

# The role of advanced cardiac imaging with multi-detector row computed tomography in the evaluation of atherothrombotic coronary artery disease.

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## Introduction

The approach to atherothrombosis has taken on a new meaning as many new and important advances in medical diagnostic modalities became available in the last decade. For many years, cardiologists as a whole have focused their attention on aggressive intervention of acute coronary syndromes and the myriad consequences of coronary atherothrombosis. In the overall scheme of the treatment of coronary atherothrombosis, aggressive intervention of acute coronary syndrome has become a treatment approach that focuses only on the tip of the iceberg. Early detection and effective prevention of this silent and dreadful complication of atherosclerosis in asymptomatic people with high and intermediate risk have become an issue of paramount importance to both physicians and investigators alike. Thus, this new era has ushered in a major paradigm

shift from focusing on secondary disease management to primary disease prevention<sup>1</sup>.

### Framingham Heart Study:

The identification of various independent risk factors for coronary heart disease such as cigarette smoking, elevated blood pressure, elevated serum total cholesterol, high density lipoprotein (LDL-C), low serum high density lipoprotein cholesterol (HDL-C), diabetes mellitus, and advancing age are a main contribution of the Framingham Heart Study but it also set the stage for establishing a platform for the design of treatment strategy for the prevention of coronary heart disease (CHD). In addition, Framingham Heart Study helped elucidate the quantitative relationship between these risk factors and CHD and also showed the additive effect of an individual having multiple

risk factors in the assessment of his/her cardiovascular risk profile 2. Framingham risk score allows the estimation of the probability of developing coronary heart disease over a given time period.

### **Identifying High Risk Patient With Increased Burden Of Atherothrombosis**

A major limitation of the Framingham Heart Study is the exclusion of many new biological markers that are potentially important in the determination of the absolute and relative risk of CHD in an individual. For example, C-reactive protein is a marker of inflammation and has been shown in prospective clinical studies to be associated with an increased risk of cardiovascular complications, such as myocardial infarction, stroke, sudden death, and peripheral vascular disease 3. However, the additive and independent effect of C-reactive protein with that of LDL cholesterol in predicting CHD was not known. More recently, Ridker et al. reported a significant increased risk of cardiovascular events associated with increasing levels of C-reactive protein irrespective of the Framingham risk score. Interestingly, increasing C-reactive protein levels were associated with increased risk of cardiovascular events in all levels of LDL cholesterol including those with levels below 130 mg per deciliter 3.

It is becomingly clear that patient risk stratification is a systemic process, with careful attention to traditional and novel risk factors for inflammation and thrombosis 4. The national cholesterol education program III (NCEP) classifies patients in low risk (0-1 coronary risk factor), moderate risk (2+ risk factors), and high-risk (heart disease equivalent) according to their likelihood of developing an acute coronary event within the next 10 years 5. In spite of the availability of the user-friendly programs for the calculation of 10-year risk programs, physicians have not completely adopted these tools to risk stratify their patients. As a result, proper estimation of atherosclerotic burden is not routinely evaluated in preventive medicine. Simultaneously, the advances in non-invasive imaging technology have opened another window of opportunity for clinicians and researchers alike to assess and quantify atherothrombotic burden in the coronary arteries using electron-beam computerized tomography (EBCT), multi-detector row CT

(MDCT) and magnetic resonance imaging. These tools are emerging as potentially useful tests for the identification of high-risk patients for cardiovascular events. In the past few years, MDCT with its rapidly improving hardware and software has leapfrogged over other imaging modalities as the non-invasive technology of choice for the assessment of the presence of coronary artery disease in high risk individuals.

### **CORONARY CALCIUM SCORE: AN INDEPENDENT PREDICTOR OF CORONARY HEART DISEASE**

Coronary calcium score is considered a highly sensitive marker for coronary atherosclerosis with prognostic value for obstructive coronary artery disease (CAD) 6. Patients with zero or low calcium scores have lower probabilities of developing clinical coronary syndromes compared to those with high calcium score (CS) values 7. Raggi et al reported an annual event rate of only 0.36% for patients with calcium score of zero 8. However, when calcified lesions are present, plaque burden interpretation is graded as minimal (CS 0-10), mild (CS 11-100), moderate (CS 101-400) or extensive (CS > 400) 9. Regarding risk assessment, an associated CS above 100 has been shown in several studies to predict cardiac events in symptomatic and asymptomatic individuals 7,9,10. Its negative predictive value is between 94-100% 11. This means that coronary artery disease can be excluded with a high degree of confidence when no coronary calcifications can be detected. Recently, investigators of the St. Francis Study reported the findings of their prospective, longitudinal, population-based study of 5585 asymptomatic patients with no previous history of coronary artery disease followed for 4.3 years. Cardiovascular events occurred in 122 patients (0.6%/year). Mean calcium scores were greater in patients with events when compared to patients without events ( $584 \pm 775$  versus  $142 \pm 381$ ;  $P < 0.0001$ ). Calcium scores predicted cardiovascular events independently from coronary risk factors and the Framingham risk score. Relative risks [95% CI] were 5.9 [3-12] for a score  $\geq 0$  and 8.0 [5-12] for a score  $\geq 600$  20.

To illustrate how noninvasive testing can influence clinical decision making, Greenland and Gaziano

used the data from a case report of an asymptomatic patient to illustrate the clinical utility of coronary calcium score and exercise stress testing in the assessment of coronary risk<sup>12</sup>. A coronary calcium score of 80 or more had sensitivity for any one of coronary events, e.g. death, myocardial infarction, and clinically indicated coronary revascularization, of 85 percent and a specificity of 75 percent. The changes of the probabilities of developing coronary events by the results of the coronary CT or electrocardiographic exercise testing were quite dramatic. It is apparent that a negative result on either test in a patient with intermediate or high risk markedly lowers that patient's predicted risk. Conversely, a calcium score of 80 or higher or a positive result on electrocardiographic exercise testing is associated with a much higher probability of developing a coronary event. In other words, additional non-invasive testing of coronary artery disease may be useful in the assessment of asymptomatic individuals with intermediate risk of coronary artery disease and as such it may allow better allocation of the limited resources in primary disease prevention.

### **Non-Invasive Coronary Angiography**

The holy grail of cardiovascular medicine is to assess the coronary stenosis non-invasively and to visualize the early atherosclerotic changes in the vessel wall of the coronary arteries. Currently, the assessment and quantification of coronary stenosis can be obtained using intravenous contrast with EBCT, multi-detector row CT (MDCT), or with coronary magnetic resonance angiography (CMRA). A recent review from our group summarized the advantages and limitations of each technique<sup>13</sup>. The key advantage of MDCT is the ability to assess the entire coronary artery tree within a scan time of less than 20 seconds. CMRA offers excellent soft tissue contrast but still lacks the temporal resolution to capture the rapid and complex movement of the coronary arteries and a beating heart. Currently in certain states in the United States, cardiac CT angiography using 16 or more MDCT may be used to rule out the presence of significant coronary artery disease in patients with equivocal stress test, coronary anomalies, pulmonary embolism, and aortic dissection. A major limitation of contrast MDCT angiography is the presence of calcium significantly hinders the ability to interpret

the degree of luminal narrowing due to the blooming or beam hardening effect (Figure 1). Nevertheless, MDCT may provide important information on the tissue characteristic or the composition of the obstructive coronary lesion.

### *Advances in MDCT*

Noninvasive coronary CT angiography (CTA) is performed after the intravenous administration of iodinated contrast agent, with simultaneous ECG synchronization and during breath-holding to minimize motion artifacts. The data acquired with CT are initially reconstructed into two-dimensional axial images. Subsequent three-dimensional postprocessing – multiplanar reformat, maximum intensity projection, volume rendering or virtual angiography (Figure 2) – can be performed and thus be useful in the assessment of coronary stenosis.

The critical role of a dedicated cardiovascular workstation for performing cardiovascular CT imaging cannot be minimized. Our group preferred the use of a vendor-neutral advanced cardiovascular workstation for our every day clinical practice and investigative work. In our practice, we interpret cardiovascular images that are scanned using 16-detector row MDCT scanners from all three major manufacturers, i.e. Siemens, General Electrics, and Philips. All the images in this article were obtained from either a Siemens Sensation 16 or a Siemens Sensation Cardiac Scanners and all the image processing were performed on TeraRecon workstations (Aquarius workstation, TeraRecon, Inc. San Mateo, CA, USA). Our workstations also allow remote access and manipulation of 3-dimensional cardiovascular data sets, an essential feature of a user-friendly imaging post-processing system for the practicing cardiologists or radiologists who may need to review the data from afar in order to facilitate their clinical decision making process.

Initial work on coronary CTA was performed with EBCT. Due to its higher spatial resolution compared to EBCT, majority of the published reports in the last few years have focused primarily on MDCT. A recent review of ten studies including 583 patients

reported an overall sensitivity of 87% and specificity of 91% for EBCT in the detection of at least 50% stenosis. An average of 16% of coronary segments were considered non-evaluable, usually because of motion artifacts due to cardiac or breathing movements and/or severe calcification<sup>14</sup>. Eight studies using 4-slice MDCT and involving 513 subjects showed an overall sensitivity and specificity of 59% and 89% respectively for the detection of significant coronary stenoses. 31% of the coronary segments were considered non-assessable. These results are inferior to those obtained with EBCT. However, a recent comparison between 4-slice MDCT and EBCT showed no significant differences in diagnostic accuracy<sup>15</sup>. Additionally, two studies have already been published using 16-slice MDCT. One of them reported a sensitivity and specificity of 95% and 86% respectively, and with only 7% of non-evaluable arteries<sup>16</sup>. The other showed a sensitivity of 92% and specificity of 93% after the exclusion of 12% of arteries that were considered of sub-diagnostic image quality<sup>17</sup>. Both studies demonstrated a negative predictive value of 97%. Therefore, the newer generations of MDCT scanners appear to offer markedly improved diagnostic capability. Our group recently reported our own experience on the optimal reconstruction protocol using 16-detector row MDCT and found that inclusion of end systolic images during image reconstruction significantly improves the chance of obtaining acceptable and good quality coronary images (Figure 3)<sup>21</sup>. Additionally there is growing interest in the ability of MDCT to detect non-calcified atherosclerotic plaques that may be more prone to rupture (Figure 4). Initial reported experience in exploring the potential of MDCT for identifying the different plaque components appeared to be quite promising although the current spatial resolution of the most advanced scanners is still inadequate for precise and detailed characterization and differentiation of various components in an atherosclerotic plaque<sup>18</sup>. In spite of some inherent limitations of MDCT, other clinically useful applications of MDCT include the visualization of areas of myocardial hypoperfusion (Figure 5) or the evaluation of systolic cardiac function<sup>19</sup> without the need of additional contrast or radiation exposure.

### **Conclusion:**

Atherothrombosis plays an important role in the pathogenesis of cardiovascular disease and is a major cause of morbidity and mortality in this country. Risk stratification of patients based on the time-honored traditional risk factors of coronary artery disease has been quite useful clinically. However, new biological markers and advanced imaging techniques have opened a new window of opportunity for the primary prevention of atherothrombotic coronary artery disease. C-reactive protein and coronary calcium score are two important new markers of cardiovascular disease and as such each contributes significantly and independently to the ever-evolving and complex algorithm of preventive therapy for intermediate to high-risk patients. The introduction of advanced MDCT coronary imaging furthers our ambitious goal to come closer to replace x-ray coronary angiogram, the gold standard of coronary lumenography. Furthermore, MDCT, with its ever improving temporal and spatial resolution, offers the unique opportunity to visualize subtle changes in the vessel wall including the formation of calcified and non-calcified coronary plaques and a valuable imaging tool to follow the progression and more importantly the regression of atherothrombotic lesions in response to pharmacological treatment or risk factor modification.

## Figures:

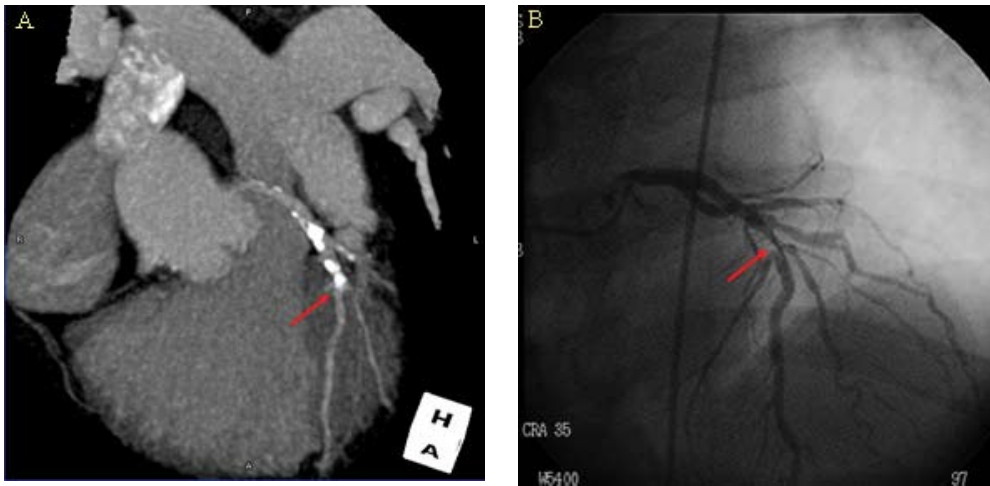


Figure 1 Panel A is a maximum intensity projection (MIP) Image from a CT angiography performed using a 16 detector CT scanner on a patient with atypical chest pain symptoms. This patient also had a conventional x-ray angiography performed shortly following the CT study. Calcified lesions are noted in the proximal left anterior descending artery (LAD) with a red arrow pointing to a high-grade lesion as shown on the still frame from the x-ray angiogram (Panel B) of the same patient.

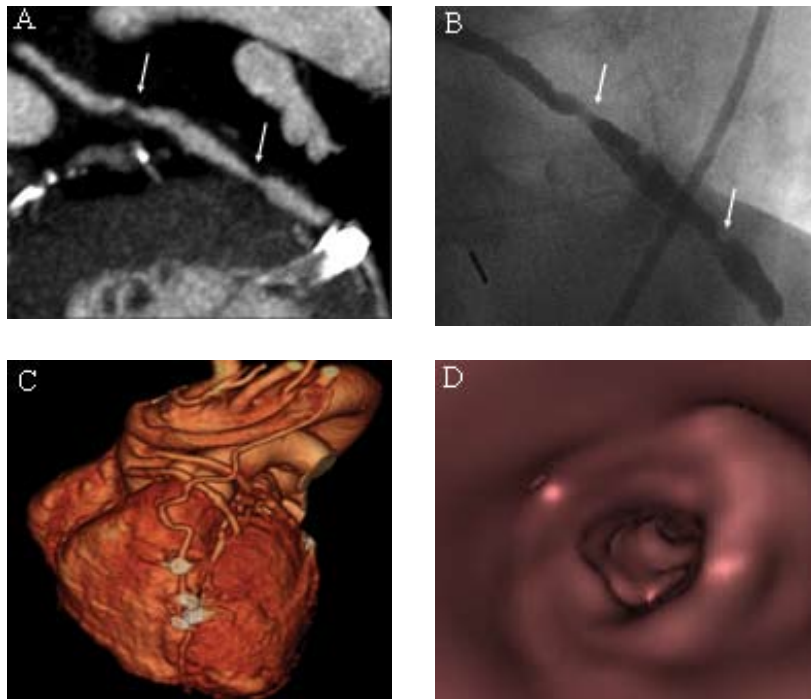
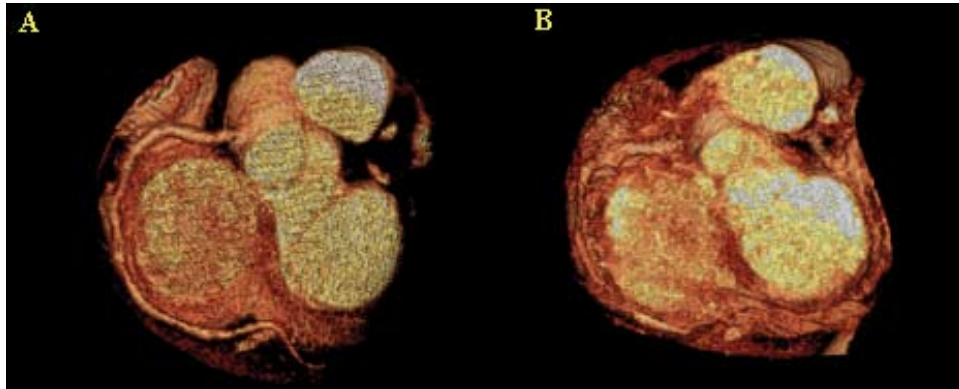
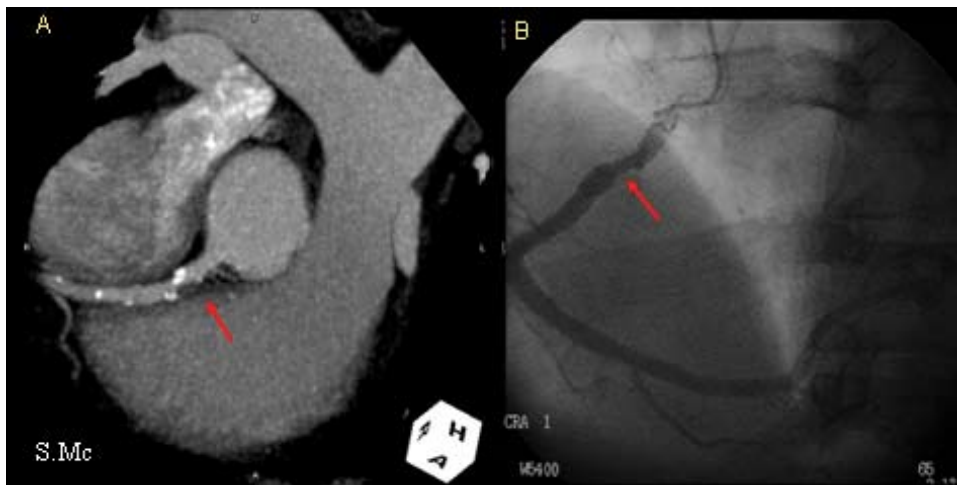


Figure 2: A) Maximum intensity projection (MIP) image. Patent saphenous vein graft (SVG) to the second obtuse marginal branch (OM) with significant stenoses detected along its course at its mid and distal segments (white arrows).

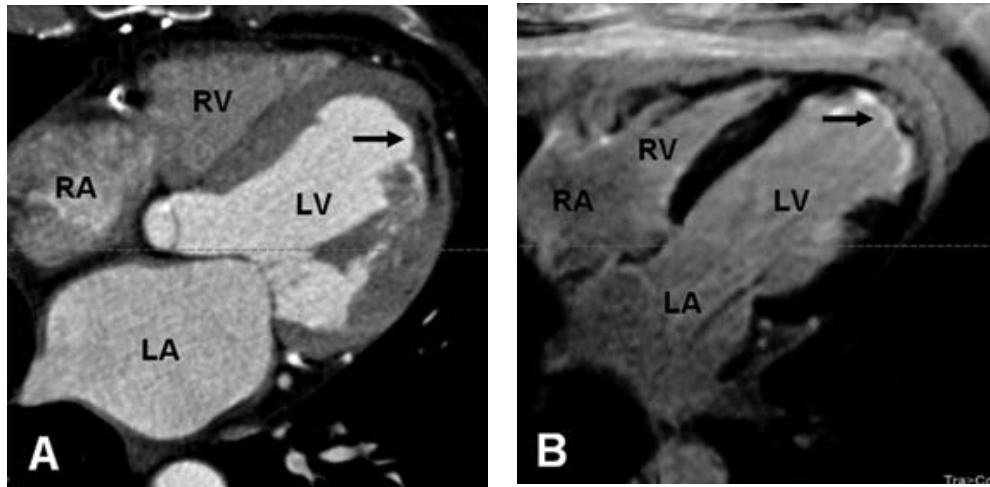
B) X-ray angiography depicts the vein graft stenoses (white arrows). C) 3-D Volume rendering (VR) image of the heart showing arterial and venous by-pass grafts. Patent SVG to the OM, SVG to first diagonal branch (DB) and left internal mammary artery (LIMA) to the left anterior descending artery (LAD). Ocluded SVG to right coronary artery (RCA). Surgical clips are depicted at the anastomoses sites with the native coronary arteries. D) A fly-through (virtual angiography) view of the SVG to OM shows the endoluminal view.



*Figure 3 Volume-rendered reconstruction of the right coronary artery. Panel A shows a reconstruction centered in mid-diastole, when coronary motion is less, and allows complete visualization in the artery. Panel B illustrates a proto-diastolic reconstruction, the conventional approach, with severe motion artifacts and impossibility to assess the patency of the vessel.*



*Figure 4 Panel A is a maximum intensity projection (MIP) image from a CT angiography performed using a 16 detector CT scanner on a patient with atypical chest pain symptoms. This patient also had a conventional x-ray angiography performed shortly following the CT study. A non-calcified lesion (red arrow) is noted in the proximal right coronary artery (RCA). On the still frame image from the x-ray angiography (Panel B) of the same patient, a non-obstructive lesion (red arrow) is shown.*



*Figure 5 Contrast-enhanced MDCT (Panel A) and delayed-enhancement (DH) MRI (Panel B) of a 68 year-old male patient with a history of coronary artery disease and myocardial infarction. In the contrast-enhanced MDCT images, an area of decreased attenuation is seen in the apical and anterior region of the left ventricular wall (Panel A, black arrow). In the same area of Panel B, an area of DH corresponding to an area of chronic myocardial infarction (Panel B, black arrow). (LV = left ventricle, RV = right ventricle, LA = left atrium, RA = right atrium).*

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