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Noninvasive Modalities for Coronary Angiography

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1. Introduction

Optimal diagnostic quality non-invasive alternatives for visualization of the coronary arteries has been a major goal with the advent of newer cardiovascular imaging modalities such as coronary computed tomography angiography (CCTA) and magnetic resonance coronary angiography (MRCA). The challenges in imaging coronaries are obvious. The technology must be capable of visualizing arteries as small as 1.5 mm to delineate luminal and wall pathology which becomes challenging as many of the arteries are engulfed in tissue of similar composition. Coronary arteries exhibit rapid motion which poses major issues with blurring of images due to substantial limitations of temporal resolution. Invasive coronary angiography current enjoys the best temporal resolution (less than 20 msec) for real time visualization of coronaries and its branches but comes with its obvious limitations. CCTA has rapidly risen to this challenge and is already widely employed using 64 slice detector technology and is outstanding for exclusion of CAD with substantial advances in radiation reduction and speed of acquisition. MRCA has made significant improvements in technology which has made coronary imaging less challenging using navigator gating, whole heart imaging and using 3Tesla magnets, with the big advantage of no radiation and capability of non-contrast coronary imaging and most of all the promise of a true " one stop " comprehensive assessment. However, it is still suboptimal compared to CCTA as discussed subsequently in detail. This chapters aims to discuss MRCA and CCTA with regards to coronary imaging and compare and contrast both these imaging modalities with one another and also highlight some emerging comparisons of CCTA to invasive coronary luminal assessment technologies.

2. Magnetic Resonance Coronary Angiography (MRCA)

Introduction: MRCA has been performed for close to 20 years with numerous advances in technical and imaging aspects during this period although slower than CCTA explaining its slower adoption [1]. Initially 2 dimensional k space segmented imaging was done, but most centers now use whole heart free breathing navigator coronary MRI or targeted 3D imaging to enable better reconstruction capabilities. Published studies from experienced centers have shown excellent accuracy and superiority to conventional coronary angiography (CA) using 2 and 3 dimensional k space gradient echo MRCA (Table 1)[2]..

Although whole heart MRCA was initially performed with 4 channel cardiac coils and a parallel imaging factor of 2 [3, 4] it has been limited due longer acquisition times and image deterioration from diaphragmatic drift. Thirty two channel cardiac coils and higher parallel imaging factor of 4 [5] has potential for enhanced coronary imaging with whole heart MRCA. 3T MRCA gives higher signal to noise ratio (approximately 30%) but has its own limitations such as constructive/destructive interference in images causing dark and bright areas due to inherent in-homogeneities which worsen with strong magnetic fields [6]. Also specific absorption rates can increase upto 4 fold with 3T systems limiting use of certain imaging sequences. There are multiple components of MRCA namely cardiac triggering to suppress cardiac motion, respiratory motion suppression (navigator, breath hold) pre-pulses to enhance contrast noise ratio and image acquisition to enhance coronary arterial image quality. Overall image sequences for coronaries include black blood (fast spin echo and dual inversion) bright blood (segmented k space gradient echo and SSFP) all of which can be used either with 2D or 3D imaging.

Investigator	Technique	Respiratory Compensation	Number of Subjects	RCA	LM	LAD	LCX
Manning, 1993	2D GRE	BH	25	100%	96%	100%	76%
Pennell, 1993	2D GRE	BH	26	95%	95%	91%	76%
Duerinckx, 1994	2D GRE	BH	20	100%	95%	86%	77%
Sakuma, 1994	2D GRE cine	BH	18	100%	100%	100%	67%
Masui, 1995	2D GRE	BH	13	85%	92%	100%	92%
Davis, 1996	2D GRE	BH	33*	100%	100%	100%	100%
Li, 1993	3D GRE	Multiple Averages	14	100%	100%	86%	93%
Post, 1996	3D GRE	Retro Nav G	20	100%	100%	100%	100%
Wielopoiski, 1998	3D Seg EPI	BH	32	100%	100%	100%	100%
Botnar, 1999	3D GRE	Pro Nav G/C	13	97%	100%	100%	97%
Weber, 2003	3D SSFP	Pro Nav G/C	12	100%	100%	100%	100%

Abbreviations: BH, breath hold; GRE, gradient echo; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LM, left main coronary artery; PRO Nav GAC, prospective navigator gating with correction; RCA, right coronary artery; Retro Nav, retrospective navigator gating; Seg EPL, segmented EPI; SSFP, steady state free precession, 3D

Table 1. Successful visualization of native coronary arteries using 2 and 3 dimensional k space gradient echo MRCA [2].Obtained with permission

3. Challenges for MRCA

Achieving optimal spatial and temporal resolution, accurate motion compensation, wide anatomical coverage, and high signal and contrast to noise ratios are inherent challenges in MRCA. Improvement in one parameter occurs at the expense of another. Other factors that limit its widespread application in the acute setting include longer exam time, limited clinical monitoring in the scanner, device implants and other metallic objects that may need clearance prior to scanning.

Cardiac motion compensation deserves special mention. Since the heart moves due to both inherent motion and due to diaphragmatic movement and as the magnitude of this motion is greater than the diameter of the coronary vessels substantial blurring occurs if motion suppression techniques are not utilized [7]. A regular cardiac rhythm and reliable ECG gating is crucial for cardiac motion suppression techniques to work. Also time intervals of acquisition has to be determined in advance to plan the preparatory pulses which is a limitation. Acquisition is usually in mid-diastole due to least coronary motion and lasts for 50-150 milliseconds per cardiac cycle [8, 9].

As breath holds may be long during coronary imaging and impossible for some patients free breathing MRCA is an alternative and numerous correction techniques such as multiple averaging, chest wall bellows and navigator techniques have been attempted of which the latter is the most widely used [10].

MRCA Acquisition Methods:

1.   **Pulse sequences:**

Pulse sequence design has evolved from black blood spin echo sequences to bright blood sequences such as gradient echo and steady state free precession (SSFP) imaging. Currently GRE is the chosen acquisition scheme in the majority of MRCA studies.

2.   **Acquisition strategies:**

This includes k-space acquisition, contrast –enhanced (intrinsic and extrinsic) MRCA, 2D and 3D acquisitions. Despite many advances, the speed of acquisition and signal to noise ratio (SNR) remain limited. New strategies such as real time, parallel, time resolved and whole heart imaging have been developed.

1.   CONVENTIONAL SPIN ECHO MRI: A spin echo signal results from a 90^0 RF pulse followed by a 180^0 pulse which refocuses the dephased spins up to a decay curve determined by the T2 relaxation time.

2.   2D SEGMENTED k SPACE GRADIENT ECHO MRI: The most widely available MRCA sequence is a 2D segmented k-space gradient echo acquisition usually performed in a single breath hold of fewer than 12 heartbeats. Thick slices and breath hold variability can limit registration of images from slice to slice however this sequence is adequate for applications such as evaluation for anomalous coronaries.

3. 3D MRI: The use of navigator respiratory gating has given access to three-dimensional (3D) coronary magnetic resonance imaging techniques, allowing a 3D dataset to be obtained in a single acquisition. It provides higher spatial resolution and is less operator dependent. However, it relies on a reproducible respiratory pattern, which is not always present. Furthermore, 3D techniques are hampered by the saturation of blood signal, which decreases the signal to-noise ratio and the contrast of blood to myocardium.

4. CONTRAST ENHANCED CORONARY MRI: The use of interstitial paramagnetic contrast agents allows an improvement of signal and contrast. The disadvantage is the rapid leakage out of the intravascular space, amounting to 50% during the first pass. Multiple injections are necessary to cover the whole coronary artery tree. With the introduction of intravascular paramagnetic contrast agents [11, 12], the signal from blood no longer relies on inflow of blood but rather on the presence of the contrast agent itself. The imaging time can be prolonged with potential increased signal and in contrast, allowing a larger volume coverage and higher resolution.

5. 3T MRI: Imaging at higher field strength can enhance signal-to-noise ratio (SNR) and enable higher spatial resolution. However, image quality may be hampered by increased susceptibility artifacts and RF inhomogeneity which may be addressed by shortening the TE and acquisition time. High-field imaging at 3 Tenhances spiral MRCA. A number of research groups already have demonstrated the feasibility of cardiac imaging at 7 T and beyond and have shown improved contrast between blood and epicardial fat, better coronary vessel sharpness, and increased blood signal intensity of the coronaries are obtained at 7 T than at 3 T [13].

Clinical Applications:

1. Anomalous coronary arteries:

C-MRA provides a 3D spatial relationship to great vessels, allowing evaluation of the origin and course of anomalous coronary arteries. Accurate delineation of proximal course has been shown with a sensitivity of 88-100% and specificity of 100% [14-19] MRI can often provide a definitive diagnosis in patients in whose X ray angiography is inconclusive. See Table 2

Investigator	Number of patients	Correctly Classified Anomalous Vessels
McConnell, 1995	15	14 (93%)
Post, 1995	19	19 (100%)
Vilegen, 1997	12	11 (92%)
Taylor, 2000	25	24 (96%)
Bunce, 2003	26	26 (100%)
Razmi, 2001	12	12 (100%)

Table 2. Anomalous coronary assessment by MRCA.[2] (reproduced with permission)

2.   Coronary Artery Disease:

Clinical studies have produced variable results. Kim et al [20] performed the first multicenter trial in 109 patients with suspected CAD. Overall sensitivity and specificity was 93 and 42%, respectively. 84% of coronary segments were of diagnostic quality. Table 1 shows the comparative sensitivities of MRCA to CA. An example of MRCA coronary artery delineation is shown in Figures 1A and 1B

Sakuma et al [21] evaluated over 130 patients with significant CAD and found an overall accuracy of 87%, per patient sensitivity of 82% and specificity of 90%
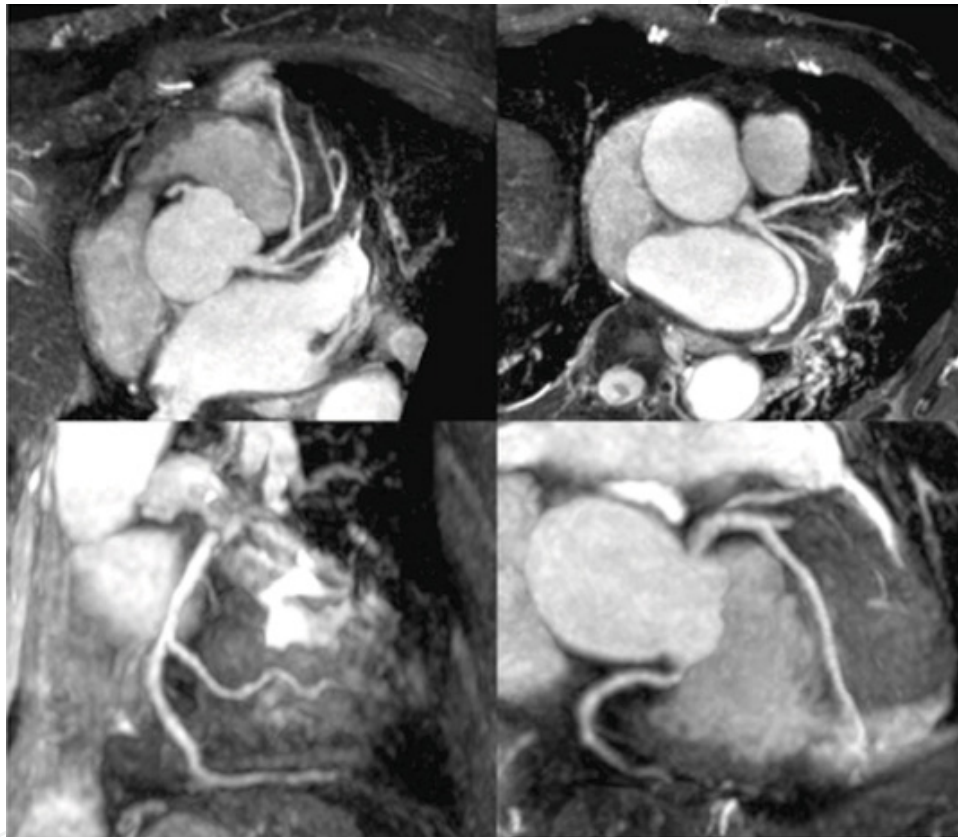

Figure 1. Sliding partial MIP images of 3 T whole heart coronary MRA acquired with a patient-specific narrow acquisition window (50 ms) in the cardiac cycle Journal of Cardiovascular Magnetic Resonance **Vol.** 11 **Issue** Suppl 1 2009-01-2

4. Coronary Computed Tomoraphy Angiography (CCTA)

Introduction: CCTA has been rapidly adopted in a short time span by institutions across the world as the most widely used anatomic noninvasive imaging modality for coronary artery assessment. A major reason for this is the existing wide use of CT for non-cardiac applications and most institutions have access to a CT scanner. Thus, investing in a state of the art

CT scanner serves multiple purposes and makes financial sense with opportunity for cardiac and non-cardiac use. Although initially limited to electron beam scanners in the 1980's where imaging of the heart arteries took several seconds and processing several hours, with the advent of multi-detector coronary computed CT technology (MDCT or multi slice (MSCT)) in the late 1990's, rapid advancement in scanner technology has enabled rapid whole heart acquisitions in a few seconds. With such scanners post processing capabilities on a 3D dataset is usually achievable in about 15-20 minutes.

CCTA requires high temporal resolution to minimize motion artifacts caused by cardiac motion and breathing. This requires a fast gantry rotation with multiple detectors. Because the coronaries are seen best when there is least motion, the diastolic phase is most optimal for imaging and thus the temporal resolution must be less than the length of the diastolic phase. High spatial resolution is also necessary to allow imaging of the coronary arteries which are small and tortuous. At present, 64-detector row CT systems are the most widely employed platform for performing CCTA. The 64 detectors allow an x-,y- axis (in-plane) spatial resolution of near 0.4mm and the z-axis spatial resolution or slice thickness is almost 0.6mm. Fast contiguous coverage of the heart is required to allow imaging of the entire heart in one breath hold. This requires the multi-slice helical CT technique, each slice of the heart is collected in one or more heartbeats. There is a 30%-50% overlap between each slice. The scan must be triggered to the heartbeat to allow gating so that imaging in multiple slices occurs across multiple heartbeats. Table 3 below, is a summary of the state of art 64 slice CT scanners with their various technical specifications [22].

Scanner	X-ray sources, n	Detector rows, n	Detector-row x-axis dimension, mm[*]	Total nominal beam width, mm	Fastest gantry rotation time, second	Temporal resolution for each cross-sectional image, second[†]
GE Discovery CT750 HD	1	64	0.625	40	0.35	0.175
Hitachi SCENARIA	1	64	0.625	40	0.35	0.175
Philips Brilliance iCT	1	128[‡]	0.625	80	0.27	0.135
Siemens SOMATOM Definition FLASH	2 (95° apart)	64[‡]	0.6	40	0.28	0.075
Toshiba Aquilion ONE	1	320	0.5	160	0.35	0.175

*Values measured at scanner isocenter.
†Values do not reflect the use of multisegment reconstruction.
‡Uses z-axis flying focal spot to sample each detector twice per rotation.

Table 3. Reproduced under permission from [22]

Patient preparation:

On the day of the test, patients should take medications as scheduled especially betablockers. Metformin should be avoided because of the potential adverse effects when used concomitantly with iodinated contrast agents. Phosphodiesterase inhibitors should be avoided 48 hours before a CCTA because nitrates are needed to dilate the coronary arteries. Premedication with mucomyst and hydration are recommended if the creatinine is elevated. If a contrast allergy is present, premedication with steroids and antihistamines is required. A right

antecubital IV that is at least 18-gauge is preferred. If heart rate is not low enough with oral beta-blockers, IV beta-blockers may be useful.

Data Acquisition:

Two types of ECG gating are possible, prospective and retrospective. Prospective is where the scanner emits radiation only at a predefined point after the R wave. Mid-diastole occurs at 70-75% of the R-R interval and during this time in the cardiac cycle, there is minimum amount of motion enabling better coronary imaging. The CT beam is off during all other points in the cycle. This requires a regular heart rate and is the preferred method of imaging because of the low radiation dose. In retrospective triggering a continuous heart scan is utilized. Imaging is performed throughout systole and diastole. Left ventricular function data is hence available. This method of gating is used if the patient's heart rate is irregular or not low enough for 64 slice CT scanners. Figure 2 below shows the different modes of CCCT acquisition [22].
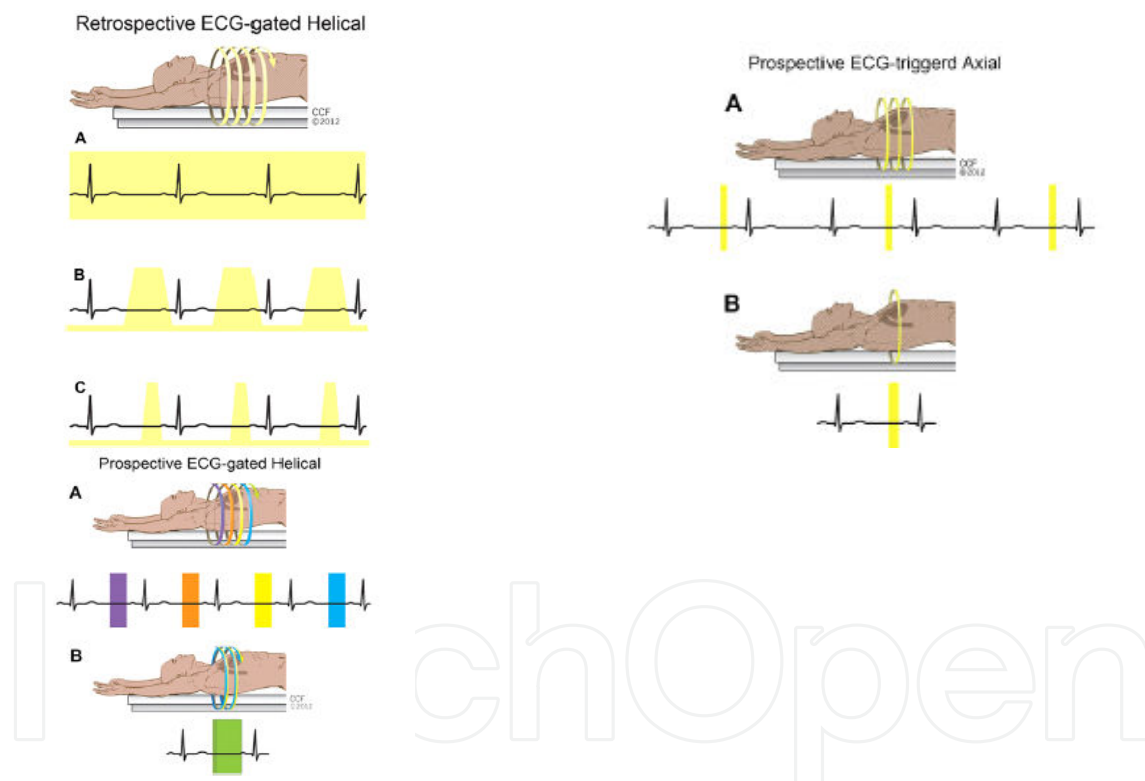

Figure 2. Reproduced under permission from [22]

Radiation Exposure: Reported CTA effective radiation dose is higher than many other cardiac diagnostic procedures as described by the International Commission on Radiological Protection (ICRP) 60 [23]. The rapid expansion of CCTA magnifies the importance of dose reduction within the population. The clinical acceptance of CCTA will partially depend on the radiation exposure and its consequences, particularly if it is going to be used at an earlier stage of CAD detection. Some commonly used dose reduction strategies include:

1. Restricting scan field to anatomy of interest (~1 cm above left main to ~1 cm below heart)

2. Reducing peak mAs based on body size (non-contrast scout films may be used to estimate image noise)

3. Using ECG dependant current modulation with lowest mAs during systole. Narrowing the width of the peak mAs phase

4. Reducing kV to 100 if body Wt is <85 kg

5. Use prospective gating if available.

With regards to radiation exposure numerous algorithms and acquisition techniques have been developed as discussed previously to reduce exposure specifically prospective triggered acquisition [24] and high pitch acquisition with dual source CCTA [25].

5. Limitations

There are several limitations with CCTA. Patients unable to cooperate with scanning instructions should be considered for other imaging modalities. Uncontrollable arrhythmias can result in significant motion artifacts and multiple uninterpretable coronary segments. Contraindications to iodinated contrast use include pregnancy, prior severe/anaphylactic contrast reaction and renal insufficiency (but end-stage renal disease is not a contraindication) for contrast-induced nephropathy. Certain conditions should raise concerns for the use of pre-scan beta-blocker (chronic obstructive pulmonary disease/asthma, decompensated heart failure, and advanced atrioventricular block) and nitroglycerin (severe aortic stenosis, hypertrophic cardiomyopathy, recent phosphodiesterase-5 inhibitor use). Metallic objects such as pacemakers, intra-cardiac defibrillator leads, prosthetic valves cause beam-hardening and streaking artifact over adjacent coronary arteries. Dense concentric coronary calcification causes a blooming artifact, which often leads to overestimation of degree of stenosis.

Clinical Applications:

Most Important Appropriate indications for CCTA

Chest pain evaluation after an uninterpretable or equivocal stress test
Chest pain evaluation in patients with an intermediate probability, an uninterpretable EKG and unable to exercise
Acute chest pain evaluation, an intermediate pretest probability, no EKG changes, and serial enzymes negative
Suspected coronary anomalies in symptomatic patients
Coronary evaluation in new onset heart failure

Table 4.

1. **Anomalous coronary arteries:** CTA provides a 3D spatial relationship to great vessels, allowing evaluation of the origin and course of anomalous coronary arteries in a non–invasive manner. It is the "gold standard" test for evaluating anomalous coronary arteries and has the highest level of appropriateness use for this indication.
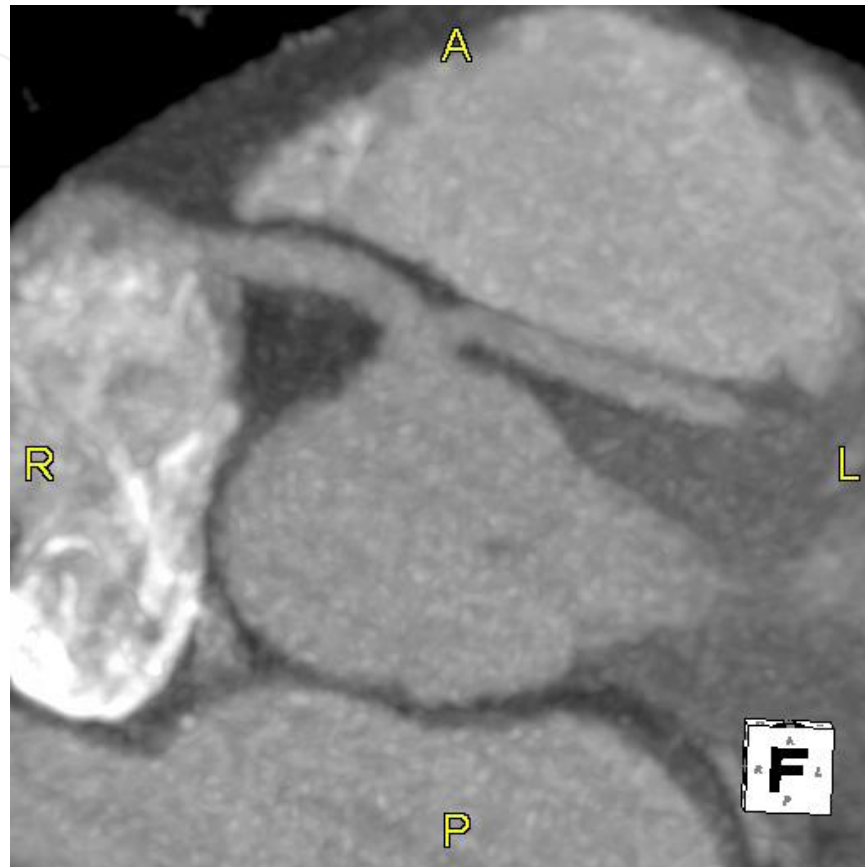

Figure 3. 40 year old male with syncope during exercise. CCTA shows anomalous left main coronary artery take off from right coronary cusp between aorta and RVOT

2. **Coronary artery disease**

i. **Detection of Coronary Stenosis:** With ongoing technical development, the diagnostic performance of CT with respect to detection and quantification of obstructive CAD is steadily improving. The confidence and accuracy to assess stenosis is better in larger branches and in the absence of extensive coronary calcification. For the assessment of individual coronary segments, the sensitivity to detect significant coronary artery stenosis ranges between 64-99%, the specificity between 84- 98%, with pooled average sensitivity of 87% and specificity of 96%. The positive predictive value is approximately 80% whereas the negative predictive value has been consistently high in all the studies with a pooled average of 98%. Calcified coronary disease causes blooming artifacts, which increases apparent stenosis severity of a lesion. The ability to quantify coronary stenosis severity has been modest com-

pared to invasive angiography given the limited spatial resolution of CT and blooming artifacts of calcified lesions. There are numerous single-center [26-34] and three multicenter studies [35-37] using different scanner technologies (Table 4) [35-37] in symptomatic patients with suspected CAD.

| Author | Year | Patients | CAD prevalence (%) | Per-patient base analysis | | | |
				Sensitivity	Specificity	Positive predictive value	Negative predictive value
Budoff *et al.*	2008	230	25	95	83	64	99
Miller *et al.*	2008	291	56	85	90	91	83
Meijboom *et al.*	2008	360	68	99	64	86	97

CAD, coronary artery disease.

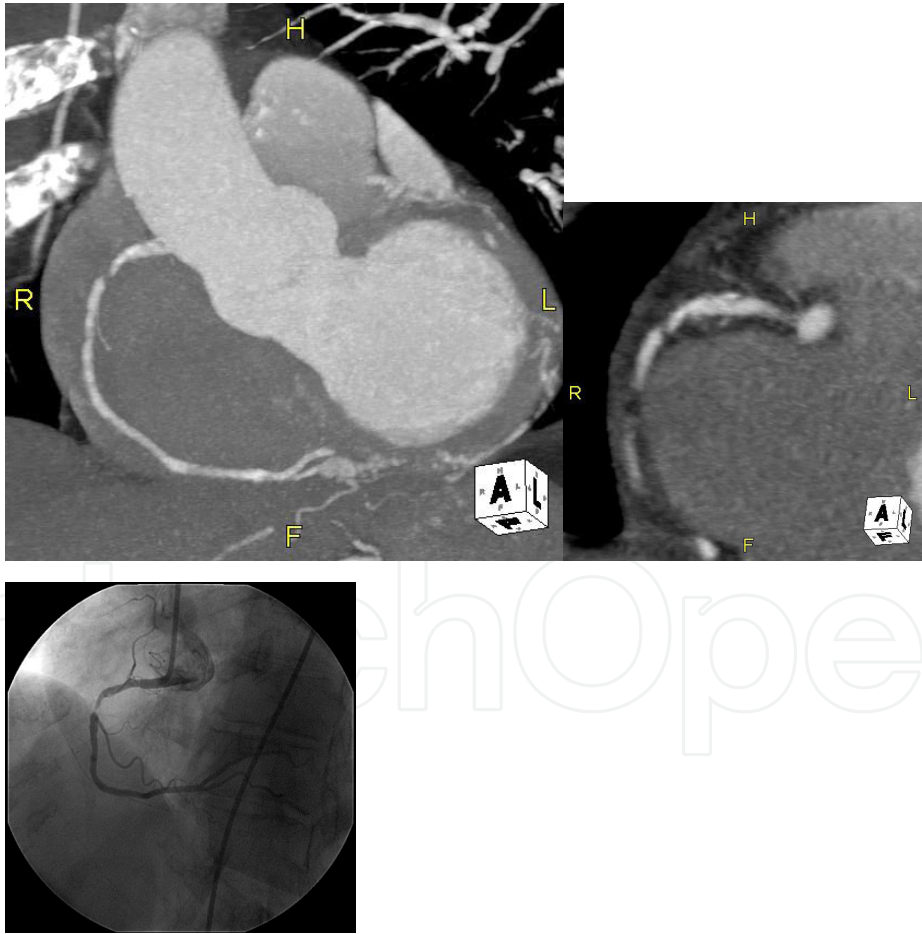**Table 5.** Adapted with permission from Chang et al [38].

Figure 4. CCTA of a 60 year old smoker with atypical chest pain and sub-maximal negative stress echo. Thick maximum intensity projection (MIP) images and multiplanar reconstruction images (MPR) are shown showing focal high grade stenosis in proximal-mid RCA accompanied by scattered calcified plaques throughout RCA, Coronary angiogram was performed confirming CCTA findings.

ii. **Stents:** CCTA is not optimal for the evaluation of coronary stents because the spatial resolution is not quite good enough to visualize the intrastent lumen, thus should not be routinely used for the evaluation of coronary stents. Small stents tend to cause blooming and beam hardening issues leading to poor delineation of lumen. Lack of contrast in lumen is a sign of in-stent restenosis. Currently, larger stents >3.5-4.0 mm may be adequately assessed [39].
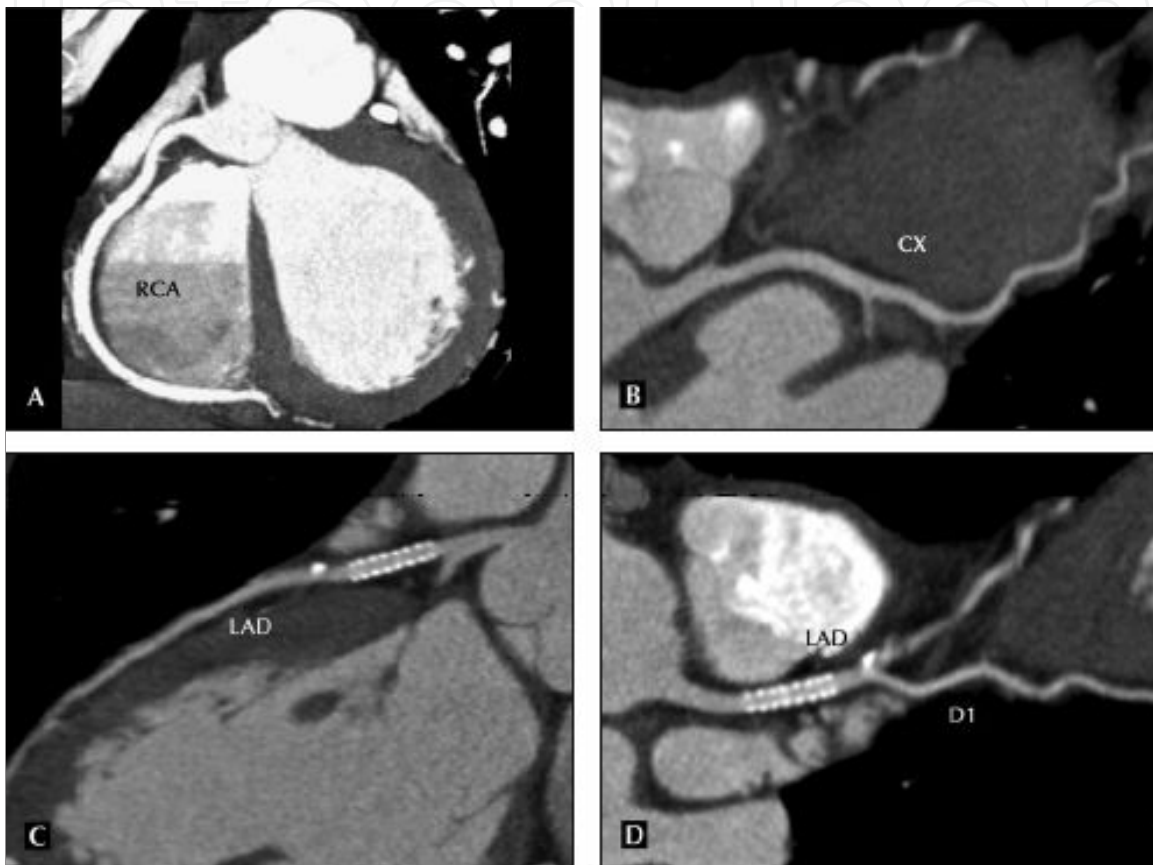

Figure 5. Shows multiplanar reformats of the left anterior descending coronary artery with clear visualization of patent stents and normal right and left circumflex coronary arteries. Reproduced from Cademartiri et al [39].

iii. **Bypass Graft Analysis:** CCTA may be used to assess bypass graft patency as well as to evaluate the patient undergoing repeat bypass surgery. In repeat bypass surgery CCTA is utilized to identify the location of a previously utilized graft. Clips may often create challenges in assessing bypass grafts because of beam hardening artifact and their potential to obscure the graft lumen or anastomosis point. Below is an example of a 3d surface rendering of patient with prior coronary artery bypass surgery (Figure 6) [40]. The saphenous vein graft (SVG) to the right coronary artery is seen taking off from the aorta and inserting into the RCA. The origins of 2 other SVG are also noted adjacent to the SVG to RCA going to the left coronary system. The maximum intensity projection reveals a significant stenosis in the insertion site of the SVG to RCA [40].
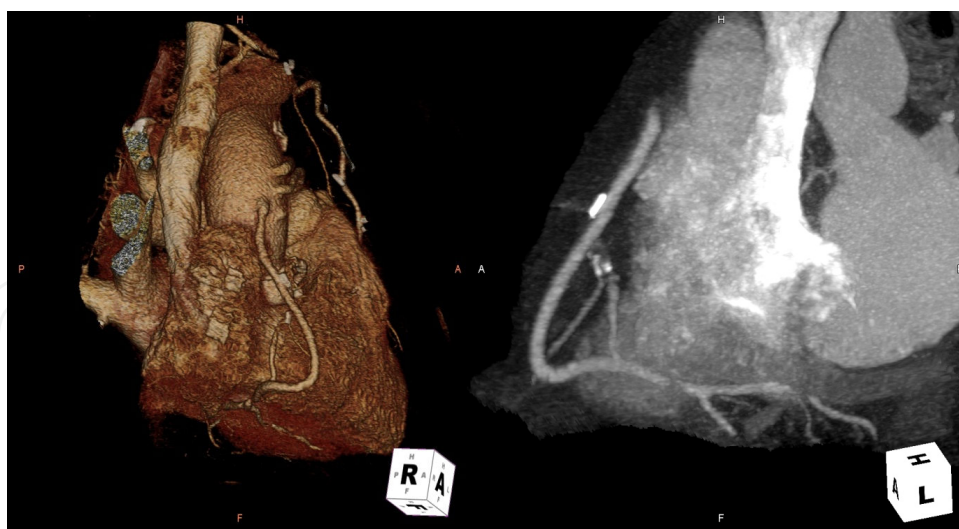
Figure 6.

3.   Role of CCTA in Emergency Department:

A significant amount of money is wasted on inappropriate chest pain evaluations and admissions. Given CTA's high NPV, the test would most benefit the intermediate-probability patients in the ED. By using CTA, hospitalization could be avoided in patients presenting to ED with chest pain. Logistic issues such as ED scanner availability and 24 hour expertise in CTA interpretation limit use of CTA in most institutions. Triple rule out protocols have been developed and studied to rule out coronary disease, pulmonary embolism and aortic dissection [27, 41, 42]. These are however not used widely due to logistic issues and since often one or more of these 3 etiologies can be ruled out clinically. A recent meta analysis by Samad et al [43] synthesized data from 9 studies involving 1349 patients presenting to the emergency room with suspected acute coronary syndrome (ACS). Endpoint was the diagnostic performance of CTA for ACS. The bivariate summary estimate of sensitivity of CTA for ACS diagnosis was 95% (95% CI 88-100) and specificity was 87% (95% CI 83-92), yielding a negative likelihood ratio of 0.06 (95% CI 0-0.14) and positive likelihood ratio of 7.4 (95% CI 4.8-10). Based on this meta analysis of all the clinical studies, coronary CTA with its high sensitivity and a low negative likelihood ratio of 0.06, is effective in ruling out the presence of ACS in low to intermediate risk patients presenting to the ED with acute chest pain. More recently the role of CCTA in ER has been studied in 2 important randomized trials the ACRIN-PA [44] and the ROMICAT-2. Both studies showed that CCTA has an outstanding negative predictive value with low subsequent event rates although conventional management including stress testing also achieved comparable results. There was shorter length of stay and quicker discharge directly from ED in CCTA arm although costs were the same between CCTA and conventional testing in ROMICAT-2. Also radiation doses and downstream testing were higher in CCTA arm in ROMICAT-2 [45]. An important point with regards to use of CCTA in ED is that although a zero calcium score makes obstructive CAD highly unlikely as a cause of chest pain it is now clear that young patients (age < 50, smokers) may present

with non-calcified obstructive disease and thus should not be triaged based on a negative calcium score alone (see Figure 7 below)
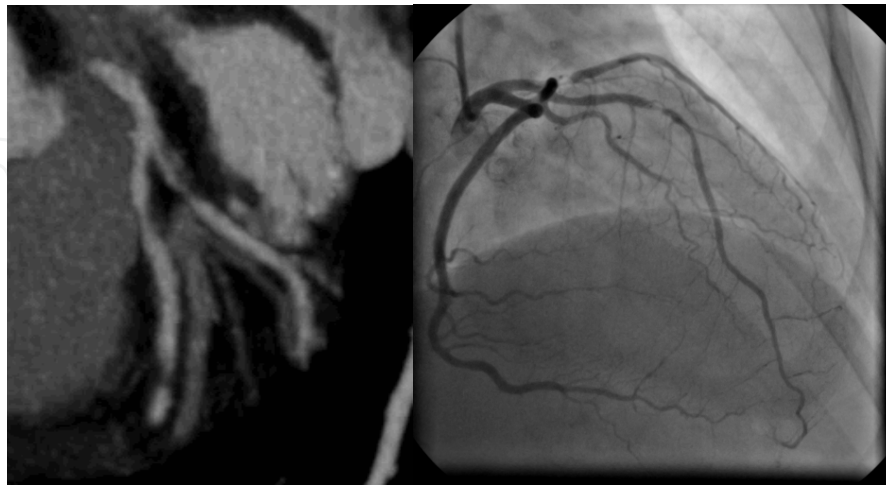

Figure 7. 30 year old male with history of 15 pack history of smoking, cocaine abuse presents with intermittent substernal pressure of 3 days duration. Coronary CT was done. Non-contrast scan showed zero calcium score but CCTA showed high grade stenosis in the LAD and diagonal. The image on left is a view of the mid LAD showing mainly non-calcified obstructive plaque. Coronary angiography confirms high grade LAD.

4. Role of CCTA in Assessing Etiology of Cardiomyopathy

It is extremely important to define the etiology of cardiomyopathies to enable appropriate management and therapies. CCTA can be of critical importance to rule out ischemic cardiomyopathy in a non-invasive manner. CCTA has immensely robust accuracy at evaluating the proximal vascular bed with accuracy approaching almost 97-100%. This attribute becomes most relevant in the context of ischemic cardiomyopathy which per the standardized definition proposed by Felker et al [46][Patients with 75% stenosis of left main or proximal LAD, patients with 75% stenosis of two or more epicardial vessels] yields a very high diagnostic odds ratio for ischemic cardiomyopathy. Several studies have evaluated the diagnostic accuracy of CCTA in comparison with invasive angiography. We performed a meta analysis of all 6 studies involving 452 patients with cardiomyopathy of undetermined cause who underwent CTA. All patients also underwent diagnostic invasive angiography. The pooled summary estimate of sensitivity was 98% and specificity 97% yielding a negative likelihood ratio of 0.06 for ischemic cardiomyopathy. The receiver operator curve analysis showed a robust discriminate diagnostic accuracy of ischemic etiology with an AUC of 0.99(Figure 8). With a pooled sensitivity of 98%, an ischemic etiology of left ventricular systolic dysfunction can be accurately "ruled out" with CTA (>16 slices). A negative study hence essentially excludes the presence of ischemic cardiomyopathy. A positive CTA effectively "rules in" the probability that an underlying cardiomyopathy could be related to significant epicardial coronary stenosis. Hence, CTA can be considered as an invaluable imaging modality for evaluating patients with left ventricular dysfunction of a suspected ischemic etiology [47].
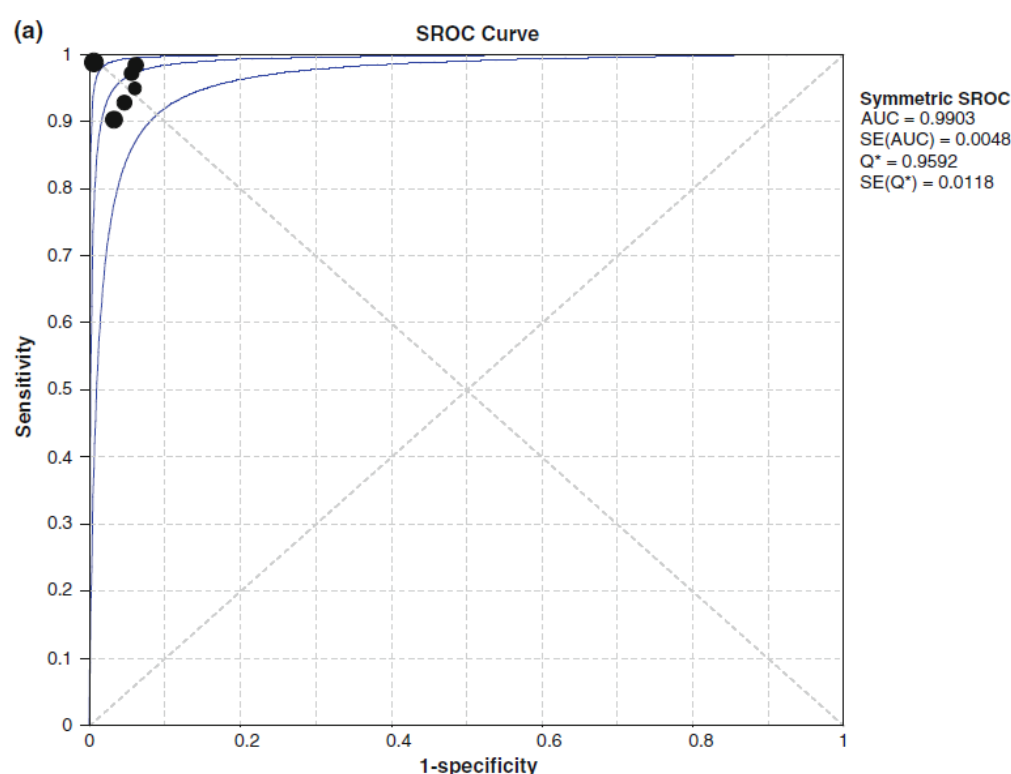
Figure 8. Diagnostic accuracy of CCTA for ischemic cardiomyopathy. Adapted with permission from Bhatti et al [47].

6. Comparison of MSCT angiography and Invasive angiography

Since the first report of Moshage et al over 17 years ago [48], numerous studies and meta analyses have been published confirming the superior diagnostic performance of MSCT in comparison with invasive angiography as the reference standard.. The largest meta analysis to date collated data from 89 studies with 7516 patients [49]. Bivariate analysis yielded a mean sensitivity and specificity were 97.2% (95% CI, 96.2% to 98.0%) and 87.4% (CI, 84.5% to 89.8%) for CT. Negative likelihood ratio was 0.03 (0.02-0.04) whereas the positive likelihood ratio was modest at 7.7(6.2-9.5) area under the curve was 0.98 (CI, 0.96 to 0.99) for CT. The resulting sensitivity of 98.1% for scanners with more than 16 detector rows was significantly higher ($P < 0.050$) than that for scanners with a maximum of 16 rows (95.6%). The high negative predictive value of CTA best suites it as an effective rule-out test for significant CAD.

Despite the use of newer generation scanners (>64 slice), coronary calcification remains the Achilles heel of CTA. A recent analysis from the CORE 64 study demonstrated that the robust AUC of CTA (0.93) significantly decreased to (0.81) in patients with calcium score >600 [50]. Furthermore, the negative predictive value of CTA decreased from 0.93 in patients with Calcium score <100 to 0.75 in patients with calcium score >100. High pretest probability of CAD and high calcium score negatively impacts the diagnostic performance of CTA and must be carefully considered in test selection.

7. Prognostic value

Whereas the diagnostic accuracy of CCTA has been rigorously established, increasing number of studies have also evaluated the prognostic value of CCTA. A recent meta analysis included eighteen studies involving 9,592 patients with a median follow-up of 20 months for adverse cardiac events [51]. The authors computed a pooled annualized event MACE rate of 8.8% for obstructive (any vessel with >50% luminal stenosis) disease versus 0.17% per year for normal CCTA (p < 0.05) and 3.2% versus 0.15% for death or MI (p < 0.05) Figure 9. Furthermore, the pooled negative likelihood ratio for MACE after normal CCTA findings was 0.008 (95% CI: 0.0004 to 0.17, p < 0.001). Patients with a normal CTA can hence be confidently reassured given a very low risk of death, MI or revascularization fairly comparable to an otherwise healthy population(<1%). Furthermore, the low event rate for normal CTA (0.16%) is comparable to other well established non invasive risk stratification modalities including stress echocardiography (0.45%) and myocardial perfusion stress imaging (0.54%). CTA has hence emerged as a well established clinical tool that carries not only robust diagnostic accuracy but also has powerful predictive accuracy as well [51].
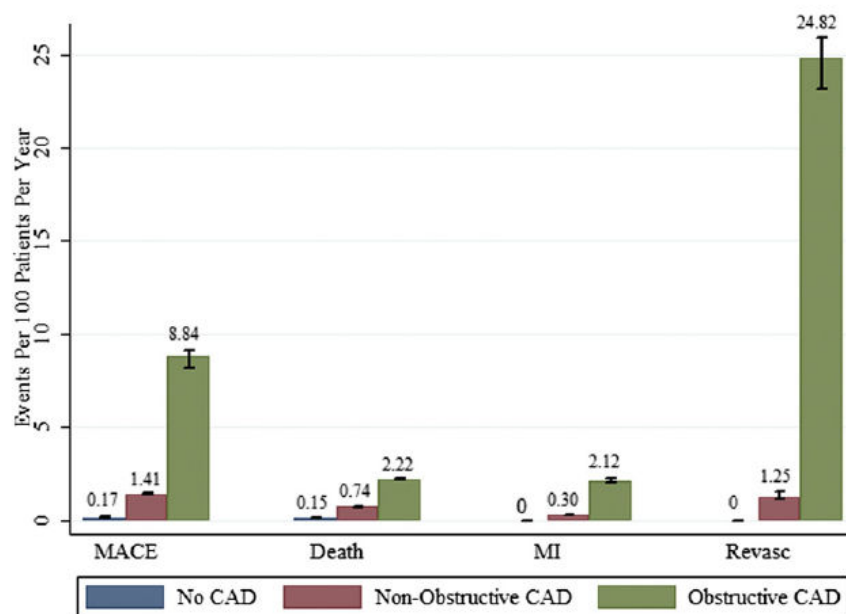

Figure 9. Adapted with permission from Hulten et al [51]

8. Physiological significance of stenoses identified by CTA

That, coronary angiography is merely a "luminogram" and does not provide much insight into the hemodynamic significance of a stenotic lesion, is a fact that has been rigorously established for the past two decades. This well-recognized limitation has been documented re-

peatedly by intravascular ultrasound imaging and stress testing. It has been known that coronary angiography often leads to overestimation of the functional significance of epicardial coronary stenoses. In this regard, fractional flow reserve (FFR) has emerged as a powerful catheter based tool that provides robust information about the functional severity of the lesion. FFR calculated from coronary pressure measurement, is a reliable, invasive index to indicate if a stenosis is ischemia-related and can be determined in the catheterization laboratory in a simple and rapid way. By taking the ratio of the coronary pressure measured distal to the stenosis to aortic pressure as the normal perfusion pressure (distal coronary pressure/ aortic pressure) and obtaining these measurements when the microvascular resistance was minimal and assumed to be constant (that is, at maximal hyperemia), the percentage of normal coronary flow, or a fraction of normal flow (i.e., FFR), can be calculated. FFR has a uniform normal value of 1.0 for every patient and every coronary artery; it is not dependent on changes in heart rate, blood pressure, or contractility; it accounts for collateral flow; and it has a sharp threshold value to indicate inducible ischemia: FFR < 0.75 always indicates inducible ischemia; FFR > 0.80 excludes ischemia in 90% of the cases [15, 17-20, 23, 46, 52-54]. The grey zone is very limited, which is important for clinical decision making in an individual patient. Coronary pressure measurements can be easily performed by a pressure wire, with almost identical mechanical properties as normal guide wires, and barely prolong the procedure, even when multiple vessels are interrogated. The ischemic threshold of FFR has been replicated independently with different noninvasive functional tests in numerous studies (including exercise electrocardiography, dobutamine stress echocardiography, and MPI) as well as alongside one another in the same population. An FFR >0.75 identified coronary stenoses in patients with inducible myocardial ischemia with high sensitivity (88%), specificity (100%), positive predictive value (100%), and overall accuracy (93%). FFR has a high reproducibility and low intra-individual variability. Several randomized clinical trials including DEFER, FAME and now FAME II have established the prognostic utility of FFR.Consequently, now, measurement of FFR during invasive coronary angiography is the gold standard for identifying coronary artery lesions that cause ischemia and improves clinical decision-making for revascularization.

Similar limitations of stenoses especially in the intermediate range (50-70%) are widely seen in CT angiograms. This poses both diagnostic and therapeutic challenges. Meijboom et al [55] evaluated 89 lesions in 79 patients with stable angina. Lesion correlation with invasive angiography was performed and FFR of stenoses was measured. The authors demonstrated very poor correlation between CTA and invasive coronary angiography with hemodynamically significant stenosis (FFR<0.75); diagnostic accuracy 64% for FFR <0.8 and 49% for FFR< 0.75. CTA overestimated the functional significance of coronary stenoses (poor specificity/ high false positive rate) even after excluding segments with high calcification and coronary motion. Hence patients with intermediate stenoses on CTA require further evaluation by either FFR evaluation of stress testing.

Recently, evaluation of FFR from CCTA data (FFRCT) has been proposed as a noninvasive method for identifying ischemic lesions. This employs the concept of computational fluid dynamics (CFD) Koo et al [56] correlated FFR from CT data with invasive FFR in 103 pa-

tients (159 vessels) in a prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained via Noninvasive Fractional Flow Reserve) study. On a per-vessel basis, the accuracy, sensitivity, specificity, positive predictive value, and negative predictive value were 84.3%, 87.9%, 82.2%, 73.9%, 92.2%, respectively, for FFRCT and were 58.5%, 91.4%, 39.6%, 46.5%, 88.9%, respectively, for CCTA stenosis yielding an AUC of 0.9 for FFR CT and 0.75 for CTA. There was fair correlation between invasive FFR and FFRCT (r = 0.717, p < 0.001) although FFR Ct had slight underestimation (0.022 ± 0.116, p = 0.016). The results of the larger 285 patient DEFACTO trial comparing CT FFR and invasive FFR are awaited later this year and would further consolidate the role of non invasive FFR in the evaluation of intermediate coronary lesions see on CTA.

9. Complimentary role of CTA in guiding complex PCI like Chronic total occlusion (CTOs)

The unprecedented spatial resolution and 3D reconstruction of the epicardial coronary vessels has led to its role as an indispensable tool in guiding complex coronary interventions including recanalizing chronic total occlusions (CTO); the most challenging subset of complex coronary lesions. The display of CTA images as a 3D roadmap, side-by-side with live angiography images is instrumental in providing the interventional team access to the occluded channel. Furthermore, synchronization of the CTA image orientation with the C-arm, allows for selection of the ideal treatment projection angle without additional contrast medium or radiation exposure. Several studies have validated the use of CTA in guiding CTO intervention [57].

10. Diagnostic accuracy of CTA for in-stent restenosis

Despite the introduction of drug eluting stents, instent restenosis (ISR) from neointimal hyperplasia remains a real issue. For patients with recurrent chest pain following stent implantation, invasive coronary angiography is often performed to evaluate the presence of ISR. However, the need for a noninvasive alternative approach for ISR detection is more desirable. The experience with older generation CTA systems (4 and 16 slice) in evaluation of ISR was very disappointing largely related to motion and blooming artifacts. The improved spatial and temporal resolution with 64,128 and 256 slice scanners seems to have ameliorated those limitations. Carrabba et al [58] performed a meta analysis of nine studies involving 598 participants with 978 stents evaluated for ISR with CTA (64 slice) using invasive coronary angiography as the reference standard. More than 60% of the studied stents were >3 mm in diameter. Approximately 10% of the stents were unassessable. The pooled sensitivity and specificity of CTA was 86% (95% CI 80-91%) and 93%(95% CI 91-95%) respectively yielding an AUC of 0.94 for per stent analysis. The calculated positive and negative predictive values were 70.4% and 97.2%, respectively. CTA can hence 64-MDCT can hence reliably rule out ISR and further evaluation by means of invasive coronary angiography can be avoided.

Caution is still advised for smaller stents and the fact that almost 10% of the studies were still uninterpretable despite the use of 64 detector scanners.

11. Comparison of coronary computed tomography angiography and magnetic resonance coronary angiography

This section aims to compare the techniques of coronary computed tomography angiography (CCTA) with magnetic resonance coronary angiography (MRCA) from the standpoint of coronary and cardiac imaging.

12. Comparison of technical aspects CCTA to MRCA

Currently the majority of the institutions utilize 64 slice technology (in-plane spatial resolution of 0.4 x 0.4 mm with a slice thickness of 0.6 mm and a 360° gantry rotation in about 330 milliseconds). More recently dual source CCTA technology has pushed the envelope further and has delivered a temporal resolution of 70-83 msec with an in plane resolution of 0.4 mm [59]. Furthermore, 256 and 320 slice CT- scanners are available in limited institutions across the world which can image the entire heart in 1 beat thus obviating many limitations with current 64 slice scanners such as irregular heart rhythm, breath hold issues and opening options for perfusion CCCTA imaging.

The tremendous advantages that CCTA holds over MRCA with such high spatial resolution relates to: 1. ability to visualize small diameter vessels including distal coronary branches, 2. increased ability to quantify calcium and reduce blooming artifacts, 3. better visualization of stents, and 4. better plaque morphology assessment. The temporal resolution advances in CCTA has enabled: 1. enhanced ability to freeze cardiac motion, 2. additional reconstruction capabilities within cardiac cycle, and 3. reduced scan time.

The obvious disadvantages of CCTA compared to MRCA are: 1. radiation exposure which depending on the scanner, mode of acquisition and protocol modifications can range from 1 milliseivert to > 15 milliseiverts[60, 61], 2. use of iodinated contrast which could pose issues for patients with underlying renal dysfunction, and 3. need for slow heart rates which require use of beta-blockers.

13. One stop shop imaging : MRCA versus CCTA

A very attractive advantage with MRCA is that it can combined with detailed cardiac MRI exam to provide a "one stop shop" assessment is easily achievable where coronary disease, valves, stress/rest perfusion for ischemia and viability and overall cardiac and adjacent thoracic and extra-thoracic anatomy can be all studied without concern for nephrotoxic contrast or

repetitive exposure to radiation. Furthermore, imaging sequences or views can easily be re‐
peated. Thus, a hybrid anatomic and functional assessment is clinically feasible at present in
centers with experience with MRCA. With CCTA, valves and ventricular function assessment
comes at the cost of higher radiation exposure as retrospective triggered acquisition is needed.
CT perfusion imaging for ischemia and viability is still not well validated compared to cardiac
MRI but has been performed for both viability [62, 63] and perfusion [64, 65] and is being tested
against SPECT in ongoing clinical trials. Promising new studies with CCTA with lower radia‐
tion doses encompassing a complete anatomical-functional assessment compared to tradition‐
al SPECT imaging has been published recently [66] but this aspect of CCTA is not ready for
clinical use. Although MRCA does offer high temporal resolution, good spatial resolution,
high soft tissue contrast and the ability to generate any three dimensional image without need
for ionizing radiation it is much more challenging to perform as it requires selection of the cor‐
rect pulse sequences and each pulse sequence needs many parallel slices or slab volumes to
cover the entire heart. Free breathing MRCA acquisitions can take 5-15 minutes compared to a
few seconds with current 64-320 slice CCTA. Spatial resolution of CCTA is superior to MRCA
(0.4 to -0.6 mm with CCTA compared to 1.5 mm with MRCA). The disadvantage for MRCA
compared to CCTA in terms of speed of acquisition is difficult to overcome although breath
hold MRCA may offer some improvement in time required for acquisition compared to free
breathing techniques [67]. The temporal resolution of CCTA is limited by the gantry rotation
speed and hence cannot be altered. On the contrary free breathing MRCA temporal resolution
can be flexibly determined using imaging parameters. The acquisition window position and
the length within the RR interval can be individually set [68]. This is an important advantage
with MRCA.

14. Diagnostic accuracy of CCTA versus MRCA for CAD

The diagnostic accuracy of CCTA is well established with it outstanding negative predic‐
tive value (97.2%) and moderate-to good positive predictive value (87.4%) based on cu‐
mulative data from 89 studies of 7519 patients(69). This compares much more favorably
to MRCA which has a sensitivity of 87.1% and specificity of 70.3 % based on 20 studies
of 989 patients [69]. Furthermore, in patients suspected of CAD or with acute disease at
presentation, CCTA has an outstanding negative likelihood ratio of 0.03(0.02-0.04) and
0.06(0.02-0.19) respectively [69]. A meta-analysis of CCTA versus MRCA [49] and a re‐
cent study comparing state of art 64 slice CCTA to 32 channel 3T MRCA [70] both con‐
cluded that although both modalities performed well for CAD detection CCTA
outperformed MRCA. Furthermore CCTA was completed in 13.9+/= 1.1 sec compared to
17 +/- 4.7 minutes for MRCA [70]. The expert consensus document on "appropriate" use
of CT and MRI imaging published in 2006 gave an appropriate indication for CCTA to
rule out significant CAD in patients with chest pain and intermediate likelihood of CAD.
On the contrary the document gave a recommendation of "inappropriate" for MRCA for
the same indication [71]. This reflects the lack of adequate data demonstrating the feasi‐
bility and accuracy for MRCA on a practical level across many institutions.

15. Assessment of coronary anomalies and aneurysms: CCTA versus MRCA

One important indication where MRCA could be very helpful is imaging for anomalous coronaries in children and young adults where exposure to radiation from CCTA is undesirable [72]. Coronary arteries in MRCA can be imaged without nephrotoxic contrast administration. The high T2/T1 signal in steady state free precession imaging (SSFP) acts as a natural contrast agent providing coronary lumen definition [73]. However, SSFP imaging has greater susceptibility to artifacts and newer sequences such as fast low angle shots (FLASH) show better imaging characteristics at 3.0T compared to SSFP [74] also showing a 50% reduction in scan time [75]. CCTA offers outstanding spatial resolution and is the widely preferred technique at least in adults to evaluate anomalous coronaries as long as there are no inherent contraindications to its use. ACC/AHA appropriate use guidelines for CCTA /MRI [71] gives CCTA and MRCA an " appropriate" indication score with CCTA receiving a higher score of 9 compared to MRCA which also receives a high score of 8. MRCA may also be used for serial follow-up of coronary aneurysms which can be a sequelae of Kawasaki disease particularly in adolescents and young adults who otherwise may need repeated angiography.[76, 77] CCTA again is excellent to delineate these aneurysms but suffers from limitations of repetitive radiation exposure.

16. Comparison of Technical Challenges in Imaging for CCTA and MRCA

16.1. Motion artifact issues : CCTA versus MRCA

Motion artifacts pose a significant problem with both MRCA and CCTA. In MRCA this can be intrinsic related to cardiac contraction /relaxation or extrinsic attributable to diaphragm and chest wall movement during respiration [35]. Furthermore, MRCA requires expertise to perform and interpret and is currently limited largely to academic centers with a dedicated 1.5 or a 3T cardiac magnet at least in North America. In CCTA motion artifacts are related to patient motion and respiratory based artifact (as CCTA imaging is during breath hold). In contrast 64 slice CCTA is available in most large institutions and practices and the training and interpretation process is much more feasible for physicians desiring to practice this technology.

16.2. Calcification issues: CCTA versus MRCA

Calcification of coronary arteries is seen in at least 50-70% of patients with atherosclerotic plaques [78]. Calcium poses a significant limitation for accuracy of CCTA due to blooming/beam hardening artifacts compromising lumen assessment [79]. However it is not a limitation for MRCA for assessing the lumen of the coronary arteries as MRI does not have issues with beam hardening or blooming. Thus lumen visualization is

not compromised [80]. The flip side of this is the added advantage of detection of coronary calcium during the non-contrast portion of CCTA which serves both to diagnose atherosclerosis [81] and in its absence make obstructive CAD highly unlikely both in asymptomatic patients and in patient with suspected cardiac etiology of chest pain [82, 83]. Coronary calcium also provides powerful prognostic information and is incremental in risk assessment beyond traditional risk scores like Framingham risk scores [84]. Furthermore, identifying substantial calcium may also help in decision making for the physician as the CCTA portion of the test could be cancelled and more definitive testing towards significance of underlying lesion could be pursued wither with stress testing or angiography. MRCA lack this important " heads up" diagnostic advantage that CCTA possess as part of its armamentarium due to its inability to image calcium. More recently some investigators have tried to exploit the different capabilities of CCTA and MRCA by combining both technologies in patients with significant calcification. In a small study of 18 patients who underwent 64 slice CCTA, 3D free breathing MRCA and coronary angiography, MRCA had better diagnostic image quality and performed better in detection of obstructive CAD in coronary segments with focal rather than diffuse calcification and overall performed better than CCTA in detecting significant CAD in patients with high calcium scores [80].

17. Imaging bypass grafts and stents: CCTA versus MRCA

CCTA is an outstanding modality for imaging bypass grafts. In a study by Liu and colleagues [85] 228 patients underwent 64 slice CCTA to evaluate diagnostic accuracy of CCTA for bypass graft disease. The sensitivity, specificity, positive negative predictive value and overall accuracy were reported at an impressive 93.3%, 98.1%, 93.3%, 98.1%, and 97.7 % respectively. Major disadvantages include higher contrast dose, increased radiation from longer scanning to cover the anatomy of origin and course of grafts and artifacts related to clips from surgery. The anastamotic sites in particular can sometimes be challenging to evaluate. In comparison, in a study by Langerak et al,[86] MRCA showed a sensitivity and specificity of 83 and 100% for graft occlusion,82%, and 88% for graft stenosis >/= 50% and 73% and 80% for graft stenosis >/= 70%. MRCA also suffers from signal void artifacts from metallic implants, clips, etc. In addition it seems to perform inferior to CCTA in consistently identifying severely diseased yet patent vessels [86] making its widespread applicability for bypass graft evaluation less feasible. Furthermore even though CCTA has limitations with radiation the population with CABG are older and hence the lifetime risk of cancer is less of a concern. Newer generation 64 slice CCTA has also shown promise in imaging stent lumen although stents less than 3 mm tend to cause unacceptable degree of lumen visualization and blooming artifacts (highest with tantalum stents and lowest with titanium and nitinol based alloys) and CCTA is not recommended below this size. A recent study on coronary stent patency with CCTA showed a promising 89% sensitivity and 95% specificity [87]. MRCA data with stents is limited but the stainless steel composition of stents make imaging challenging as in-stent integrity and persistent assessment can be compromised. The attractive force and

local heart generated with stent imaging at 1.5 T and 3T is not a major issue the local susceptibility artifacts can be a big problem [88, 89]. This is less of problem with tantalum compared to stainless steel stents. In the USA both Cypher and Taxus Liberte stents are approved for imaging with MRI immediately after implantation.

18. Contrast issues: CCTA versus MRCA

CCTA has to utilize iodinated contrast agents between 80-120 ml for opacification of coronary vessels. This is an obvious limitation for those with underlying chronic kidney disease particularly Stage 3 and above as it is potentially nephrotoxic. MRCA on the other hand utilizes the natural signal differences seen in SSFP imaging to visualize coronaries and does not require gadolinium contrast although it can be utilized. Currently used gadolinium compounds remain intravascular only for a short period of time thus limiting the benefit of contrast enhancement for MRCA for a short period of time. However some advances in MRI contrast agents have been made with newer agents with more prolonged intravascular time now being available. These agents increase contrast to noise ratio with MRCA and hold promise to improve diagnostic accuracy although no large scale studies have been performed as yet. It is important o note that gadolinium chelates can cause nephrogenic systemic fibrosis and are usually contraindicated in patients with glomerular filtration rates of < 30 ml/min.

19. Plaque imaging: CCTA versus MRCA

Plaque imaging is an exciting area of intense research and potential application of CCTA given its capacity to image the vessel wall and provide information beyond luminal narrowing. It can detect and characterize atherosclerotic plaques as calcified, non-calcified and mixed composition (Figure 10).[90] It is now known that regardless of degree of luminal stenosis even non-obstructive plaques as detected by CCTA carries adverse prognosis [91]. However, inter-observer variability of measurement of plaque dimensions is substantial and routine plaque measurements is not feasible at this time. However CCTA shows promise in identifying certain high risk characteristics such as bulky plaques, spotty calcification and positive remodeling all of which have been shown to be related to acute coronary syndromes [92]. With MRI, although once felt to be not possible, several investigators have imaged the coronary vessel wall and plaque successfully including subclinical wall thickening [93, 94], although from point of practical applicability this has yet to find a place in the clinical arena. Because of the lack of radiation exposure in MRCA it is ideally suited for follow-up imaging for assessing plaque progression [95] or to follow-up intermediate range stenosis where anatomy can be combined with a functional assessment of significance of lesion with stress –rest perfusion sequences [96].
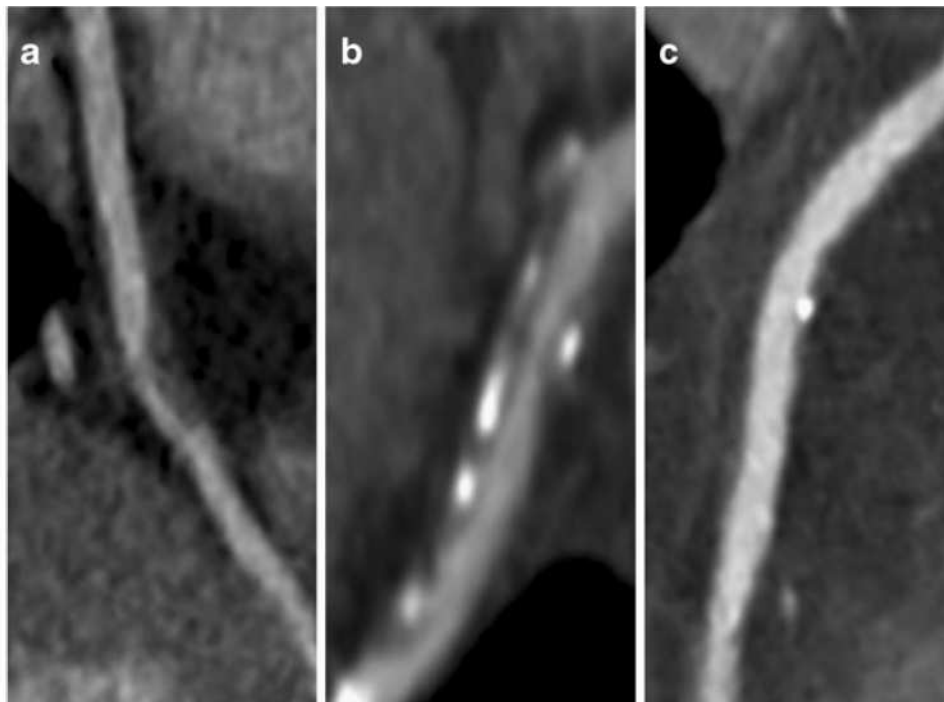
Figure 10.

20. Patient acceptance of CCTA versus MRCA

CCTA enjoys a much shorter time to completion of study compared to MRCA (20 versus 60 minutes respectively) which is a major attraction from the patient perspective [97]. For a modality to be overall successful in clinical practice it should not only be accurate, demonstrate clinical benefit and cost effective but also preferred by patients [98]. Studies have shown that patients prefer CCTA to MRCA [99]. This is mainly driven by longer imaging times, confinement in closed space and noise associated with MR imaging.

21. Training issues CCTA versus MRCA

Guidelines exist both from American College of Radiology [100] and the American College of Cardiology [101] for specific training requirements for gaining expertise in CCTA. Unfortunately no such guidelines exist for MRCA and given the complexity involved in image acquisition the degree of expertise needed to independently perform and interpret MRCA is likely to substantially greater with regards to training requirements. CCTA program clearly is easier to establish and execute than a MRCA program.

Table 5 summarizes various advantages and disadvantages from the authors perspective of CCTA and MRCA.

Properties	CTA	MRI
Time and patient preference	short duration and preffered	long duration, many breath holds, more claustrophobic
Comprehensive assessment	YES with higher radiation exposure, viability still not widely validated	one stop shop complete function, perfusion, viability and ischemic, myopathic assessment
Resolution	Higher spatial resolution	better temporal resolution
Diagnostic issues	superb negative predictive value and moderate positive predictive value	very good prognostic value in limited studies. Diagnostic values close to CT with 32C/3T
Radiation	yes	no
Calcification	interferes with interpretation	cannot be assessed. not limitation to assess coronaries
Radiocontrast	yes	no
Mettalic interference	yes but not contraindicated	currently contraindicated in pacemakers, defibrillators, metallic implants, shrapnel intracranial clips
Bypass Grafts	Excellent	Limited by artifacts
Stents	Large stents good	not good ?
Experience	Widespread	Limited
Availability	Widespread	Limited
Scanner	16Slice and Higher	1.5 T reasonable 3T better
Claustrophobia	Not a big issue	It is an issue
Irregular rhythm	Problem	Problem
Need premedication	Yes (mostly)	Not needed

Table 6.

22. Future perspectives

Noninvasive coronary angiography involving CCTA and MRCA has revolutionized delineation of coronary anatomy in a safe and fast way. CCTA has advanced much more in this aspect with fast imaging with single breath holds and 1 beat acquisition lasting a few seconds. The radiation and iodine based contrast are the major disadvantages although currently radiation doses below 1 millisievert are achievable with CCTA. MRCA with whole heart 3D imaging and 32 channel coils and 3T magnets have improved coronary imaging significantly but still lags behind and is not available widely. We foresee that CCTA will become mainstream for coronary imaging in low to intermediate risk populations with chest pains syndromes in the near future with exciting prospects of comprehensive cardiac imaging of perfusion and viability and plaque imaging.

Acknowledgements

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