Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Imaging

# Non-Invasive Diagnostic Workup of Patients With Suspected Stable Angina by Combined Computed Tomography Coronary Angiography and Magnetic Resonance Perfusion Imaging

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***Background:*** To evaluate additional adenosine magnetic resonance perfusion (MRP) imaging in the diagnostic workup of patients with suspected stable angina with computed tomography coronary angiography (CTCA) as first-line diagnostic modality.

***Methods and Results:*** Two hundred and thirty symptomatic patients (male, 52%; age, 56 year) with suspected stable angina underwent CTCA. In patients with a stenosis of >50% as visually assessed, MRP was performed and the quantitative myocardial perfusion reserve index (MPRI) was calculated. Coronary flow reserve (CFR) using invasive coronary flow measurements served as the standard of reference. CTCA showed non-significant CAD in 151/230 (66%) patients and significant CAD in 79/230 patients (34%), of whom 50 subsequently underwent MRP and CFR. MRP showed reduced perfusion in 32 patients (64%), which was confirmed by CFR in 27 (84%). All 18 cases of normal MRP (36%) were confirmed by CFR. The positive likelihood ratio of MRP for the presence of functional significant disease in patients with a lesion on CTCA was 4.49 (95% confidence interval [CI] 2.12–9.99). The negative likelihood ratio was 0.05 (95%CI 0.01–0.34).

***Conclusions:*** CTCA as first-line diagnostic modality excluded coronary artery disease in a high percentage of patients referred for diagnostic workup of suspected stable angina. MRP made a significant contribution to the detection of functional significant lesions in patients with a positive CTCA. (*Circ J* 2011; **75:** 1678–1684)

**Key Words:** Computed tomography; Coronary angiography; Coronary artery disease; Coronary flow reserve; Magnetic resonance imaging

The use of computed tomography coronary angiography (CTCA) in the diagnostic workup of suspected coronary artery disease (CAD) is rapidly expanding. While CTCA reliably excludes severe CAD, the technique cannot accurately measure the severity of coronary obstructions or assess their hemodynamic importance. Prior studies with invasive coronary angiography (CAG)[1,2] have indicated that an anatomically significant lesion does not always equate with functional significance. With the introduction of CTCA this problem has reoccurred as nearly 50% of the significant lesions on CTCA were not functional relevant.[3,4] Recently, adenosine magnetic resonance perfusion (MRP) imaging has emerged as a safe technique for evaluating the functional significance of a stenosis.[5] We hypothesized that MRP could identify which patients with an abnormal CTCA result require further invasive investigation. We therefore investigated the additive value of MRP in symptomatic patients where CTCA was used as the first-line diagnostic tool and additional testing was indicated, using invasive coronary flow reserve (CFR) as our standard of reference.

Editorial p1575

## Methods

### Study Population

Between September 2007 and February 2009 CTCA was

Received November 24, 2010; revised manuscript received February 13, 2011; accepted March 8, 2011; released online June 10, 2011
Time for primary review: 22 days

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ISSN-1346-9843 doi:10.1253/circj.CJ-10-1154

part of the routine workup of patients with stable chest complaints and suspected CAD. During this period most patients with a visually estimated obstruction of ≥50% in at least one coronary vessel on CTCA were referred for CAG at the discretion of the physician, using the information of patient history, risk factors and additional non-invasive stress testing if performed. All referred consecutive patients were approached to undergo MRP and CFR measurements during invasive CAG. The pre-test probability for obstructive CAD was estimated using the Diamond and Forrester score based on the type of chest discomfort, age and gender, regarding <20% as low, 21–80% as intermediate, and >80% as high probability.[6] Exclusion criteria were (1) previous myocardial infarction, (2) previous percutaneous coronary intervention or coronary artery bypass grafting, (3) contraindications for magnetic resonance imaging (MRI), (4) possible pregnancy and/or breast feeding, (5) inability to hold breath for up to 15 s, (6) inability to give reliable informed consent, (7) known claustrophobia, (8) unstable CAD, (9) known allergy to contrast material; (10) renal insufficiency with glomerular filtration rate <60 ml·min$^{-1}$·1.73 m$^{-2}$; (11) chronic obstructive pulmonary disease; (12) persistent arrhythmias. The institutional review board of the Erasmus University Medical Centre in Rotterdam approved the study and all participating patients gave written informed consent.

## CTCA

CTCA was performed with a 64-slice dual-source CTCA scanner (Siemens Definition, Forchheim, Germany). A 80–100-ml bolus of iopromide (Ultravist 370 mg I/ml, Schering, AG, Berlin, Germany) was injected at a rate of 5.0–5.5 ml/s, followed by a 40-ml saline bolus chaser at an identical injection rate. Data acquisition was synchronized with contrast enhancement of the coronary arteries by means of a bolus tracking technique. A spiral CTCA scan was performed with the following parameters: tube voltage 120 kV, nominal tube current 380–412 mA/rotation, rotation time 330 ms, temporal resolution 83 ms, variable table feed of 0.20–0.34 depending on the heart rate, collimation 32×0.6 mm with double Z-axis sampling resulting in a 64-slice acquisition. Prospectively ECG-triggered tube modulation with selective tube output during the desired cardiac phase, mid-diastolic for heart rates <65 beats/min and from end-systolic to mid-diastolic for higher heart rates, was used to reduce the radiation dose. The mean radiation dose was 11.3±2.8 mSv, including preparation scans. The scan time varies between 5 and 10 s, depending on the table feed. All patients received nitroglycerin (0.4 mg/dose) sublingually, before scanning, no additional $\beta$-blockers were used. The average heart rate during acquisition was 66± 12 beats/min. Using retrospective ECG-gating, 0.75-mm slices were reconstructed at 0.4-mm intervals during mid-diastole and/or end-systole depending on the tube modulation protocol, with a medium smooth kernel (B26f).

Axial source, multiplanar reformations and maximum intensity projections were used for qualitative assessment of the coronary arteries. Vessels were qualitatively scored as significantly stenosed (≥50% diameter narrowing) or not significantly stenosed (<50%). Two experienced observers unaware of the MRP, CFR and clinical results of the patients analysed the CTCA based on consensus reading. Borderline lesions were considered significant. Additionally based on left or right dominance, the left ventricular segments (AHA model) were determined as being perfused by either the left or right coronary artery.

## Cardiac MRP Imaging

**Scan Protocol** A 1.5-Tesla scanner with an 8-element phased-array receiver coil was used for imaging (Signa CV/*i*, GE Medical Systems, Milwaukee, WI, USA). Repeated breath holds and gating to the ECG were applied to minimize the influence of cardiac and respiratory motion on data collection. Cine MRI was performed using a steady-state free-precession technique (FIESTA). Sequence details have been published before.[7] To cover the entire ventricle 10–12 cine breath-hold short-axis images were acquired. After rest cine imaging, rest perfusion imaging was performed. During a breath hold, the extravascular contrast media, gadolinium diethyltriaminepentaacetic acid (Magnevist, Schering, Germany) was injected via the intravenous catheter (0.05 mmol/kg at 3 ml/s; Medrad). Its first pass was monitored using a presaturation scheme with a notched excitation followed by a segmented gradient echo/echo-planar read-out with the following imaging parameters; field of view 32–36×32–36, rectangular field of view 0.75, repetition time 6.8 ms, echo time 2.0 ms, inversion time 150–175 ms, preparation pulse 90°, time to echo 1.2, train length 4, number of averages 0.75, bandwidth 125 kHz, flip angle 20, matrix 128/96, slice thickness 8 mm. Voxel size was 2.5–2.8 mm vs. 2.5–2.8 mm vs. 8 cm. The temporal resolution per slice of 120 ms allowed imaging of 3–5 slices per R-R interval. Perfusion imaging covered the basal mid and apical part of the left ventricle. Fifteen minutes after rest perfusion vasodilatation was induced by adenosine (140 $\mu$g·kg$^{-1}$·min$^{-1}$ body weight over 3 min) a second bolus of gadolinium diethyltriaminepentaacetic acid was injected via the intravenous catheter (0.05 mmol/kg at 3 ml/s) and stress first-pass perfusion images were acquired using the same pulse sequence and orientations used for rest perfusion. Approximately 10 min the later delayed enhancement MRI was performed with an inversion recovery gradient echo sequence 10–20 min after gadolinium injection. Imaging parameters have been published previously.[8] Slice locations of the delayed enhancement images were copied from the cine images.

**CMR Data Analysis** All images were transferred to a Microsoft Windows™-based personal computer for analysis (CAAS-MRV, version 3.2.1; Pie Medical Imaging, Maastricht, The Netherlands). Left ventricular volumes and ejection fraction (EF) were analyzed using the additional information of the long-axis to limit the extent of volume at the base and the apex of the heart.[7] Papillary muscles and trabeculations were considered as being part of the blood pool volume. A 16-segment model, excluding the apex, was used to analyze the myocardial wall in each patient.

For perfusion analysis, the mean signal intensity for each myocardial segment was registered over time, displayed as signal intensity–time curves. The maximum upslope of the signal intensity was determined by using 5 consecutive points on the curve, a straight-line model was used for a linear fit of the data. The maximum upslope of the signal intensity of the myocardial segment was divided by the maximum upslope of the signal intensity of the left ventricular cavity. This was calculated during rest and during the hyperemic phase. The myocardial perfusion reserve index (MPRI) was calculated by division of the corrected upslope of the stress examination by the corresponding segment's corrected upslope value of the rest examination. A MPRI of 2.0 was used to define a functional important stenosis.[9,10] The MRP scans were evaluated by an experienced observer unaware of the results of CTCA and CFR.

**Table. Patient Demographics**

| | CTCA ≥50% (n=79) | CTCA <50% (n=151) | P value |
|---|---|---|---|
| **Age (years)** | 62±7 | 55±9 | <0.05 |
| **Men** | 54 (68) | 62 (41) | <0.05 |
| **Risk factors** | | | |
| Smoking | 22 (29) | 41 (27) | 1.00 |
| Diabetes mellitus | 12 (15) | 15 (10) | 0.15 |
| Hypertension | 39 (49) | 66 (44) | 0.72 |
| Hypercholesterolemia | 32 (41) | 57 (38) | 0.49 |
| Family history of ischemic heart disease | 28 (35) | 69 (45) | 0.25 |
| **Pre test probability of CAD*** | | | |
| Low (0–20%) | 11 (14) | 30 (19) | 0.18 |
| Intermediate (21–80%) | 51 (64) | 103 (68) | 0.09 |
| High (81–100%) | 17 (22) | 18 (12) | <0.05 |

Values are number (%) or mean±standard deviation.
*According to the Diamond and Forrester criteria.[24]
CTCA, computed tomography coronary angiography; CAD, coronary artery disease.

### Intracoronary Flow Wire

All patients underwent ICA through the femoral artery using a 6 or 7 French guiding catheter. After injection of 2 mg isosorbide dinitrate, angiograms of the left and right coronary arteries were acquired in multiple projections using standard techniques. In each vessel with a significant stenosis as detected on CTCA, CFR measurements were performed using a combo wire (model 9500, volcano, Zaventem, Belgium). The intracoronary flow wire was passed through the catheter to a position distal to the stenosis and a Doppler signal was derived. The wire was rotated and repositioned to obtain a typical flow pattern. If unsuccessful the wire was positioned into a side branch and flipped to obtain a more central position in the vessel and to derive a good flow signal. In each vessel the intracoronary average peak velocity was measured at rest and during maximal hyperemia after injection of adenosine ($140\,\mu g \cdot kg^{-1} \cdot min^{-1}$) with continuous monitoring of symptoms, heart rate, blood pressure and ECG. CFR was calculated as the ratio of the hyperemic average peak velocity divided by the rest average peak velocity. The CFR was determined in an average of 2 stable consecutive beats at rest and during hyperemic stress. In this study a significant reduction in CFR was defined as a CFR <2.0 based on previous results.[11]

All data were analyzed in a random order with the investigator blinded to the clinical information and the previous results.

### Statistical Analysis

Continues variables are expressed as mean±standard deviation. Categorical variables are expressed as numbers and percentages. The diagnostic performance of MRP in patients with a positive CTCA for the detection of functional significant CAD as defined by CFR is presented as sensitivity, specificity, positive predictive value, negative predictive value with the corresponding 95% confidence intervals (CI), and positive and negative likelihood ratios (LRs) with corresponding 95%CI were calculated. All data analysis was performed with SPSS for Windows 15.0.0 (SPSS Inc, Chicago, IL, USA).

## Results

### Patient Cohort and CTCA Results

Of the 260 patients with chest pain without a history of cardiovascular disease that visited our outpatient clinic, 230 did not have clinical contraindications for CTCA. For the cohort of patients undergoing CTCA the pre-test likelihood of CAD was low, intermediate and high in 19% (44 of 230), 67% (154 of 230) and 15% (35 of 230), respectively. The median interval between CTCA and CAG was 30 days (25th and 75th percentiles, 16–46), without any interventions or events during that period for any of the patients. Baseline patient characteristics are presented in Table. The average age was higher and male gender and a high pre test probability was more prevalent in the patient group with significant CAD on CTCA.

CTCA showed no significant lesions in 151 (66%) patients and a significant lesion in 79 patients (34%). In patients without a lesion on CTCA, lifestyle changes were advised and medical therapy initiated following primary prevention guidelines.[12] Further follow-up of these patients was performed by a general practitioner. After 1 year, patients were contacted by telephone by the initial investigators. None of the patients without CAD on CTCA had undergone revascularization in the 1-year follow-up period.

In 79 patients, a significant stenosis on CTCA was detected in 118 vessels: in 66 vessels in the left coronary artery, in 25 vessels in the left circumflex and in 27 vessels in the right coronary artery.

Of the 79 patients with significant stenosis on CTCA, 17 were not referred for CAG because on CTCA all these patients had small vessel disease (visual estimated vessel diameter <2 mm) in side branches of major coronary arteries and secondary prevention was started. Of the 62 patients referred for CAG after CTCA, 50 patients consented and participated in this study and underwent CMR. Of the remainder, 4 had contraindications to MRI (all claustrophobic), 5 refused to be enrolled, in 1 patient the MPRI could not be determined because of the limited image quality due to triggering problems and 2 patients could not be enrolled due to logistic reasons (Figure 1). Despite the fact that none had a known history of myocardial infarction, 5 patients showed delayed myocardial enhancement suggestive of prior ischemic injury. None of these infarcts were in the region of the vessel with a stenosis on CTCA and thus did not influence the MPRI.

### Diagnostic Performance of MRP

Mean left ventricular EF was 64±6%, end-diastolic volume

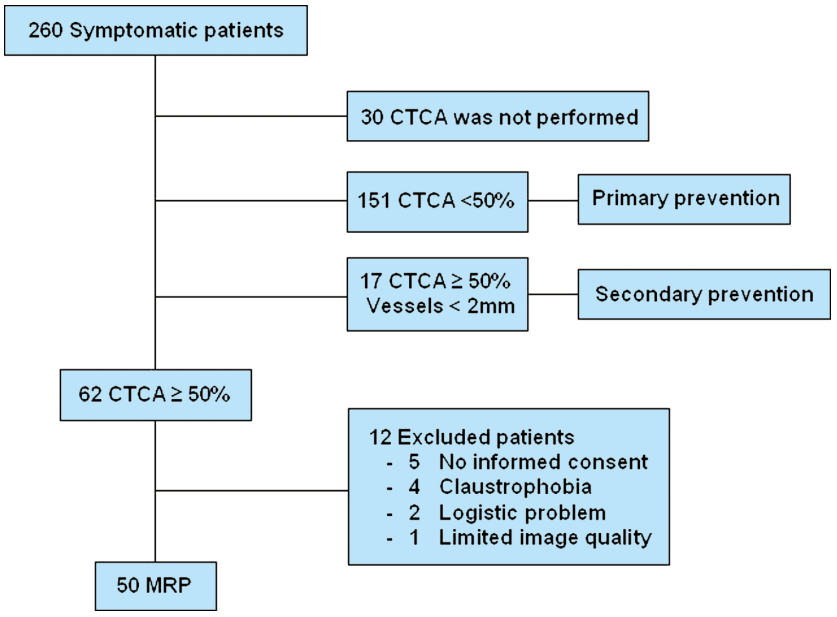


**Figure 1.** Flow diagram according to the STARD criteria. CTCA, computed tomography coronary angiography; MRP, magnetic resonance perfusion.

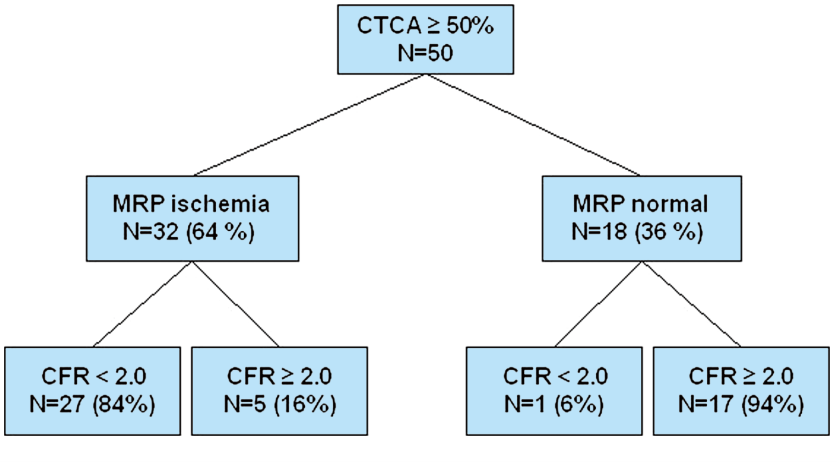


**Figure 2.** Flow chart describing the relationship between computed tomography coronary angiography (CTCA), adenosine magnetic resonance perfusion (MRP) and coronary flow reserve (CFR). This flow chart illustrates the additional value for MRP in patients with obstructive coronary artery disease on CTCA.

index was 80±16 ml/m$^2$, and end-systolic volume index was 29±9 ml/m$^2$. In 17 (34%) patients, MRP correctly ruled out functional significant CAD (ie, CFR >2; **Figures 2,3**). In 1 patient, MRP showed no significant perfusion defect although CFR was <2.0. Of the patients with a positive MRP scan (n=32), 27 had a CFR <2, indicating coronary insufficiency. For 5 patients with a perfusion deficit on MRP the CFR was within normal limits (**Figure 4**).

Pre-test probability of a reduced CFR in patients with a positive CTCA was 54% (27/50). The post-test probability after MRP was 84%. The positive LR for the presence of functional significant disease was 4.49 (95%CI 2.12–9.99). The negative LR was 0.05 (95%CI 0.01–0.34). Sensitivity, specificity, and positive and negative predictive values for MRP for the detection of a reduced CFR in patients with a positive CTCA scan were 96% (79–99), 78% (61–95), 84% (71–98) and 95% (72–99).

### Multivessel Disease

Of the 50 patients with significant obstructive CAD on CTCA, 20 (40%) patients had multivessel disease and of them, MRP showed a reduced perfusion index in multiple perfusion territories in 15 patients. In the other 5 patients multivessel diseased was ruled out, which was confirmed by CFR. Of the 15 patients with a positive MRP, only 7 could be confirmed as having multivessel disease.

## Discussion

We demonstrated that, in this study group with an overall low prevalence of disease in patients referred for evaluation of chest pain suspected as CAD, an initial normal CTCA scan occurred in the majority (66%) of these patients, ruling out obstructive CAD in a fast and reliable manner. In the patients with an abnormal CTCA scan MRP correctly excluded the presence of a functionally significant lesion in 34% of the patients, thereby avoiding referral for invasive coronary evaluation. An abnormal MRP resulted in an increased presence of functional significant CAD from 54% to 84% with a positive LR of 4.49.

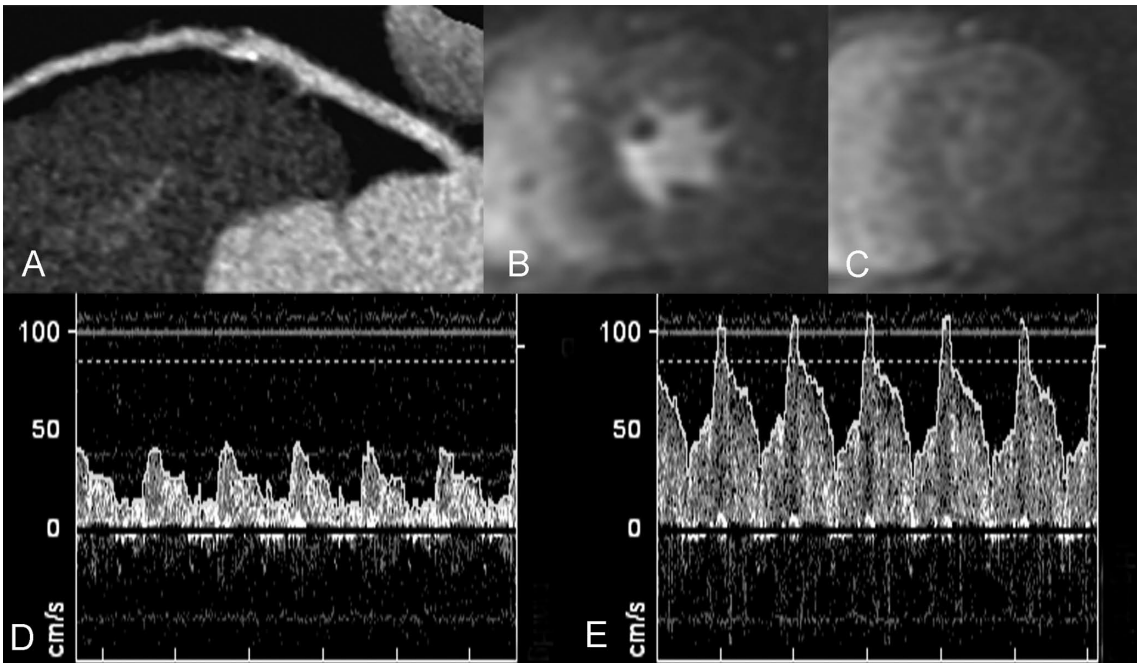


**Figure 3.** (**A**) CTCA image showing significant lesion in the mid-LAD. MR perfusion image during adenosine stress (**B**) and during rest (**C**) with normal perfusion of the myocardium in the perfusion territory of the LAD; the MPRI in this region was 2.3. CFR image of flow during rest (**D**) and during adenosine stress (**E**). The CFR in this patient was 2.6. CFR, coronary flow reserve; CTCA, computed tomography coronary angiography; LAD, left anterior descending; MPRI, myocardial perfusion reserve index; MR, magnetic resonance imaging.

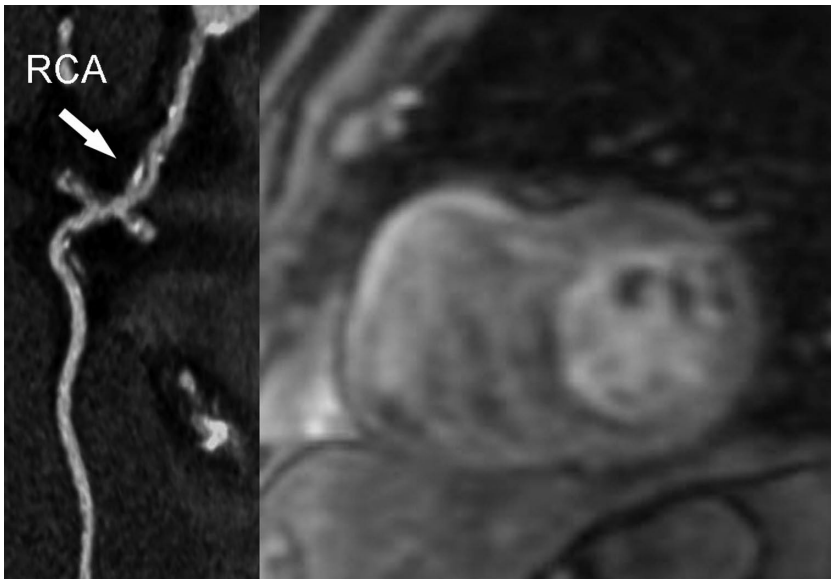


**Figure 4.** Patient with a significant lesion in the RCA on CTCA (**Left**) and a perfusion defect in the inferoseptal wall on MRP (**Right**), the CFR in this patient was 1.9. CFR, coronary flow reserve; CTCA, computed tomography coronary angiography; RCA, right coronary artery.

## CTCA as First-Line Diagnostic Test

Whether CTCA or functional testing should be used first in patients with chest pain and a low to intermediate risk for CAD is still under investigation. In this study MRP was added to CTCA, which served as the first-line diagnostic modality. Arguments in favor of CTCA are the high negative predictive value, mostly observed in studies of patients with a high prevalence of disease,[13–15] and excellent long-term outcome in a patient group without significant stenosis and a low prevalence of disease.[16] At the current time few medical centers have the facilities or resources to perform MRP on a routine basis and MRP is a complex technique not very suited as a first-line test in the general population because it takes almost an hour for an experienced team to acquire the full protocol,

including stress and rest perfusion imaging, functional imaging and delayed enhancement. Also, the post-processing for quantitative analysis can be cumbersome and the associated costs currently inhibit the widespread use of MRP as a first-line diagnostic test. CTCA is a faster test, with interpretable results in nearly all patients; it is less expensive as compared to MRP and a strategy based on performing CTCA first is further enforced as faster scanners with lower radiation dose are now available. However, evaluating a calcified lesion is difficult and vulnerable to overestimation of the degree of stenosis.[17] In the case of calcified lesions, visual estimation took into account the calcium-related blooming artifacts, which give an increased appearance of obstruction. Non-contrast-enhanced CTCA has limited value in patients with a high coronary calcium score (Agatston score >400), although image quality is constantly improving with the hardware and software developments, resulting in a better anatomical diagnosis in these patients.[18]

### MRP as Functional Test

MRI is one of several imaging techniques available to detect inducible myocardial hypoperfusion,[19,20] which includes single-photon emission computed tomography (SPECT), positron emission tomography and echocardiography. The advantages of MRP are its high spatial resolution, the absence of ionizing radiation, no need for an acoustic window, the possibility of combining the stress-test with sensitive infarct imaging, and reproducible evaluation of ventricular function. Also, a normal MRP is associated with excellent long-term survival.[21] MRP, as with most non-invasive perfusion imaging techniques, provides information about the blood supply to the myocardium, which is affected by epicardial and microvasculature disease. Microvascular perfusion, which also may cause chest pain, can be reduced in patients with hypertension,[22] diabetes[23] or obesity.[24] Based on this knowledge we compared non-invasive MRP to invasive CFR measurement, which is similarly affected by both the epicardial vessels as well as the microvasculature.

### Combined Use of CTCA and MRP

Our study confirmed the acknowledged and long-known poor correlation between anatomy and function for stenoses of intermediate severity in particular.[1,2] Despite the presence of obstructive CAD on CTCA, 36% of the present patients showed no inducible perfusion abnormality on MRP, and 47% had a normal CFR. Poor correlation between anatomy and function has similarly been demonstrated for CFR or fractional flow reserve (FFR) vs. QCA,[25] as well as SPECT and FFR vs. CTCA,[3,11,26] and recently of CTCA compared with MRP.[27] In the study by van Werkhoven et al,[27] normal perfusion was observed in 33% of the patients with significant obstructive CAD on CTCA. Furthermore, comparing CTCA with invasive FFR measurements demonstrated that a significant lesion on CTCA was not functionally relevant in approximately 50% of the patients;[3] in our population also, no functionally significant lesion was detected in 45% of those with significant obstructive CAD on CTCA. Based on this knowledge, revascularization decisions have to be based on both anatomical and functional information. Using the combined approach, 27 of 32 (84%) patients with a positive CTCA and MRP were confirmed by the reference standard, which is a post-test probability sufficient to warrant invasive CAG. A negative rule out could be obtained in 151 of 230 (66%) patients with one test, and 22 (10%) underwent both tests without having functional CAD. These numbers strongly support the proposed algorithm of CTCA as first-line diagnostic test followed by MRP in patients with a positive CTCA. This strategy has to be confirmed with larger studies with longer follow-up and cost-effectiveness analysis.

### Study Limitations

First, in patients with a negative CTCA scan MRP was not performed. However, it is known that patients with suspected CAD and no or minimal coronary arteriosclerosis on CTCA may be safely deferred.[28,29] Also, we did not observe any revascularization in patients where CTCA was negative. A second limitation was that in 17 patients with a positive CTCA the routine clinical workup did not support invasive analysis, because of small vessel disease, and therefore they could not be part of this study. None of those patients had major cardiac events or invasive test during the 12-month follow-up, confirming the original conservative strategy of the treating physician.

## Conclusion

Given the previously discussed findings and the consistently high negative predictive value for CTCA in different patient populations we can conclude that in patients with chest pain suspected as CAD a combined approach using anatomy and function may best identify, in a fast and effective manner, the patients who will most likely benefit from further invasive CAG.

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