Assessment of Fractional Flow Reserve in Patients With Recent Non–ST-Segment–Elevation Myocardial Infarction
Comparative Study With 3-T Stress Perfusion Cardiac Magnetic Resonance Imaging

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Background—The use of fractional flow reserve (FFR) in acute coronary syndromes is controversial. The British Heart Foundation Fractional Flow Reserve Versus Angiography in Guiding Management to Optimize Outcomes in Non-ST-Elevation Myocardial Infarction (FAMOUS-NSTEMI) study (NCT01764334) has recently demonstrated the safety and feasibility of FFR measurement in patients with non–ST-segment–elevation myocardial infarction. We report the findings of the cardiac magnetic resonance (CMR) substudy to assess the diagnostic accuracy of FFR compared with 3.0-T stress CMR perfusion.

Methods and Results—One hundred six patients with non–ST-segment–elevation myocardial infarction who had been referred for early invasive management were included from 2 centers. FFR was measured in all major patent epicardial coronary arteries with a visual stenosis estimated at ≥30%, and if percutaneous coronary intervention was performed, an FFR assessment was repeated. Myocardial perfusion was assessed with stress perfusion CMR at 3 T. The mean age was 56.7±9.8 years; 82.6% were men. Mean time from FFR evaluation to CMR was 6.1±3.1 days. The mean±SD left ventricular ejection fraction was 58.2±9.1%. Mean infarct size was 5.4±7.1%, and mean troponin concentration was 5.2±9.2 μg/L. There were 34 fixed and 160 inducible perfusion defects. There was a negative correlation between the number of segments with a perfusion abnormality and FFR (r=−0.77; P<0.0001). The overall sensitivity, specificity, positive predictive value, and negative predictive value for an FFR of ≤0.8 were 91.4%, 92.2%, 76%, and 97%, respectively. Diagnostic accuracy was 92%. The positive and negative predictive values of FFR for flow-limiting coronary artery disease (FFR≤0.8) in patients with non–ST-segment–elevation myocardial infarction (n=21) who underwent perfusion CMR before invasive angiography were 92% and 93%, respectively. Receiver operating characteristic analysis indicated that the optimal cutoff value of FFR for demonstrating reversible ischemia on CMR was ≤0.805 (area under the receiver operating characteristic curve, 0.94 [0.9–0.99]; P<0.0001).

Conclusions—FFR in patients with recent non–ST-segment–elevation myocardial infarction showed high concordance with myocardial perfusion in matched territories as revealed by 3.0-T stress perfusion CMR.

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Key Words: acute coronary syndrome ■ fractional flow reserve, myocardial ■ magnetic resonance imaging ■ myocardial infarction ■ percutaneous coronary intervention

Fractional flow reserve (FFR) has an established role in guiding percutaneous coronary intervention (PCI) in stable coronary artery disease (CAD). In this setting, the use of FFR has been associated with improved long-term outcomes and reduced healthcare costs compared with angiographic-based strategies.1 Rates of urgent revascularization are reduced when
WHAT IS KNOWN

• Fractional flow reserve is a well-validated technique to guide revascularization decisions among patients with stable angina.
• There is a paucity of data on the accuracy of fractional flow reserve in patients with acute non-ST-segment-elevation myocardial infarction.

WHAT THE STUDY ADDS

• There is a high level of concordance between inducible perfusion defects revealed by stress perfusion cardiac magnetic resonance imaging and fractional flow reserve among selected patients with non-ST-segment-elevation myocardial infarction.

Compare with contemporary medical therapy. The validity of FFR is predicated on the ability to produce maximal hyperemia to achieve a linear relationship between pressure and flow. Maximal hyperemia may be less readily achieved in patients with recent myocardial infarction (MI) because of microvascular dysfunction. Evidence on the potential diagnostic accuracy of FFR in patients with a recent acute coronary syndrome (ACS) is lacking.

In primary PCI for acute ST-segment-elevation MI (STEMI), FFR values are influenced and may reflect severe microvascular dysfunction in the territory of reperfused culprit artery. The natural history of non-STEMI (NSTEMI) is different with most patients who are medically stabilized presenting without coronary occlusion. In these patients, the microcirculation may have recovered and stabilized sufficient vasodilator capacity that FFR may be a valid measure of lesion-level flow. Recent clinical studies support the notion that contemporary FFR thresholds retain diagnostic accuracy among medically stabilized patients with MI. For example, FFR correctly identified inducible ischemia on single-photon emission computed tomography in 57 patients >6 days after MI, and in a follow-up study of 124 patients with ACS, deferring revascularization in lesions with an FFR of ≥0.75 was safe. On the basis of invasive measurement of coronary vasodilator capacity (resistive reserve ratio), we found that patients with stable angina and NSTEMI have a similar vasodilator reserve. Thus, although recent studies are informative, more data concerning the validity of FFR in NSTEMI are needed.

The recent British Heart Foundation Fractional Flow Reserve Versus Angiography in Guiding Management to Optimize Outcomes in Non-ST-Elevation Myocardial Infarction (FAMOUS-NSTEMI) study (NCT01764334) is the largest randomized controlled trial of FFR in ACS to date. In FAMOUS-NSTEMI, 350 medically stabilized patients with NSTEMI were randomized to FFR-guided management versus standard care with angiography-guided management. FFR was measured in all of the participants, but in the control group, clinicians and patients were blinded to the FFR results. FFR was feasible and safe in >99% of the participants, and intravenous adenosine was well tolerated. Compared with angiography-guided management, FFR-guided management reduced revascularization, and health outcomes were similar between the groups at 1 year. A prespecified substudy was conducted to assess the relationships between invasively measured FFR and myocardial perfusion with cardiac magnetic resonance (CMR) at 3.0-T. The purpose of this study was to examine the ability of FFR to predict reversible ischemia when compared with a noninvasive gold standard in a large cohort of medically stabilized patients with NSTEMI.

Methods

Study Population

One hundred six patients were enrolled between November 2011 and June 2013 from 2 of the participating hospitals in the vicinity of the CMR center. One of the hospitals was a nonacademic regional hospital, and the other was an academic cardiothoracic center and the lead site for the FAMOUS-NSTEMI trial. The CMR study population consisted of patients with recent NSTEMI who had been referred for early invasive management guided by coronary angiography (NCT02073422). Exclusion criteria included coronary artery bypass graft surgery, severe valvular heart disease, and standard contraindications for CMR. At the time of coronary angiography, FFR was measured in all major patent epicardial coronary arteries with a visual stenosis estimated at ≥50%. An FFR assessment after PCI was also performed. Patients were scheduled for a pharmacological stress perfusion CMR scan at 3.0 T after discharge from hospital. CMR was also performed in a subset of patients who had been discharged from hospital for early urgent outpatient coronary angiography/PCI.

The protocol was approved by the regional ethics committee, and the study was undertaken in accordance with the Declaration of Helsinki. All of the participants gave written informed consent.

CMR Protocol

A description of the CMR protocol used in this study is available in the Data Supplement. Higher field (3.0 T) contrast-enhanced CMR was adopted as a reference method for assessing myocardial perfusion, as well as left ventricular function and MI. Heart imaging was carried out on a Siemens MAGNETOM Verio (Erlangen, Germany) 3.0-T scanner with an 8-element phased array cardiac surface coil. The CMR protocol included assessment of left ventricular function using steady-state free precession, MI using late gadolinium enhancement, and myocardial perfusion was assessed by first-pass dynamic contrast-enhanced CMR.

For perfusion, dynamic contrast-enhanced CMR was acquired in basal, midventricular, and apical short axis slices during the first pass of 0.05 mL/kg of 1 mol/L of gadolinium–based contrast agent (Gadovist, Bayer) injected with a power injector at a flow rate of 4 mL/s.

Hypermia was achieved with an intravenous infusion of adenosine at 140 μg/kg per minute for 3 to 4 minutes. All patients had desisted from caffeine for at least 12 hours before the scan and had otherwise complied with their standard medication.

Rest perfusion imaging was acquired using the same dynamic contrast-enhanced CMR protocol 15 minutes after the stress scan with the administration of 0.05 mL/kg of contrast agent (Gadovist, Bayer).

Late gadolinium enhancement CMR was performed with a T1-weighted–segmented gradient-echo phase-sensitive inversion-recovery sequence [10]. Images were collected 15 to 20 minutes after the last injection of contrast.

CMR Analysis

CMR data acquisition were performed independently by a separate team of staff from the staff who performed the invasive catheter laboratory procedures and FFR measurements. The CMR scans
were deidentified and analyzed in random order on an image review workstation by CMR observers with at least 3 years of experience of perfusion CMR (C.B., D.C., and S.W.). J.L. coordinated the study. The CMR readers were blinded to all of the clinical, angiographic, and FFR results.

Analysis of Stress/Rest Perfusion CMR
Stress and rest perfusion CMR images were analyzed side-by-side using dedicated software (Argus Dynamic Signal, Siemens, Erlangen, Germany). The stress and rest myocardial perfusion scans were viewed simultaneously. The perfusion scans were visually assessed for normal and abnormal myocardial hyperperfusion, and segments with abnormal perfusion were assigned to coronary territories using the American Heart Association coronary arterial 16-segment model. In cases of disagreement between observers, a third blinded observer adjudicated, and the observers also prospectively evaluated image quality. Two patients were excluded because of poor image quality.

A myocardial perfusion abnormality at rest or during pharmacological stress was classified as significant according to the presence of reduced perfusion in 2 segments of a 32-segment model (16-segment AHA model divided into subendocardial and subepicardial layers): >60° in either the basal or the midventricular slices or >90° in the apical slice or any transmural defect or 2 adjacent slices.

Invasive Coronary Angiography and Coronary Pressure Wire
All patients received an initial intravenous bolus of 5000 U of unfractionated heparin with an additional bolus of heparin as required to maintain an activated clotting time of 250 s. All patients had been pretreated with aspirin and clopidogrel. A 6-F coronary guiding catheter was used routinely, and 200 µg of intracoronary nitroglycerin was administered during left and right coronary angiography. A 0.014" coronary pressure–sensing guidewire was calibrated and then equalized to the guiding catheter pressure with the guidewire sensor placed in the aorta at the ostium of the coronary artery. The wire was then passed beyond the stenosis into the distal third of the vessel. Systemic hyperemia was then established using intravenous adenosine at a dose of 140 µg/kg per minute. Myocardial FFR was taken as the ratio of distal coronary to proximal aortic pressure during steady state hyperemia. An FFR of ≤0.8 was used as a measure of stenosis significance. An FFR value of 0.5 was given to patients with an occluded or subtotally occluded vessel.

Safety
All patients were prospectively evaluated for safety, including in relation to intravenous adenosine administration and coronary instrumentation with the diagnostic guidewire. Adverse events were recorded by the clinical and research staff in an electronic case report form administered by the Pharmacovigilance Service of the Robertson Center for Biostatistics, a trials unit registered with the National Institute for Health Research.

Diagnostic Accuracy Study Methodology
This analysis was conducted according to standards for reporting of diagnostic accuracy, and the study was reported in accordance with the established best practice (Data Supplement).

Statistical Analyses and Indicative Sample Size Calculation
Statistical analyses were carried out using IBM SPSS Statistics software, version 21.0 (Armonk). Normality was tested with the Shapiro–Wilk test. All results are given as mean±SD, unless otherwise stated. Correlations were tested by the Pearson or Spearman method as appropriate. Comparisons of normally distributed continuous data were undertaken using the Student t test. Between-group comparisons of non-normally distributed data were performed with a Mann–Whitney test. P<0.05 was considered statistically significant.

Receiver operating characteristic analysis was used to determine the optimal cutoff value for FFR to predict a perfusion defect on CMR. The area under the receiver operating characteristic curve (AUC) was used as a measure of test accuracy.

To predetermine the sample size, we estimated that at least 40% of the study participants would have an FFR value of ≤0.80 at the time of the index procedure, and ≈20% of the participants would have functionally significant residual obstructive coronary disease at the end of the procedure reflecting incomplete revascularization of nonculprit coronary lesions (potentially as part of a staged management plan or lesions that were not amenable to revascularization). We therefore estimated that the prevalence of regional perfusion defects overall by stress perfusion CMR will be 30%. Theoretically, there should be close to a 1:1 correspondence with an inducible perfusion abnormality on stress CMR and an FFR of ≤0.80. Assuming a true underlying agreement rate of 90% and only one artery studied per patient, a sample size of 104 patients would have >85% power to exclude an agreement rate <80% based on a 1-sided 95% confidence interval. In reality, >1 artery could be studied on a per-patient basis, hence increasing the power further.

Results
Of 251 medically stabilized patients with NSTEMI who were randomized in the clinical trial in the 2 hospitals that participated in the CMR study, 106 (42.2%) were enrolled and had evaluable CMR data. A total of 1696 myocardial segments were available for analysis. Thirty-two segments (2 patients) were excluded from the analysis because of nondiagnostic image quality; so, 1664 myocardial segments with evaluable perfusion CMR data were finally included. Of these, 793 segments were spatially matched with a coronary artery territory in which FFR was measured. The flow diagram for the CMR substudy is shown in Figure 1. A typical clinical case including the CMR, angiography, and FFR observations is shown in Figure 2.

The demographics and characteristics of the patients with NSTEMI are shown in Table 1. The mean age of the participants was 56.7±9.8 years, and 82.6% were men. The mean time from symptom onset to FFR evaluation was 6.1±3.1 days. The mean time from FFR evaluation to CMR was 4.4±2.5 days.

A total of 21 patients with NSTEMI had CMR examinations before coronary angiography/PCI, and 83 patients had stress CMR after angiography/PCI (Figure 3). Of these 83 patients, 66 underwent PCI before the CMR. Of the 21 medically stabilised NSTEMI (intermediate-high risk) Referred for coronary angiography n=106 (Nov 2011 – Jun 2013)

Figure 1. Flow diagram of patients enrolled in the fractional flow reserve (FFR)-cardiac magnetic resonance study. MRI indicates magnetic resonance imaging; and NSTEMI, non-ST-segment-elevation myocardial infarction.
Patients studied before coronary angiography, 8 patients underwent PCI and 1 patient went on to have coronary artery bypass graft. The mean time interval between the CMR and FFR for this group was 6.6±3.7 days.

There were no adverse events related to intravenous adenosine infusion during for the whole cohort either the invasive procedure for FFR or the stress perfusion CMR scan. No adverse events occurred in relation to coronary instrumentation with the diagnostic guidewire or with intravenous adenosine for FFR measurement.

Coronary Angiography and Physiology
A total of 168 coronary arteries were assessed, 96 (57%) in the infarct-related arteries and 72 (43%) in the noninfarct-related arteries. As reported by the interventional cardiologist in the catheter laboratory, and based on all of the clinical information at the time of the procedure, the infarct-related artery was the left anterior descending coronary artery in 47 patients with NSTEMI, the left circumflex in 17 patients, and the right coronary artery in 18 patients. In 1 patient, the identity of the culprit artery was unclear. The mean FFR for the population was 0.85±0.13.

CMR Findings
The mean±SD left ventricular ejection fraction was 58.2±9.1%, and the mean infarct size was 5.4±7.1%. There were 194 segments with a perfusion abnormality, including 34 (18%) fixed and 160 (82%) inducible perfusion defects. The 160 inducible segmental perfusion defects occurred in 41 patients. Thirty (73%) of these perfusion defects involved the infarct-related artery territory, and 11 (27%) occurred in the noninfarct artery territory. There were 57 inducible perfusion defects (14 vessels) among patients imaged before and 103 defects (28 vessels) in those patients imaged after coronary angiography. There were 40 inducible transmural perfusion defects. Five (5%) patients had CMR evidence of perfusion abnormalities in multiple coronary artery territories. There was a negative correlation between the number of segments with an inducible perfusion defect and FFR (r=−0.77; P<0.0001; (Table 2).

When looking only at the infarct-related culprit artery territory (n=89), there was a moderate negative correlation between the number of segments (n=113 segments) with an inducible perfusion abnormality on stress CMR and FFR (r=−0.8; P<0.001) When the analysis is restricted to coronary arteries with occlusive disease (ie, arteries with an FFR allocation of 0.5 ascribed for severe, flow limiting stenosis/chronic occlusion), the correlation was moderate (r=−0.69; P<0.0001; n=66 arteries; 59 segments).

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for an FFR of ≤0.8 were 91.4%, 92.2%, 76%, and 97%, respectively. The diagnostic accuracy was 92%. The sensitivity, specificity, PPV, and NPV for an FFR of ≤0.75 were 88.2%, 95%, 83%, and 96%, respectively.

Receiver operating characteristic analysis indicated that the AUC for FFR predicting an inducible perfusion defect on stress CMR was 0.94 (0.90–0.99), P<0.0001 (Figure 4). The optimal cutoff value was 0.805, and this was associated with a sensitivity of 91.2% and a specificity of 92.2%. Looking specifically at the infarct-related culprit artery, the AUC was 0.91, P<0.001. The optimal cutoff value was again an FFR of 0.805, and this was associated with a sensitivity of 86% and a specificity of 95%.

On a per-segment analysis, the FFR cutoff value of ≤0.8 was associated with 87.2% sensitivity, 91.9% specificity, PPV of 65%, and NPV of 97%.

CMR Before Versus After Angiography
Patients with NSTEMI who had stress perfusion CMR before invasive angiography (n=21) had an altered clinical profile

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
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<tr>
<td>Men (%)</td>
<td>86 (82.6)</td>
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<tr>
<td>Age±SD</td>
<td>58.7±9.8</td>
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<tr>
<td>Diabetes mellitus, n (%)</td>
<td>13 (12.6)</td>
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<tr>
<td>Smoker, n (%)</td>
<td>77 (73.3)</td>
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<td>Hypertension, n (%)</td>
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<td>Hypercholesterolemia, n (%)</td>
<td>34 (33)</td>
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<tr>
<td>Multivessel disease, n (%)</td>
<td>55 (52.9)</td>
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<tr>
<td>Previous PCI, n (%)</td>
<td>8 (5.1)</td>
</tr>
<tr>
<td>Troponin, μg/L (±SD)</td>
<td>5.2±9.5</td>
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<tr>
<td>BMI (±SD)</td>
<td>29.17±4.7</td>
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<tr>
<td>GRACE (±SD)</td>
<td>163.6±35</td>
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<tr>
<td>Syntax score (±SD)</td>
<td>12.4±7.7</td>
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<tr>
<td>Approach score (±SD)</td>
<td>21.8±12.9</td>
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</tbody>
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Table 1. Demographics and Treatment of Study Population
compared with those patients imaged after PCI/angiography. The mean Grace score was lower (Grace score before angiography 140.0±52.3 versus 164.2±34.8 [P=0.63]) as was the mean FFR (mean FFR before angiography 0.7±0.2 versus mean FFR after angiography 0.87±0.13; P=0.004).

Other clinical characteristics for patients with CMR before versus after angiography were similar, including patient age (57.8±10.6 versus 56.4±9.6 years; P=0.6), body mass index (30.6±4.6 versus 28.7±4.7 kg/m²; P=0.87), time from CMR to FFR assessment (6.1±3.7 versus 5.9±3.1 days; P=0.84), or Syntax score (13.9 versus 12.06; P=0.51).

The PPV of FFR for flow-limiting CAD (FFR≤0.8), compared with stress perfusion CMR perfusion before invasive angiography, was higher when compared with patients’ imaged after invasive management (sensitivity, 92%; specificity, 93.3%; PPV, 92%; and NPV, 93%), and accuracy was otherwise similar.

Figure 3. Flow diagram providing an overview of the study population. MRI indicates magnetic resonance imaging; and PCI, percutaneous coronary intervention.

Discussion
The most important finding of this study is the high diagnostic accuracy of FFR at established thresholds for lesion-level flow limitation when compared against myocardial perfusion revealed by stress perfusion CMR at 3.0 T. We have shown that as a diagnostic test for detecting flow-limiting CAD, the performance of FFR was excellent with an AUC of 0.94. Before our study, the validity of FFR and its established ischemic thresholds of 0.80 and 0.75 in medically stabilized patients with NSTEMI was uncertain. The high prevalence of multivessel coronary disease and the impractical use of noninvasive tests in the acute setting support the theory that FFR might have potential diagnostic values in this population. Because the performance of FFR could rule-out the need for deferral of treatment to obtain a noninvasive stress test to assess the functional significance of bystander coronary disease, FFR has potential clinical utility in the context of a single diagnostic and therapeutic procedure in patients with NSTEMI during urgent ad hoc invasive management.

Use of 3-T CMR as Noninvasive Reference Standard
Comparing FFR with a noninvasive reference standard for diagnosing ischemia is a point of contention within the medical literature particularly because FFR was originally compared with noninvasive imaging for its own validation. However, with the continued improvements in CMR imaging and with a lack of a clear gold standard for noninvasively diagnosing ischemia, CMR was chosen as a reference standard to assess the accuracy of FFR.

Concerns on the Use of FFR to Guide Management in ACS
Culprit Arteries
In the setting of emergency primary PCI for acute STEMI, severe microvascular injury precludes maximal hyperemia such that FFR is not valid as a diagnostic test. In the NSTEMI setting, the nature of the microvascular injury is typically different because the culprit coronary artery remains patent with normal antegrade flow, which is the usual finding during invasive angiography. In some patients with NSTEMI, the natural history may involve intermittent coronary occlusion (eg, because of vasospasm and thrombus burden), but typically, the occlusion is transient. Furthermore, microvascular injury may also be transient such that initial measurements of FFR may be artificially elevated, but after stabilization of the coronary microcirculation, FFR reflects the true hemodynamic effect.
of the coronary stenosis. In our study, FFR was restricted by protocol to coronary arteries with normal flow, and in the case of chronic total occlusions or severely obstructed arteries, an FFR value of 0.5 was assigned. Furthermore, in patients with NSTEMI, invasive angiography is generally performed on a subacute basis usually 24 hours or more after initial presentation during which time antithrombotic treatments are given. Theoretically, maximal coronary vasodilatation that is required to establish the critical linear relationship between pressure and flow necessary for the assessment of FFR may still not be achieved. The attainment of maximal hyperemia is predicated on preserved microcirculatory function because the distal coronary microcirculation is the major contributor to coronary vascular resistance. However, using cardiac positron emission tomography, Uren et al provided evidence of impaired microcirculatory function in the infarcted region compared with healthy controls ≤6 months after acute MI. Thus, in patients with recent MI microvascular injury, stunning and edema may result in a failure to achieve minimal resistance, and FFR values may be falsely elevated. Tamita et al highlighted this by demonstrating a higher post-PCI FFR in patients with STEMI compared with patients with stable angina despite similar intravascular ultrasound parameters. Patients with thrombolysis in MI II flow also had a higher FFR compared with those patients with thrombolysis in MI III flow. Thus, in patients with severe microvascular dysfunction, the assessment of FFR may be unreliable.

We have demonstrated a good correlation between inducible ischemia demonstrated on a noninvasive gold standard and FFR in the culprit artery of patients with NSTEMI. Furthermore, we have shown excellent test accuracy with an AUC of 0.91, a sensitivity of 86%, and a specificity of 95%. Indeed, the optimal cutoff value for FFR was 0.8. This excellent concordance provides further evidence for the validity of FFR measurements in the culprit vessel of patients with recent NSTEMI and supports previous findings.

**Nonculprit Arteries**

Several studies have clearly demonstrated that altered blood flow patterns and impaired vasodilator response in territories remote from the culprit vessel could potentially have implications for the assessment of FFR in nonculprit vessels in patients presenting with ACS.

**FFR Thresholds in ACS**

In patients with stable CAD, a myocardial FFR of ≤0.80 is an evidence-based physiological threshold indicative of lesion-level ischemia because of obstructive CAD that may be amenable for revascularization. The original validation studies that determined the FFR threshold for ischemia were all performed in stable patients. However, there have been several studies that have aimed to establish and validate FFR thresholds for ischemia in patients with ACS. In 48 stabilized patients with recent MI, Samady et al compared FFR in the infarct-related artery to noninvasive findings using single-photon emission computed tomography and myocardial contrast echocardiography. Patients had a mean time to angiography of 3.7 days; 73% of patients presented with STEMI. The group demonstrated that an FFR of ≤0.75 had 91% sensitivity, 93% specificity, and a diagnostic accuracy of 92% for detecting reversible ischemia. They provided an optimal cutoff FFR value of ≤0.78 for detecting reversible ischemia using receiver operating characteristic analysis. Furthermore, Ebersberger et al reported the findings of a similarly designed FFR versus CMR study at 3.0 T in 116 patients with stable angina. They demonstrated sensitivity, specificity, PPV, and NPV of 89%, 95%, 87%, and 96%, respectively. Our data are in accordance with these findings and support the diagnostic utility of FFR in patients with NSTEMI in the culprit and nonculprit territories at 4 days after MI to identify reversible ischemia.

Our findings are similar to those of Samady et al and higher than the threshold originally put forward for patients with stable angina and may reflect higher microvascular resistance in patients with recent NSTEMI compared with controls in line with recent observations by our group.

**Current Evidence for Benefit of FFR in ACS**

The FAME trial also included patients with NSTEMI/unstable angina. FFR-guided revascularization was associated with a similar magnitude of treatment effect over angiography-guided PCI in patients with recent NSTEMI/unstable angina compared with those with stable angina. However, the pooling of patients with unstable angina and NSTEMI, the lack of information on the timing of the index infarction or troponin values, and risk stratification (e.g., with the GRACE score) supported the case for further studies investigating the relationship between FFR and NSTEMI.

Most data relating to FFR in NSTEMI thus far have been retrospective or observational. Potvin et al demonstrated that in 201 unselected patients presenting to the catheter laboratory, the use of an FFR threshold of ≤0.75 was safe to allow deferral of stenting. However, only 21% of patients had a recent STEMI/NSTEMI, and the use of FFR was not...
randomized or blinded. Thus, although helpful, these studies were in relatively stable patients and not powered to detect any effect of FFR-guided management on health outcomes or to determine the clinical utility of FFR or optimal cutoff in patients with ACS.

Lopez-Palop et al recently have published the results of an observational nonrandomized cohort of 107 patients with NSTEMI who had FFR evaluation of nonculprit stenoses. They demonstrated no difference in outcome between patients who had revascularization deferred on the basis of FFR compared with those who underwent angiographically guided revascularization. In addition, Ntalianis et al evaluated the assessment of nonculprit stenoses in 26 patients with an acute NSTEMI (within 72 hours) and 126 patients with STEMI and showed that FFR values in the nonculprit vessel were unchanged when measured again ≥5 weeks later. Thus, the use of FFR to evaluate nonculprit stenoses has been shown to be reasonably accurate and reproducible in different NSTEMI populations, including from this analysis also.

The British Heart Foundation FAMOUS-NSTEMI study recently confirmed the feasibility and safety of routine FFR measurement in patients with NSTEMI. Although there was no difference in major adverse cardiac events at 12-month follow-up, there was a significant change in management strategy after FFR disclosure with an increase in the prescription of medical therapy and a reduction in revascularization. The results from our study are in accordance with FAME and provide further evidence of the validity of FFR in this population.

Potential Benefits of FFR-Guided Stenting in Patients With ACS
Contemporary guidelines recommend making revascularization decisions for culprit lesions in patients with convalescent STEMI and NSTEMI/unstable angina in the same manner as stable angina. This strategy seems to improve symptoms and reduce rates of death and nonfatal MI at long-term follow-up. However, there has been discordance in the literature with respect to standard angiographic classifications (eg, coronary artery surgery score and DUKE jeopardy score) and also coronary collateral supply.

Discordance Between FFR and CMR
We observed discordance between FFR and CMR diagnosis of ischemia in 63 magnetic resonance imaging segments. However, this most commonly involved an isolated segment within an already ischemic territory. As this did not meet the prespecified CMR definition of ischemia, the diagnostic utility of FFR was preserved. Because of the small numbers, we could not define a relationship between discordance and timing of magnetic resonance imaging/clinical presentation.

Limitations
A minority of the patients with NSTEMI in our study had stress perfusion CMR before invasive management, whereas the majority had CMR afterward. This meant that a significant proportion of patients had revascularization before the CMR. However, CMR was performed on average 6 days after invasive management allowing time for microvascular dysfunction related to the PCI procedure (performed after FFR) to improve. Nevertheless, the time interval between CMR and FFR and PCI-related microvascular injury may be confounding factors for the FFR versus perfusion CMR relationship.

Because many centers perform intervention on patients with NSTEMI within 48 hours of presentation, the generalizability of our results is limited to patients who present within a similar time frame. However, because FFR was performed within 5 days of presentation to hospital and a predefined inclusion was that the patients must have pain within the last 5 days (or have had their NSTEMI in the last 72 hours), our data remain relevant.

We found evidence of a high sensitivity and a specificity of FFR for flow-limiting coronary disease, as revealed noninvasively by stress perfusion CMR. Our results are in keeping with established data but should be interpreted on the basis that the participants with NSTEMI had a high pretest likelihood of CAD. This fact is also relevant when considering the higher PPV of FFR for abnormal myocardial perfusion in patients undergoing CMR before invasive angiography and revascularization.

Although we have demonstrated excellent concordance between FFR and stress CMR, we should not expect one-to-one concordance between FFR and myocardial perfusion because fundamentally, the tests are different. FFR is an invasive guidewire-based pressure-derived index of coronary blood flow that can be anatomically specified to individual coronary lesions with a readout displayed in real time on a hemodynamic monitor. Perfusion magnetic resonance imaging is noninvasive and provides information on myocardial perfusion based on dynamic changes in myocardial contrast kinetics and signal intensity in just a few heart beats. In clinical practice, the signal changes are assessed visually. We have assumed spatial concordance for the coronary artery instrumented for FFR measurement and its distribution on the myocardial perfusion scan, but other biological factors may affect this relationship including subject-specific variations in coronary anatomy with respect to standard angiographic classifications (eg, coronary artery surgery score and DUKE jeopardy score) and also coronary collateral supply.

Conclusions
This is the first study to date to examine the diagnostic accuracy of FFR in a reasonably large cohort of patients with recent NSTEMI versus a high-fidelity noninvasive reference method. Our results indicate that FFR and stress perfusion CMR at 3.0 T were highly concordant and add further evidence for the utility of FFR in this population.

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Disclosures
Dr Berry has been a Principal Investigator on institutional research grants supported by St Jude Medical, and he has acted as a consultant to St Jude Medical with institutional reimbursement. Dr Oldroyd has grants supported by St Jude Medical, and he has acted as a consultant to St Jude Medical and VOLCANO Corporation. The other authors report no conflicts.

References


Layland et al.  FFR vs MRI in NSTEMI


Assessment of Fractional Flow Reserve in Patients With Recent Non–ST-Segment–Elevation Myocardial Infarction: Comparative Study With 3-T Stress Perfusion Cardiac Magnetic Resonance Imaging


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STROBE Statement—Checklist of items that should be included in reports of cohort studies Item

Title and abstract: Background/rationale

Objectives: Indicate the study's design with a commonly used term in the title or the abstract. Provide in the abstract an informative and balanced summary of what was done and what was found.

We have done this in our title and in our abstract.

Introduction: Explain the scientific background and rationale for the investigation being reported. State specific objectives, including any prespecified hypotheses.

This is included in our introduction.

Methods

Study design: Present key elements of study design early in the paper.

We have included this in the methods.

Setting: Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.

This is clearly explained in the methods and in figure 1.

Participants: Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. For matched studies, give matching criteria and number of exposed and unexposed.

There is clear inclusion criteria mentioned in the methodology.

Variables: Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.

These are mentioned as best we can for a correlative study.

Data sources/measurement: For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.

This is clearly written in the methods section.
Bias Describe any efforts to address potential sources of bias

Bias is briefly discussed in the limitations section.

Study Size Explain how the study size was arrived at.

Sample size calculation is discussed in the methods

Quantitative variables. Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why

Statistical methods Describe all statistical methods, including those used to control for confounding. Describe any methods used to examine subgroups and interactions. Explain how missing data were addressed. If applicable, explain how loss to follow-up was addressed. Describe any sensitivity analyses

All statistical methods clearly documented in the statistics section.

Results

Participants: Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give reasons for non-participation at each stage. Consider use of a flow diagram

All patients considered and excluded patients (and reasons for) are given in methods/results.

Descriptive data: Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)

Demographics clearly shown in Data Tables and Text

Outcome data: Report numbers of outcome events or summary measures over time

This was not an outcome trial

Main results: Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
All results expressed as mean/median with standard deviations/Interquartile range as appropriate.

Other analyses: Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

ROC curve, sensitivity, specificity analyses are clearly reported.

Discussion

Key results: Summarise key results with reference to study objectives

Results are clearly presented in the discussion.

Limitations: Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.

There is a long discussion concerning the limitations of the study

Interpretation: Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence

Generalisability: Discuss the generalisability (external validity) of the study results

Interpretation and generalizability are clearly presented.

Other information

Funding: Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.

The funding for the study is presented at the end of the paper.

Detailed CMR Protocol

Higher field (3.0 Tesla) CMR was adopted as a reference method for assessing myocardial perfusion, as well as function and infarction. Heart imaging was carried out on a Siemens MAGNETOM Verio (Erlangen, Germany) 3.0 Tesla scanner with an 8-element phased array cardiac surface coil. The CMR protocol included assessment of left ventricular function using Steady State Free Precession (SSFP), myocardial infarction
using late gadolinium enhancement (LGE), and myocardial perfusion was assessed by first-pass dynamic contrast-enhanced CMR (DCE-CMR).

Cine SSFP images with two-fold accelerated parallel imaging (GRAPPA) were acquired in a stack of short-axis views of the LV. Imaging parameters were: repetition time (TR) 3.4 ms, echo time (TE) 1.51 ms, flip angle (FA) 50°, typical field of view (FOV) (340 x 286)mm², matrix 256 x 216, slice thickness 7 mm, slice gap 3 mm, receiver bandwidth (BW) 977 Hz/px, 25 cardiac phases.

For perfusion, DCE-CMR was acquired in basal, mid-ventricular, and apical short axis slices during the first pass of 0.05 ml/kg of a 1-molar gadolinium based contrast agent (Gadovist, Bayer) injected with a power injector at a flow rate of 4mls/s.

Hyperaemia was achieved with an intravenous infusion of adenosine at 140 µg/kg/min for 3-4 minutes. All patients had desisted from caffeine for at least 12 hours prior to the scan and had otherwise complied with their standard medication.

DCE-CMR was performed with a fast gradient echo sequence with non-selective saturation recovery preparation pulse (T_{SR} = 100ms) and two-fold acceleration (GRAPPA). Perfusion sequence readout parameters were: TR/TE/FA = 2.4 ms/1.07 ms/12°; FOV (340-400 x 340-400 mm²); matrix 160 x 120; BW = 651 Hz/px. Slice thickness was 8 mm, with 8 mm gap.

Rest perfusion imaging was acquired using the same DCE-CMR protocol 15 min after the stress scan with the administration of 0.05 ml/kg contrast agent (Gadovist, Bayer).

LGE CMR was performed with a T1-weighted segmented gradient-echo phase-sensitive inversion-recovery (GRE PSIR) sequence, with following parameters: TE/TR/FA = 760 ms/1.56 ms/20°. The inversion time (TI) was adjusted for optimal suppression of signal from normal myocardium (TI~340ms). Typical FOV was (350 x 262)mm², matrix 256 x
192, slice thickness 7 mm, slice gap 2.8 mm, and BW = 465 Hz/px. Images were collected 15-20 minutes after the last injection of contrast.

**CMR analysis**

CMR data acquisition and were performed independently by a separate team of staff from the staff who performed the invasive catheter laboratory procedures and FFR measurements. The CMR scans were de-identified and analyzed in random order on an image review work-station by CMR observers with at least 3 years experience of perfusion CMR (C.B., D.C., S.W.). J.L. coordinated the study.

*Analysis of stress/rest perfusion CMR:*

Stress and rest perfusion CMR images were analyzed side-by-side using dedicated software (Argus Dynamic Signal, Siemens, Erlangen, Germany). The stress and rest myocardial perfusion scans were viewed simultaneously. The perfusion scans were visually assessed for normal and abnormal myocardial hypoperfusion and segments with abnormal perfusion were assigned to coronary territories using the American Heart Association coronary arterial 16-segment model. In cases of disagreement between observers, a third blinded observer adjudicated. The observers also prospectively evaluated image quality. Two patients were excluded due to poor image quality.

A myocardial perfusion abnormality at rest and/or during pharmacological stress was classified as significant according to the presence of reduced perfusion in 2 segments of a 32 segment model (16-segment AHA model divided into sub-endocardial and sub-epicardial layers) i.e.: > 60 degrees in either the basal or the midventricular slices or > 90 degrees in the apical slice or any transmural defect or two adjacent slices.