Computed tomography coronary angiography : from quantification of coronary atherosclerosis to risk stratification of patients

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Chapter 2

Computed tomography angiography and other applications of CT

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Abstract

Patients presenting with acute chest pain constitute a common and important diagnostic challenge. This has increased interest in using computed tomography (CT) for non-invasive visualization of coronary artery disease in patients presenting with acute chest pain to the emergency department; particularly the subset of patients who are suspect of having an acute coronary syndrome, but without typical ECG changes and normal troponin levels at presentation. As a result of the rapid developments in coronary CT angiography technology, high diagnostic accuracies for excluding coronary artery disease can be obtained. It has been shown that these patients can be discharged safely. The accuracy for detecting a significant coronary artery stenosis is also high, but the presence of coronary artery atherosclerosis or stenosis does not necessarily imply that the cause of the chest pain is related to coronary artery disease. Moreover, the non-invasive detection of coronary artery disease by CT has been shown to relate with an increased use of subsequent invasive coronary angiography and revascularization, and further studies are needed to define which patients benefit from invasive evaluation following coronary CT angiography. Conversely, the implementation of coronary CT angiography can significantly reduce the length of hospital stay, with a significant cost reduction.

Additionally, CT is an excellent modality in patients whose symptoms suggest other causes of acute chest pain such as aortic aneurysm, aortic dissection, or pulmonary embolism. Furthermore, acquisition of the coronary arteries, thoracic aorta, and pulmonary arteries in a single CT examination is feasible, allowing ‘triple rule-out’ (exclusion of aortic dissection, pulmonary embolism and coronary artery disease). Finally, other applications such as the evaluation of coronary artery plaque composition, myocardial function and perfusion or fractional flow reserve are currently being developed and may also become valuable in the setting of acute chest pain in the future.

Introduction

The present chapter is an update of the previous book chapter.[1] Those parts on which new literature is available have been updated, whereas other parts have been inserted unchanged. Since the introduction of CT in the early 1970s the technique has evolved into an essential imaging tool in general medicine. With this technique, non-invasive high resolution cross-sectional imaging of internal structures such as the brain, thorax and abdomen was permitted, thereby gradually replacing the more invasive radiographic techniques.[2] Moreover, CT angiography has evolved as a very accurate tool for visualization of the aorta and pulmonary arteries. However, high-quality imaging of the coronary arteries remained challenging because of their small vessel size, movement, and tortuous anatomy requiring high temporal, spatial and contrast resolution. In the late 1990s, the first 4-slice spiral CT scanner was developed with sufficient resolution to allow visualization of the coronary arteries, establishing the potential of multi-slice CT for detecting significant coronary artery stenosis in comparison to invasive coronary angiography (ICA).[3-5] Since then, multi-slice CT coronary angiography has developed into a promising non-invasive alternative to ICA. With each successive generation of scanners from 4-slice to the present 64-, 256- and 320- slice scanners, temporal and spatial resolution improved markedly due to faster gantry rotation times, thinner detectors, and volumetric coverage. These new developments currently allow motion-free visualization of the entire coronary artery tree with high diagnostic accuracy for detecting coronary artery stenosis.[6, 7] Thanks to these rapid developments, interest has been raised in using CT for the evaluation of patients presenting with acute chest pain. In the intensive cardiac care unit (ICCU), acute chest pain is the most common clinical presentation of coronary artery disease (CAD). The diagnosis of acute coronary syndrome (ACS) is straightforward in high risk patients with typical chest pain, typical ECG changes, and elevation of serum cardiac markers (enzymes), whereas it is difficult in patients presenting with atypical chest pain, non-diagnostic or normal ECG, and normal markers on presentation. Indeed, up to 8 % of patients with ACS are misdiagnosed and inappropriately discharged home.[8] Conversely, only a minority of 'low risk' patients (i.e. those with initially normal ECGs and cardiac enzymes) actually suffer from myocardial ischemia.[9] Therefore, the conventional approach for patients with acute chest pain leads to many unnecessary hospital admissions and is both time-consuming and expensive and thus, resource-intensive. Therefore, a non-invasive and rapid examination to establish or exclude CAD as the underlying cause of symptoms could substantially improve the clinical care of patients admitted to the ICCU, reducing hospital admissions and costs. This chapter focuses on the evolving role of coronary CT angiography (CTA) (including coronary artery calcium (CAC) scoring) in the diagnosis of patients presenting with acute chest pain. An overview of a wide range of other CT applications is also provided, including triple rule-out, evaluation of plaque composition, myocardial function, and perfusion.

CT coronary angiography: patient preparation, acquisition, post-processing

CT is an imaging modality which has an X-ray source (tube) and detectors on opposite sides of a gantry that continuously rotates around the patient. During the CT scan the patient is moved through the gantry. Subsequently, the X-ray source emits photons collimated into a fan beam which are, after partial absorption and dispersion, reabsorbed by the detectors. Computer systems process these data into three-dimensional (3D) volumetric information, which can be transferred to CT workstations and evaluated using multiple post-processing techniques.

Patient preparation

Proper patient preparation is important for obtaining diagnostic image quality. Therefore, before referring a patient for coronary CTA, a short patient history should be obtained. Overall, a history of a severe allergic reaction to contrast agents, impaired renal function (glomerular filtration rate <30 mL/min), presence of atrial fibrillation, and pregnancy are considered contraindications. The patient should refrain from food and liquids preferably 3 hours before the examination, to prevent nausea as a reaction to the contrast agent. Moreover, a low and stable heart rate in the range of approximately 50–60 beats/min is preferred during image acquisition. To achieve a low and stable heart rate, a β-blocker is frequently administered prior to the examination, unless contraindicated. Preferably, sublingual nitrates (0.4mg) are administered to the patient. The resulting vasodilatation facilitates the assessment of small coronary arteries.[10] Lastly, to ensure rapid delivery of the contrast agent bolus for coronary CTA, an intravenous catheter should be present for delivery of the contrast agent, preferably in the right antecubital vein (18–20 gauge).

Acquisition

The scan range of the current 64-slice scanners is not large enough to cover the entire heart in one rotation and therefore several heart cycles are needed to image the entire heart. To compensate for cardiac motion and synchronize the start of the systole, ECG gating is needed to obtain phase-compatible images. Currently, the majority of cardiac CTs are acquired using prospective triggering, in which the start of scanning is triggered by the preceding R-wave. Most often the scan is triggered in the relatively motion-free phase of mid diastole (70–80 % of the R–R interval) to minimize motion artefacts. Depending on the scanner type, imaging can be performed in helical ('spiral') mode with continuous table movement and modulated acquisition, or in step-and-shoot mode with multiple volumetric acquisitions reconstructed into a single data set. A wide-volume detector allows full cardiac acquisition in a single gantry rotation, e.g. a 256- or 320-detector-row scanner that allows a maximum of 16 cm scan range in a single rotation.[11, 12] Novel dual-source CT scanners, equipped with two X-ray tubes and two detectors at a 90 degree angle provide high temporal resolution. As a result, these scanners are able to produce images of high quality in patients with high heart rates. Besides, with these 64-slice dual-source CT scanners, using a high-pitch spiral technique, the entire heart can be depicted in one cardiac cycle with ultra-low radiation dose (<1mSv).[13]

For CAC scoring, a low-dose ECG triggered non-contrast-enhanced scan is performed before the contrast-enhanced CT examination and reconstructed to 3-mm slices. Additionally, this scan can be used to determine the proper location and scan range for coronary CT imaging. For a regular CTA, a rapid infusion of 60–100 mL of contrast material with a flow rate of 5 mL/s is used, followed by a saline flush. Typical scan parameters are a pitch of 0.375, rotation time of 333–500 ms, tube voltage of 100 or 120 kV and tube current of 300-500 mA (depending on body mass index). However, with novel iterative reconstruction algorithms, lower radiation exposure can be achieved by lowering tube voltage and current with preserved image quality. When using a bolus-triggered start of the CT scan, the start is automatically initiated if the preset contrast-enhancement threshold level in the descending aorta is reached. Alternatively, a test bolus injection can be used to determine the contrast transit time. Subsequently, data acquisition is performed at half-inspiratory breath hold of approximately 10 s.

Post-processing

After data acquisition, images are reconstructed and sent to a dedicated workstation for post-processing. Commonly, coronary CTA data sets are reconstructed with continuous images using thin increments (typically 0.5–0.6 mm slice thickness). For post-processing, various types of algorithms are available.

- The thin axial slices, as depicted in Figure 1, are considered the source information of CT imaging. Accordingly, the cardiac structures and coronary arteries can easily be evaluated by scrolling through the images in axial direction.
- Curved multiplanar reconstructions (MPR) allow visualization of the entire coronary artery in a single image which is useful for depicting the entire coronary lumen and evaluating degree of stenosis.

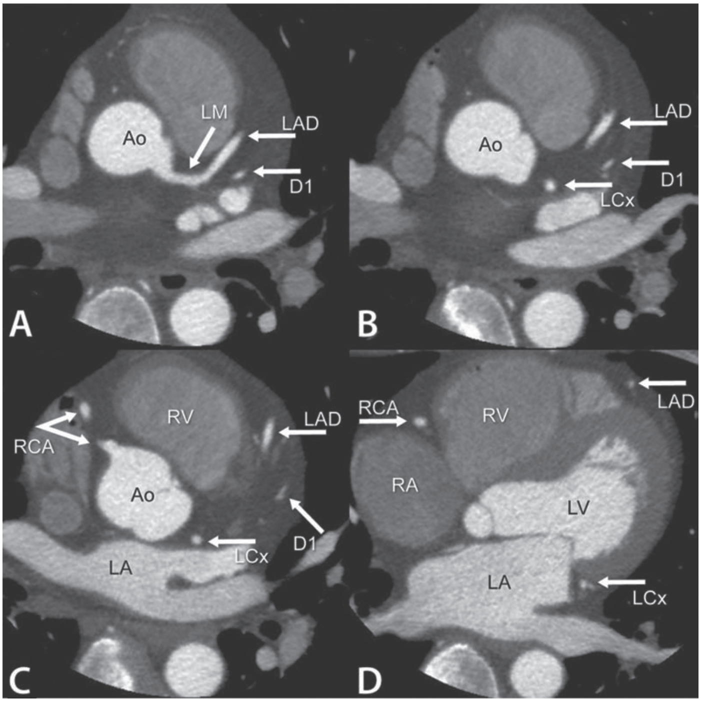

Figure 1. Typical example of axial contrast-enhanced images.
This image with a 0.5-mm slice thickness, can be used to evaluate cardiac structures (such as the left ventricle (LV), left atrium (LA), right ventricle (RV), and aorta (Ao)) and coronary arteries by scrolling through the slices in the cranio-caudal direction. Four images have been selected to demonstrate the anatomy of the heart. A. Axial image showing the left main (LM) coronary artery at the level of the ostium which arises from the left coronary cusp and bifurcates first into the left anterior descending coronary artery (LAD). B. Slightly more distal axial image showing the left circumflex coronary artery (LCx) and the first diagonal branch (D1) which has originated from the LAD. C. Axial image demonstrating the origin of the right coronary artery (RCA) from the right coronary cusp and the mid segments of the LCx, LAD, and D1. (D) Axial image at midventricular level which shows the mid segment of the right coronary artery (RCA) and distal segments of the LAD and LCx (the latter is seen in the left atrioventricular groove).

- Maximum intensity projections (MIP) can be reconstructed which represent a series of contiguous CT slices stacked into a single image ('slab'). Moreover, MIPs are very suitable for assessment of longer length of vessel segments and may facilitate in evaluating the degree of stenosis.
- 3D volume rendering provides a 3D image of the heart and vessels. An excellent overview of the coronary anatomy is provided, although 3D volume rendering is generally not used for assessing the stenosis severity. Figure 2 provides an example of a 3D volume rendered image.

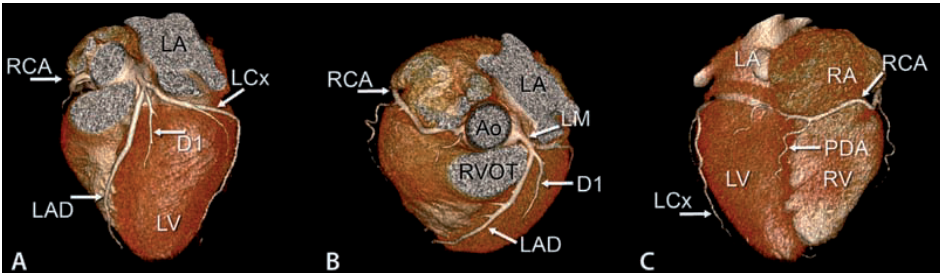

Figure 2. Surface-rendered volumetric 3D images of the coronary arteries and side branches. This type of image provides a 3D overview of the coronary artery tree and their relative position to the underlying cardiac structures, including the left ventricle (LV) and right ventricle (RV). A. Anterior view of the left circulation demonstrating the left anterior descending coronary artery (LAD) with first diagonal branch (D1). In addition, the left circumflex coronary artery (LCx) can be identified. The left atrium (LA), aorta (Ao), and right ventricular outflow tract (RVOT) can be also appreciated in this view.B. Cranial view demonstrating a volume-rendered image of right coronary artery (RCA) and left main coronary artery (LM) and their main branches originating from the right and left coronary cusp, respectively. C. Posterior view of the RCA and the posterior descending coronary artery (PDA).

Interpretation of coronary artery disease on coronary CT angiography

A systematic approach is important when evaluating a coronary CTA. If CAC scoring has been performed, the Agatston score is reported on a patient and vessel basis. Thereafter, the coronary CTA is interpreted to assess coronary atherosclerosis and stenosis severity. In addition to the analysis of the coronary arteries, the entire scan range should be examined to detect potential extra-cardiac findings.

Coronary artery calcium score

For quantification of the coronary calcifications, the Agatston method (a method that multiplies the calcified area by a density factor based on the highest Hounsfield values within this area) is routinely used.[14] Total CAC scores are generally stratified into normal (zero calcium), mild (1–100), moderate (101–400), and severe (> 400).[15] Several population based studies have demonstrated that the CAC score increases with higher age, thereby reflecting the natural progression of atherosclerosis. In addition, men tend to have higher CAC scores than women of similar age. Therefore, the CAC score should be ranked in percentiles according to the distribution within age and gender[16, 17] Although newer quantification methods have been introduced (calcified volume (mm^3) and mass (mg) measurements), these metrics are not commonly used in clinical practice.[18] With novel algorithms the quantification of CAC on contrast enhanced scans is feasible.[19] However, these techniques are currently not used in clinical practice.

Coronary CT angiography

With regard to the coronary CTA, the quality of the scan should be mentioned as this influences the diagnostic certainty of the study. Findings are commonly reported similar to the reporting of invasive coronary angiography (ICA). Typically, each coronary segment of the American Heart Association 17-segment model[20] is described as normal, mild (<30% wall irregularities), non-significant (30–50% stenosis), significant (>50% stenosis), severe stenosis (> 70%), and occlusion. In addition to stenosis severity, the plaque composition of each lesion should be described as non-calcified, calcified, or mixed (i.e. a combination of calcified and non-calcified plaque). Presence and patency of stents and bypasses are reported, if evaluable. Segments that are uninterpretable due to severe calcifications, motion, or breathing artefacts should be mentioned as such in the report.

Extra-cardiac findings

Beyond evaluating the coronary arteries, other cardiac findings and/or extra-cardiac findings may be identified during coronary CTA. Interestingly, extra-cardiac findings provide an explanation for chest pain complaints in 4–8% of patients or may be incidental findings not related to chest complaints.[21, 22] Clinically important findings that require immediate therapy, intervention, additional diagnosis, or follow-up are reported in approximately 13% of cardiac CT examinations.[23, 24] These include suspected malignancy which may necessitate immediate therapeutic actions, or the presence of acute pulmonary embolism or pneumonia.[21, 25-27] Incidental lung cancers are found in 0.24% of patients.[23] For coronary artery assessment, a zoomed-in small field of view focused on the heart is reconstructed to obtain maximal spatial resolution for evaluation. However, this focused view reveals only 36% of the total chest volume, whereas 70% of the total chest volume has been exposed to radiation.[27] Substantially more significant extra-cardiac pathology is found on maximum full-field reconstructions than on small-field reconstructions.[23] Therefore the maximum full-field reconstructions should be reviewed for optimal identification of extra-cardiac pathology.[21, 23, 25, 27, 28]

Patients with non-acute chest pain

Coronary artery calcium score

It has been widely verified that the presence of coronary artery calcification only occurs in the presence of coronary artery atherosclerosis.[29] Both electron beam CT (EBCT) and multi-slice CT have been used over the past years for the noninvasive evaluation of coronary artery calcifications, both demonstrating high sensitivities for the detection of CAD indicating that a large proportion of patients with CAD are accurately detected by CAC scoring.[17, 30] The relation between the presence of obstructive CAD and the presence and extent of CAC has been extensively studied.[31] The CAC score has a high sensitivity and negative predictive value for the presence of obstructive CAD, but its specificity is limited.[31, 32] The high negative predictive value indicates that patients without CAC virtually never have obstructive CAD. In contrast, the lower specificity indicates that patients without obstructive CAD still often present with CAC. For instance, Haberl *et al.* evaluated 1,764 patients who underwent both EBCT (CAC score) and ICA. The absence of CAC was associated with an extremely low probability of disease (<1%) and thus highly accurate to exclude obstructive CAD. However, specificity was only 23% in men and 40% in women. Therefore, the technique may be more suited to provide an estimate of total plaque burden rather than stenosis severity.

Furthermore, numerous investigations have shown that the extent of CAC provides prognostic information. CAC scoring has therefore been proposed as a tool for cardiac risk stratification. Several large trials have reported that elevated CAC scores have predictive value for cardiovascular events, both independently and incrementally to cardiovascular risk factors.[33, 34] Budoff *et al.* assessed the prognostic value of CAC scoring in 25,253 asymptomatic individuals over a mean follow-up period of 6.8 years. The survival of individuals without CAC was excellent (99.6%), with a gradual reduction in survival rates with increasing CAC score.[33]

Coronary CT angiography

With the current generation 64-slice CT scanners, with improved temporal and spatial resolution, a good diagnostic accuracy for detection of obstructive CAD has been reported, both for the proximal as well as the distal part of the coronary arteries. In comparison with ICA, a high sensitivity (85–99%) and high specificity (83–90%) has been reported for the detection of obstructive stenoses.[6, 7] More importantly, as demonstrated by the high negative predictive value, coronary CTA is an excellent tool to exclude significant CAD. This implies that in the presence of normal coronary arteries on coronary CTA, no further testing is required and patients can be reassured. The positive predictive value however, is lower (64–93%), and the severity of atherosclerotic lesions is frequently overestimated on coronary CTA.

Recently, new low-radiation-dose algorithms have been introduced, which resulted in a significant reduction in radiation, A meta-analysis of these studies confirmed the diagnostic accuracy[35]; pooled data from 15 studies (with varying novel CT scanners) included 960 patients, reported a sensitivity of 100% with a specificity of 89%. The NPV was 99%, with a PPV of 93%, indicating overestimation of stenosis severity in 7% of patients. Moreover, the diagnostic performance of coronary CTA is influenced by the pretest likelihood of obstructive CAD. Indeed, as shown in Table 1, the benefit from CT is highest in patients with a low to intermediate pretest likelihood for CAD due to the high accuracy to exclude obstructive CAD.[36]

In line with these observations, Henneman *et al.* demonstrated that coronary CTA was able to exclude coronary artery atherosclerosis in 58% of patients with low pretest likelihood of CAD, with no need for further routine visits to the outpatient clinic.[37] Conversely, coronary CTA demonstrated atherosclerosis and/or stenosis in 83% of patients with a high pretest likelihood of CAD. These patients may thus benefit more from non-invasive testing for ischemia and/or direct ICA with fractional flow reserve assessment, to determine optimal therapy (medical management or revascularization. Indeed the recent European Society of Cardiology guidelines for stable CAD indicate that coronary CTA is particularly useful in patients with low-intermediate pretest likelihood of CAD (recommendation class IIa).[38]

In addition to the diagnostic value, coronary CTA provides prognostic information. Chow *et al.* reported in the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes) registry (with 14,064 patients in 12 different centers) that a normal coronary CTA was associated with an annual mortality rate of 0.65% over a mean follow-up of 22.5 months (Figure 3).[39] Conversely, patients with obstructive CAD had an annual mortality rate of 2.9%, which increased to almost 5% in patients with 3-vessel, left-main and or proximal LAD disease. It is important to realize that the annual mortality in the CONFIRM registry was only 1.1%, indicating a relatively low risk population.

A recent meta-analysis by Bamberg *et al.* focused on the prognostic value of coronary CTA, and included 9 studies with 3,760 patients with an average follow-up varying from 14 to 78 months.[40]

The overall event rate was 6.8%, but it should be noted that two-third of the events were coronary revascularizations. (Early) Revascularization is not an ideal end-point since the findings on coronary CTA may have triggered the revascularization. Patients with a normal coronary CTA had an event rate of 0.4%. Patients with obstructive CAD had a 6-fold increased risk for death, infarction or ACS. Importantly, a significant

Table 1. Diagnostic accuracy of 64-slice coronary CT angiography for detection of significant stenosis (≥ 50%) categorized according to pretest probability.

Pretest probability	N	Sens(%)	Spec(%)	PPV(%)	NPV(%)
Low	66	100	93	78	100
Intermediate	83	100	84	80	100
High	105	98	74	93	89

Data adapted from Meijboom *et al.*[36]

Abbreviations: NPV: negative predictive value, Sens: sensitivity, Spec: specificity, PPV: positive predictive value

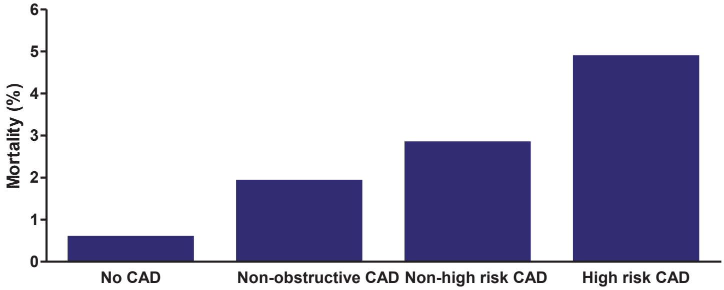

Figure 3. Bar graph illustrating the prognostic value of coronary CTA for the prediction of all-cause mortality.
Non-obstructive CAD was defined as <50% stenosis, non-high risk CAD was defined as ≥50% stenosis and high risk CAD included left main stenosis (≥50%) or 3-vessel disease (≥70%) or 2-vessel disease (≥70%) including the proximal left anterior descending artery.
CAD: coronary artery disease
Adapted from Chow, Circulation Cardiovascular Imaging 2011

stenosis on coronary CTA remained predictive of events after correction for CAC score and cardiovascular risk factors.

Patients with suspected acute coronary syndrome

Coronary artery calcium score

The prognostic value of the CAC score has been widely established in patients with stable angina, but some studies evaluated the use of CAC score in patients with acute chest pain. Earlier studies with EBCT reported a high negative predictive value of the CAC score, demonstrating that patients with a CAC score of 0 had an excellent prognosis.[41-43] Georgiou *et al.* reported in 192 patients with acute chest pain that the absence of coronary artery calcifications had a very low risk for future cardiac events (<1%), whereas the presence of CAC was a strong predictor of events[41]. More recently, Nabi and co-workers reported on the use of CAC score in 1031 patients with acute chest pain using 16-slice CT.[44] In the 625 (61%) patients with zero CAC score, the cardiac event rate was <1%, whereas the event rate increased in parallel with an increasing CAC score. The various prognostic studies using CAC score in patients with acute chest pain and/or suspected ACS are summarized in Table 2. The results of six studies, with a total of 3035 patients were included in the pooled analysis.[45] In total, 62% of patients with acute chest pain or suspected ACS presented with a CAC score of 0 (indicating relatively low risk populations). However, there was a large variation in incidence of CAC score of zero between studies, ranging from 36%

Table 2. Diagnostic accuracy of a coronary artery calcium score of 0 for the prediction of acute coronary syndrome or events.

Author	N	No. (%) CAC=0	Follow-up	Sens(%)	Spec(%)	PPV(%)	NPV(%)
Chang et al[48]	1047	795 (76)	Prospective, 30 days	67	77	4	99
Georgiou et al[41]	192	76 (40)	Prospective, 50 ± 10 months	97	64	48	97
Hoffman et al[51]	368	197 (54)	Prospective, 6 months	97	58	18	99
Laudon et al[42]	263	133 (51)	Prospective, 6 months	97	57	23	99
McLaughlin et al[43]	134	48 (36)	Prospective, 30 days	88	37	8	98
Nabi et al[44]	1031	625 (61)	Prospective, 6 months	94	62	7	99
Pooled *	3035	1874(62)	-	93	65	14	99

*Data adapted from Tota-Maharaj *et al.*[45]

Abbreviations: CAC: coronary artery calcium, NPV: negative predictive value, Sens: sensitivity, Spec: specificity, PPV: positive predictive value

to 76%. The pooled analysis demonstrated a negative predictive value of 99% for the occurrence of future events. In contrast, the positive predictive value was only 14%. The long-term prognostic value of CAC score patients with suspected ACS has also been evaluated. Forouzandeh and colleagues acquired long-term follow-up data (median 3.3 years) in 760 patients presenting with acute chest pain who underwent 16-slice CT.[46] Events occurred in 45 (6%) patients; the long-term event rate was 0.4% in patients without CAC, and increased to 11% in patients with a CAC score >400. Although a CAC score of zero has been associated with an excellent prognosis, it has simultaneously been observed that patients with ACS or acute infarction can present without CAC in the culprit vessel[47]. Thus, particularly in the acute setting, the absence of CAC may not always imply the absence of atherosclerotic plaque. This was demonstrated by Chang *et al* showing that obstructive atherosclerosis was present in 17 of 795 (2%) patients with a suspected ACS and CAC 0. [48] In addition, 12% of the patients with a CAC 0 had non-obstructive CAD. Accordingly, Biegel *et al.* performed coronary CTA in 785 consecutive patients with acute chest pain.[49] Of the 255 patients with CAC score 0, significant CAD was observed on ICA in 2.7% of patients. Figure 4 provides an example of a patient with an obstructive non-calcified plaque despite a CAC score of zero.

Coronary CT angiography

Previous studies have demonstrated that coronary CTA has a high sensitivity and specificity for the detection of CAD compared to ICA in patient with stable CAD. More importantly, due to the high negative predictive value, coronary CTA can reliably exclude significant CAD, which is of potential value in patients presenting with

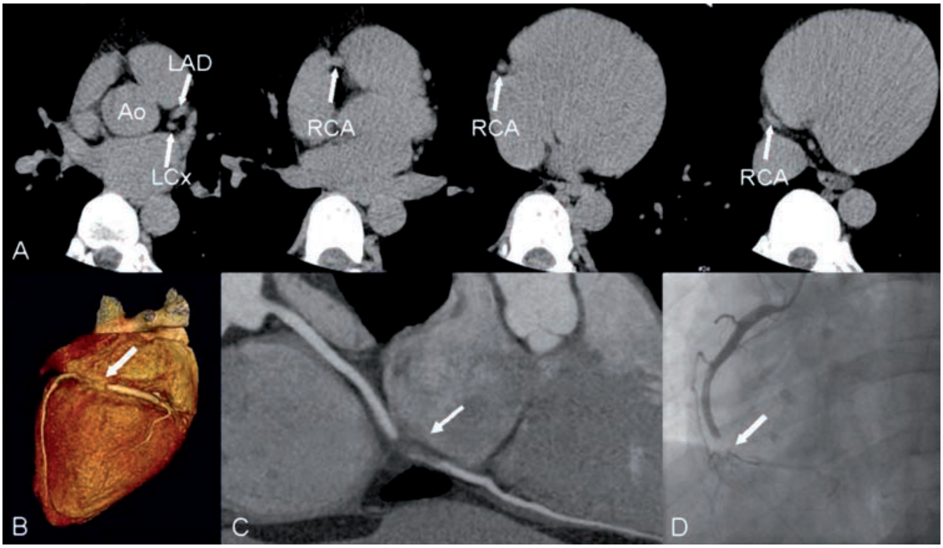

Figure 4. Example of a patient presenting with suspected ACS.
In this patient coronary artery calcium (CAC) scoring and contrast-enhanced coronary CT angiography were performed to exclude CAD. Although the CAC score was zero (A), an obstructive non-calcified plaque with a superimposed thrombus in the right coronary artery (RCA) was detected on coronary CT angiography (B, C). The volume-rendered 3D reconstruction (B) and curved multi-planar reconstruction (C) show an occlusion in the mid segment of the RCA (white arrows). (D) This finding was confirmed on invasive coronary angiography (white arrow). Ao, aorta; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery. From Henneman MM, Schuijf JD, Pundziute G, *et al.* Noninvasive evaluation with multislice computed tomography in suspected acute coronary syndrome: plaque morphology on multislice computed tomography versus CAC score. *J Am Coll Cardiol* 2008; **52** (3):216–222, with permission.

suspected ACS in the emergency room, but without specific ECG abnormalities and serum troponin levels in the normal range on admission. Limited studies are available that assess the diagnostic value of coronary CTA for the detection of significant CAD compared to ICA in patients presenting with suspected ACS. Meijboom *et al.* evaluated 104 patients with non-ST elevation ACS using 64-slice CTA compared with ICA.[36] In total 88 patients (85%) presented with significant CAD on ICA. Reported sensitivity and specificity of coronary CTA for detecting or excluding significant coronary artery stenosis were 100% and 75% respectively. Figure 5 shows an example of a patient presenting with suspected ACS with a significant stenosis in the RCA. More importantly, several investigations have addressed the predictive value of coronary CTA for the detection of ACS in patients with acute chest pain. Table 3 demonstrates the diagnostic accuracy of coronary CTA for the detection of ACS. In the most of these studies ACS is defined as either acute myocardial infarction or unstable angina pectoris according to the ACC/AHA-criteria[50], preferably with evidence of myocardial

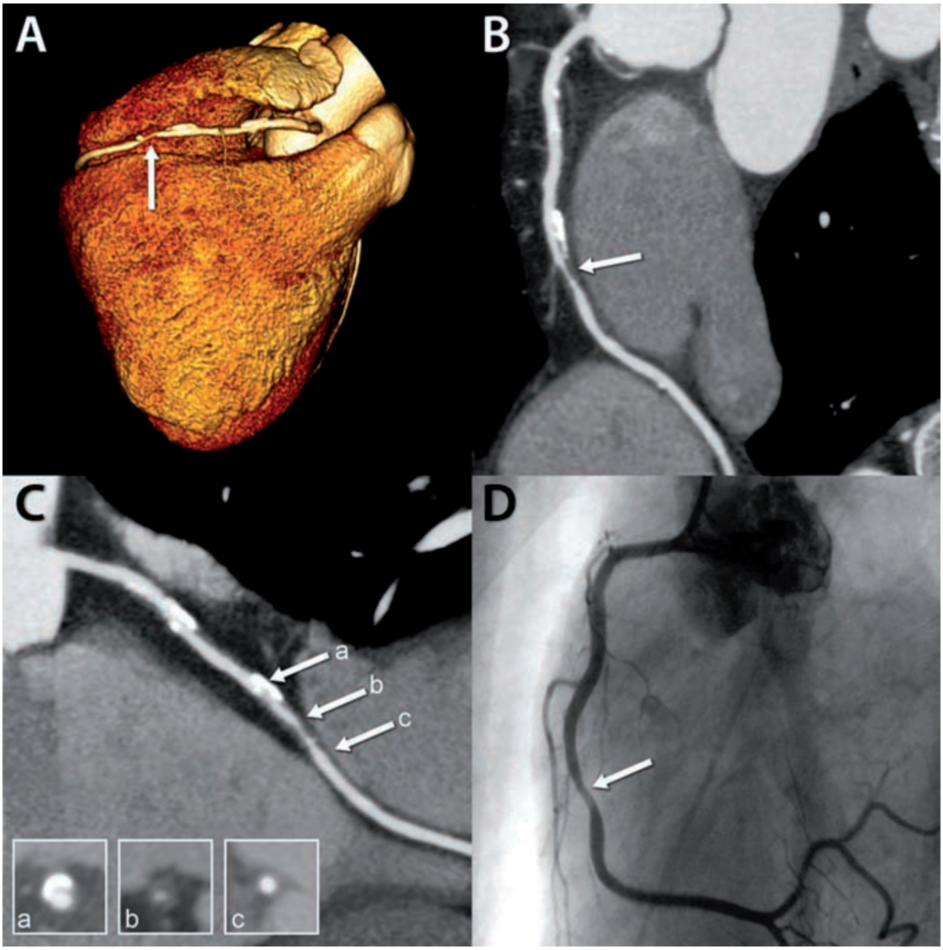

Figure 5. Example of non-invasive coronary angiography with CT in a patient presenting with suspected ACS.
In (A), a 3D volume-rendered reconstruction is provided, showing a large dominant right coronary artery (RCA) with signs of luminal narrowing (white arrow). B. A curved multiplanar reconstruction (MPR) of the RCA is shown demonstrating the presence of significant luminal narrowing in the mid segment (arrow). C. Another curved MPR in a different view, revealing the presence of significant stenosis (arrows). Cross-sectional CT images (inlays) show the presence of calcified plaque proximal to the stenosis (a), exclusively non-calcified plaque within the stenosis (b), and no coronary plaque distal from the stenosis (c). D. Conventional coronary angiography confirming the presence of significant luminal narrowing of the RCA (arrow).

ischemia on functional testing.[51] In the ROMICAT I study, 368 patients presenting with chest pain and possible ACS (but normal initial troponin and non-ischemic ECG) underwent 64-slice CTA.[51] Of these 368 patients, 8% eventually developed an ACS according to the definition described above. On 64-slice CT, 183 did not have any coronary atherosclerosis (no CAD), whereas 117 had non-obstructive coronary artery

Table 3. Diagnostic accuracy of CTA for the detection of acute coronary syndrome.

Author	N	Pre-test probability	% ACS	% patients negative CTA	Definition ACS	Sens(%) (TP/(TP+FN))	Spec(%) (TN/(TN+FP))	PPV(%) (TP/(TP+FP)	NPV(%) (TN(TN+FN)
White *et al.* [69]	69	Low - high	17	82	Clinical	83 (10/12)	96 (55/57)	83 (10/12)	96 (55/57)
				86	Clinical				
Gallagher *et al.*[103]	85	Low	8			86 (6/7)	92 (72/78)	50 (6/12)	99 (72/73)
Hoffman *et al.* [104]	40	All	13	65	Clinical	100 (5/5)	74 (26/35)	38 (5/14)	100 (26/26)
Hoffman *et al.*[105]	103	Low	14	71	Clinical	100 (14/14)	82 (73/89)	47 (14/30)	100 (73/73)
Olivetti *et al.*[106]	31	Low- Intermediate	58	52	ICA	83 (15/18)	100 (13/13)	100 (15/15)	81 (13/16)
Sato *et al.*[107]	31	Low	71	29	Clinical	95 (21/22)	89 (8/9)	95 (21/22)	89 (8/9)
Goldstein *et al.* [54]	99	Low	8	89	Clinical	100 (8/8)	97 (88/91)	73 (8/11)	100 (88/88)
Meijboom *et al.* [36]	33	Low^{+}	85	12	ICA	100 (28/28)	75 (4/5)	96 (28/29)	100 (4/4)
Rubinshtein *et al.*[108]	58	Intermediate	34	60	Clinical	100 (20/20)	92 (35/38)	87 (20/23)	100 (35/35)
Hoffman *et al.*[51]	368	Low	8	82	Clinical	77 (24/31)	84 (293/337)	35 (24/68)	98 (293/300)
Meta-analysis *	917	-	16	72	-	92 (151/165)	89 (667/752)	64 (151/236)	98 (667/681)

$^{+}$ Only a portion of patients with low risk were included in this meta-analysis

* Meta-analysis adapted from Vanhoenacker *et al.*[109].

Abbreviations: ACS: acute coronary syndrome, FN: false negative, FP: false positive, ICA: invasive coronary angiography, NPV: negative predictive value, Sens: sensitivity, Spec: specificity, TN: true negative, TP: true positive, PPV: positive predictive value stenoses. Of these 300 patients, only 7 (2%) were diagnosed with ACS, yielding a NPV of 98%. Conversely, 68 patients had obstructive CAD on CTA, and 24 developed an ACS; accordingly the PPV was 35%. Similarly, Gallagher *et al.* evaluated 85 patients with suspected ACS using 64-slice CTA; 73 patients had non-obstructive or no CAD on the CT scan and 1 of these developed an ACS, resulting in a NPV of 99%. On the other hand, 6 of the 12 patients with obstructive CAD on the CT scan developed an ACS, yielding a PPV of 50%. Meta-analysis combining the results of 10 studies with a total of 917 patients confirmed a NPV of 98%, with a lower PPV of 64%. The high NPV permits rule out of future development of ACS. In contrast, significant CAD on coronary CTA has lower predictive value for the development of ACS. These observations indicate that absence of significant CAD on coronary CTA can rule out development of ACS, but the presence of significant CAD does not indicate that these patients will always develop an ACS.

In addition, coronary CTA has been used for prediction of short- and long-term outcome of patients presenting to the emergency room with suspected ACS. In the ROMICAT I study, none of the 300 patients with a 'negative coronary CTA' (defined as no coronary atherosclerosis or non-obstructive CAD) experienced a subsequent cardiovascular event during a 6 months follow-up period.[51] Based on these initial observations, subsequent studies have focused on the potential implementation of coronary CTA in management of patients presenting to the emergency room with suspected ACS (but with normal troponins and non-ischemic ECG). For example, Lit *et al.* performed a randomized controlled trial (RCT) in 1370 patients with suspected ACS.[52] Patients were randomized to either CTA or standard care. Of the 908 patients referred for CTA, 640 (70%) had a negative CTA (no atherosclerosis or non-significant CAD). These patients were discharged, and none of these patients died, or presented with myocardial infarction within the next 30 days.

At present, four large RCTs have been conducted to assess the value of a CTA-based strategy compared to standard care. The results of these four trials have been pooled in a meta-analysis by Hulten *et al.*[53] This meta-analysis analysis included the results of 1,869 patients undergoing coronary CTA and 1,397 patients receiving standard care. Of the 1,869 patients undergoing CTA, only 4.2% had a significant coronary artery stenosis (≥70% luminal narrowing) on CTA. None of the patients died during the trials. In total, 142 (7.6%) of the patients in the coronary CTA group underwent ICA, of which 76 (4.1%) were revascularized. Patients referred to coronary CTA more often underwent ICA than patients receiving standard care. As depicted in Figure 6, the ICA referral rate was 6.3% in patients receiving standard care as compared to 8.4% in patients randomized to CTA ($P = 0.003$). The absolute increase in ICA for a coronary CTA based strategy was 21 per 1,000 patients.[53] Of interest, the majority of these downstream referrals for ICA were during the index hospitalization. Similar to the

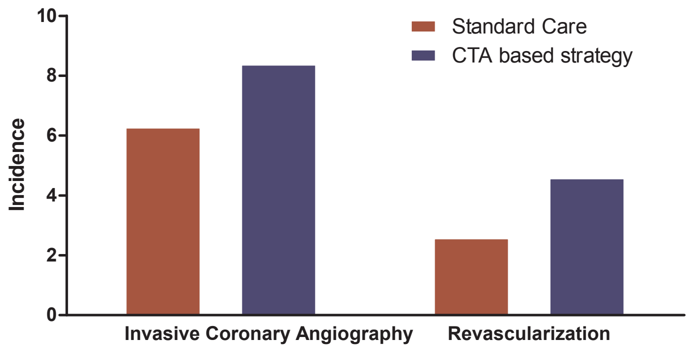

Figure 6. Difference in referral rate for invasive coronary angiography and subsequent revascularization between patients randomized to either a coronary CTA based strategy or standard care.
Adapted from Hulten *et al.* [53]

increase in ICA in the coronary CTA group, a significant increase in revascularization was observed in this group (both PCI and CABG).The revascularization rate was 2.6% in patients receiving standard care as compared to 4.6 % in patients randomized to coronary CTA (P = 0.004). The absolute increase in revascularization for a coronary CTA based strategy was 20 per 1,000 patients.

The information from these 4 RCTs underscores the value of coronary CTA in the emergency room for patients presenting with acute chest pain, suspect of ACS in the emergency room, namely exclusion of CAD. At the same time however, this approach is associated with an increased use of ICA and subsequent revascularization.

At the same time, the coronary CTA based strategy resulted in a significant reduction in the length of stay (emergency department or hospital stay) by 3.4–11.6 hours as compared to patients receiving standard care.[52, 54-56] For example, 50% of the patients randomized to coronary CTA in the ROMICAT II study could be safely discharged within 8.6 hours as compared to 26.7 hours for the patients receiving standard care (Figure 7).[55] Moreover, a coronary CTA based strategy positively affected emergency department costs: in three of the four trials a significant reduction in costs was observed in the group of patients randomized to CTA, ranging from $286 to $1321.

The number of post discharge hospitalizations for ACS is extremely low in these 4 trials (ranging from 0 to 3.1%), which further supports the safety of coronary CTA guided discharge of patients.

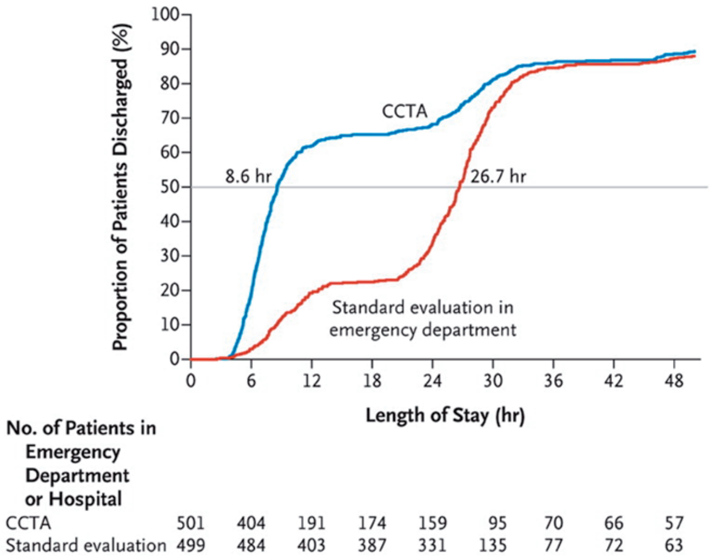

Figure 7. Difference in length of hospital stay between patients referred to CTA of standard care.
The horizontal line indicated the median length of stay in both study groups which was significantly different.
From: Hoffmann *et al.* NEJM. 2011

CT angiography of aorta and pulmonary arteries

Non-cardiac causes of acute chest pain concerning vascular structures in the thorax such as in acute aortic syndrome and pulmonary embolism can be easily visualized by CT. CT angiography of other vascular beds than the heart is less complex if non-ECG gating techniques are used. ECG gating may be used to improve image quality. In addition, contrast enhancement in the blood pool is required to visualize the vascular structures, and thus intravenous contrast is still needed. Several common principles should be applied to all imaging protocols to provide optimal diagnostic image quality such as bolus timing for optimization of contrast delivery in the vessel, fast high resolution acquisition, and administration of approximately 60–120 mL of contrast material (dependent on patient size, contrast agent used, and scanner type) injected at rapid infusion rates (4–5 mL/s).

Because of the availability, excellent image quality with good spatial resolution, high sensitivity, and fast imaging speed, multi-slice CT has become the first-choice imaging tool for the evaluation of acute aortic syndrome[57] and traumatic aortic pathology.[58] multi-slice CT is also widely used in the evaluation of non-acute pathology such as aneurysm or aortic coarctation, inflammatory and infective aortic disease, and after aortic surgery.[59]

Acute aortic syndrome encompasses a variety of life-threatening conditions that require emergency diagnosis and management, including aortic dissection (AD) (see Figure 8), intramural hematoma (IMH), penetrating aortic ulcer (PAU) and symptomatic aortic aneurysm.

If a patient presents with suspected acute aortic syndrome, the CT protocol should include a non-contrast enhanced scan from the proximal part of the arch vessels to the diaphragm, followed by CTA from the proximal part of the arch vessels to the femoral arteries. The non-contrast scan is to evaluate possible presence of an IMH as aortic wall thrombus.[59] IMH of the ascending aorta is clinically regarded at high risk for complication (evolving into dissection) and death, and surgery is usually indicated.[60]

PAU is usually located in the mid-descending thoracic aorta, where it presents as a mushroom-like contrast outpouching beyond the expected contours of the aortic lumen. PAU represents an atherosclerotic ulceration that penetrates the internal elastic lamina allowing hematoma formation within the aortic media, and may develop into IMH, aortic dissection, or vessel rupture.[61]

Thoracic aortic aneurysm

Aneurysm is defined as a permanent localized dilatation of an artery, having at least a 50% increase in diameter as compared with the normal diameter.[60] In general, an ascending aortic diameter equal to or greater than 4 cm (in an individual less than 60 years old) is considered an aneurysm. The size of the thoracic aorta increases with age and depends on sex and body size. The normal ascending aorta diameter is approximately 27 mm in 20-years old and 36 mm in 80-years old.[60] Thoracic aortic

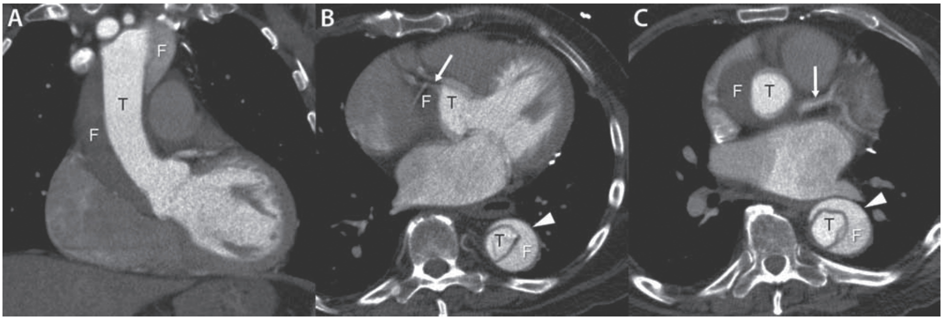

Figure 8. Thoracic CT angiography showing a type A aortic dissection(A).
The right coronary artery is contrast enhanced and has its origin from the true lumen (arrow, B). The right coronary artery has double appearance due to motion artefacts in this non-ECG gated scan. The left main coronary artery stem (arrow, C) is also contrast enhanced and had its origin from the true lumen. Carotid and subclavian arteries as well as the visceral arteries all had their origin from the true lumen. Note the almost complete disruption between the true and false lumen of the descending aorta (arrowheads B, C). F, false lumen; T, true lumen.

aneurysms can be true or false aneurysms. In a true aneurysm all three layers of the vessel wall are involved (intima, media, and adventitia) and is characterized by a fusiform shape. In a false aneurysm (or pseudo-aneurysm), the intima is disrupted and the blood is contained by the adventitia. Atherosclerosis is the most frequent cause of thoracic aneurysms (70%). Several genetic syndromes, vasculitis, and inflammatory diseases are also associated with aortic aneurysm and dissection.

Asymptomatic patients with an ascending aorta or sinus diameter larger than 5.5 cm, a growth rate more than 0.5 cm per year in aorta aneurysm less than 5.5 cm, and patients with genetically mediated syndromes and thoracic aorta aneurysm exceeding 4.0 to 5.0 cm, are candidates for elective surgical repair. Symptomatic patients suggestive of expansion of a thoracic aneurysm should be evaluated for prompt surgical intervention.[60]

CT angiography is the most robust tool for evaluating aortic aneurysms and some key features should be evaluated when using CT such as the maximal aortic diameter, presence of thrombus, shape and extent of the aneurysm, involvement of aortic branches, relationship to adjacent structures, and presence of aortic calcifications. In 23% of cases a thoracic aneurysm coexists with an abdominal aortic aneurysm, and thus evaluation of the entire aorta is indicated. Most importantly, CT shows excellent accuracy for characterizing important features of aneurysms.[62]

Pulmonary embolism

The well-known Wells' clinical decision rule is used to risk stratify patients suspected of pulmonary embolism.[63] This is a scoring method based on various clinical risk factors and stratifies patients as low, intermediate, or high risk. If a patient has a score of 4 or more, further testing is required. In routine clinical practice, multi-slice CT pulmonary angiography has become the first-choice imaging method for evaluating the pulmonary arteries when pulmonary embolism is suspected (see Figure 9).[64] A normal CT pulmonary angiography can safely exclude pulmonary embolism without need for additional tests.[65] On CT, pulmonary emboli are shown as filling defects of the contrast-enhanced central or segmental pulmonary arteries. In patients with pulmonary embolism, cloth burden is related to right ventricular dysfunction, where the measure of a right to left ventricular diameter ratio exceeding 1.0 is at risk for short term death.[66]

Triple rule-out CT

The concept of the 'triple rule-out' protocol is to simultaneously exclude all three potentially life-threatening causes of acute chest pain (ACS or infarction, acute aortic dissection or syndrome, and pulmonary embolism) in a single CT examination. A triple rule-out scan protocol includes coverage of the entire thorax cavity including

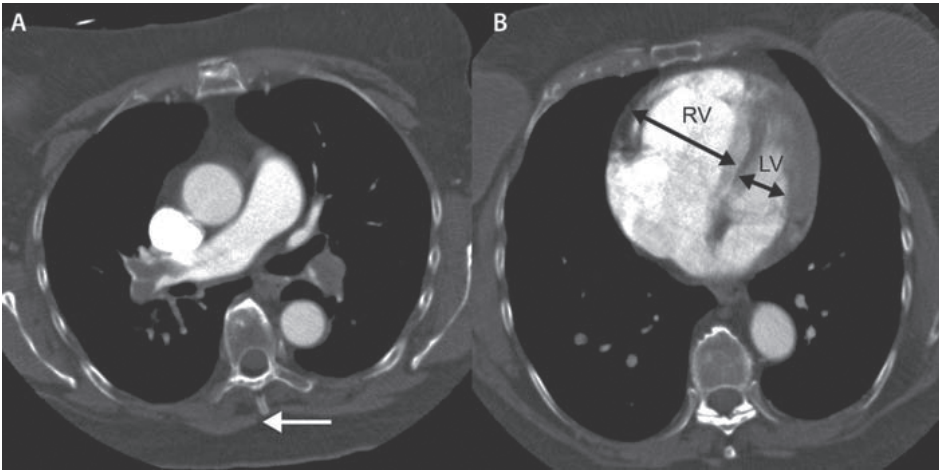

Figure 9. Patient with acute pulmonary embolism and high embolus load.
Massive emboli in the left and right pulmonary arteries can be observed (arrows, A). Note severe dilatation of the right ventricle (RV, B) with interventricular septum shift to the left and compression of the left ventricle (LV) due to high embolus load. Normally the RV diameter does not exceed that of the LV.

the aortic arch. State-of-the-art 64-slice scanners with wide anatomical coverage are able to scan the entire thorax including the pulmonary arteries, thoracic aorta, and coronary arteries in a single breath hold of approximately 15–20 s. An important technical challenge of a triple rule-out scan protocol is to ensure that high contrast enhancement is present simultaneously in both the pulmonary and systemic circulation to evaluate the pulmonary arteries and aorta including the coronary arteries. Injection protocols should be adapted to scanner type and acquisition settings.

Triple rule-out approach may improve the triage of patients presenting to the emergency department with acute chest pain, and provide a faster algorithm to make a diagnosis. However, it is crucial that patients should be carefully selected to ensure the appropriate use of a triple rule-out CT protocol. If the triple rule-out protocol involves retrospective gating of the entire thorax, radiation dose is high, even more than the radiation dose observed in dedicated coronary CT angiography.[67, 68] Prospective gating techniques strongly reduce radiation dose, but may not be applied effectively in patients with high or irregular heart rates. Therefore, patients with symptoms highly suggestive for ACS, acute pulmonary embolism, or acute aortic dissection, should be referred for a work-up specifically designed for this purpose (such as ICA if a patient has a high risk for ACS). As discussed before, the presence of a significant stenosis on coronary CTA does not automatically confirm the presence of ACS. In the remaining patients with uncertain cause of chest pain, a triple rule-out protocol can be considered.

Initial studies suggest that a triple rule-out CTA protocol for evaluation of patients with acute chest pain is feasible and that quantitative parameters of image quality may be comparable to the conventional, dedicated coronary and pulmonary CTA protocol. [69, 70] A study evaluating the diagnostic value of triple rule-out with 64-slice CT in 55 patients admitted to the emergency department demonstrated that this technique facilitated the differential diagnosis of chest pain.[70] Furthermore, the triple rule-out protocol could potentially identify a subset of patients with acute chest pain who can safely be discharged from the emergency department without adverse events during a 30-day follow-up.[71] A recent study in 100 patients with acute chest pain and an intermediate cardiac risk profile used either coronary CTA or a triple rule-out protocol in case of elevated D-dimer levels. Based on a negative coronary CTA or triple rule-out findings, 60 of 100 patients were discharged the same day, without major cardiac events at 90-days follow up. Also, those patients with significant coronary artery stenosis were identified.[72] The use of this protocol in intermediate cardiac risk profile patients was calculated to reduce the number of hospitalized patients and total health costs.[73] Indeed, more RCTs are needed to determine how the triple rule-out protocol is best applied to improve clinical decision making and justified use.

Technical developments

Coronary artery plaque quantification

Currently, assessment of stenosis severity on coronary CTA is performed visually. This requires however significant experience and is characterized by limited reproducibility.[74] Novel software tools have become available to (automatically) quantify stenosis severity on CTA, so-called quantitative CTA (QCT).[75, 76] These algorithms usually consist of various steps. First, the coronary tree is extracted from the CTA dataset and a multiplanar reformation is created of each coronary artery or side branch. Thereafter, the lumen and vessel wall are delineated on these MPR images. Based on these segmented contours, the severity of coronary artery stenosis can be quantified, but also the amount of coronary atherosclerosis (the plaque burden) can be derived (see Figure 10.) Previous investigations using QCT have demonstrated a good agreement between stenosis severity as assessed with QCT compared to ICA and intravascular ultrasound (IVUS).[75, 76] It was also shown that stenosis severity derived from QCT was related with the presence of ischemia on SPECT perfusion imaging.[77] Besides these geometrical parameters, it is also feasible to automatically assess and quantify coronary plaque composition with QCT. In a head-to-head comparison between QCT and IVUS with virtual histology, a good agreement was shown for assessment of different plaque types (calcified, mixed or non-calcified).[78] QCT will improve

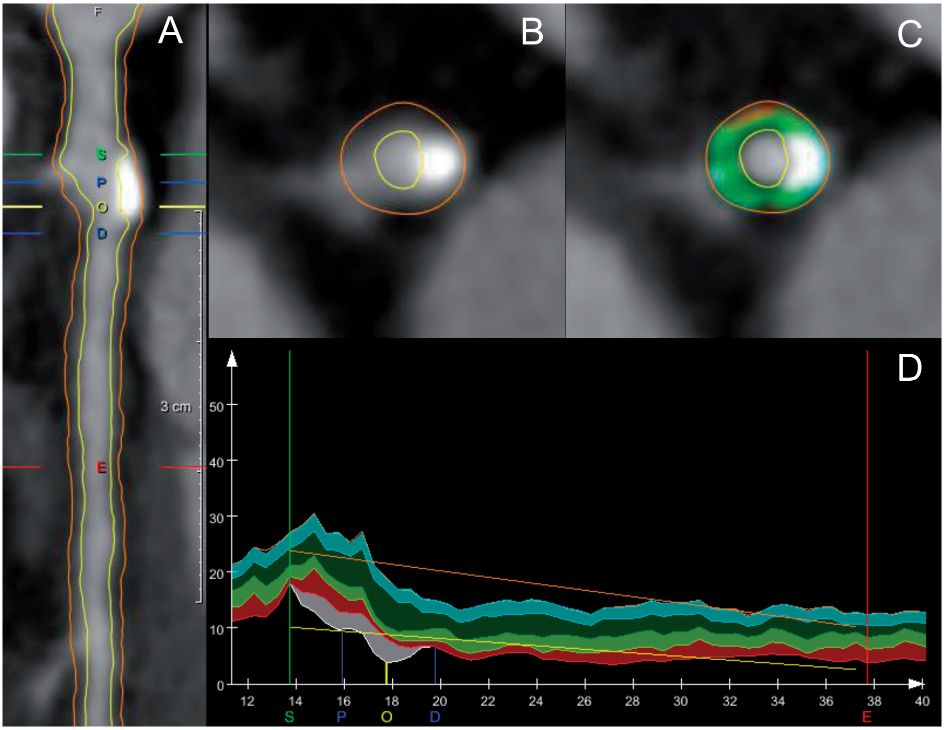

Figure 10. Example of quantitative CTA analysis of a 48 year old male patient referred for the evaluation of stable chest pain.
Panel A demonstrates a stretched multiplanar reformation (MPR) of the LAD with a calcified lesion. QCT was used to detect both lumen (yellow) and vessel wall (orange) contours. Longitudinal lumen and vessel wall contours are shown in panel A; whereas transversal lumen and vessel wall contours at the level of the minimal lumen area (MLA) are shown in panel B. Panel C show the quantification of coronary plaque constitution. Calcium is labeled in white, fibrotic tissue labelled in dark green, fibro-fatty tissue in light green and necrotic core labeled in red. Quantification of the calcified lesion was performed using proximal (green) and distal (red) reference markers as well as lumen (yellow) and vessel wall (orange) reference lines, as illustrated in panel D. In this graph, the x-axis represents the distance from the coronary ostium in mm. The y-axis represents the area of either the lumen (lower part of graph) or the vessel wall (upper part of graph) in mm2. The part between the two graphs shows the plaque constitution. Stenosis severity was quantified as 35%.

quantification of coronary stenosis and assessment of plaque composition and may be of particular value in serial evaluations to assess a potential effect of medication on atherosclerosis progression/regression and plaque composition.[79] Recently, the incremental predictive value of these QCT parameters (over visual interpretation) for development of a subsequent ACS, has been established.[80] Versteylen *et al.* compared the coronary CTA results in 25 patients who subsequently developed an ACS (over a mean follow-up period of 26 months) to 101 control patients without events. In the patients who developed an ACS, the total plaque volume, the plaque burden and the non-calcified plaque volume were significantly larger. Moreover, these quantitative CTA parameters provided incremental prognostic value over the clinical risk profile and the visual interpretation of the coronary CTA results.

Developments in CT scanners

The technology of the CT scanners is evolving rapidly. With the introduction of 256- and 320-slice scanners complete volume coverage of the heart becomes possible in a single heartbeat,[11, 12] This may potentially reduce motion artefacts, particularly in patients with irregular heart rates or rhythm abnormalities. Moreover, dual-source CT scanners with 2 × 128 detector rows have been introduced and these systems demonstrated a high temporal resolution of 75 ms (approximately half of the temporal resolution of the fastest 64-slice scanners) making possible to freeze cardiac motion and obtain diagnostic quality images of the coronary arteries regardless of heart rate or rhythm. Initial studies with dual-source coronary CT in patients presenting with chest pain have reported high negative predictive values approaching 100%, enabling to reliably excluded coronary artery stenoses also in patients with higher heart rates.[81] Very recently, high-pitch ECG triggered ('Flash Spiral') dual-source CT scanners have shown promising results.[13] The novelty of this technique lies in the very high pitch which results in fast image acquisition without cardiac motion artefacts and a very low radiation exposure (<1 mSv).[13] Currently only limited data in selected patients are available with these newer scanners, and larger studies are needed to determine the value of these novel equipment in routine clinical practice.

Novel applications of cardiac CT

Assessment of coronary artery plaque composition

Since coronary CTA allows for the visualization of the coronary vessel wall, coronary atherosclerosis on coronary CTA can be further characterized (beyond stenosis severity), permitting assessment of plaque composition. The plaques can be divided into non-calcified, calcified and mixed plaques. Interestingly, coronary plaque composition has been linked to clinical presentation: patients presenting with an ACS were shown to have more non-calcified and/or mixed plaques in the coronary arteries, whereas patients with stable CAD present with more calcified plaques.[82] In addition, it has been suggested that plaque composition may provide prognostic information.

Specifically, non-calcified plaques with low attenuation values, positive remodeling, and spotty calcifications have been associated with subsequent development of ACS.[83] Moreover, Gaemperli *et al.* evaluated 220 patients with known or suspected CAD using 64-slice coronary CTA and demonstrated worse outcome of patients with mixed or non-calcified plaques.[84] This was further confirmed by Hou *et al.* in 4,425 patients with suspected CAD with a follow-up period of nearly 3 years. The authors demonstrated that patients with non-calcified plaque were at 5 times higher risk for the combination of death, infarction or revascularization, as compared to patients with calcified plaques, and the risk of patients with mixed plaques was nearly 10 times higher.[85] Interestingly, it was shown in 163 patients with chest pain and suspected CAD that mixed plaques were also correlated with the presence of ischemia on SPECT perfusion imaging.[86]

Evaluation of myocardial perfusion

Recent developments in CT scanner technology have enabled evaluation of left ventricular myocardial contrast attenuation enabling CT myocardial perfusion imaging (of the left ventricle). This functional information is of particular importance to determine the hemodynamical significance of intermediate coronary artery stenoses (around 50% luminal narrowing). Standard CT perfusion (CTP) protocols include a rest study for the evaluation of the coronary arteries and the resting myocardial perfusion, followed by an adenosine-induced stress study to determine the stress perfusion.[87] Similar to perfusion imaging with SPECT or magnetic resonance imaging (MRI), reversible or fixed perfusion defects can be detected indicating ischemia or scar tissue respectively. [88-91] A major advantage of CTP is the combination of coronary artery anatomy (CTA) and function (CTP) in one examination. Blankstein *et al.* demonstrated with 64-slice CT that an adenosine stress CT protocol can identify stress-induced myocardial perfusion defects with a diagnostic accuracy comparable to SPECT.[92] Additionally, the average radiation required in this protocol was similar to the radiation dose of SPECT perfusion imaging. It is anticipated that with improved dose reduction protocols, the radiation dose will be reduced significantly. Recent studies have indicated an improved diagnostic accuracy for CTP compared to coronary CTA alone for the detection of myocardial ischemia.[87, 93] George *et al.* demonstrated in 53 patients with an intermediate to high pre-test likelihood of CAD that the diagnostic accuracy of CTP to predict reversible ischemia on SPECT was higher than coronary CTA.[87]

Evaluation of myocardial infarction

Over recent years, MRI has been successfully employed to image the presence of infarcted myocardium with delayed contrast enhancement imaging. However, several studies have demonstrated that the presence of infarction can be also identified on CT.[88] Because of the pharmokinetics of the contrast material, a difference between the accumulation of contrast in infarcted and normal myocardium can be visualized. Accordingly, early hypo-enhancement can be observed on the CT images during the first pass of contrast medium at the area of infarcted myocardium. In addition, delayed hyper-enhancement of infarcted tissue can be detected similarly to MRI. Good correlations between infarct imaging with CT and other imaging modalities such as MRI and SPECT imaging have been demonstrated.[88-90] Moreover, a good correlation between enhancement patterns (both early hypo-enhancement and late hyper-enhancement) and recovery of myocardial function at a follow-up of 3 months post-infarction was reported, suggesting that CT may be useful to predict functional recovery after infarction.[91] However, it is important to realize that in general, delayed enhancement imaging with CT requires additional imaging and thus involves additional radiation exposure. Also, a larger amount of contrast agent is required for delayed enhancement imaging as compared to imaging the coronary arteries alone.

Fractional flow reserve (FFR)

It has been shown in the FAME (FFR vs. Angiography for multivessel evaluation) trial that revascularization guided by invasive assessment of FFR is superior in terms of outcome over revascularization driven by angiographic stenosis severity.[94] This observation highlights that functional (ischemia) assessment may be preferred over anatomical assessment (stenosis severity) to guide the need for revascularization. Invasive assessment of FFR however, may not be the first choice in patients with stable chest pain, and a non-invasive approach may be preferred. With the application of computational fluid dynamics and complex mathematical calculations, novel software tools allow for the non-invasive assessment of FFR from coronary CTA datasets (FFRct) without additional imaging, modification of CT acquisition protocols, or administration of medication.[95] An example of this approach (as compared to ICA and

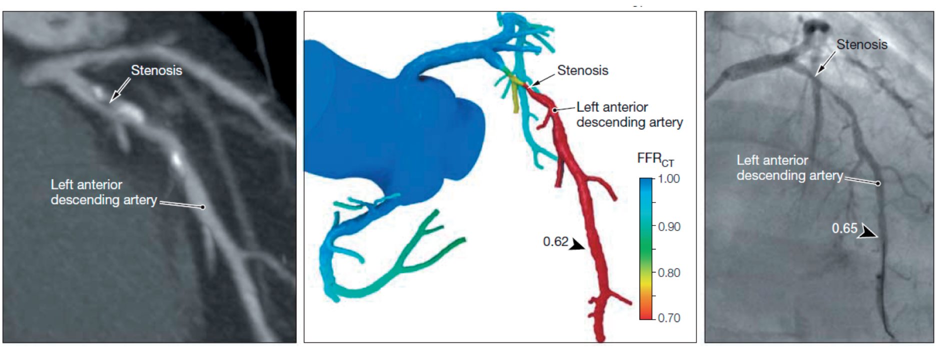

Figure 11. Case example of FFRct with corresponding invasive coronary angiogram.
Multiplanar reformat of a coronary CT angiogram demonstrating obstructive stenosis of the proximal portion of the left anterior descending (LAD) coronary artery and a computed fractional flow reserve (FFRCT) value of 0.62, indicating ischemia. Invasive coronary angiography demonstrates obstructive stenosis of the proximal portion of the LAD and measured fractional flow reserve (FFR) values of 0.65, indicating ischemia.
From: Min *et al.*, JAMA 2012

invasive FFR) is shown in Figure 11. In the DISCOVER FLOW (diagnosis of ischemia-causing stenoses obtained via noninvasive fractional flow reserve) trial, Koo *et al.* have demonstrated good agreement between FFRct and invasive FFR in 103 patients in whom 159 coronary arteries were evaluated.[96] At present, FFRct is not suitable for implementation in the daily practice since FFRct calculations are time consuming (calculation of FFRct may require up to 5 hours) and requires sophisticated computation which is not available in routine clinical imaging departments.[96]

Transluminal attenuation gradient

Another method to improve assessment of the hemodynamic significance of a coronary stenosis with CTA could be the calculation of the transluminal attenuation gradient (TAG). [97] For this purpose a MPR is generated of each coronary. Along the center-line of this MPR the luminal intensity is measured at 1mm increments. TAG is then defined as the slope of the regression line of the decrease in luminal intensity from the proximal to the distal part of the coronary (Figure 12). A steep decrease in intensity (i.e. a more negative TAG) was associated with the presence of an obstructive lesion in that coronary.[97] Recently Wong *et al.* have reported the incremental value of TAG measurements on 320-row CTA over CTA alone for the prediction of invasive FFR significant lesions.[98] However, until present the exact clinical value of TAG is unknown and requires further trials and investigations.

Evaluation of myocardial function

Besides assessment of the coronary arteries, cardiac CT imaging also permits assessment of left ventricular volumes and function. If data have been collected during the whole cardiac cycle, images can be retrospectively reconstructed in several phases to derive left ventricular ejection fraction from the left ventricular volumes. Indeed, numerous studies have shown that global left ventricular function assessed by CT correlates well with echocardiography and MRI, although CT appeared to minimally overestimate end-systolic volume and may thus slightly underestimate left ventricular ejection fraction.[99, 100] In addition, regional wall motion abnormalities can be reliably evaluated as compared to MRI. [101] However, as images should be acquired throughout the cardiac cycle, left ventricular function protocols are associated with increased radiation exposure and CT may not be the first choice technique, but could be considered as an alternative for patients who are not suitable to undergo MRI.[102]

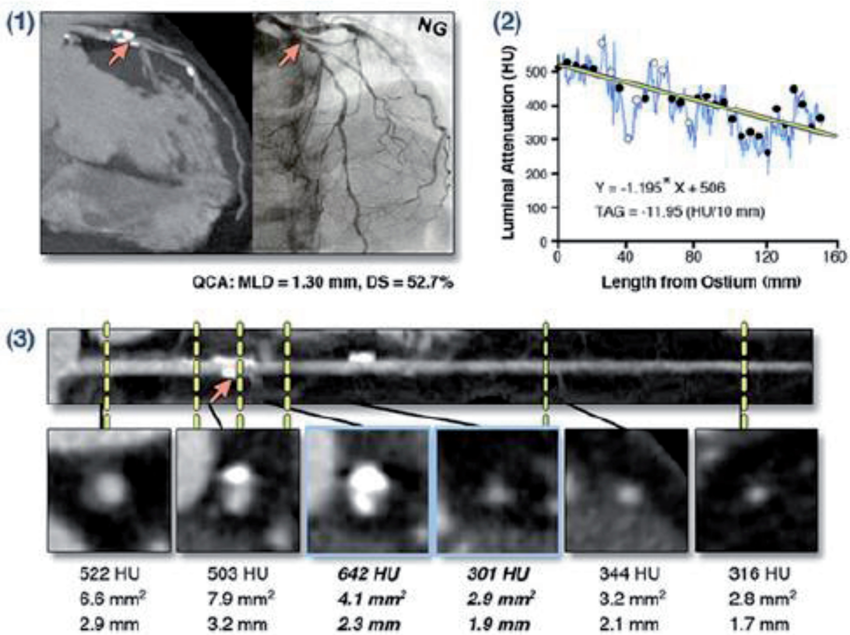

Figure 12. Patient example of transluminal attenuation gradient (TAG) calculation.
Panel 1: Coronary CTA demonstrates calcified lesions in the proximal LAD coronary artery and moderate stenosis in the mid LAD traject, confirmed by invasive coronary angiography.
Panel 2: Luminal attenuation plot. Black dots represent 5-mm intervals at which intraluminal attenuation (in Hounsfield units, HU) and luminal area (in mm^2) were measured. TAG is shown by the yellow line and was -11.95 (HU/10mm).
Panel 3: Axial and representative cross-sectional views of coronary CTA.
MLD: minimal lumen diameter, QCA: quantitative coronary angiography
From: Choi *et al.*, JACC: cardiovascular imaging 2011

Conclusion

Patients presenting with acute chest pain to the emergency room, suspect for an ACS but without the diagnostic ECG and troponin criteria. This poses an important dilemma in clinical cardiology: on the one hand, this population constitutes a large number of patients with a low prevalence of ACS, but on the other hand a substantial number of patients appear to develop an ACS once discharged. Coronary CT angiography is a feasible technique for non-invasive, fast, and accurate exclusion of obstructive CAD in patients presenting with acute chest pain. Moreover, a normal coronary CTA permits safe discharge with good short- to mid-term prognosis. This has increased interest in using CT for non-invasive assessment of CAD in the emergency department, and in addition the technique can evaluate the presence/absence of other causes of acute chest pain such as aortic aneurysm, aortic dissection, or pulmonary embolism.

Four RCTs have been performed comparing a CT-based approach in the emergency room versus a standard of care approach. These trials confirmed the value of coronary CTA to exclude CAD, with good outcome after discharge, and a reduction in hospital stay and costs. At the same time, an increase in ICA and revascularization rate was observed in patients with CAD on coronary CTA; this warrants further studies to determine the precise relation between the coronary CTA findings and referral for ICA. Finally, other applications such as the evaluation of coronary artery plaque composition, myocardial function and perfusion or fractional flow reserve are currently being developed and may also become valuable in the setting of acute chest pain in the future.

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