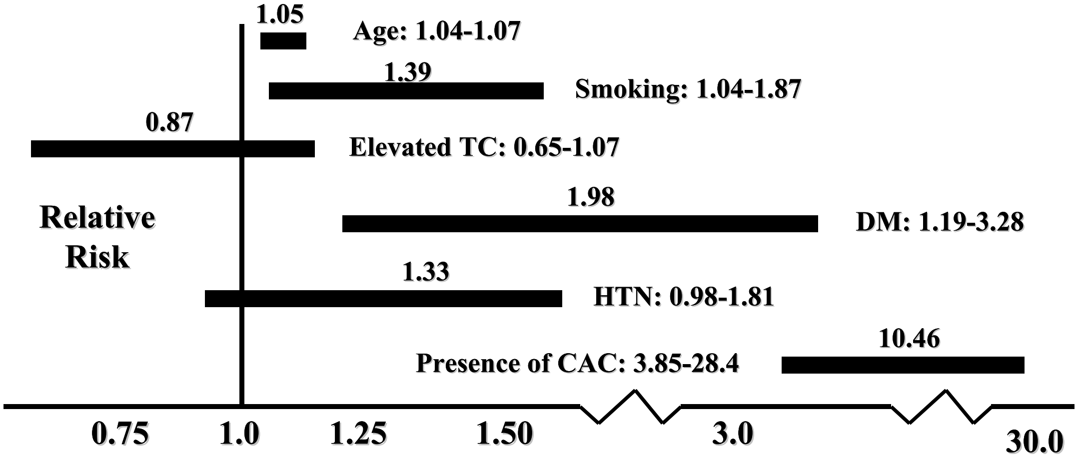

Figure 2: CAC (EBT coronary artery calcium score): absence or presence of CAC, percent of individuals with initial score above the 50th or 90th percentile for age and gender. First myocardial infarction in young previously asymptomatic individuals versus control subjects.. Ages are between 19 and 59 years with an average age of 41+10 years. The data are based upon 102 patients and 102 control subjects matched for age, gender, and conventional risk factor profile. Adapted from data presented in Reference 60. See text for details.