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Groothuis, J.G.J.

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Chapter 8

General considerations and future perspectives

Jan G.J. Groothuis

GENERAL CONSIDERATIONS

General considerations

Until recently, the non-invasive diagnostic work-up of patients with chest pain and low to intermediate likelihood of having significant CAD was based on detection or ruling out of myocardial ischemia, by X-ECG, dobutamine stress echocardiography or nuclear myocardial perfusion imaging. Such a strategy is in line with recent studies that have confirmed the superiority of ischemia driven revascularization rather than anatomy based therapy. (1,2) However, with the growing use of CTCA the diagnostic evaluation of patients with suspected CAD is more and more based on the assessment of coronary anatomy rather than ischemia. Although CTCA can reliably rule-out significant CAD, the positive predictive value for detection of hemodynamically significant CAD is low. Therefore, to avoid large numbers of unnecessary invasive procedures, additional non-invasive functional testing is warranted when obstructive CAD is detected by CTCA.

In this thesis we have shown that CMR may be the ideal functional test in addition to CTCA. We proposed a new diagnostic workup of patients with chest pain and low to intermediate pre-test likelihood. CTCA is used as first line technique to reliably rule out significant CAD. When obstructive CAD is detected by CTCA, patients will undergo CMR for the evaluation of the hemodynamic significance of the lesions. This work-up improves diagnostic accuracy for detection of significant CAD, reduces the number of patients that will undergo myocardial perfusion imaging and allows the detection of alternative (extra-) cardiac causes of chest pain, without the cost of additional radiation. However, several issues of such a new non-invasive diagnostic evaluation of patients with suspected CAD remain unanswered.

Additional value of CTCA to CCS

The additional value of CTCA to CCS remains question of debate. In clinical practice most cardiac CT protocols consist of two parts, coronary calcium scan and coronary angiography. Due to beam hardening artifacts, the image quality of CTCA in patients with extensive calcified plaques (high coronary calcium scores) is reduced and therefore exclusion of significant CAD is less reliable. (3) For this reason, one might decide ad hoc, to abort the CT coronary angiography when the calcium score is high. However, with the rapid technological development of CTCA image quality is becoming better, even in calcified coronary arteries, and observers are becoming more experienced. Furthermore, recently it was shown that in addition to CCS, the pre-test probability of the patient has large impact of the diagnostic accuracy of CTCA. (4). Therefore we believe that an exact threshold of CCS to abort the CTCA does not exist. Most important is the assessment of the patients pre-test probability of suspected CAD. Only patients with low to intermediate risk should then be referred for cardiac CT. Conversely, as the prevalence of significant lesions in patients without coronary calcification is very low (3, 5) one might decide to abort the CT coronary angiography when the CCS is zero. However, conflicting data exist about the

exact prevalence of significant CAD in patients with a CCS of zero. (6). Especially in the younger patients and/or with more acute symptoms, significant CAD without any calcification is not rare (6, 7). As cardiac CT is used as (definitive) first line rule-out technique to exclude suspected CAD, we recommend that CTCA should not be aborted in patients with a coronary calcium score of zero.

Management of non-significant CAD on CTCA

In our proposed non-invasive diagnostic work-up, CTCA is used as first line technique as it can reliably exclude significant CAD and is able to detect (non-significant) CAD. In clinical practice patients with non-significant CAD on CTCA often are prescribed medication (statin, ace-inhibitor and aspirin). Although several studies have shown that CAD detected by CT has additional prognostic value to more conventional risk factors, especially in intermediate risk patients (8), no study has yet shown that patients with non-significant CAD on CTCA should receive medication. However, with the growing wealth of data on the prognostic value of CAD detected by CT (9), it may be unethical to start a study randomizing patients with non-significant CAD to placebo or medication. Moreover, large patient cohorts are needed to perform such research given the low incidence of cardiac events in patients with a low-intermediate risk profile and non-significant CAD on CT.

Validation of new diagnostic strategies

Although several studies have shown the superiority of CTCA and CMR myocardial perfusion imaging over X-ECG for the detection of CAD (10-12), it remains unknown whether a combined strategy of CTCA and CMR myocardial perfusion imaging will improve risk stratification when compared with X-ECG. While it has been shown that X-ECG cannot reliably detect significant CAD (13), its prognostic value has been validated extensively (14). Recently several studies have shown the significant prognostic value of either CTCA or CMR (9, 15-21), however, studies that directly compared the prognostic value of X-ECG with CTCA or CMR are scarce (22, 23). In contrast, several studies have shown the additional prognostic value of SPECT myocardial perfusion imaging to X-ECG. (24, 25) Therefore, long term outcome studies are needed in which patients with low or intermediate likelihood CAD are randomized to either a conventional work-up consisting of X-ECG or CTCA and/or CMR.

Cost effectiveness of new diagnostic strategies

It is clear that with increasing health costs, the cost-effectiveness becomes increasingly important when introducing new diagnostic techniques. Although the cost-effectiveness depends on many factors such as downstream test utilization and local organization of health costs, and these factors may vary overtime, several studies have investigated the cost effectiveness of either CTCA and CMR and showed promising results. (26-28). In a study

by Min et al (27) it was shown that using CTCA instead of nuclear SPECT myocardial perfusion imaging as first line technique in patients with intermediate likelihood of disease is more cost-effective. Furthermore, recently Francis et al (28) showed that CMR perfusion imaging is more cost-effective than nuclear perfusion imaging for the evaluation of patients with intermediate pre-test probability CAD.

In contrast, studies comparing the cost-effectiveness of the combined use of CTCA/CMR and conventional strategies using X-ECG and SPECT do not exist. However, we believe that the combination of CTCA and CMR can be cost effective. In addition to data on the superior diagnostic accuracy of both CTCA over X-ECG(10-11), and CMR in relation to SPECT, (29-30) and the cost effectiveness of either CTCA or CMR in relation to conventional strategies (26-28), further supportive data are the suggested prices of different diagnostic modalities presented by the Nederlandse Zorgautoriteit (31), see table 1. Given the relatively high price of X-ECG and the combined stress and rest SPECT myocardial perfusion imaging, the cost-effectiveness of a combined CTCA-CMR work-up seems promising.

Table 1. Recommended prices of different diagnostic modalities according to the Nederlandse Zorg Autoriteit

Diagnostic modality	cost price (euro)*
X-ECG	97,74
Echocardiography	51,35
CT heart	195,83
MRI thorax (heart not available)	160,01
SPECT myocardium	265,08 (stress), 199,41 (rest)
Invasive coronary angiography	789,35

*According to the Nederlandse Zorg Autoriteit. (31)

FUTURE PERSPECTIVES

The growing wealth of data showing that CTCA and CMR each are very powerful new modalities for the non-invasive diagnostic work-up of patients with suspected CAD and the growing availability of both techniques will result in a significant increase of use in clinical practice. However, further research and development is needed.

New developments of cardiac CT

The rapid technical improvements from 16-row to 64- and even 320-row multidetector CT and the use of dual source scanners have improved temporal resolution significantly while reducing radiation dose. (32, 33) In this way, image quality is less dependent on (slow) heart rates and patients will not need high doses of beta-blocker before CT scanning. (34, 35) On the other hand, higher temporal resolution will lead to higher image quality that may result in higher diagnostic accuracy. In contrast to ICA, CTCA visualizes not only the vessel lumen, but also the vessel wall, together with other (thoracic) structures. Therefore it is able to optimally visualize distinct abnormalities, such as coronary anomalies, with their relation to other cardiac structures. See addendum 1 and 2 for two case examples. With the growing availability of CTCA we believe that CTCA will be performed regularly in addition to, or instead of, ICA for further evaluation when such abnormalities are suspected. On the other hand, as more patients undergo (non-invasive) evaluation of coronary anatomy, more coronary anomalies may be detected. (36) This may herald outcome studies to investigate how these patients should be managed.

In contrast to ICA, CTCA visualizes coronary plaque in addition to the vessel lumen, therefore plaque burden can be measured. In figure 1 a case example is presented that shows how CTCA provides additional information to ICA about plaque burden, that was confirmed by intravascular ultrasound (IVUS). Recently, several studies have focused on coronary plaque characterization by CTCA (37, 38). Among risk characteristics for plaque rupture as detected by IVUS are the amount of necrotic core tissue and the density of thin-cap fibroatheroma. Several studies have shown a correlation between plaque composition measured by CTCA and IVUS data. (39-41). However, these were only small single center studies and the clinical consequences of these new data remains unknown.

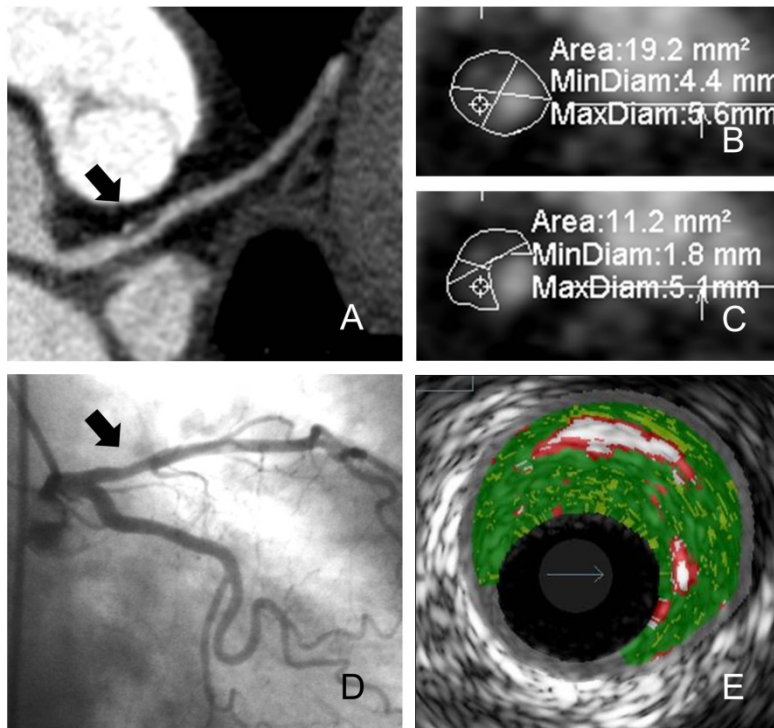


Figure 1. Underestimation of coronary plaque burden by ICA as compared to CTCA and IVUS. Panel A: CTCA curved multiplanar reconstruction of left anterior descending coronary artery (LAD) showing a mixed plaque (calcified and non-calcified plaque), arrow. Panel B and C: CT coronary angiography image showing cross sectional view of LAD at the sight of the mixed plaque with total vessel area of 19.2 mm and plaque area of 11.2 mm. Panel D: Invasive coronary angiography image of right anterior oblique view of LAD showing only mild stenosis in proximal LAD (arrow). Panel E: intravascular ultrasound image at the sight of lesion in LAD confirming large plaque burden (60%) consisting mainly of fibrotic tissue (green) and calcified plaque (white).

In a recent case report we showed how CTCA could visualize a myocardial perfusion defect in an acute traumatic myocardial infarction (see addendum 4). Recently, several studies have shown that myocardial perfusion imaging using CTCA can accurately detect significant CAD as defined by SPECT, ICA and FFR. (43-46) In contrast to CMR, CTCA has the advantage, that the concentration of ionated contrast agents has a linear relation to its signal intensity. Although these data are promising, further research is needed to overcome several issues such as the injection of high volumes of ionated contrast agents, high radiation dosage and the optimal timing of the perfusion scans.

Recently a novel CT derived FFR method was presented, using computational fluid dynamic-based algorithms to calculate a fractional flow reserve from CTCA data. Although the diagnostic accuracy of CT-FFR for detection of hemodynamically relevant CAD was high in a single center study, (47), this could not be reproduced in a larger multi-center study. (48)

New developments of CMR

Recently several studies have investigated the performance of first pass myocardial perfusion imaging on systems with higher field strength (3 Tesla) (49, 50). The higher signal to noise ratio can be used to increase spatial and/or temporal resolution and thus results in better image quality. It was shown that CMR perfusion imaging at 3 Tesla resulted in a significantly higher diagnostic accuracy for detection of significant CAD than at 1.5 Tesla (51, 52). Furthermore, higher spatial resolution, and thus image quality, may result in better differentiation of subepicardial from transmural and endocardial defects and this may lead to more insights into the pathophysiology of microvascular function. (53-54). Although CMR perfusion imaging at 3 Tesla seems promising, cine imaging using steady state free precession (SSFP), that is the corner stone of CMR imaging and an important part in a CMR ischemia protocol, is less stable and more susceptible to artifacts at 3 Tesla. (55) Therefore, further research in this field is needed.

Recently several new techniques have been introduced to further accelerate myocardial perfusion imaging and thus improving temporal resolution. Highly constrained back-projection reconstruction (56), and compressive sensing (57) are promising new techniques. For quantitative analysis of myocardial perfusion imaging more research is needed to overcome the problem of the non-linear relation between contrast concentration and signal intensity. Although several possible correction methods have been presented (58-60), these need further incorporation into clinically available post-processing software. Furthermore, development of motion correction software and automatic contour detection of CMR myocardial perfusion images will be pivotal to reduce analysis time and increase observer reliability. Then, automatic quantitative analysis can be very important in clinical decision making, eg. for detection of (balanced) 3-vessel disease. It will provide many research applications e.g. in the field of myocardial perfusion related to microvascular dysfunction and follow-up of new therapies.

Although CTCA has surpassed MR coronary angiography for the detection of CAD, recently, several studies have shown promising results using 3D whole heart coronary angiography imaging sequences. (61, 62). Using this sequence, prognostically important left main disease and 3 vessel disease could be reliably ruled out (negative predictive value 99%). Especially in heavily calcified coronary arteries CMR may have additional value (63). However, acquisition time can be very long (> 15 minutes) and spatial resolution is still relatively low. With the development of new sequences at higher field strengths, these problems may be overcome and MR coronary angiography may be integrated in a CMR ischemia scan protocol.

Although CT-MR hybrid scanners do not exist, recently image fusion software for CTCA and CMR images was presented, in line with hybrid techniques using PET-CT or SPECT-CT. (64-65) It was shown that by using this technique the culprit atherosclerotic coronary segment could be allocated exactly to the corresponding perfusion defect. However, we believe that in low to intermediate risk patient population, a step wise strategy, rather than

hybrid protocol is more appropriate, thus taking maximal advantage of the high negative predictive value of CTCA, which will decrease the number of patients that will undergo additional functional testing.

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