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Comparison of treadmill exercise stress cardiac MRI to stress echocardiography in healthy volunteers for adequacy of left ventricular endocardial wall visualization: A pilot study

Paaladinesh Thavendiranathan, MD^{1,*}, Jennifer A. Dickerson, MD¹, Debbie Scandling, BS², Vijay Balasubramanian, MS^{2,†}, Michael L. Pennell, PhD³, Alice Hinton, MS³, Subha V. Raman, MD, MSEE^{1,2,4}, and Orlando P. Simonetti, PhD^{1,4,2}

¹Division of Cardiovascular Medicine, Department of Internal Medicine, The Ohio State University, Columbus, OH, USA

²Davis Heart and Lung Research Institute, The Ohio State University, Columbus, OH, USA

³Division of Biostatistics, College of Public Health, The Ohio State University, Columbus, OH, USA

⁴Department of Radiology, The Ohio State University, Columbus, OH, USA

Abstract

Purpose—To compare exercise stress cardiac magnetic resonance (cardiac MR) to echocardiography in healthy volunteers with respect to adequacy of endocardial visualization and confidence of stress study interpretation.

Materials and Methods—28 healthy volunteers (aged 28 ± 11 years, 15 males) underwent exercise stress echo and cardiac MR one week apart assigned randomly to one test first. Stress cardiac MR was performed using an MRI-compatible treadmill; stress echo was performed as per routine protocol. Cardiac MR and echo images were independently reviewed and scored for adequacy of endocardial visualization and confidence in interpretation of the stress study.

Results—Heart rate at the time of imaging was similar between the studies. Average time from cessation of exercise to start of imaging (21 vs. 31 seconds, $p < 0.001$) and time to acquire stress images (20 vs. 51 seconds, $p < 0.001$) was shorter for cardiac MR. The number of myocardial segments adequately visualized was significantly higher by cardiac MR at rest (99.8% versus 96.4%, $p = 0.002$) and stress (99.8% versus 94.1%, $p = 0.001$). The proportion of subjects in whom there was high confidence in the interpretation was higher for cardiac MR than echo (96% vs 60%, $p = 0.005$).

Conclusion—Exercise stress cardiac MR to assess peak exercise wall motion is feasible and can be performed at least as rapidly as stress echo.

Address for correspondence: Orlando Simonetti, The Ohio State University, 473 W. 12th Ave, Suite 200, Columbus, OH 43210, Phone: 614-293-0739, Fax: 614-247-8277, orlando.simonetti@osumc.edu.

*current affiliation: Peter Munk Cardiac Center, University Health Network of Toronto, Toronto, Ontario, Canada

†current affiliation: EXCMR, Inc., Columbus, OH

VB is currently employed by EXCMR, Inc.

SVR and OPS have applied for a patent on the MRI-compatible treadmill and have ownership interest in EXCMR, Inc., a company commercializing this device. SVR and OPS receive research support from Siemens Healthcare.

Keywords

Exercise stress cardiac magnetic resonance imaging; exercise stress echocardiography; endocardial visualization index

Introduction

Exercise stress echocardiography remains one of the most commonly used methods for detection of coronary artery disease (CAD) with good sensitivity and specificity (1,2). It provides assessment of post-peak exercise stress systolic wall motion abnormalities as a marker of myocardial ischemia, and provides prognostic information (3,4) (1,5). However, this technique is not without limitations. Since the detection of CAD requires observation of contractile dysfunction of myocardial segments at rest or with stress, complete visualization of all LV endocardial borders is necessary (6). However, many patient factors such as obesity and lung disease, excessive cardiac motion, and hyperventilation can result in non-diagnostic or poor quality images in from 15% to 30% of patients(6,7). These challenges can increase inter-observer variability and reduce inter-institutional reproducibility(8). The use of harmonic imaging and contrast agents to improve endocardial border delineation has reduced, but not overcome these limitations (9,10) as even contemporary studies illustrate that endocardial visualization can still be limited in some patients, reducing the confidence to rule out regional wall motion abnormalities in up to 26% of patients(9).

Cardiac MR in general provides superior image quality with respect to contrast to noise ratio and signal to noise ratio compared to echo, allowing superior assessment of endocardial borders(11,12). Naturally, this has resulted in the use of stress cardiac MR for assessment of CAD. There is now a substantial body of literature illustrating the sensitivity, specificity, and accuracy of vasodilator and dobutamine stress cardiac MR for the assessment of coronary artery disease(4,13–17). Although these are excellent methods of stress testing, they lack the corresponding diagnostic and prognostic information provided by exercise stress (18,19).This includes heart rate (HR) and blood pressure response, ability to reproduce the symptoms, exercise duration, maximum METs, and arrhythmias. As a consequence there has been some interest in exercise stress cardiac MR with supine bicycle (20)and treadmill exercise stress testing.

With respect to treadmill exercise stress cardiac MR, there has been progression from placing a treadmill outside the cardiac MR room(21), followed by moving the treadmill to the corner of the room(22–24), to more recently a fully MRI compatible treadmill placed adjacent to the MRI system analogous to the setup used for stress echocardiography(25). This provides the ability to assess post exercise wall motion following a procedure similar to stress echo in a rapid and safe fashion without limitations of acoustic window. Initial experience with this latter treadmill setup in healthy volunteers(25) has been previously published. However, a direct comparison of exercise stress cardiac MR to echocardiography has not been performed to assess feasibility, adequacy of endocardial wall visualization, and reader confidence in image interpretation.

The objective of this study was to compare exercise stress cardiac MR to echocardiography in healthy volunteers with respect to (1) feasibility of the stress protocol, (2) adequacy of left ventricular endocardial visualization, and (3) reader confidence in the interpretation of the stress study.

Methods

Study Population and Study Protocol

Healthy volunteers were recruited to undergo both exercise stress cardiac MR and stress echocardiography. Baseline demographics, cardiac risk factors, and cardiac disease history were all obtained at the time of enrollment and those with any previous history of cardiac disease were excluded. Volunteers were randomly assigned to first having one of the two stress modalities followed by the second stress study within one week. This study was approved by our local Institutional Review Board.

Exercise Stress Cardiac Magnetic Resonance Imaging

Cardiac MR exercise stress testing was performed using a fully MRI-compatible treadmill placed adjacent to the MRI patient table(25). The MRI system used was a 1.5 Tesla scanner (Siemens Avanto, Erlangen, Germany) with a 32-channel phased-array coil (Rapid MRI, Columbus, OH). This setup has been previously described in detail(25). In the MRI room, volunteers were first positioned on the scanner table using individualized molds created from deflatable cushions (Vac-Lok, CIVCO Medical Solutions, Kalona, IA) that allowed easy return to the same position post exercise(22). Resting cine images consisting of 5 short axis, and 4 long axis slices were performed using a non-triggered real-time steady-state free precession (SSFP) acquisition with temporal generalized autocalibrating partially parallel acquisition (TGRAPPA) acceleration factor of 4 with the following scan parameters: repetition time (TR) 2.2ms, echo time (TE) 1.0ms, flip angle 58°, receiver bandwidth (BW) 1360Hz/pixel, forty frames, temporal resolution 51.8ms, slice thickness 8mm, average in-plane spatial resolution of 3.9×2.6 mm, scan time of 2 seconds per slice, and an average field of view (FOV) of 281 mm $\times$ 373 mm.

Upon completion of rest imaging, the volunteer was brought out of the scanner and connected to a 12-lead electrocardiography system (Cardiosoft, GE Healthcare, Waukesha, WI); electrocardiogram (ECG) and blood pressures were measured in the supine and standing positions. The volunteer then practiced getting back onto the table into the “mold” prior to initiation of the Bruce treadmill stress(26) protocol. All volunteers exercised to at least 85% of maximal predicted heart rate with termination of study determined by volunteer fatigue(26). The prototype, fully MRI-compatible treadmill was located adjacent to the MRI patient table analogous to the setup in a stress echocardiography lab (25). During stress, vital signs and symptoms were recorded by a supervising physician.

At completion of exercise, the volunteer immediately returned to the same position on the MRI patient table using the previously-molded cushion and was returned to the scanner isocenter based on pre-stress positioning. The start button on the magnet housing was pressed by a technologist in the MRI room to initiate scanning. Non-breath held stress real-time cine imaging covering 9 slice positions (total time approximately 18 seconds) was performed using a protocol identical to that described at rest. At the completion of cine imaging, the volunteer was immediately brought out of the scanner, re-connected to the 12-lead ECG system and allowed to recover in the supine position with close monitoring of ECG and blood pressure. Timing to initiate and complete imaging was recorded.

Exercise Stress Echocardiography

All exercise stress echocardiography studies were performed by one experienced sonographer using a General Electric system (Vivid 7) with a 1.7/3.4 MHz 2-D transducer (MS4, GE Healthcare, Waukesha, W). Baseline images were obtained in the standard parasternal, short axis, and apical long axis views. Imaging settings were optimized at the time of acquisition to ensure the best endocardial visualization. Harmonic imaging was used

for all studies. Treadmill exercise stress testing was then performed using the standard Bruce Protocol. Heart rate, blood pressure, and 12-lead ECG were monitored throughout the exercise test. All volunteers exercised to at least 85% of maximal predicted heart rate with termination of exercise determined by volunteer fatigue. At completion of exercise, the volunteer quickly returned to the echocardiography bed for peak stress imaging in the same planes acquired at rest. An echocardiography bed drop out was used to improve image acquisition. Stress echo studies were done in a research lab where the treadmill was placed approximately 7 feet from the ultrasound machine. Timing to begin and complete imaging from the cessation of exercise was recorded. Contrast enhancement was not used in this study.

Image Analysis

A blinded reviewer (>5 years experience reading stress echo and cardiac MR) independently reviewed de-identified cardiac MR and echo images separately in a random fashion. Each modality was reviewed without knowledge of the results of the other modality. For all 17 myocardial segments, the reviewer coded adequacy of endocardial visualization at rest and peak stress into 5 categories: 1 = adequate or excellent endocardial visualization, 2 = incomplete endocardial border visualization, 3 = epicardial border only, 4 = not visible (correct view, but not seen) and 5 = not obtained (out of plane or foreshortened)(9). The interpretation was based on integration of all available views. When a segment was visualized from more than one view, the best visualization scores were used. The reviewer also provided a global confidence of interpretation score for each stress study: 1 = high, 2 = medium, 3 = low. This was based on the reviewer's confidence that *all* segments of all coronary territories were sufficiently assessed for the study to be reported as normal. Endocardial visualization index was calculated for each subject as the number of segments with endocardial visualization score of 1 divided by the total number of segments adequately acquired (i.e. all segments with scores 1–3)(27,28).

Statistical Analysis

Continuous data with a normal distribution are expressed as mean $\pm$ SD, and non-normally distributed data as median (range). Categorical data are expressed as frequency or percentage. All data were tested for normality using the Kolmogorov-Smirnov test and an evaluation of histograms and normal quantile-quantile (q-q) plots (a probability plot that is used to compare ordered variable values from a parameter with quantiles of a normal distribution). Student's paired t-test (for normally distributed data) or Wilcoxon signed-rank test (for non-normally distributed data) was used to compare parameters between echo and cardiac MR. Global confidence scores were compared between echo and cardiac MR using the Wilcoxon Signed Rank test. The statistical analysis of continuous outcomes was performed using MedCalc (11.4.2.0, Mariakerke, Belgium).

Results

Study Population and Exercise Data

A total of 28 volunteers (age 28 ± 11 years, 15 males) were included. One volunteer had controlled hypertension. No other cardiac risk factors were present in any of the volunteers. Timing, hemodynamic, and exercise parameters are summarized in the Table 1. The hemodynamics were comparable between the two tests. Although the peak heart rate was marginally higher in the echo study, the HR at the time of image acquisition was similar between the studies. The latter is likely a reflection of the fact that the time from cessation of exercise to image acquisition was longer with stress echo (21 vs. 31 seconds, $p < 0.001$). The time to complete imaging (from cessation of exercise) was shorter for stress cardiac MR

compared to echocardiography (20 vs. 51 seconds $p < 0.001$). The exercise ECG was of diagnostic quality in all volunteers for both tests and was negative for ischemia in all.

Endocardial Visualization

The frame rate for echo images at rest was 64 ± 10 frames per second (fps), while at peak stress it was 59 ± 12 fps. Adequate images for analysis were obtained for all subjects with both stress echocardiography and cardiac MR. A case example of rest and peak stress echo and cardiac MR images in one volunteer is illustrated in Figure 1 and in the video files included as Supporting Information. The percentage of segments with an endocardial visualization score of 1 both at rest and peak stress for both modalities is illustrated in Figure 2. A greater proportion of segments had adequate or excellent endocardial visualization by cardiac MR compared to echocardiography at both rest (99.8% versus 96.4%, $p = 0.002$) and peak stress (99.8% versus 94.1%, $p = 0.001$). The median (range) number of segments inadequately visualized at rest and stress by echo were 1 (1–4) and 2 (1–6), respectively, while by cardiac MR it was one segment in one subject at both rest and stress. The mean $\pm$ SD endocardial visualization index at stress for echo and cardiac MR were 0.94 ± 0.10 and 1.0 ± 0.01 , respectively ($p = 0.001$).

Amongst the included subjects, three had at least two myocardial segments inadequately visualized on rest echocardiography images. As per American Society of Echocardiography (ASE) guidelines, these subjects would meet criteria for contrast administration for endocardial border definition(6). Therefore we re-analyzed the number of segments with endocardial visualizations score of 1 at peak stress with these subjects excluded. There was still a significant difference between the two techniques in the number of segments with a score of 1 (96.2% versus 99.8%, $p = 0.008$).

Confidence of Interpretation

The confidence of interpretation of the entire stress study is summarized in Figure 3. With cardiac MR the proportion of subjects in whom the interpretation was possible with medium or high confidence was significantly higher compared to stress echo ($p = 0.001$). With the 3 subjects who would have met criteria for contrast administration with echocardiography removed, the confidence of interpretation was still higher with stress cardiac MR ($p = 0.008$). With stress echo, amongst the patients with low confidence of interpretation at peak stress, 3 out of 4 had good quality resting echocardiography images. In the 4th patient the image quality was limited at rest with 4 segments inadequately visualized, however, at peak stress several additional segments could not be sufficiently assessed.

Discussion

The present study demonstrates the feasibility of exercise stress cardiac MR for assessment of peak stress wall motion. In a group of healthy volunteers the stress ECG was diagnostic in all subjects, image acquisition was initiated as quickly as with stress echo, and the image acquisition was completed within a shorter time span. The adequacy of endocardial visualization was better with cardiac MR compared to echo both at rest and at peak stress. Finally, the confidence in interpretation of the stress study was higher with stress cardiac MR.

In our study, exercise stress cardiac MR was successfully completed in all subjects. The ECG recording was of diagnostic quality for assessment of ST segments and arrhythmias in all subjects; this result is consistent with previous work illustrating that when exercising at least 80cm from the MRI magnet bore entrance the ECG recordings are not affected(29). An important component of exercise stress testing is to initiate stress imaging immediately after

peak exercise to ensure that peak stress wall motion abnormalities are captured. Our time to start peak stress imaging was comparable to a previous publication using the same treadmill setup with healthy volunteers (21 versus 24 seconds)(25) and to the time required to start stress echocardiography imaging (31 s) in this study. The longer timing to initiate imaging with stress echo was a reflection of our treadmill setup. In the clinical setting where the treadmill is adjacent to ultrasound system, the patient usually quickly moves directly from the treadmill to the bed to initiate imaging, allowing imaging to be started well within 20 seconds of peak exercise. However, with our setup the volunteer had to wait for the treadmill to stop, walk from the treadmill to the bed, lie down and be re-positioned before initiation of imaging. Since the HR at the time of image initiation was similar between the two modalities, this does not affect our imaging findings; however, the time to initiate echo imaging in practice would be significantly less than the 31 s found in this study.

The time to acquire stress images was significantly shorter for stress cardiac MR (20 versus 51 seconds, $p < 0.001$) than for stress echo, and the total time to start and complete imaging after exercise ($21 \text{ s} + 20 \text{ s} = 41 \text{ s}$) was well within the stress echo guidelines for timing of image acquisition(30,31). The time to acquire stress echo images was longer than that often seen in clinical practice due to several factors. First, for the comparison with cardiac MRI we obtained more views of the ventricle (3 long axis and 3 short axis images) than would be typical for a clinical scan; second, since these were young healthy volunteers, heart rates and respiratory rates at peak stress were higher than may be encountered in typical patients, requiring greater time to obtain the correct planes to start imaging; and finally, we were extremely meticulous in our imaging to ensure that we obtained the best quality images for comparison with cardiac MR.

Our endocardial visualization data can be compared to a recent randomized cross-over study of patients with suspected CAD who had stress echo both with and without contrast administration(9). In this study from an experienced center, up to 28% of myocardial segments at rest and 33% at peak stress were inadequately visualized resulting in low confidence in interpretation of the stress echo study in up to 28% of the patients(9). The administration of contrast agents for endocardial border definition significantly improved the number of segments adequately visualized both at rest and stress increasing the confidence of interpretation of the reader. In comparison, in our study of healthy volunteers, suboptimal endocardial visualization with stress echo was only seen in 3.6% of the segments at rest and 5.9% of the segments at peak stress resulting in low confidence of interpretation in only 14%. This discrepancy likely reflects the fact that our study consisted of young healthy volunteers with generally good image quality. However, similar to the effect of contrast administration in the study by Plana et al(9), cardiac MR provided excellent endocardial visualization in all the volunteers with suboptimal quality in only 0.2% of the segments both at rest and peak stress. Cardiac MR also resulted in a high level of confidence in interpretation of the stress study in all but one subject. This is higher (96% versus 74%) than the improvement in confidence seen with contrast administration in stress echo in the study by Plana et al(9).

With ongoing improvement in echo technology it is necessary to consider whether the effort invested in performing stress cardiac MR will provide additional clinical benefit. Although our study was focused on the assessment of peak stress wall motion, stress cardiac MR can also provide, in a single study, assessment of peak stress myocardial perfusion and high resolution assessment of myocardial scar with the administration of gadolinium contrast agents(22,23). Therefore an integrated stress cardiac MR exam with peak stress wall motion, myocardial perfusion, and scar assessment likely affords a more accurate assessment of coronary artery disease. This, however, needs to be tested formally in a larger cohort of patients with suspected CAD. Also, although the difference in endocardial visualization and

confidence scores were small between the two modalities, in patients this difference is likely to be larger as those with suspected CAD also tend to be overweight and have lung disease both of which affect echo windows. Therefore, the expected benefit of cardiac MR in a patient population is likely to be even higher.

Our work comparing exercise stress cardiac CMR to echo is unique when compared to several previous publications comparing chemical stress cardiac MR to echo(2,4,11,17,32). Since the patients have to come off the cardiac MR table for exercise, the need to get the patient back into the exact same position to obtain comparable post exercise image is a unique challenge. Furthermore, exercise results in significant respiratory motion that can impact peak stress imaging. Neither of these are a concern with chemical stress cardiac MR. Therefore data from chemical stress cardiac MR with respect to endocardial visualization cannot be translated to exercise CMR. Finally we have unique exercise data as well as peak stress ECGs which are not available with chemical stress cardiac MR.

Limitations

Despite the potential benefits with exercise cardiac MR stress testing, there will remain a proportion of patients who will be unable to undergo treadmill exercise stress due to physical limitations. Pharmacological stress cardiac MR will remain a good alternative in these patients. We did not administer contrast agents for left ventricular opacification as we wanted to compare stress echo as it is performed at most centers. However, given the criteria for contrast administration suggested in the ASE guidelines only 3 volunteers would have met the criteria for contrast administration(6,33). Despite removing these subjects from the analysis the endocardial visualization and confidence of interpretation remained higher with stress cardiac MR.

Although our results are encouraging, our data is based on a small sample of healthy subjects, and further validation is necessary in a large cohort of patients. This study was performed as a pilot study to compare stresses cardiac MR to stress echo for feasibility, endocardial wall visualization, and confidence of interpretation. As a consequence, we are also unable to provide data on the differences in diagnostic benefit of cardiac MR compared to echo or meaningful cost/benefit comparison. Therefore, the next step would be to assess the overall diagnostic benefit of stress cardiac MR in comparison to stress echo in patients with suspected CAD. This, however, does not compromise our study's significance as we provide important information about feasibility which is an important step prior to studying patients with suspected CAD.

In conclusion, exercise stress Cardiac MR is feasible and can be performed as rapidly as stress echo. Stress Cardiac MR was superior to echo in adequacy of endocardial wall assessment and confidence of study interpretation. The potential superiority of stress Cardiac MR for ischemia detection requires formal evaluation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Illustration of echocardiography and cardiac MR images from one volunteer. Panels A and B are rest diastolic and systolic frames. The anterior lateral wall was not adequately seen both in systole and diastole but is clearly seen in the corresponding cardiac MR slice positions (Panels E and F). At peak stress (Panels C and D) the echocardiographic endocardial walls were difficult to assess in multiple segments while all segments were clearly seen on cardiac MR images (Panels G and H). Heart rate at time of peak images was 162 for echocardiography and 155 for cardiac MR. Cardiac MR and echocardiography images from this same subject are shown in accompanying video files.

Figure 2.

Comparison of the proportion of myocardial segments with adequate endocardial visualization (score 1) between echocardiography and cardiac MR both at rest and peak stress. Although small, with cardiac MR there was a higher percentage of segments with excellent or adequate endocardial visualization (score 1) both at rest and peak stress.

*($p < 0.05$ for comparison of cardiac MR versus echo).

Figure 3.

Comparison of confidence of interpretation of the entire stress study by cardiac MR versus echocardiography. The distribution of the degree of confidence (low, medium, or high) of interpretation was different between the methods with a larger proportion of studies interpreted with higher confidence with cardiac MR compared to echocardiography.

Table 1

Patient demographics and exercise stress data.

	Stress Echocardiography	Stress cardiac MR	p value*
Resting Variables			
HR, bpm	73 ± 12	74 ± 13	0.7
Systolic BP, mmHg	117 ± 16	111 ± 13	0.05
Diastolic BP, mmHg	71 ± 8	70 ± 9	0.5
Exercise Variables			
Exercise duration, mins	11.6 ± 2.2	11.1 ± 2.3	0.07
METs	13.6 ± 2.5	13.0 ± 2.7	0.08
Peak HR, bpm	181 (143–199)	173 (146–196)	0.01 [†]
Peak systolic BP, mmHg	155 ± 19	158 ± 19	0.3
Peak diastolic BP, mmHg	70 (60–98)	79 (60–90)	0.002 [†]
Time to start stress imaging, seconds	31 ± 6	21 ± 2	< 0.001
HR at time of peak cine images, bpm	150 ± 16	148 ± 14	0.7 [†]
Time to complete stress imaging, seconds[‡]	51 ± 9	20 ± 2	< 0.001

* paired t test unless specified;

[†] Wilcoxon Rank Sum Test for paired data,[‡] Corresponds to the duration of imaging.

HR, heart rate; bpm, beats per minute; BP, blood pressure; mmHg, millimeters of mercury; min, minutes; cardiac MR, cardiac magnetic resonance imaging; METs, metabolic equivalent.