DEBATE ARTICLES: WHICH IMAGING IS THE BEST FOR DETECTING CAD ?− REVIEW ARTICLE

Coronary CTA is the Best Approach to Detect Coronary Artery Disease

Alexander R. van Rosendael, MD[1), 2)], Jeff M. Smit, MD[1)] and Arthur J.H.A. Scholte, MD, PhD[1)]

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Abstract

In patients with suspected coronary artery disease (CAD), an anatomical or functional approach can be used to guide further patient management. Functional techniques are able to assess the presence and extent of myocardial ischemia, whereas coronary computed tomography angiography (CTA) can assess the presence and extent of coronary atherosclerosis. Coronary CTA has a high sensitivity to detect obstructive CAD in patients with a low to intermediate probability and is therefore commonly used to rule out coronary atherosclerosis. To improve its specificity, novel techniques as fractional flow reserve using CT (FFRct) and CT myocardial perfusion imaging (CTP) are emerging. This review will summarize the latest trials that investigated how coronary CTA can be applied in clinical practice and compare this technique to other imaging modalities.
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Coronary computed tomography angiography (CTA) provides direct visualization of the coronary arteries and aims to detect and quantify the amount of coronary atherosclerosis. Each individual coronary plaque can be identified and information regarding a patient's total coronary artery disease (CAD) extent (number of diseased vessels), severity (luminal stenosis), location (proximal or non-proximal coronary artery segments) and composition (calcified plaque, partially calcified plaque or non-calcified plaque) can be obtained. The severity of CAD is traditionally divided into non-obstructive (0-49% luminal stenosis) or obstructive CAD (≥50% stenosis). All this information combined can aid the physician to clarify the cause of chest pain, assess the prognosis and determine further patient management. Post coronary CTA decision making is addressed in a recent reporting system (CAD-RADS − Coronary Artery Disease Reporting and Data System) that has been created to standardize the communication of coronary CTA findings and to facilitate decision making (1). Based on stenosis severity and number of diseased coronary arteries, appropriate patient management is advised. Consideration of preventive therapy and risk factor management is recommended for patients with minimal or mild non-obstructive CAD. For patients with moderate obstructive stenoses (50-69%), management can be complemented with functional testing and symptom guided anti-ischemic therapy. In patients with severe lesions (70-99% stenosis), besides functional testing, invasive coronary angiography (ICA) can be considered. ICA is recommended as next step for patients with left main stenosis ≥50% or 3 vessels with ≥70% (1).

Diagnostic accuracy of coronary CTA versus myocardial perfusion imaging

Myocardial perfusion imaging (MPI) is a widely used technique to determine the extent and severity of myocardial ischemia in symptomatic patients. Whilst CTA is able to evaluate the location, characterization, extent and severity of coronary artery stenoses, MPI can assess the hemodynamic consequences of coronary stenoses. Because obstructive coronary stenoses on CTA (≥50% stenosis by visual assessment) result in myocardial ischemia in only 50% of the patients, MPI can provide important functional information in

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1) Alexander R. van Rosendael, Jeff M. Smit, Arthur J.H.A. Scholte
Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands
E-mail: a.j.h.a.scholte@lumc.nl

2) Alexander R. van Rosendael
The Netherlands Heart Institute, Utrecht, the Netherlands

addition to CTA (2).

Recently, the diagnostic performance of CTA and SPECT MPI were compared using ICA as a reference standard (≥50% stenosis in ≥1 coronary artery) in 391 symptomatic patients (3). The area under the receiver operator characteristic curve (AUC) was significantly higher for CTA compared to SPECT MPI (0.91 vs. 0.69; P < 0.001), predominantly due to the higher sensitivity of CTA (0.92 vs. 0.62; <0.001). However, as CTA and ICA (used a as reference standard in this study) are both anatomical tests and SPECT MPI is a functional test, this may partly underlie the favorable diagnostic accuracy of CTA. The high diagnostic accuracy of CTA to rule-out CAD could be an important reason for the increasing use of this technique worldwide. For instance, a 21.9% increase in coronary CTA procedures was observed in the Japanese population from 2011-2015 (4).

In a recent meta-analysis by Danad et al. invasive FFR was used as a reference standard to determine the diagnostic performance of CTA and SPECT MPI (5). On a patient-based analysis, CTA showed a high sensitivity (0.90; 95% CI 0.86-0.93), confirming the potential of CTA to rule out ischemia-causing CAD accurately. In contrast, SPECT MPI showed only a moderate sensitivity (0.70; 95% CI 0.59-0.80) for the detection of ischemia-causing CAD. Because SPECT MPI is based on the principle of relative flow reserve, at least 1 normal vascular territory is needed for the assessment of ischemia-causing CAD. In case of significant three-vessel CAD, no ischemia may be detected by SPECT MPI ("balanced ischemia") limiting the capability of this technique to accurately rule-out hemodynamically relevant CAD.

Currently, positron emission tomography (PET) is considered the gold standard MPI technique for the detection of ischemia-causing CAD (6). Because PET MPI is able to measure absolute myocardial blood flow, high diagnostic accuracy is retained also in case of "balanced ischemia". However, PET MPI has a limited availability due to high costs and the use of complex tracers for which an on-site generator or cyclotron is needed. Therefore, CTA may be considered a more appropriate and cost-effective first step to rule-out obstructive CAD. If the presence of obstructive CAD cannot be excluded by CTA, PET MPI could be a useful technique to determine the hemodynamic consequences of coronary artery stenoses (7).

Diagnostic role of coronary CTA compared with functional testing

In patients presenting with chest pain, the primary goal of coronary CTA is to assess the presence of obstructive CAD, whereas the primary goal of functional testing is to identify myocardial ischemia. This paragraph will explain two recent randomized trials showing the strength of coronary CTA to aid in the diagnostic process of patients with stable chest pain compared with functional tests.

In the Scottish Computed Tomography of the Heart (SCOT-HEART) trial, 4,146 patients with suspected angina were randomly assigned to standard care plus coronary CTA or standard care alone (existing predominantly of functional testing). The primary endpoint was the certainty of a physician to relate the chest pain symptoms to coronary heart disease. Use 6 weeks after randomization, an almost 4-fold increase in certainty of angina due to coronary heart disease was observed in the coronary CTA group. Furthermore, information derived from coronary CTA led to a change to more appropriate anti-anginal (9% vs 1%) and preventive medical therapy (18% vs 4%) and planned invasive and non-invasive coronary testing (15% vs 1%) compared with standard care. It seems likely that these changes were caused by increased knowledge of a patient's CAD burden.

A post hoc analysis of this trial explored the consequences of coronary CTA-guided management on the effectiveness of ICA and clinical outcomes. At 6 weeks, coronary CTA was associated with more cancellation of ICA's (29 vs 1, P= 0.0008) and request of new ICA's (94 vs 8, P<0.0001). Over the total trial follow up period, no difference in total number of ICA's was observed (409 vs 401, P=0. 451); however, coronary CTA led to less ICA's showing normal coronary arteries (20 vs 56, P<0.001) and more ICA's showing obstructive CAD (283 vs 230, P=0.005). Overall, there was a trend for more revascularizations (233 vs 201, P = 0.061) in the coronary CTA group. Finally, although the study was not powered and initiated to detect differences in clinical outcome, a 38% reduction (P=0.052) in fatal and non-fatal myocardial infarction was observed in the coronary CTA group compared with functional testing. Hence, SCOT-HEART showed that an initial approach of coronary CTA leads to improvements in diagnostic certainty, selection for referral to ICA and possibly improved outcome.

In the CRESCENT (Computed Tomography vs. Exercise Testing in Suspected Coronary Artery Disease) trial, 350 patients with stable chest pain were randomized (in a 2:1 fashion) to a cardiac CT approach (consisting of a calcium scan and selective performance of coronary CTA) or functional testing, aiming to compare clinical effectiveness, defined as the absence of chest pain complaints after 1 year (8). At baseline, a similar pattern of chest pain typicality was present between groups; a quarter having typical angina, half having atypical chest pain and a quarter having non-anginal chest pain. In the CT group, more patients were symptom free at 1 year (39% vs 25%) and a lower angina frequency at 1-year follow-up (P=0.012) was observed compared with functional testing. Moreover, the final clinical diagnosis was made significantly earlier after the initial non-invasive test for CT

(P<0.001) and fewer patients required another, secondary test (25% vs 53%, P<0.0001). Finally, a non-significant trend in higher proportion of ICA's followed by revascularization (72 % vs 58%) was observed for the CT group. This study reproduces the strengths of coronary CTA to aid in the diagnostic process of patients presenting with stable chest pain and select patients that should undergo ICA compared with functional testing.

Prognostic role of coronary CTA

Quantification of CAD with coronary CTA enables accurate prediction of future events. Multiple series from the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) have consistently shown that increasing extent of CAD burden is associated with worse outcome and that coronary CTA provides incremental risk prediction beyond clinical risk scores (9-12). Absence of CAD has a very low rate of adverse events and obstructive three vessel or left main disease carries the highest risk. For this risk group, Schulman-Marcus et al. showed an approximately 12 times elevated rate of myocardial infarction among 5,632 patients without known CAD with 5 years of follow up (13). In comparison with functional imaging that only detects the functional consequence (myocardial perfusion defects or wall motion abnormalities) of hemodynamically significant CAD, coronary CTA can detect CAD in an earlier stage. Increasing evidence arises that the presence and extent of non-obstructive stenosis (which mainly do not cause myocardial ischemia) are prognostically important (14-16). Among 2,583 patients without prior CAD and without obstructive CAD on coronary CTA, the presence of non-obstructive CAD was associated with a (CAD risk factor adjusted) 2 fold increased mortality hazard (17). Patients with non-obstructive lesions in 3 epicardial vessels or 5 diseased coronary segments were at an approximately 5 fold increased risk. Moreover, Mushtaq et al. investigated the prognostic value of a coronary plaque score (computed tomography–adapted Leaman score) that incorporates the lesion localization, stenosis degree, and plaque composition into one single number. They observed that the event free survival for patients with a high score was similar when subdivided into obstructive and non-obstructive CAD, indicating that the total CAD burden is prognostically more important than lesion severity alone.

The PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) study randomly assigned patients with stable chest pain and intermediate pretest probability for obstructive CAD to functional testing or coronary CTA. Hoffmann et al. investigated the prognostic value of anatomical vs functional testing to predict major adverse cardiac events (18). Compared with normal test results, hazard ratios for mildly, moderately or severely abnormal test results

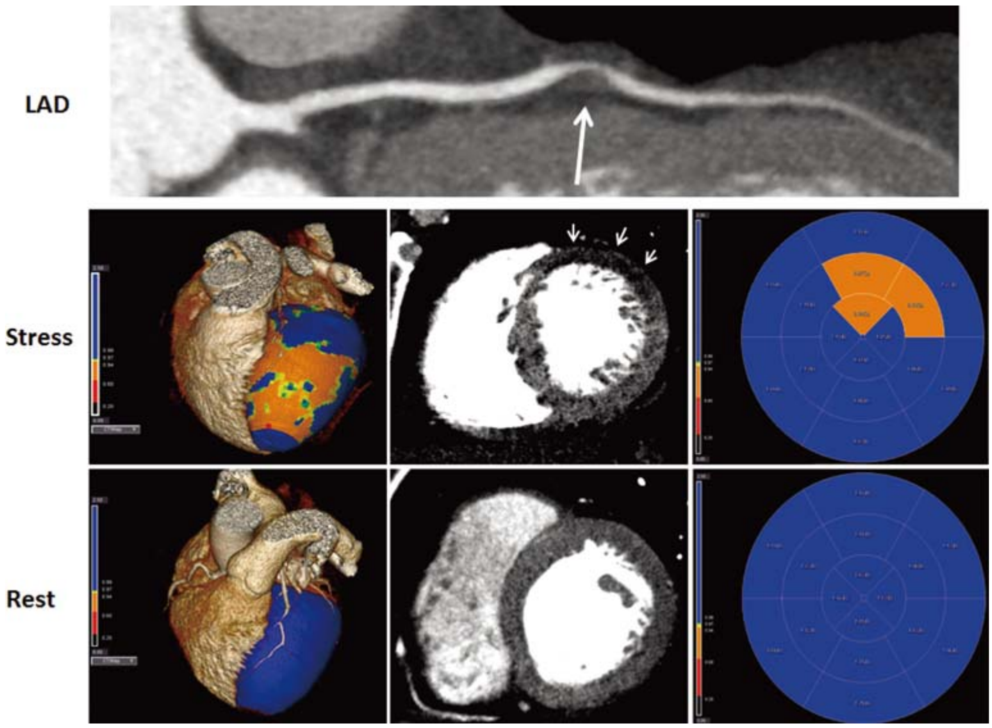

Fig. 1 Coronary CTA with CT myocardial perfusion imaging.
An example of a patient showing a severe non-calcified lesion in the left anterior descending coronary artery (LAD). A subsequently performed CT myocardial perfusion scan shows myocardial ischemia in the anterior wall, corresponding to the LAD vascular territory. Modified with permission from van Rosendael et al., J Nucl Cardiol 2016 (26).

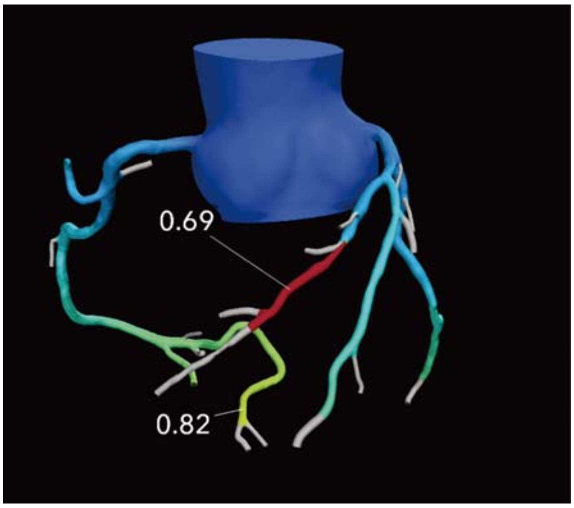

Fig. 2 FFRct case.
A 3D reconstructed coronary tree model showing a severe lesion in the mid-LAD with an FFRct value of 0.69 distal to the stenosis (hemodynamically significant).

increased proportionally for coronary CTA but less for functional testing categories: HR 2.94, 7.67, 10.13 for coronary CTA vs HR 0.94, 2.65, 3.88 for functional testing. The discriminatory ability of coronary CTA was significantly better than of functional testing (c-index 0.72 vs 0.64, P=0.04). By the ability of coronary CTA to identify non-obstructive CAD – which does generally not lead to myocardial ischemia – increased prediction of events was observed compared with functional testing. Specifically, this study reinforces the clinical importance of non-ischemic coronary lesions that result in an abnormal coronary CTA but will result in normal functional tests.

Functional imaging with cardiac CT

By the introduction of fractional flow reserve – computed tomography (FFRct) and CT myocardial perfusion (CTP), it is possible to derive functional information of coronary stenosis with cardiac CT. By the application of computational fluid dynamics to conventional coronary CTA images, coronary lesion specific FFR values can be calculated, which correlate well with invasive FFR (19). CTP requires an additional CTA during pharmacological stress (mainly adenosine infusion) and myocardial ischemia or scar can be detected as myocardial areas with relative hypo-enhancement (20). By combining coronary CTA with one of these new techniques (FFRct or CTP), integrated anatomical and functional information can be obtained within one procedure. Both techniques provide incremental diagnostic accuracy compared with coronary CTA alone, predominantly by increasing the specificity while remaining high sensitivity, as compared with invasive FFR (21, 22). The clinical utility of FFRct was demonstrated in the PLATFORM (Prospective Longitudinal Trial of FFRCT: Outcome and Resource Impacts) trial. 380 patients who were already referred for ICA by their physician were allocated to either direct ICA or coronary CTA with selective FFRct calculation (mainly when ≥30% stenosis was detected). After receiving the coronary CTA/FFRct results, 61% of ICA's were cancelled. Among the patients that underwent ICA after coronary CTA/FFRct, only 12.4% did not show obstructive CAD, compared with 73.3% among the patients that directly underwent ICA (risk difference 60.8%, P<0.0001). At 1 year, mean costs were 33% lower for coronary CTA/FFRct ($8,127 vs $12,145, P<0.0001) and rates of major adverse events were similar and low (23). Currently, there is limited literature available on CTP. The largest trial performed is the CORE 320 study (The Coronary Artery Evaluation using 320-row Multidetector Computed Tomography Angiography and Myocardial Perfusion) that tested the diagnostic accuracy of a combined protocol of coronary CTA plus CTP compared with obstructive CAD by ICA plus corresponding perfusion defect diagnosed with SPECT MPI as reference (20). The addition of CTP significantly increased the overall diagnostic accuracy when compared to coronary CTA alone (area under the receiver operating characteristic curve 0.87 vs 0.84, P=0.02) by increasing its specificity (51% for coronary CTA and up to 83% for the combined protocol with an abnormal CTP defined as a summed stress score ≥5). Recently, the prognostic importance at 2 year follow-up of combining CTA and CTP in comparison with combined ICA and stress SPECT as reference showed similar results (24). Van Rosendael et al. investigated clinical impact of adding CTP to coronary CTA when obstructive CAD is observed among 384 patients presenting with stable chest pain (25). This study showed that 95% of patients with an abnormal CTP were referred for ICA and 76% underwent revascularization; only 31% with a normal CTP were referred for ICA and 15% underwent revascularization.

Conclusion

Coronary CTA provides direct visualization of coronary atherosclerosis and informs about the severity, extent and location of the CAD. It has a higher sensitivity to detect CAD than functional imaging and is therefore commonly used to rule out obstructive CAD. Trials have shown that coronary CTA as initial test among symptomatic patients with suspected CAD has led to improved clarification of the diagnosis of chest pain, fewer ICA's showing no CAD and possibly a reduction in subsequent myocardial infarction compared with functional testing. Moreover, coronary CTA is able to identify prognostically important non-obstructive CAD that does generally not lead to myocardial ischemia and will not be detected with MPI. Identification of this CAD can initiate preventive medical therapy and life style changes at early stages. Finally, the novel techniques CTP and FFRct can increase the specificity to detect hemodynamically significant lesions (which are the target for revascularization) and clinical utility evidence is emerging for these techniques.

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Conflicts of interest

None.

Abbreviations

CAD: coronary artery disease

CMR: cardiac magnetic resonance

CTA: computed tomography angiography

CTP: computed tomography myocardial perfusion imaging

FFR: fractional flow reserve

FFRct: fractional flow reserve using computed tomography

ICA: invasive coronary angiography

MPI: myocardial perfusion imaging

PET: positron emission tomography

SPECT: single-photon emission computed tomography

Reprint requests and correspondence:

Arthur J.H.A. Scholte, MD, PhD

Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, 2300 RC, the Netherlands

E-mail: a.j.h.a.scholte@lumc.nl

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