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Chapter 1

Advances in Cardiac Computed Tomography

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Abstract

Coronary cardiac computed tomography (CCTA) has seen rapid improvements in technology including hardware and postprocessing techniques that have contributed to its rapid growth and enabled it to remain in the forefront on diagnostic imaging. Important technological advances include wider detectors for greater coverage with less gantry rotation times, dual-source computed tomography (CT) with improved temporal resolution, dual-energy CT where simultaneous imaging at different energies to increase the contrast difference between different tissues enhances diagnostic accuracy, and emergence of spectral CT to enhance atherosclerotic imaging through nanoparticle technology. Software advances include iterative reconstruction methodologies to reduce noise and radiation doses, plaque imaging and quantification tools to assess plaque morphology and stenosis severity. Processing advances using computational fluid dynamics now enables the determination of fractional flow reserve (FFR). Another important advancement in CCTA physiologic imaging is CCTA perfusion imaging to detect ischemia and compares favorably with myocardial perfusion imaging and coronary angiographic stenosis. Finally, large registry studies and single-center studies have now been published assessing the incremental value of coronary calcium score, CT plaque severity of disease and have demonstrated that the CCTA carries strong prognostic value over and above traditional risk assessment in predicting adverse outcomes.

Keywords: coronary computed tomography angiography, CT advances, CT perfusion imaging, CT fractional flow reserve, prognosis

1. Introduction

Cardiac computed tomography (CT), specifically coronary CT angiography (CCTA), has made major progress and currently is one of the leading noninvasive modalities for diagnosis of coronary artery disease (CAD) during the past years. The progress can be attributed to many

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reasons but chief among them are progressive establishment of CCTA as a front-line imaging modality for diagnosis and prognosis of coronary artery disease. This was shown by randomized trials and multicenter registry-based evidence totaling tens of thousands of patients. The second important factor contributing to the rapid rise of CT is advancements in CT technology in hardware and new software solutions, such as refined image reconstruction methods. Due to such advances, CCTA has enjoyed progressive enhancements in image quality and achieved better temporal and spatial resolution. Most importantly, CCTA is now possible with much lower radiation doses than a traditional SPECT scan. Furthermore, with some advanced scanners and scanning methodologies current doses approach the 1-milliseivert range which is a mind-boggling advance since the inception of the technique not too long ago in early 2000.

2. Historical perspective

The first CCTA was performed using electron-beam CT in the 1990s [1]. X-ray beams were produced by an electron beam, and were directed toward stationary targets around the patient. This image was produced at a temporal resolution of 100 ms but was insufficient to image coronaries given a slice thickness of 1.5–3 mm. However, this laid the groundwork for manufacturers to move the field forward with the multislice CST (MSCT), and the first four-slice CT in 2000 for coronary visualization had a gantry rotation time of 500 ms and a temporal resolution of 250 ms [2]. Subsequently, this evolved into 16-, 40-, and then 64-slice CT. There was slight improvement in slice thickness but now with an ability to image the heart in 4–8 heart beats. This led to reduction in less breath hold times, lesser artifacts, higher speed of contrast use, and thus lesser contrast volume. Multiple studies have now established the diagnostic accuracy of 64-slice CCTA using retrospective helical acquisition techniques [3, 4].

3. Equipment advances in CCTA

Although 64-slice CCTA remains the workhorse of coronary imaging, manufacturers have worked continuously to move technology forward. While some have just increased the number of slices in detectors which then translates to greater scan coverage and thus acquisition of the image needed in shorter number of heart beats, others have used dual-scanner technology (dual-source CT at 90° angle) to enable increasing temporal resolution by a factor of 2.

1. **Wide detector CT:** By increasing the number of CT scanner detector width (number of slices), a great amount of coverage of the heart in a single gantry rotation can be achieved. Each detector row has a width (collimation) of 0.5–0.6 mm. So, a 64-slice detector can cover 64 × 0.5 = about 38 mm of scan coverage. Thus, a wider detector array such as 320-detector CT would provide a single gantry rotation coverage of 320 × 0.5 = 160 mm. Since the approximate coverage to scan the entire heart is about 120 mm, a 65-slice scanner would need about 4 gantry rotations, and a 320-slice scanner could cover the entire heart in one rotation. The disadvantage of wide detector CT is that due to extra rotation at the beginning and end of scan to avoid cone beam reconstruction artifact (over ranging), there is extra radiation burden to patient and also additionally areas not in the field of interest also being exposed

to radiation. **Table 1** provides a comparison of CT scan characteristics and acquisition parameters over a wide range of detector widths, and **Figure 1** provides a comparative illustration of detector coverage depending on the number of detector rows in MSCT.

2. **Dual-source CT:** The principle behind dual-source CT scanners is two sources of radiation with the corresponding detectors set at 90° to each other. Thus, image acquisitions are much faster cutting short time by 50% which is a key factor in improving image quality by decreasing artifacts related to breath hold [5]. Furthermore, temporal resolution is also improved (83 ms). Whereas a 64-slice single-detector MSCT requires half of gantry rotation (180°) for image reconstruction, the same information can be obtained with a DSCT for one-fourth of the gantry rotation (90°). The heart rate factor also is of less importance with DSCT although HR has to be steady and significant tachycardia is not optimal [6]. Another important factor is that radiation doses are also decreased even though two radiation sources are used because the radiation source is on for less than half of the time narrowing electrocardiogram (ECG)-pulsing window for image acquisition given the DSCT technology. Investigators have now pushed the limits of this scanner further with recent high-pitched prospective gated acquisition which enables whole heart acquisition in250 ms in a single heart beat [7]. This if combined with excellent heart rate controls (<60 bpm) can achieve extremely low radiation doses reaching 1 milliseivert [8]. **Figure 2** shows the CT image quality with 320-slice and with high-pitch prospective CT-scanning technology.

3. **Dual-energy CT:** Apart from using dual source, using different energies could have the advantage of assessing iodine from other tissues by varying the voltage (kilovolts). This has the impact of demonstrating the nonlinear variation of different tissues at varying voltages. This could help improve contrast between structures. The dual-energy concept can either be with two sources alternating the voltages or by using detectors with elements capable of detecting varying energies. Although the full role of this technique is not clear, it could help in separating calcium from contrast-enhanced lumen and in detecting perfusion defects in CT perfusion imaging [9]. One other intriguing advantage of dual energy is in radiation reduction. By using virtual-unenhanced image reconstruction (VUE) techniques employing iodine subtraction algorithms, early studies have shown that it is possible to obtain calcium score and contrast-enhanced corona angiographic information from a single image which can translate to dose reduction ranging from 20 to 50% by avoiding non-contrast calcium score scans [10, 11]. **Table 2** outlines some of the applications of dual-energy CT technology

4. **Spectral CT:** Along the same lines as dual-source CT, spectral CT also adopts the principle of varying photo energies to characterize different tissues and can be used in conjunction with nanoparticles to further characterize atherosclerosis. In contrast to two levels of energy in dual source which poses limits to detecting different energy spectra, a photon-sensitive spectral CT detector can sample a bin the incident photon based on the current pulse generated at a specific energy level. This allows multiple photon energies to be sampled. This technology is in its earliest stages but studies are being done and detector technology is being evaluated [12, 13]. **Table 2** outlines some of the applications of spectral energy CT technology.

5. **Flat panel CT:** Flat panel CT as the name implies employ a flat panel of digital detectors achieving isotropic resolution (0.2 mm) and represent a totally different technology from the current generation of CT scanners in every aspect. These provide volumetric coverage

Number of detector slices	4	16	64	256	320
Detector collimation (mm)	4 × 1 4 × 1.25	16 × 0.5 16 × 0.625 16 × 0.75	64 × 0.5 64 × 0.65 2 × 32 × 0.6*	2 × 128 × 0.625*	320 × 0.5
Slice width (mm)	1.3	0.8–1.0	0.5–0.8	0.6	0.5
Spatial resolution (mm)	1	0.6	0.4–0.6	0.4	0.35
Rotation time (s)	0.5	0.375–0.420	0.33–0.40	0.27	0.35
Temporal resolution (ms)	250	188–210	165–200‡	135	175§
z-axis coverage (mm)	4–5	8–12	32–40	80	160
Scan time to cover the entire heart volume (s)	40	15–20	6–12	1–2	>1

* Double *z*-sampling. ‡Temporal resolution can be improved to 83 ms with dual source acquisitions in single-energy applications. §Temporal resolution can be improved to 58 ms with multisegment acquisition and multisegment reconstruction

Abbreviation: MDCT, multidetector CT

Schuleri K.H. *et al. Nat. Rev. Cardiol*. **6**, 699–710 (2009); doi:10.1038/nrcardio.2009.172

Table 1. Technical and acquisition parameters for cardiac examinations with MDCT.

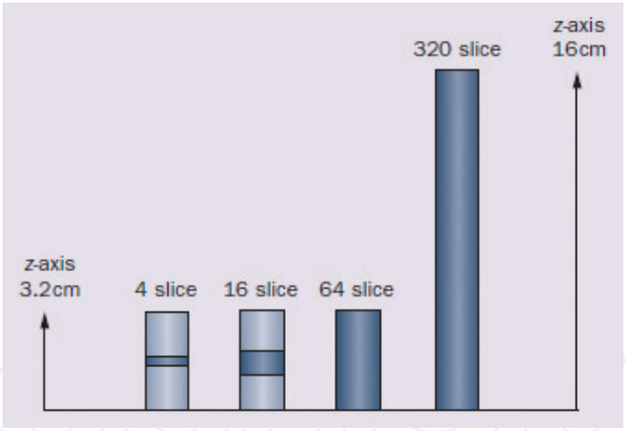


Figure 1. Technical progression of scanner technology. Improvement in coverage of the *z*-axis with 4-, 16-, and 64-slice detector rows, relative to wide-range 320-slice detector rows. With the wide-range technology, the entire heart is covered in one gantry rotation. Schuleri, K. H. *et al. Nat. Rev. Cardiol*. **6**, 699–710 (2009); doi:10.1038/nrcardio.2009.172.

of the entire heart and deliver extremely high spatial resolution capable of imaging distal small coronary arteries, much better stented lumen delineation, and less artifacts from calcium. The major limitations currently are poor temporal resolution (2 s) and poor contrast resolution (5–10 Hounsfield units compared to 1 Hounsfield unit for MSCT) [14]. Currently as most evidence is limited to preclinical and animal studies, further research and studies are needed in this field.

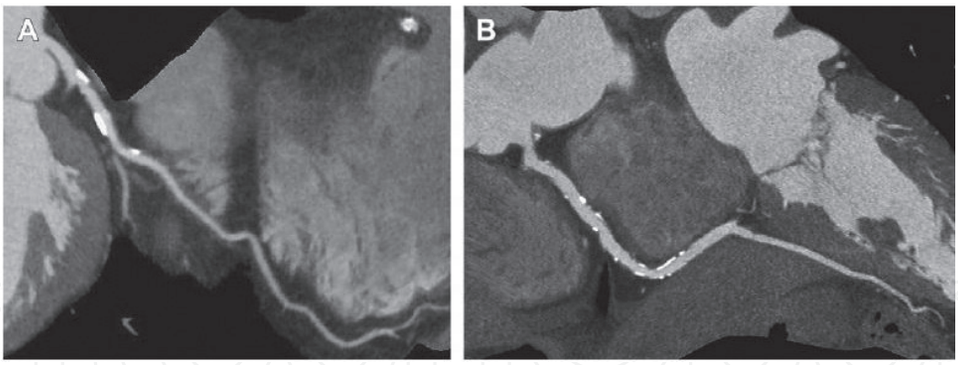


Figure 2. (A) Coronary CT with 320-slice CT. (B) Coronary CT with high-pitch prospective scanning. Achenbach S et al. Cardiol Clin 30 (2012) 1–8.

Parameter	Dual source	kVp switching	Double-layer detector
Method	Two X-ray tubes with 90° offset each tube can operate at a two different kVp energy levels	One X-ray tube voltage switches between low- and high-energy setting (e.g., 80 and 140 kVp) continuously during spiral 360° acquisitions	One X-ray tube exposes a detector system consisting of two layers. The first (top) layer encountered by photons absorbs most of the low energy (soft spectrum), whereas the bottom detector layer absorbs the remaining higher energy (hard spectrum)
Advantages	No significant lag time between low-energy and high-energy scans	No image mis-registration Monochromatic image acquisitions possible	No time lag for kVP switching; suitable for rapid imaging in cardiac motion Photon counting possible to sort spectral subranges in order to form images based on their attenuation profile; enables high-sensitivity acquisitions for targeted contrast agents
Disadvantages	Image mis-registration possible Reduced temporal resolution Currently only polychromatic image acquisitions	Dual-energy time lag between low and high energy depends on switching time Limited temporal resolution Currently only polychromatic image acquisitions	X-rays are generated as polychromatic beam Limited temporal resolution

Schuleri, K. H. *et al. Nat. Rev. Cardiol.* **6**, 699–710 (2009); doi:10.1038/nrcardio.2009.172

Table 2. Current applications of dual-energy and spectral CT techniques.

4. Advances in temporal and spatial resolution

Continuing advances are being made in the development of faster scanners and in the pipeline is GE.

Revolution CT TM (GE Healthcare, Milwaukee, WI) with a wider *z*-axis coverage and a gantry rotation time of 0.2 s providing wider *z*-axis coverage and single beat image acquisition (Revolution CT 2014; available at www.gehealthcare) and the Seimens Somatom Force TM

(Seimens AG, Erlangen, Germany) providing very high temporal resolution of 66 ms and spatial resolution of 0.24 s and able to image the heart in a single beat with Turbo Flash mode with the need for breath hold. These superb technological advances need formal clinical validation (Somatom Force TM available at www.seimens.com).

Typical MSCT detectors have solid-state ceramic detectors which help to convert X-rays to visible light followed by conversion to analog electrical signal which then gets converted to a digital signal for image formation. The detectors all have septate electric boards which are all then linked to each other.

However, with breakthrough in technology one vendor has introduced a new detector system called Stellar Detector (Stellar Detector TM, Seimens AG, Erlangen, Germany) which combines all detectors into single electric board and claims superior spatial resolution and decrease in image noise.

GE has introduced Gemstone Detector which is a garnet-based substance which has much shorter decay and after-glow times enabling much rapid processing of signal improving spatial resolution and decreasing image noise. This concept has proven useful in reading CTAs in stent, determining intrastent diameter and area due to decrease in image noise [15]. It appears to be compatible with dual-energy scanners too.

5. Software advances in CCTA

a. **Iterative reconstruction (IR):** Although filtered back-projection remains a common method of reconstruction, IR techniques are more commonly being used where image information is used to simulate expected image based on CT measurements and then these simulated data are modified in subsequent image reconstruction. This technique has been shown to reduce image noise and reduction in radiation doses [16, 17]. **Figure 3** shows an example of noise reduction with IR.

b. **Motion correction:** Motion artifact is one of the most important limitations in CCTA affecting overall accuracy. Techniques such as heart rate control and faster scanning with wide detector and dual source technologies are ways to limit motion artifact. Recently, GE Healthcare has introduced Snapshot FreezeTM where the software evaluates multiple adjacent cardiac phases within the same cardiac cycle to evaluate and plot coronary artery motion and eliminate residual coronary motion artifact. This promises to further minimize motion artifact improving the image quality and interpretability [18].

c. **Arrhythmia detection:** Occurrence of arrhythmias causes significant issues with missing data and artifacts in CCTA. Advances in arrhythmia detection include using of complex arrhythmia detection algorithms to enable stopping the scan when arrhythmia occurs and restarting scans after arrhythmia subsides to enable capturing data in the right cardiac cycles (Seimens Healthcare, Forcheim, Germany). Other advances include image reconstruction using identical filling concepts isovolumetric phases (which contain best image data) are used in image reconstruction [19].

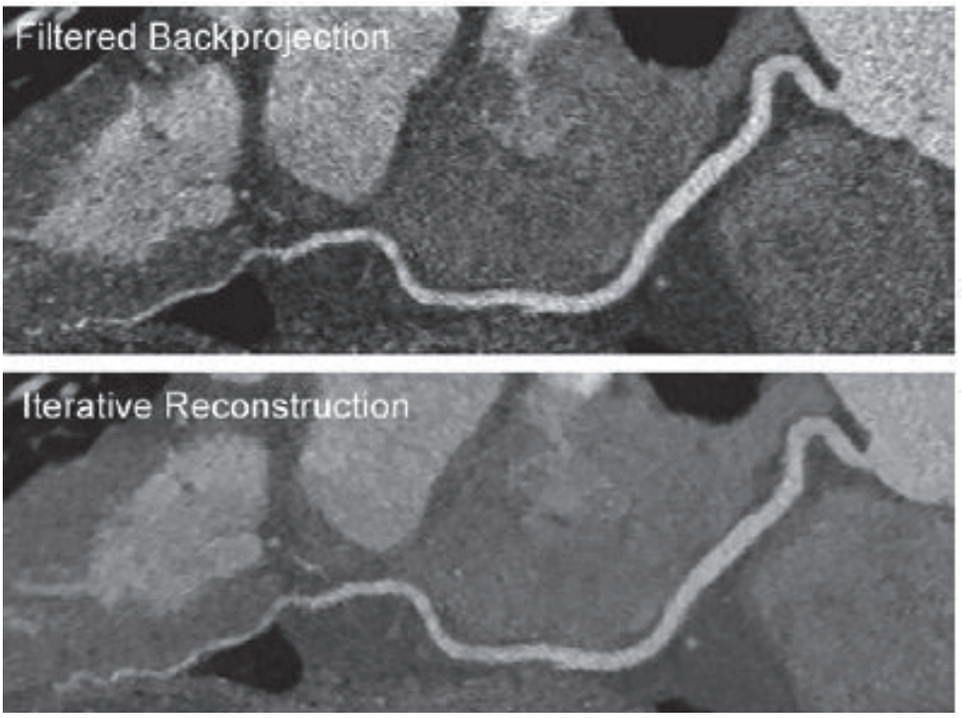


Figure 3. Image noise reduction with iterative reconstruction technology. Achenbach S et al. Cardiol Clin 30 (2012) 1–8.

d. **Radiation reduction:** Apart from prospective gating, traditional ECG tube current modulation, wide detector coverage, and dual source high-pitch-scanning techniques all of which dramatically reduce radiation; further advances are being done to do real-time modulation of attenuation-based adjustments in tube potential, thus driving radiation doses down even further (Care Dose4D TM; Seimens Healthcare, Forcheim, Germany).

6. Advances in CCTA beyond traditional noninvasive coronary angiography

CCTA has been recognized as a cost-effective noninvasive diagnostic modality [20]. Evolving literature has established that revascularization has clinical benefit when performed in stenosis with hemodynamic significance [21, 22]. An intermediate stenosis on CT scan is not a good predictor of physiological significance [23–25]; this calls for additional tools which can provide complementary physiological data to available anatomy. Noninvasive fractional flow reserve (FFR) evaluation on CT, myocardial CT perfusion, and transluminal attenuation gradient (TAG) are the three techniques with clinical evidence. We will talk briefly about these in this section of the chapter.

6.1. Noninvasive fractional flow reserve evaluation on CCTA: physiology

FFR is defined as the ratio of the mean coronary pressure distal to a coronary stenosis to the mean aortic pressure during maximal coronary blood flow. An FFR value of 0.80 or less suggests

lesion-specific hemodynamic significance [26]. Incorporation of FFR in CT does not call for any modification of CCTA protocols, additional image acquisition, or administration of medications. The calculation is performed by segmentation of coronary tree and left ventricular mass and application of computational fluid dynamics (see **Figure 4**). While no adenosine administration is performed, the conditions to simulate the same can be established.

6.1.1. Clinical evidence

FFR incorporation into routine CT has been compared to visual estimation alone in multiple studies. We now have evidence from an integrated analysis of data from three prospective, international, and multicenter trials, which assessed the diagnostic performance of FFR CT using invasive FFR as a reference standard [27]. The key trials outlining the value of CT FFR were the DISCOVER-FLOW, DeFACTO, and the NXT trials. These studies with cumulative over 600 patients concluded that with intermediate coronary stenosis, FFR CT remained both highly sensitive and specific with respect to the diagnosis of ischemia. Specifically, CT FFR had higher sensitivity than CT (81 vs. 53%) Additionally, when compared to invasive FFR evaluation, FFR CT had higher diagnostic accuracy (86 vs. 71%) in the identification of hemodynamically significant lesions.

More exciting data have suggested an economic benefit associated with a 12% reduction in adverse cardiovascular events at 1 year with the use of CT FFR when compared to angiography with stenosis-based PCI [28]. In their study, Hlatky et al. applied a decision analysis comparing five clinical strategies constructed as follows: (1) angiography with stenosis-based PCI; (2) angiography with FFR-guided PCI; (3) coronary CTA followed by angiography and

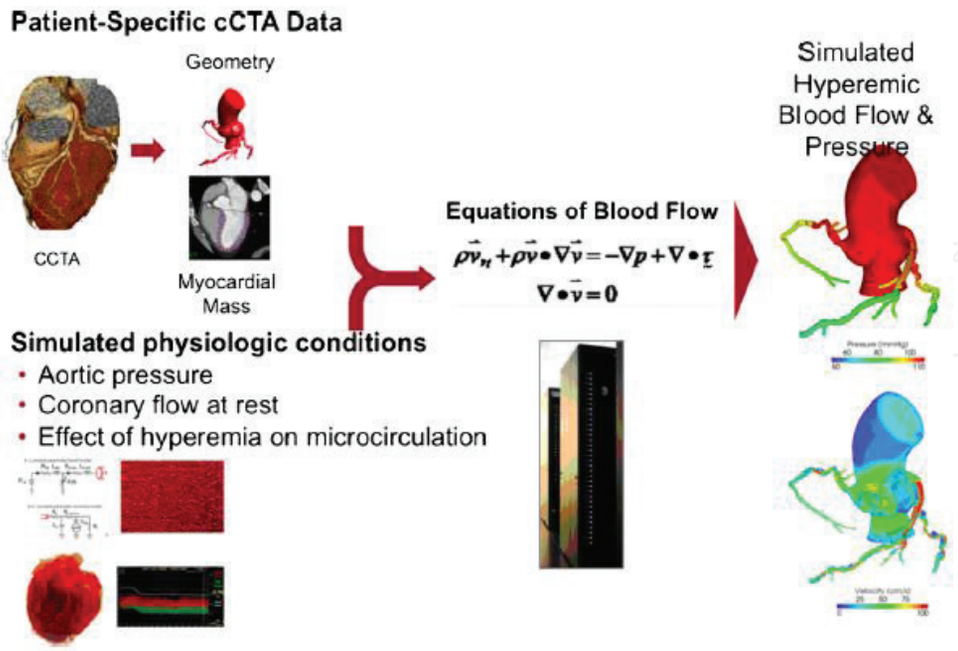


Figure 4. Simplified scheme of computational fluid dynamic techniques for simulating hyperemic flow and pressure applied to CTA data. Min JK. JCCT 2011;5(5);301-9.

stenosis-based PCI; (4) coronary CTA followed by angiography and FFR-guided PCI and (5) coronary CTA–FFR CT followed by FFR CT-guided PCI. The projected initial management costs were highest for angiography with stenosis-based PCI and lowest for the coronary CTA–FFR CT followed by FFR CT-guided PCI. Inspired from this concept, we now have a prospective, controlled utility trial evaluating patients with an intermediate likelihood of CAD PLATFORM (Prospective Longitudinal Trial of FFR CT: Outcome and Resource IMpacts) [29]. Patients referred for noninvasive evaluation formed the first cohort and those referred for invasive coronary angiogram comprised the second cohort. These were evaluated by using standard care approach (first phase) and coronary CTA with physiologic FFR evaluation (second stage). The primary result was that among those with intended ICA (FFRCT-guided = 193; usual care = 187), no-obstructive CAD was found at ICA in 24 (12%) in the CTA/FFRCT arm and 137 (73%) in the usual care arm ($P < 0.0001$), with similar mean cumulative radiation exposure (9.9 vs. 9.4 mSv, $P = 0.20$). Invasive coronary angiography was cancelled in 61% after receiving CTA/FFRCT results. Clinical event rates within 90 days were low in both the arms. This is just another example of how CT FFR is a feasible and safe alternative to invasive angiography and was associated with a significantly lower rate of invasive angiography showing no-obstructive CAD (**Figure 5a** and **b**).

We await the results of the multicentric registry ADVANCE (assessing diagnostic value of noninvasive FFRCT in coronary care) which will evaluate the clinical and economic impacts of FFR CT (NCT02499679).

6.1.2. Clinical applications

Enhanced specificity and accuracy in the available data has established FFR incorporation to CT as a promising new dimension in noninvasive modalities. It may serve as a "gate-keeper" to escalation to invasive coronary angiography in suitable patient population. We await many more exciting studies to define the niche for its role in daily clinical practice.

6.1.3. Limitations

1. Presence of heavy calcification, mis-registration, and motion artifacts may affect FFR calculation with CT since the calculation relies on accurate anatomic models.
2. Computational simulation of adenosine-induced hyperemia is performed without the actual use of adenosine which may incorporate errors, especially in the presence of microvascular dysfunction.
3. Presence of viable or scarred myocardium also affects the FFR value.

6.2. Myocardial CT perfusion (myocardial CTP)

Myocardial CTP protocol is composed of a stress phase acquisition and a rest phase acquisition, as with nuclear myocardial perfusion imaging [30]. Iodinated contrast is administered in both the stress and rest acquisition (60–75 ml for each acquisition), for a total contrast dose of

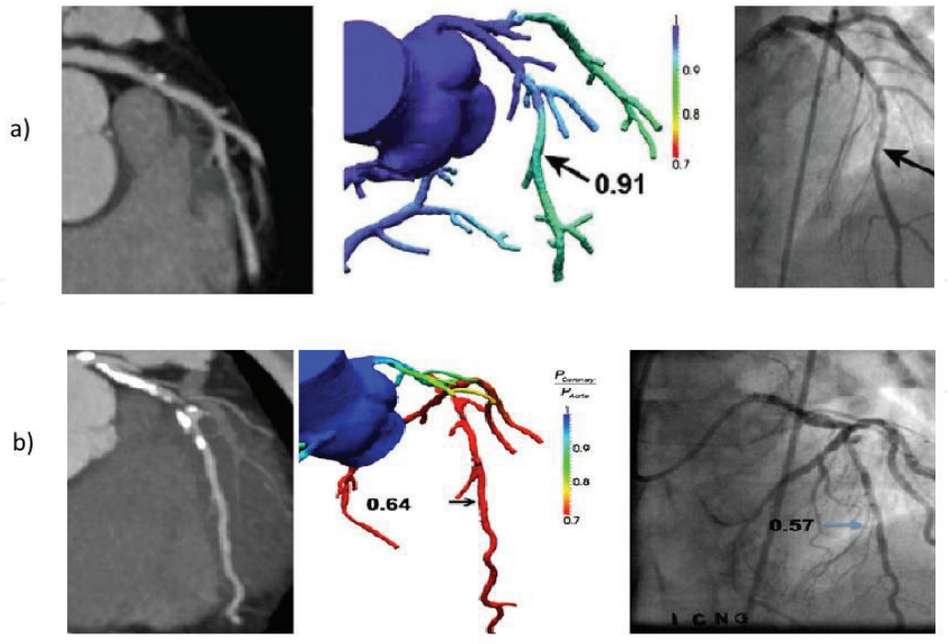


Figure 5. (a) Examples of a no-obstructive CAD on CTA and corresponding normal CT FFR and correlative coronary angiographic FFR of patient from the DeFACTO study. (b) Example of patient with obstructive coronary disease in left anterior descending coronary artery on CTA and corresponding abnormal CT FFR and correlative coronary angiographic FFR from the DeFACTO study.

approximately 130–150 ml. The pharmacological stress agents include adenosine, dipyridamole or regadenosin. Although it has been shown in many studies that pharmacological and exercise stress testing have comparable diagnostic characteristics, exercise is the preferred method of stress in myocardial perfusion imaging when possible [31].

There are two ways in which to set up a stress and rest myocardial CTP protocol based on the order of scan acquisition, namely stress phase first followed by rest phase, or vice versa (as illustrated in **Figure 6**).

As expected, the main consideration is that the first scan will be a "clean" acquisition, and that the contrast used in the first acquisition can cross-contaminate the second acquisition if the interval between the scans is less than approximately 30 min. On the other hand, when doing a stress phase acquisition first, the detection of myocardial ischemia is optimized by not having contamination of contrast; however, the second scan can underestimate the presence of infarct in the myocardium if a short scan interval is used. This is so because the contrast from the stress scan would accumulate in an area of myocardial infarct due to the slow wash-out phenomenon, leading to persistent perfusion defect during rest imaging. Thus, possible underestimation of myocardial infarction specifically if the second scan is done within 10 min of the first one. A coronary CTA acquisition can be acquired simultaneously with the rest acquisition, and beta-blockers and sublingual nitroglycerin can be given to optimize the second scan (**Table 3**)

6.2.1. Clinical evidence

The smaller initial studies have been conducted at various institutions with differences in protocols and reference standards. The unifying conclusion is that perfusion defects on myocardial

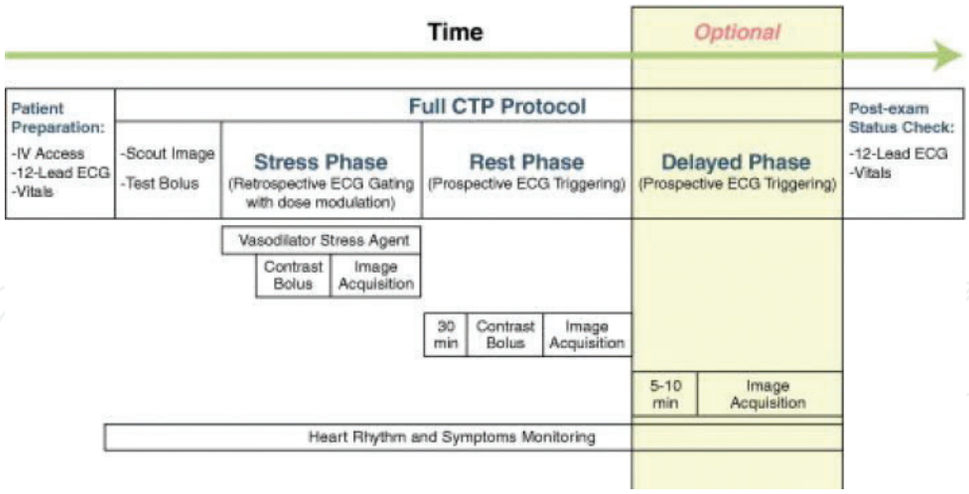


Figure 6. Full CTP Protocol: The protocol includes patient preparation and post-examination checkup (including an optional delayed phase acquisition (shaded box). All steps are as listed in sequence. Heart rhythm and symptoms are monitored throughout the entire examination. (Adopted with permission from Ref [31]).

Sequence	Advantages	Disadvantages
Stress → Rest	Better sensitivity of stress scan (ability to detect ischemia). Coronary CTA can be optimized with second acquisition by giving medications without interfering with perfusion assessment	Contrast contamination, leading to appearance of late-contrast enhancement during rest acquisition (decreased sensitivity for infarct)
Rest → Stress	Ability to stop protocol after rest phase (if no or minimal disease is evident). Better sensitivity of rest scan (ability to detect infarct)	Contrast contamination, leading to appearance of late-contrast enhancement during stress acquisition (decreased sensitivity for ischemia). Beta-blocker given during first acquisition can underestimate myocardial ischemia

Table 3. Advantages and disadvantages of different CTP protocol sequences (adopted with permission [30]).

CTP correlate well with those on SPECT and also in some studies with stenosis on quantitative coronary angiography. We briefly present some of these studies.

George et al. [32] used a 64-detector MDCT or a 256-detector MDCT for image acquisition with adenosine as the stress agent. The combined analysis of all patients (including both scanner types) in this study showed a per-vessel territory sensitivity, specificity, positive-predictive value (PPV), and negative-predictive value (NPV) of 75, 87, 60, and 93%, respectively, when compared with QCA and SPECT. Using the same stress agent, Blankstein et al. [33] acquired myocardial CTP images using a dual-source CT scanner, which has higher temporal resolution. They confirmed that myocardial CTP is equivalent to SPECT in detecting coronary artery stenosis by QCA, with comparative sensitivity and specificity to prior study. One interesting derivation from this study was similar radiation exposure with full myocardial CTP when compared to SPECT MPI. Rocha-Filho et al. [34] demonstrated that adding perfusion information obtained from stress myocardial CTP to coronary CTA improves all diagnostic characteristics of CTA alone, with most significant impact on specificity and PPV. The size and severity evaluation of perfusion defect at rest and

stress have been shown to be concordant between myocardial CTP and SPECT [35]. This concordance has been further validated in the form of excellent validation by a five-point scale and a total perfusion deficit score [36]. Myocardial CTP has proven equivalent to SPECT in the detection of stenosis found on QCA (sensitivity and specificity: 88 and 79% for myocardial CTP and 69 and 71% for SPECT, p = NS) with dipyridamole on a 64-detector MDCT scanner [37].

An additional concept is the utilization of dynamic myocardial perfusion. Ho et al. [38] demonstrated that stress and rest dynamic perfusion imaging can detect myocardial perfusion defect with good diagnostic accuracy when compared with SPECT MPI (per-segment sensitivity, specificity, PPV, and NPV of 83, 78, 79, and 82%, respectively) and with QCA (per-segment sensitivity, specificity, PPV, and NPV of 95, 65, 78, and 79%, respectively) and allows for defining time-attenuation curves with the potential for quantification of myocardial blood flow. This comes at the price of a much higher radiation dose when compared to static imaging.

6.2.2. Limitations

1. CT-related artifacts should be recognized in an attempt to minimize them. One major culprit is beam hardening, which is a phenomenon that occurs when X-ray beams pass through objects of high density, leading to a selective attenuation of lower-energy beams and increased mean energy of the remaining beams. The resulting appearance is a hypoenhanced region that may mimic areas of true perfusion defect. Such hypoenhanced region is usually triangular and appears to originate from the region of high attenuation next to it, and does not conform to vascular territories [39]. A particularly common location includes the basal inferolateral wall, due to proximity to the descending aorta with iodinated contrast and dense vertebral bodies. Attempts to develop an algorithm to minimize beam-hardening artifacts are ongoing, with the use of iterative reconstruction.
2. Myocardial CTP is also prone to motion artifacts similar to coronary CTA, particularly during the stress phase acquisition, due to the increased heart rate. Cardiac motion during the acquisition leads to hypoenhanced areas that can mimic true perfusion defects. Enhanced temporal resolution of CT has led to marked decrease in this artifact.

It cannot be emphasized enough that a careful review of multiple phases of the cardiac cycle is a robust method to differentiate a true perfusion defect from an artifact.

In summary,

- Myocardial CTP has the potential to become a robust clinical tool for the evaluation of chest pain patients.
- The available literature is in a very preliminary stage with only single-center preliminary experiences. These are flawed by referral bias and absence of any standardized protocol.
- More research is needed in order to further define, optimize, and validate the modality.

7. Transluminal attenuation gradient

TAG is a modality that is based upon the kinetics of iodinated contrast media within coronary arteries. It is the linear regression coefficient between the lumen attenuation and axial distance along the vessel from the ostium. This method is based upon the contrast attenuation difference across a stenosis which may predict functional significance [40].

7.1. Clinical evidence

Changes in coronary opacification across a stenosis were found to predict abnormal resting coronary blood flow in a study by Chow et al. [41]. The comparison of coronary opacification after normalization to aorta was performed to severity of stenosis and thrombolysis in myocardial infarction flow in the coronary arteries at invasive coronary angiography. TAG significantly improves both sensitivity and specificity over CCTA stenosis degree alone [40].

7.2. Clinical applications

The addition of TAG to CCTA may supplement detection of hemodynamic significance of coronary stenosis especially in severely calcified lesions. An advantage of TAG over FFR supplementation of CT is that there is no complex computation required [42].

7.3. Limitations

The evidence on the role of TAG in CCTA is limited. Further validation of both diagnostic and prognostic role of this approach is required in larger studies.

8. Take home points

The single most attractive characteristic of the summarized techniques is that they provide both anatomical and functional assessments of CAD. The current studies have demonstrated that these methods are feasible for noninvasive assessment of CAD and have the potential to provide incremental value in detecting functionally significant coronary stenosis over CCTA alone. The available data are preliminary, but definitely promising. This calls for dedicated research to identify the prognostic value and clinical outcomes of decision making based on these techniques.

9. CCTA and prognosis

In an era where coronary artery disease (CAD) is the leading cause of death worldwide, noninvasive cardiac imaging is essential for the diagnosis and prognosis of patient with suspected or known coronary artery disease. While nuclear positron emission tomography (PET), SPECT,

cardiac magnetic resonance imaging, and stress echocardiography are well-established modality with excellent diagnostic accuracy, coronary computed tomographic angiography (CCTA) has emerged in the past couple of decades and is rapidly growing as noninvasive testing modality for the detection of coronary artery disease (CAD). CCTA provides excellent anatomic information that is comparable with invasive coronary angiography and in addition can provide significantly more information about subclinical atherosclerosis [43–46].

This has attracted particular interest to explore prognostic implication of the CCTA in cardiology field. Several single- and multiple-center studies, including meta-analysis of large registry, have been done to evaluate its prognostic value and compare it to the traditional risk factors [47].

9.1. Clinical evidence

Prognostic value of the CCTA was studied in a variety of patient population including symptomatic and asymptomatic subset of patients. Hadamitzky et al. analyzed large patient population of 17,793 from the international CONFIRM registry in patient with suspected coronary artery disease. Combining the CCTA data and the clinical risk scores, a modeled score was developed with end-point assessment being all-cause mortality at 2-year follow-up. The optimized score developed improved risk stratification and overall risk prediction beyond the clinical risk scores. Incremental prognostic value was noted particularly with plaque burden and vessel stenosis, with a proportional correlation for proximal segment involvement [48]. Similar outcome was replicated at longer 5-year follow-up studies [49].

Other studies evaluated the prognostic value of the CCTA based on the plaque location and whether the atherosclerotic plaque is obstructive or not and the number of vessels involved. Cheruvu et al. analyzed the CCTA prognosis in asymptomatic patients without modifiable cardiovascular risk factors [50]. A total number of 1884 patients from 12 different centers were enrolled and followed up for approximately 5 years. Both obstructive and non-obstructive CADs were found to predict MACE with increased HR associated with higher degree of stenosis. MACE ranged from 5.6% in patients with no CAD to 36.28% in patients with obstructive CAD. **Figure 7** shows the obstructive severity on CTA and clinical implications. **Table 4** provides a summary of some of prognostic studies in CCTA.

The additive information of the CCTA on atherosclerotic plaque features offers the promise to provide a more comprehensive view on total plaque burden. In emergent data, atherosclerotic plaque characteristics have been associated with plaque vulnerability; hence, several observational and prospective studies are done to correlate their ability to predict future cardiovascular events [51–54]. Feuchtner et al. characterized CTA features associated with worse clinical outcomes. The evaluation of the CTA findings was based on lesion severity, plaque types (the spectrum from different degrees of calcified to non-calcified), and high-risk plaque criteria (low attenuation by HU, napkin-ring, spotty calcification, and remodeling index). The study concluded that the low attenuation plaque of <60 HU and napkin-ring sign were the most powerful predictors for MACE. Prognosis was established as excellent long term if CTA is negative but worsens with increasing non-calcifying plaque component [55]. Similar

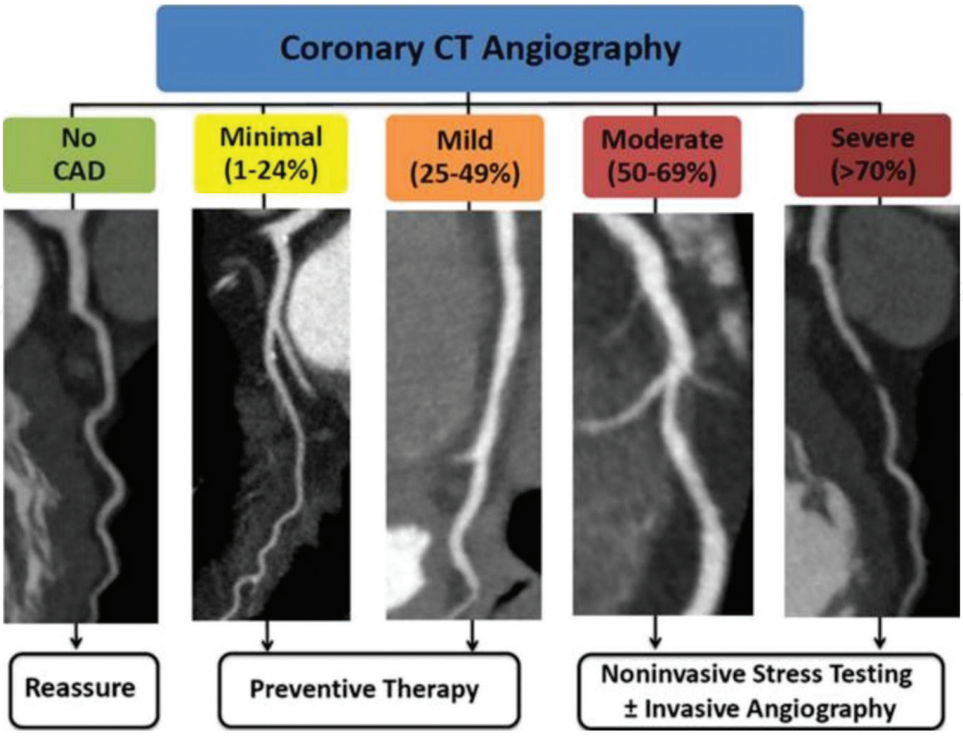


Figure 7. Coronary artery disease (CAD) severity identified by coronary CT angiography and recommended management. Patients with a normal coronary CT angiography can be safely reassured. Follow-up for preventive therapy is recommended for non-obstructive (<50%) CAD. For obstructive CAD (≥50% stenosis), further testing is recommended to guide management [55].

concept was entertained by Nadjiri et al., who performed a semi-quantitative analysis of all non-calcified plaques or partially calcified plaques to quantify the low attenuation plaque volume (LAPV), total non-calcified plaque volume, and remodeling index. All these plaque characteristics were associated with increased MACE independently from the clinical risk presentation. The strongest prognosis was associated with LAPV, which carried additional information beyond the calcium score and the conventional coronary CTA [56]. High-risk plaque and plaque progression were also found to be independent risk factors for predicting ACS [57, 58]. **Figures 8–10** demonstrate images of different histologic plaque types, their quantitative measurements, and plaque-specific-associated risk.

Considering the well-known correlation of the diabetes mellitus and CAD, particular attention was directed of the CCTA implication in diagnosing diabetic patients with subclinical CAD and assessing the prognostic value in this subset of patients. On prospective evaluation of 525 asymptomatic diabetic patients, Van den Hoogen et al. found a proportional increase in event rates in patients with increased CAC category and coronary stenosis severity. What was even more importantly noted was that patients with normal CTA had an excellent prognosis [59]. Whether or not asymptomatic diabetic patients would benefit from screening for CAD remains controversial. Muhlestein et al. demonstrated in a prospective study of 900 patients that CTA screening showed no survival benefit compared to optimized medical therapy in asymptomatic patients with type 1 and type 2 diabetes mellitus [60].

Study	Study aim	Patients (*N*)	Population characteristics	Major findings
Puchner S. et al. [58] (ROMICATII TRIAL)	Plaque characteristics predicting ACS.	472	Acute chest pain, low risk for ACS.	Presence of high-risk plaques was an independent *predictor of ACS*
Hadamitzky M et al. [48, 49]	Predict cardiac events at 5 years follow-up.	1584	Suspected CAD, not previously diagnosed	Severity of CAD and total plaque score predicted cardiac events over standard clinical events
Feuchtner G et al. [55]	Prospective assessment of the CCTA and MACE.	1469	Low to intermediate risk patients for CAD	Strongest predictors for MACE were LAP and napkin-ring sign with HR of 4.96 and 3.85, respectively.
Nadjiri J et al. [56]	Plaque characteristics and associated prognosis	1168	Patient with suspected CAD	Napkin-ring sign lesions and LAVP found to be predictors for MACE with LAVP carrying the strongest prognostic value HR 1.12, $p < 0.0001$
Cheruvu C et al. [50]	Predict MACE in long-term follow-up.	1884	Symptomatic patient with angina-equivalent	MACE were 5.6% in patients with non-obstructive CAD and 36.28% in patients with obstructive CAD
Van den Hoogen IJ et al. [59]	Prognostic assessment of the CCTA in patient with diabetes mellitus	525	Asymptomatic diabetic patients with no known history of CAD	Excellent prognosis in patient with CCTA negative. Prognosis was worse and directly proportional to the *number and severity of stenosis*
Linde et al. [61] (CATCH TRIAL)	CCTA-guided management and clinical outcomes.	600	Symptomatic patient with chest pain but negative troponin and ECG	CCTA-guided strategy appears to improve clinical outcomes in these patient population with HR: 0.36; $p = 0.04$

CCTA, coronary computed tomographic angiography; *CAD*, coronary artery disease; *HR*, hazard ratio; LAVP, low attenuation volume plaque; LAP, low attenuation plaque; MACE, major adverse cardiac events.

Table 4. Major studies assessing prognostic value of CCTA.

Symptomatic patients are another subgroup of patients where the role of CTA and its clinical implication was assessed. ROMICATT II and CCATCH trials [61, 62] addressed the clinical impact of CTA-guided therapy in patients with acute chest pain and negative ECG and cardiac biomarkers were evaluated in 600 randomized patients. Almost half underwent CTA guided and other half standard care (exercise MPI/EKG). MACE (cardiac death, myocardial infarction, hospitalization for unstable angina, symptom-driven revascularization, and readmission for chest pain) was significantly better in CTA group.

In conclusion, the above review has summarized the advances in CCTA and emerging data reflecting the very promising role CCTA carries in diagnosis and prognosis over the traditional risk assessment. Its unique ability to provide complete assessment of anatomy, plaque characteristics, and prognosis makes the CCTA's future very promising and crucial in enhancing patient care.

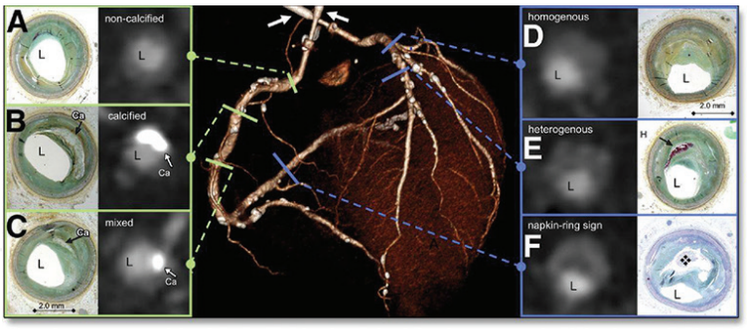


Figure 8. CCTA image of the coronaries with traditional plaque classification and the corresponding histology slides. There are non-calcified (A), calcified (B), and mixed plaque (C) noted. Based on plaque attenuation, there is homogeneous (D), heterogeneous (E), and napkin-ring sign (F) plaques [56].

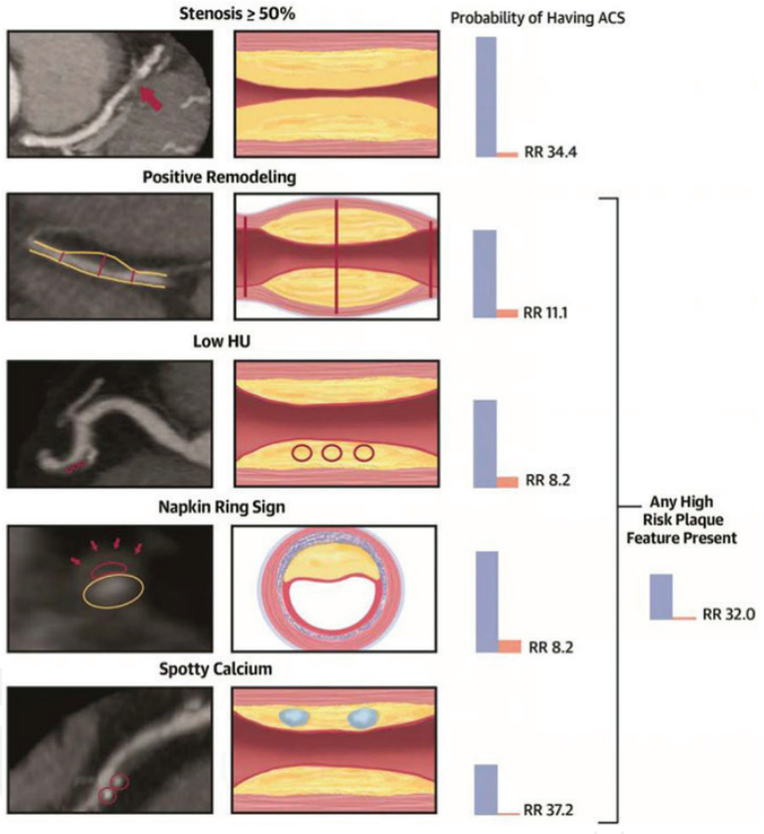


Figure 9. Probability of having acute coronary syndrome during the index hospitalization according to coronary computed tomography characteristics. Central Illustration: Significant stenosis and high-risk coronary plaque features and their association with the probability of having acute coronary syndrome during the index hospitalization. Stenosis of ≥50%—Severe stenosis of the mid-left anterior descending coronary artery (Bold arrow). Non-calcified plaque with positive remodeling in the distal right coronary artery (arrowhead). Positive remodeling—The two dotted red lines (image insert) demonstrate the vessel diameters at the proximal and distal reference (both 1.8 mm) and the full red line demonstrates the maximal vessel diameter in the mid portion of the plaque (2.7 mm)—the remodeling index is 1.5 Low HU plaque—Partially calcified plaque in the mid-right coronary artery with low <30 HU plaque. The red circles demonstrate the three regions of interest with the mean CT number of 22, 19, and 20 HU Napkin-ring sign—Napkin-ring sign plaque in the mid-left anterior descending coronary artery. Schematic cross-sectional view of the napkin-ring sign. The red line demonstrates the central low HU area of the plaque adjacent to the lumen (ellipse) surrounded by a peripheral rim of the higher CT attenuation (arrows). Spotty calcium—Partially calcified plaque in the mid-right coronary artery with spotty calcification (diameter of <3 mm in all directions; circles) [58].

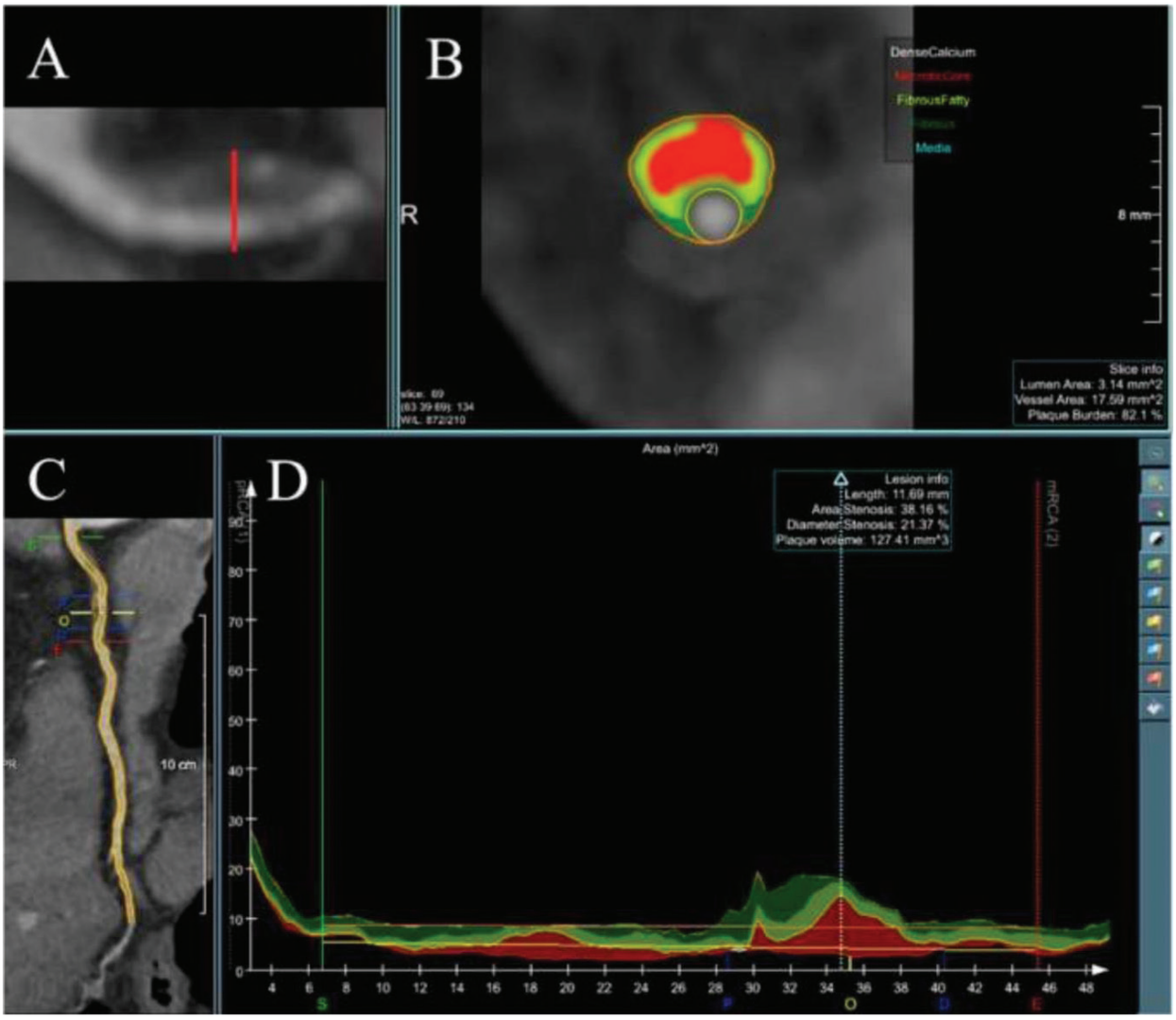


Figure 10. An example of the quantitative plaque measurements. **Panel A** – The large coronary plaque in the proximal right coronary artery (RCA) showed in long-axis view in the multiplanar reformatted image. **Panel B** – The cross-sectional view of the proximal RCA demonstrates a large plaque. The software detects plaque components with low CT attenuation <30HU, 31 to 60HU and 61 to 130HU. **Panel C** – The curved multiplanar reformatted image of the RCA. The proximal and distal normal cross sections are selected manually by the reader to mark the beginning and end of the plaque. The software automatically selects the minimal luminal area (stenosis). **Panel D** – The software provides quantitative measurements of the selected coronary plaque including total plaque volume (127 mm^3), remodeling index (2.04), stenosis degree (21%) and plaque length (11.7 mm). The volumes of plaque subcomponents are also reported [62].

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