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CLINICAL RESEARCH

High-Resolution Cardiac Magnetic Resonance Imaging Techniques for the Identification of Coronary Microvascular Dysfunction

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ABSTRACT

OBJECTIVES This study assessed the ability to identify coronary microvascular dysfunction (CMD) in patients with angina and nonobstructive coronary artery disease (NOCAD) using high-resolution cardiac magnetic resonance (CMR) and hypothesized that quantitative perfusion techniques would have greater accuracy than visual analysis.

BACKGROUND Half of all patients with angina are found to have NOCAD, while the presence of CMD portends greater morbidity and mortality, it now represents a modifiable therapeutic target. Diagnosis currently requires invasive assessment of coronary blood flow during angiography. With greater reliance on computed tomography coronary angiography as a first-line tool to investigate angina, noninvasive tests for diagnosing CMD warrant validation.

METHODS Consecutive patients with angina and NOCAD were enrolled. Intracoronary pressure and flow measurements were acquired during rest and vasodilator-mediated hyperemia. CMR (3-T) was performed and analyzed by visual and quantitative techniques, including calculation of myocardial blood flow (MBF) during hyperemia (stress MBF), transmural myocardial perfusion reserve (MPR: $MBF_{HYPEREMIA}$ / MBF_{REST}), and subendocardial MPR (MPR_{ENDO}). CMD was defined dichotomously as an invasive coronary flow reserve <2.5, with CMR readers blinded to this classification.

RESULTS A total of 75 patients were enrolled (57 $\pm$ 10 years of age, 81% women). Among the quantitative perfusion indices, MPR_{ENDO} and MPR had the highest accuracy (area under the curve [AUC]: 0.90 and 0.88) with high sensitivity and specificity, respectively, both superior to visual assessment (both $p < 0.001$). Visual assessment identified CMD with 58% accuracy (41% sensitivity and 83% specificity). Quantitative stress MBF performed similarly to visual analysis (AUC: 0.64 vs. 0.60; $p = 0.69$).

CONCLUSIONS High-resolution CMR has good accuracy at detecting CMD but only when analyzed quantitatively. Although omission of rest imaging and stress-only protocols make for quicker scans, this is at the cost of accuracy compared with integrating rest and stress perfusion. Quantitative perfusion CMR has an increasingly important role in the management of patients frequently encountered with angina and NOCAD. (J Am Coll Cardiol Img 2020;■:■–■)

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ABBREVIATIONS AND ACRONYMS

AUC = area under the curve

CMD = coronary microvascular dysfunction

CMR = cardiac magnetic resonance

CFR = coronary flow reserve

CI = confidence interval

Endo/Epi = hyperemic subendocardial to subepicardial blood flow ratio

MBF = myocardial blood flow

MPR = myocardial perfusion reserve

MPR_{ENDO} = subendocardial myocardial perfusion reserve

NOCAD = nonobstructive coronary artery disease

ROC = receiver-operating characteristic

Angina and nonobstructive coronary artery disease (NOCAD) is an increasingly recognized diagnosis, accounting for nearly one-half of all patients undergoing invasive angiography (1). Within this heterogeneous group of patients, those with coronary microvascular dysfunction (CMD) have a greater risk of major adverse cardiovascular events (2). With emerging evidence that CMD represents a modifiable therapeutic target, accurate diagnosis of this condition has become ever more paramount; however, current diagnostic pathways require invasive physiological assessment during angiography (3–5). Cardiac magnetic resonance (CMR) has recently shown promise in detection of CMD among stable angina populations using semi-quantitative analysis of hyperemic myocardial blood flow (6). Transmural maldistribution of myocardial blood flow (MBF) during hyperemia is a hallmark of CMD, suggesting that high-resolution perfusion CMR with quantification of MBF across myocardial layers may have greater accuracy at identifying this condition compared with measuring flow across the whole myocardium (7,8). Higher throughput sequences increasingly forgo acquisition of rest perfusion images and rely on visual assessment alone in the interest of time, and while this approach is acceptable when ruling out obstructive coronary artery disease, the impact of these abbreviations on the accuracy for diagnosing CMD is unclear (9,10).

We hypothesize that quantitative analysis of high-resolution perfusion images will identify CMD with greater accuracy than visual assessment alone. Among the quantitative perfusion techniques, we also sought to evaluate whether both hyperemic and rest images are required or whether the assessment of hyperemic images alone is sufficient.

METHODS

STUDY POPULATION. Patients undergoing elective diagnostic angiography for investigation of angina pectoris were enrolled into the study. Inclusion criteria were preserved left ventricular systolic function (ejection fraction >50%) and unobstructed coronary arteries (<30% diameter stenosis or fractional flow reserve >0.80). Exclusion criteria were intolerance to adenosine, chronic kidney disease (estimated glomerular filtration rate <30 ml/min/m^2), concomitant valve disease (greater than mild on echocardiography), recent acute coronary syndrome, or cardiomyopathy. Antianginal medications were withheld, and patients abstained from caffeine 24 h before all study visits. Subjects gave written informed consent in accordance with the protocol approved by the UK National Research Ethics Service (17/LO/0203). The study was registered with the National Institute for Health Research UK Clinical Research Network portfolio database (Central Portfolio Management System identifier: 33170).

CATHETERIZATION PROTOCOL. Catheterization was performed via the right radial artery using standard coronary catheters. A dual pressure and Doppler sensor-tipped 0.014-inch intracoronary wire (ComboWire; Philips Volcano, Rancho Cordova, California) was used to measure distal coronary pressure and average peak flow velocity in the left anterior descending artery. Hemodynamic measurements were recorded under resting conditions and during intravenous adenosine-mediated hyperemia (140 μg/kg/min). Signals were sampled at 200 Hz, with data exported into a custom-made study manager program (Academic Medical Centre; University of Amsterdam, Amsterdam, Netherlands) and analyzed on custom-made software, Cardiac Waves (King's College London, London, United Kingdom). Coronary flow reserve (CFR) was calculated as hyperemic flow divided by resting flow. Patients were classified off-line as reference group (CFR ≥2.5) and CMD (CFR <2.5), with researchers blinded to this classification throughout the study protocol (11).

3-T PERFUSION CMR PROTOCOL. All scans were performed on a dedicated 3-T CMR scanner (Achieva TX; Philips Healthcare, Best, the Netherlands). Contiguous short-axis slices were acquired from the base to the apex for calculation of left ventricular function and mass (CVI42, v5.1.1, Circle Cardiovascular Imaging, Calgary, Ontario, Canada). Following 3 min of intravenous adenosine (140 μg/kg/min) with symptoms and signs confirming hyperemia, stress

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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perfusion data were acquired in 3 short-axis slices using a saturation-recovery *k-t* sensitivity encoding accelerated gradient-echo method (*k-t* factor 5 and 11 training profiles with a repetition time of 3.0 ms, echo time of 1.0 ms, flip angle of 15°, in-plane spatial resolution at 1.3 × 1.3 mm^2, slice thickness of 10 mm) (12,13). A dual-bolus gadobutrol (Gadovist; Bayer, Berlin, Germany) contrast agent scheme was used to correct for signal saturation of the arterial input function as previously described (14). Resting perfusion imaging was performed 15 min following stress, before acquisition of late gadolinium enhancement imaging (total contrast agent dose 0.2 mmol/kg) (15). A proton density acquisition was performed before stress and rest acquisitions to correct for spatial inhomogeneities of surface coils (16). Prior to quantitative analysis, the perfusion images were motion corrected according to published methods (17). Quantitative analysis was performed as previously described by Fermi-constrained deconvolution; myocardial blood flow (MBF) was quantified in ml/min/g during rest and hyperemic stress and myocardial perfusion reserve (MPR) was defined as hyperemic MBF / rest MBF (8). MPR was also assessed specifically in the subendocardial layer (MPR_{ENDO}) (defined as hyperemic MBF_{ENDO} / rest MBF_{ENDO}). Endocardial to epicardial perfusion (Endo/Epi) ratios were calculated during hyperemic stress by dividing stress MBF estimates within the inner and outer layers of myocardium. Unless otherwise specified, all quantitative analysis was carried out globally across basal, mid, and apical left ventricular slices. As a separate analysis, MPR was calculated in specific coronary territories; left anterior descending artery, left circumflex artery, and right coronary artery, based on the American Heart Association 17-segment model (18). Visual analysis was carried out by a level-3 accredited operator (European Association of Cardiovascular Imaging) with >10 years expertise in perfusion imaging (P.G.M.); the CMR reader was aware that all these patients had NOCAD but was blinded to the physiological classification and other demographic data. A perfusion abnormality was defined visually according to the criteria previously described in the MR-INFORM (MR Perfusion Imaging to Guide Management of Patients With Stable Coronary Artery Disease) trial (19), as a delayed wash-in of contrast persisting for ≥5 dynamics in ≥1 American Heart Association segments compared with normal remote myocardium. Scans were adjudged to display "ischemia" or "no ischemia" as binary endpoints.

STATISTICAL ANALYSES. The primary hypothesis of this study was to determine if MPR was superior to visual assessment of CMD using high-resolution imaging. On 1.5-T imaging, visual analysis has not demonstrated the ability to discriminate between CMD and reference group patients (20). Pilot data demonstrate an area under the curve (AUC) of 0.6 using visual analysis of 3.0-T perfusion imaging, and assuming an AUC of 0.78 using quantitative MPR, 75 patients would provide 80% power ($\alpha = 0.05$) to detect a difference between both techniques (20). The diagnostic performance of CMR indices for detecting CMD (as defined by invasive coronary physiology testing) was assessed by using the receiver-operating characteristic (ROC) curve, reporting sensitivity, specificity, accuracy, positive predictive values, and negative predictive values with 95% confidence intervals (CIs) where appropriate. Likelihood ratios were used to determine optimal cutoff values and the difference between 2 indices was assessed using the DeLong ROC comparison analysis (where comparison was performed against visual assessment). Continuous normally distributed data are expressed as mean ± SD and compared using unpaired and paired Student's *t*-tests where appropriate, while categorical variables were compared with chi-square tests. For all analyses, a p value of 0.05 was considered significant, and all p values were 2-sided. Statistical analyses were performed using Prism 8.0 (GraphPad Software, San Diego, California) and MedCalc Statistical Software 19.2.0 (MedCalc Software, Ostend, Belgium).

RESULTS

A total of 75 patients were recruited into the study (45 were classified as CMD and 30 as the reference group with normal invasive CFR); a higher proportion had CMD, as these patients were more likely to have cardiovascular risk factors and refractory symptoms warranting angiography. Groups were well matched for cardiovascular risk factors and pre-procedural medications (**Table 1**).

CMR MEASURES. Reference group and patients with CMD were well matched in terms of left ventricular function and mass, and no patients had evidence of scar during late gadolinium enhancement imaging (**Table 2**). Patients with CMD had higher resting MBF, lower stress MBF, and therefore lower MPR compared with reference patients (1.38 ± 0.38 ml/min/g vs. 1.14 ± 0.20 ml/min/g; p = 0.004; 2.67 ± 0.69 ml/min/g vs. 2.99 ± 0.53 ml/min/g; p = 0.04; and 2.00 ± 0.43 ml/min/g vs. 2.68 ± 0.47 ml/min/g; p < 0.001, respectively). In patients with CMD, territorial MPR in the

TABLE 1 Patient Characteristics and Long-Term Medication Prior to Angiography

	Reference Group (n = 30)	CMD (n = 45)	p Value
Demographics			
Female	22 (73)	39 (87)	0.15
Age, yrs	56 ± 10	57 ± 11	0.48
Hypertension	18 (60)	24 (53)	0.57
Diabetes mellitus	6 (20)	11 (24)	0.65
Hypercholesterolemia	15 (50)	22 (49)	0.93
Smoker	10 (33)	10 (22)	0.29
Medication prior to angiography			
Aspirin	9 (30)	12 (27)	0.75
Statin	16 (53)	23 (51)	0.85
ACE inhibitor/ARB	7 (23)	12 (27)	0.79
Beta-blocker	10 (33)	13 (29)	0.68
CCB	6 (20)	8 (18)	0.81
Invasive coronary physiology			
FFR	0.93 ± 0.05	0.92 ± 0.05	0.24
CFR	3.2 ± 0.6	1.9 ± 0.3	<0.001

Values are n (%) or mean ± SD.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium-channel blocker; CFR = coronary flow reserve; CMD = coronary microvascular dysfunction; FFR = fractional flow reserve.

left anterior descending artery, left circumflex artery, and right coronary artery territories were 1.95 ± 0.38 versus 2.03 ± 0.46 versus 1.99 ± 0.46 (p = 0.10 and p = 0.35 compared with left anterior descending artery, respectively). Examples of perfusion maps with corresponding MPR and CFR values are shown in Figure 1.

TABLE 2 CMR Imaging Measures in Reference Group Versus CMD

	Reference Group (n = 30)	CMD (n = 45)	p Value
CMR hemodynamic data			
Rest heart rate, beats/min	68 ± 10	71 ± 12	0.42
Stress heart rate, beats/min	100 ± 14	104 ± 14	0.41
Rest SBP, mm Hg	129 ± 13	131 ± 14	0.68
Stress SBP, mm Hg	128 ± 13	129 ± 23	0.79
Rest RPP	8,759 ± 1,592	9,251 ± 1,848	0.38
Stress RPP	12,804 ± 2,227	13,414 ± 2,988	0.49
LV structural parameters			
LV ejection fraction, %	65 ± 5	67 ± 6	0.22
LV mass index, g/m^2	45 ± 17	43 ± 11	0.67
Rest CMR parameters			
Rest MBF, ml/min/g	1.14 ± 0.20	1.38 ± 0.38	0.004
Rest Endo/Epi	1.01 ± 0.03	1.01 ± 0.02	0.45
Stress CMR parameters			
Stress MBF, ml/min/g	2.99 ± 0.53	2.67 ± 0.69	0.04
Stress Endo/Epi	1.04 ± 0.11	0.95 ± 0.09	0.001
Stress and rest CMR parameters			
MPR	2.68 ± 0.47	2.00 ± 0.43	<0.001
MPR_{ENDO}	2.68 ± 0.52	1.87 ± 0.44	<0.001

Values are mean ± SD.

CMD = coronary microvascular dysfunction; CMR = cardiac magnetic resonance; Endo/Epi = subendocardial to subepicardial myocardial blood flow ratio; LV = left ventricular; MBF = myocardial blood flow; MPR = myocardial perfusion reserve; MPR_{ENDO} = subendocardial myocardial perfusion reserve index; RPP = rate-pressure product; SBP = systolic blood pressure.

QUANTITATIVE PERFUSION ANALYSIS DIAGNOSTIC PERFORMANCE. Visual assessment of first-pass perfusion data for the detection of CMD yielded an accuracy of 58% (95% CI: 46% to 69%), sensitivity of 41% (95% CI: 27% to 57%), and specificity of 83% (95% CI: 65% to 94%) against invasive CFR values. The positive predictive value was 79% (95% CI: 61% to 90%) and the negative predictive value was 48% (95% CI: 41% to 55%). Using ROC analysis, the AUC was calculated as 0.60.

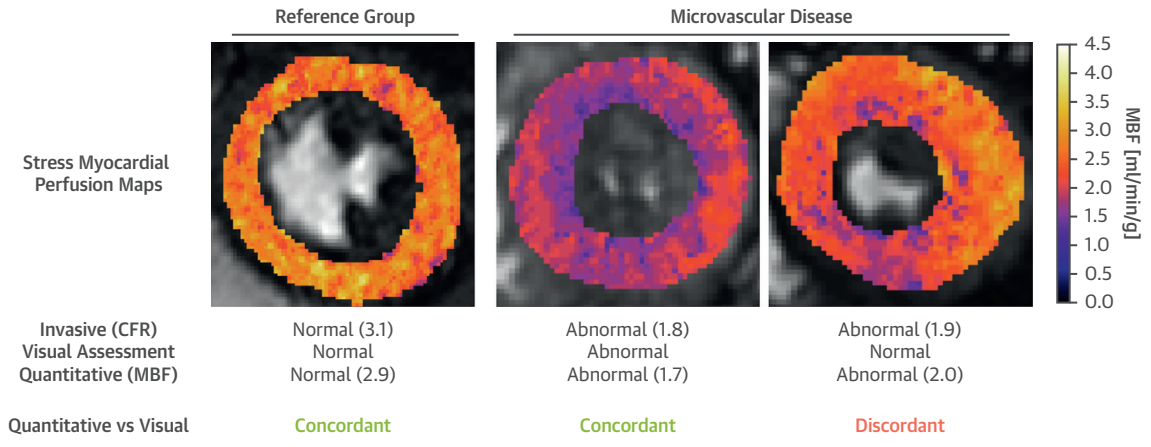
Among quantitative perfusion indices, MPR_{ENDO} (AUC: 0.90) and MPR (AUC: 0.88) were superior to visual analysis (both $p < 0.001$), while stress Endo/Epi numerically performed better (AUC: 0.79; $p < 0.001$) and almost reached statistical significance when compared directly with visual analysis ($p = 0.06$). Stress MBF performed similarly to visual assessment (AUC: 0.64 vs. 0.60; $p = 0.69$) (Figure 2).

An MPR threshold of 2.19 showed excellent specificity for detecting CMD on ROC analysis, with a sensitivity of 70% (95% CI: 53% to 83%), specificity of 90% (95% CI: 74% to 98%), accuracy of 79% (95% CI: 68% to 88%), positive predictive value of 90% (95% CI: 76% to 97%), and negative predictive value of 70% (95% CI: 59% to 79%). An MPR_{ENDO} threshold of 2.41 showed excellent sensitivity for detecting CMD on ROC analysis, with a sensitivity of 95% (95% CI: 83% to 99%), specificity of 72% (95% CI: 52% to 87%), accuracy of 85% (95% CI: 75% to 92%), positive predictive value of 82% (95% CI: 72% to 89%), and negative predictive value of 91% (95% CI: 72% to 98%).

DISCUSSION

This is the first study to compare contemporary 3-T CMR techniques including high-resolution fully quantitative perfusion and to determine the ability to identify CMD as defined by an invasive reference standard. CMD is associated with homogenous circumferential inducible ischemia with a greater predilection for the subendocardial layer of the myocardium and can be identified with high accuracy using 3-T CMR with quantitative perfusion. Compared with visual assessment, quantitative perfusion analysis techniques had a higher accuracy for correctly identifying the presence of CMD. If only hyperemic images are obtained, transmural blood flow distribution (stress Endo/Epi) yields greater accuracy for identifying CMD. The change in

FIGURE 1 Quantitative Perfusion Maps

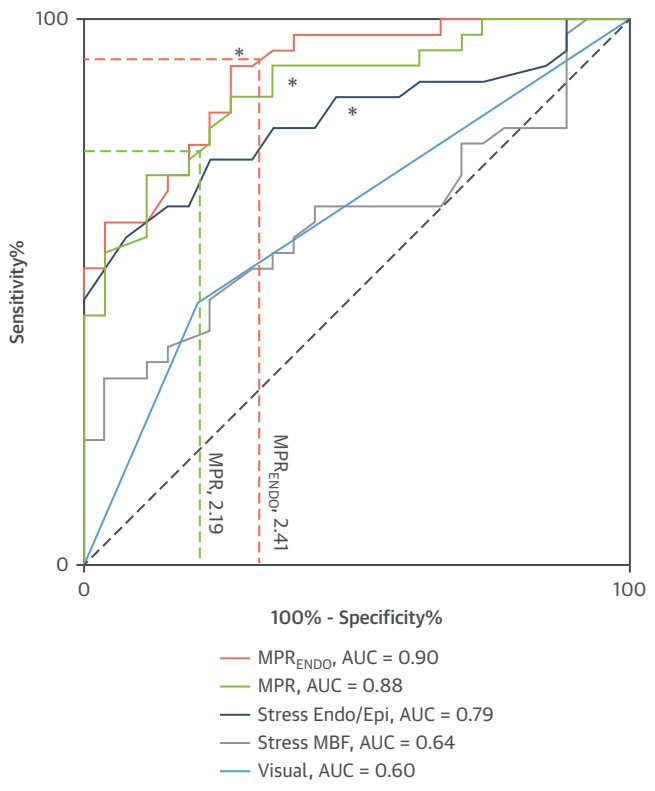


These cases identify concordant normal **(left)**, concordant abnormal **(middle)**, and discordant abnormal cases **(right)**, whereby visual perfusion fails to correctly identify coronary microvascular dysfunction. CFR = coronary flow reserve; MBF = myocardial blood flow.

subendocardial perfusion from rest during vasodilator-mediated hyperemia performed the best out of the quantitative techniques with excellent sensitivity, demonstrating the importance of acquiring both rest and hyperemic perfusion images and incorporating high spatial resolution imaging and quantitative techniques (**Central Illustration**).

SUBENDOCARDIAL HYPOPERFUSION. Myocardial perfusion abnormalities occur early in the ischemic cascade, while the subendocardial layer is the most vulnerable to ischemia during periods of increased myocardial oxygen demand (21). Tests designed to interrogate the latter stages of the ischemic cascade such as exercise electrocardiography and stress echocardiography have demonstrated poor accuracy for identifying CMD, with sensitivity of 18%, specificity of 80% and sensitivity of 29%, specificity 57%, respectively (22). Nuclear perfusion imaging, hampered by limited spatial resolution, has fared similarly poorly, with sensitivity of 51% and specificity of 52% (23). Semi-quantitative analysis using 1.5-T vasodilator stress CMR has demonstrated greater performance in identification of CMD (73% sensitivity and 74% specificity) and if extrapolating from published data for the detection of coronary artery disease, the use of 3-T imaging should be associated with greater diagnostic performance still (20,24). The significantly higher diagnostic accuracy of 3-T perfusion found in our study can be attributed to an increased signal-to-noise ratio enabling the acquisition of high spatial resolution series, the assessment of subendocardial hypoperfusion and the reduced occurrence of dark-rim artifact (24). With higher throughput clinical sequences, rest perfusion images are increasingly sacrificed; however, global assessment of stress myocardial blood flow alone is insufficient even at 3-T (9,10). Abnormalities in subendocardial perfusion correlate well with exertional ischemia in patients with NOCAD (25). In this scenario, measuring Endo/Epi ratio during stress will increase the sensitivity and overall accuracy of this technique to detect CMD, and indeed subendocardial hypoperfusion is often considered the pathophysiological hallmark of the microvascular disease process (7). Kotecha et al. (6) recently demonstrated that stress MBF can be used to identify patients with CMD when defined by measuring the thermodilution derived index of microvascular resistance calculated during vasodilator-mediated hyperemia. This paradigm has recently been challenged, in which it has been demonstrated that over one-half of all patients with CMD have preserved coronary flow during vasodilator hyperemia, but diminished vasodilator flow reserve, or "functional" CMD (25). In the context of NOCAD, dynamic changes in invasive measurement of CFR correlate better with exercise pathophysiology and risk of major adverse cardiovascular events compared with static measures of microvascular resistance, and indeed this remains the most widely used index recommended for the identification of CMD (23,26). Our data demonstrate the importance of rest perfusion image acquisition to accurately identify all CMD endotypes; the biologic basis of this has recently been discovered, in which

FIGURE 2 Diagnostic Performance of Cardiac Magnetic Resonance Techniques in the Identification of Coronary Microvascular Dysfunction



The areas under the curve (AUCs), p values, and 95% confidence intervals (CIs) were as follows: for visual analysis (AUC: 0.60; 95% CI: 46% to 69%; $p = 0.09$), stress myocardial blood flow (MBF) (AUC: 0.64; 95% CI: 49% to 77%; $p = 0.06$), subendocardial to subepicardial MBF during hyperemia (stress Endo/Epi) (AUC: 0.79; 95% CI: 77% to 92%; $p < 0.0001$), myocardial perfusion reserve (MPR) (AUC: 0.88; 95% CI: 78% to 96%; $p < 0.0001$), and subendocardial MPR (MPR_{ENDO}) (AUC: 0.90; 95% CI: 82% to 97%; $p < 0.0001$). An MPR threshold of 2.19 has sensitivity and specificity values of 70% and 90%, and an MPR_{ENDO} threshold of 2.41 has sensitivity and specificity values of 95% and 72%, respectively. Using DeLong receiver-operator characteristic (ROC) comparison analysis, MPR_{ENDO} and MPR both performed better than visual analysis (both $p < 0.001$), while stress Endo/Epi and stress MBF did not reach statistical significance ($p = 0.06$ and 0.69, respectively). Apart from visual analysis and stress MBF, all tests identified coronary microvascular dysfunction with good accuracy. **Asterisks** denote tests reaching statistical significance with ROC analysis ($p < 0.05$).

nitric oxide dysregulation underlies resting perfusion abnormalities and pathophysiology consistent with a CMD diagnosis (25,27). Previous studies have demonstrated that in patients with risk factors for CMD, while MPR was lower compared with healthy control subjects, resting flow was similar between groups; our study demonstrates that in patients with CMD confirmed on invasive testing, abnormalities in resting flow is a frequent pathological finding (28).

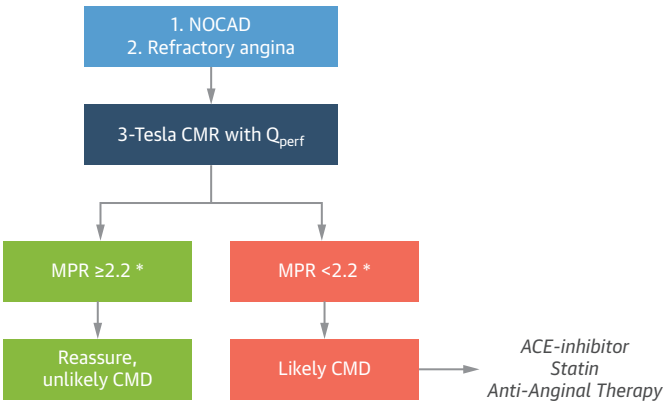
DIAGNOSTIC PATHWAYS. Coronary computed tomography angiography has recently gained a class I indication for assessment of recent onset chest pain in the European Society of Cardiology guidelines, yet this approach can yield a NOCAD diagnosis upwards of 90% (26,29). Although it is impractical to perform invasive testing in this entire cohort, noninvasive functional testing may have a role as a gatekeeper test for identifying those with CMD. Risk-stratifying those who have an ischemic substrate of chest pain represents a challenge to appropriate use of health care resources, particularly as risk factors and typicality of symptoms do not necessitate the presence of CMD (30). An angiographic diagnosis of NOCAD can now be readily stratified by use of pressure and flow wire-based measurements, yet invasive testing is still associated with a small risk of complications and higher initial resource cost (5,31). High-resolution perfusion CMR with quantitative analysis represents a powerful gatekeeper to identifying CMD in patients with refractory symptoms despite normal coronary computed tomography angiography, potentially circumventing the need for invasive testing in several patients. Indeed, among patients who have persistent refractory symptoms despite a normal coronary computed tomography angiography and perfusion CMR, coronary reactivity testing may be considered, as coronary vasospasm and endothelial dysfunction currently remain invasive diagnoses (11,32). This patient-centric pathway serves to minimize invasive burden to patients, while maximizing diagnostic yield (**Figure 3**). Prospective studies will be required to further validate the outcomes utilizing this approach and indeed among patients with high pre-test probability for CAD, perfusion CMR has recently been shown to reduce the rate of "unnecessary angiography and angioplasty" without additional risk of harm to patients (19). CMR may have a role in identifying distinct endotypes of CMD and facilitate development of stratified therapy in this large patient population (27). Quantitative perfusion CMR has been limited in the past by the intense and time-consuming post-processing required to generate detailed perfusion maps (33,34). Recent technical advances permit robust full automation of quantitative analysis, and this is likely to become the method of choice in the years to come on the basis of high diagnostic accuracy, strong prognostic value, and independency from operators training (34–39).

As we increasingly recognize that NOCAD is not a benign clinical entity, clarity into patient groups at risk of cardiovascular morbidity and mortality is

warranted. With lack of exposure to ionizing radiation and the benefit of myocardial function and tissue characterization, perfusion CMR may form the cornerstone tool of assessing patients with suspected angina.

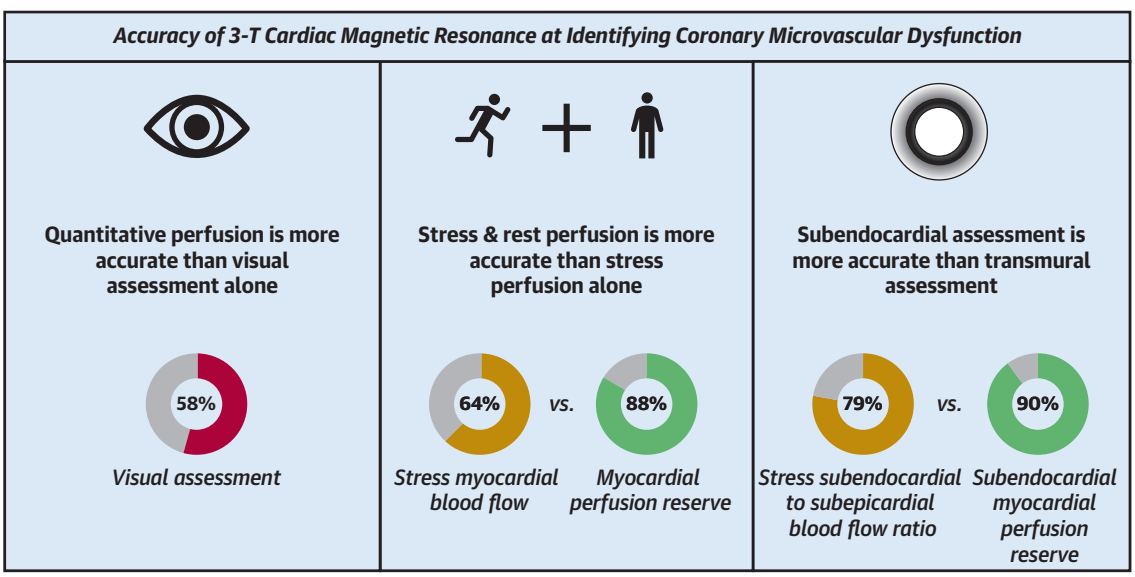
STUDY LIMITATIONS. This was a small single-center study; however, to date, it is the largest NOCAD population in which both invasive coronary physiology and high-resolution myocardial perfusion data with absolute quantification have been acquired. This was a group of patients known to have NOCAD, a larger study would need to include patients with epicardial CAD to assess the discriminatory power of novel quantitative perfusion parameters. Furthermore, CFR was only assessed in the left anterior descending artery, while all patients had NOCAD; therefore, microvascular physiology would be expected to be similar across perfusion territories, subtle regional variations in flow may exist. Patients with normal CFR are not true control subjects, as they still have symptoms of angina that have warranted angiography and indeed may have occult abnormalities such as endothelial dysfunction and coronary

FIGURE 3 CMR Pathway for Diagnosis of CMD



The **asterisk** indicates that an MPR value can be substituted with an MPR_{ENDO} value of 2.41, which will have greater sensitivity at the cost of specificity. An MPR threshold of 2.19 has sensitivity and specificity values of 70% and 90%, and an MPR_{ENDO} threshold of 2.41 has sensitivity and specificity values of 95% and 72%, respectively.
ACE = angiotensin-converting enzyme; CMD = coronary microvascular dysfunction; CMR = cardiac magnetic resonance; NOCAD = nonobstructive coronary artery disease; Q_{perf} = quantitative perfusion; other abbreviations as in Figure 2.

CENTRAL ILLUSTRATION Incremental Value of Quantitative Stress and Rest Perfusion Cardiac Magnetic Resonance in Identifying Coronary Microvascular Dysfunction



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Techniques need to be incorporated to ensure that adequate vasodilator hyperemia is achieved. Endo/Epi = subendocardial to subepicardial blood flow ratio; MBF = myocardial blood flow; MPR = myocardial perfusion reserve; MPR_{ENDO} = subendocardial myocardial perfusion reserve.

vasospasm; however, prognostic data in the NOCAD population comprise mainly studies assessing the response to endothelial-independent vasodilatation with adenosine. Additionally, these findings may not necessarily extend to other patient populations like heart failure or renal failure, who may exhibit different patterns of microcirculatory abnormalities and perfusion defects. Gadobutrol contrast dose administration was in accordance with the Society for Cardiovascular Magnetic Resonance guidance; however, it is unclear whether these findings will be replicated with lower total doses of gadolinium contrast administration in a recently approved trial by the Food and Drug Administration (NCT01890421). Further studies would be required to test reproducibility across all scanner vendors. Finally, this study did not directly compare 3.0-T with contemporary 1.5-T image acquisition, and indeed the latter may have been suitable for identifying CMD with sufficient fidelity using modern post-processing tools; however the higher rate of dark-rim artifact is likely to be problematic when assessing subtle subendocardial perfusion abnormalities.

CONCLUSIONS

High-resolution quantitative perfusion CMR can diagnose CMD with high accuracy. Accuracy is improved by acquisition of vasodilator stress and rest perfusion imaging compared with stress perfusion alone and by the use of high spatial resolution sequences. With increasing recognition that angina and NOCAD represents a heterogeneous cohort at risk of cardiovascular morbidity, CMR may represent an ideal risk-stratification tool and should form an integral part of chest pain algorithms. Prospective outcome studies will be required to assess if this potentially cost-saving measure will be associated with better patient outcome.

AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: CMD is associated with a poor prognosis and is usually diagnosed by invasive coronary physiology testing. We have now shown that high-resolution CMR can accurately diagnose CMD but only when quantitative analysis is performed.

TRANSLATIONAL OUTLOOK: Quantitative perfusion CMR can be used to diagnose coronary microvascular dysfunction in patients with unobstructed epicardial arteries in routine clinical practice and future research protocols.

REFERENCES

1. Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. N Engl J Med 2010;362:886–95.

2. Pepine CJ, Anderson RD, Sharaf BL, et al. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study. J Am Coll Cardiol 2010;55:2825–32.

3. Ford TJ, Stanley B, Good R, et al. Stratified medical therapy using invasive coronary function testing in angina: the CorMicA trial. J Am Coll Cardiol 2018;72:2841–55.

4. Ong P, Camici PG, Beltrame JF, et al. International standardization of diagnostic criteria for microvascular angina. Int J Cardiol 2018;250:16–20.

5. Rahman H, Corcoran D, Aetesam-Ur-Rahman M, Hoole SP, Berry C, Perera D. Diagnosis of patients with angina and non-obstructive coronary disease in the catheter laboratory. Heart 2019;105:1536–42.

6. Kotecha T, Martinez-Naharro A, Boldrini M, et al. Automated pixel-wise quantitative myocardial perfusion mapping by CMR to detect obstructive coronary artery disease and coronary microvascular dysfunction: validation against invasive coronary physiology. J Am Coll Cardiol Img 2019;12:1958–69.

7. Panting JR, Gatehouse PD, Yang GZ, et al. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. N Engl J Med 2002;346:1948–53.

8. Schuster A, Sinclair M, Zarinabad N, et al. A quantitative high resolution voxel-wise assessment of myocardial blood flow from contrast-enhanced first-pass magnetic resonance perfusion imaging: microsphere validation in a magnetic resonance compatible free beating explanted pig heart model. Eur Heart J Cardiovasc Imaging 2015;16:1082–92.

9. Kwong RY, Ge Y, Steel K, et al. Cardiac magnetic resonance stress perfusion imaging for evaluation of patients with chest pain. J Am Coll Cardiol 2019;74:1741–55.

10. Kramer CM, Barkhausen J, Bucciarelli-Ducci C, et al. Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update. J Cardiovasc Magn Reson 2020;17:22.

11. Rahman H, Demir OM, Ryan M, et al. Optimal use of vasodilators for diagnosis of microvascular angina in the cardiac catheterization laboratory. Circ Cardiovasc Interv 2020;13:e009019.

12. Plein S, Schwitter J, Suerder D, Greenwood JP, Boesiger P, Kozerke S. k-Space and time sensitivity encoding-accelerated myocardial perfusion MR imaging at 3.0 T: comparison with 1.5 T. Radiology 2008;249:493–500.

13. Modi BN, Rahman H, Sherif SA, et al. Is heart rate response a reliable marker of adenosine-induced coronary hyperemia? Int J Cardiovasc Imaging 2018;34:1117–25.

14. Ishida M, Schuster A, Morton G, et al. Development of a universal dual-bolus injection scheme for the quantitative assessment of myocardial

perfusion cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2011;13:28.

15. Kramer CM, Barkhausen JR, Flamm SD, Kim RJ, Nagel E. Standardized cardiovascular magnetic resonance (CMR) protocols 2013. J Cardiovasc Magn Reson 2013;15:91.

16. Kremers FP, Hofman MB, Groothuis JG, et al. Improved correction of spatial inhomogeneities of surface coils in quantitative analysis of first-pass myocardial perfusion imaging. J Magn Reson Imaging 2010;31:227–33.

17. Scannell CM, Villa ADM, Lee J, Breeuwer M, Chiribiri A. Robust non-rigid motion compensation of free-breathing myocardial perfusion MRI data. IEEE Trans Med Imaging 2019;38:1812–20.

18. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 2002;105:539–42.

19. Nagel E, Greenwood JP, McCann GP, et al. Magnetic resonance perfusion or fractional flow reserve in coronary disease. N Engl J Med 2019; 380:2418–28.

20. Thomson LE, Wei J, Agarwal M, et al. Cardiac magnetic resonance myocardial perfusion reserve index is reduced in women with coronary microvascular dysfunction. A National Heart, Lung, and Blood Institute-sponsored study from the Women's Ischemia Syndrome Evaluation. Circ Cardiovasc Imaging 2015;8:e002481.

21. Nesto RW, Kowalchuk GJ. The ischemic cascade: temporal sequence of hemodynamic, electrocardiographic and symptomatic expressions of ischemia. Am J Cardiol 1987;59:23C–30C.

22. Cassar A, Chareonthaitawee P, Rihal CS, et al. Lack of correlation between non-invasive stress tests and invasive coronary vasomotor dysfunction in patients with non-obstructive coronary artery disease. Circ Cardiovasc Interv 2009;2:237–44.

23. Bairey Merz CN, Pepine CJ, Walsh MN, Fleg JL. Ischemia and no obstructive coronary artery disease (INOCA): developing evidence-based therapies and research agenda for the next decade. Circulation 2017;135:1075–92.

24. Cheng AS, Pegg TJ, Karamitsos TD, et al. Cardiovascular magnetic resonance perfusion imaging at 3-Tesla for the detection of coronary artery disease: a comparison with 1.5-Tesla. J Am Coll Cardiol 2007;49:2440–9.

25. Rahman H, Ryan M, Lumley M, et al. Coronary microvascular dysfunction is associated with myocardial ischemia and abnormal coronary perfusion during exercise. Circulation 2019;140: 1805–16.

26. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41: 407–77.

27. Rahman H, Demir OM, Khan F, et al. Physiological stratification of patients with angina due to coronary microvascular dysfunction. J Am Coll Cardiol 2020;75:2538–49.

28. Zorach B, Shaw PW, Bourque J, et al. Quantitative cardiovascular magnetic resonance perfusion imaging identifies reduced flow reserve in microvascular coronary artery disease. J Cardiovasc Magn Reson 2018;20:14.

29. Douglas PS, Hoffmann U, Patel MR, et al. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med 2015; 372:1291–300.

30. Mygind ND, Michelsen MM, Pena A, et al. Coronary microvascular function and cardiovascular risk factors in women with angina pectoris and no obstructive coronary artery disease: the iPOWER Study. J Am Heart Assoc 2016;5: e003064.

31. Wei J, Mehta PK, Johnson BD, et al. Safety of coronary reactivity testing in women with no obstructive coronary artery disease: results from the NHLBI-sponsored WISE (Women's Ischemia Syndrome Evaluation) study. J Am Coll Cardiol Intv 2012;5:646–53.

32. Beltrame JF, Crea F, Kaski JC, et al. International standardization of diagnostic criteria for vasospastic angina. Eur Heart J 2017;38:2565–8.

33. Lockie T, Ishida M, Perera D, et al. High-resolution magnetic resonance myocardial perfusion imaging at 3.0-Tesla to detect hemodynamically significant coronary stenoses as determined by fractional flow reserve. J Am Coll Cardiol 2011;57: 70–5.

34. Hsu LY, Jacobs M, Benovoy M, et al. Diagnostic performance of fully automated pixel-wise quantitative myocardial perfusion imaging by cardiovascular magnetic resonance. J Am Coll Cardiol Img 2018;11:697–707.

35. Villa ADM, Corsinovi L, Ntalas I, et al. Importance of operator training and rest perfusion on the diagnostic accuracy of stress perfusion cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2018;20:74.

36. Sammut EC, Villa ADM, Di Giovine G, et al. Prognostic value of quantitative stress perfusion cardiac magnetic resonance. J Am Coll Cardiol Img 2018;11:686–94.

37. Scannell CM, Chiribiri A, Villa ADM, Breeuwer M, Lee J. Hierarchical Bayesian myocardial perfusion quantification. Med Image Anal 2020;60:101611.

38. Scannell CM, Veta M, Villa ADM, et al. Deep-learning-based preprocessing for quantitative myocardial perfusion MRI. J Magn Reson Imaging 2020;51:1689–96.

39. Dewey M, Siebes M, Kachelrieß M, et al. Clinical quantitative cardiac imaging for the assessment of myocardial ischaemia. Nat Rev Cardiol 2020;17:427–50.

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