



Correlation of FFR-derived from CT and stress perfusion CMR with invasive FFR in intermediate-grade coronary artery stenosis

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Abstract

Only one-third of intermediate-grade coronary artery stenosis (i.e. 40–70% diameter narrowing) causes myocardial ischemia, requiring most often additional invasive work-up with invasive fractional flow reserve (FFR). To evaluate the correlations between FFR estimates derived from computed tomography (FFR_{CT}) and adenosine perfusion cardiac magnetic resonance (CMR) with invasive FFR in intermediate-grade stenosis. Thirty-seven patients (mean age 61 ± 9 years; 25 men) who underwent adenosine perfusion CMR, quantitative coronary angiography and FFR in the work-up for intermediate-grade stenoses (n = 39) diagnosed at coronary CT angiography were retrospectively evaluated. Blinded FFR_{CT} analysis was computed on each intermediate-grade lesion and correlated to the FFR values. On adenosine CMR, subendocardial time-enhancement maximal upslopes, normalized by respective left ventricle cavity upslopes, were obtained distal to a coronary stenosis (RISK area) and in remote myocardium (REMOTE area). The perfusion was subsequently assessed without (uncorrected RISK) and after correction for remote perfusion (relative myocardial perfusion index = REMOTE/RISK ratio), and then correlated to the FFR values. Differences in correlations were tested with z statistics and considered statistically significant different at a p < 0.05 level. The average FFR value was 0.85 ± 0.10 (0.60–0.98 range), 28% (n = 11) was ≤ 0.80. FFR value correlated poorly with uncorrected RISK upslopes (r = 0.151; p = 0.36), but equally strongly with FFR_{CT} (r = 0.675; p < 0.001) and the relative myocardial perfusion index (r = -0.63) (p < 0.001; z = 6.72) for assessment of lesion-specific ischemia. Both FFR_{CT} and adenosine perfusion CMR strongly correlate with invasive FFR measurements for intermediate-grade stenosis. These preliminary findings pave the way for further studies evaluating non-invasively intermediate coronary stenosis in clinical practice.

Keywords Coronary stenosis · Fractional flow reserve · Myocardial · Adenosine · Magnetic resonance imaging · Computed tomography angiography

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Abbreviations

FFR	Fractional flow reserve
FFR _{CT}	FFR estimates derived from computed tomography
CMR	Cardiac magnetic resonance
CTA	Computed tomography angiography

Introduction

Intermediate-grade coronary artery stenoses (i.e. 40–70% diameter reduction) at coronary computed tomography angiography (CTA) and coronary angiography represent a therapeutic challenge as multiple studies have shown the poor accuracy of anatomical parameters to predict the functional significance [1–4]. Adequate selection of hemodynamically significant lesions is important, as patients without ischemia—approximately 2/3rds of intermediate stenoses—do not benefit from revascularization [5]. Further functional assessment during coronary angiography, including fractional flow reserve (FFR), is required in these lesions to guide coronary revascularization. However, FFR remains invasive and expensive, with procedure-related complications [4, 6].

Non-invasive tests for anatomical and physiological assessment of coronary stenoses are among the pivotal aims of the current CT developments. Coronary CTA allows non-invasive FFR estimation (FFR_{CT}), providing additional functional information in one single examination without supplementary radiation or contrast injection [7]. Preliminary studies show a higher diagnostic performance of FFR_{CT} to exclude ischemia in intermediate-grade stenoses compared with coronary CTA alone [8, 9]. However, FFR_{CT} has not yet been compared with other noninvasive diagnostic strategies in these lesions.

Cardiac magnetic resonance (CMR) evaluates the myocardial perfusion without ionizing radiation exposure under resting and drug-induced (adenosine) vasodilatation, based on the enhancement profile of the myocardial microvasculature after a bolus injection of a gadolinium chelate [10]. Although no study did specifically evaluate intermediate-grade stenosis on adenosine CMR in a clinical setting (i.e., using visual and semi-quantitative analyses), its diagnostic value to rule out ischemic coronary artery disease is generally excellent, exceeding that of other non-invasive imaging modalities [11, 12].

We therefore hypothesized that both FFR_{CT} and adenosine CMR correlate with invasive FFR-measurement in intermediate-grade stenosis. The objective of this study was to evaluate the lesion-specific correlations of FFR_{CT} and adenosine perfusion CMR with invasive FFR in intermediate-grade stenosis.

Materials and methods

Patients and study protocol

This study protocol was approved by the hospital Ethics Committee, and all patients provided written informed consent. All patients older than 18 years with an intermediate-grade coronary stenosis on coronary CTA, and workup with adenosine CMR perfusion and invasive FFR measurement within 4 months in our institution between 2010 and 2013 were eligible for a retrospective FFR_{CT} analysis. Usual contraindications to all examinations applied.

Imaging protocol

Coronary CTA technique

Coronary CTA was performed with a 64-detector CT-scanner (LightSpeed VCT or Discovery CT 750 high-definition, GE Healthcare) with prospective or retrospective electrocardiographic gating according to the Society of Cardiovascular Computed Tomography guidelines [13]. Patients with baseline heart rate > 65 beats/min were given 5 mg of bisoprolol (Emconcor mitis, Merck) orally the evening before and the morning of the examination. For the patients with heart rate remaining > 65 beats/min an intravenous bolus of 5–15 mg of metoprolol (Seloken, AstraZeneca) was given prior to examination. 2 min before scanning, 0.4 mg of sublingual nitroglycerin was administered, after which coronary CTA was acquired during a bolus injection of 70–90 mL of iodinated contrast material (Iomeron 400 mg/mL, Bracco imaging) depending on patient's body mass index, followed by a saline chaser of 40 mL at a rate of 4.5–6 mL/s.

In all patients, an initial reconstruction was performed at 75% of the RR interval. The section thickness was 0.625 mm and the increment 0.625 mm with the use of a small- or medium-sized cardiac field of view. In case of motion artifacts on this phase, multiphase reconstructions were obtained for the data acquired with prospective and retrospective ECG triggering with 5% and 10% steps, in the range of 65–85 and 0–100% of the RR intervals respectively. Images were reconstructed using a standard reconstruction algorithm.

Computation of FFR_{CT}

Computation of FFR_{CT} was performed in blinded fashion by the FFR_{CT} core laboratory (HeartFlow Inc). The algorithm used flow dynamics computations after semi-automated segmentation of coronary arteries to calculate resting coronary blood flow from left ventricular mass and resistance from the

vessel diameter measurements, repeating the process after simulating resistance with adenosine stress, as previously reported [8]. The FFR_{CT} ratio was obtained by dividing the mean pressure distal to the coronary stenosis by the mean aortic pressure.

CMR imaging protocol

All adenosine first-pass CMR examinations were performed on a 1.5 T magnetic resonance imaging (MRI) unit (Avanto, Siemens Medical) under continuous heart rate and blood pressure monitoring. All patients were asked to suspend the intake of beta-blockers and all competitive antagonists of adenosine (caffeinated beverages) 24 h before the examination. Stress perfusion CMR was performed during maximal vasodilatation (i.e., 3 min after beginning the injection of 140 $\mu\text{mol/kg/min}$ of adenosine [Adenocor, Sanofi-Aventis]) using selective saturation-prepared T1-weighted steady-state free precession (SSFP) slices.

First-pass CMR acquisition started simultaneously with the injection of 0.1 mmol/kg of body weight of a gadolinium chelate contrast agent [gadodiamide, Omniscan], and a 30 mL saline flush, both were given at an injection rate of 4 mL/s. During a single breath hold, fifty measurements were acquired of the three slices per heartbeat.

After clearance of adenosine and contrast diffusion equilibrium (i.e., approximately 10 min after the start of the intravenous injection of contrast agent), myocardial LGE imaging was performed using breathhold phase-sensitive inversion recuperation sequences.

Catheter coronary angiography

Patients underwent coronary angiography by catheterization of a common femoral artery using a 7-French catheter with at least 2 orthogonal projections for all segments as described in the AHA guidelines [14] after contrast injection (Hexabrix 320 mgI/mL, Guerbet) and 100–200 μg intracoronary nitroglycerin infusion. QCA measurements were performed off line with the Xcelera R3.1L1 system (Philips Medical Systems) to assess lesions' morphological characteristics.

Pressure wire-derived fractional flow reserve (FFR) measurements

FFR measurements were performed by an interventional cardiologist, using previously described standard procedures [15]. FFR was performed using a 0.014 inch pressure wire with a pressure-sensing guidewire system (FloWire® Doppler Guide Wire image Volcano Corporation) across the diseased artery. FFR was determined as the ratio of the mean distal coronary to the mean aortic pressure during maximal

myocardial hyperemia, i.e., 30–60 s after the intracoronary injection of 15–20 mg of papaverine (papaverine STEROP 100 mg/3 mL).

Image analysis

Blinded integration of FFR and FFR_{CT}

To enable direct comparison of FFR_{CT} with the invasive FFR measurement distal of the stenosis at the presumed position where the FFR was measured, the 3D FFR_{CT} view was used to match the location of the intermediate-grade stenosis on the coronary CTA and the invasive angiogram.

Semi-quantitative CMR

Semi-quantitative analyses were performed using dedicated software (Syngo Via VA 30, cardiac Engine-perfusion module, Siemens Medical) after correction of respiratory motion with navigator-guided motion correction (MOCO) (Syngo Via-VA 30, Siemens Medical).

First, a visual analysis was performed in consensus by two experienced observers having full knowledge of the location of the coronary stenosis on coronary CTA, but blinded to the FFR data to assess the functional significance of the intermediate lesion. They determined the RISK area downstream a coronary artery stenosis taking the coronary dominance into account. The segment with the greatest transmural extent of the stress-induced myocardial perfusion defect was considered for further measurements when the RISK area involved more than one segment of the left ventricle representation. This segment was equally divided in subendocardial and subepicardial regions by outlining the endocardial and epicardial borders. Special emphasis was placed to avoid dark rim artifacts and adjacent tissue and blood from these tracings. Similar steps were performed for a remote myocardial segment with no > 40% diameter reduction stenosis on the supplying artery (Fig. 1).

Then, for each subendocardial RISK and remote myocardial segments, the mean maximal initial upslope of the contrast enhancement phase was normalized by its respective left ventricle cavity upslope (measured under a circular region of interest of 10 mm² in the center of the cavity) during stress perfusion [16]. If necessary, manual correction was made to adjust the region of interest placement (Fig. 1).

When no myocardial inducible defect was visualized, the RISK area was defined distal to the anatomic location of the coronary stenosis, and the remaining steps were performed as when a perfusion defect could be visually detected.

We analyzed during maximal hyperaemia the uncorrected upslopes in RISK myocardium and the relative myocardial perfusion index (= REMOTE/RISK ratio), which is similar to the initial FFR validation correcting in-flow confounders

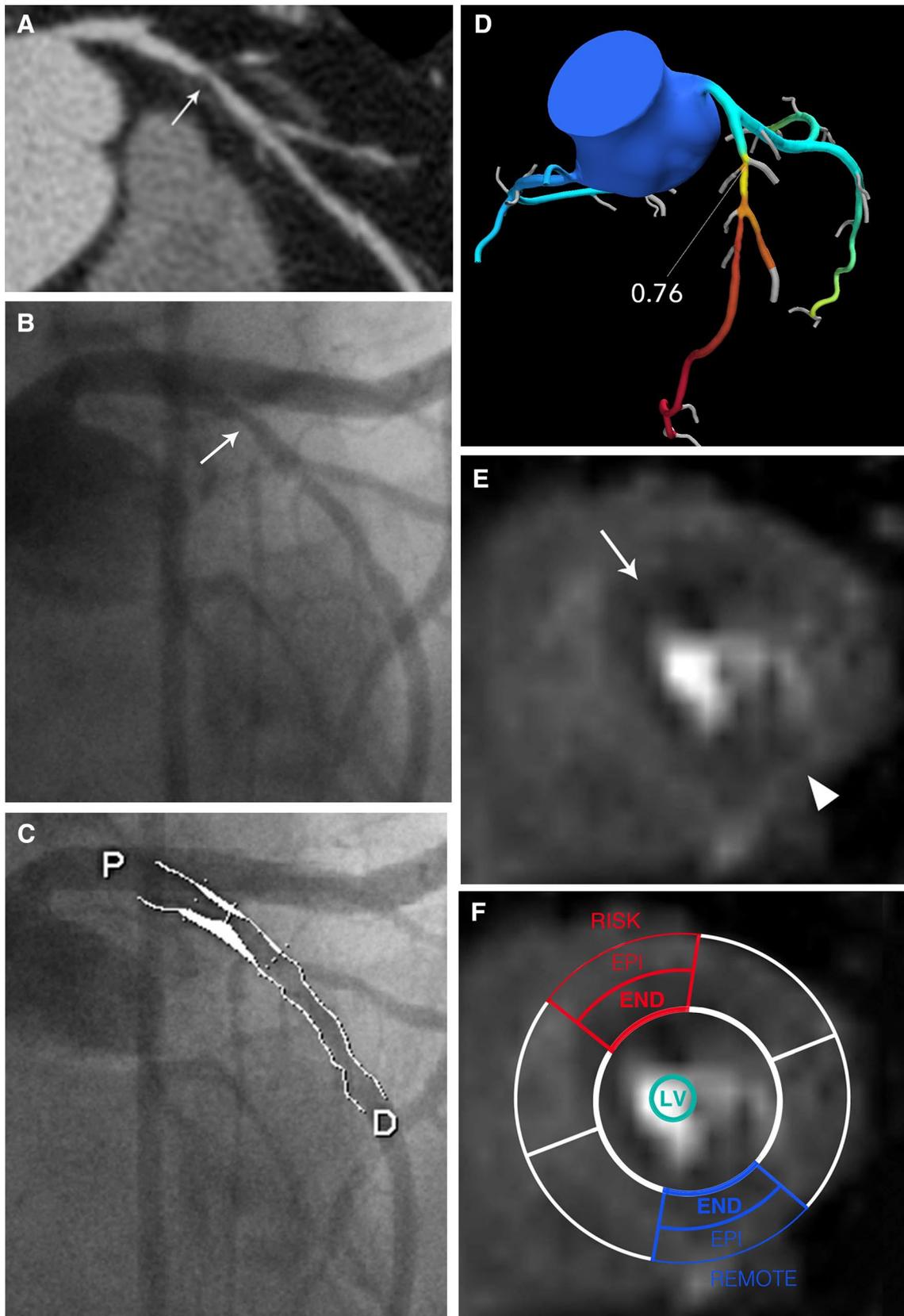


Fig. 1 Detailed steps for semi-quantitative cardiac magnetic resonance analysis in a 58-year-old female with intermediate-grade coronary artery stenosis of the mid portion of the left anterior descending artery with a minimal lumen diameter of 1.2 mm and a 54% diameter narrowing on CCTA (**a**), and a minimal lumen diameter of 1.1 mm and a 57% diameter narrowing on catheter coronary angiography with QCA measurement (**b**, **c**). Stenosis length was 8 mm, owing to a soft plaque with external remodeling on CCTA (**a** white arrow). FFR estimates derived from CT (FFR_{CT}) was 0.76 (**d**), while the invasive FFR value was 0.73. Peak myocardial enhancement on adenosine first-pass cardiac magnetic resonance showed an anterior wall mid-left ventricular area of low signal intensity (arrow, segment 7 in **e**) in the area-at-risk (RISK), whereas the remote area (REMOTE) (arrowhead, segment 10 in **e**). No abnormal enhancement was present on late-enhancement imaging (not shown). Equally divided subendocardial (bold lines, END) and subepicardial (thin lines, EPI) regions of interest are drawn in the RISK (red color) and REMOTE segments (blue color) after outlining the endocardial and epicardial borders of the myocardium during maximal hyperemia (**f**). After normalization by respective left ventricle cavity upslopes, the subendocardial RISK upslope and the relative myocardial perfusion index during stress perfusion were available for further analysis. CCTA coronary computed tomography angiography, QCA quantitative coronary angiography, FFR fractional flow reserve, [END] subendocardial, [EPI] subepicardial, upslope maximal upslope value of the contrast enhancement during maximal hyperemia, RISK area-at-risk, REMOTE remote myocardium, CMR cardiac magnetic resonance, relative myocardial perfusion index REMOTE/RISK upslopes

such as microvascular disease and microcollaterals [17, 18], as described in Fig. 1.

In patients with one intermediate-grade stenosis on two different vessels, each corresponding area of supply was assessed separately.

Statistical analysis

Statistical analyses were performed using SPSS v 24.0. Continuous data with a normal distribution (based on Shapiro–Wilk tests) are expressed as the means \pm standard deviations (SDs) and categorical variables are presented as frequency and percentage. Two-tailed Pearson correlations were calculated between the FFR value and different variables including FFR_{CT} , uncorrected RISK upslope and the relative myocardial perfusion index. Differences between correlations were analyzed (two-tailed Fisher's r -to- z transformation). A p -value of <0.05 indicated statistical significance.

Results

Patient and coronary stenosis characteristics

Our initial search yielded 81 patients with intermediate coronary stenosis on CCTA (Fig. 2). Stenoses with minimal diameter reduction of $<40\%$ ($n=12$) or $>70\%$ ($n=12$) on quantitative coronary angiography (QCA) were reclassified

as mild or severe stenosis, and excluded. Due to possible hemodynamic interactions between distinct coronary territories, we excluded all patients with more than one epicardial coronary stenosis of $>70\%$ minimal diameter reduction on different vascular territories ($n=3$) and those with more than one stenosis of $>70\%$ minimal diameter reduction on the same coronary artery based on the QCA reports ($n=3$), as well as patients with a myocardial infarct on CMR ($n=5$). FFR_{CT} analysis was not possible due to previous stenting on the same artery, motion artefacts or misregistration on coronary CTA ($n=9$). In total, 37 patients (mean age 61 ± 9 years) including 25 men (mean age 59 ± 9 years) and 12 women (mean age 67 ± 8 years) were included in this study. The demographics and cardiovascular risk factors are given in Table 1. The mean time interval between CMR and FFR measurement was 24 ± 28 days (range 0–110 days). Two patients had FFR measurements of one intermediate-grade stenosis on 2 distinct coronary arteries, resulting in a total number of 39 intermediate stenoses.

The lesions had a mean percentage of diameter reduction of $55.5\% \pm 8.0\%$ on QCA; 28% ($n=11$) of the stenoses were located on the right coronary artery, 59% ($n=23$) on the left anterior descending artery and 13% on the left circumflex coronary artery ($n=5$). The average FFR value in all stenoses was 0.85 ± 0.10 , with a range of 0.60–0.99; 28% lesions ($n=11$) had a $FFR \leq 0.80$ (range 0.60–0.79).

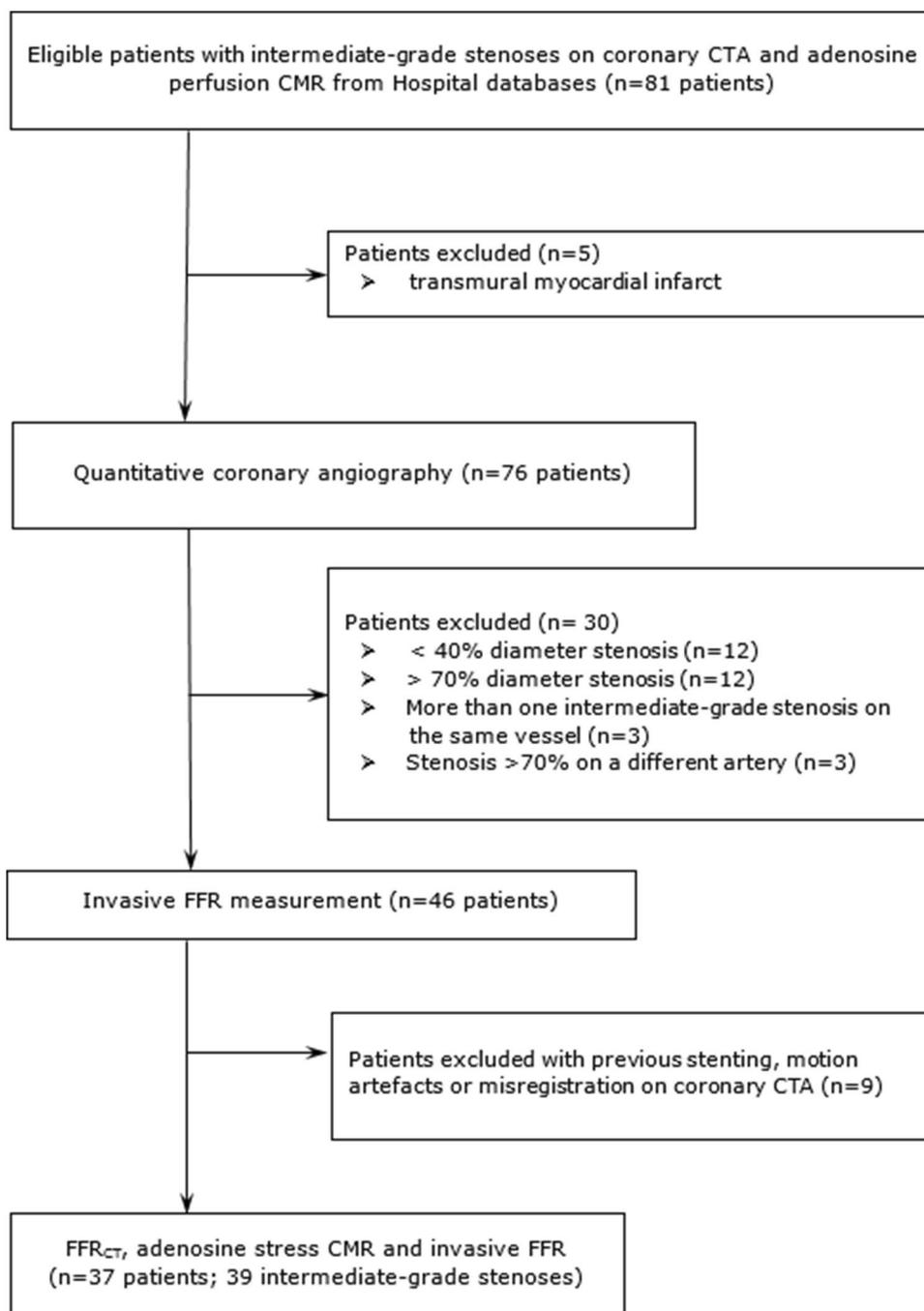
Correlations of FFR_{CT} and adenosine CMR with FFR

The uncorrected RISK upslopes did not correlate with FFR ($r=0.151$; $p=0.36$). In contrast, FFR had a strong positive correlation with FFR_{CT} ($r=0.675$; $p<0.001$) (Fig. 3), and an equally strong negative correlation with the relative myocardial perfusion index ($r=-0.63$; $p<0.001$). Figure 4 represents the scatterplots between the FFR values and the FFR_{CT} estimates (A), the uncorrected RISK upslopes (B) and the relative myocardial perfusion index (C). In addition, correlation with FFR showed larger 95% CI limits for uncorrected RISK upslope, as compared to FFR_{CT} and the relative myocardial perfusion index.

Discussion

This study demonstrated a strong correlation with invasive FFR of both FFR_{CT} and adenosine CMR in the assessment of lesion-specific ischemia in intermediate-grade coronary stenoses. Using CMR, only the relative myocardial perfusion index (i.e., after correction for perfusion in remote myocardium) allowed this outcome. These findings are supported by the concept of FFR [17] and previous studies evaluating the functional significance of coronary artery stenosis with Positron Emission Tomography. In these studies, correction

Fig. 2 Study flowchart. *CTA* computed tomography angiography, *FFR_{CT}* fractional flow reserve calculation derived from CT, *FFR* fractional flow reserve, *CMR* cardiac magnetic resonance



of the hyperemic myocardial blood flow in a stenotic area by the myocardial blood flow in remote areas resulted in better correlations with FFR, as compared to the uncorrected myocardial blood flow assessment [19–21].

The correlation was low between the FFR value and the perfusion in the myocardium downstream a coronary stenosis, in contrast with previously reported correlations [22–25]. This poor correlation would suggest that visual analysis is outperformed by quantitative analyses accounting for perfusion changes in remote myocardium, for the assessment

of myocardial ischemia induced by an intermediate-grade stenosis. This is in contrast to recent meta-analyses of adenosine perfusion CMR reporting excellent diagnostic values for visual assessment, but including also low- and high-grade stenoses [12, 13, 21]. Several reasons might be responsible for the low correlation including the narrower FFR range (0.60–0.98) of the lesions in our study compared to previous studies that included lesions with much lower FFR values. Physiologically, microvascular disease may be another cause of discrepancy. The microvascular tone theoretically affect

Table 1 Patient demographics and cardiovascular risk factor

Patient characteristic	Non-ischemic (n=28)	Ischemic (n=11)	p-value
Age (years) ^a	60 ± 9 [44–80]	64 ± 10 [48–80]	0.205
Gender (male) ^b	20 (71)	7 (64)	0.635
BMI (kg/m ²) ^a	29 ± 5 [21–39]	28 ± 4 [24–35]	0.144
Resting heart rate (beats/min) ^a	69 ± 11 [51–100]	67 ± 9 [54–81]	0.682
Family history of coronary disease ^b	8 (29)	8 (73)	0.012
Personal history of coronary disease ^b	4 (14)	9 (81)	<0.001
Diabetes mellitus ^b	8 (29)	9 (81)	0.002
Current tobacco smoker ^b	9 (32)	4 (36)	0.801
Elevated blood lipid profile ^b	21 (75)	9 (82)	0.649
Systemic hypertension ^b	24 (86)	6 (55)	0.037
Agatston coronary calcium score ^a	302 ± 303 [0–1354]	561 ± 534 [1–1483]	0.211

Correlation is significant at the 0.05 level (two-tailed)

^aMean ± standard deviation [range]

^bNumber of patients (%)

the difference between coronary flow estimated on CMR and pressure estimated on FFR [26]. In addition the variability of the microvascular bloodflow that affects the myocardial perfusion is not predictable by essence, reaching up to 35% in highly controlled settings [18].

The correlation between FFR_{CT} and FFR in our study was higher than in previous studies evaluating intermediate-grade coronary stenoses ($r=0.5-0.6$) [8, 26], probably due to the technical advances of the model. On the other hand, the restriction to intermediate-grade coronary lesions in our study probably resulted in a lower correlation with FFR compared to the NXT trial [7].

Other factors than stenosis or patient selection may explain the “imperfect” correlations of both non-invasive techniques with FFR. Technically, image artefacts such as motion, low contrast, misregistration and blooming due to severe calcification on CT angiography may limit the accuracy of the anatomic models of the coronary lumen on FFR_{CT}. Likewise, image artefacts, bolus dispersion and vasodilatation failure are potential pitfalls for perfusion CMR. Using FFR_{CT}, multiple assumptions (e.g. relative coronary microvascular resistance based on vessel size) may limit the physiological models to population-specific and patient-specific data [27].

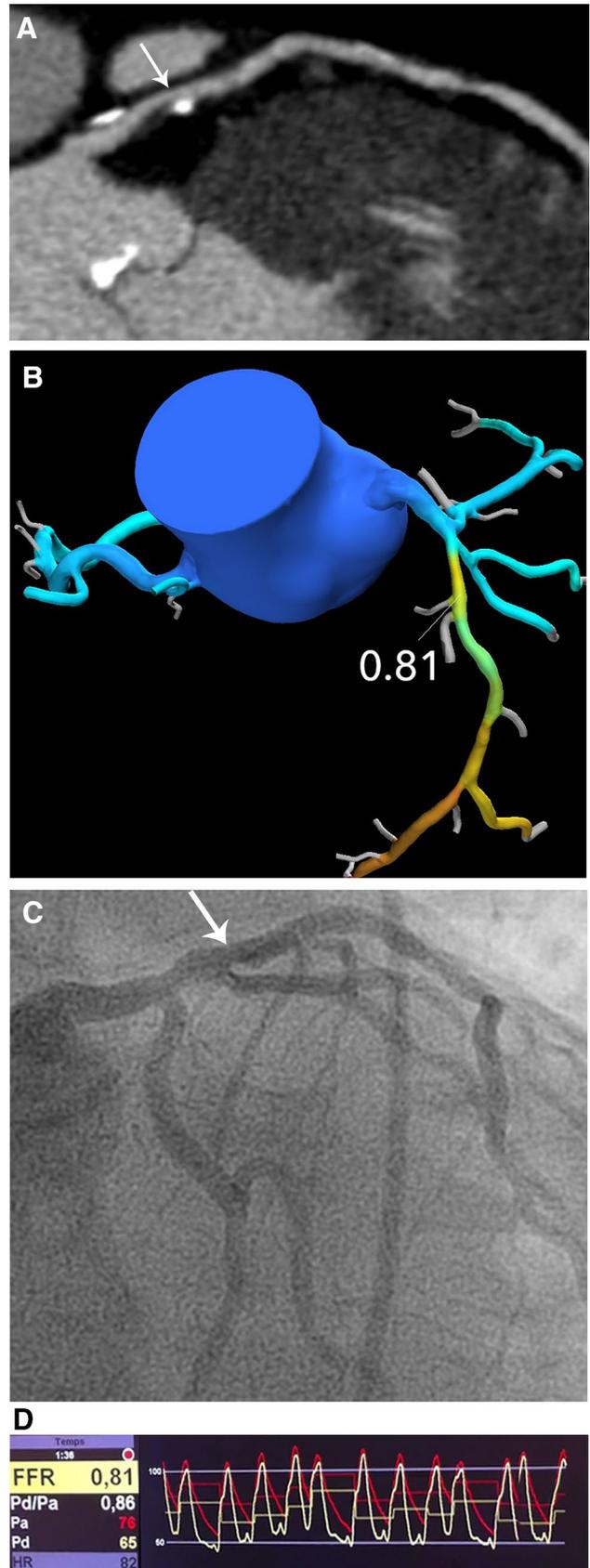
Compared to perfusion CMR, FFR_{CT} has the added benefit of being able to pinpoint the specific lesion that causes ischemia, whereas the latter assesses myocardial perfusion that may be affected by an array of causes, including epicardial stenosis but also endothelial dysfunction and microvascular disease [8].

There are limitations to our study, including the small sample size of intermediate coronary lesions. Therefore, we did not report diagnostic values of FFR_{CT} and adenosine perfusion CMR in the current study since confidence intervals

will be large. FFR has a continuous relation to adverse events that differs between revascularization and medical treatment, rather than a risk versus benefit FFR threshold of 0.80 in borderline flow-limiting intermediate-grade coronary stenoses [28, 29]. Our findings will need confirmation in future analyses with larger cohorts and address the value of these techniques as alternative to invasive FFR in clinical practice. Second, FFR_{CT} and CMR analyses were unblinded for stenosis location. Third, our data were not controlled for risk factors of microvascular disease, which may have different effects on the FFR, FFR_{CT} and myocardial first-pass CMR correlations [22, 27]. These confounders limit the validity of our data to patients with similar cardiovascular risk factors for microvascular disease. Fourth, the use of intracoronary papaverine for invasive FFR measurements is different from the validation studies of FFR_{CT}, although similar maximal hyperaeremia can be obtained compared to intravenous adenosine administration [30]. Fifth, semi-quantitative adenosine perfusion CMR parameters were used to correlate with the FFR value, which are not assessable by visual analysis. However, the semi-quantitative CMR analysis can also be used clinically. Finally, as only intermediate stenoses were included, we cannot comment on the performance of FFR_{CT} or perfusion CMR for mild stenoses (e.g. <40% stenoses).

In conclusion, this study shows that both FFR_{CT} and adenosine perfusion CMR strongly correlate with invasive FFR measurements for intermediate-grade coronary stenosis. These preliminary findings pave the way for further studies evaluating non-invasively intermediate coronary stenosis in clinical practice.

Fig. 3 Diagnostic work-up in a 64-year-old male with intermediate-grade coronary artery stenosis on the proximal left anterior descending artery after the bifurcation of the first diagonal branch on coronary CT angiography (white arrow in **a**) and catheter coronary angiography (white arrow on **c**). Both FFR estimates derived from CT (FFR_{CT}) and the invasive FFR measurement were 0.81 (**b**, **d**). FFR_{CT} fractional flow reserve calculation derived from CT, FFR fractional flow reserve



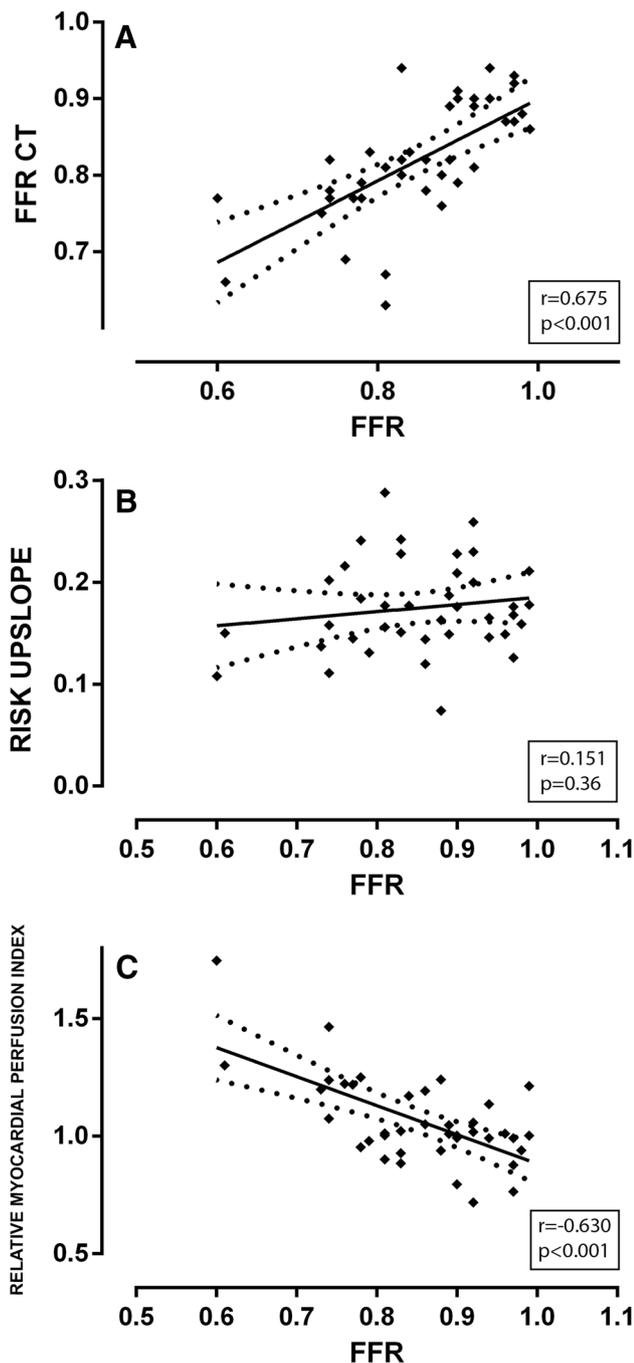


Fig. 4 Scatterplots between the observed FFR values and the predictions of the FFR, based on FFR_{CT} (a), and semi-quantitative first-pass adenosine CMR parameters of the uncorrected RISK upslope (b) and the relative myocardial perfusion index (c). *Upslope* maximal upslope value of the contrast enhancement, *RISK* area-at-risk, *REMOTE* remote myocardium, *relative myocardial perfusion index* REMOTE/RISK upslope, FFR_{CT} fractional flow reserve calculation derived from CT, *FFR* fractional flow reserve, *CMR* cardiac magnetic resonance

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Compliance with ethical standards

Conflict of interest Jonathon Leipsic: Grant/Research Support: Edwards Lifesciences, Neovasc, Tendyne, HeartFlow, Samsung; Consultant: Circle CVI, Edwards, HeartFlow, Samsung; Stock Options: Arineta, Pi Cardia. The other authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Ethical approval Institutional Review Board approval was obtained.

Statistics One of the authors, Dominique Hansen, has significant statistical expertise.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

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