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ORIGINAL RESEARCH

Comparative Prediction of Cardiac Events by Wall Motion, Wall Motion Plus Coronary Flow Reserve, or Myocardial Perfusion Analysis

A Multicenter Study of Contrast Stress Echocardiography

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OBJECTIVES This study sought to determine whether the increasing difficulty of assessing wall motion (WM), Doppler coronary flow reserve on the left anterior descending coronary artery (CFR-LAD), and myocardial perfusion (MP) during stress echocardiography (SE) was justified by increasing prognostic information in patients with known or suspected coronary artery disease.

BACKGROUND The use of echocardiographic contrast agents during SE permits the assessment of both CFR-LAD and MP, but their relative incremental prognostic value is undefined.

METHODS This study followed a multicenter cohort of 718 patients for 16 months after high-dose dipyridamole contrast SE for evaluation of known or suspected coronary artery disease. The ability of WM, CFR-LAD, and MP to predict cardiac events was studied by multivariable models and risk reclassification.

RESULTS Abnormal SE was detected as a reversible WM abnormality in 18%, reversible MP defect in 27%, and CFR-LAD <2 in 38% of subjects. Fifty cardiac events occurred (annualized event rate 6.0%). A normal MP stress test had a 1-year hard event rate of 1.2%. The C-index of outcomes prediction based on clinical data was improved with MP ($p < 0.001$) and WM/CFR-LAD ($p = 0.037$), and MP ($p = 0.003$) added to clinical and WM data. Net risk reclassification was improved by adding MP ($p < 0.001$) or CFR-LAD (net reclassification improvement $p = 0.001$) in addition to clinical and WM data. The model including clinical data, WM/CFR-LAD, and MP performed better than that without MP did ($p = 0.012$).

CONCLUSIONS The multiparametric assessment of WM, CFR-LAD and MP during stress testing in patients with known or suspected coronary artery disease is feasible. Contrast SE allowed better prognostication, irrespective of the use of CFR-LAD or MP. The addition of either CFR-LAD or MP assessment to standard WM analysis and clinical parameters yielded progressively higher values for the prediction of cardiac events and may be required in today's intensively treated patients undergoing SE, because their average low risk of future cardiac events requires methods with higher predictive sensitivity than that available with standalone WM assessment. (J Am Coll Cardiol Img 2013;6:1–12) © 2013 by the American College of Cardiology Foundation

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Pharmacological stress echocardiography (SE) using wall motion (WM) analysis is an established technique for the detection and prognostication of coronary artery disease (CAD) (1,2). Indeed, the prediction of cardiac events with SE is incremental to clinical, rest echocardiographic, and angiographic parameters (3). Assessment of long-term outcome of contrast SE is important because this test may identify both high-risk patients who would benefit from invasive intervention and lower-risk patients in whom additional procedures and intensive medical follow-up are not required. The use of echocardiographic contrast agents has improved the accuracy of SE (4). Although the risk of events is low in patients without WM abnormalities, an at-risk subgroup can be identified with myocardial perfusion (MP) defects alone (5–8). Contrast SE also facilitates the measurement of the left anterior descending coronary artery flow reserve (CFR-LAD) using transthoracic Doppler, and CFR-LAD shows incremental value to WM analysis (9–11). Whether these 3 parameters, sequentially assessed during the same stress test, provide incremental, complementary, or redundant prognostic information remains to be determined. In the present study, we sought to determine the association between contrast high-dose dipyridamole SE (DipSE) findings with future cardiac events in a large, prospective, contemporary, and multicenter cohort of patients (n = 718) with suspected or known CAD and to define the potential complementary value of WM, CFR-LAD, and MP analysis.

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CFR-LAD = Doppler coronary flow reserve on the left anterior descending coronary artery

CI = confidence interval

DipSE = dipyridamole stress echocardiography

HR = hazard ratio

LV = left ventricle

MI = myocardial infarction

MP = myocardial perfusion

MPD = myocardial perfusion defect(s)

SE = stress echocardiography

WM = wall motion

WMA = wall motion abnormality

METHODS

Study population. Between January 2009 and March 2011, we enrolled 752 patients undergoing contrast DipSE for evaluation of chest pain with suspected or known CAD at 3 Italian hospitals: University Hospital, Parma (n = 470), Umberto I Hospital, Mestre-Venice (n = 161), and Andria Hospital, Bari (n = 121). All patients met the following inclusion criteria: 1) stable chest pain; 2) absence of absolute contraindications to dipyridamole; 3) absence of known allergy to sulphonamide-containing products; 4) enrollment in a follow-up program. Exclusion criteria were: 1) inadequate acoustic window; 2) severe valvular or congenital heart disease; 3) suspected pregnancy; 4) significant comorbidity reducing life expectancy to <1 year; 5) unwillingness to give informed consent.

Traditional risk factors for CAD, including arterial hypertension (blood pressure ≥140/90 mm Hg or use of antihypertensive medication), hyperlipidemia (total cholesterol ≥200 mg/dl or treatment with lipid-lowering medications), current or prior smoking, diabetes mellitus (fasting glucose level ≥126 mg/dl or the need for insulin or oral hypoglycemic agents), history of CAD, and a family history of CAD were recorded. The study was conducted in accordance with the institutional review board standards of all participating centers.

Contrast stress echocardiography. This protocol is summarized in Figure 1 and has been already described in detail elsewhere (12). Briefly, 2-dimensional echocardiography, 12-lead electrocardiography, and blood pressure monitoring were performed in combination with high-dose dipyridamole (0.84 mg/kg over 6 min) in accordance with a standard protocol (1). Transthoracic stress echocardiography was performed with commercially available ultrasound machines (iE33 Philips Ultrasound, Andover, Massachusetts) using multifrequency phased-array probes (S5), second harmonic, and low-mechanical index power modulation technology. Apical 2-, 3-, and 4-chamber views were obtained both for WM and MP; a modified 3-chamber view for CFR-LAD imaging was integrated into the imaging sequence. Contrast WM, CFR-LAD, and MP were sequentially assessed using the same probe (S5) by activation of the appropriate preset. The left ventricle (LV) was divided into 17 segments (13). Repeated 0.5-ml SonoVue boluses (Bracco Imaging Italia SRL, Milan, Italy) were administered at rest and at peak stress, followed by low-power (mechanical index = 0.10) contrast-specific imaging for MP and a different preset (LV opacification, with harmonic imaging and mechanical index = 0.27) for contrast WM analysis; the standard 2-dimensional preset was resumed (WM monitoring) after microbubbles were cleared. For MP assessment, flash-replenishment sequences were acquired, both in the continuous (40 frames/s) or triggered mode (end-systolic at every cardiac cycle). Just before administration of the contrast bolus, the low mechanical index setting was activated and optimized for gain and power so that no signal was detectable from the myocardium;