Integrating CT myocardial perfusion and CT derived FFR in the workup of coronary artery disease.

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Integrating CT myocardial perfusion and CT derived FFR in the workup of coronary artery disease.

Abstract

Objectives
This study investigates the individual and combined accuracy of dynamic CT myocardial perfusion imaging (CT-MPI) and CT derived fractional flow reserve (CTA-FFR) for the identification of functionally relevant coronary artery disease (CAD).

Background
Coronary CT angiography (CTA) has become an established diagnostic test for ruling out CAD, but does not allow for interpretation of the hemodynamic severity of stenotic lesions. Two recently introduced functional CT techniques are dynamic myocardial perfusion imaging and CTA-FFR using computational fluid dynamics.

Methods
From two institutions 74 patients (62 male, 61 years) planned for invasive angiography with invasive FFR in 142 vessels, underwent CTA and dynamic CT-MPI during adenosine vasodilation. A patient specific myocardial blood flow index was calculated, normalized for the remote myocardial global left ventricular blood flow. CTA-FFR was computed using an on-site, clinician operated application. Using binary regression a single functional CT variable was created combining both CT-MPI and CTA-FFR. Finally, a stepwise diagnostic work-up of CTA-FFR with selective use of CT-MPI was simulated. Diagnostic performance of CT-MPI, CTA-FFR and CT-MPI integrated with CTA-FFR were evaluated using C statistics with invasive FFR with a threshold of 0.80 as reference.

Results
Sensitivity, specificity and accuracy were 73% (61-86%), 68% (56-80%) and 70% (62-79%) for CT-MPI, and 82% (72-92%), 60% (48-72%) and 70% (63-80%) for CTA-FFR. For CT-MPI integrated with CTA-FFR diagnostic accuracy was 79% (71-87%), with improvement of the AUC from 0.78 to 0.85 (p<0.05). Accuracy of the stepwise approach was 77%.

Conclusions
CT-MPI and CTA-FFR both identify functionally significant CAD, with comparable accuracy. Diagnostic performance can be improved by combining both techniques. A stepwise approach, reserving CT-MPI for intermediate CTA-FFR results, also improves diagnostic performance while omitting nearly half of the population from a CT-MPI examination.
Condensed abstract:

CT myocardial perfusion imaging (CT-MPI) and CT derived FFR (CTA-FFR) are different approaches to improve the diagnostic accuracy of cardiac CT in the detection of functional coronary artery disease (CAD). Dynamic CTA-MPI and on-site CTA-FFR were integrated to detect functional CAD defined by invasive FFR. From two institutions 74 patients, with 142 vessels with invasive FFR were investigated. The AUC of the integrated approach (0.85) was superior to CTA (0.70), CT-MPI (0.78) or CTA derived FFR (0.78) alone. A stepwise approach, reserving CT-MPI for intermediate CTA-FFR results, also improved diagnostic performance while omitting a considerable proportion of patients from a CT-MPI examination.

Abbreviations:

AIF: arterial input function
CAD: coronary artery disease
CTA: Coronary CT angiography
CTA-FFR: Coronary CT angiography derived fractional flow reserve
CT-MPI: CT myocardial perfusion imaging
DSCT: dual-source CT scanner
FFR: fractional flow reserve
MBF: myocardial blood flow
MBF(LV)75%): Myocardial blood flow of the myocardial segment representing the 75 percentile
TAC: time-attenuation curve
On-site CT derived FFR versus dynamic CT myocardial perfusion imaging for functional assessment of coronary artery disease.

Introduction

CT angiography (CTA) has become an established diagnostic technique to assess coronary artery disease (CAD). However, CTA provides only anatomical information and tends to overestimate stenosis severity, particularly in the presence of calcifications (1,2). Over the past decade functional parameters have become more important for management decisions, in particular with regard to mechanical revascularization. Catheter-based fractional flow reserve (FFR) is currently regarded as the reference for the assessment of the hemodynamic severity of CAD (3-5). The relation between angiographic stenosis and function significance is diffuse. Compared to invasive FFR the specificity of CTA with a conventional 50%-stenosis threshold is low (6-8).

Several strategies have been developed for functional assessment of CAD by cardiac CT. In this study we investigated the diagnostic performance CTA and two recently introduced functional cardiac CT techniques: dynamic CT myocardial perfusion imaging (CT-MPI) and CTA based computational FFR (CTA-FFR) using an application that can be performed locally on-site.

Methods

Study design

At two centers 76 patients with known or suspected CAD underwent CTA and CT-MPI <14 days before clinically indicated invasive coronary angiography (9). By study protocol, FFR measurements were performed in vessels with a visual diameter stenosis between 30-90%.

Exclusion criteria: age below 40 years, invasive FFR measurement not performed,
impaired renal function, possible pregnancy or breast feeding, body weight over 120kg, use of clopidogrel, total occlusion of a dominant coronary artery, non-diagnostic CTA image quality, or contra-indications for iodine contrast material or adenosine.

The study protocol was compliant with the declaration of Helsinki and received approval from the Research Ethics Committee at each institution. All patients provided written informed consent.

**CTA**

All patients received sublingual nitroglycerine before the CTA. Beta-blockers were only used very selectively before CTA because of potential interaction with the adenosine response needed for the dynamic CT-MPI. The prospective ECG-trigged axial scan mode was used with an exposure window during diastole and/or systole depending on the heart rate. Tube current and tube voltage were selected semi-automatically based on body size. A test bolus acquisition was performed using 15 mL of contrast medium followed by 40 mL saline chaser. For the CTA a contrast bolus of 50-60 mL (depending on iodine concentration) was injected to achieve an iodine delivery rate of 2.2 g/iodine per second, followed by a 40 mL saline bolus chaser. Images were reconstructed with a medium smooth kernel (B26, Bv40), slice thickness of 0.5 mm and an increment of 0.3 mm.

The CTAs were evaluated by an experienced reader, blinded to all other modalities. On a per vessel basis stenosis were classified as recommended by the Society of Cardiovascular Computed Tomography: normal: 0% lumen diameter reduction; minimal: 1-24%; mild: 25-49%; moderate: 50-69%; severe 70-99%; occluded: 100% (10). A stenosis grade of 50% or greater at CTA was considered to indicate angiographically significant stenosis. The most severe stenosis at
coronary CT angiography proximal to the FFR pressure wire position was defined as the lesion of interest.

**Dynamic CT-MPI**

All patients were instructed to withhold from caffeine intake 24 hours prior to the examination. In both antecubital veins a 18-gauge cannula was placed. Blood pressure and ECG were monitored during the examination. 71 patients were scanned with a second-generation dual-source CT scanner and 3 with a third-generation dual-source system (SOMATOM Definition Flash and SOMATOM Force, Siemens, Forchheim, Germany).

The scan range of the dynamic CT-MPI was planned using a low-dose non-contrast scan acquired during systole. Adenosine was infused over 3-6 minutes at 140 µgram/kg/min. 50 or 60 mL contrast media was injected resulting at an iodine delivery rate of 2.2 g of iodine per second, followed by a saline bolus of 40 mL. CT-MPI examinations were started 5 seconds after contrast injection was started, using an axial scan mode triggered at 250 ms after the R wave (end-systolic). Imaging of the complete left ventricle required a shuttle-mode acquisition technique. By moving the table back and forward after each acquisition two series of images were collected that together cover the entire myocardium. Depending on the heart rate scans were performed every second or third heart cycle, resulting in a series of 10-15 phases acquired over a period of approximately 30 seconds (11).

The following scan parameters were used:

2nd generation DSCT: collimation 2×64×0.6 mm, gantry rotation time 280 ms, temporal resolution 75 ms, tube voltage/current 100 kV/300 mA or 80 kV/370 mA per rotation, shuttle-
mode z-axis coverage 73 mm.

3rd generation DSCT: collimation 2×96×0.6 mm, gantry rotation time 250 ms, temporal resolution 66 ms, Care-kV was used reference setting of a tube voltage/current of 80 kV/300 mA, shuttle-mode z-axis coverage 102 mm.

CT-MPI post processing

The CT-MPI images were reconstructed using a dedicated kernel for reduction of iodine beam hardening artifacts (b23f, Qr36), and analyzed using a CT-MPI software package (Volume Perfusion CT body, Siemens, Forchheim, Germany). Motion correction was applied if necessary to correct for breathing related displacement of the left ventricle. The change of attenuation in the myocardium over time was computed from time-attenuation curves (TAC). For quantification of the MBF the influx of contrast medium was measured using the arterial input function (AIF). The AIF was sampled in the descending aorta. Precision of the AIF was increased by including both the cranial and caudal sections (double sampling). For quantification of the MBF the myocardial TACs were coupled with the AIF using a hybrid deconvolution model. The model uses a simplified impulse residue function for modeling of the interaction between intra- and extracellular compartments. On a per voxel basis MBF was computed by dividing the convoluted maximal slope of the myocardial TAC by the maximum AIF (11-13). MBF maps were reconstructed as a stack of color-coded images with a slice thickness of 3 mm and an increment of 1.5 mm.

CT-MPI image analysis

CT-MPI images were analyzed with disclosure of which vessels were interrogated by invasive
FFR, as well as coronary dominance to ensure correct coronary-myocardial interpretation. Readers were blinded to the CTA and invasive coronary angiography and all other medical information.

From the MBF map the slice best representing the myocardium associated with the vessel of interest was selected. Within this cross-section a polygonal region of interest (ROI) with a minimal area of 50 mm², was placed to sample the MBF within the suspected perfusion defect (Syngo Via 2.0, Siemens, Forchheim, Germany).

Because CT-MPI studies have demonstrated that the global MBF value varies between patients, an index MBF value was applied with normalization for inter-individual differences in myocardial flow.\(^{(12,14,15)}\)

A prototype software (Cardiac Functional Analysis; Siemens) was used to generate a polar map for MBF, fitting the modified 17-segment AHA myocardial model onto the CT-MPI MBF maps.\(^{(16)}\) The index MBF value was calculated as the ratio between the MBF sample and the MBF of the myocardial segment representing the 75 percentile (MBF\(_{LV}\)\(_{75\%}\)).

\[
\text{Indexed MBF} = \frac{\text{Measured MBF}}{\text{MBF}(LV)_{75\%}}
\]

**CTA-FFR**

On-site CTA-FFR was computed using a dedicated clinician-operated prototype application (cFFR version 1.4, Siemens, Forchheim, Germany; currently not commercially available). From a CTA datasets with optimal image quality a 3D coronary model was semi-automatically segmented, after which markers were manually placed proximal and distal to each stenotic lesion. The CTA-FFR algorithm is composed of a hybrid model using a reduced-order model in the non-stenotic regions and pressure drop models in the stenotic regions. Based on allometric
scaling laws the resting total coronary blood flow is estimated based on the left ventricle mass derived automatically from the CTA.(17) The resting total coronary blood flow is distributed over the 3D coronary model. By reducing the microvascular resistance with a factor of 0.21, similar to values achieved by adenosine infusion, a hyperemic state can be simulated (18). By comparing the computed pressures in the aorta and distal to the coronary lesion during simulated hyperemia an FFR value can be determined. FFR values are computed throughout the coronary arteries, and can be superimposed as color gradients onto a 3D coronary model (19).

After the CTA-FFR map was rendered, the sample location of the invasive FFR pressure wire was released. Without making any changes to the CTA-FFR model, or revealing the invasive FFR results, the simulated FFR value at the corresponding invasive FFR pressure wire position was recorded (Figure 2). A CTA-FFR value ≤0.80 was considered as hemodynamically significant.

**Invasive angiography and fractional flow reserve**

Invasive coronary angiography was performed according to local clinical standards. By study protocol, invasive FFR was performed in all vessels with a diameter reduction between 30-90%. An FFR pressure wire (PressureWire Aeris/Certus, St. Jude Medical, St. Paul, USA or Prime/Combo Wire, Volcano, San Diego, USA) was positioned distal to the stenosis of interest, after which hyperemia was induced by intravenous infusion of adenosine at 140 µg/kg/min. An FFR ≤0.80 was considered hemodynamically significant. To co-register the location of the invasive FFR measurement and CTA-FFR, an independent observer without knowledge of the angiographic or functional results, identified the invasive FFR sample location on the fluoroscopy images and marked the corresponding location onto the CTA images.
Statistics

Absolute variables are represented as totals and percentages, continuous variables as means and standard deviations (±) or median and inter-quartile (IQ) ranges. Effective radiation dose was calculated using a conversion factor of 0.014.

Combined performance of CTA, CT-MPI and CTA-FFR was investigated using binary logistic regression (Appendix 1).

A stepwise diagnostic work-up based on CTA-FFR with restrictive use of CT-MPI was designed by determining the CTA-FFR thresholds that resulted in a sensitivity of 90% (lower threshold) and specificity of 75% (upper threshold). Vessels with a CTA-FFR value between these two ranges (CTA-FFR intermediate zone) were reclassified according to the CT-MPI results.

The CT-MPI, CTA-FFR, and combined CT-MPI and CTA-FFR values for normal and ischemic territories were compared with an unpaired two-sided independent t-test. Correlation between CT-MPI and CTA-FFR was calculated using the Pearson’s correlation coefficient. The optimal threshold was calculated using the Youden index. The 95% confidence intervals were corrected for within patient clustering of data using generalized estimating equations (20). Most statistical analysis were made using SPSS (version 21, IBM Corp, Armonk NY, United States of America), while MedCalc (version 13.0; MedCalc Software, Ostend, Belgium) was used to compare the AUCs by using the method of DeLong et al (21).

Results

The study population consisted of 74 patients, in whom 142 vessels were investigated by
invasive FFR (Figure 1, Table 1). The radiation dose was 3.7 ± 3.2 mSv for the CTA and 9.3 ± 1.8 mSv for the dynamic CT-MPI. The median invasive FFR was 0.83 (IQ: 0.73-0.91), and 67 (47%) vessels were considered hemodynamically significant by an invasive FFR ≤0.80.

**CTA**

Two vessels were classified as normal, 19 as minimal, 31 as mild, 72 as moderate, 16 as severe, and two as occluded. The area under the curve (AUC) for CTA was 0.70 (Figure 3). The sensitivity and specificity of CTA were 78% (95% CI:65-90%) and 49% (38-61%) (Table 2).

**Dynamic CT-MPI**

The absolute myocardial blood flow values were 108 ml/100ml/min for the normal (invasive FFR>0.80) territories and 79 ml/100ml/min for the ischemic (FFR≤0.80) territories (p=0.001). The optimal threshold for absolute MBF was 91 ml/100ml/min. Diagnostic accuracy of absolute MBF was 68% (59-76%) (Table 2). The area under the curve (AUC) was 0.75.

The mean index MBF was 0.78 ± 0.16 for normal territories and 0.60 ± 0.17 for ischemic territories (p<0.001) (Figure 4). The Pearsons correlation coefficient with invasive FFR was 0.48. The AUC was 0.78 (Figure 3). Based on the optimal threshold of 0.71 as computed with the Youden index, dynamic CT-MPI correctly classified 100 out of 142 territories, resulting in a diagnostic accuracy of 70% (Table 2).

**CTA-FFR**

The median CTA-FFR was 0.77 (IQ: 0.66-0.86) for all 142 vessels, and 0.84 (IQR: 0.74-0.92) for normal and 0.69 (IQR: 0.55-0.78) for ischemic territories (p<0.001). Correlation with
invasive FFR was 0.61. The AUC for CTA-FFR was 0.78. The optimal threshold computed with the Youden index was 0.81, however in this analysis the standard threshold of 0.80 was used (Figure 3). The diagnostic accuracy of CTA-FFR was 70% (Table 2). CTA-FFR also correctly classified 100 out of 142 vessels.

**Integration of CTA, CTA-FFR and CT-MPI**

The combination of CTA and CT-MPI resulted in an increased AUC of 0.83, which is significantly larger than either CTA or CT-MPI alone (p<0.0001 & p=0.02). When combining CTA and CTA-FFR the AUC increased till 0.80, significantly larger than CTA alone (AUC, p=0.001), however the difference with CTA-FFR (0.78, p=0.31) was not significant. The combination of CT-MPI and CTA-FFR resulted in a diagnostic accuracy of 79% (table 2), and significantly increased the AUC (0.85) compared to either CT-MPI or CTA-FFR respectively (p=0.01 & p=0.03) (Figure 3).

Correct, and concordant classification by both CT-MPI and CTA-FFR was accomplished in 70/142 vessels/territories (49%) (Figure 5). A stepwise diagnostic work-up was simulated to identify the patients with the largest benefit from an additional CT-MPI examination following CTA-FFR evaluation. An upper threshold of CTA-FFR of 0.85 resulted in a sensitivity of 90% and a lower threshold of 0.74 resulting in an acceptable specificity of 75% (Figure 6). In 44 vessels (31%) the CTA-FFR value was between 0.74 and 0.85. The accuracy of CTA-FFR for these 44 vessel was 55% (24/44) and could be improved to 77% (34/44) if these vessels/territories were evaluated with CT-MPI instead of CTA-FFR. From the total 142 vessels this stepwise approach resulted in 110 correctly classified vessels, and theoretically avoided a CT-MPI examination in 34 (46%) patients, and 98 (69%) of the territories.
Discussion

The main findings of this paper are: 1) Both on-site performed CTA-FFR and dynamic CT-MPI perform well in the detection of functional CAD. 2) The combination of CTA and CT-MPI improves diagnostic performance, over either alone. 3) For CTA and CTA-FFR this increase was small and not significant. 4) CTA-FFR and dynamic CT-MPI provide complementary information, and integrated interpretation (as a single variable) improves diagnostic performance significantly. Alternatively, both techniques can also be used in sequence, where selective use of CT-MPI improves hemodynamic classification for intermediate CTA-FFR results (0.74-0.85).

Dynamic CT-MPI, as opposed to the previously introduced static CT-MPI, acquires a series of images during the transit of contrast medium through the myocardium, which allows for quantification of the myocardial blood flow in a way resembling quantitative MBF acquired by PET perfusion imaging (11,12). Based on the known variation in (measured) global myocardial blood flow during hyperemia between scans, we applied a normalized MBF index instead of an absolute MBF threshold to classify the presence of myocardial ischemia. (12,14,15). However, indexation in a way sacrifices the absolute potential of dynamic CT-MPI, potentially leading to false negative results in the presence of three vessel disease. A recent study from Stuijfzand et al. showed that in oxygen-15-labeled water PET perfusion a relative flow reserve did not significantly perform better than quantitative MBF assessment (22). The average radiation dose of a dynamic CT-MPI was 9.3 mSv, which is relatively high. However, with newer generation CT scanners acquisition of dynamic CT-MPI at lower tube voltage levels became available further reducing the radiation dose.

The diagnostic performance of CTA-FFR alone in this study was slightly lower than in
previous single center on-site CTA-FFR studies (23-25). Nakazato et al. investigated the
diagnostic performance of CT derived FFR application in a sub-study of the intermediate
stenosis severity vessels in the DEFACTO study. The diagnostic accuracy of 69% and AUC
(0.79) were similar to the results found in our study of 70% and 0.78 (26). However, when
compared with the AUC (0.93) of the NXT trial diagnostic performance of this study is lower
(27). The application used in the DEFACTO and NXT trial is a full order application from
Heartflow inc.. Apart from differences in the CT derived FFR methodology, differences in
prevalence of hemodynamic significant disease (47% in this study compared with 21% in NXT)
may have contribute to the difference in diagnostic performance (27).

In this study CT-MPI and CTA-FFR performed similarly well. FFR is a derivative of the
coronary blood flow based on the measurement of pressure. Although there is good correlation
between FFR and coronary flow, they are not entirely similar (28). In our study the combination
of both techniques significantly improved diagnostic performance in comparison to invasive
FFR, supporting the notion that each technique provides incremental value. In a recent study by
Yang et al. the combination of either static CT-MPI with CTA and CT derived FFR with CTA
improved diagnostic performance compare with CTA alone, however this study used static CT-
MPI instead of the dynamic method used in this study. (29).

For various reasons it is unlikely that in clinical practice both techniques will be routinely
applied in each patient. As CTA-FFR requires no additional testing, we simulated a diagnostic
workup where CTA-FFR would be performed first, and CT-MPI only in case of an intermediate
CTA-FFR results. Interpreted as a binary test it is expected that most misclassifications occur
around the threshold. Using the sensitivity-specificity plot CTA-FFR values (0.85) above which
sensitivity was ≥90%, and values (0.74) below which specificity was ≥75%, were considered
conclusive. Within the intermediate range our results indicate that CT-MPI improves interpretation of the hemodynamic significance of CAD.

**Study limitations:**

By the design of the study, and the invasive comparator, we investigated a moderate number of patients with a high disease burden. Whether the investigated techniques perform similarly in standard populations with a lower disease prevalence is currently unknown. A consecutive inclusion of patients was complicated by logistic factors as availability of researchers and competitive studies. While the non-consecutive enrollment was mainly based on logistic factors some degree of selection bias cannot be excluded. CTA-FFR and CT-MPI are fundamentally different techniques for which no perfect (single) reference is available. Because invasive FFR is currently regarded as the clinical reference to assess functional significance of CAD we selected this technique as the most optimal comparator. Derived thresholds for both dynamic CT-MPI and the combination of CTA-FFR and CT-MPI are based on this cohort and ideally would be validated in an external cohort. The on-site CTA-FFR used in this study was based on a prototype software and is currently also only being used in a research setting. It is uncertain whether our results can be extrapolated to other CTA-FFR or myocardial perfusion techniques. The average radiation dose of a dynamic CT-MPI was 9.3 mSv, this is relatively high. However, with newer generation CT scanners acquisition of dynamic CT-MPI at lower tube voltage levels became available. Preliminary observations in our institution suggest this would further reduce the radiation dose.
Conclusion:
On-site CTA-FFR and dynamic CT-MPI are promising approaches towards functional interpretation of coronary artery disease detected on cardiac CT, each demonstrating good diagnostic accuracy in comparison with invasive FFR. Integrated interpretation of both modalities further improves diagnostic accuracy. A stepwise workup where CT-MPI is reserved for patients with an intermediate CTA-FFR result (0.74-0.85), would also improve diagnostic accuracy, and could avoid a MPI examination in a substantial proportion of patients.

Clinical competencies
In the workup of stable chest pain an integrated approach combining myocardial perfusion imaging and CT derived FFR improves diagnostic accuracy. A diagnostic workup where an intermediate CT derived FFR result is followed by a myocardial perfusion scan could identify patients most benefitting for an additional myocardial perfusion scan, while the remaining patients avoid an additional examination.

Translational outlook
In this study CT derived FFR and CT myocardial perfusion imaging are intergraded. The algorithm used in this study for integration of CT derived FFR and dynamic MPI can be used in future diagnostic studies. Clinical outcomes studies will be needed to investigate the additional patient benefit and cost effectiveness of an integrated approach in detection and treatment of CAD.

References


Figure legend:

Figure 1: Inclusion flow chart, in total 84 subjects were recruited over two sites. Ten patients were excluded, resulting in a total of 74 patients and 142 vessels/territories included in the study.

Figure 2: Case example of a 65 year old man presenting with stable exercise related chest pain. CTA demonstrated sequential partly calcified moderate stenoses in the LAD (A). The CTA-FFR simulation demonstrated a significant pressure drop (CTA-FFR 0.63) (B). CT-MPI, image fused with the anatomical CT for illustration purposes, shows a perfusion defect in the anterior wall, classified as ischemic with a measured index MBF value of 0.56 (C). The corresponding invasive angiography shows the sequential stenosis in the LAD, with an invasively measured FFR of 0.71 (D). Secondary not shown directly, the LCx also had a hemodynamically relevant stenosis with an invasive FFR of 0.70, the RCA was directly stented.

FFR: fractional flow reserve, CT-MPI: CT myocardial perfusion imaging, MBF: myocardial blood flow, CTA-FFR: CT derived FFR. LAD: left anterior descending, LCx: left circumflex coronary artery. S1: septal branch, D1: first diagonal branch

Figure 3: Receiver operator curve. Analysis per vessel/territory, using invasive FFR as reference. The area under the curve (AUC) for CT-MPI/FFR (0.85) was significantly higher than CT-MPI (0.78, p=0.01), CTA-FFR (0.78, p=0.03) and CTA (0.70, p=0.002).

Abbreviations as in Figure 2

Figure 4: Distribution of CT-MPI, CTA-FFR, and CT-MPI combined with CTA-FFR shown displaying the predicted probabilities. The median is displayed as a horizontal line.

Abbreviations as in Figure 2

Figure 5: Diagnostic classification by CT-MPI and CTA-FFR. The size of the charts was scaled towards the number of vessels/territories. Out of the 49 territories vessels classified as positive for ischemia by CTA-FFR and CT-MPI, 40 (82%) were confirmed by invasive FFR. Of the 33 territories/vessels were both CTA-FFR and CT-MPI indicated a non-functional stenosis 30 (91%) were confirmed as not functionally obstructed by invasive FFR.

Abbreviations as in Figure 2

Figure 6: Sensitivity and specificity with invasive FFR as reference plotted against CTA-FFR thresholds. An intermediate zone was defined between a sensitivity of 90% and a specificity of 75%, corresponding to CTA-FFR values between 0.74-0.85.

Abbreviations as in Figure 2
Appendix: Combined analysis of continuous variables CTA, CT-MPI and CTA-FFR

Combined diagnostic performance was investigated using a binary logistic regression, with a value of 1 coding for a hemodynamic significant stenosis (FFR≤0.80) and 0 for a non-significant stenosis (FFR>0.80). This resulted in a constant of 9.0, a beta of -5.6 for CT-MPI (index MBF) (p<0.001), and -7.0 for CTA-FFR (p<0.001). Predicted logit is a single value representing the outcomes from both CT-MPI and CTA-FFR.

CTA and CTA-FFR: Predicted Logit = 2.8 + (0.7 × CTA ) −(6.4 × CTA derived FFR)
CTA and CT-MPI: Predicted Logit = 1.5 + (1.0 × CTA ) −(6.2 × index MBF)
CT-MPI and CTA-FFR: Predicted Logit = 9.0 −(5.6 × index MBF) − (7.0 × CTA derived FFR)

From this formula a vessel/territory based individual predicted probability was calculated using the following formula:

\[
\text{Predicted probability} = \frac{e^{\text{Predicted Logit}}}{1 + e^{\text{Predicted Logit}}}
\]

\[e = Euler's\ number\ (2.71828)\]

The predicted probability is a number between 0 and 1. The lesions has a higher change of being hemodynamically significantly obstructed when the predicted probability is closer to 1. A value close to 0 represents a lesion with a low probability of a hemodynamic significant stenosis.

A predicted probability ≥0.50 was classified as hemodynamically significant.
Erasmus Medical Center, Rotterdam
Recruited 43 subjects

Centre for Advanced Cardiovascular Imaging, London
Recruited 41 subjects

Excluded:
- Incomplete coverage CTA (n=1)
- Failed CT-MPI examination (n=1)
- CTA non-diagnostic image quality (n=8)

Included:
- 74 subjects
- 142 vessels/territories, with invasive FFR measurements.
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</tr>
<tr>
<td><strong>CT-MPI negative</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=21</td>
<td>n=3</td>
</tr>
<tr>
<td></td>
<td>n=15</td>
<td>n=30</td>
</tr>
</tbody>
</table>

- Red: invasive FFR $\leq 0.80$
- Blue: invasive FFR $>0.80$
### Table 1: Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, ( n )</td>
<td>74</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.9±9.1</td>
</tr>
<tr>
<td>Male gender, ( n ) (%)</td>
<td>62 (84)</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))(^*)</td>
<td>26.9±3.6</td>
</tr>
<tr>
<td>Cardiovascular risk factors, ( n ) (%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>40 (54)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>45 (61)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15 (20)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>27 (37)</td>
</tr>
<tr>
<td>Smoking within the last year</td>
<td>33 (45)</td>
</tr>
<tr>
<td>Prior myocardial infarction, ( n ) (%)†</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Prior percutaneous coronary intervention, ( n ) (%)†</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>Agatston coronary calcium score(‡)</td>
<td>289 (74-849)</td>
</tr>
</tbody>
</table>

Values are reported as mean ± standard deviation or absolute number \( n \) and percentage (%).

CAD, coronary artery disease;

\(^*\) In two patients length and weight data were not available.

\(†\) Not in the vessel territories interrogated by invasive FFR.

\(‡\) Represented in median and (inter-quartiles).
Table 2: Diagnostic performance

<table>
<thead>
<tr>
<th>Modality</th>
<th>TP</th>
<th>FP</th>
<th>TN</th>
<th>FN</th>
<th>Sens (%)</th>
<th>Spec (%)</th>
<th>PPV  (%)</th>
<th>NPV  (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTA</td>
<td>52</td>
<td>38</td>
<td>37</td>
<td>15</td>
<td>78% (65-90%)</td>
<td>49% (38-61%)</td>
<td>58% (48-68%)</td>
<td>71% (56-87%)</td>
<td>63% (55-71%)</td>
</tr>
<tr>
<td>Absolute MBF</td>
<td>50</td>
<td>29</td>
<td>46</td>
<td>17</td>
<td>75% (63-86%)</td>
<td>61% (47-75%)</td>
<td>63% (51-76%)</td>
<td>73% (62-84%)</td>
<td>68% (59-76%)</td>
</tr>
<tr>
<td>CT-MPI (Index MBF)</td>
<td>49</td>
<td>24</td>
<td>51</td>
<td>18</td>
<td>73% (61-86%)</td>
<td>68% (56-80%)</td>
<td>67% (55-80%)</td>
<td>74% (63-85%)</td>
<td>70% (62-79%)</td>
</tr>
<tr>
<td>CTA-FFR</td>
<td>55</td>
<td>30</td>
<td>45</td>
<td>12</td>
<td>82% (72-92%)</td>
<td>60% (48-72%)</td>
<td>65% (55-75%)</td>
<td>79% (68-90%)</td>
<td>70% (63-80%)</td>
</tr>
<tr>
<td>CTA and CTA-FFR</td>
<td>43</td>
<td>18</td>
<td>57</td>
<td>24</td>
<td>64% (51-77%)</td>
<td>76% (66-86%)</td>
<td>71% (59-82%)</td>
<td>70% (59-82%)</td>
<td>70% (62-79%)</td>
</tr>
<tr>
<td>CTA and CT-MPI</td>
<td>51</td>
<td>17</td>
<td>58</td>
<td>16</td>
<td>76% (65-87%)</td>
<td>77% (67-88%)</td>
<td>75% (64-86%)</td>
<td>78% (68-89%)</td>
<td>77% (70-84%)</td>
</tr>
<tr>
<td>CT-MPI and CTA-FFR</td>
<td>49</td>
<td>12</td>
<td>63</td>
<td>18</td>
<td>73% (61-86%)</td>
<td>84% (75-93%)</td>
<td>80% (70-91%)</td>
<td>78% (68-88%)</td>
<td>79% (71-87%)</td>
</tr>
</tbody>
</table>

Diagnostic performance with invasive FFR and a threshold of ≤0.80 as reference. Dynamic CT-MPI, absolute MBF using a threshold of 91 ml/100ml/min. CTA-MPI (index MBF) using a threshold of 0.71. CTA-FFR using a threshold of 0.80. A predicted probability below ≥0.50 was used as a threshold for all the combined (CTA and CTA-FFR, CTA and CT-MPI, and CT-MPI and CTA-FFR) analyses.