# Diagnostic Performance of Treadmill Exercise Cardiac Magnetic Resonance: The Prospective, Multicenter Exercise CMR's Accuracy for Cardiovascular Stress Testing (EXACT) Trial

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***Background***—Stress cardiac magnetic resonance (CMR) has typically involved pharmacologic agents. Treadmill CMR has shown utility in single-center studies but has not undergone multicenter evaluation.

***Methods and Results***—Patients referred for treadmill stress nuclear imaging (SPECT) were prospectively enrolled across 4 centers. After rest $^{99m}$Tc SPECT, patients underwent resting cine CMR. In-room stress was then performed using an MR-compatible treadmill with continuous 12-lead electrocardiogram monitoring. At peak stress, $^{99m}$Tc was injected, and patients rapidly returned to the MR scanner isocenter for real-time, free-breathing stress cine and perfusion imaging. After recovery, cine and rest perfusion followed by late gadolinium enhancement acquisitions concluded CMR imaging. Stress SPECT was then acquired in adjacent nuclear laboratories. A subset of patients not referred for invasive coronary angiography within 2 weeks of stress underwent coronary computed tomography angiography. Angiographic data available in 94 patients showed sensitivity of 79%, specificity of 99% for exercise CMR with positive predictive value of 92% and negative predictive value of 96%. Agreement between treadmill stress CMR and angiography was strong (κ=0.82), and moderate between SPECT and angiography (κ=0.46) and CMR versus SPECT (κ=0.48).

***Conclusions***—The multicenter EXACT trial indicates excellent diagnostic value of treadmill stress CMR in typical patients referred for exercise SPECT. (*J Am Heart Assoc*. 2016;5:e003811 doi: 10.1161/JAHA.116.003811)

**Key Words:** coronary disease • exercise • ischemia • magnetic resonance imaging • stress

The burden of coronary artery disease (CAD)—in both lives lost and dollars expended—is staggering, causing over 500 000 deaths annually in the United States alone.[1] Stress imaging with exercise single photon emission computed tomography (SPECT) is a common method for diagnosing CAD.[2] However, SPECT involves radiation exposure,[3] and techniques to correct for soft tissue attenuation may only partially overcome limitations on specificity. In a landmark study of nearly 400 000 patients undergoing elective invasive coronary angiography (ICA),[4] only 41% of those who underwent noninvasive testing prior to ICA had obstructive CAD. These data underscore the need for improved methods of evaluation.

Magnetic resonance is an established modality for cardiac imaging (CMR) without ionizing radiation or limitations imposed by the acoustic window. Stress CMR traditionally requires pharmacologic agents such as inotropes and vasodilators; diagnostic and prognostic value are excellent for both dobutamine stress cine CMR[5,6] and adenosine stress

perfusion CMR.[7,8] However, pharmacologic stress does not provide any of the standard information provided by treadmill exercise such as (1) reproduction of exertional symptoms and correlation of symptoms with ECG and stress imaging findings, (2) comparison of functional capacity to the extent of any ischemia, and (3) the Duke treadmill score with its well-established prognostic value.[9] Our group recently developed a completely MR-compatible treadmill system that can be placed immediately next to the MR scanner table, minimizing the time to stress CMR image acquisition.[10,11] Although single-center data suggest feasibility of in-room exercise CMR,[12,13] prospective evaluation in a multicenter trial including both community and academic practices has been lacking. In this work we evaluated the diagnostic performance of exercise stress testing by CMR compared to SPECT as the reference standard with additional comparison to coronary angiography.

## Methods

### Study Population

The prospective, observational EXACT trial (Exercise CMR's Accuracy for Cardiovascular Stress Testing) sought to directly compare the diagnostic performance of treadmill stress CMR to SPECT. Patients at 4 participating centers who were clinically referred for treadmill stress SPECT for evaluation of known or suspected CAD were screened for enrollment. Individuals aged ≥18 years with preserved renal function (glomerular filtration rate >30 mL/min per 1.75 m²) and weight under 160 kg able to provide informed consent and lie flat for up to 30 minutes were screened for the following exclusion criteria: allergy to gadolinium-based contrast media, non-MR-compatible implant or foreign body, claustrophobia, and pregnancy. Contraindications to exercise stress testing[14] included additional exclusion criteria: acute myocardial infarction, high-risk unstable angina, uncontrolled cardiac arrhythmias, active endocarditis, symptomatic severe aortic stenosis, decompensated heart failure, acute pulmonary embolus or pulmonary infarction, acute noncardiac disorder that may be aggravated by exercise, acute myocarditis or pericarditis, and physical disability that would preclude safe and adequate test performance. Patients with known left main coronary stenosis without revascularization, significant stenotic valvular heart disease, major electrolyte abnormalities, tachyarrhythmias or bradyarrhythmias, atrial fibrillation with uncontrolled ventricular rate, hypertrophic cardiomyopathy, high-degree atrioventricular node block, or uncontrolled hypertension were also excluded. Indication of exercise stress SPECT was rated per appropriate use criteria[15] for each subject who completed the imaging protocol. The study was done in accordance with the Declaration of Helsinki. The study protocol was approved by each institution's committee for human subjects' research, and written informed consent was obtained from all enrolled subjects.

### Stress Protocol

Each participant underwent acquisition of complete rest and stress SPECT and CMR images with 1 single treadmill exercise test (Figure 1). After the resting myocardial perfusion imaging (MPI) SPECT was performed (Myosight or Ventri, GE Healthcare; Forte, Skylight, or Cardio 60, Philips Healthcare), the subject was taken to the nearby CMR suite (1.5 Tesla Avanto or Espree, Siemens Healthcare), where resting cine imaging was obtained using non-breath-holding sequences. After resting cines, the scanner table was moved out of the magnet bore for baseline supine 12-lead ECG recording. Then the subject moved to an MRI-safe treadmill positioned next to the scanner table, where a standing 12-lead ECG was recorded followed by symptom-limited Bruce protocol stress conducted by an exercise physiologist or nurse experienced in cardiac stress testing. Heart rate, cardiac rhythm, and 12-lead ECG were recorded throughout stress. Blood pressure was monitored using an MRI-compatible sphygmomanometer before and at each stage of the test with additional measurements performed as needed.

Peak stress was targeted based on achieving a heart rate of at least $0.85 \times (220 - \text{age})$, with age in years. Stress was also stopped for any of the standard indications to terminate exercise stress such as signs of poor perfusion, sustained arrhythmia, and at the subject's request.[14] When peak stress was imminent, the stress SPECT radioisotope dose was injected and allowed to circulate for up to 90 additional seconds as tolerated. On exercise termination, the patient immediately lay back on the scanner table, and rapid multiplane cine imaging was repeated, followed by multiplane perfusion imaging, both without breath holding. For perfusion imaging, 0.1 mmol/kg gadolinium contrast agent was injected using a power injector at a rate of 4 mL/s. During this time, heart rate and rhythm were continuously recorded via an MRI-compatible 3-lead wireless ECG system monitored by clinical staff. After completion of stress imaging, the scanner table was moved out from the magnet bore for recovery 12-lead ECG and blood pressure monitoring. Recovery monitoring was done in accordance with guidelines in the supine position for 6 to 8 minutes or longer if needed.[14] Duke treadmill scores were computed from available stress data.[16] Postrecovery imaging included multiplane cines, resting perfusion, and single-heartbeat multiplane late gadolinium enhancement (LGE) acquisitions. The patient then returned to the nearby SPECT suite for stress MPI acquisition, typically 30 minutes after the stress radioisotope was injected. Detailed CMR scan parameters are provided in Table 1.
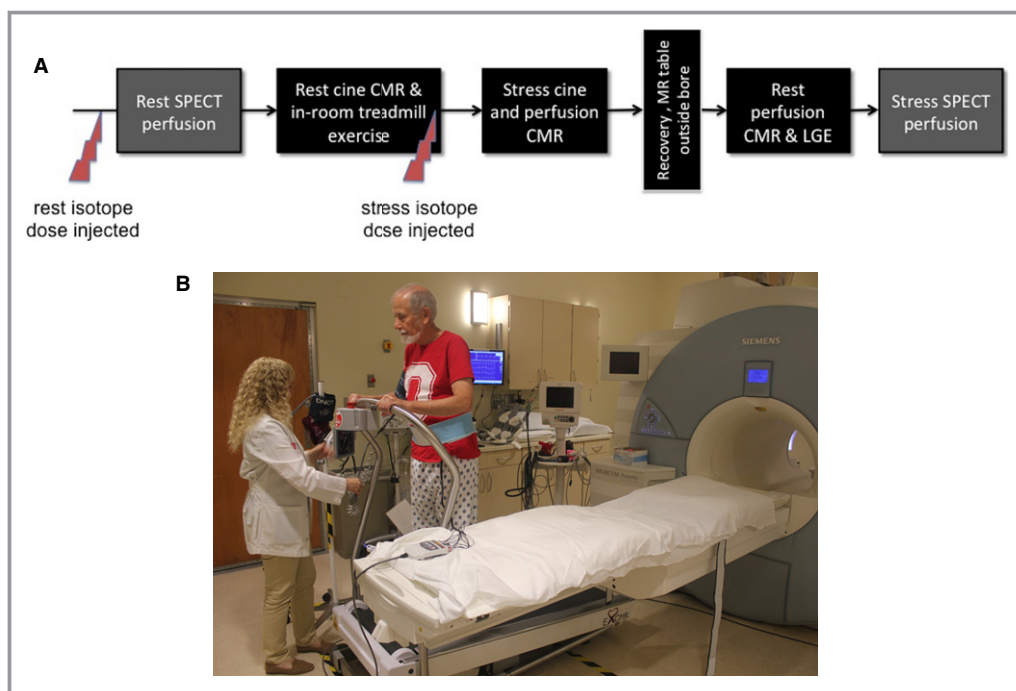
**Figure 1.** Hybrid exercise CMR-SPECT stress imaging. A, Protocol: After initial injection of the rest dose of sestamibi, SPECT perfusion imaging is acquired. The subject then undergoes resting cine imaging and treadmill exercise stress in the MR scanner room, with injection of the stress sestamibi dose ~90 seconds prior to termination of exercise. On termination of exercise, the subject quickly returns to the prestress position on the scanner table, and stress cine and perfusion images are acquired within a goal of 60 seconds poststress. The MR table is pulled out so that recovery monitoring can be performed, and once sufficient recovery has occurred the subject is returned to the isocenter to complete rest perfusion CMR and LGE imaging. Finally, stress SPECT perfusion images are acquired. The CMR components of the protocol (black boxes) are completed within 1 hour, well within the typical waiting period for patients undergoing rest/stress SPECT examination. B, Room setup. A subject is shown walking on the treadmill while a staff member measures his brachial artery blood pressure. In-room display of continuous electrocardiographic monitoring is shown on a screen just behind the subject's right side. On completion of exercise stress, the subject will return to the scanner table where deflatable cushions around his head and feet molded prior to rest cine imaging facilitate return to his prestress position. Both individuals gave informed consent for obtaining this photograph and permission for its publication.

## Coronary Angiography

Referral for invasive coronary angiography (ICA) was performed at the referring physician's discretion, and ICA when ordered was performed using established clinical techniques. Patients not referred for ICA by 2 weeks after stress imaging were recruited to undergo research coronary computed tomography angiography (CTA). Standardized protocols at each site included either prospective ECG-triggered acquisition (Brilliance iCT 256, Philips) or retrospectively gated acquisition with tube current modulation (Somatom64, Siemens).

## Image Analysis

Data for each exercise SPECT and CMR exam were reviewed in random order by 2 reviewers blinded to the results of the other stress imaging study. The consensus diagnosis recorded for each stress SPECT was 1 of the following: (1) normal, (2) positive for ischemia (reversible defect), (3) fixed defect without ischemia, or (4) infarct with ischemia. Similarly, the consensus diagnosis recorded for each stress CMR was 1 of the following: (1) normal, (2) positive for ischemia (reversible perfusion defect with or without wall motion abnormality), (3) infarct scar without ischemia, or (4) infarct scar with ischemia. Additionally, any noninfarct LGE abnormalities were recorded. ICA studies were interpreted by a single interventional cardiologist blinded to other data, recording presence/absence of disease defined as ≥70% stenosis in the left main, left anterior descending coronary artery and branches (LAD), right coronary artery and branches (RCA), and left circumflex coronary artery (LCx) and branches. In the presence of bypass grafts, patency of the graft and vessel distal to the graft anastomosis was recorded as absence of

**Table 1.** Exercise Stress CMR Scan Parameters

| | Sequence Type | Mag. Prep. | Echo Train | TR, ms | TE, ms | Flip Angle, Deg | Bandwidth, Hz/Pixel | Temporal Resolution, ms* | Matrix PE×FE | FOV PE×FE* | Slice Thick | Acceleration Rate | Prep Delay, ms* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cine | bSSFP | n.a. | n.a. | 2.6 | 1.0 | 62.1±2.2* | 1488 | 51.5±5.5 | 88×160 pixels | 357±48 mm×386±10 mm | 10 mm | 4 | n.a. |
| Perfusion | GRE-EPI | SR | 4 | 5.6 | 1.1 | 25 | 1806±214 | 67.2±7 | 92×160 pixels | 339±18 mm×390±18 mm | 10 mm | 2 | 101±7.6 |
| LGE | bSSFP | IR | n.a. | 2.5 | 1.0 | 40 | 1422±164 | 170±22 | 112×192 pixels | 356±15 mm×375±18 mm | 10 mm | 2 | 286±32 |

FE indicates frequency encoding; IR, inversion recovery; LGE, late gadolinium enhancement; Mag prep, magnetization preparation; PE, phase encoding; SR, saturation recovery; TE, echo time; TR, repetition time.
*Parameters represent average values across all 210 completed exams.

≥70% stenosis in that territory (eg, patent internal mammary artery graft to a native LAD with ≥70% stenosis was recorded as absence of disease in the LAD). CTA images were reviewed in the original axial reconstructions as well as multiplanar reformats by consensus of 2 reviewers blinded to the results of other imaging procedures, assessing each major native coronary segment: left main, LAD and branches, LCx and branches, RCA and branches. Presence/absence of disease defined as ≥70% stenosis was recorded, and nonevaluable segments were noted; bypass grafts were handled similarly as with invasive angiography.

## Follow-Up

Occurrence of cardiovascular events at 12 months after stress imaging was recorded for all subjects by telephone contact and chart adjudication. Cardiac events were defined as death due to cardiovascular disease or hospitalization for acute coronary syndrome, heart failure, or arrhythmia.

## Statistical Analysis

The results of the CMR and SPECT were converted to dichotomous variables (positive or nonpositive based on presence or absence of ischemia), and an angiographic outcome was generated for each subject from available cardiac catheterization and CTA data to yield a dichotomous variable (positive or nonpositive); together, CMR, SPECT and angiography dichotomous variables were used for Spearman rank correlation analysis. The κ statistic was used to assess intertest agreement. Correlations between stress imaging and angiography were computed using Pearson product-moment correlation. All statistics were performed on the R statistics package version 3.2.1.

## Results

A total of 227 subjects were initially enrolled. Four individuals experienced severe claustrophobia on entering the MR scanner, which required termination of the procedure. In 5 subjects, the stress protocol was changed to pharmacological stress as inability to perform adequate treadmill exercise became apparent only after arrival. Four subjects developed dyspnea, chest pain, back pain, or left bundle branch block, prompting termination of stress testing prior to image acquisition. Malfunction of the MRI-compatible treadmill precluded its operation in 2 subjects, and scheduling constraints prevented 2 additional subjects from undergoing the hybrid test. The remaining 210 subjects successfully completed treadmill exercise stress and the hybrid SPECT–CMR imaging protocol (Table S1). Of those, 94 completed invasive x-ray or noninvasive CT coronary angiography with

diagnostic results of adequate quality; the characteristics of these 94 subjects are summarized in Table 2. Within this 94-patient cohort, stress SPECT was clinically ordered to diagnose suspected CAD in 72 patients and to evaluate disease significance in 22 patients with known CAD. SPECT appropriate use was met in 78 (83%), whereas utilization was of uncertain appropriateness in 10 (11%) and inappropriate in 6 (6%).

## Stress Testing and Timing

The 94 subjects with angiographic outcomes completed on average 8.5±3.2 minutes of Bruce protocol treadmill stress. Heart rate averaged 97.1±10.3% of age-predicted maximum heart rate (APMHR) at the end of exercise, with subjects achieving a double product of 26 994±4255 mm Hg-bpm and 10.1±3.1 metabolic equivalents (METs). Cine imaging

**Table 2.** Characteristics of All Study Participants With Angiographic Data (N=94)

| Characteristic | Value |
|---|---|
| Age, y, mean±standard deviation (SD) | 57.1±10.6 |
| Male, N (%) | 51 (54) |
| Race, N (%) | |
|    White | 81 (86) |
|    Black | 12 (13) |
|    Asian | 1 (1) |
|    Pacific Islander | |
| Nonsmoker, N (%) | 82 (87) |
| Hypertension, N (%) | 35 (37) |
| Diabetes mellitus, N (%) | 12 (13) |
| Known CAD, N (%) | 22 (23) |
| Medications | |
|    Aspirin and/or clopidogrel | 58 (62) |
|    Beta blocker | 29 (31) |
|    ACEI or ARB | 34 (36) |
|    Statin | 54 (57) |
| Standing blood pressure, mm Hg, mean±SD | |
|    Systolic | 134±18 |
|    Diastolic | 81±12 |
| Standing heart rate at rest, beats per minute, mean±SD | 80±16 |
| Indication for stress test, N (%) | |
|    Chest pain/angina | 59 (63) |
|    Shortness of breath without chest pain | 16 (17) |
|    Other | 19 (20) |

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease.

was done at 83±11% of APMHR, and perfusion imaging at 76±11% of APMHR. After exercise termination, cine imaging commenced at 25±13 seconds, stress cine imaging was completed within 46±16 seconds, and perfusion imaging was completed by 87±36 seconds. Symptoms during stress testing included dyspnea in 27 (29%) subjects, chest pain in 6 (6%), and arrhythmias including isolated ventricular premature beats (10 [11%]), atrial premature beats (4 [4%]), and ventricular couplet in 1 (1%). Median [IQR] Duke treadmill score was 8 [5−10]. ST segment monitoring was inadequate in 2 subjects due to artifact; in the remaining 92 recordings, 12 (13%) demonstrated ST depression, and findings were indeterminate in 8 (9%).

## Imaging and Angiographic Findings

In 94 subjects with angiographic outcomes, 87.2% had no ischemia by stress CMR, and 87.2% had no ischemia by stress SPECT. The remaining results for CMR/SPECT were as follows: 3.2%/3.2% positive for ischemia without infarct scar, 7.4%/5.3% infarct without ischemia, and 2.1%/4.3% infarct plus ischemia. SPECT demonstrated a reversible defect consistent with ischemia in 4.8% and a fixed defect without ischemia in 7.6%.

Twenty-one subjects were referred clinically for cardiac catheterization, and CTA was performed in 113 (3 of whom also had invasive angiography performed). CTA was not performed in 57 who refused, 15 who could not be reached for scheduling, and 3 who reported allergy to iodinated contrast. CTA was nondiagnostic in 37 cases due to severe calcification or artifact, yielding 94 subjects with an angiographic outcome (Table 3). Comparison between CMR and coronary angiography showed a

**Table 3.** Results of Angiography (N=94)

| | CTA | ICA | Combined* |
|---|---|---|---|
| Extent of disease, no. of vessels | | | |
| 0 | 70 | 10 | 80 |
| 1 | 2 | 6 | 8 |
| 2 | 1 | 5 | 6 |
| 3 | 0 | 0 | 0 |
| Location of disease | | | |
| LM | 0 | 0 | 0 |
| LAD | 1 | 7 | 8 |
| RCA | 2 | 3 | 5 |
| LCx | 1 | 6 | 7 |

CTA indicates coronary computed tomography angiography; ICA, invasive coronary angiography; LAD, left anterior descending; LCx, left circumflex; LM, left main; RCA, right coronary artery.
*Three patients underwent both CTA and ICA.

**Table 4.** Test Characteristics Compared to Angiography (70% Stenosis Cutoff)

| | Sensitivity, % | Specificity, % | Positive Predictive Value, % | Negative Predictive Value, % |
|---|---|---|---|---|
| Exercise stress CMR | 78.6 (48.8–94.3) | 98.7 (92.3–99.9) | 91.7 (59.7–99.6) | 96.3 (88.9–99.0) |
| Exercise stress SPECT | 50.0 (24.0–76.0) | 93.7 (85.4–97.7) | 58.3 (28.6–83.5) | 91.5 (82.7–96.2) |

CMR indicates cardiac magnetic resonance; SPECT, single photon emission computed tomography.

strong positive correlation ($\rho$=0.825, $P$<0.0001), whereas SPECT versus coronary angiography showed a moderate positive correlation ($\rho$=0.467, $P$<0.001). When angiographic stenosis of 70% was used as a cutoff, sensitivity, specificity, positive predictive value, and negative predictive value of each stress modality could be calculated (Table 4). For 66 patients with a history of CAD, exercise CMR showed ischemia in 8 and infarct scar in 20. Because these subjects did not have prior LGE-CMR, we could not assign these as new infarct or old. The test was effective in identifying ischemia in the presence of preexisting disease and MI: 8 of 66 subjects with known CAD had ischemia by exercise CMR, and in all 8 angiography confirmed obstructive disease in one or more segments lacking patent PCI or bypass graft.

Agreement between CMR and SPECT was moderate (Figures 2 and 3), indicated by a $\kappa$ statistic of 0.42 (0.23–0.60) ($P$<0.0001). LGE-CMR demonstrated subendocardial infarct scar in 8 patients with normal SPECT images (Figure 4), whereas SPECT demonstrated a fixed defect in 9 patients without LGE abnormality by LGE-CMR. Additionally, 6 patients had midwall fibrosis by LGE, indicating nonischemic myocardial disease. CMR identified additional abnormalities not evident by SPECT, including LV thrombus in 1 subject and apical hypertrophic cardiomyopathy in 2 subjects (Figure 5).

Analysis of stress cine CMR data without perfusion or LGE data (ie, noncontrast exercise stress CMR) showed high specificity (97.5 [90.4–99.6]%) but low sensitivity (35.7 [14.0–64.3]%) in this cohort. Only 1 of the 9 subjects whose wall motion was "negative" in the presence of >70% stenosis by either invasive angiography or CTA went on to revascularization. In both of 2 subjects whose wall motion was "positive" in the face of a negative angiographic outcome, there was global
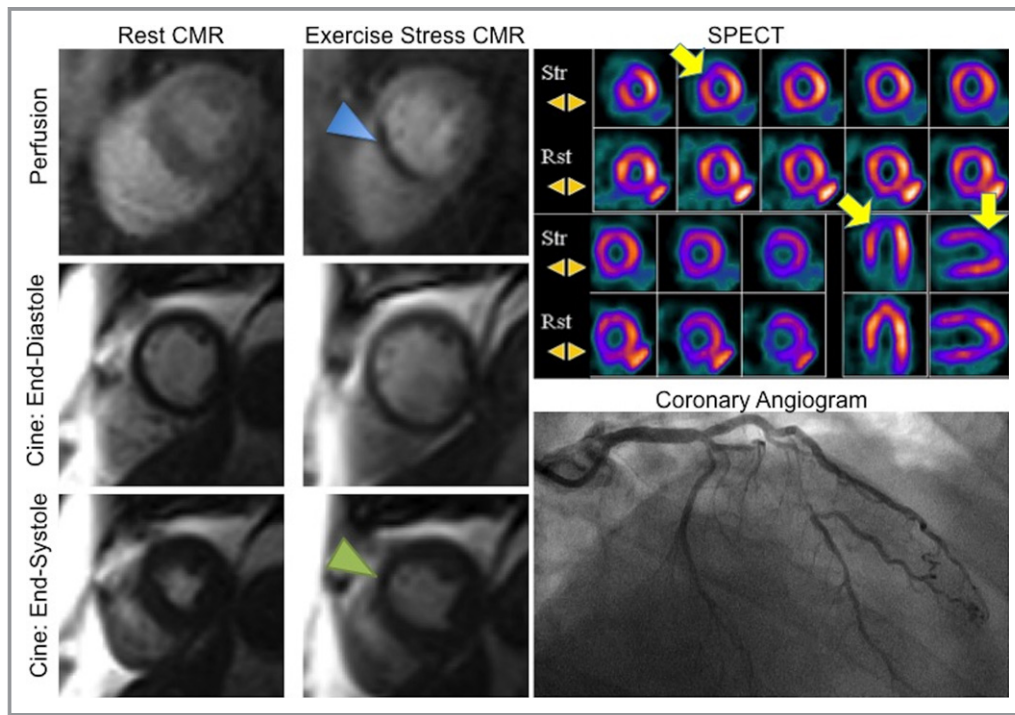


**Figure 2.** Ischemia by treadmill stress CMR and SPECT. A 59-year-old male referred for exercise SPECT underwent the hybrid treadmill stress CMR-SPECT protocol. SPECT (upper right color image) demonstrated reversible perfusion abnormality in the anteroseptum and apex (yellow arrows). Similarly, cine and perfusion CMR showed both wall motion and perfusion abnormalities present only on stress images (blue and yellow arrowheads, respectively), with viable myocardium, ie, absence of scar by LGE (not shown). Invasive angiography (lower right) confirmed high-grade left CAD. CAD indicates coronary artery disease; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; SPECT, single photon emission computed tomography.
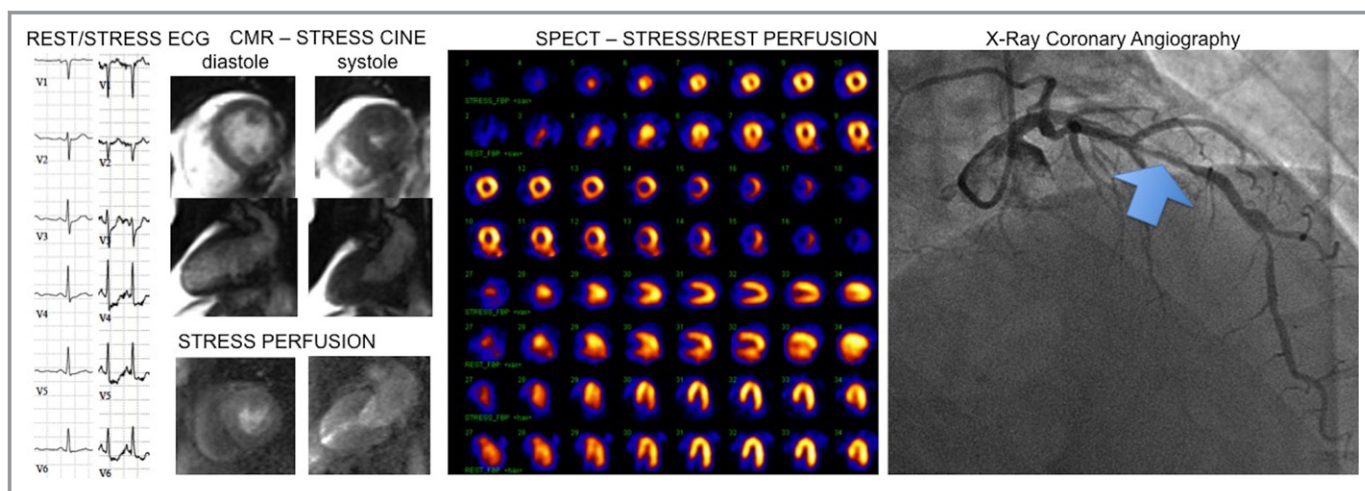
**Figure 3.** Exercise-induced ST depression without wall motion or perfusion abnormalities. A 62-year-old male with exertional dyspnea in the setting of hypertension and a family history of coronary artery disease was referred for stress imaging. Exercise was terminated at 7.5 minutes due to fatigue, the patient having reached 108% of his age-predicted maximum heart rate. Although ST depression developed with exercise, no appreciable wall motion or perfusion abnormalities were seen by either CMR or SPECT. Clinically directed invasive angiography demonstrated an anatomic stenosis in the proximal left anterior descending coronary angiography prompting subsequent percutaneous revascularization. Of note, fractional flow reserve was not measured prior to PCI. CMR indicates cardiac magnetic resonance; ECG; electrocardiogram; SPECT, single photon emission computed tomography; PCI, percutaneous coronary intervention.

dysfunction with stress and midwall fibrosis by LGE consistent with lack of contractile reserve in the setting of nonischemic cardiomyopathy. Older age and male gender both predicted greater positive stress test and angiographic results ($P<0.001$ for gender versus stress CMR, $P=0.001$ for gender versus stress SPECT, $P=0.018$ for gender versus angiography using a 70% cutoff).

## Follow-Up

Eleven subjects were lost to follow-up. In the remaining subjects, 2 individuals suffered strokes, and 1 subject died of breast cancer during the follow-up period. No adverse cardiac events occurred in this cohort at 12 months follow-up.

## Discussion

This is the first multicenter trial demonstrating the diagnostic performance of treadmill stress CMR in a large symptomatic patient population. Our study demonstrated excellent agreement between exercise treadmill CMR and coronary angiography, with more moderate agreement between exercise treadmill SPECT and angiography. Test performance was superior with CMR versus SPECT when measured against anatomic coronary artery disease by either invasive or noninvasive angiography.

In a prior single-center study, we demonstrated treadmill CMR's excellent accuracy in patients who subsequently underwent invasive coronary angiography, and a negative
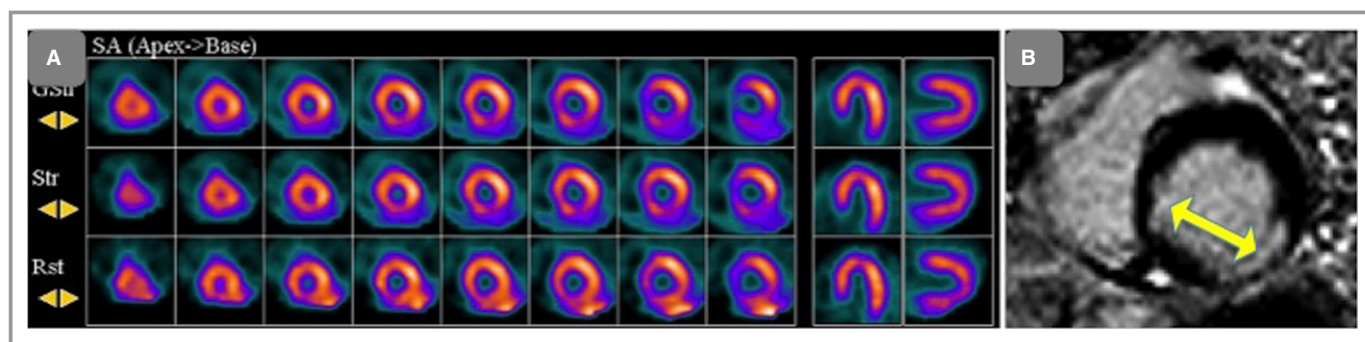


**Figure 4.** Subendocardial infarct scar by CMR and negative stress SPECT. A 57-year-old female referred for stress SPECT underwent the hybrid treadmill stress protocol with no ischemia by SPECT (A) or CMR perfusion imaging; however, LGE-CMR identified infarct scars in 2 regions (B, arrowheads). CMR indicates cardiac magnetic resonance; LGE, late gadolinium enhancement; SPECT, single photon emission computed tomography.
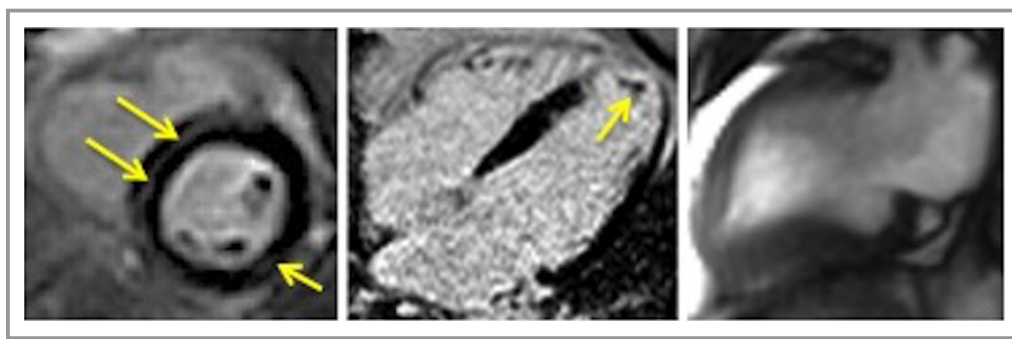
**Figure 5.** Non-CAD diagnoses afforded by CMR in patients referred for stress SPECT. Additional findings afforded by CMR included midwall fibrosis indicating nonischemic myocardial disease (left panel), LV thrombus that preceded subsequent thromboembolic stroke (middle panel), and typical morphology of apical hypertrophic cardiomyopathy explaining abnormal ECG findings (right panel). CAD indicates coronary artery disease; CMR, cardiac magnetic resonance; ECG; electrocardiogram; LV, left ventricular; SPECT, single photon emission computed tomography.

treadmill CMR exam predicted freedom from cardiovascular events with comparable prognostic value as a normal stress SPECT exam.[12] In addition to identifying obstructive epicardial coronary heart disease, we have also shown that this modality can diagnose exercise-induced microvascular disease.[17] Finally, preliminary data in patients with congenital heart disease suggest that treadmill CMR can uniquely quantify biventricular contractile reserve.[18] Building on these data, the present work suggests feasibility of the procedure for the evaluation of ischemic heart disease (IHD) in typical ambulatory patients referred for stress cardiac imaging in both academic and community-based practices.

Dobutamine stress CMR cine imaging alone may be falsely negative in elderly patients due to greater LV concentricity and lower LV preload and myocardial oxygen demand.[19] Combined perfusion and wall motion imaging with exercise stress may better distinguish microvascular from epicardial disease. In leveraging comprehensive myocardial imaging, exercise stress CMR also helps identify other conditions such as nonischemic cardiomyopathy and pericardial disease whose presentations may mimic ischemic heart disease (IHD).

Stress CMR using supine cycle ergometry is feasible,[20] but this approach has made limited inroads into clinical care; this may reflect limiting skeletal muscle fatigue that precludes adequate cardiopulmonary stress in individuals not accustomed to high-intensity cycling. Treadmill stress CMR was first reported in 2003 using a standard treadmill placed outside the scanner room.[21] The time needed for typical cardiovascular disease patients to go from outside the scanner room to the scanner table and then to isocenter may push postexercise wall motion imaging beyond the 60 seconds advocated by guidelines,[22] which show that exercise-induced functional abnormalities dissipate rapidly once exercise stops.

## Limitations

Perfusion CMR may have achieved higher sensitivity if the perfusion scan were run first following exercise rather than following cine imaging, which may explain the false-negative case shown in Figure 3. For this initial multicenter study, we chose to complete cine imaging first because the cine scans are run without ECG triggering, whereas the perfusion scans are triggered. If perfusion images were acquired first after exercise, any problem with triggering would potentially impose a significant delay on the start of cine imaging, whereas acquiring cine images first avoided this issue.

Prior stress imaging trials focused on a high pretest likelihood of disease population, enrolling only patients undergoing invasive coronary angiography. We instead enrolled patients from the stress SPECT laboratory, recognizing that very few would go on to clinically referred angiography, to insure relevance of study findings to typical patients referred for stress imaging. CTA's utility is in its high negative predictive value; however, the high prevalence of obscuring coronary calcifications and unevaluable segments due to artifact limited CTA's ability to serve as a consistent surrogate for ICA in comparing stress imaging to stenosis severity. Ideally, fractional flow reserve (FFR) measures would have been available as a superior reference standard, particularly as CTA may overestimate stenosis; κ values for stress imaging versus angiography would likely have differed for stress imaging versus FFR. Lack of angiographic data in a considerable proportion of subjects who did not complete CTA may bias results, though mandating angiography would have selected a different population, itself impacting overall study results. The normality rate in our study was high for both for SPECT and CMR, albeit in a similar range as some SPECT reports,[23] reflecting referral patterns at the enrolling

institutions where patients with high pretest probability of CAD are more likely scheduled directly for ICA rather than for stress imaging. Although all SPECT exams were conducted in highly experienced nuclear laboratories in real-world patients, we recognize that the sensitivity of the SPECT testing procedure for identifying >70% stenosis in this study was lower than typically reported values.

Cine-only imaging performed poorly in this study, possibly as a result of considerable excursion of LV segments during heavy breathing, a limitation not seen in dobutamine stress, where breath-hold cine imaging also predominates. Prognostic assessment was limited by no adverse events at 1-year follow-up. Studies in higher-risk cohorts are needed to know the prognostic value of this modality, although we are encouraged by a recent study showing incremental prognostic value with treadmill stress outside the scanner room followed by cine CMR.[24,25] The current study was not designed to assess differences in cost of initial and downstream care; the ongoing multicenter EXACT-COST trial, which randomizes patients to treadmill stress with either SPECT or CMR, should provide important insights in this regard (NCT01875315).

## Conclusions

In this prospective multicenter study, we identified high diagnostic performance of treadmill exercise CMR testing. Further long-term studies are warranted to better define the impact on morbidity, mortality, and resource utilization of this novel approach to cardiac stress imaging.

## Sources of Funding

## Disclosures

S. V. Raman, J. W. Arnold, and O. P. Simonetti have applied for a patent on the MRI-compatible treadmill and have ownership interest in EXCMR, Ltd, a company commercializing this device. Raman and Simonetti receive research support from Siemens. J. K. Min has received research support from Philips Healthcare. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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SUPPLEMENTAL MATERIAL

Table S1. Characteristics of All Study Participants who Completed Imaging (N=210)

| Characteristic | Value |
|---|---|
| Age in years, mean ± standard deviation (SD) | 57.3 ± 10.6 |
| Male, N (%) | 126 (60) |
| Race, N (%) | |
| White | 178 (85) |
| Black | 27 (13) |
| Asian | 4 (2) |
| Pacific Islander | 1 (<1) |
| Nonsmoker, N (%) | 181 (86) |
| Hypertension, N (%) | 77 (37) |
| Diabetes, N (%) | 30 (14) |
| Known coronary artery disease, N (%) | 66 (31) |
| Medications | |
| Aspirin and/or clopidogrel | 132 (63) |
| Beta blocker | 78 (37) |
| ACEI or ARB | 83 (40) |
| Statin | 128 (61) |
| Standing blood pressure in mmHg, mean ± SD | |
| Systolic | 134 ± 18 |
| Diastolic | 80 ± 11 |
| Standing heart rate at rest in beats per minute, mean ± SD | 78 ± 15 |
| Indication for stress test, N (%) | |
| Chest pain/angina | 135 (64) |
| Shortness of breath without chest pain | 25 (12) |
| Other | 50 (24) |