Debate

Atypical Chest Pain in a Patient with Multiple Cardiovascular Risk Factors: CT Coronary Angiography Is the Route to Go

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Introduction

The feasibility of computed tomography angiography (CTA) for coronary imaging was first described in 1995 where electron beam CT was used to image the coronary arteries in 27 patients (1). The technology while providing high temporal resolution had substantial limitations in spatial resolution and image noise. The introduction of the first four-slice multidetector CT in the late 1990s provided improved spatial resolution and shorter acquisition times, allowing for the rapid advancement in this technology over recent years. Current-generation 64-detector scanners allow imaging of the entire heart over 5 to 7 beats, with newer generation scanners allowing imaging of the entire heart in a single cardiac cycle.

Cardiac CT imaging is ideally performed in those in sinus rhythm with heart rates <65 beats per minute to provide optimal image quality. Oral or intravenous beta-blockade, in the absence of contraindications, may be administered to achieve such heart rates. Sublingual nitrates are often administered at most institutions, to provide maximal coronary vasodilatation at the time of coronary imaging. Iodinated contrast is required to provide visualization of the coronary arteries and hence contrast allergy or significant renal impairment would represent relative contraindications to the procedure.

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Acute Chest Pain

Coronary CT has been demonstrated to have a role in the assessment of acute chest pain presentations to the emergency department. The high negative predictive value and sensitivity for detection of coronary plaque, as illustrated in the ROMICAT trial (2, 3), allows for earlier risk stratification and discharge from hospital in the absence of coronary plaque. Additionally, emergency department presentations with acute chest pain syndromes are not infrequently related to noncardiac causes, making the use of cardiac CT in a "triple rule-out" fashion appealing for the exclusion of other significant pathologies, particularly pulmonary embolism and aortic dissection. Takakuwa et al. (4) demonstrated in their cohort that 11% of patients studied using a "triple rule-out" had an identifiable noncoronary source for their symptoms. Additionally, it is suggested that coronary CT in the emergency department setting may be more cost and time efficient when compared to standard functional assessments. While significant differences exist in costs across different institutions and countries and depending on the stress testing modality of choice, the CT-STAT trial (5) suggests that coronary CT may carry significant cost reductions and time savings when compared to current standard of care.

CTA Diagnostic Accuracy

Current international consensus guidelines, including both North American and European societies, suggest that cardiac CT has a role in the diagnosis and risk assessment of patients with low or intermediate risk for coronary artery disease; the assessment of coronary arterial graft patency; and the evaluation of suspected coronary anomalies (6, 7). Additionally, it is also useful in cardiac structural and functional evaluation. Cardiac CT has been studied extensively over the years with strong data to support its use in these settings.

Cardiac CT had been extensively evaluated against the current gold standard of conventional invasive coronary angiography across numerous single center and multicentre trials. Trials have recurrently shown that the absence or presence of mild coronary disease on coronary CT is associated with a very high negative predictive value for more significant disease. However, the positive predictive value of this technology is lower, resulting from overestimation of disease burden and positive vessel remodeling. A meta-analysis of 28 studies by Mowatt et al. (8) illustrated this, showing a pooled sensitivity of 99%, specificity of 89%, positive predictive value of 93%, and negative predictive value of 100%. These results were later confirmed by the larger multicenter trials: ACCURACY (9), CORE 64 (10) and that published by Meijboom et al. (11). These studied a total of 880 patients, again illustrating the test's high sensitivity (95%, 85% and 99%, respectively) and negative predictive value of (99%, 83% and 97%, respectively); while suffering from issues related to overestimating disease resulting in modest specificity (83%, 90% and 64%, respectively) and positive predictive values (64%, 91% and 86%, respectively) (9–11). These findings compare favorably with functional stress imaging studies which report sensitivities and specificities of 68% and 77%, respectively, for ECG stress testing; 80–85% and 84-86% for exercise stress echocardiography; 85–90% and 70–75% for exercise myocardial perfusion imaging; 40–100% and 62–100% for dobutamine stress echo; and 83–94% and 64–90% for vasodilator stress myocardial perfusion imaging (12) (Table 1).

Table 1.
Comparison of CT Coronary angiography with exercise ECG stress testing.

Author	Significant disease on invasive angiogram	CTCA sensitivity	CTCA specificity	CTCA PPV	CTCA NPV	EST sensitivity	EST specificity	EST PPV	EST NPV
Dewey *et al.*[25]	≥ 50% stenosis	91%	83%	98%	91%	73%	31%	67%	65%
Mollett *et al.*[26]	≥ 50% stenosis	100%	87%	96%	100%	78%	67%	89%	47%
Nieman *et al.*[27]	≥ 70% stenosis	96%	24%	34%	94%	80%	64%	53%	86%
Cademartiri *et al.*[28]	≥ 50% stenosis	100%	90%	97%	100%	89%	67%	88%	50%
Maffei *et al.*[29]	≥ 70% stenosis	96%	65%	74%	94%	47%	53%	51%	49%
Chinnaiyan *et al.*[23]	> 50% stenosis	93.7%	37%	70.6%	79.1%	69.4%	40.0%	62.5%	47.6%

CTCA , computed tomography coronary arteries; EST, exercise ECG stress test; PPV, positive predictive value; NPV, negative predictive value.

CTA Compared to other Noninvasive Imaging

Coronary CT carries advantages over echocardiographic stress imaging, as imaging is not limited to suitable acoustic windows and ultrasonographic tissue properties, which does not infrequently make imaging and test interpretation technically difficult. The disadvantages of coronary CT include an inability to provide physiological data, such as exercise capacity, heart rate and blood pressure response to exercise, which has been previously demonstrated to carry prognostic information in the setting of functional stress testing. This, however, makes coronary CT well suited to the assessment of patients who have a poorer functional capacity or other conditions which would limit their exertional tolerance, as this group frequently requires the administration of pharmacological stress agents with which such physiological parameters would be uninterpretable. Other limitations include artifact caused by coronary stents and significant coronary arterial calcification which can make luminal interpretation suboptimal, and this group of patients may be better assessed by functional stress imaging.

Coronary CT angiography has been compared to nuclear myocardial perfusion imaging (13, 14) to cardiac magnetic resonance (15, 16) and MR stress perfusion (17), to intravascular ultrasound (18, 19) and to stress echocardiography (20, 21). These tests, however, are answering different questions: CCTA provides information on coronary anatomy, plaque and stenosis; whereas stress nuclear/MR/echo provide information on myocardial perfusion. "Anatomy versus function" has been an ongoing debate in the cardiology literature for decades. The PROMISE trial (clinicaltrials.gov NCT01174550) is an NIH-sponsored multicenter comparative effectiveness trial enrolling 10,000 patients, and is expected to define the cost-effectiveness and prognostic value of anatomic assessment with CCTA versus functional assessment with conventional stress testing.

Direct comparison between coronary CT, stress imaging and invasive coronary angiography has primarily involved exercise stress with SPECT myocardial perfusion imaging. Exercise stress ECG has been demonstrated to be inferior to coronary CT across numerous studies, as illustrated in Table 1, with both poorer sensitivity and specificity. Comparative data for stress echocardiography demonstrated that coronary CT is more sensitive but less specific in the detection of hemodynamically significant lesions causing a >70% luminal stenosis, when compared to dobutamine stress echocardiography (91% vs. 70% and 74% vs. 84%, respectively) (22). Stress echocardiography, however, fared less well when a lower cut-off of >50% coronary stenosis was used at invasive angiography (sensitivity 93.7% vs. 40.8%, specificity 37.9% vs. 48.9%) (23). Coronary CT also compares favorably with myocardial perfusion imaging with improved sensitivity and specificity as illustrated in Table 2. Interestingly, in the study by Kajander et al. (24) comparing positron emission tomography (PET), myocardial perfusion imaging and coronary CT to invasive fractional flow reserve assessments, PET performed superiorly compared to other published studies using single-photon emission computed tomography (SPECT) scanning. In this

Table 2.
Comparison of CT coronary angiography with myocardial perfusion imaging.

Author	Significant disease on invasive angiogram	CTCA sensitivity	CTCA specificity	CTCA PPV	CTCA NPV	EST sensitivity	EST specificity	EST PPV	EST NPV
Schuijf *et al.*[30]	≥ 50% stenosis	100%	81%	82%	100%	59%	48%	55%	62%
Budoff *et al.*[31]	> 70% stenosis (or > 50% for left main stenosis)	94%	96%	92%	97%	81%	78%	89%	64%
Ravipati *et al.*[32]	≥ 50% stenosis	100%	73%	92%	100%	69%	36%	78%	27%
Hamirani *et al.*[33]	> 70% stenosis	89.7%	86.4%	92.1%	82.6%	57.7%	43.2%	64.3%	36.5%
Kajander *et al.*[24*]	≥ 50% stenosis with positive FFR testing	95%	87%	81%	97%	95%	91%	86%	97%
Chinnaiyan *et al.*[23]	> 50% stenosis	93.7%	37%	70.6%	79.1%	64.7%	29.4%	59.2%	34.5%

CTCA, computed tomography coronary arteries; MPI, myocardial perfusion imaging; PPV, positive predictive value; NPV, negative predictive value; FFR, fractional flow reserve.
*Positron emission tomography (PET) scanning used in this paper. All other cases used single-photon emission computed tomography (SPECT) scanning.

single trial, though both PET and coronary CT showed excellent negative predictive value, coronary CT was less useful in assessing the severity of coronary stenosis. Overall results for the multicenter ACIC registry (23), while subject to the biases of only evaluating abnormal noninvasive imaging tests with invasive angiography and assessing stenosis >50% on invasive angiography as hemodynamically significant, demonstrate superior sensitivity and specificity for coronary CT when compare to all forms of stress testing (60.4% and 34.2% vs. 93.7% and 37.9%, respectively).

Studies have also demonstrated additive benefit from combining the functional assessment provided by functional stressing testing with anatomical information provided by coronary CT (23, 24, 34–36). De Azevedo and colleagues (36) demonstrated that in patients with inconclusive stress tests, coronary CT could be used to further risk stratify patients: with those with no disease on coronary CT having an excellent long-term prognosis.

Function versus Anatomy

Newer CT perfusion techniques allow the combined assessment of anatomy and perfusion using coronary CT. Images are acquired early during first-pass circulation as contrast transits through the coronary arteries into the myocardium (37). Myocardial CT perfusion protocols comprise rest and stress phase acquisitions, utilizing vasodilators such as adenosine, regadenoson, or dipyridamole. Unlike myocardial perfusion scanning, the time between the acquisitions is short and contrast from the first acquisition may still be present within the myocardium during the second acquisition (37). Reduced myocardial perfusion is represented as hypoattenuated areas. CT perfusion scanning has been subject to numerous studies with comparisons made against various reference standards including myocardial perfusion imaging, magnetic resonance imaging with myocardial perfusion imaging, invasive angiography with myocardial perfusion imaging, and invasive fractional flow reserve assessment. These are well summarized in a review by Ko et al. (37), with CT perfusion having a sensitivity between 79% and 97% and specificity of 72% to 98%. Two studies, published by Bamberg et al. (38) and Ko et al. (39), have directly compared CT perfusion with invasive fractional flow reserve assessment. Bamberg et al. (38) reported a per-vessel sensitivity of 93%, specificity of 87%, positive predictive value of 75%, and negative predictive value of 96.7% when combination CT angiography and perfusion was used, with a radiation exposure of 12–13 mSv. Ko et al. (39) reported a per-vessel sensitivity of 76%, specificity of 84%, positive predictive value of 82%, and negative predictive value of 79% when CT perfusion was used alone. Specificity rose significantly when this was used together with CT angiography: with the combination of a ≥50% stenosis with associated perfusion defect were associated with 98% specificity for detection of myocardial ischemia, and <50% stenosis on CTA and normal perfusion being 100% specific for the exclusion of ischemia. The mean radiation dose for CT perfusion alone and combined CT angiography with perfusion was 5.3 and 11.3 mSv, respectively.

Further work has evaluated dynamic real-time (as opposed to static) CT stress perfusion myocardial imaging, with promising results (40). Dual-energy CT, harnessing the differential attenuation of iodine when exposed to beams of differing kV, also offers the ability to evaluate myocardial viability using computed tomography (16).

CTA and Prognosis

Prognostic implications of coronary CT findings have been definitively demonstrated in the large prospective CONFIRM registry (41) studying 23,854 patients across multiple centers, clearly demonstrating that no identifiable coronary artery disease on coronary CT is associated with an excellent long-term prognosis (annualized mortality 0.28%). Unsurprisingly, those with obstructive coronary disease were associated with a significantly worse prognosis with a 2.6 times higher risk of death, with long-term outcome inversely related to the number of coronary arteries demonstrating obstructive lesions. While similar data exist supporting the prognostic value of stress imaging (42), limited head-to-head comparison data exist comparing the prognostic value of coronary CT with stress imaging. Three such studies comparing coronary CT lesions of less than 50% severity with no evidence of inducible ischemia on myocardial perfusion imaging demonstrated an excellent long-term prognosis in both groups with no statistically significant difference in patient long-term outcomes (43–45). However, the CONFIRM registry (41) also demonstrated that those patients with mild nonobstructive coronary disease carried a worse prognosis than those with normal coronaries, with a 1.6 times higher mortality risk. This group would not otherwise be identifiable on stress imaging and may highlight a role for coronary CT in the further risk stratification of lower risk groups. While no data is currently available directly demonstrating the value of treating this mild coronary disease identified on coronary CT, it is conceivable from available primary prevention data that the early treatment of this cohort of patient may be associated with improved longer term prognosis.

Radiation

Concerns exist over patient radiation exposure in all forms of medical imaging (46). Retrospective-ECG gated coronary CT acquisitions have previously been associated with an effective radiation dose of 12.5 ± 5.6 mSv, which are comparable to those found using SPECT myocardial perfusion imaging with effective radiation doses of 7.2–17.6 mSv (47, 48). However, current techniques including tube modulation and prospective ECG gating have resulted in significant decreases in the effective radiation dose without reduction in image quality, as demonstrated in the PROTECTION I, II, and III trials (49–52). Tube-current modulation allows for a reduction in the tube current and radiation exposure during systole, where cardiac motion would otherwise prevent successful coronary arteries reconstruction. The use of this technique reduces the effective dose by 33% for retrospective acquisitions (47). Prospective-gated acquisitions are useful in those patients with regular and slow heart rates, allowing imaging to be performed in diastole alone with the tube switched off in between acquisitions, also known as a "step and shoot" acquisition. This allows mean effective radiation doses to be reduced to just 3.4 ± 1.4 mSv, which is considerably less than achievable with myocardial SPECT imaging (47, 52). Newer technologies such as dual-source high-pitch and broad detector (256- and 320-slice scanners) enable the entire heart to be imaged in a single heartbeat. This allows for further improvements in radiation dose while maintaining diagnostic imaging quality (53–55).

Conclusion

Coronary CT angiography has a significant role to play in the assessment of chest pain syndromes. It is both a useful standalone investigation and can be complementary to information provided by stress imaging, particularly in the noninvasive diagnosis of atheroslerosis. Coronary CT is particularly useful in patients with low or intermediate risk of coronary artery disease. In this group of patients where coronary CT is likely to demonstrate normal coronaries or mild disease, anatomical assessment with coronary CT provides patients with definitive confirmation of the absence of flow limiting coronary disease with high negative predictive values. It allows the identification of mild disease, which may otherwise be missed on stress imaging due to the lack of hemodynamic significance, so as to allow the earlier implementation of aggressive risk factor modification with the hope of altering longer term prognosis. As with all technologies, technical limitations do nonetheless exist and users need to be aware of these in order to ensure the appropriate and optimal use of available techniques. Further data, especially the "PROMISE" trial, will clarify the role of anatomic versus functional imaging in the patient presenting with chest pain.

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