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Patient Outcome Following 2 Different Stress Imaging Approaches

A Prospective Randomized Comparison

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Objectives The study sought to prospectively compare patient outcome after stress real-time myocardial contrast echocardiography (RTMCE) versus conventional stress echo (CSE), where contrast is used to optimize wall motion (WM) analysis.

Background Myocardial perfusion imaging with RTMCE may improve the detection of coronary artery disease (CAD), and predict patient outcome.

Methods Patients with intermediate to high pre-test probability referred for dobutamine or exercise stress echocardiography were prospectively randomized to either RTMCE or CSE. Definity contrast was used for CSE only when endocardial border delineation was inadequate (63% of studies). Studies were interpreted by either an experienced contrast reviewer (R1; n = 1257), or 4 Level 3 echocardiographers (R2) with basic contrast training (n = 806). Death, nonfatal myocardial infarction (MI), and revascularizations were recorded at follow-up.

Results Follow-up was available in 2,014 patients (median 2.6 years). Mean age was 59 ± 13 years (53% women). An abnormal RTMCE was more frequently observed than an abnormal CSE ($p < 0.001$), and more frequently resulted in revascularization ($p = 0.004$). Resting WM abnormalities were also more frequently seen with RTMCE ($p < 0.01$), and were an independent predictor of death/nonfatal MI ($p = 0.005$) for RTMCE, but not CSE. The predictive value of a positive study, whether with CSE or RTMCE, was significant for both R1 and R2 reviewers in predicting the combined endpoint, but R1 was better than R2 at predicting patients at risk for death or nonfatal MI.

Conclusions Perfusion imaging with RTMCE improves the detection of CAD during stress echocardiography, and identifies those more likely to undergo revascularization following an abnormal study. (J Am Coll Cardiol 2013;61:2446–55)

Real-time myocardial contrast echocardiography (RTMCE) is a technique that allows for the simultaneous analysis of myocardial perfusion and wall motion during stress echocardiography (1–3). Retrospective studies have shown that myocardial perfusion data obtained with RTMCE may be incremental to wall motion analysis in detecting coronary artery disease (CAD), and improve the predictive value of the test (4–8). However, these studies may have been hampered by selection bias, and the inability to accurately determine what effect a normal or abnormal study has on subsequent revascularization rate. There have been no prospective randomized studies to date examining the effect of 1 stress imaging modality versus another in predicting patient outcome. Therefore, in this study, we prospectively compared RTMCE to conventional stress echocardiography (CSE) in patients presenting for suspicion of CAD, to determine whether the differences in test performance for detecting CAD lead to differences in the rate of angiography and revascularization, as well as predicting death or nonfatal myocardial infarction (MI). Secondly, we determined what effect training experience with contrast imaging had on the predictive value of either CSE or RTMCE.

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Methods

Study population. Consecutive patients referred to the echocardiography laboratory at the University of Nebraska Medical Center between 2007 and 2011 were asked to participate in the study if they were considered to have intermediate to high pre-test probability for CAD, and scored between 7 and 9 for appropriateness indications for stress echocardiography (9). This included both outpatient and inpatient subjects who were admitted for chest pain or shortness of breath with normal or equivocal troponin values. Exclusion criteria included those with known hypersensitivity to contrast agents, low pre-test probability of CAD, pregnancy or breastfeeding, or ventricular paced rhythm. All patients gave written informed consent, and the study protocol was approved by the University of Nebraska Medical Center Institutional Review Board. Those who consented to participate in the study were randomized, using an internet-based site, to undergo either CSE or RTMCE as their imaging technique (NCT00575549).

A total of 4 experienced stress echo readers who had Level III training in the performance and interpretation of echocardiography using 2008 COCATS (Core Cardiology Training Symposium) guidelines (10), and who had interpreted over 100 CSE and RTMCE studies with contrast, served as 1 group of reviewers (R2), and were compared with a Level III echo-trained physician who had interpreted over 1,000 contrast studies (R1). All interpreting physicians had access to clinical indications, and were aware of patient risk factors at the time of their interpretations.

Imaging techniques with contrast. The contrast agent used for the study was the commercially available lipid encapsulated microbubble, Definity (Lantheus Medical Imaging, North Billerica, Massachusetts). This agent was administered as a 3% intravenous continuous infusion at 4 to 6 ml/min under resting conditions and during stress. RTMCE was performed using ultrasound scanners equipped with low-mechanical index real-time pulse sequence schemes (4–8). This utilized a mechanical index of <0.2, frame rates of 20 to 25 Hz, time gain compensation higher in the near field, focus at the mitral valve plane or below, and overall gain settings adjusted so that brief high mechanical index impulses clear the myocardial segments of any signals. For CSE, Definity contrast was administered only when 2 contiguous segments could not be visualized, as recommended by the 2008 American Society of Echocardiography guidelines (8).

The decision to perform dobutamine or exercise treadmill stress echocardiography was made by the referring physician. In either case, patients were instructed to discontinue beta-blocker drugs at least 24 h prior to the stress test. Patients undergoing treadmill stress underwent maximal symptom-limited exercise according to the Bruce protocol. Patients undergoing dobutamine stress echocardiography (DSE) received intravenous dobutamine infusion at a starting dose of 5 μ/kg/min, followed by increasing doses of 10, 20, 30, 40, up to a maximal dose of 50 μ/kg/min, in 3- to 5-min stages. Atropine (up to 2.0 mg) was injected in patients not achieving 85% of the predicted maximal heart rate. Subsequent angiograms and revascularizations (percutaneous coronary interventions or coronary bypass surgery) were performed if clinically indicated in the judgment of the referring cardiologist, who had access to the results of the stress echocardiogram. A >50% diameter stenosis at angiography was considered a significant stenosis.

Abbreviations and Acronyms

CAD = coronary artery disease

CSE = conventional stress echocardiography

DSE = dobutamine stress echocardiography

EFS = event-free survival

MI = myocardial infarction

RTMCE = real-time myocardial contrast echocardiography

WM = wall motion

Image analysis. All studies were analyzed by the reviewer at the time of the study. Perfusion and wall motion (WM) were both assessed using a 17-segment model (11). In the CSE arm, the reviewers had access to at least 2 clips of cardiac cycles obtained at or following peak stress, to compare side by side with at least 1 cardiac cycle of resting images in both parasternal and apical windows. These digitized loops of the 3 apical windows were displayed side by side for rest and stress comparisons. For RTMCE, both perfusion and WM were analyzed simultaneously during the replenishment phase of contrast following brief high mechanical index impulses as previously described (12), at baseline and at or following peak stress. For CSE, WM was analyzed (with or without the aid of enhanced border delineation with contrast) at baseline and at or following peak stress. If resting WM abnormalities were present, stress images were compared with the low dose dobutamine images (10 μg/kg/min) to assess whether the abnormalities were fixed or inducible. With treadmill exercise, ischemia was considered present (instead of infarction) only if hypokinesis (at rest) became akinesis during stress. Studies were considered abnormal if either fixed or inducible abnormalities were present.

Data and safety monitoring plan. Formal interim monitoring of the study was to be done 3 times, after approximately 33%, 66%, and 100% of the expected enrollment with sequential boundaries determined using The O'Brien-Fleming spending function (13,14). This was conducted by an independent 3-member Data and Safety Monitoring Committee.

Statistical analysis. The primary outcome was event-free survival (EFS), defined as the time to death, nonfatal MI, or revascularization. Nonfatal MI was defined as a presentation with chest discomfort or shortness of breath associated with a serial troponin elevation or ST segment elevation in 2 contiguous leads. The anticipated total number of subjects to be enrolled was 3,000, as it was pre-determined that this sample size would achieve 90% power to detect a hazard rate of 0.66 when the proportion who are alive and free of nonfatal MI are 0.90 and 0.93 using a 2-sided log-rank test. Patient characteristics were descriptively summarized for each group, and compared with chi-square tests, or *t* tests as appropriate. In order to determine what effect revascularization had on other outcomes, it was analyzed not only as a separate endpoint, but also as a time-dependent covariate using only death and nonfatal MI as endpoints. Survival distributions were estimated following the method of Kaplan and Meier and compared using the log-rank test. Cox proportional hazards regression was conducted to look for univariate predictors of death+nonfatal MI. Most of the variables included in the multivariate analysis were highly correlated, so a backward selected model was also performed, with an alpha of 0.10 and forcing techniques to stay in the model.

Results

As required by our Data Safety and Monitoring Board, we performed an interim analysis after enrollment of 66% of the patients (2,063 total patients), which indicated the outcome of patients undergoing CSE versus RTMCE would not be different for death or nonfatal MI, but would be different for the combined endpoint of death, nonfatal MI, and revascularization.

Table 1 presents the demographic data of the patients included in the study. Patients in each group were similar with respect to age, gender, prevalence of hypertension, diabetes, and smoking. There was a slight, but significant, 1% higher ejection fraction in the CSE group. Hyperlipidemia and use of beta-blockers prior to the stress test were more common in the RTMCE group, and more patients in the RTMCE group had prior percutaneous coronary intervention and remote history of MI.

Dobutamine and exercise stress test hemodynamics. During DSE, the average increase in heart rate and systolic blood pressure was not different between CSE and RTMCE groups (Table 2), and there were no differences in those who failed to attain 85% of their target heart rate. Patients randomized to RTMCE had a higher incidence of ventricular arrhythmias and more frequently experienced chest pain at peak stress (both p values <0.05 compared with CSE). These arrhythmias were isolated premature atrial or ventricular contractions, and occurred following the brief high mechanical index pulse used to clear contrast from the myocardium. Abnormal EKG responses (>0.1 mV ST-segment depression) were seen in 22% of abnormal CSE studies, 28% of abnormal RTMCE studies, 9.6% of normal CSE studies, and 8% of normal RTMCE studies.

Effect of contrast use on image interpretation in the CSE and RTMCE groups. A total of 655 patients (63%) in the CSE group received contrast to optimize WM detection. The abnormal rate in the CSE group was not different in patients that received contrast (22% abnormal) versus those that did not (21% abnormal). Of the 310 abnormal RTMCE studies, 31 (10%) were abnormal for perfusion only (WM normal), while the remainder were read as both abnormal WM and perfusion.

The number of patients who had resting WM abnormalities was higher in the RTMCE group (13%) compared with the CSE group (9%; $p = 0.004$). The resting WM abnormality in the RTMCE was accompanied by a resting perfusion defect in 110 patients (75%), which aided in delineating a subendocardial resting WM abnormality. Patients who randomized to RTMCE were more likely to have abnormal stress studies (30% vs. 22% for CSE; $p < 0.001$). The pattern of abnormality (single- vs. multivessel territory) was also more likely to be multivessel in the patients randomized to RTMCE (39% vs. 26% of CSE studies; $p < 0.001$).

Angiographic and revascularization outcomes of CSE versus RTMCE. A total of 145 of the 310 patients (47%) with abnormal RTMCE, and 81 of 226 abnormal CSE studies (36%), proceeded to heart catheterization following abnormal studies. Proceeding to angiography after an abnormal CSE or RTMCE was not a predictor of death or nonfatal MI in these patients. Coronary angiography demonstrated at least 1 >50% obstructive lesion in 1 of the 3 major epicardial vessels in 112 of the RTMCE cases (positive predictive value 77%) and 59 of the CSE cases (positive predictive value 73%). However, the number of revascularizations was more frequent following an abnormal RTMCE study (26% of all abnormal studies) than following an abnormal CSE study (15% of all abnormal studies; $p < 0.001$ compared with RTMCE). Of the 81 revascularizations following an abnormal RTMCE, 55 were percutaneous revascularizations, and 26 were coronary bypass procedures. Of the 33 revascularizations following an abnormal CSE, 21 were percutaneous and 12 were coronary bypass procedures.

Predictive value of CSE versus RTMCE. Figure 1 demonstrates the consolidated standards and reporting trials diagram, which includes the outcomes for the patients randomized to CSE or RTMCE. Of the 2,063 patients enrolled on the study, 2,014 have follow-up data. There were 84 (4.1%) deaths, 20 (1%) nonfatal MIs, and 142 revascularizations (7.0%) over the follow-up period. The range of troponin elevations in the nonfatal MI patients was 0.12 to 12.87 ng/ml. Of the 142 patients that were revascularized, 6 (4.1%) subsequently died and 4 (2.7%) had an MI, and thus the death/nonfatal MI rate in the revascularized group alone was 10 of 142 (7.0%).

There were 1,979 alive at last contact with a median follow-up of 2.6 years (range 0 to 4.3 years). Overall, the event rate for death or nonfatal MI was 104 (5.2%) of the 2,014 patients with follow-up data. As shown in Figure 2, death and nonfatal MI rates were significantly higher in patients with abnormal studies by CSE or RTMCE when compared with normal studies. There was no difference in death/nonfatal MI rates in the RTMCE group in those with perfusion defects only (6.5%) versus those with both perfusion defects and wall motion abnormalities (7.2%).

When considering the combined endpoint of death, nonfatal MI, and subsequent revascularization, the predictive

Table 1 Baseline Characteristics All Patients (n = 2,063)

	Total (N = 2,063)	CSE (n = 1,035)	RTMCE (n = 1,028)	p Value
Age, yrs	59.6 ± 12.5	59.4 ± 12.8	59.8 ± 12.2	0.43
Sex				
Female	1,069 (52%)	544 (53%)	525 (51%)	0.50
Male	994 (48%)	491 (47%)	503 (49%)	
Family history of CAD				
No	1,375 (67%)	691 (67%)	684 (67%)	0.91
Yes	688 (33%)	344 (33%)	344 (33%)	
Smoking status				
Current	469 (23%)	230 (22%)	239 (23%)	0.84
Former	243 (12%)	124 (12%)	119 (12%)	
Never	1,351 (65%)	681 (66%)	670 (65%)	
Hyperlipidemia				
No	951 (46%)	506 (49%)	445 (43%)	0.011
Yes	1,112 (54%)	529 (51%)	583 (57%)	
Diabetes				
No	1,530 (74%)	773 (75%)	757 (74%)	0.59
Yes	533 (26%)	262 (25%)	271 (26%)	
HTN				
No	795 (39%)	407 (39%)	388 (38%)	0.46
Yes	1,268 (61%)	628 (61%)	640 (62%)	
Previous PTCA				
No	1,822 (88%)	936 (90%)	886 (86%)	0.0027
Yes	241 (12%)	99 (10%)	142 (14%)	
Previous CABG				
No	1,901 (92%)	956 (92%)	945 (92%)	0.71
Yes	162 (8%)	79 (8%)	83 (8%)	
Previous MI				
No	1,871 (91%)	951 (92%)	920 (89%)	0.062
Yes	192 (9%)	84 (8%)	108 (11%)	
Ejection fraction	59.4 ± 9.2	60.2 ± 9.0	58.6 ± 9.3	<0.001
Antiplatelet (clopidogrel)				
No	1,945 (94%)	982 (95%)	963 (94%)	0.24
Yes	118 (6%)	53 (5%)	65 (6%)	
Beta-blockers				
No	1,230 (60%)	641 (62%)	589 (57%)	0.032
Yes	833 (40%)	394 (38%)	439 (43%)	
ACE inhibitors or ARB				
No	1,454 (70%)	728 (70%)	726 (71%)	0.89
Yes	609 (30%)	307 (30%)	302 (29%)	
Aspirin				
No	1,314 (64%)	669 (65%)	645 (63%)	0.37
Yes	749 (36%)	366 (35%)	383 (37%)	
Test result				
Normal result	1,518 (74%)	803 (78%)	715 (69%)	<0.001
Abnormal result	536 (26%)	226 (22%)	310 (30%)	
Incomplete test	9 (0.4%)	6 (0.6%)	3 (0.3%)	
More experienced reviewer				
Yes	1,257 (61%)	618 (60%)	639 (62%)	0.25
No	806 (39%)	417 (40%)	389 (38%)	

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CSE = conventional stress echocardiography; HTN = hypertension; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; RTMCE = real-time myocardial contrast echocardiography.

value of a negative CSE and negative RTMCE was the same, but this combined endpoint was significantly higher in patients with an abnormal RTMCE (Fig. 3). Most of these revascularizations (60 following RTMCE and 21 following CSE) were within 90 days of the stress echocardiogram. Three-year EFS (death and nonfatal MI only),

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Table 2 Hemodynamic Variables With Stress

Variable	DSE			ESE			Overall		
	RTMCE (n = 627)	CSE (n = 587)	p Value	RTMCE (n = 401)	CSE (n = 448)	p Value	RTMCE (n = 1,028)	CSE (n = 1,035)	p Value
Arrhythmias	32.6	30.3	0.42	22.1	15.7	0.02	28.5	24.0	0.02
Chest pain	15.6	10.9	0.02	7.7	6.9	0.75	12.5	9.2	0.02
Dyspnea	1.1	1.1	0.78	10.7	10.3	0.94	4.9	5.1	0.91
Conduction Abnormality at stress	3.8	3.9	0.95	2.0	2.2	0.97	3.1	3.2	1.00
Peak systolic BP, mm Hg	151 ± 34	154 ± 30	0.10	152 ± 20	153 ± 19	0.46	152 ± 29	153 ± 26	0.41
Peak diastolic BP, mm Hg	67 ± 19	68 ± 19	0.36	81 ± 8	82 ± 9	0.09	73 ± 17	74 ± 17	0.18
Peak heart rate	143 ± 13	143 ± 14	1.00	155 ± 21	155 ± 22	1.00	148 ± 18	149 ± 19	0.22
Percentage of maximal predicted heart rate, %	90 ± 11	91 ± 10	0.10	97 ± 46	94 ± 11	0.18	93 ± 30	92 ± 10	0.31
Rate-pressure product	21,323 ± 4,975	21,651 ± 5,290	0.27	23,783 ± 5,326	23,579 ± 4,929	0.56	22,162 ± 5,223	22,540 ± 5,211	0.10

Values are % or mean ± SD.
BP = blood pressure; DSE = dobutamine stress echocardiography; ESE = exercise stress echocardiography; other abbreviations as in Table 1.

when using revascularization as a time-dependent covariate, was 90.0% after an abnormal RTMCE, and 91.2 % after an abnormal CSE (not significant), and negative studies in this context had similar 3-year EFS (96.2% following a negative RTMCE and 95.2% following a negative CSE). In patients with prior CAD, there were no difference in death, nonfatal MI, or subsequent revascularization rates following normal CSE or RTMCE studies, but these rates were significantly higher following abnormal RTMCE studies compared with abnormal CSE studies ($p = 0.026$). In patients with no prior CAD, these rates also trended higher following abnormal RTMCE studies ($p = 0.11$).

Death or nonfatal MI following abnormal CSE or RTMCE studies were significantly higher when the experienced reviewer (R1) read a study as abnormal versus normal, but were not significantly different with less experienced R2 reviewers (Fig. 4). However, when looking at the combined endpoint of death, nonfatal MI, and subsequent revascularization; abnormal and normal studies read by R1 versus R2 reviewers had equivalent predictive value.

Univariate and multivariate predictors of death and nonfatal MI in CSE versus RTMCE groups. When combining CSE and RTMCE patients, the univariate predictors of death or nonfatal MI included test result, prior revascularization, and presence of a resting wall motion abnormality (Table 3). Online Table 1 for shows the confidence intervals. A resting WM abnormality was the only multivariate predictor of events in all patients. Overall, the 3-year event rates were 7.6% in the patients who had a multivessel pattern of abnormality (82% of which were in the RTMCE group), 4.2% in patients with a single-vessel distribution abnormality (79% of which were in the CSE group) and 4.2% in the normal studies ($p = 0.029$ comparing multivessel pattern to normal or single-vessel pattern).

In the CSE patients alone, there were no univariate or multivariate predictors of death or nonfatal MI (Table 4). See Online Tables 2A and 2B for confidence intervals. This model included age, prior revascularization, clinical risk factors, presence of a resting WM abnormality, test result, and extent of abnormal result. In patients randomized to RTMCE, only the presence of a resting wall motion abnormality was a significant univariate and multivariate predictor of death or nonfatal MI (Fig. 5). When the CSE patients that received contrast and those that did not were analyzed separately, resting WM abnormalities were still not predictive of death or nonfatal MI in either group.

Discussion

This is the first prospective randomized trial to examine the clinical outcome of patients after 2 different imaging approaches for pharmacologic or exercise stress. Retrospective studies have shown that perfusion information obtained during demand stress improves the predictive value of DSE for predicting death and nonfatal MI (4,15). Unlike retrospective studies examining the predictive value of 1

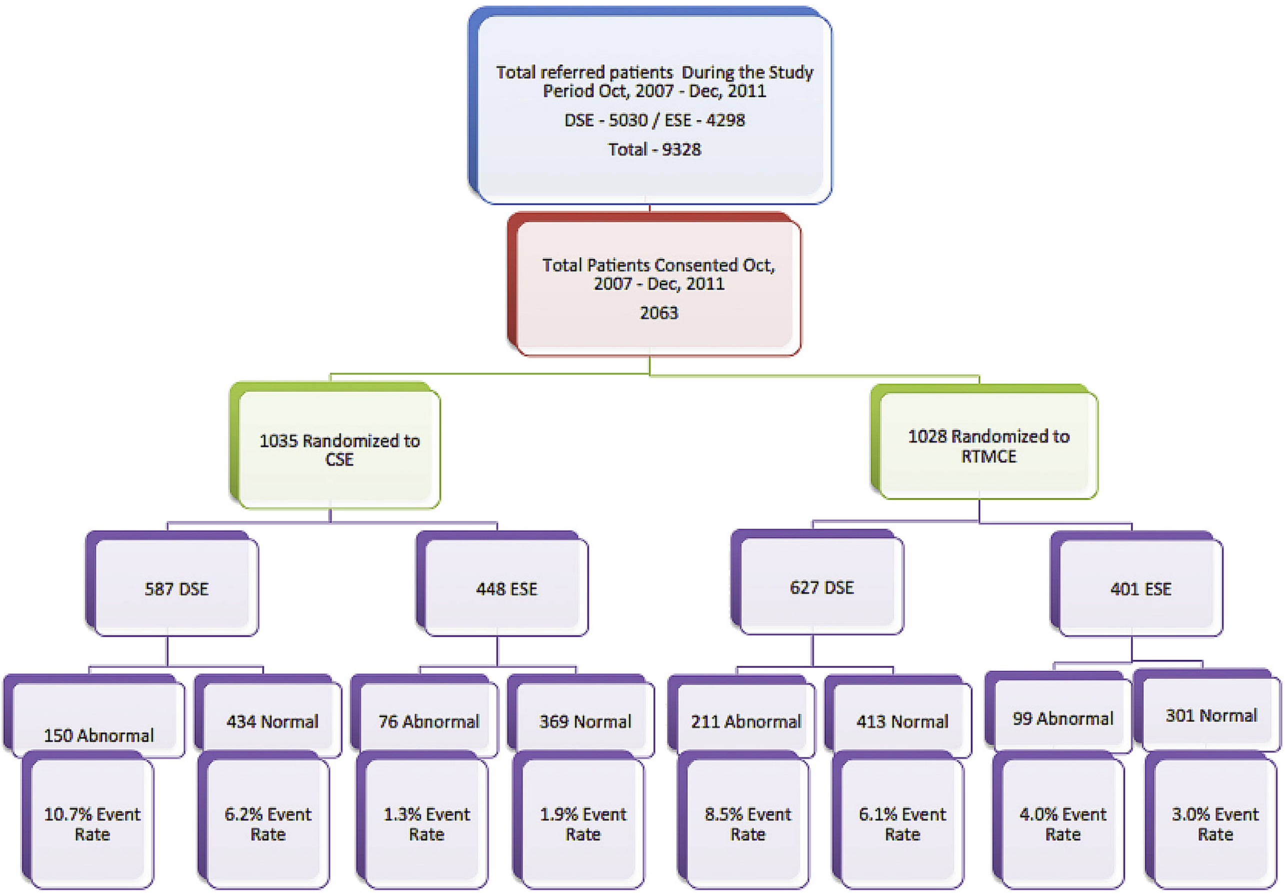

Figure 1 Consolidated Reporting Diagram

The consolidated standards and reporting trials diagram showing the number of patients referred to the University of Nebraska Echocardiography Laboratory during the study period, and those who consented to participate. Their subsequent randomized assignments, and outcomes, are shown. CSE = conventional stress echocardiography; DSE = dobutamine stress echocardiography; ESE = exercise stress echocardiography; RTMCE = real-time myocardial contrast echocardiography

imaging modality, the current study examined the value of 2 optimized imaging approaches in predicting patient outcome. This allows one to examine both the ability of the test to identify those who will eventually need revascularization, as well as predict death or nonfatal MI. In this context, death, nonfatal MI, and revascularization numbers were significantly higher following an abnormal RTMCE versus abnormal CSE study.

Previous retrospective studies examining the predictive value of 1 particular imaging technique (stress echo or stress radionuclide imaging) have had difficulties in assessing the predictive value of abnormal (or positive) studies, because revascularizations occurring after the stress study resulted in either patient exclusion or censoring at the time of the revascularization (4–6,16). However, radionuclide stress perfusion studies have demonstrated that subsequent revascularization after a stress test significantly impacts the rate of death or nonfatal MI, especially as the extent of inducible ischemia increases (17,18). In the current study, the RTMCE arm had a higher abnormalcy rate and a higher frequency of inducible ischemia in a multi-vessel pattern. This may have led to significantly higher revascularization rates following angiography in RTMCE patients, despite similar positive predictive values in detecting a coronary stenosis. Therefore, the higher number of abnormal studies in the RTMCE group may have helped in identifying patients most likely to benefit prognostically from revascularization, and explain the similar death or nonfatal MI rates following abnormal CSE versus RTMCE studies. These differences may have also been found if quality of life measures were assessed in the different patient populations.

Conversely, a negative test (CSE or RTMCE) in predicting hard events was excellent in this intermediate risk patient population, with 3-year event rates of <5%, similar to previous studies (4,5). Revascularizations were much less likely to occur in these groups, with a death, nonfatal MI, or revascularization rate of <2.5% per year. Because revascularizations in the setting of a negative study would most likely be for acute

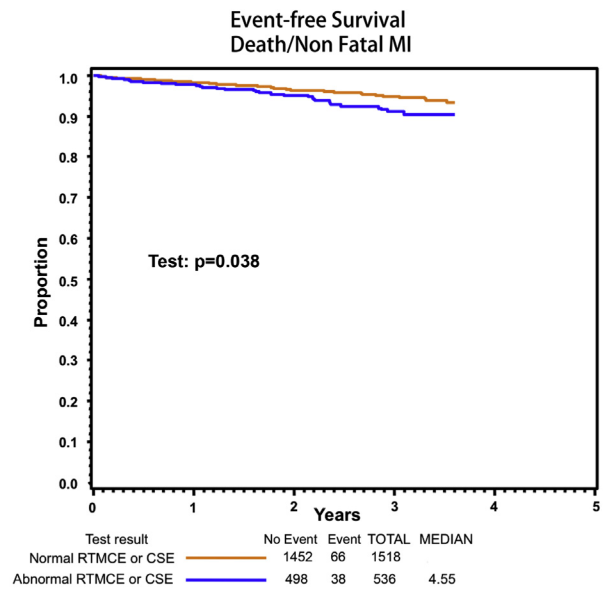

Figure 2 **Overall Event-Free Survival**

Event-free survival (death or nonfatal myocardial infarction [MI]) in patients with an abnormal stress echo (conventional stress echocardiography [CSE] or real-time myocardial contrast echocardiography [RTMCE]) versus those with a normal result.

coronary syndrome or medically refractory symptoms, a negative study by either imaging technique appears to identify a patient at much lower risk for this clinical scenario.

Although one would assume that CSE should be better for detecting resting WM abnormalities due to the higher frame rate to detect tardokinesis (19), it was a resting WM abnormality detected by RTMCE that was the only significant predictor of death or nonfatal MI in the univariate and multivariate analyses. One explanation for this may be the potential for RTMCE to better identify a critical resting stenosis. When such a stenosis is present, subendocardial wall thickening is affected more than subepicardial wall thickening, and blood flow is reduced only in the subendocardium (20). Therefore, the resultant subendocardial perfusion defect (which could only be visualized when using RTMCE) may have improved the delineation of a subendocardial wall motion abnormality. Because CSE can only analyze transmural wall thickening, it would have more difficulty in detecting a wall thickening abnormality confined to the subendocardium. In this setting, resting wall motion abnormalities combined with resting perfusion defects with contrast echocardiography have been shown to identify the highest risk subgroup of patients presenting with potential acute coronary syndromes, even within 12 h of the episode of chest pain (21). Patients presenting to the emergency department with chest pain and negative or equivocal troponin values were included in our study, and

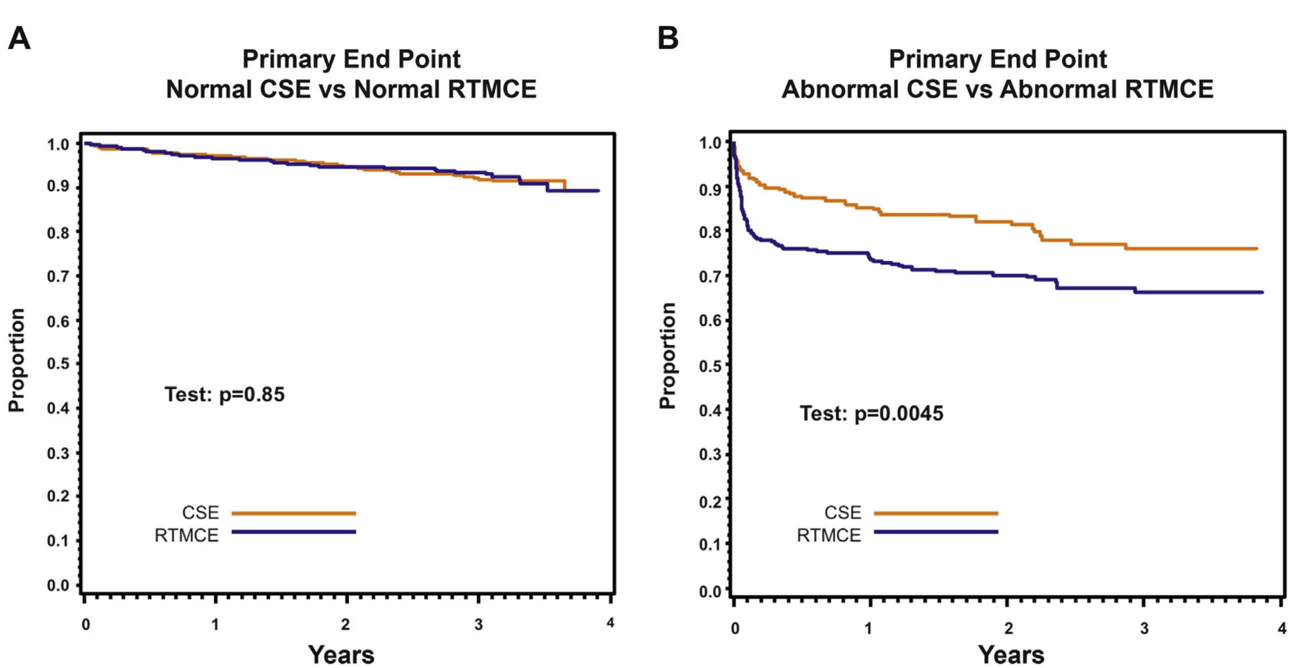

Figure 3 **Differences in Event-Free Survival for Primary Endpoint**

Event-free survival (death, nonfatal MI, or subsequent revascularization) in those with a normal CSE and RTMCE exam **(A)**, and in those with an abnormal CSE and RTMCE exam **(B)**. Abbreviations as in Figure 2.

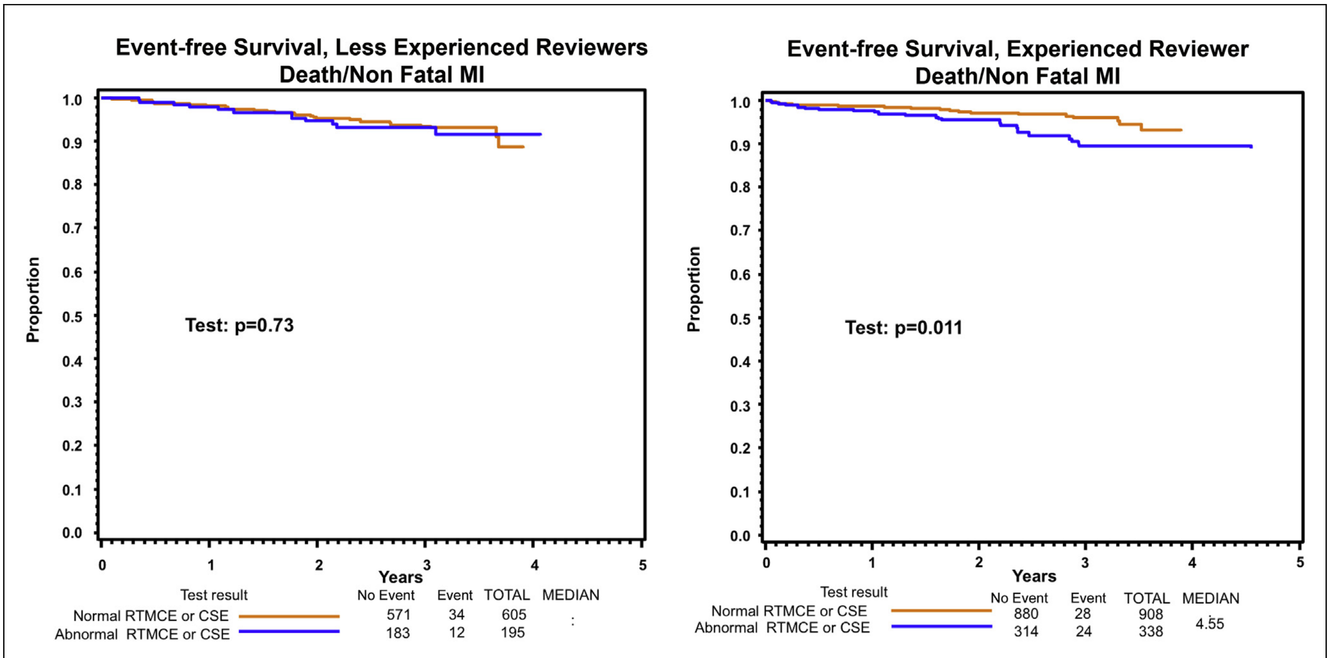

Figure 4 **Reviewer Experience and Outcome**

EFS (death or nonfatal MI) in patients with an abnormal versus normal stress echo based on reviewer experience. R1 (Fig. 3A) is a reviewer with experience in reviewing over 1,000 RTMCE and CSE studies. R2 are the reviewers who had Level 3 training in echocardiography, and who had interpreted over 100 contrast studies for left ventricular opacification and for perfusion imaging. Abbreviations as in Figure 2.

resting RTMCE may have aided in detecting a high-risk subgroup of patients in this category.

Study limitations. Reviewer experience plays a role in the evaluation of contrast-enhanced images, independent of whether it is being utilized for CSE or RTMCE. Although an abnormal study read by an experienced versus less experienced reviewer was equivalent in predicting subsequent revascularization, death, or nonfatal MI, only the experienced reviewer was able to predict death or nonfatal MI when revascularization was considered as a time-dependent covariate. This was true for both RTMCE and CSE studies, and emphasizes the critical role of formal contrast training in both of these imaging approaches. Unfortunately, no formal guidelines exist for contrast echo training within current American College of Cardiology/American Heart Association Guidelines(8), while at least 300 performed and interpreted studies are required for Level 2 training in other established imaging techniques. Based on the differences in contrast experience between R1 versus R2, it would appear that a Level 2 training equivalent of 300 contrast cases would be needed to improve an interpreter's ability to predict outcome.

The RTMCE group had a higher proportion of patients with prior MI and prior percutaneous intervention. This may indicate some recruitment bias toward patients with higher pre-test probability when certain interpreters were reading, and patients with more advanced disease being randomized to RTMCE. Therefore, it is reasonable to assume from our study that the prevalence of more advanced disease was higher in the RTMCE patients. RTMCE identified this more advanced disease resulting in higher revascularization numbers, which may have equalized the death and nonfatal MI rates following abnormal studies in the 2 groups.

Table 3 **Univariate and Multivariate Models of EFS (Death+MI)**

Variable	Univariate	Full Multivariate	Backward Selected Model
Technique (RTMCE vs. CSE)	0.64	0.95	0.78
Age >70 vs. ≤70 yrs	0.071	0.088	0.087
EF <50% vs. ≥50%	0.055	0.70	
Prior revascularization (PTCA or CABG)	0.061	0.61	
DM	0.19	0.24	
Hyperlipidemia	0.82		
Antiplatelet (clopidogrel)	0.90		
Aspirin	0.78		
Resting wall motion abnormality (yes vs. no)	0.004	0.13	0.005
ECHO result (abnormal vs. normal)	0.040		
More experienced reviewer (yes vs. no)	0.36		
Extent of abnormality (≥2 territories vs. normal/ single vessel)	0.029	0.81	
Revascularization following stress echo	0.17	0.52	

Values are p values.
DM = diabetes mellitus; ECHO = echocardiography; EF = ejection fraction; EFS = event-free survival; other abbreviations as in Table 1.

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Table 4 Univariate and Multivariate Models of EFS (Death+MI)

Variable	CSE Patients			RTMCE Patients		
	Univariate	Full Multivariate	Backward Selected Model	Univariate	Full Multivariate	Backward Selected Model
Age >70 versus ≤70 yrs	0.25			0.16	0.22	
EF <50% versus ≥50%	0.31			0.11	0.85	
Prior revascularization (PTCA or CABG)	0.64			0.044	0.45	
DM	0.061	0.098	0.061	0.99		
Hyperlipidemia	0.58			0.84		
Antiplatelet (clopidogrel)	0.67			0.81		
Aspirin	0.28			0.17	0.73	
Resting wall motion abnormality (yes vs. no)	0.67			0.001	0.014	0.001
Echo result (abnormal vs. normal)	0.17	0.48		0.15		
More experienced reviewer (yes vs. no)	0.97			0.19	0.13	
Extent of abnormality ≥2 territories vs. normal/single vessel	0.14	0.50		0.11	0.73	
Revascularization following stress echo	0.48			0.25		

Values are p values.
Abbreviations as in Tables 1 and 3.

Because this study was multireader but not multicenter, institutional biases may have played a role in outcome. For example, contrast use for conventional stress echo was higher at our institution than what is being used in the general population. Because contrast use has been shown to improve the diagnostic quality of a conventional stress echocardiogram (22), its higher use in the CSE arm may have improved both the detection and exclusion of ischemia. In institutions where contrast use during CSE is less, the predictive value of the test may not be the same.

Conclusions/Clinical implications. Therefore, in this prospective clinical comparison, both RTMCE and CSE appear to be excellent at risk stratifying patients at intermediate risk for CAD. When performed properly, RTMCE identifies more patients with CAD and extensive ischemia, and those more likely to require revascularization. A resting WM abnormality detected with RTMCE is highly predictive of adverse outcomes, while it is not predictive of outcome with CSE. Therefore, although the prognostic values of RTMCE and CSE are similar when revascularization is considered as a time dependent covariate, stress RTMCE should be the preferred technique for detecting those who may need revascularization, and RTMCE is better for detecting a resting WMA (*wall motion*

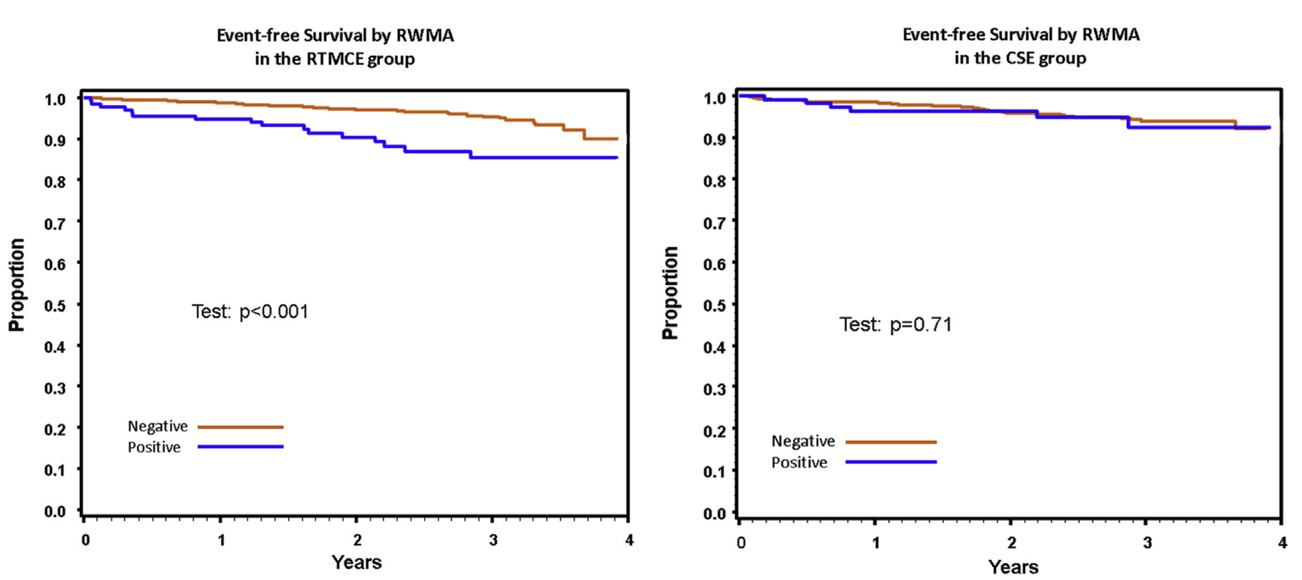

Figure 5 Outcome With RWMA

EFS (death or nonfatal MI) in patients with resting wall motion abnormalities (RWMA) detected by RTMCE versus CSE. Note that only in RTMCE patients was a resting wall motion abnormality predictive of death or nonfatal MI. Abbreviations as in Figure 2.

abnormalities) that will impact outcome. Revascularization following an abnormal RTMCE may have altered the clinical course of the disease with respect to subsequent death or nonfatal MI. Further studies will be required to verify this important possibility.

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Key Words: coronary artery disease ▪ perfusion imaging ▪ stress echocardiography.

APPENDIX

For supplemental tables, please see the online version of this article.