

# The Role of Ultra-fast Computed Tomography in the Assessment of Suspected or Known Coronary Artery Disease

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The use of electron beam computed tomography (EBCT) for non-invasive assessment of coronary artery calcium is growing in popularity but remains controversial. There is uncertainty regarding the place this test has in clinical practice and the conclusions that may or may not be drawn from test results. However, it is clear that EBCT can be used to address defined clinical questions regarding the presence and severity of the atherosclerotic process. On the horizon, there is developing potential for non-invasive coronary imaging using new electron beam technology that may soon rival existing multi-detector computed tomography and coronary angiography for imaging of coronary arteries. Frustratingly, despite continuing research in this exciting area, there remains a paucity of evidence to guide the application of this modality to daily clinical practice.

The purpose of non-invasive cardiac imaging is to address questions related to the optimal treatment of a patient in the context of currently available therapies. Cardiologists are challenged to identify the presence of coronary artery disease (CAD) in symptomatic patients without prior documented CAD (diagnostic evaluation) and to assess the severity/risk of known CAD (prognostic evaluation). In selected patients with cardiac risk factors it may also be possible to identify the presence of pre-clinical disease, that is presence of atherosclerotic disease prior to development of significant (>50%) epicardial disease as evaluated by coronary angiography (screening evaluation).

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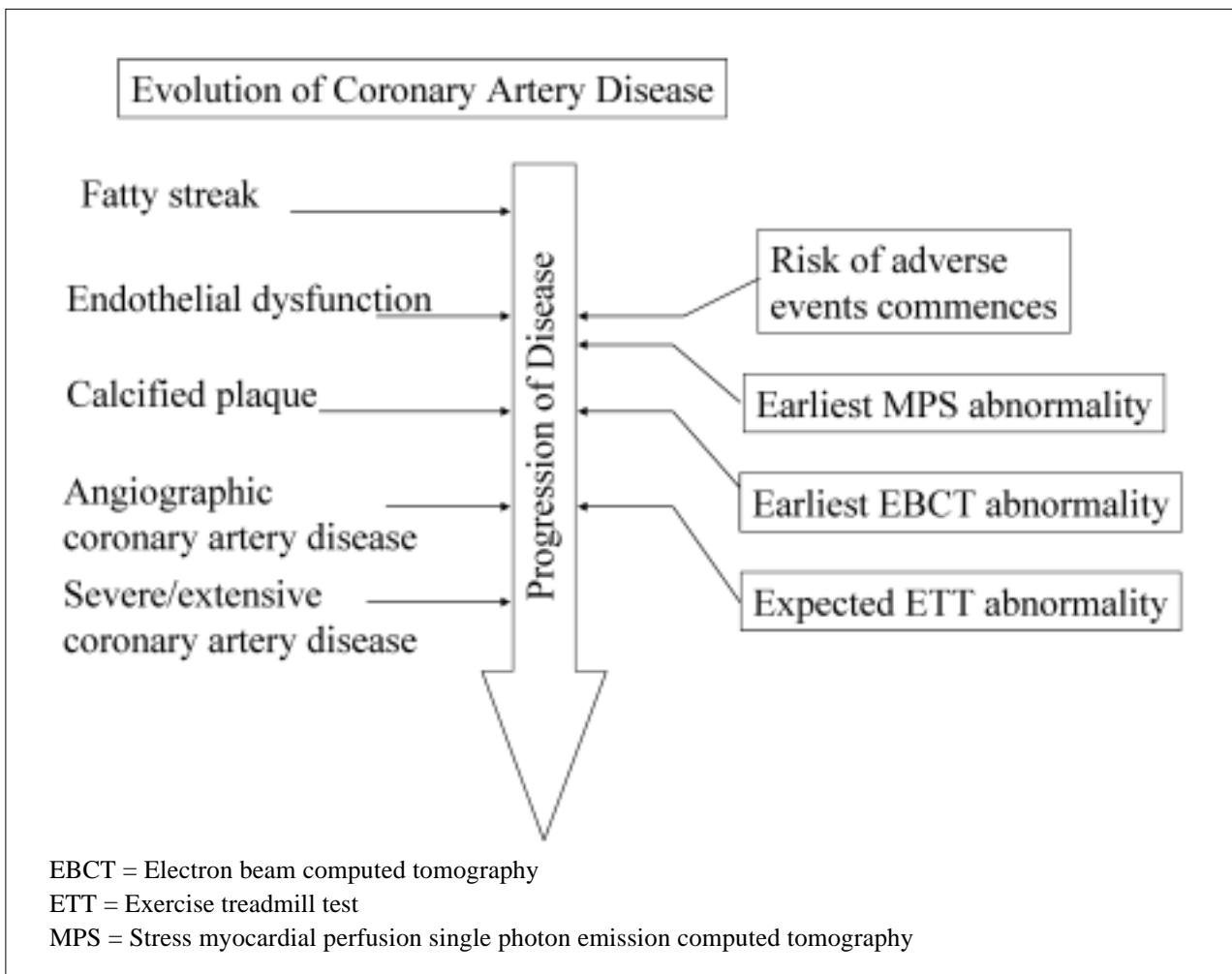
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The quantification of coronary artery calcium by EBCT is a powerful indirect marker of the total atherosclerotic plaque burden.<sup>1,2</sup> It is known that atherosclerotic plaques calcify over time, that acute plaque rupture is related to the balance between inflammation and mechanical stressors and that rupture is less likely in a "stable" calcified plaque than in a non-calcified lipid rich minor plaque. The amount of calcium burden measured by computerized tomography is related to the likelihood of epicardial stenoses being present.<sup>3-7</sup> The total calcium burden in body increases with advancing years and most men over the age of 60 have measureable levels of calcium. It has also been shown that the observed risk of subsequent myocardial events is increased in patients with high coronary artery calcium scores (Figure 1).<sup>8-12</sup> Conventional risk factors explain very little of observed variation in calcium scores. This finding may in part be explained by the recent findings of the Epidemiology of Coronary Artery Calcification (ECAC) study group who reported that 43.5% of the variation in coronary artery calcium quantity could be attributed to genetic factors.<sup>13</sup>

## Asymptomatic Patients with Risk Factors: Screening Evaluation

Interest in the use of EBCT for screening for atherosclerotic disease is driven by the knowledge that large number of patients present with life threatening cardiac events as their initial manifestation of CAD. Currently we rely on risk factor identification and modification in an effort to prevent or delay onset of CAD. However, EBCT can potentially identify those asymptomatic patients with risk factors who already have calcifying atherosclerotic disease.

The routine use of EBCT for screening for CAD in asymptomatic individuals was recommended against



**Figure 1.** *Evolution of Coronary Artery Disease. In assessing the role of non-invasive imaging it is useful to remember the natural history of coronary artery disease and the points along this time line at which various tests potentially become abnormal. EBCT is a highly sensitive test for the presence of coronary artery calcium, however non-calcified lipid rich plaque is inherently less stable than calcified plaque. The absence of calcium does not preclude any risk from acute coronary events associated with abnormal risk factors and does not negate the need for risk factor modification.*

by the American College of Cardiology (ACC) and American Heart Association (AHA) expert consensus document and Prevention Conference V, on the basis that EBCT does not provide clear additional information over traditional risk factor assessment.<sup>8,14</sup> An ideal observational study evaluating the role of EBCT as a test to predict outcome in asymptomatic individuals is unlikely to be undertaken given today's knowledge of the importance of risk factor modification and the bias introduced by referral to catheterization on the basis of the calcium score.

Studies of asymptomatic patients to date have shown that cardiac event rates can be predicted by coronary artery calcium scoring. Arad and associates reported that a threshold Agatston score of 80 had an excellent negative predictive value of 99% for prediction of coronary events (death, MI, revascularization) in a predominantly male population with multiple cardiac risk factors.<sup>15</sup> However, the positive predictive value of EBCT at this threshold calcium score was only 10%. This finding of high sensitivity and poor specificity is typical of the literature in coronary artery calcium

scoring of asymptomatic patients.<sup>8,9,15,16</sup> In this study, traditional risk factors remained predictive of events, independent of the calcium score. Importantly, the patients with lower calcium scores who had multiple CAD risk factors remained at increased risk of events and 7/39(18%) of the total events occurred in patients with calcium scores <97. Thus, concern remains about the value of EBCT as a screening test for predicting likelihood of events in populations with multiple risk factors and this is the population most in need of screening.

It has been demonstrated by several studies and in pooled analysis of data that the risk of events increases as the coronary calcium burden increases.<sup>8,9,15</sup> From the multivariable analysis in Arad's paper, the odds ratio for death, MI or revascularization increased from 14.3 to 20.2 with increasing calcium score threshold  $\geq 80$  to  $\geq 600$ .

A recent publication from Wayhs et al.<sup>10</sup> reported an extremely high annualized event rate of 25% in a group of 89 patients with calcium scores over 1000 who were followed for  $17 \pm 11$  months. Although other studies have found that event rates increase as calcium scores increase, the absolute event rate observed in this population was unusually high.

While the value of coronary calcium as an independent predictor of patient outcome has been demonstrated, the value of EBCT over traditional methods of screening for the presence of CAD has not been clearly determined. However, patient and physician demand is such that the use of this test for screening continues. Patients should be advised that although event rates are low in patients with very low calcium scores, the absence of measurable calcium does not preclude future cardiac events and should not alter management of cardiac risk factors. The finding of any coronary calcium is a marker for the presence of atherosclerosis and may serve to reinforce the need for risk factor modification. There is anecdotal evidence that a few asymptomatic patients with extremely high calcium scores have had subsequent angiography on the basis of the high score and have been found to have left main coronary artery stenosis. From the existing literature however, this finding is probably highly unusual. Overall there is no evidence to support the routine use of EBCT results in selecting therapy or guiding referral to further testing in asymptomatic patients.

## Symptomatic Patients with Risk Factors: Diagnostic Evaluation

The place of calcium scoring in the evaluation of patients with risk factors and symptoms is evolving and there is a need for longitudinal studies to help to define where this test best fits into a testing algorithm. In symptomatic populations, the sensitivity of calcium scoring is again high but specificity is poor (Pooled data sensitivity 90%, specificity 49%).<sup>8</sup> Therefore it is likely that the test will need to be combined with another test in order to enhance specificity. Additionally, it is crucial to remember that calcium scoring does not give any information about the presence of inducible ischemia or the left ventricular function and does not have established value as an alternative to currently available stress imaging techniques. Several different potential approaches to calcium scoring in symptomatic patients are feasible:

1. EBCT and exercise treadmill testing. The first possible approach is to combine treadmill exercise test results with calcium scoring in order to reduce the rates of patients with false positive treadmill results referred to catheterization. Shavelle and colleagues<sup>17</sup> found the specificity of EBCT for the prediction of >50% angiographic stenosis was improved from 47% to 83% by the addition of exercise treadmill testing results to EBCT results (Threshold Calcium score >0 and positive exercise treadmill test). However, in this study the overall accuracy of technetium stress was equivalent to the EBCT/exercise treadmill test combined and technetium stress testing was more sensitive for the detection of flow limiting epicardial stenosis.<sup>17,18</sup>
2. EBCT and stress imaging. The second possible approach is to send all patients with a coronary calcium score above a threshold level to stress imaging. Patients with calcium scores below this threshold would receive aggressive risk factor management and close follow up (with referral to further testing if symptoms failed control by medical therapy). Using this approach, patients referred for stress imaging have a greater likelihood of significant coronary disease. The selected threshold level of calcium score should represent the level at which

sensitivity is maintained, specificity increases and the risk of future events is at an acceptably low level for patients below the cut off to justify medical management. The limitation of this approach, however, is demonstrated by the fact that approximately 4% of patients having calcium score assessments following documented MI have no detectable calcium. Calcium scoring gives no information about inducible ischemia and there is no evidence that it is superior to any existing modality for the diagnosis of occlusive CAD.

3. EBCT and coronary angiography. This possible approach accepts the premise that presence of calcium represents evidence for atherosclerosis, potentially justifying referral to coronary catheterization to rule out significant epicardial stenosis. Haberl and colleagues reported that absence of calcium was associated with <1% risk of significant CAD defined by catheterization.<sup>6</sup> For detection of >50% stenosis by catheterization the sensitivity was 99% in men and 100% in women using a calcium score criteria of "any calcium" but specificity was consequently very low (23% for men and 40% for women). Therefore this approach would subject large numbers of patients without flow limiting lesions to an expensive invasive test that also carries a small but significant risk. This approach fails to recognize that calcium score by EBCT is a marker for atherosclerosis but not epicardial stenosis.
4. EBCT and stress imaging or coronary angiography. A combination of the last two approaches could be to undertake stress imaging in patients with calcium scores up to a threshold level and direct referral to catheterization in patients with very high calcium scores. This approach potentially reduces rates of unnecessary catheterization and avoids missing the presence of ischemia in patients with low calcium scores who have risk factors and symptoms.
5. Normal stress imaging and EBCT. The final potential approach in the symptomatic patient is to use the calcium score as a second-line investigation following normal stress imaging. If a calcium score is zero, then the physician may have increased

confidence that there is no evidence for atherosclerotic disease. Alternatively, an elevated calcium score is evidence for atherosclerosis and the patient should receive medical therapy including the most aggressive risk factor modification.

In certain populations where exercise treadmill testing may be considered less reliable (e.g. women) EBCT may also potentially be an alternative to ETT in diagnostic evaluation. The greatest role of EBCT may be to further define risk in patients determined to be at intermediate risk by conventional assessment of risk factors. Currently there is inadequate published data to determine the ideal place of EBCT in the diagnostic algorithm. Studies of different management strategies are needed to determine the best approach to calcium scoring in the evaluation of symptomatic patients.

### **Patients with Known Coronary Artery Disease: Prognostic Evaluation**

It has been suggested that there is a potential role for EBCT in monitoring the progression or regression of disease in terms of plaque burden. Although early studies reported mean inter-scan calcium score reproducibility of only 14-38%, subsequent advances in hardware, acquisition protocols and calcium score calculation methods have improved aspects of reproducibility.

It should be noted that patients with CAD are not all suitable for EBCT evaluation of calcium scores. Coronary artery bypass grafts calcify at a variable rate and the use of EBCT in patients with grafts is not recommended. In patients with known CAD, it has been shown that calcium scores increase over time. Rates of increase are greater in patients with occlusive coronary artery disease and in patients with end stage renal disease.<sup>19,20</sup> This rate of progression slows with statin therapy and calcium scores may even regress with aggressive lipid lowering.<sup>21</sup>

For EBCT to be used in this context, the error of variability at the site undertaking repeated studies must be minimal. This variability assessment should include assessment of inter-scan variability, intra and inter-observer variability and a decision regarding the type of calcium scoring method to be used (Agatston score

vs calcium volume score).<sup>22</sup> Carefully performed assessments using newer software systems InSight and AccuImage have been reported excellent (>98%) inter and intra observer reproducibility in a recently published paper by Yamamoto et al.<sup>23</sup> However, the overall inter-scan variability was marginally lower using a console based method than the newer software and was significantly lower for calcium volume scoring than Agatston score (13.3% vs 17%). Importantly, inter scan variability using the Agatston method was up to 23.9% in patients with lower calcium scores (<66).

The routine use of calcium scoring for tracking disease progression is not recommended. However, in selected subsets of patients with higher calcium scores EBCT may provide a non-invasive marker of disease progression or regression with therapy. Evidence that this will provide superior prognostic information to that already available is yet to be presented.

### **New Horizons for Computed Tomography in Non-invasive Assessment of CAD**

There have been developments in multi-detector computed tomography (MDCT) that have improved imaging times and resolution. Many centers are using MDCT for calcium scoring as a low cost alternative to EBCT, however there is inadequate data to show the relationship between MDCT calcium scores and EBCT calcium scores and the necessary validation studies are awaited.

Coronary artery imaging using MDCT or EBCT is a desirable addition to calcium score data. However, until now limited temporal resolution has meant that only the proximal portions of coronary arteries have been clearly visualized. In the race for coronary imaging by computed tomography, the 16-slice MDCT has looked most promising to date in terms of temporal and spatial resolution. In expert hands, this technology appears accurate for the detection of significant proximal epicardial stenosis, albeit with a moderate radiation exposure to the patient.

General electric/Imatron claims dramatic improvements in temporal resolution of up to 33 ms and imaging speed of 30 frames per second with the new "e-speed" EBCT. These advances give potential

for EBCT to provide coronary artery imaging, cardiac wall motion imaging and cardiac volume quantification in addition to improved accuracy of calcium scoring. This technology has limited availability at this point but is a major potential advance towards a complete non-invasive assessment of coronary artery disease risk using EBCT. Validation studies of this latest technology are anticipated in the near future.

### **Conclusion**

The role of EBCT in screening, diagnosis and prognosis continues to evolve. It has been established that EBCT calcium scoring reflects the degree of atherosclerotic plaque burden, that patients with higher calcium scores are at greater risk of adverse cardiac events and, in symptomatic patients, the likelihood of occlusive CAD increases as a function of calcium score.

However, enthusiastic incorporation of EBCT into routine clinical practice should be tempered by careful assessment of the available literature. To date, there is no evidence that screening asymptomatic patients provides incremental prognostic information over established risk factors. There is additionally, a paucity of evidence to support the use of the calcium score as the basis for adjusting risk modification therapy or as justification for invasive testing in asymptomatic patients. In patients with risk factors who have had EBCT performed and have a very high calcium score it is appropriate to perform a test for inducible ischemia as the next step and not to perform a coronary angiogram based solely on the calcium score. In the diagnosis of CAD in symptomatic patients, the low specificity of EBCT makes it unsuitable as a stand-alone non-invasive test but specificity can be improved by combining EBCT with a test of inducible ischemia.

Given recent technological advances in temporal resolution, EBCT may well play an important future role in the management of patients with suspected coronary artery disease. Appropriate and cost-effective inclusion of EBCT in the assessment of patients with suspected or known coronary artery disease will need to follow if there is evidence that the calcium score provides incremental or independent value over existing techniques for diagnosis and risk assessment.

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