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Value of Cardiovascular Magnetic Resonance Stress Perfusion Testing for the Detection of Coronary Artery Disease in Women

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OBJECTIVES We wanted to assess the value of cardiovascular magnetic resonance (CMR) stress testing for evaluation of women with suspected coronary artery disease (CAD).

BACKGROUND A combined perfusion and infarction CMR examination can accurately diagnose CAD in the clinical setting in a mixed gender population.

METHODS We prospectively enrolled 147 consecutive women with chest pain or other symptoms suggestive of CAD at 2 centers (Duke University Medical Center, Robert-Bosch-Krankenhaus). Each patient underwent a comprehensive clinical evaluation, a CMR stress test consisting of cine rest function, adenosine-stress and rest perfusion, and delayed-enhancement CMR infarction imaging, and X-ray coronary angiography within 24 h. The components of the CMR test were analyzed visually both in isolation and combined using a pre-specified algorithm. Coronary artery disease was defined as stenosis ≥70% on quantitative analysis of coronary angiography.

RESULTS Cardiovascular magnetic resonance imaging was completed in 136 females (63.0 ± 11.1 years), 37 (27%) women had CAD on coronary angiography. The combined CMR stress test had a sensitivity, specificity, and accuracy of 84%, 88%, and 87%, respectively, for the diagnosis of CAD. Diagnostic accuracy was high at both sites (Duke University Medical Center 82%, Robert-Bosch-Krankenhaus 90%; $p = 0.18$). The accuracy for the detection of CAD was reduced when intermediate grade stenoses were included (82% vs. 87%; $p = 0.01$ compared the cutoff of stenosis ≥50% vs. ≥70%). The sensitivity was lower in women with single-vessel disease (71% vs. 100%; $p = 0.06$ compared with multivessel disease) and small left ventricular mass (69% vs. 95%; $p = 0.04$ for left ventricular mass ≤97 g vs. >97 g). The latter difference was even more significant after accounting for end-diastolic volumes (70% vs. 100%; $p = 0.02$ for left ventricular mass indexed to end-diastolic volume ≤1.15 g/ml vs. >1.15 g/ml).

CONCLUSIONS A multicomponent CMR stress test can accurately diagnose CAD in women. Detection of CAD in women with intermediate grade stenosis, single-vessel disease, and with small hearts is challenging. (J Am Coll Cardiol Img 2008;1:436–45) © 2008 by the American College of Cardiology Foundation

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Coronary artery disease (CAD) continues to be the leading cause of death in women despite efforts to improve prevention and treatment of heart disease in females (1). Awareness of risk and specific aspects of cardiovascular disease in women is suboptimal even among health care professionals (2). This is partly due to the fact that women are often underrepresented in studies on noninvasive testing as well as interventional trials. Frequently, diagnostic and therapeutic decisions in female patients are made based on results from studies on middle-aged men. Improvements in the diagnosis and treatment of CAD in women can only be achieved on the basis of studies focusing specifically on female populations.

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Noninvasive diagnostic testing with and without imaging for detection of CAD in women presents challenges not encountered in men. Prevalence of CAD in women, even with typical angina, is lower compared to men, thus reducing predictive accuracy due to Bayesian principles (3,4). Female patients more frequently have single-vessel disease and intermediate grade stenosis, which in combination with smaller heart sizes imposes additional difficulties on stress tests (4–8). A recent evidence report from the U.S. Agency for Health Care Research and Quality stated that the accuracy of exercise ECG and thallium single-photon emission computed tomography (SPECT) for the diagnosis of CAD is lower in women than in men due to both poor sensitivity and specificity. Furthermore, the accuracy of exercise echocardiography is believed to be better than either ECG or SPECT; however, this assertion is supported by limited data (3 studies including 296 women) (9). A separate issue is that assessment of quality of the studies on stress testing in women is difficult (which is also the case in men) as these data are frequently subject to different forms of bias—mainly pre-test and work-up or post-test referral bias—which hampers calculation of test accuracy (10).

Recently, a combined stress perfusion and infarction imaging cardiovascular magnetic resonance (CMR) imaging stress test with the use of a systematic interpretation algorithm for visual analysis has been shown to accurately diagnose CAD in the clinical setting in a mixed gender population (11). The aim of the present study was to evaluate the diagnostic accuracy of this CMR stress test for the detection of CAD in women with invasive coronary angiography as the gold standard. We applied this test in an appropriate patient group—women with intermediate to high CAD risk (12). A rigorous study design was followed to reduce both pre-test bias, by including only women without known heart disease, and post-test referral bias by having all patients undergo the reference test independent of the CMR results. We further assessed the effect of factors known to reduce accuracy of established stress tests, namely single-vessel disease, intermediate grade stenosis, and small heart size on the performance of the CMR stress test (4–8). To provide information on the relative significance of the CMR stress test to the established clinical CAD evaluation in women, all patients underwent a detailed clinical assessment including medical history and blood tests for CAD risk factor assessment.

METHODS

Population. Women with chest pain or other signs and symptoms suggestive of CAD, who were referred to the Duke University Medical Center in Durham, North Carolina (Duke), and to Robert-Bosch-Krankenhaus Hospital in Stuttgart, Germany (RBK), for elective coronary angiography (CA) were screened for study enrollment. Patients were contacted by telephone the day before admission for scheduled angiography, and the first patient meeting study criteria who agreed to participate was recruited. We excluded all patients with known CAD, including those with prior myocardial infarction (MI) or revascularization procedures. The only other exclusion criteria were contraindications to magnetic resonance imaging (e.g., pacemaker) or adenosine (e.g., high-grade atrioventricular block). Written informed consent was obtained from all enrolled patients. All patients underwent X-ray angiography within 24 h of CMR. The majority (78%) had an abnormal nuclear, echocardiography, or treadmill stress test as part of their clinical work-up prior to elective angiography. In 30 patients (22%), symptoms were strongly suggestive of CAD, and angiography was deemed indicated by the treating physician without a preceding stress test. Some of the results on the first 49 Duke patients were reported previously in a mixed gender study (11). All eligible women from this prior report were included in the present study.

Protocol. Within 24 h before the CMR stress test, a complete medical history including responses to a

ABBREVIATIONS AND ACRONYMS

CA = coronary angiography
CAD = coronary artery disease
CMR = cardiovascular magnetic resonance
DE-CMR = delayed-enhancement cardiovascular magnetic resonance
LV = left ventricular
MI = myocardial infarction
RBK = Robert-Bosch-Krankenhaus
SPECT = single-photon emission computed tomography

Rose chest pain questionnaire was obtained. Blood samples were drawn after an overnight fast for glucose, lipid profile, and high-sensitivity C-reactive protein. Coronary artery disease risk factors were defined using the Framingham Heart Study definitions (13). A 12-lead electrocardiogram was registered and scored for Q waves and bundle-branch block using Minnesota codes (14).

CMR imaging. The CMR stress test consisted of 4 protocols that were performed in the following order: 1) cine imaging at rest for assessment of left ventricular (LV) function; 2) adenosine gadolinium first-pass imaging for assessment of stress perfusion; 3) repeated first-pass imaging without adenosine 15 min later for assessment of rest perfusion; and 4) delayed-enhancement CMR (DE-CMR) for assessment of MI. The identical image acquisition protocol was followed at both sites and was completed in about 45 min.

At both study centers, a 1.5-T scanner (Siemens Sonata, Erlangen, Germany) with a phased-array receiver coil was used. Steady-state free-precession cine images were acquired in multiple short-axis (every centimeter throughout the LV) and 3 long-axis views. After cine imaging was completed, adenosine (140 $\mu g \cdot kg^{-1} \cdot min^{-1}$) was infused under continuous ECG and blood pressure monitoring for approximately 3 min, with contrast injection at 2 to 2.5 min. Perfusion CMR images were acquired as previously described (11) using gadolinium contrast (0.07 mmol/kg gadoversetamide [Mallinckrodt, Hazelwood, Missouri] at Duke, or gadodiamide [GE Healthcare, Buckinghamshire, United Kingdom] at RBK). A saturation-recovery, single-shot, gradient-echo sequence (90°-pre-pulse before each slice; echo time, 1.1 ms; delay time, 85 to 100 ms; temporal resolution, 110 to 125 ms; voxel size, 3.1 × 1.8 to 2.5 × 8 mm) was typically set up for 4 short-axis slices (matched to cine locations excluding most basal and apical slices) per heartbeat. In order to speed up imaging either 4 k-space lines were acquired per excitation (echo-planar hybrid) or parallel imaging (15) with 2-fold acceleration was employed. Five minutes after rest perfusion (additional 0.07 mmol/kg gadoversetamide or gadodiamide), DE-CMR was performed using a segmented inversion-recovery technique in the identical views as cine-CMR (16).

CMR analysis. Scans were analyzed by consensus of 2 observers who were blinded to patient identity, clinical information, and the angiography results. One observer performed most reads at Duke and all reads at RBK; the second observer was different at Duke and RBK. Each observer had previously performed and interpreted over 150 CMR stress perfusion studies according to the same protocol. The individual CMR protocols and combinations were scored independently by rapid visual assessment as follows: cine alone, stress and rest perfusion alone, DE-CMR alone, perfusion with DE-CMR (using the interpretation algorithm), and cine with the algorithm. The interpretation algorithm has been previously described (11). Briefly, it was shown that DE-CMR has a high specificity for CAD detection and that the combination of DE-CMR with perfusion CMR (which has a modest specificity) in a systematic fashion results in a significant improvement of overall test specificity and accuracy. For the combination of the Duke algorithm with cine-CMR, the observers were told to consider the cine findings when the perfusion results were equivocal, that is, increasing level of confidence if concordant wall motion abnormalities are encountered and vice versa.

Regional parameters were assessed using a 17-segment model as previously described (11,16) for cine and DE-CMR. A perfusion defect was defined as a regional dark area that: 1) persisted for >2 beats while other regions enhanced during the first-pass of contrast through the LV myocardium; and 2) involved the subendocardium. Stress and rest images were assessed using 16 segments (segment 17 at apex was not visualized) and each segment was scored using a 4-point scale: 0, normal; 1, probably normal; 2, probably abnormal; 3, definitely abnormal. This scoring system was chosen to allow dichotomization of results into normal (≤1) and abnormal (≥2) and, at the same time, to provide a range of scores for receiver-operator characteristic curve analysis.

Standard methods were used to quantify LV volumes (end-diastolic and -systolic), ejection fraction, and mass using Argus software (Siemens, Erlangen, Germany) on short-axis cine images (17).

Coronary angiography (CA). X-ray coronary angiography was performed by standard techniques and analyzed masked to identity, clinical information, and CMR results. In patients with stenosis >40% determined visually by the consensus of 2 experienced cardiologists, computer-assisted quantification of luminal diameter stenosis (quantitative CA) was performed (except for subtotal stenosis). Significant CAD was defined as ≥70% narrowing of the luminal diameter of at least 1 major epicardial artery, or ≥50% narrowing of the left main artery (18). Additionally, we evaluated the detection of

intermediate grade stenosis by applying a cutoff of ≥50%.

Statistical analysis. Continuous data are expressed as mean ± standard deviation. Comparisons between groups were made using 2 sample *t* tests for continuous data and chi-square tests for discrete data. The Fisher exact test was used when the assumptions of the chi-square test were not met. The McNemar test was used to compare sensitivities, specificities, and the diagnostic accuracy of techniques within groups. The receiver-operator characteristic curve analyses were performed to compare the diagnostic performance of techniques. Statistical tests were 2-tailed; $p < 0.05$ was considered statistically significant.

RESULTS

Study population. A total of 147 women (59 at Duke, 88 at RBK) were enrolled in the study; CMR stress testing was completed in 136 patients. Eleven women (3 from Duke, 8 from RBK) did not have a complete CMR test. In 1 case, scanner operator error led to incomplete data, and 1 patient requested to stop the scan due to discomfort in the scanner. In 9 cases, imaging was omitted because of non-CMR related issues: 2 had xanthines in the morning before the scan; 1 had beta-blockers within 12 h before the scan; 2 withdrew consent; in 3, intravenous access could not be obtained; and in 1, there was severe adenosine-induced dyspnea, which led to early termination of the protocol. The woman with dyspnea, which quickly resolved after stopping adenosine, had the only adverse event during stress testing.

Table 1 summarizes the patient characteristics. The majority (89%) reported chest pain or discomfort, and 68 (50%) women had typical angina by Rose chest pain questionnaire. The proportion of women with typical angina was similar in the groups with and without obstructive CAD. Patients had several CAD risk factors (3.6 ± 1.3); however, prevalence of CAD risk factors was similar in women with CAD and those without CAD. The only differences noted were older age and higher prevalence of hyperlipidemia in females with CAD. The majority (90%) were Caucasian. The mean body mass index was 28.5 ± 5.1 kg/m^2 in the entire group, and was similar in both women with (28.6 ± 4.8 kg/m^2) and without CAD (28.5 ± 5.3 kg/m^2; $p = 0.93$).

CMR stress test. The infusion duration for adenosine was 3.1 ± 0.5 min. The heart rates were 72 ± 12 beats/min at rest and 96 ± 16 beats/min at peak stress. Most women (84%) had mild symptoms during adenosine infusion; the most frequent being chest discomfort described as pain, pressure, tightness, or burning, followed by shortness of breath, flush, and nausea. In 98 (72%) women, the gradient-echo sequence with parallel imaging was used, and in 38 (28%) women, the echo-planar hybrid sequence was used, yielding on average 3.6 ± 0.6 images per heartbeat. Among the 136 women who completed imaging, 2 had atrial fibrillation and 5 had frequent ventricular ectopy chronically and during imaging. All 136 were considered to have evaluable images and are included in the analysis.

Detection of CAD. Significant CAD (≥70%) on CA was present in 37 women (27%), and 46 women (34%) had stenosis ≥50%. Table 2 shows the diagnostic performance of the combined CMR stress test using the interpretation algorithm according to disease severity. Sensitivity, specificity, and accuracy for the diagnosis of CAD (≥70%) were 84%, 88%, and 87%, respectively. The accuracy for detection of CAD including intermediate grade lesions (≥50%) was lower (82%; $p = 0.01$). Although the specificity of the algorithm remained high for both stenosis severity cutoffs, the sensitivity for detection of moderate disease (cutoff 50%) was reduced.

When the individual components of the CMR stress tests were analyzed separately, perfusion CMR alone had a moderate sensitivity (78%) but only modest specificity (56%) and accuracy (62%) for the detection of CAD. By adding the information of DE-CMR, both specificity (88%) and accuracy (87%) were significantly improved compared to perfusion CMR alone ($p < 0.0001$). The improvement in specificity and accuracy using the algorithm was due to the high specificity of DE-CMR (98%). The diagnostic accuracy of the combination of perfusion and delayed enhancement was significantly greater than perfusion alone independent of the cutoff chosen for an abnormal stress test (area under the receiver-operator characteristic curve: 0.91 ± 0.05 vs. 0.81 ± 0.05; $p = 0.002$) (Fig. 1). The combined perfusion and DE-CMR analysis had also an improved specificity and accuracy compared to perfusion alone when a cutoff of 50% was chosen (88% vs. 57% for specificity, 82% vs. 63% for accuracy; $p < 0.0001$ for both). The accuracy for both perfusion pulse sequences was similar, alone ($p = 0.55$) and in combination with DE-CMR ($p = 0.27$).

Table 1. Baseline Characteristics

Characteristic	Entire Group (n = 136)	CAD* (n = 37)	No CAD (n = 99)	p Value
Age (yrs)	63.0 ± 11.1	66.5 ± 10.0	61.7 ± 11.4	**0.02**
CAD risk factors				
Diabetes	30 (22%)	10 (27%)	20 (20%)	0.39
Hypertension	93 (68%)	29 (78%)	64 (65%)	0.13
Cigarette smoking	42 (31%)	12 (32%)	30 (30%)	0.81
Hyperlipidemia	77 (57%)	28 (76%)	49 (49%)	**0.006**
Family history of CAD	72 (53%)	19 (51%)	53 (54%)	0.94
Menopause	120 (89%)	32 (86%)	88 (90%)	0.59
Obesity (BMI ≥30 kg/m^2)	52 (38%)	14 (38%)	38 (38%)	0.96
Number of risk factors	3.6 ± 1.3	3.9 ± 1.3	3.4 ± 1.4	0.09
Rose chest pain questionnaire				
Angina	68 (50%)	21 (58%)	47 (47%)	0.27
Medications				
Statins	39 (29%)	13 (35%)	26 (26%)	0.31
Beta-blockers	58 (43%)	18 (49%)	40 (40%)	0.39
Aspirin	78 (57%)	28 (76%)	50 (51%)	**0.008**
ACE inhibitors	61 (45%)	16 (43%)	45 (46%)	0.82
Nitrates	10 (7%)	3 (8%)	7 (7%)	0.84
Diuretics	30 (22%)	4 (11%)	26 (26%)	0.053
Hormone replacement†	54 (45%)	11 (34%)	43 (49%)	0.16
Blood tests‡				
Fasting glucose (mg/dl)	98.0 ± 14.9	102.3 ± 15.0	96.6 ± 14.8	0.10
Lipids				
Total cholesterol (mg/dl)	218.6 ± 42.5	236.4 ± 45.6	212.3 ± 39.7	**0.004**
LDL (mg/dl)	131.6 ± 37.8	148.1 ± 42.7	125.4 ± 34.1	**0.002**
HDL (mg/dl)	59.4 ± 16.2	55.5 ± 17.8	60.9 ± 15.4	0.09
Triglycerides (mg/dl)	137.7 ± 71.0	155.5 ± 63.8	131.1 ± 72.7	0.08
hs-CRP (mg/l)	4.8 ± 5.7	5.5 ± 6.6	4.5 ± 5.4	0.39
Indication for angiography				0.16§
Positive stress nuclear study	37 (27%)	12 (32%)	25 (25%)	
Positive stress echo study	20 (15%)	6 (16%)	14 (14%)	
Positive treadmill ECG study	49 (36%)	11 (30%)	38 (38%)	
Clinical symptoms alone	30 (22%)	8 (22%)	22 (22%)	
12-lead ECG				
Q-wave‖	7 (5%)	2 (5%)	5 (5%)	1.00**
RBBB¶	3 (2%)	1 (3%)	2 (2%)	1.00**
LBBB#	6 (5%)	0 (0%)	6 (6%)	0.19**

Values in **bold** indicate statistical significance. *CAD was defined by X-ray coronary angiography (see text). †Current or ever users (peri- or post-menopausal women). ‡Blood tests were acquired within 24 h of CMR in 104 patients for fasting glucose (nondiabetic patients only), 130 patients for lipids, and 125 patients for hs-CRP. §The p value pertains to the comparison between the CAD and No CAD groups in the distribution of patients according to indication for coronary angiography. ‖Minnesota codes 1-1-1 to 1-2-7. ¶Minnesota codes 7-2-1 and 7-2-2. #Minnesota codes 7-1-1 and 7-1-2. **Fisher exact test (2-tailed).
ACE = angiotensin-converting enzyme; BMI = body mass index; CAD = coronary artery disease; ECG = electrocardiogram; HDL = high density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LBBB = left bundle branch block; LDL = low density lipoprotein; RBBB = right bundle branch block.

Resting wall motion abnormalities were only modestly sensitive (49%) but had high specificity (84%) for the detection of CAD. However, the specificity was not higher than for DE-CMR (98%), and the addition of cine-CMR to the interpretation algorithm did not improve the diagnostic accuracy (interpretation algorithm: 87% vs. interpretation algorithm with cine: 86%; p = 0.56).

In Table 3, results are shown according to extent of disease. All patients with multivessel disease (16 patients) and all patients with left main disease (5 patients) were correctly identified by the combined CMR stress test. Six women with single-vessel disease were false negatives: 2 had disease >80%, and in the 4 others, stenosis degree was 70% to 80%.

Table 4 shows the results of quantitative analysis of cardiac volumes and function. To evaluate the influence of small heart size on the sensitivity of the CMR stress test, patients were divided in tertiles of LV mass. Test sensitivities in women with LV mass

Table 2. Diagnostic Performance of the CMR Stress Test for the Detection of CAD According to Disease Severity

	Combined CMR Stress Test		
	Sensitivity	Specificity	Accuracy
CAD ≥ 70%*	84% (31/37)	88% (87/99)	87% (118/136)†
CAD ≥ 50%	70% (32/46)	88% (79/90)	82% (111/136)

*Or ≥50% left main disease. †p = 0.01 compared to CAD severity cutoff of ≥50%.
CMR = cardiovascular magnetic resonance; other abbreviation as in Table 1.

≤90 g, 90 to 111 g, and >111 g were 75%, 83%, and 92%. The sensitivity of the combined CMR stress test in women with a LV mass of ≤97 g was lower compared with women with LV mass > 97 g (69% vs. 95%; p = 0.04). This difference was even more significant after accounting for end-diastolic volumes (70% vs. 100%; p = 0.02 for LV mass indexed to end-diastolic volume ≤1.15 g/ml vs. >1.15 g/ml). The prevalence of CAD was similar in women with small and large hearts (29% vs. 26%; p = 0.66).

The results of the CMR stress test were similar at both study sites. The sensitivity, specificity, and accuracy for stress/rest perfusion alone at Duke (n = 56) were 80%, 46%, and 55%, the corresponding results at RBK (n = 80) were 77%, 62%, and 66% (p = 0.84, 0.12, and 0.20, respectively). The results for detection of CAD in women using perfusion imaging and DE-CMR at Duke were 80%, 83%, and 82%, and 86%, 91%, and 90% at RBK (p = 0.60, 0.20, and 0.18, respectively).

Women without obstructive CAD. There were 99 (73%) women without obstructive CAD (≥70% stenosis) on CA. The multicomponent CMR stress test identified 87 correctly as not having CAD, and 12 were false positives. In 2 of those 12 women, CMR detected silent myocardial infarction (involving 7 and 3 segments), but CA showed nonobstructive CAD in both patients (Fig. 2, bottom row). Thus per definition, they were coded as "negative" for CAD (no stenosis ≥70%), despite finding sequelae of CAD on CMR. In the other 10 women, there was no evidence of infarction, and CA showed nonobstructive stenosis in 5, and no disease in 5 patients. In 1 woman, perfusion defects involving more than 1 coronary territory and extending beyond the subendocardium were found on stress perfusion imaging, without epicardial coronary stenosis (Fig. 2, middle row). This finding is similar to the previously described perfusion abnormalities in patients with microvascular disease (19). The prevalence of risk factors for microvessel disease, such as diabetes and hypertension, were higher in the false positive patients compared with true negative patients, although statistically not significant (33% vs. 18%, p = 0.23 and 83% vs. 62%, p = 0.15).

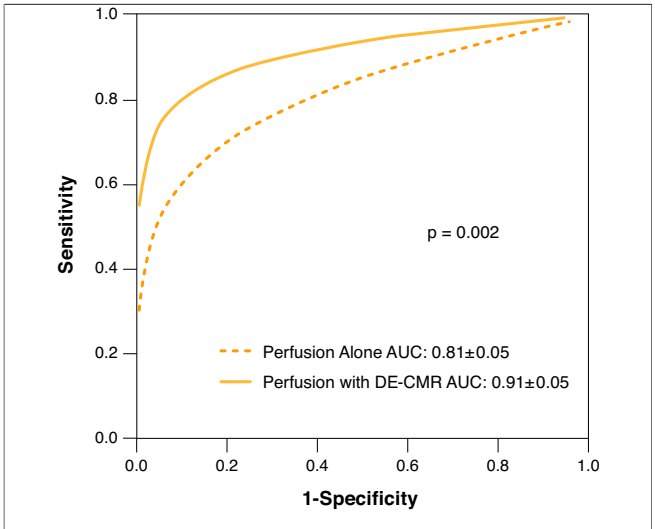

Figure 1. Receiver-Operator Characteristic Curves

Receiver-operator characteristic curve analysis comparing the combined perfusion and delayed enhancement cardiovascular magnetic resonance (DE-CMR) stress test using the interpretation algorithm to perfusion CMR alone for the detection of coronary artery disease. The diagnostic accuracy of the combined CMR stress test was significantly greater (p = 0.002). AUC = area under curve.

DISCUSSION

The major finding of the present study is that a multicomponent CMR stress test using an algorithm for visual image interpretation can accurately diagnose CAD in women in the clinical setting. The sensitivity of 84% and specificity of 88% was obtained in a cohort of patients considered to be good candidates for noninvasive diagnostic testing—women with intermediate or high pre-test probability for CAD (12). In addition, we did not enroll women with known CAD or previous myocardial infarction or normals because it is known

Table 3. Diagnostic Performance of the CMR Stress Test According to the Extent of Coronary Disease (Stenosis ≥70% or Left Main ≥50%)

	Combined CMR Stress Test		
	Sensitivity	Specificity	Accuracy
Single-vessel disease	71% (15/21)	88% (87/99)	85% (102/120)
2-vessel disease	100% (9/9)	88% (87/99)	89% (96/108)
3-vessel disease	100% (7/7)	88% (87/99)	89% (94/106)
Multivessel disease	100% (16/16)*	88% (87/99)	90% (103/115)

*p = 0.06 compared with sensitivity for single-vessel disease.
Abbreviations as in Tables 1 and 2.

Table 4. Quantitative Cine CMR Results

Parameter	Entire Group* (n = 133)	CAD† (n = 36)	No CAD (n = 97)	p Value
LV ejection fraction (%)	66.3 ± 11.6	65.0 ± 11.9	66.8 ± 11.5	0.45
LV-EDV (ml)	106.2 ± 29.0	98.3 ± 26.7	109.1 ± 29.4	0.06
LV-ESV (ml)	37.5 ± 22.2	35.7 ± 20.4	38.1 ± 22.9	0.58
LV mass (g)	106.6 ± 29.1	108.4 ± 38.6	105.9 ± 25.0	0.66
LV-EDV index (ml/m^2)	58.3 ± 14.8	54.7 ± 12.1	59.7 ± 15.5	0.09
LV-ESV index (ml/m^2)	20.7 ± 12.3	19.7 ± 9.8	21.0 ± 13.1	0.59
LV-mass index (gm/m^2)	58.7 ± 15.3	60.5 ± 19.6	58.0 ± 13.4	0.49

*In 3 patients, raw image data were not available for quantitative analysis. †CAD was defined by X-ray coronary angiography (see text).
EDV = end-diastolic volume; ESV = end-systolic volume; LV = left ventricle; other abbreviations as in Tables 1 and 2.

that such pre-test referral bias can inappropriately raise test sensitivity and/or specificity. The reference test—invasive CA—was performed in all patients independent of the CMR results to also reduce post-test referral bias.

To date, only limited data exist on the value of CMR for CAD detection in women. To our knowledge, only 1 study evaluated CMR perfusion imaging specifically in women referred for diagnostic CA. In the study by Doyle et al. (20), women

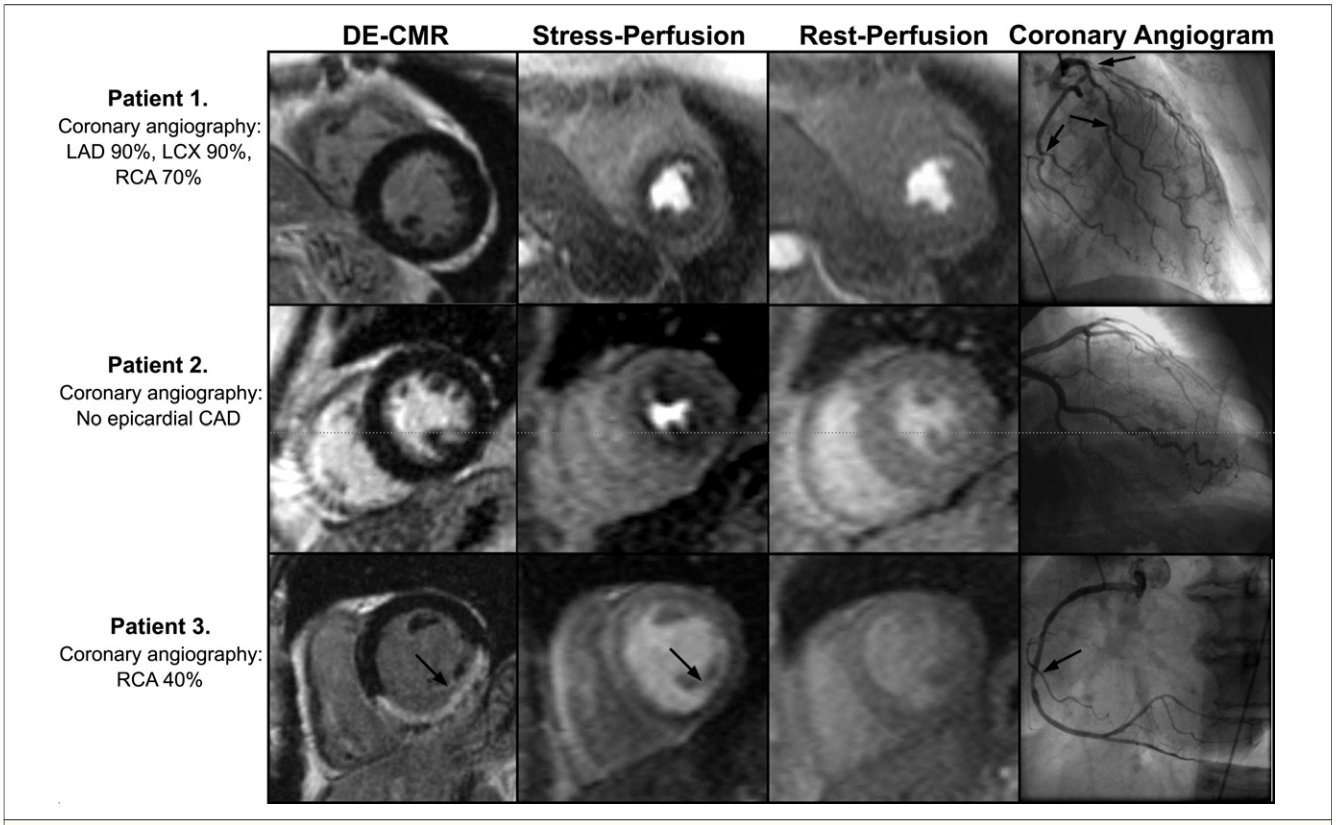

Figure 2. Patient Examples of CMR Stress Test in Women

Patient #1 is a 70-year-old, post-menopausal woman with typical angina and 3 coronary artery disease (CAD) risk factors. There is no evidence of prior infarction on delayed-enhancement (DE) images; however, stress perfusion indicates defects in all 3 vascular territories. Coronary angiography demonstrated 3-vessel coronary disease. Patient #2 is a 50-year-old, post-menopausal woman without chest pain. However, she has diabetes, hypertension, hyperlipidemia, and a positive family history for CAD. A reversible perfusion defect was noted, which was not confined to 1 coronary territory. Her coronary angiogram revealed no epicardial disease, thus microvascular disease may be suspected in this patient. Patient #3 is a 63-year-old woman with typical angina but no prior history of myocardial infarction. She is also post-menopausal and has 3 CAD risk factors. On DE-cardiovascular magnetic resonance (CMR), a transmural infarct is noted in the territory of the right coronary artery (RCA), with a corresponding dense perfusion defect in the same location. However, her coronary angiogram demonstrated only a 40% stenosis in the RCA. Although this was a false-positive CMR study, secondary CAD prevention therapy is certainly warranted in this woman. LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery.

underwent both CMR and gated SPECT imaging studies, and the accuracy for detection of angiographic stenosis ≥ 70% was similar for both techniques (76% and 79%, respectively). However, both SPECT and CMR had only modest sensitivities of 62% and 57%, respectively, which was lower compared to the present study (20). Several differences in study population and scanner hard- and software may be attributed to the higher sensitivity in our study: First, disease prevalence in the study by Doyle et al. (20) was lower, with only 14% having significant CAD on angiography and the majority of those (85%) having single-vessel disease; whereas in our study, 27% had CAD, with only 57% having single-vessel disease. Medication known to reduce sensitivity of perfusion imaging was withheld for a shortened period of 12 h in the previous study compared to the 24 h in the present study (21). There are some technical differences reflecting the rapid development of cardiac MR imaging technology: the pulse sequence used by Doyle et al. (20) allowed only the acquisition of 1 to 2 images per heartbeat; whereas the newer, now widely available sequences with fast imaging techniques used in the present study provide up to 5 images per heartbeat at different slice locations throughout the left ventricle. The increased spatial coverage of the LV myocardium, which is achieved with those newer sequences, allows the detection of small perfusion defects. We used a different receiver coil to gain a signal from the myocardium (phased-array receiver coil), which likely resulted in higher signal-to-noise ratio than the body coil used previously.

Women present frequently for the evaluation of chest pain symptoms, but angina is more commonly atypical as compared with men and less often associated with exertion (4,22). Even when women experience typical angina, obstructive CAD is less frequently found on angiography than in men (23). In our cohort, the majority of women (89%) referred to invasive X-ray angiography had chest pain or discomfort. However, only 50% met the criteria for typical angina based on the Rose questionnaire, and the rate of women reporting typical angina was not different in those with and without obstructive CAD. Thus, assessment of symptoms is of limited utility to predict the presence of CAD in women.

Risk factor assessment is also frequently used to estimate a patient's probability for CAD. In addition to established risk factors, gender-specific risk factors such as hypoestrogenemia, which occurs naturally with menopause, and novel risk markers measuring inflammation have been identified. Despite their utility to predict future cardiovascular events, they provide only limited guidance in the diagnostic work-up of women with chest pain (4). In our study, women with CAD were older and more frequently had hyperlipidemia, the other risk factors, however, had similar frequencies in females with and without CAD. The difficulties of diagnosing CAD in women based on symptoms and risk factors lead to a high number of normal coronary angiograms in symptomatic women. Efforts to avoid this undesirable result by using stress imaging for selecting women with a high likelihood of obstructive coronary disease are limited by suboptimal specificities of most tests. The specificities in published meta-analyses (4) for exercise electrocardiography, stress echocardiography, and stress SPECT in women are only 70%, 73% to 79%, and 64% to 69%, respectively. Thus it is not surprising that although in the present study the majority of women (78%) were included into the study with an abnormal stress test as the cause of referral, only 37 (27%) had obstructive coronary disease. The specificity of the CMR stress test (88%) compares favorably to the above-mentioned averaged specificities for established stress tests. Hence, the improved specificity of adenosine CMR and its high negative predictive value (94%) could have major implications on health care expenses.

We assessed the effect of factors known to reduce accuracy of established noninvasive methods for CAD detection: extent of disease (single-vessel vs. multivessel), severity (various cutoffs for CAD), and small heart size. First, although overall sensitivity was high, detection of single-vessel disease with perfusion CMR remains challenging. Second, the sensitivity of the CMR stress test was lower for intermediate degree of stenosis CAD. This finding is consistent with previous animal experiments showing that clinically relevant (≥70%) stenosis of coronary vessels (causing ≥2-fold regional differences in vasodilated blood flow) are reliably detected on perfusion MR imaging (24). The lack of perfusion defects in some patients with an intermediate degree of stenosis may thus reflect physiology of myocardial blood flow rather than technical limitations. Third, we found the sensitivity to be lower in women with small hearts, especially in those who have a small LV mass with relatively large end-diastolic volume. Further research is necessary to corroborate this finding and to investigate the mechanism for reduced sensitivity in small hearts. One may speculate that the spatial resolution (pixel size approximately 3.0 × 2.0 mm)

achieved by perfusion CMR at 1.5-T in combination with an unfavorable ratio of field-of-view (determined by relative large chest circumference including breasts) to heart size (small number of image pixels within the LV wall) is suboptimal. It is possible that higher field strength may be useful to overcome some of these difficulties for perfusion CMR. As has recently been shown by Cheng et al. (25), perfusion CMR at 3.0-T provides higher signal-to-noise ratios and contrast-to-noise ratios with improved sensitivity for CAD detection (100% vs. 90% for stenosis ≥70%) compared to 1.5-T. Thus higher field strength allows the use of higher spatial resolution without signal loss. Of note, the sensitivity of perfusion CMR in the study by Cheng et al. was higher than in the present study (100% vs. 84%), which may reflect in part the different patient population (25% vs. 100% women). The specificity, however, of perfusion CMR was moderate even at 3.0-T (76% for stenosis ≥50% and 55% for ≥70%), which underscores the potential utility of the combined perfusion—delayed enhancement protocol applied in the present study.

In women evaluated for chest pain, prevalence of obstructive CAD on CA is low, ranging between 14% and 33% (4,25,26). Likewise, in our study, 73% of women referred for CA did not have obstructive CAD. The mechanisms for women to have frequent and chronic chest pain without angiographic CAD has been attributed to vasospasms in the setting of endothelial dysfunction (27), esophageal pain (28), chest wall syndrome (29), and psychosomatic causes (30). In addition, ischemia and chest pain may result from disease of the small rather than the large epicardial vessels in the setting of diabetes, hypertension, collagen disease, and without concomitant predisposing diseases (syndrome X). Different techniques, such as invasive blood flow measurements (31), radionuclide techniques (32), phosphorus-31 nuclear magnetic resonance spectroscopy (33), and CMR (19) have been used to assess the presence of ischemia as the cause of chest pain in microvessel disease. It is possible that some of our patients with stress perfusion defects without angiographic CAD had small vessel disease. Further studies are required to investigate this issue and to define the role of CMR for assessment of microvascular disease. Importantly, however, despite the potentially confounding effects of microvascular disease on CMR perfusion findings, we note that the specificity for the detection of epicardial CAD of the multicomponent CMR stress test was high.

Study limitations. The present study has the following limitations. Not all potential sources of pre-test referral bias were removed, because patients were selected from those already scheduled for invasive angiography. Post-test referral bias was not completely eliminated, as patients had undergone stress testing prior to CA as part of their clinical CAD evaluation. In addition, invasive CA is not necessarily the ideal gold standard for comparison as functional significance of coronary obstruction and luminal diameter stenosis are moderately correlated (34).

CONCLUSIONS

The present study demonstrates that CMR adenosine stress and rest perfusion in combination with delayed enhancement infarction imaging is accurate for the detection of CAD in women. A reduced diagnostic accuracy is encountered in women with small hearts and single-vessel disease. The accuracy of the CMR stress test for detection of intermediate grade stenosis (≥50%) is lower than for stenosis ≥70%, which may however reflect true physiology rather than technical limitations.

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