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

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 echocar-

diographic 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.

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;
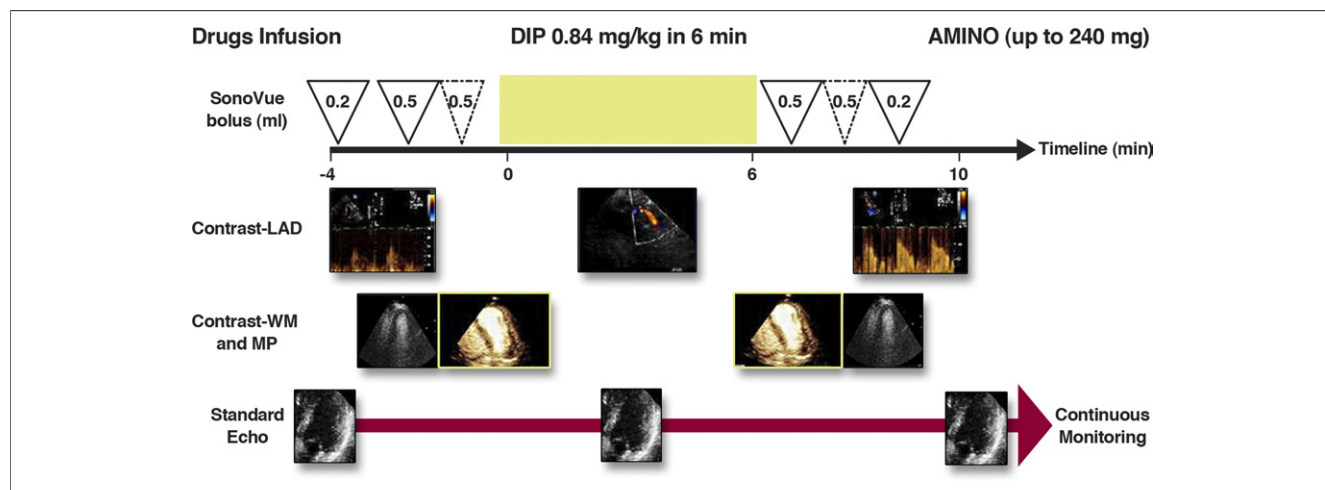
Figure 1. Schematic of the Contrast SE Protocol

AMINO = aminophylline; contrast-LAD = Doppler sampling of the mid-distal left anterior descending artery; contrast-WM = contrast wall motion; DIP = dipyridamole; MP = myocardial perfusion; SE = stress echocardiography.

after 0.5-ml SonoVue bolus, the start of acquisition of the MP flash-replenishment sequences was approximately 10 s after peak video intensity, this delay being used to avoid saturation.

Coronary flow in the mid-distal LAD was sought in the low parasternal long-axis or modified 2-chamber view, guided by color Doppler flow mapping. Color-coded blood flow from the LAD was visualized both at rest and peak stress using contrast enhancement (SonoVue, 0.2-ml intravenous bolus); flow velocities were measured at baseline and at peak stress (before aminophylline injection). For both color Doppler flow mapping and pulsed-wave velocity measurements, the standard setting for CFR-LAD was adjusted after contrast bolus by lowering the mechanical index down to 0.1. At each time point, the 3 best profiles of peak diastolic Doppler flow velocities were measured, and the results were averaged.

Interpretation of test results. Segmental WM was graded as follows: normal = 1; hypokinetic = 2; akinetic = 3; and dyskinetic = 4. Reversible ischemia was defined as the occurrence of a stress-induced new dyssynergy or worsening of rest hypokinesia in ≥ 1 segment.

Abnormal perfusion post-dipyridamole was assigned if ≥ 1 segment was not fully replenished 1.5 s after the end of the flash. Rest perfusion was deemed abnormal if replenishment occurred >4 s after the flash impulse. Myocardial perfusion defect (MPD) was scored as fixed or reversible based on its presence at rest. LV segments were excluded from MP interpretation if they were not clearly visualized

due to shadowing artifacts or low ultrasound penetration. Coronary blood flow velocity reserve was defined as the ratio between hyperemic and basal peak diastolic coronary flow. CFR-LAD ≥ 2.0 was considered normal (1,9–11).

The assessment of the contrast SE was performed at each center by consensus of 2 investigators. Readers used a binary score of normal/abnormal for all of the 3 assessed SE parameters, whatever the image quality of the test; if at least 1 reader evaluated at least 1 parameter as "uninterpretable," the patient was excluded from the study. Intraobserver and interobserver agreement data for WM, MP, and CFR-LAD have previously been published for each participating center (12,14), but a specific assessment of interobserver variability with an expert external reader (T.H.M.) on 20 randomly selected study cases was also performed for both wall motion abnormalities (WMA) and MP, and reported as a percentage with a corresponding kappa value.

Follow-up and definition of study endpoints. Follow-up information was obtained from the start of the study until June 2011. Outcomes were determined from patient interview at the outpatient clinic, hospital chart reviews, and telephone interviews with the patient, close relatives, or the referring physician. Data were prospectively collected at least 3 months after the contrast SE examination (median: 16.5 months, interquartile range: 8 to 22 months). Death, nonfatal MI, and acute coronary syndrome requiring urgent revascularization were registered as clinical events. Coronary revasculariza-

tion (surgery or percutaneous intervention) was also recorded. Overall mortality was considered to avoid misclassification of the cause of death (15). MI was defined by typical symptoms and electrocardiographic and cardiac enzyme changes. Follow-up data were analyzed for the prediction of the primary combined endpoint of death, nonfatal MI, and acute coronary syndrome requiring urgent revascularization (total cardiac events) and, secondarily, for death or nonfatal MI (hard events).

Statistical analysis. Continuous variables are expressed as mean $\pm$ SD, whereas categorical data are given as numbers and percentages. Patients undergoing test-driven coronary revascularization (defined as revascularization within 90 days) were censored at the time of their procedure, which was not considered a cardiac event. Only the first event was taken into account.

SURVIVAL ANALYSIS AND MULTIVARIABLE MODELING. Event-free survival and the rates of hard and total cardiac events were estimated with Kaplan-Meier curves, and the log-rank test was used to compare survival curves between groups. Univariable and multivariable Cox proportional hazard models were used to identify features associated with both hard and total cardiac events. Variable selection for the multivariable models was based on clinical knowledge and/or association with $p < 0.1$ at univariable analysis. A ratio of >10 events per degree of freedom was maintained.

To assess the value of SE measurements over clinical parameters for event prediction, SE variables were sequentially included in multivariable models with relevant clinical predictors. Overall, chi-square and likelihood ratio tests were used to compare the prognostic value of the clinical model with models comprising SE parameters. C-statistics and Akaike information criterion were used to compare model strengths.

RECLASSIFICATION. The impact of contrast SE variables on reclassification of patient risk with respect to total cardiac events was determined using net reclassification improvement (16). For each patient, the predicted risk of total cardiac events was determined based on each model, followed by assessment of the impact of additional information on patient reclassification; net reclassification improvement represents the net number of patients with improved reclassification, summing reclassification in patients with events and patients without events. We examined reclassification using thresholds of 3% and 10% total cardiac events per year to define low-,

intermediate-, and high-risk groups. We considered these thresholds appropriate, based on the total cardiac event rate of 6% per year in our study.

Due to the small number of hard events, model comparison and reclassification analysis were limited to the composite endpoint. Statistical analyses were performed using standard software (STATA release 10 and R 2.11, StataCorp, College Station, Texas). A p value <0.05 was considered statistically significant for all the analyses.

RESULTS

Patient characteristics. The test was deemed uninterpretable for at least 1 of the 3 tested parameters in 29 patients (4%), who were excluded. Of the 723 patients remaining, 5 (0.7%) were lost to follow-up, leaving a final study cohort of 718 patients.

Approximately one-third of the patients had a history of CAD, and those without this diagnosis had a high prevalence of risk factors. Ischemia (reversible WMA) was present in 18% of patients, compared with 27% with inducible MPD and 38% with reduced CFR-LAD (<2.0). Patients with positive MP imaging had 2.6 ± 1.5 reversible defects, and only 28 had <2 segments with reversible perfusion defects. A complete overview of the baseline characteristics of the study group is illustrated in Table 1.

The interobserver agreement of DipSE with an external blinded expert reader (T.H.M.) on 20 randomly selected study cases was 80% (k = 0.60) for MP and 95% (k = 0.86) for WM.

Outcomes. Fifty events (7.0%) occurred during follow-up, including death in 8 patients (1.1%), nonfatal infarction in 20 (2.8%), and acute coronary syndrome requiring urgent revascularization in 22 (3.1%); 85 patients (11.8%) undergoing test-driven revascularization (within 3 months of SE) were censored at that time. Annual hard and total cardiac event rates were, respectively, 2.8% and 6.0% in the entire population, 2.1% and 4.1% in patients without known CAD, 4.5% and 10.4% in patients with known CAD.

Prediction of composite endpoint. Patients with any SE abnormality showed a higher annual event rate than did subjects with normal SE (10.8% vs 2.1%, $p < 0.001$). The few patients with abnormal WM/CFR-LAD but normal MP findings had low event rates (2.2%/year). In contrast, patients with abnormal MP alone (15.9%/year) or with both abnormal MP and WM/CFR-LAD (20%/year) showed higher annual event rates. Figure 2 shows the total cardiac event rate in relation to the positivity of each

Table 1. Clinical Characteristics and Echocardiographic Findings in 718 Recruited Patients

Age, yrs	65 ± 11
Sex, M/F	442/276
Risk factors and patient history	
Hypertension*	485 (68)
Hypercholesterolemia†	422 (59)
Current smokers	168 (23)
Diabetes mellitus	200 (28)
Family history of CAD	238 (33)
Reduced ejection fraction, LVEF <50%	172 (24)
Known CAD	226 (31)
Previous myocardial infarction	135 (19)
Previous revascularization	221 (31)
Medications	
ACE inhibitors/ARB	481 (67)
Statin	435 (61)
Beta-blockers	459 (64)
ASA	468 (65)
Contrast stress-echocardiography	
Patients with reversible WMA	129 (18)
Patients with CFR-LAD <2	275 (38)
Patients with reversible MPD	198 (27)
Patients with reversible WMA and CFR-LAD <2	83 (12)
Patients with reversible WMA or CFR-LAD <2	321 (45)
Patients with reversible WMA or CFR-LAD <2 or reversible MPD	351 (49)

Values are mean ± SD or n (%). *Blood pressure ≥140/90 mm Hg or treatment of hypertension. †Total cholesterol >200 mg/dl or treatment of hypercholesterolemia.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; ASA = acetylsalicylic acid; CAD = coronary artery disease; CFR-LAD = Doppler coronary flow reserve on the left anterior descending coronary artery; LVEF = left ventricular ejection fraction; MPD = myocardial perfusion defects; WMA = wall motion abnormalities.

contrast SE variable and relevant combinations, whereas Figure 3A shows the related Kaplan-Meier event-free survival curves.

The features associated with total cardiac events are shown in Table 2. Of the baseline patient data, hypercholesterolemia, diabetes mellitus, known CAD, and aspirin therapy at the time of testing predicted total cardiac events. Reduced LV ejection fraction at rest echo and all contrast SE variables (reversible WMA, reversible MPD, CFR-LAD <2, and the combination of reversible WMA or CFR-LAD <2) predicted events. CFR-LAD <2 (hazard ratio [HR]: 2.25, 95% confidence interval [CI]: 1.21 to 4.17) and MPD (HR: 5.97, 95% CI: 3.02 to 11.78) remained predictive of total events in the multivariate analysis of the 3 SE variables, whereas WMA did not ($p = 0.37$).

The incremental value of WMA, CFR-LAD, MPD, and their combination for prediction of total cardiac events in a Cox proportional hazards model is summarized in Table 3. The clinical model (based on diabetes, hyperlipidemia, and known CAD) had a C-index of 0.667. The addition of WMA significantly increased the C-index to 0.70, whereas the addition of CFR-LAD exceeded this (C-index: 0.739), and MPD carried even more predictive power (C-index: 0.795). The combination of the 3 contributed a minor increment in predictive power.

Table 4 summarizes the incremental benefit of adding each layer of complexity of imaging to the model, including the reclassification index. Either WM/CFR-LAD or MPD variables significantly added prognostic value to the model based on clinical data (respectively, $p = 0.037$ and $p < 0.001$ for C-index comparison), whereas only MPD significantly added to the model comprising clinical data and WMA ($p = 0.003$ for C-index comparison). These data indicate that the model including both WM/CFR-LAD and MPD along with clinical data performed significantly better than the model with WMA/CFR-LAD and clinical data (model 5 vs. model 3, $p = 0.012$ for C-index comparison).

Classification groups were set at annual total cardiac event rates of 0% to 3%, 3% to 10%, and >10%. Whereas WMA alone was not able to significantly reclassify risk incremental to clinical data ($p = 0.81$), the addition of either WMA/CFR-LAD <2 ($p = 0.001$) or MPD ($p < 0.001$) significantly improved risk reclassification over clinical data. An improvement in risk reclassification was also detected for the model including WM/CFR-LAD and clinical parameters with respect to the model including only WMA and clinical data ($p < 0.001$). The addition of MPD to clinical parameters also provided an improvement in risk prediction in comparison to models with clinical data and WMA ($p < 0.001$) or WMA/CFR-LAD <2 ($p = 0.021$). Models including both the WM/CFR-LAD and MPD along with clinical parameters improved risk prediction with respect to models considering WMA ($p < 0.001$) or WM/CFR-LAD ($p = 0.025$) in addition to clinical variables, whereas there was no difference compared with the model including clinical parameters and MPD only ($p = 0.54$).

Prediction of hard events. Of baseline patient data, the only variables associated with hard cardiac events were sex (HR: 2.766, 95% CI: 1.04 to 7.35), diabetes mellitus (HR: 2.64, 95% CI: 1.22 to 5.73), and hypercholesterolemia (HR: 3.36, 95% CI: 1.27 to 8.92). Reduced LV ejection fraction at rest echo
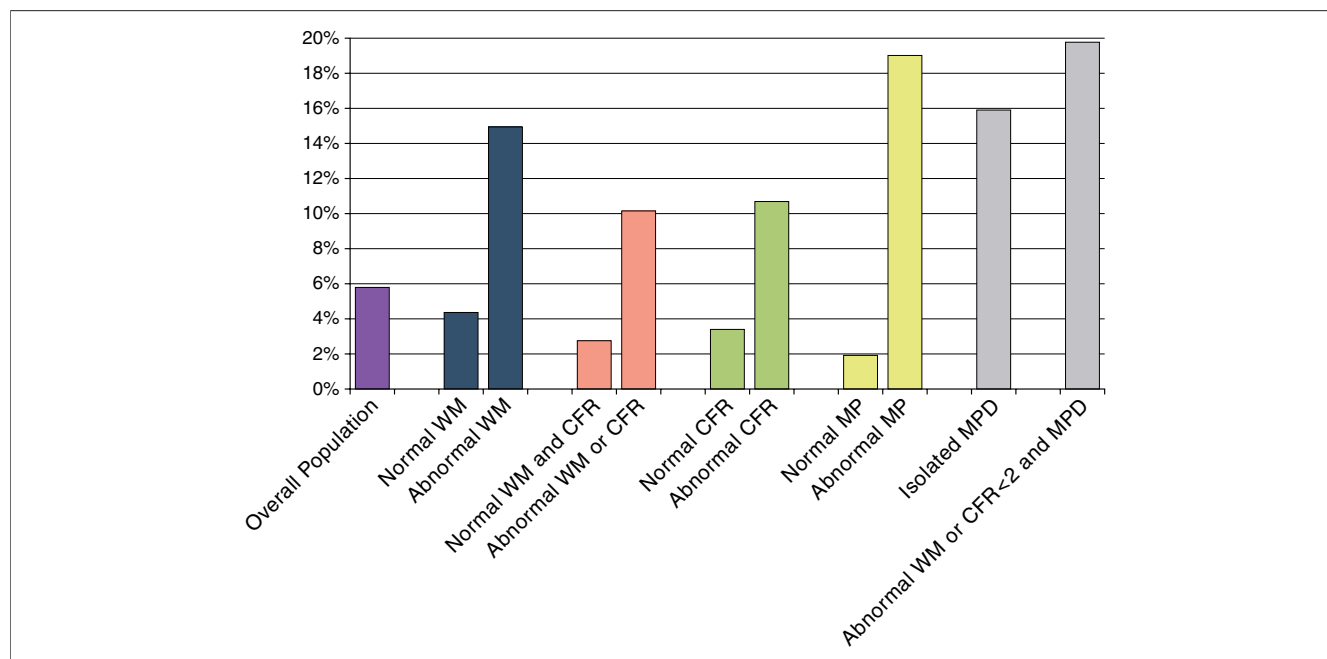
Figure 2. Total Cardiac 1-Year Event Rate

Total cardiac 1-year event rate in the overall population and classified based on stress-echocardiography findings. Compared with standard wall motion (WM) analysis, the addition of Doppler coronary flow reserve on the left anterior descending coronary artery (CFR-LAD) data added more sensitivity but less specificity for prediction of cardiac events, whereas using myocardial perfusion (MP) data increased both sensitivity and specificity, with normal MP predicting the lowest incidence of events and a positive MP predicting the highest incidence of events. Note that the same events are shared by overlapping subgroups; for example, if a patient with abnormal WM and MP has an event, it is counted in both the "abnormal WM" and "abnormal MP" subgroups. MPD = myocardial perfusion defect(s).

(HR: 2.3, 95% CI: 1.7 to 5) and all contrast SE variables—reversible WMA (HR: 4.74, 95% CI: 2.15 to 10.48), reversible MPD (HR: 4.44, 95% CI: 2.05 to 9.61), CFR-LAD <2 (HR: 3.03, 95% CI: 1.38 to 6.68), and the combination of reversible WMA or CFR-LAD <2 (HR: 4.18, 95% CI: 1.76 to 9.95)—were univariate predictors of hard events. None of the C-indices for univariable prediction of hard events was significantly different from the others.

Hard event-free survival differed significantly between patients depending on the SE results (Fig. 3B). The annual event rate with any abnormal contrast SE finding was 3-fold increased compared with normal findings (4.7% vs. 1.4%, p = 0.001), whereas this was not the case selectively for abnormal dipyridamole-induced WMA (0.8% per year) or CFR-LAD <2 (2.2% per year). Patients with an abnormal MPD, both without or with WMA or CFR-LAD <2, showed a higher annual event rate (isolated MPD: 3.9%, MPD + WM/CFR-LAD: 9.8%, log-rank p < 0.001).

DISCUSSION

In the current study, both comparison of multivariable models and risk reclassification analysis dem-
onstrate that the addition of CFR-LAD and MP during SE progressively improve prognostication of future total cardiac events over usual WM assessment and clinical data. Importantly, to make WM assessment as repeatable and accurate as possible, WM was assessed using LV cavity opacification. The superiority of MP and CFR-LAD in this context is important, as it emphasizes that the results are unlikely to change with alterations to the WM analysis.

Myocardial perfusion versus wall motion. Existing diagnostic studies of WM and MP have emphasized superiority of specificity with the former, and sensitivity with the latter (12,17). Generally, MP is more useful to diagnose less severe (50% to 70%) and less diffuse CAD. From a prognostic standpoint, the predictive value of a negative test is very high with both negative WM and MP (5,18). The SE literature has shown MP to add incremental prognostic value to WM in the prediction of major events using the dobutamine-atropine protocol (5,6) and dipyridamole protocol (19), as well as a number of studies showing an improvement of composite endpoints (7,8,20). The practical problem in the incorporation of these data into practice has been that MP and CFR-LAD have remained technically challenging, in particular at the
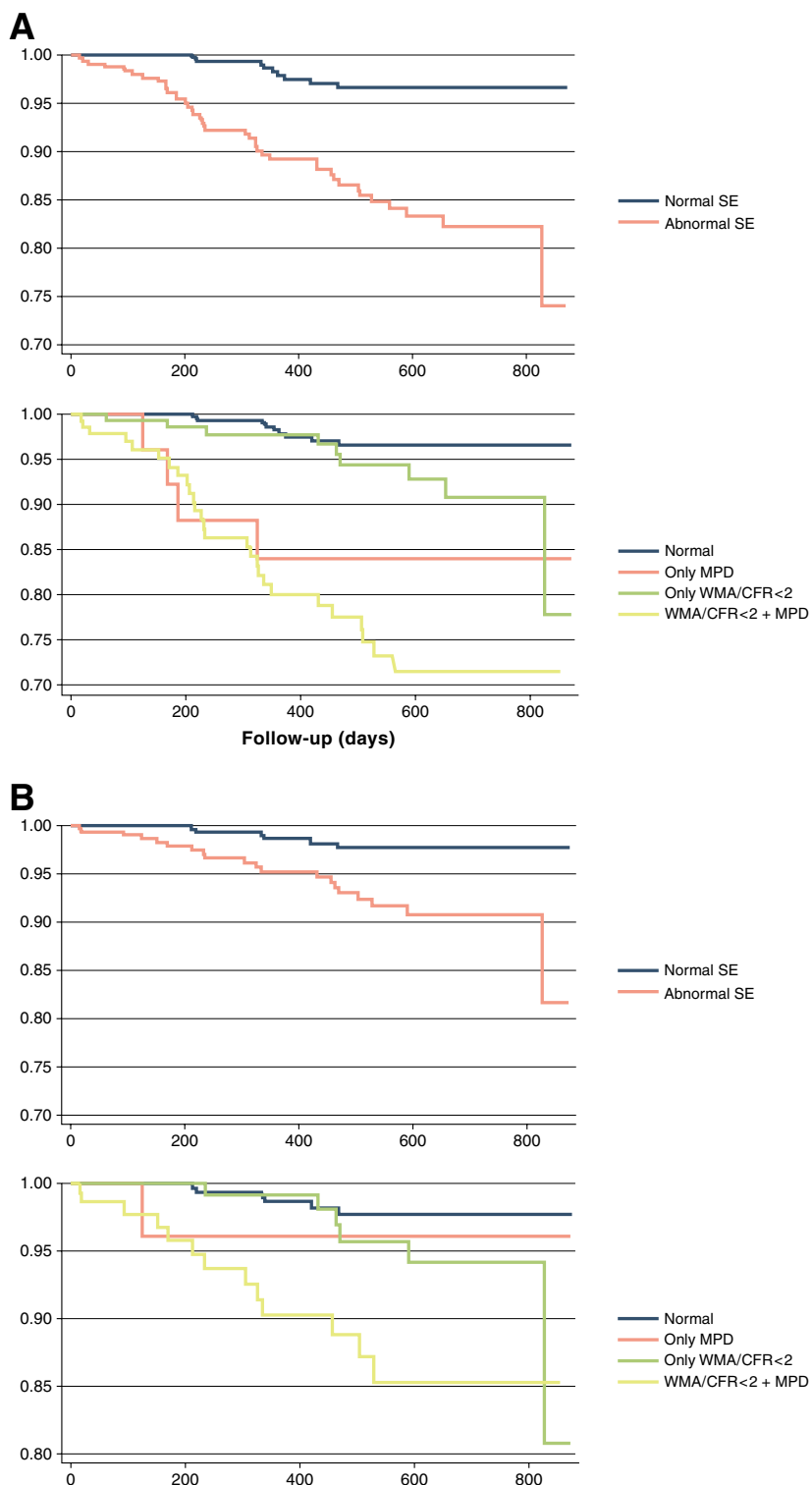
Figure 3. Total Cardiac and Hard Event-Free Survival Rates

(A) Total cardiac event-free survival rates classified by positivity of at least 1 contrast SE variable (either WMA, CFR-LAD <2, or MPD) or by possible combinations of contrast SE variables. Patients testing positive for both MPD and the combination of WMA/CFR-LAD <2 had the worst event-free survival (log-rank p value <0.001). **(B)** Cardiac hard event-free survival rates classified by positivity of at least 1 contrast SE variable (either wall motion abnormality [WMA], CFR-LAD <2, or MPD) or by possible combinations of contrast SE variables. Abbreviations as in Figures 1 and 2.

Table 2. Univariable and Selected Multivariable Cox Regression Analysis of the 3 SE Variables for the Prediction of Total Cardiac Events

	Univariate			Multivariate	
	Harrell C-Index (95% CI)	HR (95% CI)	p Value	HR (95% CI)	p Value
Demographics/cardiac risk factors					
Age, yrs	0.528 (0.45–0.61)	1.01 (0.99–1.04)	0.387		
Sex	0.550 (0.48–0.62)	1.62 (0.87–3.02)	0.127		
Family history of CAD	0.493 (0.42–0.56)	1.01 (0.56–1.83)	0.965		
Smoking habit	0.514 (0.45–0.58)	1.04 (0.54–1.99)	0.913		
Hypercholesterolemia	0.601 (0.54–0.66)	2.44 (1.27–4.68)	0.007		
Diabetes mellitus	0.595 (0.52–0.67)	2.28 (1.29–4.01)	0.004		
Hypertension	0.557 (0.50–0.62)	1.49 (0.79–2.82)	0.217		
Obesity	0.514 (0.48–0.55)	0.74 (0.27–2.05)	0.562		
CV history					
Previous MI/known CAD/revascularization	0.595 (0.52–0.67)	1.99 (1.13–3.51)	0.016		
Previous MI	0.558 (0.49–0.62)	1.72 (0.91–3.25)	0.095		
Previous revascularization	0.580 (0.50–0.65)	1.96 (1.09–3.51)	0.024		
Therapy at the time of stress test					
ASA	0.599 (0.54–0.66)	2.81 (1.36–5.80)	0.005		
Beta-blockers	0.562 (0.50–0.63)	1.56 (0.85–2.87)	0.151		
ACE	0.537 (0.47–0.60)	1.36 (0.72–2.58)	0.337		
Statins	0.554 (0.49–0.62)	1.60 (0.87–2.95)	0.128		
Stress echo					
Reduced LVEF, <50%	0.583 (0.51–0.65)	2.25 (1.28–3.95)	0.005		
CFR-LAD <2	0.654 (0.59–0.72)	3.58 (1.99–6.45)	0.000	2.25 (1.21–4.17)	0.01
WMA	0.589 (0.52–0.66)	3.01 (1.62–5.61)	0.001	0.72 (0.36–1.46)	0.37
MPD	0.735 (0.67–0.80)	6.57 (3.67–11.75)	0.000	5.97 (3.02–11.78)	<0.001
WMA or CFR-LAD <2	0.667 (0.60–0.73)	4.27 (2.27–8.06)	0.000		

CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; SE = stress echocardiography; other abbreviations as in Table 1.

high heart rate typical of the dobutamine-atropine protocol.

It has already been demonstrated that Doppler CFR-LAD measurement during DipSE can additionally stratify cardiac risk; the results of our study build on the previous work, showing the incremental benefit of CFR-LAD to be only a little less than MP for the prediction of future cardiac events relative to WMA. The C value was not significantly higher in models substituting MPD with combined WM/CFR-LAD, although they were higher when MPD was added to WM/CFR-LAD. These results support the contention that at least 1 of the 2 additional parameters (CFR-LAD or MP) should be used in addition to WM assessment for better stratification of risk during DipSE, and their additive value is clinically particularly useful when no WMA can be elicited by the stressor.

Approximately 140 patients had abnormal WM/CFR-LAD with normal MP, most because of a reduced CFR-LAD and normal WM, among whom abnormal but borderline (1.9 to 2.0) CFR-LAD results were present in 66 patients. The significance of this pattern is unknown; we suspect that it may relate to error in CFR measurement, but decreased CFR could also be due to microvascular impairment/endothelial dysfunction secondary to hypertension/diabetes/hypercholesterolemia. The clinical and prognostic meaning of this pattern cannot be addressed in this study design and requires a cross-sectional study with another functional marker of CAD, such as fractional flow reserve.

Previous SE studies and outcome risk stratification. In the largest published studies regarding the prognostic value of dipyridamole SE, the annual rate of hard events is typically close to 3% for patients with suspected CAD and close to 6% for patients with known CAD (2,3). In our population, which has similar clinical characteristics and a similar ratio of suspected versus known CAD, the annual hard event rate in the entire population was lower (2.8%), similar to the hard event rate of patients with suspected CAD in the previous studies. Several reasons could explain a lower event rate in our study, but the most intriguing hypothesis is that our study enrolled patients from current cardiology practice (between 2009 and 2011), whereas the above-mentioned landmark studies used historical

Table 3. The Multivariable Models Alternatively Incorporating Each of the Tested SE Parameters (WM, WM/CFR, MPD) or Combination of WM/CFR-LAD and MPD Risk Stratified Total Cardiac Events Better Than Clinical Parameters Only (Model 1) and Progressively Better From Model 2 Through Model 5

	Total Cardiac Events Multivariable Cox Models														
	Model 1—Clinical Parameters Only			Model 2—Clinical Parameters + WMA			Model 3—Clinical Parameters + WMA/CFR <2			Model 4—Clinical Parameters + MPD			Model 5—Clinical Parameters + WMA/CFR <2 + MPD		
	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
Hypercholesterolemia	2.03	(1.04–3.96)	0.04	1.97	(1.01–3.84)	0.05	1.92	(0.98–3.77)	0.06	1.72	(0.88–3.37)	0.10	1.69	(0.86–3.31)	0.13
Diabetes	1.89	(1.06–3.36)	0.03	1.76	(0.98–3.14)	0.06	1.72	(0.96–3.09)	0.07	1.80	(1.01–3.20)	0.04	1.75	(0.98–3.11)	0.06
Previous MI/ known CAD	1.84	(1.04–3.23)	0.04	1.63	(0.92–2.91)	0.10	1.65	(0.94–2.92)	0.08	1.52	(0.86–2.69)	0.21	1.46	(0.82–2.59)	0.20
CFR															
WMA				2.40	(1.27–4.55)	0.01									
MPD										5.72	(3.18–10.3)	0.00	4.11	(2.10–8.05)	0.00
WMA or CFR-LAD <2							3.87	(2.04–7.32)	0.00				1.99	(0.96–4.12)	0.07
AIC		588.28			583.90			570.31			555.33			553.78	
Harrell C-index		0.667 (0.596–0.738)			0.703 (0.633–0.772)			0.739 (0.673–0.805)			0.795 (0.734–0.855)			0.799 (0.739–0.858)	
Global chi-square					6.39			19.97			34.95			38.51	
p value for likelihood ratio test (compared with Model 1)					0.011			<0.001			<0.001			<0.001	

AIC = Akaike information criterion; WM = wall motion; other abbreviations as in Tables 1 and 2

databases of patients enrolled since 1995, when medical therapy was less intensive than at present. In our study, approximately two-thirds of patients were on therapy shown to have prognostic benefit (Table 1). In particular, 104 (77%) of the 135 patients with a prior MI were on therapy with high-dose/high-potency statins, defined as atorvastatin ≥40 mg or rosuvastatin ≥20 mg.

Clinical application. MP assessment was performed using repeated contrast boluses and flash-replenishment sequences, both with end-systolic triggering and in real time (Fig. 4, Online Videos 1, 2, 3, and 4).

Although continuous infusion would have been the ideal technique for analyzing contrast replenishment following a high mechanical index impulse and could have led to an even higher prognostic value of MP, we found that the bolus technique resulted in much lower contrast use, still producing satisfying results for visual analysis. Our group and others have shown that the analysis of contrast replenishment from small bolus injections of contrast is effective for detecting coronary artery disease, with accuracy values that exceed that of scintigraphic imaging (12,21).

Table 4. Summary of Model Comparisons for Total Cardiac Events Prediction, Based on Harrell C-Index and Likelihood Ratio Test

Summary Table for Model Comparison	p Value for Harrell C-Index Difference	p Value for Likelihood Ratio Test	NRI
Clinical parameters only model (Model 1) vs.			
Clinical data + WMA	0.148	**0.012**	0.810
Clinical data + WMA/CFR-LAD <2	**0.037**	**<0.001**	**0.001**
Clinical data + MPD	**<0.001**	**<0.001**	**<0.001**
Clinical parameters + WMA (Model 2) vs.			
Clinical data + WMA/CFR-LAD <2	0.242	Not feasible	**0.001**
Clinical data + WMA + MPD	**0.004**	**<0.001**	**<0.001**
Clinical data + MPD	**0.003**	Not feasible	**<0.001**
Clinical parameters + WMA/CFR-LAD (Model 3) vs.			
Clinical data + WMA/CFR-LAD >2 + MPD	**0.012**	**<0.001**	**0.025**
Clinical parameters + MPD (Model 4) vs.			
Clinical data + MPD + WMA/CFR-LAD <2	0.766	0.059	0.542

Risk reclassification is also shown, based on NRI. **Bold** values are statistically significant.
NRI = net reclassification improvement; other abbreviations as in Table 1.
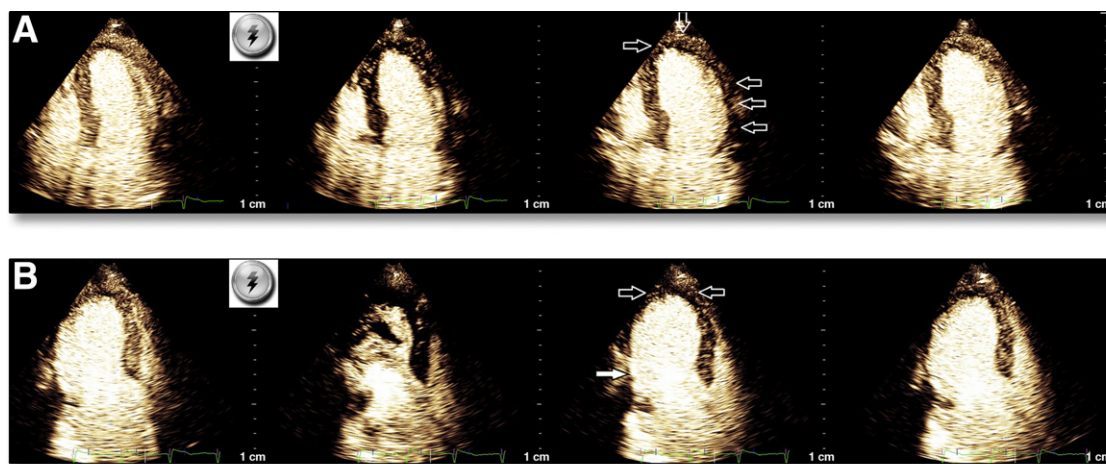
Figure 4. Example of a Flash-Replenishment Stress Perfusion Sequence

Stress perfusion sequence in apical 4-chamber **(A)** and 3-chamber **(B)** views; from **left to right**, end-systolic frame before destructive flash (see flash icon), post-flash, 2 s, and 4 s after flash. At the 2-s cutoff point for normal myocardial replenishment at stress, both the apical and lateral segments **(arrows)** show incomplete microbubble replenishment; wall motion is instead normal in the apical segments, but blunted (akinesia) in the lateral mid-basal segments both at rest (not shown) and at stress (Online Videos 1, 2, 3, and 4). The **white-filled arrow** points to an inferolateral subendocardial scar, often shown as hyperechogenic signal in the context of a fixed perfusion defect when using contrast-specific settings.

Although MP has a strong evidence base, its widespread application has been limited by technical complexity in its application and some subjectivity in its interpretation. MP is exquisitely sensitive for mild CAD, but problems with artifacts limit its interpretation in the absence of WM assessment; nonetheless, in our study, the number of segments with reversible MPD (in patients with abnormal MP) was 2.6 ± 1.5, and in this abnormal MP subgroup, only 28 patients had <2 segments with reversible MPD. This emphasizes the robustness of study findings. Moreover, although mid-apical segments for each coronary territory are usually interpretable, several perfusion assessments are incomplete because of limited feasibility in the basal myocardial segments.

Although exercise testing might be considered the best protocol in which to compare WM with other parameters, as it offers maximal stress and assessment of functional capacity, we selected pharmacological stress on the basis of the inability of many patients to exercise effectively. In addition, image degradation with exercise would make measurements of other parameters (MP, CFR-LAD) particularly difficult. The exclusion of parasternal images allowed direct comparison of all modalities in exactly the same view, but may have disadvantaged WM analysis when the apical window was poor.

Although 1 advantage of measuring CFR-LAD is that it is inherently quantitative, it should be recognized that there is a degree of subjectivity in the selection of tracings used to calculate the ratio among different measured velocities. Stenoses, tortuosity, and bridges can all lead to regional variation of measurements, both at rest and stress; consequently, the ratios can vary across the threshold of 2 in the same patient. The use of a contrast bolus enhances color Doppler signals from the mid-distal LAD, with feasibility being almost 100%. However, PW Doppler envelopes after contrast tend to be noisy, and experience is needed to obtain measurable diastolic peak velocities.

Although CFR-LAD and MP do not appear to have clear synergistic value in our study (only the addition of MPD to WM/CFR-LAD increased risk prediction assessment, and not the opposite), we demonstrated that the use of at least 1 of the 2 parameters improved prognostic stratification. The possibility of implementing WM, MP, and CFR-LAD during the same test may very well be a reason for greater use of vasodilators (dipyridamole or adenosine) for pharmacological SE in the future.

In this study, we used total cardiac events (n = 50) to be an appropriate and statistically robust endpoint. Censoring patients who undergo revascularization following a diagnostic test, as we did in the current study, is widely used to analyze prognostic studies, because of the potential confounding effect of revascularization. This excludes the highest risk patients from the study, reducing the total

number of hard events to 28, and possibly underestimating the discriminative power of the tests. In addition, censoring patients undergoing early revascularization may have led to a more pronounced underestimation of the value of WMA, because its presence and extent is used as an indication for revascularization (differential treatment selection bias).

CONCLUSIONS

Contrast SE allows for accurate risk stratification in patients with suspected or known ischemic heart disease. The multiparametric assessment of WM, CFR-LAD, and MP during stress testing is feasible, identifies patients at increased risk for cardiac events more accurately than usual standard WM assessment,

and separates them from those with normal findings who are at much lower risk. A normal MP stress test was the most reassuring result for patients undergoing SE, with a 1-year hard event rate of 1.2% and a total cardiac event rate of 2.1%. The addition of either CFR-LAD measurement or MP assessment to standard WM analysis and clinical parameters yielded progressively higher values for the prediction of total 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 is available with stand-alone WM assessment.

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