Myocardial Contrast Echocardiography Enhances Long-Term Prognostic Value of Supine Bicycle Stress Two-Dimensional Echocardiography

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Background: The aim of this study was to determine the incremental prognostic value of myocardial contrast echocardiography (MCE) over two-dimensional echocardiography (2DE) in patients undergoing supine bicycle stress.

Methods: Eighty-four patients with known or suspected coronary artery disease who underwent supine bicycle stress with 2DE and MCE (mean age, 58.5 ± 9.7 years; 68 men) were followed up for 48.3 ± 8.9 months for cardiac death (n = 1), nonfatal myocardial infarction (n = 9), and revascularization (n = 20).

Results: In sequential Cox models, the predictive power of the clinical model was strengthened by 2DE (χ^2 = 7.73 vs 12.92, P = .02) and further improved by MCE (χ^2 = 19.04, P = .01). On multivariate analysis, the only independent follow-up event predictor was ischemia on MCE (hazard ratio, 6.79; 95% confidence interval, 2.02-22.82; P = .001). Among patients with normal results on 2DE, those with normal results on MCE had greater 4.5-year event-free survival than those with abnormal results on MCE (93% vs 69%, P = .01).

Conclusions: MCE enhances the predictive power of supine bicycle stress 2DE and allows the risk stratification of patients with normal results on 2DE. (J Am Soc Echocardiogr 2009;22:1220-7.)

Keywords: Coronary artery disease, Myocardial contrast echocardiography, two-dimensional echocardiography, Supine bicycle stress, Prognosis

The accurate risk stratification of patients with coronary artery disease (CAD) has become increasingly important in determining prognosis and guiding clinical management. Exercise two-dimensional echocardiography (2DE) is an established technique for the prediction of adverse cardiac events in patients with suspected or known CAD.[1] Myocardial contrast echocardiography (MCE) is a new noninvasive imaging modality that enables the real-time assessment of myocardial perfusion (MP) and function.[2] Several studies have demonstrated that MCE performed during exercise or pharmacologic stress enhances the sensitivity and accuracy of 2DE in the detection of CAD.[3-7] This incremental benefit of MCE is explained by the spatiotemporal discrepancy between MP and wall motion (WM) abnormalities that occur with ischemia.[3,5,6,8,9] It may be speculated that because of its higher diagnostic value, MCE may improve the risk stratification of patients undergoing stress 2DE. Exercise is the preferred stress to induce ischemia in active patients, but the feasibility of exercise MCE, because of patient and respiratory movements, is still controversial. Despite these limitations, we recently showed that MCE during supine bicycle stress is feasible and improves the value of 2DE to detect myocardial ischemia.[10] So far, the prognostic value of MCE has been assessed only during pharmacologic stress,[11,12] and there is a paucity of data regarding its prognostic value during exercise. Therefore, the aim of this study was to assess whether the additional performance of MCE during supine bicycle stress 2DE provides incremental benefit for predicting outcomes in patients with known or suspected CAD.

METHODS

Study Population

The study was approved by the ethics committee of the University of Bonn and complied with the Declaration of Helsinki. Informed consent was obtained from each patient. One hundred one consecutive patients with suspected or known CAD who were scheduled for supine bicycle stress 2DE between 2002 and 2003 were enrolled in the study. Patients were not selected with respect to baseline

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Dr Tomasz Miszalski-Jamka was supported by Catholic Academic Exchange Service (Bonn, Germany).

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0894-7317/$36.00

doi:10.1016/j.echo.2009.07.020

echocardiographic image quality. Exclusion criteria were recent (≤1 month) myocardial infarction (MI), absolute and/or relative contraindications to exercise testing,[13] and/or a contraindication to SonoVue (Bracco, Milan, Italy).

Supine Bicycle Stress

The initial workload was set at 50 W and increased in 25-W increments every 2 minutes until end points according to American Heart Association and American College of Cardiology guidelines were reached.[13] Two-dimensional echocardiography was performed at rest and during each exercise stage. After peak-stress 2DE was performed, all patients continued exercise and bicycled until peak-stress MCE was carried out. Following the termination of exercise, each subject remained in the supine position on the bicycle. MCE was again performed when the subject's heart rate had returned to its preexercise value.

2DE

Two-dimensional echocardiography was performed in the apical 4-chamber, 2-chamber, and long-axis views with the System FiVe or Vivid 7 ultrasound system (GE Vingmed Ultrasound AS, Horten, Norway). Images synchronized with the QRS complex were digitally stored and compared offline side by side in quad-screen display for the presence and location of WM abnormalities. The analysis was performed by an independent, experienced viewer unaware of clinical and myocardial contrast echocardiographic data. A 17-segment model of the left ventricle was used.[14] Apical, apical septal, mid septal, apical lateral, all anterior, and all anteroseptal segments were assigned to the left anterior descending coronary artery. Mid lateral and basal lateral segments were assigned to the left circumflex artery. Basal septal, mid inferior, and basal inferior segments were assigned to the right coronary artery. The posterior wall was considered an overlap region between the left circumflex and right coronary arteries and the apical inferior segment an overlap region between the left anterior descending and right coronary arteries.[15] Segmental myocardial contractile function was assessed in terms of endocardial motion and/or systolic wall thickening as follows: 1 = normal, 2 = hypokinetic, 3 = akinetic, and 4 = dyskinetic. The development of a new or worsening (inducible) WM abnormality from rest to stress in ≥1 segment was considered indicative of ischemia. A WM abnormality present at rest and unchanged with exercise was classified as fixed. The results of 2DE were defined as abnormal if ≥1 segment demonstrated inducible or fixed WM abnormalities.

MCE

MCE was performed using the Sonos 5500 ultrasound system (Philips Medical Systems, Andover, MA). Defined equipment settings optimized for power modulation imaging were preset before supine bicycle stress. The mechanical index was kept at 0.1 and the frame rate ≥20 Hz. Ultrasound contrast agent (SonoVue) was administered intravenously in a continuous mode using an infusion pump (BR-INF 100; Bracco Research, Geneva, Switzerland). After an initial bolus (1 mL over 15 seconds), contrast infusion was started at a rate of 1.6 mL/min and adjusted to provide uniform myocardial contrast opacification without attenuation and to guarantee complete microbubble destruction with high-power frames (flash). After reaching a steady state of myocardial contrast opacification, 5 consecutive high-power frames (mechanical index, 1.5) were emitted to disrupt contrast within myocardium. Subsequently, mechanical index was switched automatically back to the low-power level, enabling the visualization of myocardial contrast replenishment. Imaging sequences of ≥15 cardiac cycles (including steady state, flash frames, and replenishment) were stored digitally for each apical view at peak exercise and after stress. The imaging sequences were assessed offline for the presence and location of WM abnormalities (left ventricular opacification [LVO] analysis) and/or MP abnormalities by two different independent, experienced viewers blinded to clinical and 2DE data. As described above, a 17-segment model of left ventricle was used, and segments were assigned to coronary artery territories.[14,15] WM abnormalities were assessed using the same scoring and positive test result criteria as for 2DE. MP was assessed in terms of myocardial contrast opacification and/or replenishment. The segments with uninterpretable myocardial contrast opacification and replenishment were excluded from MP analysis. Myocardial contrast opacification was evaluated when a steady state of contrast enhancement was reached. If a lack of enhancement resulted from artifacts, the segment was regarded as uninterpretable and excluded from MP analysis. Contrast defects limited to the basal segment were consistently attributed to attenuation. Myocardial contrast opacification of interpretable segments was graded using a 3-point scale (1 = normal, 2 = reduced, and 3 = none) on the basis of relative (ie, in comparison with the best opacified segment) assessment of myocardial contrast enhancement.[16] Segmental replenishment was evaluated in terms of the number of heart cycles required to refill a segment after microbubble destruction. Heart cycles were counted, starting with first diastole after flash. A segment was considered refilled when, during side-by-side (dual-screen format) comparison with preflash myocardial contrast opacification, visually assessed signal intensity in consecutive cardiac cycles after flash reached value similar to that before microbubble destruction. A perfusion defect was regarded as present if peak-stress myocardial contrast opacification was graded as reduced or none and/or peak stress myocardial contrast replenishment exceeded 3 cardiac cycles. Subsequently, on the basis of peak-stress and poststress comparison, perfusion defects were classified as reversible or fixed. Perfusion defects were defined as reversible when the myocardial contrast opacification score was higher at peak stress than after stress and/or when the difference between peak-stress and poststress myocardial contrast replenishment exceeded zero cardiac cycles. The remaining perfusion defects were considered fixed. A reversible perfusion defect in ≥1 segment was considered to indicate ischemia. MP was defined as abnormal when ≥1 segment exhibited a reversible or fixed perfusion defect. Cutoff values for replenishment analysis were determined in our prior study using receiver operating characteristic analysis and reference interval analysis.[10] The results of MCE were defined as abnormal when perfusion defects (MP analysis) and/or WM abnormalities (LVO analysis) were present in ≥1 segment. To determine intraobserver variability, all studies were assessed ≥2 months later in a random order by the same observer, unaware of prior results. To assess interobserver variability, all imaging sequences were evaluated by the second observer, blinded to the results obtained by first one.

Quantitative Coronary Angiography

Within 15 days of supine bicycle stress, coronary angiography was carried out using the standard Judkins technique in all patients with ischemic results on 2DE or MCE. Quantitative coronary angiography was performed by an experienced interventional cardiologist blinded to clinical and echocardiographic data using CAAS II software (Pie Medical Imaging, Maastricht, The Netherlands). Quantitative