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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