

Letter to the Editor

An Open Letter to The Hong Kong College of Cardiology Regarding Electron Beam Computed Tomography (EBT)

Dear Editor,

Ref: "Comment on Electron Beam Computed Tomography" by Dr. Patrick T H Ko. Letter to the Editor, J HK Coll Cardiol, Vol 11, 2003.

My experience with Electron Beam Computed Tomography (EBT) now dates me at over 20 years of research and clinical practice, initially in cardiac physiology, but for the past decade in coronary atherosclerosis, atherosclerosis imaging, and Preventive Cardiology. Thus, I feel I can speak from some level of authority as well as considerable experience. The point in question relates to the use of EBT and coronary calcium scoring for defining coronary disease in a non-invasive manner. I will admit, like many trained formally in traditional Cardiology and brought up with the idea that definition of coronary stenoses severity was our *standard* in defining coronary disease, that my initial efforts in using coronary calcium were directed towards that end.

Our initial studies from autopsy specimens during my tenure at the Mayo Clinic defined that coronary calcium area, by direct histologic comparisons as well as by EBT, was a valid surrogate to defining *in situ* atherosclerotic plaque.¹⁻³ The next step was to then determine application of the non-invasive EBT calcium score to defining stenosis severity in patients referred for clinically indicated invasive coronary angiography. This is where our initial efforts demonstrated that we could in fact NOT define coronary stenosis severity adequate for clinical diagnostic purposes using the EBT calcium score.^{4,5} I was initially taken-aback by these findings and also joined with my cardiology colleagues

in defining the potential for "false positive" results using EBT. In fact, however, as I have come to learn, the results were NOT false, but clearly showed that **coronary calcium in any given site is 100% specific for coronary atherosclerosis, but NOT specific for the degree of narrowing.** My Mayo Clinic colleagues and I in fact further investigated this and reported on a resolution of the problem in a separate necropsy study.⁶ What we found was that coronary calcium did continue to define coronary atheromatous plaque, but failed to define site-by-site stenosis severity due to the phenomenon of coronary artery remodeling, mentioned by Dr. Ko in his Editorial. This concept was initially reported by Dr. Glagov, at the University of Chicago, where he and his colleagues demonstrated that coronary plaque may progress by expanding the mural surfaces and yet not necessarily, until its later stages, result in luminal narrowing.⁷

The traditional view from most Cardiologists had been that a definition of "coronary artery disease" was a stenosis of significant magnitude, defined as generally representing a singular or multiple narrowing defined on a "luminogram" of >50-70%. Over the years, however, we have subsequently learned that **atherosclerosis is a diffuse disease and that focusing, as a means of defining "disease", on a stenosis of >50% vastly underestimates the severity and extent of the underlying atherosclerosis in a given individual.** Dr. Steven Nissen, Vice-Chair of Cardiology at the Cleveland Clinic, has perhaps been the best at pointing out the inadequacies of traditional coronary angiography by performing simultaneous investigations using intravascular ultrasound (IVUS). He has demonstrated that individuals may well have a "normal" coronary angiogram (i.e. luminogram) and yet have "significant" atheromatous disease⁸ due to "positive coronary remodeling". Subsequent to these investigations my colleagues and I compared "apples with apples" demonstrating that **the coronary artery calcium score**

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by EBT correlated well with IVUS definition of atheromatous plaque.^{9,10}

Dr. Ko states in his Editorial that coronary angiography is "...the *diagnostic gold standard*...". Many recent authors would dispute that statement as it relates to atheromatous plaque, as discussed above, although it does remain the clinical standard for defining the site of "significant luminal narrowing" that are targets for PCI and/or road maps for bypass surgery. His **statement** later however **that "EBCT (is)...not specific or accurate in so far as the diagnosis or the staging of clinically significant coronary disease..." is frankly and explicitly inaccurate.** The goal of EBT is to define the extent of atherosclerotic plaque and thus its "accuracy" in defining **clinically** significant disease should be better understood in its ability to predict risk of coronary events or clinically significant outcomes. The premise (or promise, more appropriately) of EBT is not to "*define significant coronary artery disease*", as implied by Dr. Ko, but to define the extent of coronary atheromatous plaque. Thus he has mis-stated his claim when he indicated that "*The premise of EBCT is thus defeated*". In fact the "promise" of EBT has been fortified by collective literature that has added incrementally to our understanding over the past decade.

Dr. Ko is indeed correct in that the formation of mural coronary artery calcification, in response to the inflammatory nature of coronary disease, may well form to provide a lattice of support in an attempt to render the plaque stable. **However**, the pathological literature shows¹¹ that **80% of the "culprit" lesions** in necropsy studies **contain histologic calcium** hydroxyapatite. However, many stable lesions show the same predilection underscoring that coronary calcium is neither a unique marker for stable nor unstable plaque. Although so called "vulnerable" plaques have been shown to be more predominantly lipid laden than calcium laden, this does not limit the value of EBT and calcium scoring in estimating the overall extent of atherosclerosis plaque present. In any given individual about 2/3 of plaque is in fact "scar" and about 1/3 is more predominantly "lipid laden". Thus EBT cannot be used to define which plaque is unstable, but can and has been shown to define disease extent (even compared with the "extent" of angiographic disease or the extent of thallium perfusion defects¹²).

The proof of the above statements must be founded in the prediction of clinical outcomes using coronary calcium by EBT as a measure of disease. Although Dr. Ko quotes one paper suggesting that EBT provided no incremental value over the sum of ALL conventional risk factors¹³ [of note and lost to most "critics" is that risk factors also failed to predict events adequately in the same cohort], **subsequent research (even from that same laboratory) has demonstrated that the coronary calcium score by EBT provided prognostic information independent and incremental to conventional risk factors.**¹⁴⁻¹⁷ Angiographic studies over the past 25 years have demonstrated that the extent of coronary disease is directly related to prognosis.^{18,19} The presence of moderate amounts of coronary calcium (i.e., EBT scores exceeding 100) has been shown in several studies to predict cardiac events in symptomatic²⁰ and asymptomatic²¹ individuals. The relative risk of a cardiac event in an individual with a moderate to high calcium score by EBT compared to an individual who has no or minimal coronary calcium has ranged from a mean of 8.66:1²² in a meta-analysis review of EBT to as high as 15:1²³ over a 2-4 year follow up time period in a more recent publication. The magnitude of the risk associated with coronary calcium is underscored when one considers the relative risks of developing symptomatic coronary artery disease in younger patients based upon conventional individual "risk factors" (15 year follow up Framingham study of initially asymptomatic men) is only 1.9:1 for an elevated Lp(a), 1.8:1 for total cholesterol >240 mg/dl., 1.8:1 for an HDL <35 mg/dl, 3.6:1 for cigarette smoking, and 1.2:1 for systolic hypertension.²⁴

The data show that, although **EBT** cannot define coronary stenosis severity, it **CAN suggest** that with higher scores, or **in the presence of symptoms**²⁴ **that further examination** such as stress testing, EBA (electron beam non-invasive coronary angiography), or even formal angiography **may be warranted.** However, this determination must be made on a case-by-case basis and is a clinical decision made by an experienced practitioner. Outcomes of such subsequent testing are then used to assist in the patient's care.

The current overall guidelines for EBT test interpretation can be expressed in several bullet points

as provided below. These statements, supported by published literature, still must function only as overall "guides" for the clinician. However, in my opinion, these interpretations are in fact being well put forward by experienced practitioners currently performing EBT examinations in Hong Kong.

Interpretation and recommendation for EBT heart scanning and CAC scoring:

- A negative test (i.e. score=0, no detectable coronary calcium) makes the presence of atherosclerotic plaque, including unstable or vulnerable plaque, highly unlikely.
- A negative test (score=0) makes the presence of significant luminal obstructive disease highly unlikely (negative predictive power by EBT on the order of 95-99%).
- A negative test is consistent with a low risk (reported to be <0.5% per year²⁶) of a significant cardiovascular event [infarction or sudden death] in the next 2-5 years.
- A positive test (i.e. a score >0) confirms the presence of a coronary atherosclerotic plaque (100% specificity for fibro-atheromatous plaque).
- The greater the EBT calcium score, the greater the atherosclerotic burden in men and women, irrespective of age, and the greater "likelihood" of more advanced luminal disease.⁵
- The total (summed) coronary calcium score correlated best with the total amount of coronary atherosclerotic plaque, although the true "atherosclerotic burden" is underestimated and, without use of contrast (as in an EBA study), "soft" plaque may not be well appreciated (but data are advancing to address this issue using non-contrast EBT²⁷).
- A high calcium score (an Agatston score >100 or any score above the 75th percentile for age and sex as compared to published EBT databases) is consistent with a moderate to high risk of a cardiac event within the next 2-5 years.
- Coronary artery calcium measurement can improve risk prediction in conventional intermediate-risk patients and such scanning should be considered in

individuals at intermediate risk for a coronary event (0.6%/year to 2.0%/year) for clinical-decision making regarding refinement of risk stratification²⁸ (recent data suggest that in low to intermediate risk patients the current goals of applying only conventional risk stratification may not be adequate in defining true risk for myocardial infarction, at least in individuals at an average age of 50 years²⁹).

- High coronary calcium scores (an Agatston score >100 or any score above the 75th percentile for age and sex) denotes advanced coronary atherosclerosis and provides a rationale for intensified LDL-c lowering therapy and assignment of coronary risk to a "coronary disease risk-equivalency" status (i.e. secondary prevention goals such as a target LDL-c range <100 mg/dl).

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