The role and added value of CT-FFR in the diagnosis of coronary artery disease

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This article summarizes the results of a recently published study [1] which assessed the added value of CT-derived Fractional Flow Reserve (CT-FFR) in the diagnosis of coronary artery disease (CAD). It was found that the use of an on-site CT-FFR based approach in patients with angina pectoris and suspected CAD led to an increase in the area under the ROC curve compared to a basic model comprising pre-test likelihood and exercise electrocardiography.

INTRODUCTION

Invasive fractional flow reserve (FFR), the physiological test that serves as a proxy for myocardial blood flow, is the generally accepted reference standard for the assessment of stenosis-specific ischemia and for the diagnosis of coronary artery disease (CAD) [2,3]. Given the frequent mismatch between anatomical and hemodynamic estimation of the severity of coronary stenosis, FFR is recommended as a complement to invasive coronary angiography (ICA) in patients with coronary stenosis of between 50-90% or in cases of multi-vessel disease [4]. The European Society of Cardiology (ESC) guidelines for Chronic Coronary Syndromes recommend that, prior to invasive testing with ICA and FFR, non-invasive tests be carried out in symptomatic patients in whom obstructive CAD cannot be excluded by clinical assessment alone. Non-invasive functional imaging for the detection of myocardial ischemia as well as coronary computed tomography angiography (CCTA) to evaluate the degree of coronary diameter reduction are recommended as initial tests in the diagnosis CAD [4]. Current non-invasive tests are, however, limited to either anatomical or functional assessments of the coronary blood flow, resulting in the need to use multiple tests in the diagnostic workflow. A balanced strategy needs to be identified in which clinical evaluation, non-invasive imaging and stress testing for risk stratification can be weighed gainst (invasive) diagnostic over-testing.

Risk stratification prior to ICA and FFR routinely includes electrocardiographic evaluation (ECG), echocardiography, X-Thorax and exercise ECG (X-ECG), but these methods are only helpful in a minority of patients. Other non-invasive imaging techniques such as CCTA, MRI, SPECT and PET-CT can improve the diagnostic process, but increase the risk of complications, exposure to radiation and contrast-agent, as well as negatively impacting the quality of life of patients and increasing costs.

The relatively recently introduced non-invasive imaging technique of CT-derived FFR (CT-FFR) combines both anatomical and functional information. CT-FFR is determined by the use of sophisticated hemodynamic flow algorithms which operate on CCTA data sets. Various algorithms have already been evaluated in multicenter studies and have shown that diagnostic accuracy is improved compared to CCTA alone, with a pooled sensitivity of 0.85 and a pooled specificity of 0.78 being reported [6]. Based on previous studies, it is reasonable to assume that complementing CCTA with CT-FFR will yield an enhanced diagnostic value, especially since no additional testing, radiation or contrast medium are required. However, to date, the diagnostic performance of CT-FFR has only been evaluated as a stand-alone, single test and not in the context of the overall clinical work-up of patients with (suspected) stable angina pectoris. To address this, we carried out a cross-sectional study evaluating the added value of CT-FFR beyond other currently used non-invasive tests in patients with angina pectoris and suspected CAD.

STUDY DESIGN AND METHODOLOGY

This single center study involved patients with a clinical suspicion of angina pectoris and an intermediate to high pre-test likelihood of CAD. To avoid referral bias, all patients underwent X-ECG, stress/rest SPECT, coronary calcium score (CCS), CCTA, CT-FFR and ICA independently of the results of the non-invasive imaging. Examples of CCTA, CT-FFR and invasive FFR images are shown in Figure 1. FFR measurements were

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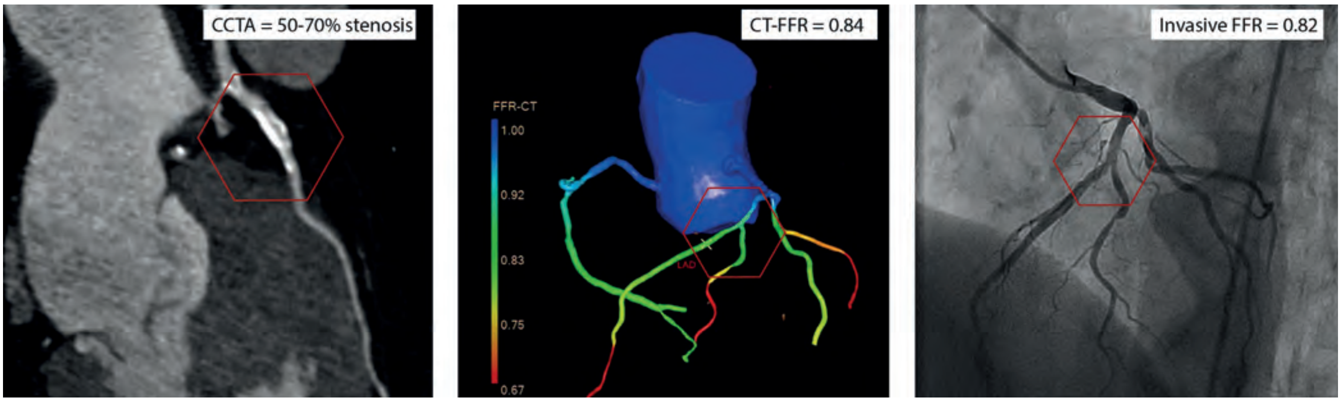

Figure 1. Examples of CCTA, CT-FFR and invasive FFR in a study patient. An Agatston CCS of 707 is observed. CCTA shows a significant stenosis of the mid LAD, whereas the CT-FFR indicates non-significant ischemia. SPECT perfusion imaging indicates mild to moderate ischemia proximal anterolateral and proximal inferoposterolateral. Invasive FFR measurements demonstrates obstructive stenosis and a FFR value of 0.82 indicating no vessel ischemia.

performed in cases of intermediate stenosis. Imaging acquisition was performed on a hybrid SPECT-CT system, consisting of a gamma camera using a weight-adjusted dose of 400-600 MBq ^{99m}Tc-sestamibi in combination with a 64-slice CT scanner (CardioMD and Brilliance 64, Philips Medical Systems, Best, The Netherlands). Prior to carrying out stress SPECT, X-ECG was performed. Rest SPECT was carried out in the case of an abnormal stress SPECT. CCS and CCTA imaging were obtained using a prospectively ECG gated scan acquisition protocol, whereas a non-enhanced acquisition was performed prior to the CCTA to calculate the Agatston CCS.

CT-FFR was calculated using an on-site CT-FFR prototype simulation algorithm (Philips Medical Systems, The Netherlands). ICA biplane views were acquired from all major coronary arteries using Allura catheterization equipment (Philips Medical Systems, The Netherlands) via femoral or radial artery access. Intermediate stenoses, defined as a diameter reduction between 50-70%, were subsequently assessed by FFR. The evaluation method and cut-off values of the various diagnostic tests are described in Table 1.

To assess the ability of the different models to distinguish between patients with and without CAD, the area under the ROC-curve and the area under the curve (AUC) were calculated. The variables were added to the multivariable model in chronological order as in clinical practice, starting with the pre-test likelihood and X-ECG. The models tested include the single and combined results of SPECT, CCS, CCTA and CT-FFR.

The primary end-point of our trial was the comparison of the areas under the receiver operating characteristic curve (ROC-curve) between the diagnostic strategies.

RESULTS

A total of 202 patients with mean age 63.1 ± 9.8 years (61.4% male) were included in the study. Five multivariable logistic regression models were used to assess the combined diagnostic value of the non-invasive tests. The basic diagnostic model used the pre-test likelihood of CAD and the result of the X-ECG. Table 2 shows the effect of the addition of one or more methodsto the basic model. It can be seen from Table 2 that the addition of SPECT, CCS and CCTA data to

Test	Evaluation method	Definition abnormal Test
X-ECG	All X-ECG were reviewed in consensus by 2 experienced cardiologist	Abnormal: horizontal shift of the ST segment at 80ms after the J-point of =0.1 mV in 3 consecutive beats. Non-conclusive: decrease of >30 mm Hg in systolic blood pressure, typical angina pectoris during stress, unable to reach >85% of the predicted heart rate without (ECG) evidence of ischemia and/or uninterpretable ECG.
SPECT	Stress and rest SPECT imaging were interpret using the QGS/QPS software package.	The definition of normal, non-conclusive and abnormal myocardial perfusion on SPECT according to segmental scores is previous described by Abidov et al.[5] SPECT classified as non-conclusive was regarded as abnormal in the analysis
CCS	Agatston calcium score	The CCS result was used as continuous variable
CCTA	Obstructive stenosis were scored in a 16-segment model in five categories using the CADRADS™.	At least 1 stenosis on CCTA =50%. Segments affected by motion artefacts or blooming due to severe calcification were not assessable and classified as non-conclusive and regarded as abnormal in the analysis.
CT-FFR	Point estimates of the computed FFR were taken at the lesion of interest - the most severe stenosis at CCTA	CT-FFR =0.80 in at least one of the vessels
ICA	The coronary tree was fully examined for the presence of stenosis according to the 16-segment model as used for the assessment of CCTA.	At least 1 stenosis on ICA =70%
FFR	An intermediate stenosis on ICA, defined as a diameter reduction between 50-70%, was by FFR	At least 1 FFR measurement = 0.80

Table 1 Interpretation and cut-off values of the (non-invasive) imaging methods

	Variables	HL-statistic (p-value)	AUC (95% CI)	p-value
Model 1	LLH CAD + X-ECG	0.29	0.79 (0.73-0.85)	<0.001
Model 2	SPECT	0.25	0.90 (0.85-0.94)	0.008
Model 3	CCS+CCTA	0.47	0.88 (0.83-0.92)	<0.001
Model 4	CCS+CCTA + CT-FFR	0.57	0.93 (0.90-0.96)	0.398
Model 5	SPECT +CCS+CCTA	0.28	0.94 (0.92-0.97)	Ref.

Table 2: Discrimination and calibration of the diagnostic models of interest.
Abbreviations: AUC area under the curve, CAD coronary artery disease, CCS coronary calcium score, CCTA coronary computed tomography angiography, CI confdence interval, CT-FFR computed tomography fractional fow reserve, LLH pretest likelihood, SPECT single photon emission computed tomography, X-ECG exercise electrocardiography.
It can be seen that the basic multivariable model of LLH CAD and XECG has an AUC of 0.790 which increased to 0.897 with the addition of SPECT (Model 2) Addition of CCTA and CCS to the basic model increased the AUC to 0.876 (Model 3); the addition of CT-FFR gave an AUC of 0.929 (Model 4). The basic model with the addition of SPECT, CCS and CCTA yielded the highest AUC of 0.94.

those of the basic model yielded the highest AUC of 0.94. However there was no significant difference (p-value = 0.398) in terms of AUC between this SPECT, CCS and CCTA model and the model including CCS, CCTA and CT-FFR which had an AUC of 0.93. Figure 2 shows the ROC-curves of the diagnostic models. All diagnostic models were found to have good calibration i.e. all had p-values above the threshold of 0.05 using the Homer-Lemeshow test of overall goodness of fit.

CONCLUSIONS AND FUTURE PERSPECTIVES

The aim of this study was to determine the added value of CT-FFR over and above other non-invasive tests which are routinely performed in patients with a clinical suspicion of having (recurrent) angina pectoris.

We found that the addition of CT-FFR improved the diagnostic performance of both SPECT and CCTA. The performance of the CT-FFR approach was not significantly different from that of the CCTA-SPECT based strategy in terms of area under the ROC-curve, suggesting that SPECT could be replaced. Such a substitution of SPECT by CT-FFR would mean a saving of 10 mSv on the doses of ^{99m}Tc-sestamibi for the stress and rest SPECT. In addition, no extra scan time would be required [7].

The addition of CT-FFR to the existing pathway increases diagnostic value after a positive or inconclusive CCTA, and does not require additional testing procedure, radiation or contrast medium. Moreover, CT-FFR is easy to use, fast and reproducible. The technique can be cost-effective even though it does require additional operator time (approximately 20 minutes). This depends heavily on the scan quality and the amount of calcification present [8,9].

CT-FFR is considered as cost effective by the UK's National Institute for Health and Care Excellence in patients with stable, recent onset chest pain [10]. The use of CT-FFR in the UK has resulted in a substantial reduction in referrals to ICA. The PLATFORM study [11] also evaluated medical costs: the mean per-patient downstream costs (i.e. without cost of initial tests, including CT-FFR) were similar for CT-FFR and usual care ($2,755 vs. $2,260, respectively).

However, generalization of these results to other countries is difficult due to differences in outcome measures, healthcare cost levels, the epidemiology of disease, patient cohorts and local expertise [12].

We hypothesize that a CT-FFR guided strategy increases cost-effectiveness by reducing the percentage of patients referred for invasive pressure measurements. The adoption of the CT-FFR based approach will also increase patient comfort and should lead to a lower rate of complications, which in turn further improves its cost-effectiveness.

To definitively establish the cost benefits of CT-FFR, more head-to-head cost-effectiveness studies are needed in different healthcare systems in addition to further studies comparing CT-FFR with methods based on invasive pressure measurements.

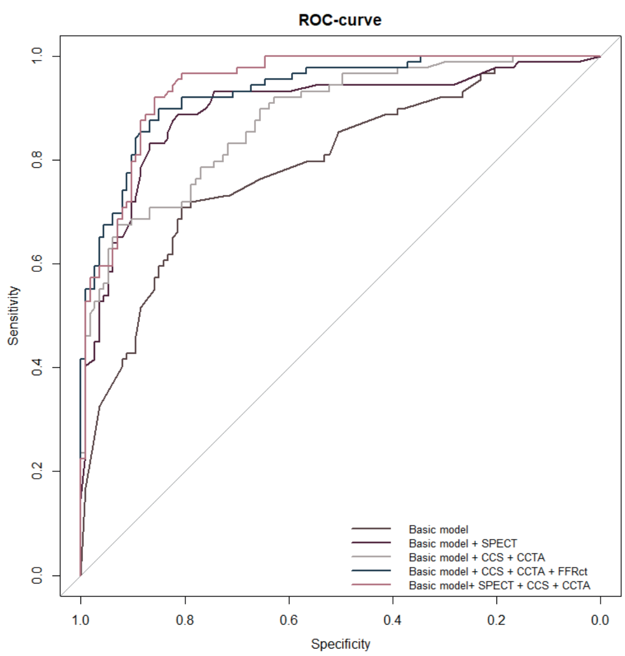

Figure 2. The Receiver Operator Characteristics curve for the five diagnostic models.

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