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Cardiac Imaging

# High-Resolution Magnetic Resonance Myocardial Perfusion Imaging at 3.0-Tesla to Detect Hemodynamically Significant Coronary Stenoses as Determined by Fractional Flow Reserve

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**Objectives** The objective of this study was to compare visual and quantitative analysis of high spatial resolution cardiac magnetic resonance (CMR) perfusion at 3.0-T against invasively determined fractional flow reserve (FFR).

**Background** High spatial resolution CMR myocardial perfusion imaging for the detection of coronary artery disease (CAD) has recently been proposed but requires further clinical validation.

**Methods** Forty-two patients (33 men, age 57.4 ± 9.6 years) with known or suspected CAD underwent rest and adenosine-stress *k*-space and time sensitivity encoding accelerated perfusion CMR at 3.0-T achieving in-plane spatial resolution of 1.2 × 1.2 $mm^2$. The FFR was measured in all vessels with >50% severity stenosis. Fractional flow reserve <0.75 was considered hemodynamically significant. Two blinded observers visually interpreted the CMR data. Separately, myocardial perfusion reserve (MPR) was estimated using Fermi-constrained deconvolution.

**Results** Of 126 coronary vessels, 52 underwent pressure wire assessment. Of these, 27 lesions had an FFR <0.75. Sensitivity and specificity of visual CMR analysis to detect stenoses at a threshold of FFR <0.75 were 0.82 and 0.94 ($p < 0.0001$), respectively, with an area under the receiver-operator characteristic curve of 0.92 ($p < 0.0001$). From quantitative analysis, the optimum MPR to detect such lesions was 1.58, with a sensitivity of 0.80, specificity of 0.89 ($p < 0.0001$), and area under the curve of 0.89 ($p < 0.0001$).

**Conclusions** High-resolution CMR MPR at 3.0-T can be used to detect flow-limiting CAD as defined by FFR, using both visual and quantitative analyses. (J Am Coll Cardiol 2011;57:70–5) © 2011 by the American College of Cardiology Foundation

Cardiac magnetic resonance (CMR) myocardial perfusion permits noninvasive detection of myocardial ischemia with high resolution, lack of ionizing radiation, and additional tissue characterization. New acquisition strategies such as *k*-space and time sensitivity encoding (*k-t* SENSE) combined with acquisition at 3.0-T allow further improved in-plane spatial resolution with favorable signal to noise ratio. High-resolution myocardial perfusion CMR at 3.0-T can detect angiographically determined coronary disease (1), but coronary angiography alone has limitations as a "gold standard" for the detection of flow-limiting coronary stenosis (2). Invasively measured fractional flow reserve (FFR) is considered to be a more reliable measure of functional stenosis significance (3). To date, there have been no studies comparing the performance of high-resolution CMR myocardial perfusion at 3.0-T with FFR.

## Methods

All subjects gave written informed consent in accordance with ethical committee approval. Forty-four patients were

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recruited with either suspected or known coronary artery disease (CAD). All patients underwent CMR before invasive coronary studies. Exclusion criteria were contraindications for CMR or gadolinium (Gd)-contrast agents, previous myocardial infarction, coronary artery bypass grafting, acute coronary syndrome, impaired left ventricular (LV) function (ejection fraction <40%), and obstructive pulmonary disease.

**CMR protocol.** CMR was performed on a 3.0-T system (Achieva, Philips Medical Systems, Best, the Netherlands) using a 6-channel cardiac phased array receiver coil. Perfusion data were acquired in 3 LV short-axis slices at end-inspiration with a saturation recovery gradient echo method (repetition time/echo time 3.0 ms/1.0 ms, flip angle 15°, effective *k-t* SENSE acceleration with 5-fold acceleration and 11 training profiles, giving a net acceleration of 3.8-fold, spatial resolution $1.2 \times 1.2 \times 10$ mm$^3$). Data were acquired during adenosine-induced hyperemia (140 μg/kg/min) and 15 min later at rest using 0.05 mmol/kg Gd-diethylene triamine pentaacetic acid (Magnevist, Schering, Germany) at 4 ml/s followed by a 20-ml saline flush. Late Gd enhancement images were acquired after 15 min.

**Table 1** Baseline Demographics of Patient Cohort

| Parameter | Data (n = 42) |
|---|---|
| Male | 33 (78.6) |
| Age, yrs | 57.4 ± 9.6 |
| Previous PCI | 8 (19) |
| DM | 8 (19) |
| Previous stroke | 1 (2.3) |
| PVD | 3 (7.1) |
| Smoker | 9 (21.4) |
| Family history of IHD | 11 (26.1) |
| Medications | |
| Statin | 31 (73.8) |
| Beta-blocker | 20 (47.6) |
| Aspirin | 35 (83.3) |
| Clopidogrel | 22 (52.3) |
| Nitrate | 17 (40.4) |
| Calcium-channel blocker | 10 (23.8) |
| Nicorandil | 3 (7.1) |
| CMR data | |
| Resting BP (MAP), mm Hg | 78 ± 11 |
| Stress BP (MAP), mm Hg | 70 ± 15 |
| Resting HR, beats/min | 71 ± 15 |
| Stress HR, beats/min | 87 ± 25 |
| Scanning time, min | 56 ± 13 |
| Late gadolinium enhancement | |
| Full thickness | 0 (0) |
| Partial thickness | 2 (4.7) |
| Adenosine symptoms | 42 (100) |
| Adenosine complications | 0 (0) |
| Angiographic data | |
| Time from CMR scan, days | 2.5 ± 4.9 (median 0.5, range 0–21) |
| ≥1 lesion (>50% visual diameter stenosis) | 38 (90) |
| Vessels FFR measured (per patient), n | 1.3 ± 0.8 |
| Vessels with FFR >0.75, n* | 25 (0.89 ± 0.06) |
| Vessels with FFR ≤0.75, n* | 27 (0.53 ± 0.17) |
| LAD, n | 17 |
| Cx, n | 3 |
| RCA, n | 7 |
| QCA in vessels with FFR >0.75 (% diameter stenosis) | 47 ± 15.4 |
| QCA in vessels with FFR <0.75 (% diameter stenosis) | 81.8 ± 16.3 |

Data are n (%) or mean ± SD unless otherwise indicated. *Mean ± SD fractional flow reserve (FFR) is presented in parentheses.

BP = blood pressure; CMR = cardiac magnetic resonance; Cx = circumflex coronary artery; DM = diabetes mellitus; HR = heart rate; IHD = ischemic heart disease; LAD = left anterior descending coronary artery; MAP = mean arterial pressure; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; QCA = quantitative coronary angiography; RCA = right coronary artery.

**Abbreviations and Acronyms**

**CAD** = coronary artery disease
**CMR** = cardiac magnetic resonance
**FFR** = fractional flow reserve
***k-t* SENSE** = *k*-space and time sensitivity encoding
**LV** = left ventricle
**MPR** = myocardial perfusion reserve
**QCA** = quantitative coronary angiography

**Catheter laboratory protocol.** A 6-F sheath was inserted into the right femoral artery for coronary angiography and a 7-F sheath into the right femoral vein to record right atrial pressure (4). One milligram of intracoronary isosorbide dinitrate was administered. The FFR was measured using standard methods (3) with a 0.014-inch coronary pressure sensor–tipped wire (Volcano Therapeutics, San Diego, California) in all vessels that showed a >50% diameter stenosis in 2 orthogonal views; lesser diameter stenoses were considered not significant. Operators in the catheter laboratory were blinded to the results of the CMR scan. Quantitative coronary angiography (QCA) was calculated for all lesions offline (Medcon Ltd., Tel Aviv, Israel) by a blinded observer.

**Visual CMR analysis.** Two experienced, blinded observers visually analyzed CMR images independently (ViewForum, Philips Medical Systems). Defects were reported for 3 perfusion territories if contrast enhancement was delayed relative to a remote segment or if a transmural enhancement gradient was seen (5). In case of disagreement, arbitration from a third observer was sought.

**Quantitative analysis.** Two separate experienced observers performed blinded quantitative analysis of perfusion CMR data. Endocardial and epicardial borders were outlined and a region of interest placed in the LV cavity (MASS, Medis, Leiden, the Netherlands). Each slice was divided into 6 equiangular segments (5). Signal intensity/time data were imported to a Fermi function deconvolution algorithm implemented in Matlaboratory (The MathWorks Inc., Natick, Massachusetts) (6). Myocardial perfusion reserve (MPR) was calculated by dividing the hyperemic myocardial blood flow estimate flow by resting flow. The segments were then assigned to the respective perfusion territory (5), and the mean value of the 2 lowest scoring segments for each perfusion territory was used for further analysis.

**Statistical analysis.** Data are presented as mean ± SD. Group means were compared using paired and unpaired Student *t* test as appropriate. Receiver-operating characteristic

(ROC) analysis was used to determine the diagnostic accuracy of visual analysis and to determine the MPR with the greatest sensitivity and specificity to detect coronary disease at an FFR cut-off of 0.75. Linear regression was used for correlation of MPR with FFR and QCA, which were compared using Seiger *Z* test. An interobserver reliability analysis was performed for the discrete data using the Cohen kappa statistic and for the continuous data using the coefficient of variability. Because 3 coronary territories were examined per patient, the intraclass correlation coefficient (ICC) was calculated to determine the design effect and the need to adjust these data for clustering (7).

## Results

Two of the 44 recruited patients (33 men, age 57.4 ± 9.6 years) were excluded: 1 because of claustrophobia and 1 owing to technical problems. A total of 126 coronary territories in 42 patients were thus available for analysis (Table 1).

**Coronary angiography.** Data are shown in Table 1. Angiography was performed 2.5 ± 4.9 days after the CMR scan. Of the 126 vessels analyzed, 53 (42.1%) contained a >50% diameter stenosis on visual assessment and underwent FFR evaluation. One vessel was not assessed because of a total occlusion. Twenty-seven of the remaining 52 lesions had an FFR <0.75, and 25 lesions had an FFR ≥0.75. There was a good correlation between FFR and diameter stenosis ($r = -0.76$ [95% confidence interval [CI]: −0.83 to −0.66], $p < 0.0001$). Subsequent QCA did not reveal any vessel with >50% diameter stenosis that was not assessed by FFR.

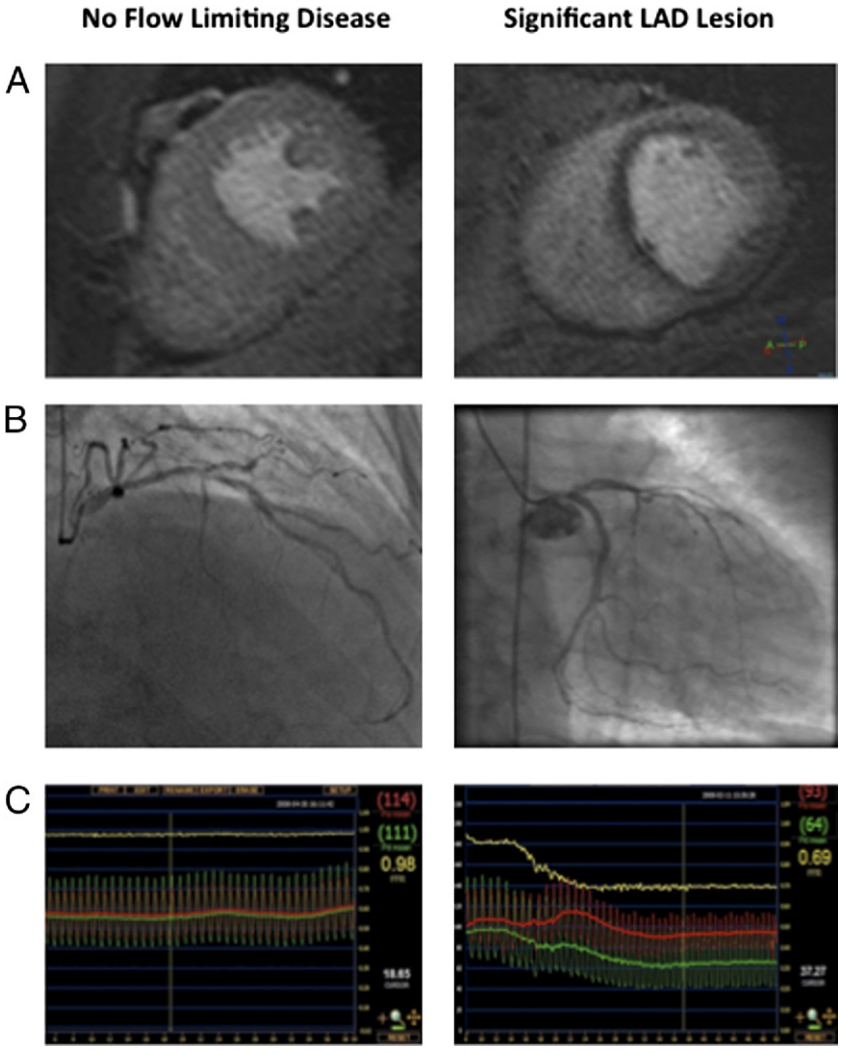


**Figure 1** Visual CMR Analysis

**Left-hand column** shows **(A)** normal cardiac magnetic resonance (CMR) perfusion scan, **(B)** moderate angiographic lesion in left anterior descending (LAD) coronary artery, and **(C)** fractional flow reserve (FFR) in the vessel of 0.98 signifying non–flow-limiting disease. **Right-hand column** shows **(A)** anterior perfusion defect, **(B)** tight lesion in the proximal LAD, and **(C)** FFR of 0.69 suggesting flow-limiting lesion.

**CMR imaging.** Mean scanning time was 56 ± 13 min, and there were no complications from the adenosine. Two (4.7%) patients had evidence of subendocardial scar based on the late Gd enhancement images; none had evidence of full-thickness transmural scar.

**Visual CMR analysis versus FFR.** Perfusion was reported as abnormal for 30 coronary territories (23.8%) and normal for 96 territories (Fig. 1). The interobserver reliability was kappa = 0.79 (95% CI: 0.69 to 0.91, $p < 0.0001$). The FFR in vessels with a visually detected perfusion defect was 0.59 ± 0.22 and was 0.93 ± 0.09 ($p < 0.0001$) in those with visually normal perfusion. Conversely, 22 of the 27 territories with an FFR <0.75 had a perfusion defect on visual CMR analysis. Five perfusion defects were reported in 99 vessels that were angiographically normal or had an FFR ≥0.75. Sensitivity of CMR perfusion to detect coronary ischemia at a threshold of FFR <0.75 was 0.82 (95% CI: 0.61 to 0.93), specificity 0.94 (95% CI: 0.87 to 0.98, $p < 0.001$), positive predictive value 0.83 (95% CI: 0.65 to 0.94), and negative predictive value 0.94 (95% CI: 0.88 to 0.98). The likelihood ratio was 16 with an area under the curve (AUC) of 0.92 (95% CI: 0.85 to 0.99, $p < 0.0001$) (Fig. 2). The agreement between visual analysis and FFR was kappa = 0.76 (95% CI: 0.63 to 0.89, $p < 0.0001$).

**Quantitative analysis.** In 4 patients, quantitative analysis of CMR perfusion data was not possible because of artifacts, leaving 114 perfusion territories in 38 patients available for analysis. The MPR in the 24 territories with an FFR ≤ 0.75 was 1.35 ± 0.5. In the 90 territories in which FFR was >0.75, MPR was 2.2 ± 0.5 ($p < 0.0001$). On ROC analysis, an MPR of 1.58 provided optimal sensitivity and specificity to detect coronary ischemia at the threshold of FFR <0.75 of 0.80 (95% CI: 0.58 to 0.94) and 0.89 (95% CI: 0.8 to 0.95), respectively, with positive and negative predictive values of 0.73 (95% CI: 0.54 to 0.88) and 0.95 (95% CI: 0.88 to 0.98), respectively. This gave a likelihood ratio of 9.3 and AUC of 0.89 (95% CI: 0.8 to 0.98, $p < 0.0001$) (Figs. 3 and 4). The agreement between MPR and FFR was kappa = 0.70 (95% CI: 0.54 to

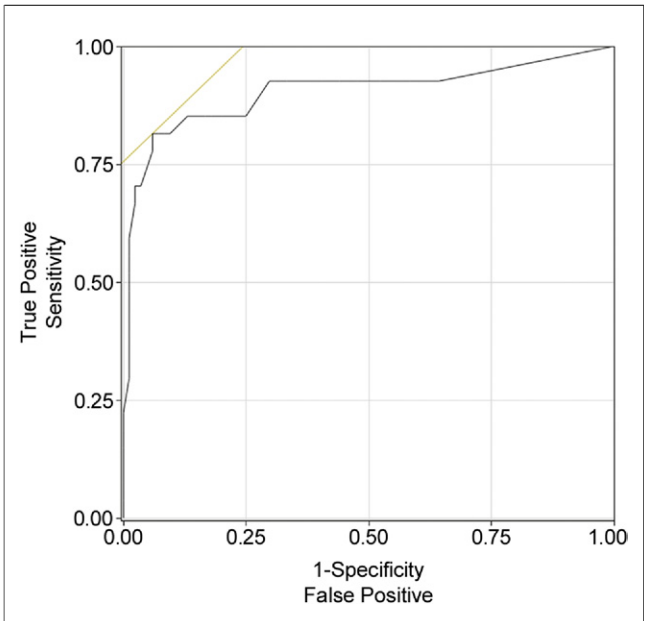


**Figure 2** ROC Showing Sensitivity and Specificity of Visual CMR Perfusion Analysis

Receiver-operating characteristic (ROC) showing sensitivity and specificity of CMR perfusion visual analysis to detect a hemodynamically significant coronary stenosis using a dichotomous value of 0.75 for FFR. The area under the curve was 0.92. Abbreviations as in Figure 1.

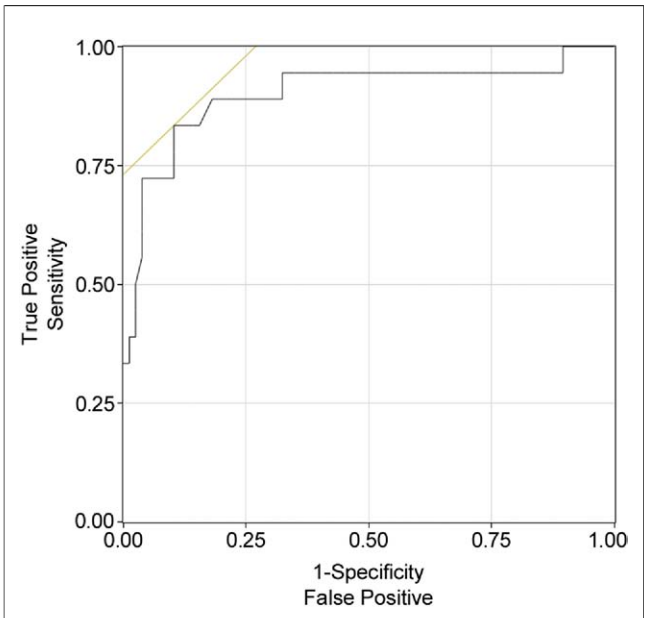


**Figure 3** ROC Showing Sensitivity and Specificity of Quantitative CMR Perfusion Analysis by MPR

ROC showing sensitivity and specificity of myocardial perfusion reserve (MPR) to detect a hemodynamically significant coronary stenosis using a dichotomous value of 0.75 for FFR. The area under the curve was 0.89. Abbreviations as in Figures 1 and 2.

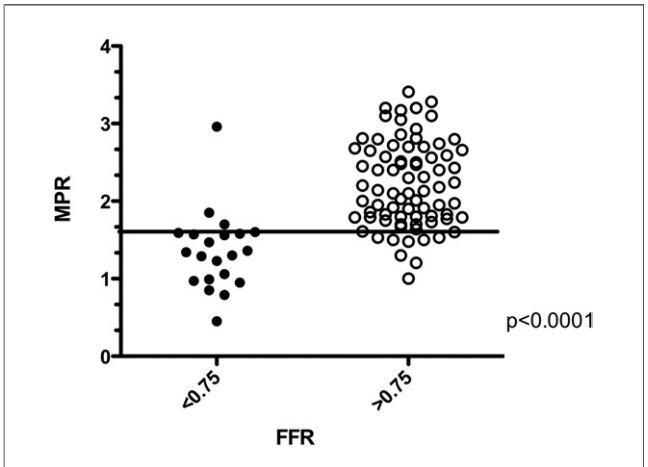


**Figure 4** Scatter Plot Showing Distribution of MPR Values According to FFR

A dichotomous cut-off of 0.75 was used to signify a significant lesion. Abbreviations as in Figures 1 and 3.

0.86, $p < 0.0001$). The coefficient of interobserver variability for MPR was 18%.

**Linear regression.** Linear regression analysis showed a closer correlation between MPR and FFR ($r = 0.59$ [95% CI: 0.43 to 0.71]; $p < 0.0001$) than between MPR and QCA ($r = -0.47$ [95% CI: −0.61 to −0.29], $p < 0.0001$; $Z = 4.73$, $p < 0.0001$). The ICC was low ($r_1 = 0.03$ [95% CI: 0.19 to 0.771], $p = 0.6$) with a design effect = 1.06 where cluster size = 3.

## Discussion

This study showed that high-resolution myocardial perfusion CMR imaging can be used for the detection of functionally significant coronary artery stenosis as determined by FFR using both visual and quantitative analysis. CMR-based measurements of myocardial blood flow correlated better with FFR than with QCA.

The majority of previous studies that have validated CMR myocardial perfusion imaging used QCA to determine the lesion severity. Our results showed that for high-resolution CMR perfusion data acquired at 3.0-T, visual and quantitative CMR allowed for accurate localization of perfusion defects to coronary territories.

Estimates of MPR correlated more closely with functional assessment of stenosis severity by FFR than with anatomic assessment by QCA. Previously, Rieber et al. (8) assessed a standard CMR perfusion sequence at 1.5-T for the detection of FFR-determined coronary disease in 43 patients. A semiquantitative analysis of upslopes of the signal-intensity profiles yielded sensitivity and specificity of 88% and 90%, respectively (8). Visual analysis was not performed. By comparison, Watkins et al. (9) used visual analysis of CMR perfusion alone with FFR in the assessment of 103 patients with CAD and were able to detect functionally significant disease with similarly high accuracy. In this later study, 25% of the patients had acute coronary syndrome and 23% had evidence of prior myocardial infarction. Although FFR has been used in these settings (10), its applicability remains uncertain (11). In addition, the presence of acutely injured myocardium or variable amounts of scar may have an unpredictable effect on the visual interpretation of myocardial perfusion. For these reasons, such patients were not included in the present study.

Both visual and quantitative analyses of myocardial perfusion CMR data have not been performed in previous studies. Although visual analysis of CMR perfusion is widely used in clinical practice, most current quantitative analysis methods are time consuming. In the present study, quantitative analysis yielded a degree of interobserver and intraobserver variability similar to previously published values (12), and both analysis methods were able to detect significant CAD as determined by FFR. The optimal MPR cut-off value of 1.58 to discriminate accurately between hemodynamically significant and nonsignificant lesions in this study is consistent with previous reports (8,13,14). It is possible that temporal filtering effects may have rendered the quantitative analysis less accurate. Such effects can be limited with recently proposed improvements of the *k-t* SENSE method that were not available at the time this study was performed (15).

**Study limitations.** Consistent with clinical practice, FFR was only measured in vessels with >50% coronary stenosis. We have studied a population with a very high prevalence of CAD who were already listed for invasive studies so that our data need to be considered preliminary and the reported accuracy is likely to represent a best-case scenario. The applicability of our results to a population with a lower pre-test probability of significant CAD needs to be determined, and the accuracy may well be lower. Artifacts may be a problem with the *k-t* SENSE method because of respiratory or cardiac motion, and quantitative analysis was not possible in 4 cases because of this. Such problems may be accentuated in patients with tachyarrhythmia or an inability to breath-hold for the scan. Because 3 perfusion territories were examined per patient, there is the potential for data loss through clustering. Although the design effect of this was low owing to a small ICC and cluster size, our results may have overestimated data correlations.

## Conclusions

In patients with stable coronary disease, high-resolution CMR perfusion at 3.0-T detected hemodynamically significant coronary stenoses as determined by FFR, using both visual and quantitative analysis methods.

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**Key Words:** coronary disease ■ fractional flow reserve ■ magnetic resonance imaging ■ myocardial perfusion.