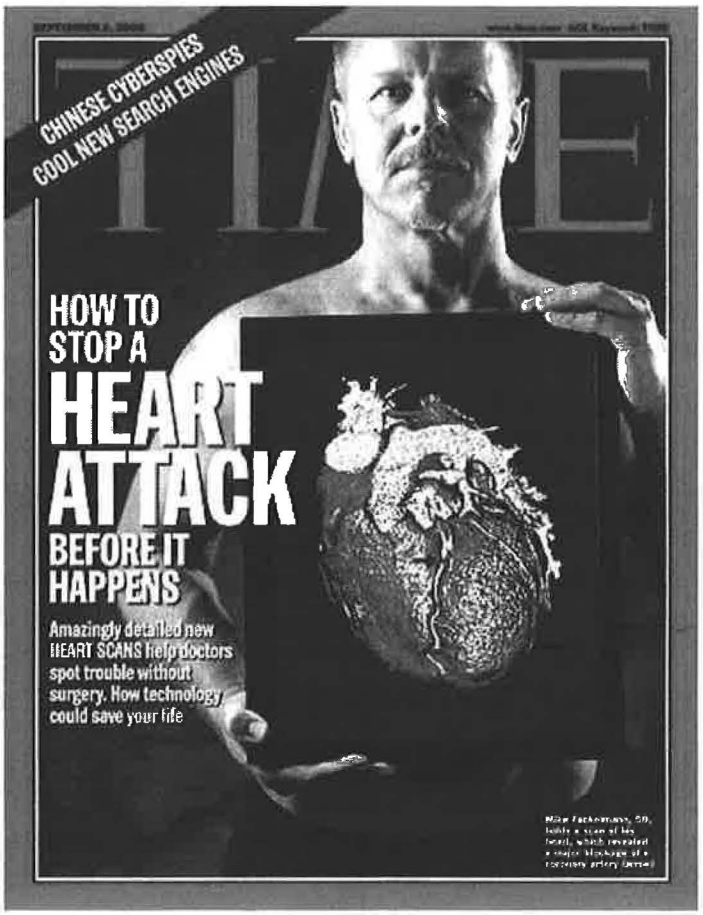
"I'm sorry to bother you at a party like this, but should I get one of those scans?" Evaluating the coronary arteries using CT and MRI in 2006 and beyond



Internal Medicine Grand Rounds
UT Southwestern Medical Center

February 2, 2006

Ronald M. Peshock, MD
Professor of Radiology and Internal Medicine
Assistant Dean for Informatics

Interests: Cardiovascular imaging, subclinical atherosclerosis, medical informatics

This is to acknowledge that Ronald Peshock, MD, has no financial interest or other relationships with commercial concerns related directly or indirectly to this program. Dr. Peshock will be discussing off-label uses in his presentation.

Collaborators: Bart Dolmatch, MD, Tulika Jain, MD, Sharon Reimold, MD, Susan Sallach, MD, Kirk Jordan, MD, Cecelia Brewington, MD, Robert Parkey, MD, Hao Lo and Rajiv Shah, Doris Duke Student Research Fellows, the Dallas Heart Study Investigators and the faculty and fellows who have referred their patients for evaluation.

On October 28, 1958, Dr. F. Mason Sones, Jr., was performing a contrast aortogram on a patient with aortic insufficiency. During the power injection the catheter whipped into the right coronary artery injecting 30cc of contrast material directly into the coronary. It is of note that the teaching at that time was that the injection of dye into one coronary artery would result in hypoxia of the coronary circulation which would lead to an electrical imbalance, fatal cardiac arrhythmias and death. In fact Sones was reported to have blurted out "we've killed him" to those present in the cath lab. Needless to say the patient did not die and the first intentional selective injection of contrast into the right coronary artery in man was done two days later (Figure 1).

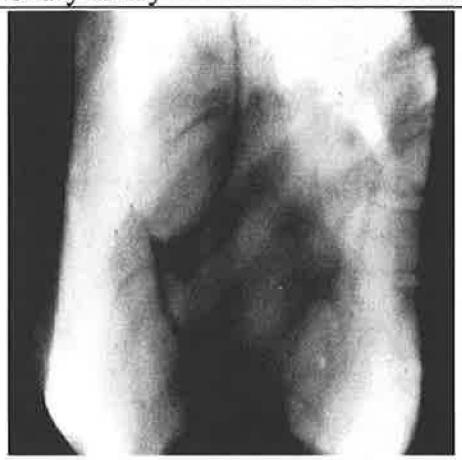
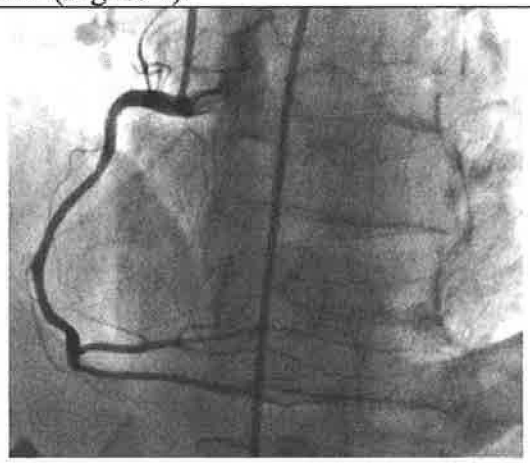


Figure 1: First selective injection of the right coronary artery by Sones. (From Ryan, TJ [1]).



Present day coronary angiogram of the right coronary artery (provided by Dr. Addo).

Our present management of patients with coronary heart disease was forever changed by the development of coronary angiography. The ability to define the location of significant narrowing of the coronary artery lumen spawned a generation of new insights and interventions including coronary artery bypass surgery, thrombolysis and other medical interventions, angioplasty and coronary artery stenting which have significantly impacted patient morbidity and mortality. However, almost 50 years later, assessment of the coronary arteries still requires invasive angiography which is not without some risk and discomfort.

Today we stand at the threshold of a new explosion in techniques for the direct, non-invasive assessment of the coronary arteries using computed tomography and magnetic resonance imaging. However, as clinicians we will need to use these tools wisely if we are to truly improve patient care and outcomes. Thus, the purpose of this review is to (1) understand why there is such interest in this area, (2) provide a basic introduction to MR and CT coronary imaging, (3) discuss the present knowledge regarding their clinical use, and (4) outline possible future developments in this area.

Why not just cath everyone?

In 2003 there were an estimated 1,414,000 inpatient diagnostic catheterizations performed in the United States. [2] Assuming a minimum payment of $2100 per outpatient procedure this accounts for an expenditure of almost $3 billion per year. Further, it is anticipated that the number of diagnostic catheterizations will continue to rise for several reasons including the aging population, the increasing number of patients (estimated 6,000,000/year) presenting with chest pain[3], continued improvements in therapy and the fact that present therapies are fundamentally palliative and not curative. Thus, in spite of our progress in the management of subclinical and clinical coronary artery disease we are facing the potential for a continued increase in the number of diagnostic coronary arteriograms.[4]

It is reasonable to ask if this is a problem. Setting the issue of the cost aside, diagnostic coronary arteriography is fundamentally a safe procedure but is associated with some finite risk.[5] Complications for coronary angiography are summarized in Figure 2.

Year(s)	Death	MI	Neurological	Arrhythmia	Vascular	Contrast	Other	Total
1979–82	0.14	0.07	0.07	0.56	0.57	—	0.41	1.82
1984–87	0.10	0.06	0.07	0.46	0.46	0.23	0.28	1.74
1990	0.08	0.03	0.06	0.33	0.40	0.37	0.48	1.77

Figure 2: Complication rates during diagnostic cardiac catheterization from the SCA&I registry. (From Bashore, et al.[6]).

Thus, although serious complications of coronary arteriography are rare, its risks appropriately impact our decision regarding its application in specific clinical patients. In one sense it boils down whether or not it is worth the risk to the patient to answer a series of questions: Is there atherosclerosis present? Is it functionally significant and the basis for the patient's chest pain? Is the patient at risk for a future event?

To focus the discussion we will consider four patients:

Case 1: 17 year old male athlete with an episode of chest pain and syncope.
Case 2: 55 year old female attorney who wants an executive physical
Case 3: 65 year old man with multiple presentations to the emergency room with chest pain
Case 4: 60 year old man with prior stent placement returns with chest pain

Who would you send to invasive coronary angiography?
Would a non-invasive alternative change your approach?

The challenge of non-invasive assessment of the coronary arteries

Non-invasive imaging of the coronary arteries is challenging for several reasons. The first major problem is the size of the vessels of interest. The left main coronary artery is largest coronary vessel and is typically has a lumen 4-5 mm in diameter.[7] All of the subsequent branch vessels are smaller and rapidly taper to less 1-2 mm vessels as they near the apex. Since we are interested in determining the degree of luminal narrowing, we really need to be able to resolve structures a fraction of a millimeter in size. Present state of the art, flat plate detector X-ray systems used in the cardiac cath lab have a resolution of approximately 0.3mm which allows us to potentially image structures of that size in a stationary phantom. Thus, any non-invasive method to assess the coronary arteries needs to resolve structures in the sub-millimeter range if it is to be of any value in even the larger proximal coronary arteries.

The second major concern is that the coronary arteries are constantly in motion. Because of their location on the surface of the heart they move towards the ventricular apex with systole and return to their original location with diastole. This motion has been carefully analyzed and can easily exceed a centimeter[8]. Luckily this motion can be addressed by "gating" or linking the acquisition of the image to a particular point in the cardiac cycle. Typically, this point is chosen at a time in the cardiac cycle (mid to late diastole) when the motion of the heart is minimized. It is important to recall that the duration of systole is generally 250-300 msec and changes relatively little with heart rate. It has also been demonstrated that there is still some residual cardiac motion in diastole and that the total time the "gate" or "shutter" can be open is limited to less than 100 msec. With this approach is possible to reduce the effect of cardiac motion to less than 1mm.

An additional source of motion is breathing. Interestingly, this has also been extensively studied and motion due to breathing is actually greater than that due to cardiac motion, typically on the order of several centimeters.[9] Thus, the effects of respiratory motion must be controlled to obtain diagnostic images. In the cath lab the patient is typically asked to hold their breath for several heart beats during the injection to minimize motion. This approach can also be used for non-invasive coronary imaging. However, it is important to realize that some non-invasive coronary imaging presently requires a longer breath-hold (typically 10-20 seconds) which can be difficult for some patients. Again, if the goal is to resolve coronary structures less than a millimeter in size, then it is necessary to reduce the effects of respiratory motion to less than a millimeter.

A third issue is the variability of coronary anatomy. Although there are typically only two coronary orifices arising from the aorta and the left main coronary artery branches into two large vessels the left anterior descending coronary artery and the left circumflex coronary artery, the subsequent branching of significant vessels is quite variable. This derives from the unusual feature of the development of the coronary vascular system.[10] Coronary vessel development involves vasculogenesis (de novo generation of blood vessels) followed by angiogenesis (generation of capillaries, veins and arteries from preexisting vessels). The coronary vessels are not derived from the cardiac mesoderm like the myocardium and endocardium but interestingly are derived from extracardiac tissue, the proepicardial organ (PEO) [Figure 3] which appears to arise from the splanchnic mesoderm.

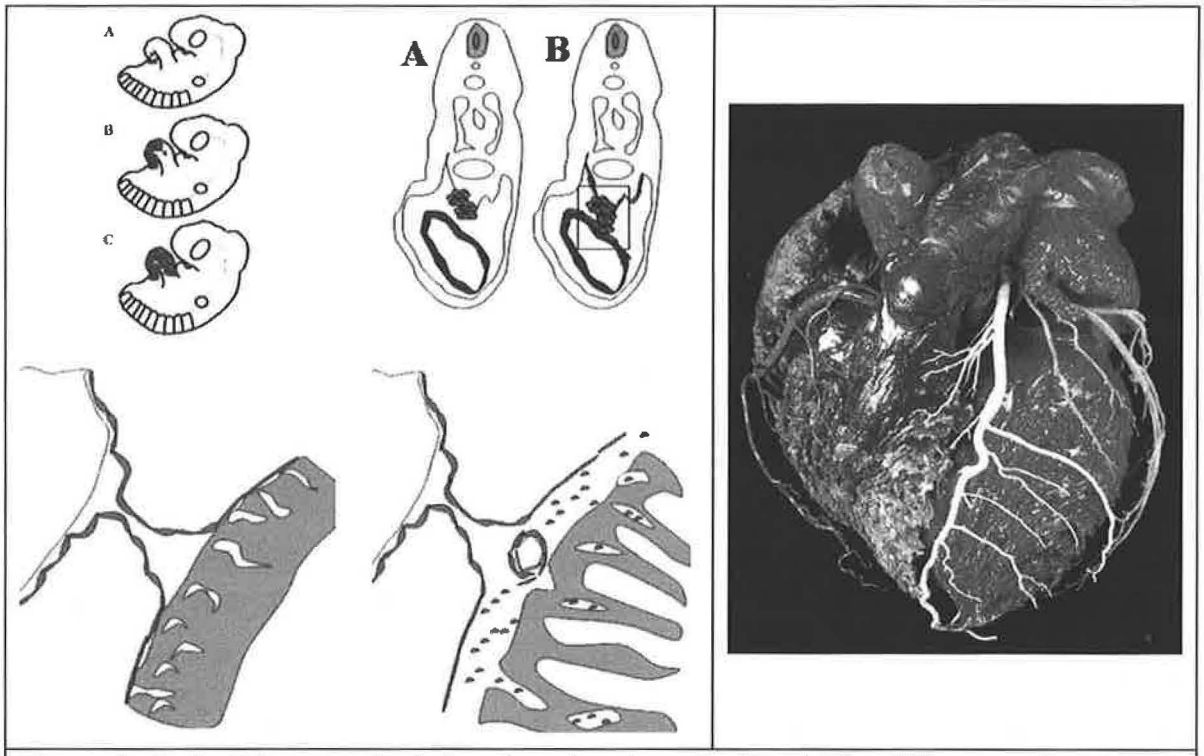


Figure 3: Left: Diagrams depicting the migration of cells which will become the coronary arteries (see Wada, et al. for details). Right: Cast of heart indicating the positions of the major coronary vessels and their branches.

The migration of epithelial cells over a developing organ is a rare event in development and is not well understood. Regulation of cell adhesion during the migration of the PEO cells is important and is regulated by VCAM-1/α4-integrin interaction. Knockout mice with functional inactivation of VCAM-1 have no subepicardial vascular development and are not viable. Loss of α4-integrin function in mice results in a failure of the cells to attach to the heart. Interestingly, the subsequent localization of these cells is not uniform suggesting that the epicardium is more sensitive to myocardial signal in certain regions. Some of the first vessels to form are in subepicardium in the atrioventricular groove which will differentiate into the circumflex and right coronary arteries. How the epicardial coronary vessels come to join the aorta is also complex and not completely understood. Several vessels approach the right and left aortic sinuses but only one in each location establishes contact to form the right and left coronary arteries. It is interesting to note that they insert exactly at the level of the coronary leaflets and that may help explain why coronary anomalies involve errors in circumferential and not longitudinal placement.

The final issue is the complexity of coronary lesions (Figure 4). As is well known, the development of coronary artery disease is a complex process which progresses through a series of pathologic stages which include initial positive remodeling without loss of luminal cross section followed by encroachment on the lumen and addition events related to plaque rupture and thrombosis. The ideal imaging approach

would permit full evaluation of the coronary lumen and wall to determine the stage of development of the plaque and its risk for rupture and thrombus formation.

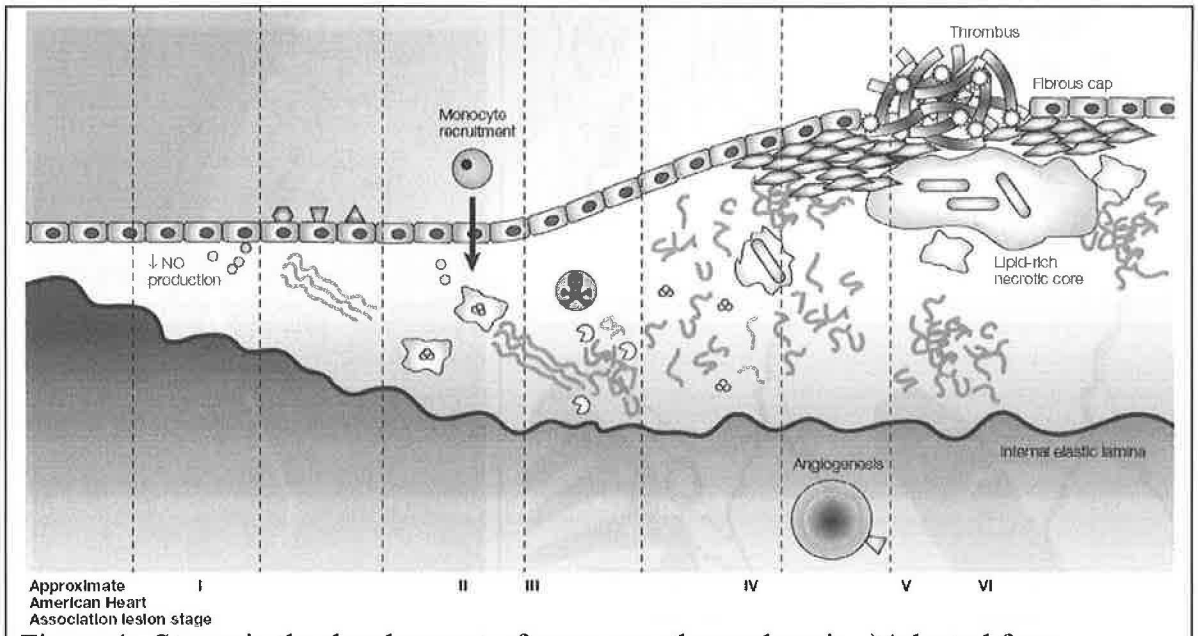


Figure 4: Stages in the development of coronary atherosclerosis.)Adapted from Choudhury RP, et al.[11])

The contenders and a little about the technology

The search for non-invasive means to examine the coronary arteries is not a new one. Many techniques have been explored including transthoracic ultrasound, intravenous subtraction angiography and synchrotron radiation with varying degrees of success. Over the past 10 years the search has involved predominately two approaches: MRI and computed tomography which includes electron beam computed tomography (EBCT) and multidectector computed tomography (MDCT). EBCT is also referred to as ultrafast CT. Multidetector CT is also referred to as multislice CT and spiral CT. The following section will briefly review how MR and CT work to image the coronary arteries.

Coronary magnetic resonance angiography: MR has become a standard tool for the evaluation of cardiac structure and function as was reviewed by Dr. Sharon Reimold in a previous Grand Rounds. As in other parts of the body, the advantages of MR include its lack of ionizing radiation, excellent soft tissue contrast and that it is intrinsically three dimensional. Its disadvantages relate to the fact that it is fundamentally utilizes a relatively weak signal resulting in relatively long scan times compared to X-ray techniques. Beginning in the mid 1990s, our group and others demonstrated that it was possible to obtain images of the coronary arteries during 20-second breath-holds sufficient to determine if the artery was occluded and to directly measure coronary artery flow.[12,13] However, these breath-holds were too long for many patients and their resolution was limited. To obtain higher resolution would require a different approach to deal with the issue of respiratory motion.

A new approach, termed the navigator echo, was described by Stuber in 1999.[14] Briefly, it uses a separate MR pulse to monitor the position of the diaphragm during the scan. One can then set a diaphragm position (typically in the mid to late expiratory phase) during which images can be acquired. This removes the restriction of completing the imaging during a breath-hold and yields free breathing images of the coronary arteries with resolution in the sub-millimeter range (Figure 5).

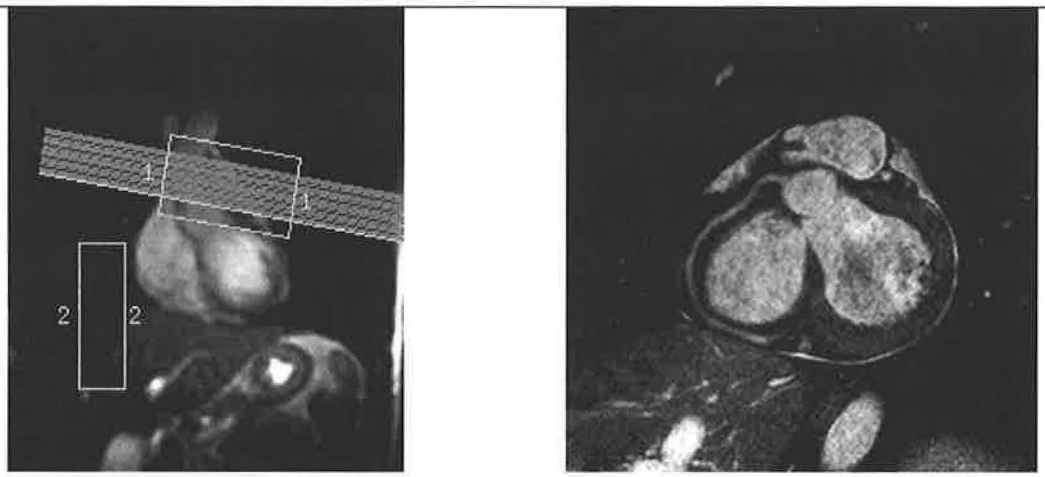


Figure 5: Navigator echo coronary MR angiography: Left panel: Box 1 and the lines indicate the imaging plane for the left anterior descending coronary artery. Box 2 is the position of the navigator used to track the position of the diaphragm during imaging. Right panel: MR angiogram of a normal right coronary artery obtained using this technique.

It is of note that these images are obtained without ionizing radiation or administration of contrast agent. The contrast between the coronary lumen and myocardial wall is generated by the adjusting the MR imaging sequence to increase signal from moving blood in the coronaries (bright blood imaging) and decreasing signal from the adjoining fat and myocardium. By changing the imaging sequence one can reduce the signal from blood (dark blood imaging) to image the coronary wall.

Coronary CT angiography: CT angiography has dramatically impacted our diagnosis and management of patients with aortic disease, pulmonary emboli, carotid disease and peripheral vascular disease. However, its application in the heart has been very limited until recently. This delay fundamentally derives from the issues of cardiac motion described previously. Standard CT scans of the chest without cardiac gating are substantially blurred making evaluation of the coronary arteries essentially impossible. To understand why this was not addressed until recently requires a basic understanding how a CT scanner works.

Briefly, in computed tomography an X-ray tube is moved around the patient while a series of detectors is rotated opposite the x-ray tube. Projections of the patient (analogous to standard projection flat plate images) are taken at multiple points. Using a mathematical technique called filtered back-projection, one can use the projections to create a tomographic image of the body. In the first CT scanners this was done with

single detector one slice at time. More recently, the use of multiple detectors has allowed one to obtain 4, 16 or even 64 slices with a single rotation without moving the patient.

However, this still does not address the motion of the heart. To stop the motion of the heart requires the rotation of the X-ray tube around the body in 100 msec (0.1 sec) or less. Calculating the centripetal force (Force = mass x velocity^2/radius, where mass of the x-ray tube is 20kg, velocity= $2\pi r/0.1$ sec, radius =0.9 m yields a force on the track of 16,000 pounds or 71,240 Newtons and a centripetal acceleration of 3562 m/s^2 [note that the acceleration due to gravity is 9.8 m/s^2 so that the tube is experiencing an acceleration of roughly 356 g's!]. Now slowing the rotation to 300 msec reduces the acceleration to 397 (~20 g's) and slowing it further to 500 msec takes it down to 142 m/s2 (~14.5 g's) which is possible.

This calculation shows that one cannot move a conventional X-ray tube fast enough to freeze the motion of the heart. However, there are two clever solutions to this problem: The first (used in electron beam CT) is not to move the tube at all but just steer the beam of X-rays electronically. The second (used in multi-detector CT) is to not acquire all of the information in a single pass of the X-ray tube but to acquire it over several cardiac cycles during a breath-hold. The information from several cardiac cycles is then combined to produce the data required to construct the image.

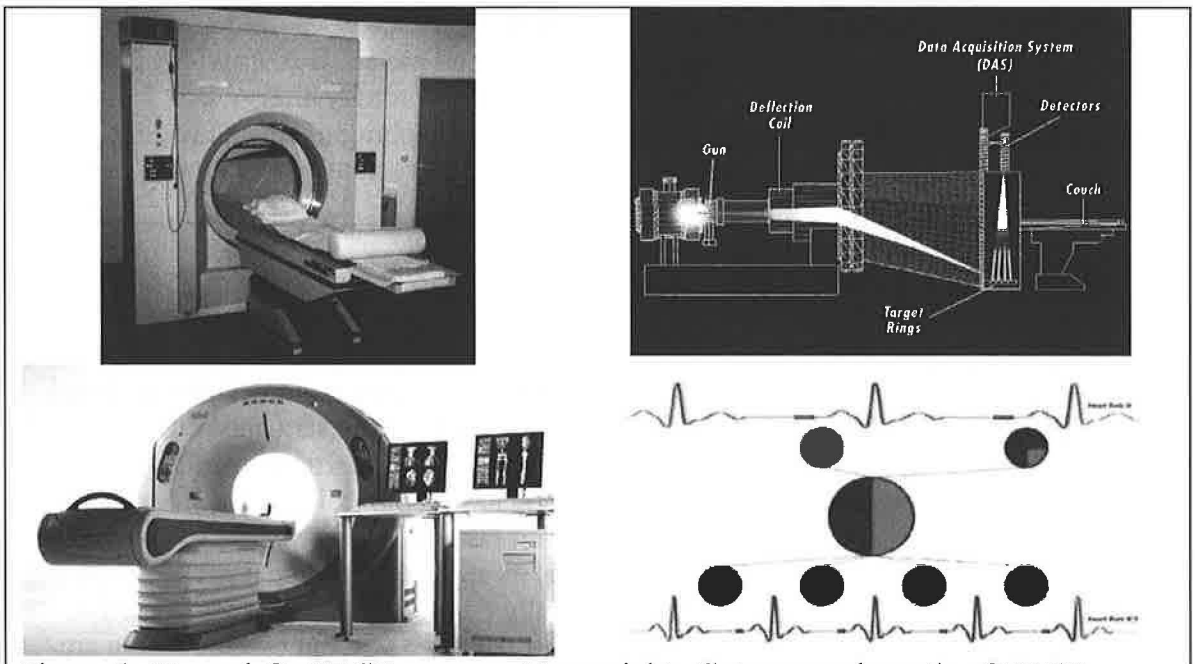


Figure 6: Upper-left: EBCT scanner. Upper right: Cut-away schematic of EBCT scanner illustrating the course of the electron beam used to generate the X-rays. Lower-left: Typical multi-detector CT scanner. Lower-left: Diagram indicating how the data required for each slice can split between multiple cardiac cycles to address the slower motion of the X-ray tube.

The electron beam CT represents an elegant technical solution to the problem. As shown in Figure 6, an electron beam used to generate the X-rays is swept electronically around the patient so that the physical structure does not move. However, it suffers from one serious limitation: the X-ray output of the device cannot be increased to penetrate

larger patients. This means that the quality of the image becomes worse in larger patients with resultant artifacts which are difficult to address.

In multi-detector CT three approaches are used to speed the acquisition of images covering the entire heart at multiple points in the cardiac cycle. First, multiple detectors are used to obtain multiple slices at the same time with a single dose of X-rays. Second, data are acquired over several cardiac slices to construct each slice. Third, all of these data are acquired as the table is moving so that the entire volume of the heart can be covered with 0.6 mm slices during a single breath-hold. As the data are being collected for each slice, the CT scanner is simultaneously recording patient position, the point in the cardiac cycle, the position of the X-ray tube. At the end of the breath-hold it is then possible to reconstruct images of the heart for each slice at multiple points in the cardiac cycle.

Note that all of this assumes that (1) the motion of the heart is reproducible during the scan, (2) motion due to respiration does not occur (i.e., the patient does not breath), and (3) there is no other motion of the body. If these conditions are not met, the reconstruction will not be correct and will contain artifacts. Thus the best candidate for MDCT of the heart is a patient with a regular, slow heart rate who can perform a very stable breath-hold. If the goal is resolution of less than a millimeter, that dictates errors in the control of motion should not exceed a millimeter. Needless to say, it is a miracle that this works at all!

An important advantage of MDCT over EBCT is that the X-ray dose can be adjusted to penetrate large patients to improve the quality of the images. The total radiation delivered is further increased by the need to obtain data for multiple slices as the patient moves through the scanner. A full discussion of how radiation exposure and its associated risk are calculated is beyond the scope of this discussion but some relevant comparisons are shown in Figure 7.[15]

TABLE 2. Effective Dose of Selected Radiological Examinations

Examination	Effective Dose, mSv
Head CT	1–2
Chest CT	5–7
Abdomen and pelvis CT	8–11
Diagnostic coronary angiogram	3–10
PA and lateral chest x-ray	0.04–0.06
Average annual background radiation in the United States	3.6

PA indicates posteroanterior.

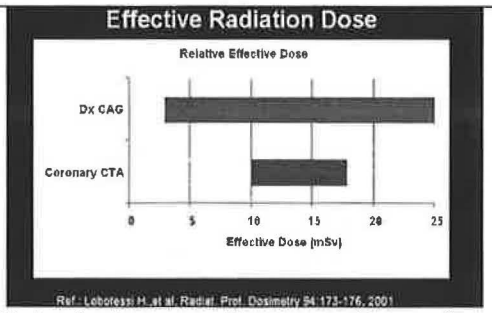


Figure 7: Left: Typical doses for standard radiological exams (from Morin, et al). Right: Effective radiation dose for present coronary CTA as compared to diagnostic catheterization.

Thus, it is clear that current CT scanners can deliver substantial doses of X-rays quite comparable to the exposure in the cardiac cath lab. It is important to note that assessment of coronary calcification alone does not require as high an X-ray exposure as coronary CTA. As an aside, comparable doses are delivered in many chest and abdominal CT exams suggesting that multiple CT exams in a single patient could result in significant radiation exposure in a short period of time.

As in other parts of the body, CT images can be obtained with and without administration of an iodinated contrast agent (Figure 8). Coronary calcium scanning does not require contrast and can be performed with a relatively low X-ray dose by both EBCT and MDCT and the results appears to be comparable.[16]

The focus of CT angiography is to move beyond the detection of calcified or "hard" plaque to the detection of non-calcified or "soft" plaque and thus requires good opacification of the coronary artery lumen. Protocols for CT coronary angiography are in a state of flux at the present time and vary from one center to another. Using 64 detector scanners it is possible to obtain 0.4x0.4x0.6mm spatial resolution with a temporal resolution of 165-200 msec. This requires a breath-hold of 8-13 seconds depending upon the heart rate and heart volume. Typically 40-80 ml of iodinated contrast material is administered at a rate of 5cc/sec which generally requires a good 18-guage antecubital intravenous line. The details of the timing of the bolus to insure good opacification have not been extensively evaluated and are quite variable from site to site.

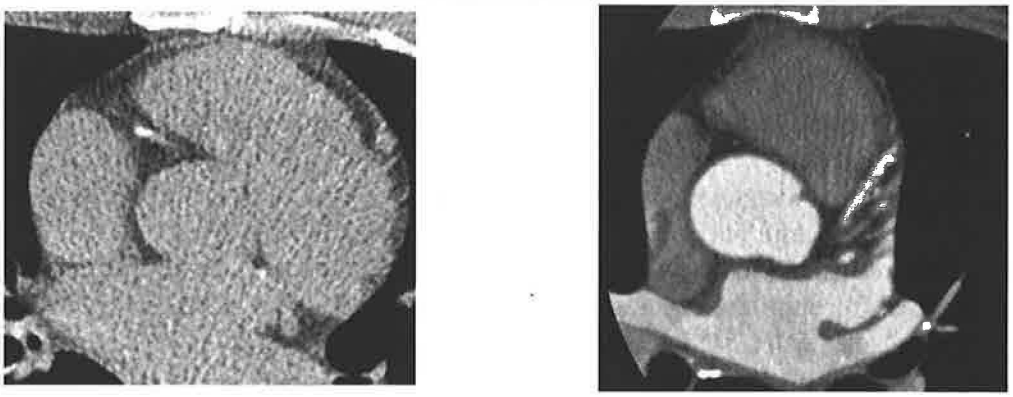


Figure 8: Left: EBCT scan for coronary calcium obtained without contrast. There is calcium in the right coronary artery just after its take off from the aorta. Fat in the anterior atrioventricular groove is seen as dark while blood and myocardium are intermediate gray. Right: MDCT scan obtained with contrast. Images are obtained as the bolus of contrast is passing through the left heart and aorta to improve opacification of the coronary artery lumen. There is also calcium present.

At present patient selection and preparation play major roles in obtaining a successful coronary CT angiogram. Clearly, patients with a contraindication to CT with contrast such as history of contrast reaction, renal insufficiency (serum creatinine >1.5), pregnancy or thyroid dysfunction should not be referred for coronary CTA. A good candidate is a patient who is able to perform a 15-20 second breath-hold, has a regular heart rate below 70, is able to follow instructions, and has excellent intravenous access. The requirement for an excellent breath-hold is more stringent than in CT angiography of the pulmonary arteries or aorta due to the need to reliable image very small vessels. The reduction of image quality with increasing heart rate has been well demonstrated in many studies. Patients with irregular rhythms, who are unable to perform breath-holds, who are unable for follow instruction and who have unreliable intravenous access will frequently have poor quality or non-diagnostic studies. In many centers the patient is given material to prepare them for the study and instructed to avoid caffeine and other stimulants prior

to the study. We ask the referring physician to premedicate the patient with beta-blockers if possible. Prior to imaging the patient will receive additional beta blockade to reduce the heart rate to 70 or less. Typical patient instructions and protocol prior to scanning are given in Figure 9.

Patient instructions:

- Do not smoke for 24 hours prior to your scan.
- Do not have any caffeine, or other foods or medications (e.g., chocolate, cola, coffee, tea, energy drinks, Excedrin or other stimulant medications) that will increase your heart rate, for 12 hours prior to your scan.
- Avoid energy or diet pills on the day before or the day of your exam.
- On the day of your exam, do not eat for 4 hours prior to the procedure.

Prior to scanning:

- At least 20 gauge antecubital IV
- 5 mg metoprolol IV up to 20 mg to achieve HR < 70 bpm
- Repeat breath-hold training with monitoring of heart rate
- Sublingual nitroglycerin

Figure 9: Left: Typical patient instructions. Right: Typical patient preparation prior to coronary CTA.

Finally, it is also important to note that coronary MRA and coronary CTA generate literally thousands of images for each patient. Thus, the interpretation of the study requires the use of computer workstations to efficiently review the images. Analysis requires identification of each of the major coronary arteries and at least their first order branches. A variety of image processing tools are used to visualize the arteries including multiplanar reformatting, curvilinear reformatting, maximum intensity projection, and volume rendering. Although volume rendered images are quite striking, they are generally not used for diagnosis (Figure 10). The primary approach is to use the original axial images to track the vessels and then use multiplanar reformatting to obtain orthogonal views of the vessels.

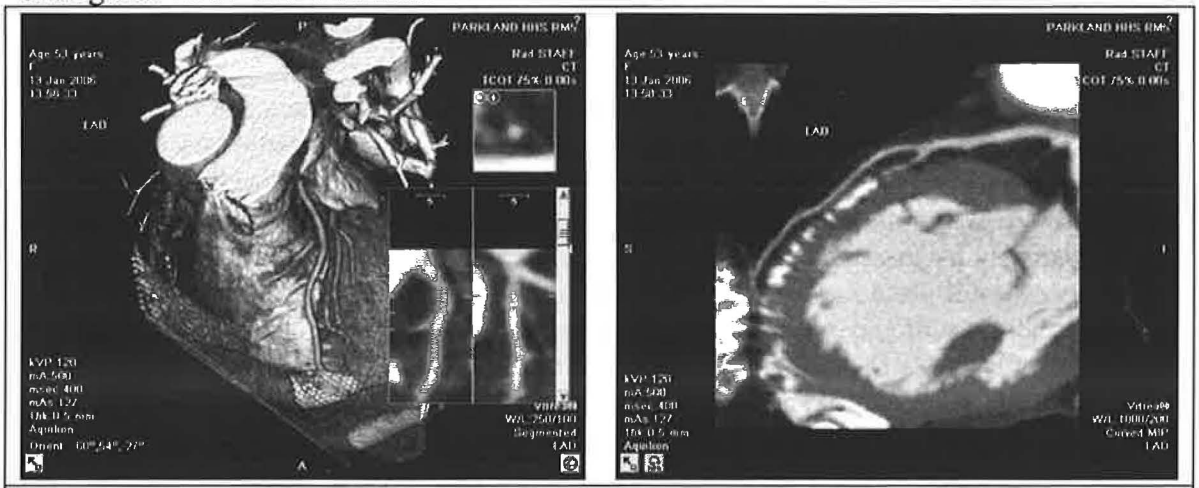


Figure 10: Left: Volume rendered image from coronary CTA Right: Multiplanar reformed images of the left anterior descending coronary artery in the same patient.

What is known today regarding how to use these tests clinically?

From a technical standpoint it's clear that both MR and CT could be used to evaluate the coronary artery lumen and wall. The questions are (1) do they work clinically and (2) when should we use them? In addressing these questions I would like to begin the discussion with the non-invasive coronary artery assessment that has the longest history: Coronary artery calcium. In spite of over 15 years of experience and hundreds of articles examining this measure, there is no topic in cardiac imaging which generates such controversy as coronary artery calcium and what to do about it. This topic was expertly review by Dr. Tom Andrews in Medical Grand Rounds in 1999[17] and the controversy continues.

Coronary artery calcium (CAC): The idea that coronary artery calcium can serve as a surrogate marker of coronary disease is enticing.[18] It reflects a process occurring in the coronary artery wall, requires a relatively low dose of X-rays and can be reasonably rapidly calculated. What appears to be accepted is that calcification does not appear to occur in the absence of atherosclerosis[19], zero scores are associated with a low rate of cardiac events, and high scores relative for age and gender do seem to correlate with a worse outcome.

Calcium Score (2, 3)	Implication	Risk of Coronary Artery Disease
0	No identifiable plaque	Very low, generally less than 5 percent
1 - 10	Minimal identifiable plaque	Very unlikely, less than 10 percent
11 - 100	Definite, at least mild atherosclerotic plaque	Mild or minimal coronary narrowings likely
101 - 400	Definite, at least moderate atherosclerotic plaque	Mild coronary artery disease highly likely, significant narrowings possible
401 or Higher	Extensive atherosclerotic plaque	High likelihood of at least one significant coronary narrowing

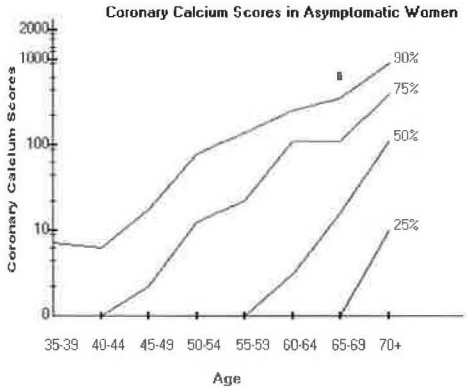


Figure 11: Left: Clinical implications of absolute calcium scores. Right: Graph showing one woman's calcium score relative to published distributions.

Possible applications include establishing the presence or absence of coronary disease in symptomatic patients, screening asymptomatic patients for coronary disease and in the assessment of response to therapy. Although it remains controversial, many investigators feel that measurement of CAC can be helpful in the patient with intermediate risk by Framingham risk.[20] It is of note that in the most recent European guidelines on cardiovascular disease prevention in clinical practice they note that "the resulting calcium score is an important parameter to detect asymptomatic individual at high risk for future CVD events, independent of traditional risk factor.[21]"

The American Heart Association has produced three consensus statements on coronary calcium screening which indicate that general clinical application will require corroborating results in larger clinical trials before the results of the small number of published studies can be used to change guidelines for coronary calcium screening.[22 23 24] Interestingly, the AHA was about to release a Scientific Statement on EBCT and MDCT

in 2004 but did not publish the article because of premature release of information to the media.[25] The role of coronary calcium in screening has been dressed repeatedly in the Journal of the American Medical Association. Greenland found that that high CAC modified predicted risk from the Framingham risk score alone.[26] More recently a commentary suggested that although EBCT improves prediction of coronary heart disease risk in asymptomatic individuals, the low underlying population risk results in a small number of individuals with a positive result who will experience a clinical event in following four to six years.[27] In addition they felt that early detection of EBCT had not been shown to reduce morbidity or mortality. Finally, there is concern that the effects of false positive tests on healthcare cost are not known. There are now a number of large trials, such as the Dallas Heart Study and the Multi-ethnic Study of Atherosclerosis (MESA) and others which are attempting to establish the value of coronary artery calcium evaluation in the general population.

With regards to the use of coronary calcium to assess response to therapy, Raggi and others have demonstrated an ability in small studies to assess progress of disease using serial measurements of CAC.[28] However, a recent larger study in which CAC could not demonstrate an effect of intensive lipid-lowering therapy compared to standard treatment[29] has raised additional concerns as to whether CAC can be used as a tool to monitor therapy[30].

Given the limitation of coronary calcification, is it possible to do better using coronary MR or CT angiography? Recently, we have had the opportunity to examine the assessment of coronary calcium in the Dallas Heart Study (DHS). As has been described in previous Grand Rounds, the DHS is multi-ethnic, population-based study of Dallas County.[31] As part of the study, extensive phenotypic characterization was performed in approximately 3,000 participants including measurement of coronary calcification using EBCT (Figure 12).[32]

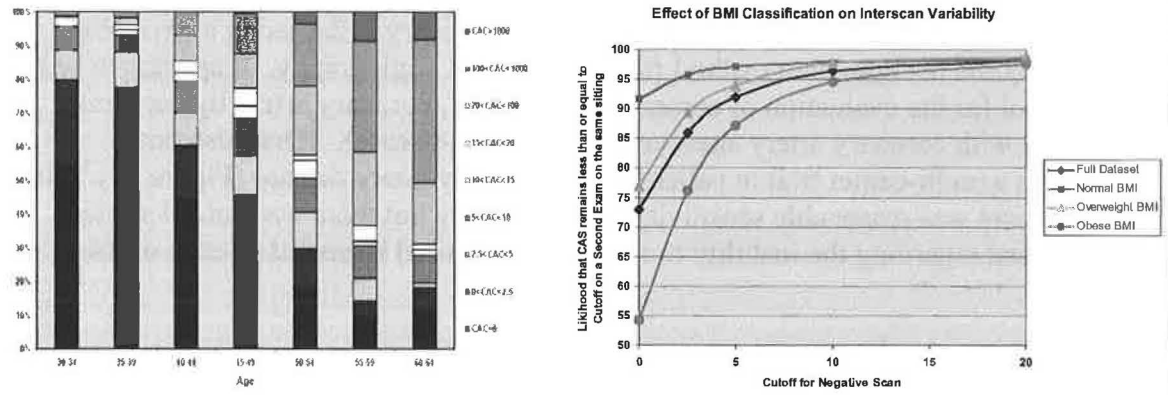
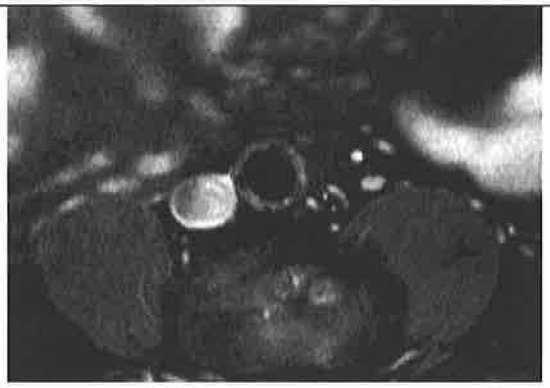


Figure 12: Left: Distribution of calcium scores in men in the Dallas Heart Study. Right effect of BMI on reproducibility of coronary calcium scores by EBCT (From Jain, et al).

The analysis of these studies revealed several interesting findings. First, in Dallas County residents ages 30-60, the overall incidence of coronary artery calcification is low, approximately 23%. Second, the high prevalence of obesity was found to be a potential contributor to false positives due to an inability to increase the X-ray dose in EBCT

(Figure 12). Third, that in a population-based sample there appears to be no difference in the prevalence of coronary artery calcium in blacks and whites.

Does the relatively low prevalence of CAC mean that atherosclerosis is not present in these individuals? In other words, does CAC underestimate the prevalence and extent of atherosclerosis? At the time of the original DHS, MR methods for directly imaging the coronary wall were not available so it was elected to examine another marker of atherosclerosis, MRI of the abdominal aorta.[33] In these images (Figure 10) it is possible to detect the presence of plaque and determine its extent. Work by Drs. Tulika Jain and Hao Lo have shown, in fact, that CAC appears to miss approximately 50% of the individuals with evidence of abdominal atherosclerosis by MRI (Figure 13).[34] These results suggest that MR could be a means of detecting the presence of alterations in the vascular wall which do not require the presence of calcification.



	AAP -	AAP +
CAC -	910 (51%)	484 (27%)
CAC +	139 (8%)	269 (15%)

Figure 13: Left: MR image of the abdominal aorta demonstrating complex plaque. Right: Concordance of CAC and the presence of abdominal atherosclerosis in the Dallas Heart Study (From Jain and Lo).

Coronary MR angiography: Free-breathing coronary MRA using a navigator echo has become the dominant method for coronary MR angiography. It appears to be an excellent tool for the evaluation of coronary anomalies[35], coronary artery bypass grafts and patients with coronary artery aneurysms (Kawasaki disease). It has also been examined in a multi-center trial in patients with coronary artery disease (Figure 14).[36] In this study there was reasonable sensitivity and specificity but there was considerable concern raised regarding the inability to analyze all required segments in each of the participants.

Variable	Left Main Coronary Artery	Left Anterior Descending Coronary Artery	Left Circumflex Coronary Artery	Right Coronary Artery	Any Coronary Artery Disease (Consensus/ Site Reading)*	Left Main Coronary Artery or Three-Vessel Disease (Consensus/Site Reading)*
No. of true negatives	81	31	49	43	18/25	74/75
No. of true positives	4	29	8	37	56/51	16/15
No. of false negatives	2	4	7	3	4/7	0/1
No. of false positives	9	29	21	17	25/18	13/10
Prevalence (%)	6	41	19	40	59	15
Sensitivity (%)	67	88	53	93	93 (88–98)/88 (82–94)	100 (97–100)/94 (89–99)
Specificity (%)	90	52	70	72	42 (32–52)/58 (48–68)	85 (78–92)/88 (82–94)
Accuracy (%)	89	65	67	80	72 (63–81)/75 (67–83)	87 (81–93)/89 (83–95)
Positive predictive value (%)	30	56	29	69	70 (61–79)/75 (67–83)	54 (44–64)/58 (48–68)
Negative predictive value (%)	98	86	86	94	81 (73–89)/77 (69–85)	100 (97–100)/99 (95–100)

*Values in parentheses are 95 percent confidence intervals.

Figure 14: Diagnostic accuracy of coronary MRA compared to invasive coronary angiography to detect stenosis greater than 50% in a multi-center trial. (From Kim, et al).

Interestingly there has been a direct comparison of MR and CT (4-slice) in the evaluation coronary disease.[37] In that study MR and CT were equivalent in the detection of significant coronary disease but both missed disease compared to selective contrast angiography. Given the relative success of the multi-center trial it is interesting to ask why this technique has not been used more widely. The primary reason may be the time required to perform the study which is on the order of 45 minutes to an hour at present standard magnetic fields (1.5 Tesla).

Who is an appropriate candidate for coronary MRA? We presently perform these studies routinely in patients referred for a question of an anomalous coronary artery which can be determined without the use of radiation or contrast agent.

Coronary CT angiography: Over the last 10 years coronary CTA has rapidly gone from a demonstration of technical possibility to clinical application. This is due in large part to continued improvement scanner technology with faster X-ray tube rotation times and increasing numbers of detector rows (from 1 to 4 to 16 and now 64 detector rows) to obtain multiple slices with each rotation. Suffice it to say this rapid progress has complicated large studies to evaluated accuracy and efficacy. However, there are as of 11/2005 over 30 single center studies (13 EBCT studies with 847 patients, 10 studies using 4 or 8 slice MDCT with 588 patients and 7 studies using 16 slice MDCT with 414 patients) which have compared coronary CTA to invasive selective angiography.[38] Given the ability of CTA to demonstrate soft plaque, there has been considerable interest in comparing measures of plaque volume from intravascular ultrasound with measures obtained with coronary CTA. In these studies there has been reasonable correlation between the two techniques (Figure 15).[39]

Table 3. Accuracy of 64-Slice CT to Detect Coronary Lesions in Comparison to IVUS

	Sensitivity	Specificity
RCA	(5/6) 83%	(6/6) 100%
LM	(5/5) 100%	(11/11) 100%
LAD	(26/30) 87%	(13/14) 93%
RCX	(10/14) 71%	(10/13) 77%
Total	(46/55) 84%	(40/44) 91%

CT = computed tomography; IVUS = intravascular ultrasound; LAD = left anterior descending artery; LM = left main artery; RCA = right coronary artery; RCX = right circumflex artery.

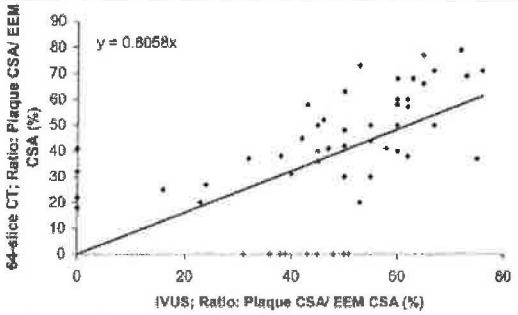


Figure 15: Left: Accuracy of 64-slice CT in the detection of coronary lesions in comparison to intravascular ultrasound. Right: Linear regression analysis of the extent of plaque as measured by CT as compared to intravascular ultrasound (From Leber)

Who is an appropriate candidate for coronary CTA? Similar to their work in the area of cardiac nuclear imaging, the American College of Cardiology has recently begun the process of establishing appropriateness criteria for cardiac CT and cardiovascular MR.[40,41] Thus, definitive criteria for the use of coronary CTA are not yet available. Interestingly, Blue Cross Blue Shield has recently produced a technology assessment report regarding the use of coronary CTA in the diagnosis of coronary disease.[42] In their report issued in May 2005 which was based on the literature available at that time, there were no studies using 64-detector row technology. In that analysis, they a felt major weakness of the literature was the frequent use individual vessel or segment analysis as opposed to analysis based on the diagnostic performance of the test using the patient as the unit of analysis. In other words, the value of a negative CTA in an individual patient is fundamentally dependent on the ability to obtain a complete analysis of all vessels. They also highlighted the requirement for a high technical success rate for CTA. If one cannot fully evaluate all vessels, the patient will have been exposed to the risks of radiation and contrast without answering the question. To help insure high technical quality in the performance and interpretation of coronary CTA, the American College of Cardiology Foundation and the American Heart Association have recently developed training standards in cardiac imaging with computed tomography and magnetic resonance.[43]

In their review of the diagnostic performance of coronary CTA, there were no studies which identified CTA as a screening test in asymptomatic subjects or subjects planned for major surgery. In patients with non-ST elevation acute coronary syndromes, there is one small study which demonstrated 99% negative predictive value for significant stenosis in vessels at least 2mm in diameter.[44] Treatment recommendations were the same for CT and invasive angiography in 19 of 22 cases (86%). In the diagnosis of coronary disease in the non-acute setting, there were multiple studies which demonstrate reasonably high sensitivities for significant stenosis on a vessel by vessel basis. However, to exclude the presence of significant stenosis requires complete evaluation of all of the coronary vessels.

Over the last 6 months the first results using 64-slice MDCT have been published (Figure 16). Overall, they confirm the results of prior studies with regards to the detection of significant stenosis on a per vessel basis. The advantages of 64-deteector scanning over previous technology appear to be related to (1) a lower prevalence of motion artifacts and (2) a better ability to evaluate segments with calcification due to

higher resolution with less partial volume effect. In addition, with the acquisition of 64 slices per rotation, breath-hold times are decreased which reduces artifacts due to respiration.

Recent results using 64-slice Coronary CTA

		n	Sens	Spec	PPV	NPN	Unevaluable segments/patients
Leber[45]	2005	59	80	97			4/59 patients
Leschka[46]	2005	67	94	97	87	99	0%
Raff[47]	2005	70	86	95	66	98	12% (segments)
Mollett[48]	2005	52	99	95	76	99	1 patient
Ropers [49]	2006	84	93	97	64	100	4% (segments)
Fine[50]	2006	66	95	96	97	92	6% (patients)

Performance for detecting >50% luminal stenoses by visual estimate

Figure 16: Summary of recent 64-detector MDCT studies in the detection of greater than 50% stenosis

Clearly, there are many unanswered questions regarding coronary CTA: Is CTA better as a primary diagnostic approach than stress echo or perfusion scanning? Should it be used primarily as a second step in the patient with an inconclusive stress test? Can the presence of soft plaque or its extent be used to predict outcomes? Preliminary results addressing each of these questions were presented at the recent American Heart Association Scientific Sessions in Dallas in November 2005. These results have not yet been subjected to peer review and published but suggest that we will soon have at least the first answers to these questions.

What future developments are on the horizon?

There are developments on the horizon which have the potential to significantly increase the role of coronary MR and CT in clinical practice. In general these involve (1) approaches to obtain higher resolution scans in less time and (2) to go beyond structural imaging to obtain information regarding the function of the vascular wall.

In the area of coronary MR, the imperative is to obtain higher spatial resolution images more quickly. It is important to recall that resolution in MRI is not dependent on the wavelength of the energy used in the imaging (the radiowaves used in MRI have wavelengths of meters). However, the amount of signal is dependent upon the number of hydrogen nuclei in each volume element so that as the volume elements become smaller (i.e. resolution becomes better), the signal becomes weaker. One approach to this problem is to increase the strength of the magnetic field used in MR from the present standard 1.5 Tesla to 3.0 Tesla. This has been applied in preliminary studies of MR coronary angiography and coronary wall imaging. In addition MR parallel acquisition techniques make it possible to divide the image tasks among an increasing number of receiver coils and processors to speed acquisition and analysis. This is now manifest in MR systems that can record information from hundreds of receivers at one time compared to the 4 or 8 channels used presently. [51]

In the case of MDCT there are now prototype systems that can acquire 256 slices of data simultaneously making it possible to obtain the images of the coronary arteries in a single cardiac cycle without cardiac gating.[52,53] In theory it is potentially possible to extend MDCT reconstruction techniques to flat plate detectors comparable to those presently used in the cath lab to obtain even more slices with each rotation. Another interesting approach to increasing the speed of the acquisition in MDCT is to use two X-ray sources simultaneously, termed dual source CT.[54] These two sources can potentially be used to reduce the total radiation dose[55] or obtain images at two different X-ray energies.

As shown earlier in the aorta, MR has major advantages in the characterization of the arterial wall. There have been major efforts to characterize carotid plaque by MRI. [56] Using standard MR imaging techniques (T1-weighted, T2-weighted and gadolinium-enhanced imaging) it is possible to characterize plaque components including the presence of the lipid rich core, calcification and fibrous components (Figure 17).

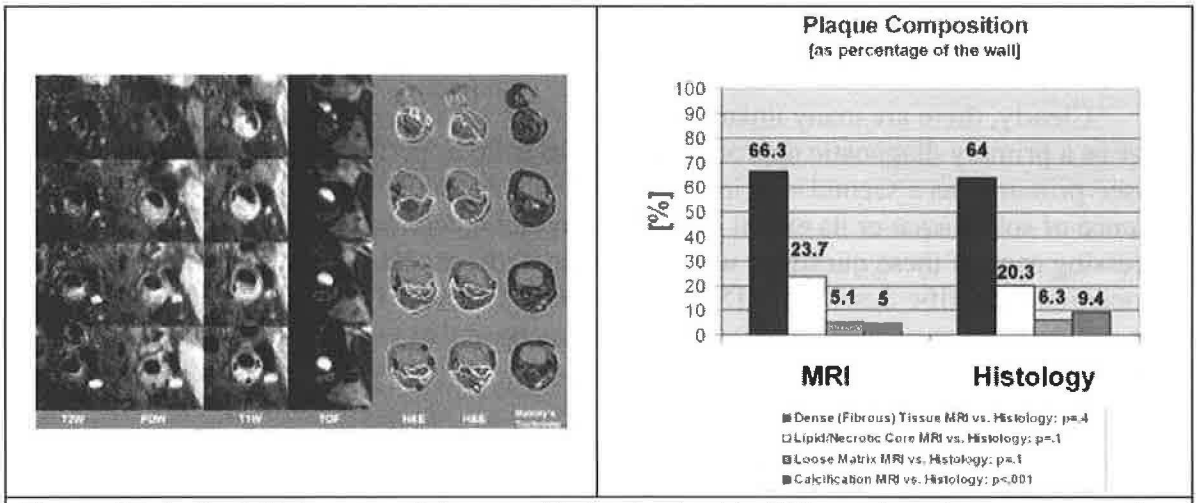


Figure 17: Left: MR images of the carotid obtained with different imaging sequences for tissue characterization. Right: Agreement of assessment of plaque composition by MR and histology (From Saam, et al).

There are now early studies attempting to similarly characterize the coronary arteries using MR. Coronary wall imaging, although technically demanding at 1.5T, has now been done at multiple centers including UT Southwestern (Figure 18) and demonstrates good reproducibility for the detection of early coronary atherosclerosis prior to the development of hemodynamically significant lesions. [57,58,59,60] There are now several studies using ex-vivo imaging of human coronaries to identify different components of atherosclerosis.[61] Finally, molecular magnetic resonance imaging of coronary thrombosis has been demonstrated in animal models.[62] The wide array studies underway in the assessment atherothrombosis and high risk plaque have recently been reviewed.[63 64]

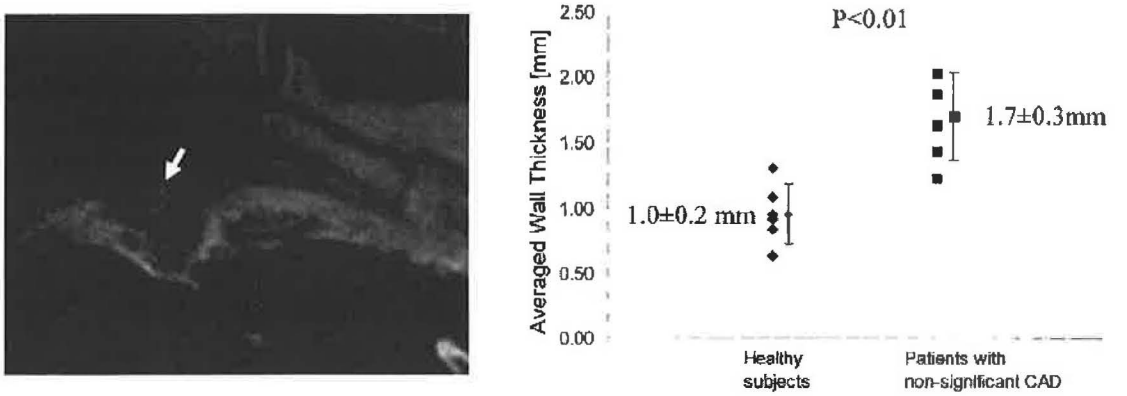


Figure 18: Left: Black blood MR imaging of the right coronary artery demonstrating focal plaque with maintenance of the lumen (From Jain, et al). Right: Coronary wall thickness by MR in healthy subjects and patients without obstructive coronary artery disease (from Kim, et al).

MDCT also has further potential for plaque characterization. The combination of positron emission tomography (PET) with CT has had a dramatic impact in oncology. There are now PET-MDCT and SPECT-MDCT devices which combine the ability to perform coronary CTA with radionuclide imaging.[65] This would offer the potential to perform perfusion scanning at the same as coronary imaging to assess the effect of lesions on coronary flow. There is also recent evidence in the carotids that a tracer as simple as 18F fluorodexyglucose can be used to detect regions of plaque activity.[66]

Conclusions

We are on the threshold of the next era in coronary imaging. The focus will be less on luminal narrowing and increasingly on the detection of active processes taking place in the vascular wall. Close collaboration between experts in vascular biology, proteomics, genetics, epidemiology and imaging will lead to important new insights and tools to improve our care of patients with coronary and vascular disease.

References

[1] Ryan, TJ. The coronary angiogram and its seminal contributions to cardiovascular medicine over five decades. Circulation 2002;106:752-756.

[2] American Heart Association. *Heart Disease and Stroke Statistics — 2006 Update.* Dallas, Texas: American Heart Association; 2006.

[3] American Heart Association. *Heart Disease and Stroke Statistics — 2006 Update.* Dallas, Texas: American Heart Association; 2006.

[4] Lucas FL, Delorenzo MA, Siewers AE and Wennberg. Temporal trends in the utilization of diagnostic testing and treatments for cardiovascular disease in the United States, 1993-2001. Circulation 2006;113:374-379.

[5] Gandelman G and Bodenheimner. Screening coronary arteriography in the primary prevention of coronary artery disease. Heart Dis 2003;5:335-344.

[6] Bashore TM, et al. American College of Cardiology/Society for Cardiac Angiography and Interventions clinical expert consensus document on cardiac catheterization laboratory standards. J Am Coll Cardiol 2001;37:2170-2214.

[7] Dodge JT, Brown BG, Bolson EL, et al. Lumen diameter of normal human coronary arteries. Influence of age, sex, anatomic variation and left ventricular hypertrophy or dilatation. Circulation 1992;86:232-246.

[8] Kim WY, Stuber M, Kissinger KV, et al. Impact of bulk cardiac motion on right coronary MR angiography and vessel wall imaging. J Magn Reson Imaging 2001;14:383-390.

[9] Kim WY, Stuber M, Kissinger KV, et al. Impact of bulk cardiac motion on right coronary MR angiography and vessel wall imaging. J Magn Reson Imaging 2001;14:383-390.

[10] Wada AM, Willet SP, and Bader D. Coronary vessel development: A unique form of vasculogenesis. Arteroscler Thromb Vasc Biol 2003;23:2138-2145.

[11] Choudhury RP, Fuster V and Fayad R. Molecular, cellular and functional imaging of atherothrombosis. Nature Reviews 2004;3:913-925.

[12] Hundley WG, Clarke GD, Landau C, Lange RA, Willard JE, Hillis LD, and Peshock RM. Noninvasive determination of infarct artery patency by cine magnetic resonance imaging. Circulation 1995;91:1347-1353.

[13] Clarke GD, Eckels R, Chaney C, Smith D, Dittrich J, Hundley WG, Li HF, Parkey RW, and Peshock RM. Measurement of absolute epicardial coronary artery flow and flow reserve using breath-hold cine phase contrast magnetic resonance imaging. Circulation 1995;91:2627-2634.

[14] Stuber M, Botnar R, Danias PG, et al. Double oblique free breathing high resolution three dimensional coronary artery magnetic resonance angiography. J Am Coll Caardiol 199;34:524-31.

[15] Morin RL, Gerber TC, McCollough CH. Radiation dose in computed tomography of the heart. Circulation 2003;107:917-22.

[16] Stanford W, Thompson BH, Burns TL, et al. Coronary artery calcium quantification at multi-detector row helical CT versus electron-beam CT. Radiology 2004;230:397-402.

[17] Andrews T. Screening for coronary artery disease. Internal Medicine Grand Rounds July 26, 1999.
[18] Agatston AS, et al. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol 1990;15:827-832.
[19] Rumberger JA and Kaufman l. A Rosetta stone for coronary calcium risk stratification: Agatston, volume and mass score in 11,490 individuals. AJR 2003;181:743-748.
[20] Grundy SM. The changing face of cardiovascular risk.(editorial). Journal of the American College of Cardiology 2005;46:173-175.
[21] De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice. Third joint task force of European and other societies on cardiovascular disease prevention in clinical practice. Eur Heart J 2003;24:1601-1610.
[22] Greenland P, Abrams J, Aurigema GP, et al. Prevention conference V: Beyond secondary prevention: identifying the high-risk patient for primary prevention: non-invasive test of atherosclerotic burden: Writing Group III. Circulation 2000;101:E16-22.
[23] O'Rourke, Brundage BH, Froelicher, 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 –140.
[24] Mosca L, Appel LJ, Benjamin EJ, et al. American Heart Association. Evidence-based guidelines for cardiovascular disease prevention in women. Circulation. 004;109:672–693.
[25] Loscalzo J, Bonow RO and Jacobs AK. Coronary calcium screening and the American heart association news embargo. Circulation 2004;110:3504-3505.
[26] Greenland P, LaBree L, Azen SP, et al. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. JAMA 2004;291:210-215.
[27] Mozaffarian, D. Electron beam computed tomography for coronary calcium: A useful test to screen for coronary artery disease? JAMA 2005;294:2897-2901.
[28] Bellasi A and Raggi P. Diagnostic and prognostic value of coronary artery calcium screening. Curr Opin Cardiol 2005;20:375-380.
[29] Schmerund A, Achenbach S, Budde T, et al. Effect of intensive versus standard lipid-lowering treatment with atorvastatin on the progression of calcified coronary atherosclerosis over 12 months. A multicenter, randomized, double-blind trial. Circulation 2006;113:427-437.
[30] Redberg RF. Coronary artery calcium: Should we relay on this surrogate marker. Circulation 2006;113:336-337.
[31] Victor RG and the Dallas Heart Study Investigators. A Population-Based Probability Sample for the Multidisciplinary Study of Ethnic Disparities in Cardiovascular Disease: Recruitment and Validation in the Dallas Heart Study. American Journal of Cardiology 2004;93:1473-1480.

[32] Jain T and the Dallas Heart Study Investigators. African Americans and Caucasians Have a Similar Prevalence of Coronary Calcium in the Dallas Heart Study. Journal of the American College of Cardiology 2004;44:1011-7.
[33] Jaffer F, et al. Age and sex distribution of subclinical aortic atherosclerosis. An MRI examination of the Framingham Heart Study. ATVB 2002;22:849.
[34] Jain T, Lo H, et al. Subclinical Atherosclerosis as Detected by EBCT and MRI in a Population-based Sample: Results from the Dallas Heart Study (manuscript in preparation).
[35] Angelini P, Velasco JA, Flamm S. Coronary anomalies: incidence, pathophysiology and clinical relevance. Circulation 2002;105:2449-2454.
[36] Kim WY, et al. Coronary magnetic resonance angiography for the detection of coronary stenosis. N Engl J Med 2001;345:163-9.
[37] Kefer J, et al. Head to head comparison of three dimensional navigator gated magnetic resonance imaging and 16-slice computed tomography to detect coronary artery stenosis in patients. J Am Coll Cardiol 2005;46:92-100.
[38] Hoffman U, Siebert U, Hossein J, et al. A systematic review of the diagnostic accuracy of CT-based detection of significant coronary artery disease. Comparison of segment and patient-based approach. AHA Scientific sessions, Dallas, 2005.
[39] Leber AW, et al. Quantification of obstructive and nonobstructive coronary lesions by 64 slice computed tomography. J Am Coll Cadiol 2005;46:147-54.
[40] Patel MR, Spertus JA, Brindis RG, et al. ACCF proposed method for evaluating the appropriateness of cardiovascular imaging. Jour Am Col of Cardiol 2005;46:1606-1613.
[41] Douglas PS, Hendel RC, Peter son ED, et al. ACCF/ASNC appropriateness criteria for single photon computed tomography myocardial perfusion imaging (SPECT MPI).
[42] Contrast-enhanced cardiac computed tomographic angiography for coronary artery evaluation. Blue Cross Blue Shield TEC assessment, Volume 20, No4. May 2005.
[43] Cohen MC, Garcia MJ, and Hodgson J, et al. ACCF/AHA clinical competence statement with cardiac imaging with computed tomography and magnetic resonance. JACC 2005;46:383-402.
[44] Dorgelo J, Willems TP, Geluk CA, et al. Multidetector computed tomography-guided treatment strategy in patients with non-ST elevation acute coronary syndromes: a pilot study. Eur Rad 2005;15:708-13.
[45] Leber AW, et al. Quantification of obstructive and nonobstructive coronary lesions by 64 slice computed tomography. J Am Coll Cadiol 2005;46:147-54.
[46] Leschka S, Alkadhi H, Plass A, et al. Accuracy of MSCT coronary angiography with 64-slice technology: first experience. European Heart Journal 2005;26:1482-1487.
[47] Raff GJ, Gallagher MJ, O'Neill WW, et al. Diagnostic accuracy of non-invasive angiography using 64-slice spiral computed tomography. J Am Coll Cardiol 2005;46:552-557.
[48] Mollet NR, Cademartiri F, van Mieghem CAG, et al. High-resolution spiral computed coronary angiography in patients referred for diagnostic conventional coronary angiography. Circulation 2005;112:2318-2323.

[49] Ropers D, Rixe J, Anders K, et al. Usefulness of multi-detector row spiral computed tomography with 64 x 0.6 collimation and 330-ms rotation for the noninvasive detection of significant coronary artery stenoses. Am J Cardiol 2006;97:343-348.
[50] Fine JF, Hopkins CB, Ruff N, et al. Comparison of accuracy of 64-slice cardiovascular computed tomography in patients with suspected coronary artery disease. Am J Cardiol 2006;97:173-174.
[51] Huber ME, Kozerke S, Pruessmann KP, et al. Sensitivity-encoded coronary MRA at 3T. Magn Reson Med 2004 ;52 :221-227.
[52] Mori S, et al. Volumetric cine image for cardiovascular circulation using prototype 256-detector row computed tomography scanner (4-dimesional computed tomography). J Comput Assist Tomogr 2005;29:26-30.
[53] Kondo C, et al. Real-time volumetric imaging of human heart without electrocardiographic gating by 256-detector row computed tomography: Initial experience. J Comput Assist Tomogr 2005;29:694-698.
[54] Flohr TG, et al. First performance evaluation of a dual-source CT (DSCT) system. European Radiology, published online 10 December 2005.
[55] Hundt W, et al. Dose reduction in multislice computed tomography. J Compuy Assist Tomogr 2005;29:140-147.
[56] Saam T, et al. Quantitative evaluation of carotid plaque composition by in vivo MRI. Arterioscler Thromb Vasc Biol. 2005;25:234-239.
[57] Fayad ZA, et al. Noninvasive in-vivo human coronary artery lumen and wall imaging using black-blood magnetic resonance imaging. Circulation 2000;102:506-510.
[58] Botnar RM, et al. Noninvasive coronary vessel wall and plaque imaging with magnetic resonance imaging. Circulation 200;102:2582-2587.
[59] Desai MY, Lai S, Barmet C, et al. Reproducibility of 3d free breathing magnetic resonance coronary vessel wall imaging. European Heart Journal 2005;June.
[60] Kim WY, Stuber M, Bonert P, et al. Three-dimensional black blood cardiac magnetic resonance coronary vessel wall imaging detects positive arterial wall remodeling in patients with non-significant coronary artery disease. Circulation 2002;106:296-299.
[61] Nikolaou K, et al. Multidetector-row computed tomography and magnetic resonance imaging of atherosclerotic lesions in human ex vivo coronary arteries. Atherosclerosis 2004;174:243-252.
[62] Spuentrup E, Buecker A, Katoh M, et al. Molecular magnetic resonance imaging of coronary thrombosis and pulmonary emboli with a novel fibrin-targeted contrast agent. Circulation 2005;111:1377-1382.
[63] Fuster V, Moreno P, Fayad, ZA, et al. Atherothrombosis and high risk plaque. Part I: Evolving concepts. J am Coll Cardiol 2005;46:97-54.
[64] Fuster V, Moreno P, Fayad, ZA, et al. Atherothrombosis and high risk plaque. Part II: Approaches by noninvasive computed tomography and magnetic resonance imaging. J am Coll Cardiol 2005;46:1209-18.
[65] Schwaiger M, Ziegler S, and Nekolla SG. PET/CT: Challenge for nuclear cardiology. J Nucl Med 2005;46:1664-1678.

[66] Davies JR, Rudd JHF, Fryer TD, et al. Identification of culprit lesions after transient ischemic attack by combined 18F fluorodexyglucose positron emission tomography and high-resolution magnetic resonance imaging. Stroke 2005;36:2642-2647.