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Prognostic Value of High-Dose Dipyridamole Stress Myocardial Contrast Perfusion Echocardiography

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Background—The addition of myocardial perfusion (MP) imaging during dipyridamole real-time contrast echocardiography improves the sensitivity to detect coronary artery disease, but its prognostic value to predict hard cardiac events in large numbers of patients with known or suspected coronary artery disease remains unknown.

Methods and Results—We studied 1252 patients with the use of dipyridamole real-time contrast echocardiography and followed them for a median of 25 months. The prognostic value of MP imaging regarding death and nonfatal myocardial infarction was determined and related to wall motion (WM), clinical risk factors, and rest ejection fraction by the use of Cox proportional-hazards models, C index, and risk reclassification analysis. A total of 59 hard events (4.7%) occurred during the follow-up (24 deaths, 35 myocardial infarctions). The 2-year event-free survival was 97.9% in patients with normal MP and WM, 91.9% with isolated reversible MP defects but normal WM, and 67.4% with both reversible MP and WM abnormalities ($P<0.001$). By multivariate analysis the independent predictors of events were age (hazard ratio 1.05, 95% confidence interval [CI], 1.02–1.08), sex (hazard ratio, 2.36; 95% CI, 1.32–4.23), reversible MP defects (hazard ratio, 3.88; 95% CI, 1.83–8.21), and reversible WM abnormalities with reversible MP defects (hazard ratio, 4.51; 95% CI, 2.25–9.07). Reversible MP defects added incremental predictive value and reclassification benefit over WM response and clinical factors ($P=0.001$).

Conclusions—MP imaging using real-time perfusion echocardiography during dipyridamole real-time contrast echocardiography provides independent, incremental prognostic information regarding hard cardiac events in patients with known or suspected coronary artery disease. Patients with normal MP responses have better outcome than patients with normal WM; patients with both reversible WM and MP abnormalities have the worst outcome. (*Circulation*. 2012;126:1217-1224.)

Key Words: coronary artery disease ■ myocardial contrast echocardiography ■ prognosis ■ stress echocardiography ■ dipyridamole

Pharmacological stress echocardiography (SE) using wall motion (WM) analysis is an established cost-effective technique for the detection and prognostication of coronary artery disease (CAD). The prognostic value has been consistently demonstrated across different patient populations.^{1–7} Myocardial contrast perfusion (MP) imaging analysis during high-dose dipyridamole real-time contrast echocardiography (DipRCE) has been shown to increase the sensitivity and accuracy of standard WM analysis for detecting angiographically significant CAD.^{8,9} The incremental prognostic value of MP during DipRCE has also been demonstrated regarding combined cardiac events, but whether this also applies to performance benchmarks when considering only hard cardiac events (death and nonfatal myocardial infarction) remains to be determined.^{10–12} In the present study, we sought to determine the prognostic value of MP and WM during DipRCE in predicting death and nonfatal myocardial infar-

tion in a wide contemporary cohort of patients who underwent DipRCE for suspected or known CAD.

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Clinical Perspective on p 1224

Methods

Patients

We analyzed the outcome of 1252 consecutive patients with known or suspected CAD who were referred for DipRCE with the use of commercially available contrast agents in our laboratory from January 2008 to June 2011. Reasons for referral were evaluation of chest pain or dyspnea in 941 (75%), preoperative risk assessment in 111 (9%), evaluation of multiple cardiac risk factors in 50 (4%), or functional assessment of known CAD in 150 (12%). The study was approved by the Institutional Review Board of the University of Parma Medical Center, and all patients gave informed consent. Follow-up was completed in January 2012. The population consisted of 757 men (60%). Mean age in the study population was 66 ± 11

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Table 1. Clinical Characteristics and Echocardiographic Findings in the 1252 Recruited Patients

| | |
|--|----------|
| Age, μ ±SD | 66±11 |
| Male sex | 757 (60) |
| Risk factors and patient history | |
| Hypertension* | 893 (71) |
| Hypercholesterolemia† | 736 (59) |
| Current smokers | 301 (24) |
| Diabetes mellitus | 326 (26) |
| Family history of CAD | 366 (29) |
| Reduced LVEF (<50%) | 321 (26) |
| Rest WM abnormality | 518 (41) |
| Known CAD | 445 (36) |
| Previous myocardial infarction | 286 (23) |
| Previous revascularization | 365 (29) |
| Medications | |
| ACE-I/ARBs | 778 (62) |
| Statin | 723 (58) |
| β -blockers | 760 (61) |
| Aspirin | 799 (64) |
| Contrast-stress echo | |
| Patients with reversible WM abnormality | 237 (19) |
| Single/multivessel reversible WM abnormality | 181/56 |
| Patients with reversible MP defect | 393 (31) |
| Single/multivessel reversible MP defect | 261/132 |
| Patients with reversible WM abnormality and MP defect | 237 (19) |
| Patients without WM abnormality but reversible MP defect | 156 (12) |
| Patients without WM abnormality or MP defect | 859 (69) |

Data presented are mean±SD or n (%) of patients. CAD indicates coronary artery disease; LVEF, left ventricle ejection fraction; WM, wall motion; MP, myocardial perfusion; ACE-I, angiotensin-converting enzyme inhibitors; and ARBs, angiotensin receptor blockers.

*Blood pressure \geq 140/90 mm Hg or treatment of hypertension.

†Total cholesterol >200 mg/dL or treatment of hypercholesterolemia.

years. Patients were followed up for a median of 25 months (range, 6–48 months). Risk factors for CAD (also see Table 1) were diabetes mellitus in 326 (26%), systemic hypertension in 893 (71%), hypercholesterolemia in 736 (59%), and cigarette smoking in 301 (24%). Two hundred eighty-six patients (23%) had a history of a previous myocardial infarction and 365 (29%) had previous coronary percutaneous interventions or bypass surgery. Seven hundred sixty patients (61%) were on β -blockers, 778 (62%) were taking angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 799 (64%) were on aspirin, and 723 (58%) were taking statins. Six hundred three patients (48%) were on both aspirin and statin therapy; 488 (39%) were on aspirin, statin, and β -blockers, and 436 (35%) were on aspirin, statin, β -blockers, and an angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker. Diabetes mellitus was defined as a fasting plasma glucose level >125 mg/dL¹³ or the need for insulin or oral hypoglycemic agents. Hypercholesterolemia was defined as total cholesterol >200 mg/dL or treatment with lipid-lowering medications. Hypertension was defined as blood pressure >140/90 mm Hg or use of antihypertensive medication.

Stress Protocol

Dipyridamole was infused at the total dose of 0.84 mg/kg in all patients. A total of 461 patients underwent a 10-minute 0.84 mg/kg dipyridamole infusion+ atropine administration (\leq 1 mg), whereas the majority of patients (n=791) underwent a 6-minute protocol,

consisting of the 0.84 mg/kg dipyridamole infusion but no additional atropine administration. Two-dimensional echocardiography, 12-lead ECGs, and blood pressure monitoring were performed in accordance to established standard protocols.¹ Aminophylline was routinely used to reverse dipyridamole effect. When an obvious new WM abnormality (\geq 1 akinetic segment) was observed by the physician performing the test, dipyridamole infusion was stopped and aminophylline administered.

DipRCE Imaging

SE was performed with a commercially available ultrasound scanner (iE33, Philips Medical Systems) equipped with low mechanical-index real-time pulse sequence schemes that deploy interpulse phase-amplitude modulation.¹⁴ DipRCE was performed using the phospholipid-encapsulated microbubble SonoVue (Bracco Imaging), either in repeated slow 0.5-mL boluses (773 patients) or continuous infusion at 0.8 to 1.2 mL/min (479 patients) by using a dedicated rotating pump.

Myocardial perfusion was studied at rest and after dipyridamole infusion by activation of low-mechanical index power-modulation imaging so that cine-loops of flash-replenishment sequences (both real-time and end-systolic triggered at every cardiac cycle) were digitally acquired in the apical 4-, 2-, and 3-chamber views. The low-mechanical index setting was activated just before administration of contrast, and the time gain compensation and 2-dimensional gain settings were adjusted to suppress any nonlinear signals from tissue at a mechanical index=0.08 to 0.12 and frame rate of >30 Hz. In case of bolus contrast administration (SonoVue 0.5 mL), the ideal timing to start acquiring the MP flash-replenishment sequences was when attenuation from left ventricular cavity contrast had resolved, usually 15 to 20 seconds after peak video intensity was reached, during the washout of contrast.

Wall motion was assessed at rest and after dipyridamole infusion by activation of a specific preset for contrast WM analysis (left ventricular opacification, with harmonic imaging, a higher mechanical index=0.27 and frame rate=40 Hz), whereas the standard 2-dimensional preset was resumed, after microbubble clearance, for continuous WM monitoring through the remainder of the stress test.

Image Analysis

The left ventricle was divided in 17 segments according to the recommendations of the European Association of Echocardiography and the American Society of Echocardiography.^{1,2}

Myocardial perfusion was visually assessed by the use of the following criteria: normal perfusion after dipyridamole was assigned if myocardium was fully replenished 1.5 to 2 seconds after the end of the flash impulse, and stress perfusion was defined as abnormal if myocardium was not fully replenished after this time in \geq 1 contiguous segment. Normal myocardial replenishment at rest was defined as complete replenishment within 4 seconds after the flash impulse. A myocardial perfusion defect was scored as fixed or reversible based on its presence at rest. Left ventricle segments were excluded from MP reading if not clearly visualized, owing to shadowing artifacts or low ultrasound penetration, especially in the basal segments. 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 \geq 1 segment.

Patients were also classified according to the extent of abnormality. They were considered to have single-vessel abnormality when the MP defect or WM abnormality involved only 1 coronary artery territory and multivessel abnormality when the MP defect or WM abnormality involved >1 coronary artery territory. The left ventricular apex, anteroseptal, distal septum, and anterior walls were assigned to the left anterior descending coronary artery, the lateral wall to the left circumflex, and the inferior wall and basal septum to the right coronary artery. The results of both MP and WM analyses were made available to the referring physicians.

Interobserver agreement data for WM and MP in our laboratory have been previously published,^{8,10} but an additional assessment with an expert external reader (T.R.P.) on 20 randomly selected

study cases was also performed and reported as a percentage with a corresponding κ value.

Follow-Up

Follow-up was obtained by review of the patient's hospital chart, electronic records, and telephone interview with the patient. The study primary end points were death from any cause and nonfatal myocardial infarction.¹⁵ Nonfatal myocardial infarction was defined by means of a serial increase in cardiac-specific enzymes and/or development of new ECG changes. Because the results of SE may have influenced whether the patients had a revascularization procedure that could have altered their subsequent event rate, any patient who underwent percutaneous coronary intervention or coronary artery bypass grafting at any time after DipRCE (n=184) were censored at the time of their procedure.

Statistical Analysis

Continuous variables are expressed as mean and SD, categorical variables as proportions.

Kaplan-Meier curves were used to estimate the distribution of time to hard events and curves were compared with the use of the log-rank test. Univariate and multivariate Cox models were used to estimate the risk of events. Subjects were either censored at the end of the follow-up period or at the time of revascularization, or revascularization was evaluated by the use of stratified models in which stratification was determined on the basis of the performance of these procedures.

Rest left ventricular ejection fraction (LVEF) was analyzed as a dichotomous variable (<50% or \geq 50%); additional clinical variables considered in the analyses were defined according to the Framingham risk score assessment. These additional variables included diabetes mellitus, hypercholesterolemia, and hypertension. Clinical variables such as history of previous myocardial infarction, known CAD, and previous revascularization were also considered. Echocardiographic parameters were rest LVEF, WM, and MP ischemic responses to dipyridamole. Aspirin, angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers, and statin therapy at enrollment were considered in univariate analysis, but, because of the unreliable nature of these data when recorded at the single time point of study enrollment and not consistently during follow-up, they were not considered further for potential inclusion in multivariate models. All other clinical and DipRCE variables with $P < 0.1$ at univariate analysis were considered for multivariate models.

A first multivariate clinical model was derived without considering DipRCE variables, then WM was added to this model, followed by MP data. The significance of additional variables to previous modeling steps was based on the likelihood ratio test. The usefulness of contrast DipRCE variables over clinical variables and rest LVEF was then verified in terms of discrimination power and reclassification.

The Harrell C index was used to evaluate discrimination, whereas the net reclassification index¹⁶ was used for risk reclassification. Because there are no universally accepted thresholds for hard events as defined in our study, we examined reclassification using thresholds of 1% and 3% hard cardiac events per year to define low-, intermediate-, and high-risk groups. The capability of a new imaging stress modality to pinpoint low-risk subjects, with <1% yearly hard event rate, has in fact been identified as a performance benchmark.¹⁷ We then considered the >3% high-risk threshold as appropriate, based on a hard event rate of 3.1% per year in our overall population.

Finally, the same strategies were then applied again to assess the consistency of DipRCE variables as prognosticators, this time including patients who had undergone coronary revascularization after enrollment and using stratified models in which stratification was determined on the basis of the performance of these procedures, instead of censoring them at the time of their revascularization procedure as it done for the main study results.

Results

There were 321 patients (26%) with baseline LVEF <50%. During the study period, 184 patients (15%) had a revascu-

larization procedure, either percutaneous (n=176) or surgical (n=8). Most of these procedures were within 3 months of the DipRCE (156 of a total 184 revascularized patients). Thirteen of those 184 patients (7%) had normal WM and MP responses to DipRCE, 19 had normal WM and abnormal MP (10%), and 152 (83%) had both abnormal WM and MP responses during DipRCE. In the remaining 1068 patients, the stress echocardiogram was interpreted as normal for WM in 983 patients (92%) and abnormal in 85 patients (8%), whereas MP was interpreted as normal in 846 patients (79%) and abnormal in 222 (21%). The results of both tests were normal in 846 (79%) and abnormal in 85 patients (8%). There were 137 patients (13%) with normal WM but abnormal MP. In the study cohort, no patient had abnormal WM with normal MP. In 27 of the 85 tests with an ischemic WM response, the dipyridamole infusion was terminated early or just after the full dose without waiting for the prescribed 2 to 4 minutes to develop its full vasodilator effect, because of an obvious WM abnormality in \geq 1 segment. The distribution of the results of WM and MP analysis are presented in Table 1, together with baseline characteristics. The interobserver agreement of DipRCE in our laboratory is 87.5% ($\kappa=0.75$) for MP and 90% ($\kappa=0.80$) for WM,⁸ but a specific assessment of interobserver agreement with an external blinded expert reader (T.R.P.) on 20 randomly selected study cases resulted 80% ($\kappa=0.60$) for MP and 95% ($\kappa=0.83$) for WM.

Outcome and Predictors of Death or Nonfatal Myocardial Infarction

The median follow-up for patients who did not experience an event was 25.7 months (lower, upper quartiles 372, 1191 days). A total of 59 (4.7%) patients had events during the follow-up. Events occurred at a median of 12 months (lower, upper quartiles 190, 470 days) after DipRCE test and included death in 24 patients and nonfatal myocardial infarction in 35 patients.

The clinical characteristics of patients with and without subsequent events are presented in Table 2.

Table 3 shows univariate and multivariate predictors of follow-up events; age (hazard ratio [HR] 1.05; 95% confidence interval [CI], 1.02–1.08), sex (HR, 2.36; 95% CI, 1.32–4.23), reversible MP defects (HR, 3.88; 95% CI, 1.83–8.21), and reversible WM abnormalities (HR, 4.51; 95% CI, 2.25–9.07) were the only independent clinical and SE predictors in the multivariate analysis. There were 2 additional variables that were significant at univariate analysis; diabetes mellitus and rest reduced LVEF, but these did not maintain significance at multivariate analysis ($P=0.07$ and $P=0.097$, respectively).

Outcome According to Stress Perfusion Defects or WM Abnormalities

The outcome of patients, according to the presence of reversible MP defect or WM abnormalities, is depicted in Figure 1. The 2-year event-free survival was 97.9% in patients with both normal MP and WM (n=18 events), 91.9% in patients with isolated reversible MP defects but normal WM (n=11 events), and 67.4% in patients with both inducible MP defects and WM abnormalities (n=28 events)

Table 2. Clinical Features of Patients With and Without Subsequent Hard Cardiac Events

| | Patients Without Events, n (%) n=1193 | Patients With Events, n (%) n=59 |
|----------------------------------|---------------------------------------|----------------------------------|
| Age, y±SD | 66±11 | 71±9* |
| Male sex | 714 (60) | 43 (73)† |
| Risk factors and patient history | | |
| Hypertension‡ | 848 (71) | 45 (76) |
| Hypercholesterolemia§ | 699 (59) | 37 (63) |
| Current smokers | 291 (24) | 10 (17) |
| Diabetes mellitus | 304 (25) | 22 (37)† |
| Family history of CAD | 351 (29) | 15 (25) |
| Reduced LVEF (<50%) | 298 (25) | 23 (39)† |
| Known CAD | 418 (35) | 27 (46) |
| Previous myocardial infarction | 274 (23) | 12 (20) |
| Previous revascularization | 343 (31) | 22 (37) |
| Medications | | |
| ACE-I/ARBs | 741 (62) | 37 (63) |
| Statin | 686 (58) | 37 (63) |
| β-blockers | 723 (61) | 37 (63) |
| Aspirin | 753 (63) | 46 (78)† |

CAD indicates coronary artery disease; LVEF, left ventricle ejection fraction; ACE-I, angiotensin-converting enzyme inhibitors; and ARBs, angiotensin receptor blockers.

* $P<0.001$.

† $P<0.05$.

‡Blood pressure $\geq 140/90$ mm Hg or treatment of hypertension.

§Total cholesterol >200 mg/dL or treatment of hypercholesterolemia.

($P<0.001$ between each of the 3 groups). The cumulative event rate for each pattern of abnormality in patients either with or without known CAD/previous myocardial infarction/revascularization is shown in Figure 2. The territorial extent of reversible ischemia (single versus multivessel territory), defined either by reversible MP defects or WM assessment, was not a determinant of prognosis (log-rank=not significant for single versus multivessel abnormality, either for WM or MP variable).

Incremental Value of MP and WM Over Clinical Characteristics to Predict Death and Nonfatal Infarction

Sequential Cox regression models were fit to test the incremental value of MP analysis over WM and over clinical variables and rest LVEF $<50\%$ on outcome prediction (Figure 3). Abnormal stress WM at DipRCE increased the χ^2 to 75.7 in comparison with clinical variables+rest LVEF $<50\%$ ($P<0.001$). However, the further addition of abnormal MP to all of these variables added significant incremental value in predicting outcome (χ^2 118 versus 107; $P=0.001$).

Model Comparison (C Statistics) and Risk Reclassification (Net Reclassification Index)

Comparison of the Harrell C index for each model showed that the addition of either stress WM or stress MP to the pre-DipRCE model, comprising only baseline clinical vari-

Table 3. Univariate Analysis of Main Clinical and Imaging Parameters and Multivariate Analysis of 6 Variables, Selected Based on Univariate Analysis Data

| | HR (95% CI) | P |
|-----------------------------|--------------------|----------|
| Univariate analysis | | |
| Age | 1.05 (1.03–1.08) | <0.001 |
| Male sex | 1.92 (1.08–3.40) | 0.026 |
| Known CAD (MI/PCI/CABG) | 1.66 (0.99–2.77) | 0.053 |
| Family history of CAD | 0.85 (0.47–1.52) | 0.577 |
| Smoke | 0.62 (0.31–1.22) | 0.165 |
| Hypercholesterolemia | 1.28 (0.75–2.17) | 0.368 |
| Diabetes mellitus | 1.86 (1.10–3.16) | 0.021 |
| Hypertension | 1.35 (0.74–2.46) | 0.324 |
| Obesity | 0.65 (0.26–1.64) | 0.365 |
| ACE-I/ARBs at enrollment | 1.197 (0.70–2.03) | 0.504 |
| Statin at enrollment | 1.477 (0.87–2.50) | 0.147 |
| β-blockers at enrollment | 1.377 (0.81–2.33) | 0.235 |
| Aspirin at enrollment | 2.46 (1.332–4.567) | 0.004 |
| LVEF reduction (<50%) | 1.78 (1.04–3.04) | 0.034 |
| Rest WM abnormality | 1.35 (0.81–2.26) | 0.25 |
| Inducible WM abnormalities* | 14.27 (8.53–23.89) | <0.001 |
| Fixed WM abnormalities | 1.58 (0.93–2.69) | 0.093 |
| Inducible MP abnormalities | 9.56 (5.49–16.67) | <0.001 |
| Multivariate analysis | | |
| Age | 1.05 (1.02–1.08) | 0.001 |
| Male sex | 2.36 (1.32–4.23) | 0.004 |
| Diabetes mellitus | 1.63 (0.96–2.77) | 0.07 |
| LVEF reduction (<50%) | 1.58 (0.92–2.70) | 0.097 |
| Inducible WM abnormalities* | 4.51 (2.25–9.07) | <0.001 |
| Inducible MP abnormalities | 3.88 (1.83–8.21) | <0.001 |

CAD indicates coronary artery disease; CI, confidence interval; MI, myocardial infarction; PCI/CABG, percutaneous/surgical coronary revascularization; ACE-I, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; LVEF, left ventricle ejection fraction; WM, wall motion; and MP, myocardial perfusion.

*All patients with inducible WM abnormalities also had reversible MP defects.

ables+ rest LVEF data, did increase significantly the C index (0.809 versus 0.688 and 0.822 versus 0.688, $P<0.001$ for both comparisons), but there was no significant difference between the C-index values obtained by substituting stress WM with stress MP on top of the pre-DipRCE model (0.809 versus 0.822, $P=0.48$). Figure 4 shows net reclassification index analysis¹⁶ demonstrating that the addition of either WM or MP data on top of clinical data significantly increased the accuracy of risk classification ($P<0.001$). Significant reclassification was observed by substituting WM data with MP in the models also comprising the pre-DipRCE variables and when adding MP data on top of WM plus pre-DipRCE data.

Continuous Infusion or Repeated Bolus Administration of Contrast Media

We analyzed the prognostic value of WM and MP separately in the first 479 enrolled patients, in whom a continuous infusion of contrast was used, and in the following 773

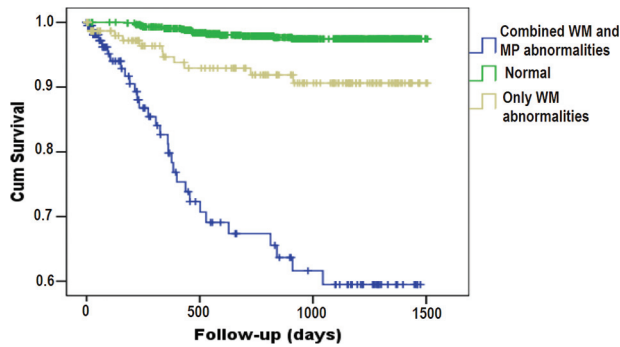


Figure 1. Kaplan-Meier curves based on the combination of WM and MP data. Differences between curves are statistically significant ($P < 0.001$). WM indicates wall motion; MP, myocardial perfusion; Cum, cumulative; and abn., abnormalities.

patients, in whom repeated small contrast boluses were used. In both groups, the model comprising the 2 DipRCE variables showed that both stress WM and MP were independently predictive of hard events (in the continuous infusion group MP HR, 6.70; 95% CI, 1.89–23.77; $P = 0.003$ and WM HR, 4.89; 95% CI, 1.89–23.77; $P = 0.001$; in the bolus group MP HR, 3.52; 95% CI, 1.27–9.76; $P = 0.016$ and WM HR, 5.35; 95% CI, 1.89–15.17; $P = 0.002$).

Revascularization Effect

Revascularization referral was driven predominantly by SE results and this relationship may have introduced a referral bias that would obfuscate the relationship between test results and subsequent patient risk because of the influence of revascularization in reducing post-SE events. To overcome this potential bias, rather than censoring the 184 patients referred to revascularization at any time after SE as was per protocol used in all previous analyses, we also evaluated Cox proportional hazards models and reclassification retaining those 184 patients in our analysis. This stratified model thus estimated the effect of predictors on hard events across strata determined by revascularization. Although the Harrell C index of the models and reclassification data did slightly change in comparison with data obtained after simply censoring revascularized patients, the selection of variables that were statistically significant and the data regarding model comparisons did not vary (Table 4).

Discussion

In this study, we specifically compared the ability of MP imaging and WM analysis during dipyridamole contrast

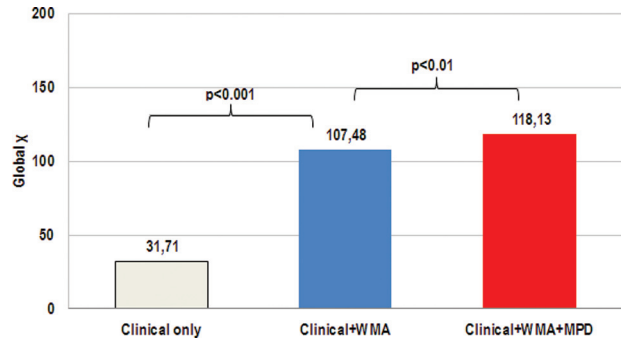


Figure 3. Incremental values (expressed on y axis as χ^2 values with incremental degrees of freedom) of abnormal WM, and abnormal MP over clinical variables+rest LVEF, using a Cox model. WM indicates wall motion; MP, myocardial perfusion; LVEF, left ventricle ejection fraction; WMA, wall motion abnormality; and MPD, myocardial perfusion defect.

echocardiography to predict hard cardiac events in patients with known or suspected CAD. Reversible MP abnormalities during DipRCE were independently (multivariate) and incrementally (global χ^2) predictive of death and nonfatal myocardial infarction; MP was also able to better reclassify true risk of hard events with respect to clinical variables+rest LVEF and WM data.

C statistics, on the contrary, did not show a significant difference between the accuracy of the model using clinical variables+rest LVEF and WM data and the one in which WM is substituted by MP. This highlights that MP should not simply substitute WM analysis during DipRCE, but the 2 variables are complementary and may have different clinical interpretation for the cardiologist. A normal MP response during DipRCE, which is the most frequent result, is always accompanied by a normal WM response and identifies a low-risk patient group (close to 1% yearly hard event rate) with a better outcome than patients with a normal WM but abnormal MP response (Figure 5). On the contrary, an ischemic WM response, which was the least frequent result and always accompanied by MP defects, predicted the highest risk for subsequent nonfatal myocardial infarction or death.

Patients with a normal MP response (69% of patients in our population) can be reassured regarding their low risk of future 1- or 2-year hard events, regardless of their clinical risk factors or previous CAD history.

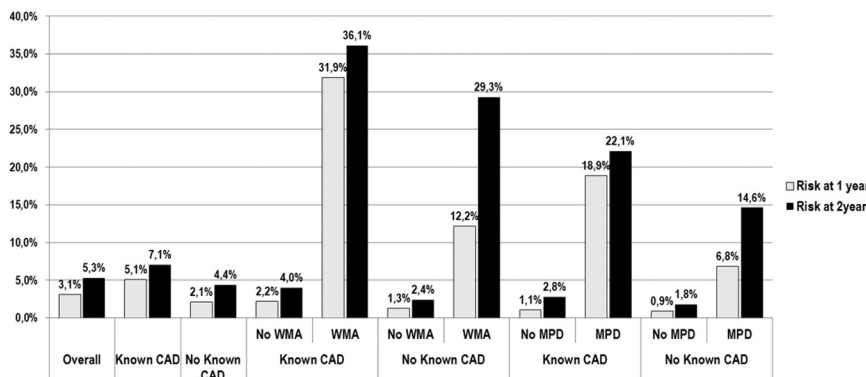


Figure 2. The cumulative 1- and 2-year hard event rate in the overall population, subsets with or without previously known CAD and for each pattern of abnormality either in patients with or without previously known CAD. CAD indicates coronary artery disease; Known CAD, previously known CAD or previous myocardial infarction or previous revascularization; WMA, wall motion abnormality; and MPD, myocardial perfusion defect.

| | CUT-OFF 1% and 3% | |
|-------------------------------|-------------------|-------------|
| | NRI | NRI P-value |
| Clinical vs Clinical+WM | 35% (18%-51%) | <0.001 |
| Clinical vs Clinical+MP | 53% (34%-71%) | <0.001 |
| Clinical+WM vs Clinical+MP | 18% (8%-28%) | 0.001 |
| Clinical+WM vs Clinical+WM+MP | 12% (2.4%-22%) | 0.014 |

Figure 4. Net reclassification operated by the addition or substitution of SE variables, according to the method proposed by Pencina et al¹⁵. WM indicates wall motion; MP, myocardial perfusion; NRI, net reclassification index; and SE, stress echocardiography.

Role of MP and WM Imaging With DipRCE in Predicting Events

The present study is the first to evaluate the role of DipRCE as a prognostic tool for hard events in patients with known or suspected CAD, and evaluates the effect of real-time perfusion echocardiography on risk reclassification. DipRCE has advantages over myocardial scintigraphy, including no irradiation, higher resolution, shorter test duration, immediate availability of results at the bedside, and the ability to perform stress and rest images in the same setting. Studies comparing DipRCE with quantitative angiography have demonstrated a significant improvement in test sensitivity with MP imaging over WM analysis^{8,9}. This study emphasizes that MP imaging, in addition to improving the sensitivity to detect CAD, also improves the predictive value of the test for future hard cardiac events. Despite the incremental value of MP imaging, our study indicates that assessing both WM and MP during DipRCE is helpful in determining risk; moreover, WM obtained higher hazard ratio for hard events prediction in comparison with MP. The relative contribution of MP and WM assessment to risk stratification during provocative testing may vary depending on the study population, the end points, the specific stressor used, or the imaging modality, each with its technical and methodological strengths and weaknesses.^{18–21} For example, studies using a dobutamine-atropine protocol demonstrated that MP had a higher hazard ratio than WM for prediction of hard events.^{18,19} This may be due either to the different stress mechanism of the dobutamine-atropine protocol or to the lower-than-ideal frame rate that could technically be used in that study for analyzing WM, especially given the high heart rate typical of dobutamine-atropine protocol. In this context, temporal resolution (ie, frame rate) was not an issue for MP assessment.

In the present study, the Cox sequential regression model indicated that both WM and MP analyses added significant

value to the prediction of outcome. Second, patients with both WM and MP abnormalities had the worst prognosis, indicating improved specificity for the prediction of events when results of both techniques are abnormal.

The extent of MP defects or WM abnormalities (single versus multivessel territory) did not show additional predictive value. This should be interpreted with caution for several reasons, because (1) a significant number of patients with multivessel territory ischemia (41 of 56 with multivessel WM abnormalities, 64 of 132 with multivessel MP defects) were excluded (censored) from main analysis because they underwent revascularization, (2) our protocol, as described in Methods, was routinely stopped/reversed as soon as the first WM abnormality became evident, which may prevent the detection of multivessel WM or MP abnormalities, and (3) vasodilator SE tends to be a suboptimal stressor for identification of multivessel abnormalities, with the worst coronary territory often obscuring less diseased territories.

MP during DipRCE has consistently been more sensitive, but less specific, than WM for CAD detection, and its utility consequently maximized when less severe CAD, in terms of stenosis percentage and number of affected territories, is to be addressed. This study demonstrates that MP behaves similarly regarding prognostication of hard cardiac events, significantly expanding the identification and number of patients truly at risk in comparison with WM (higher sensitivity). However, this also resulted in a slightly lower hazard ratio of MP compared with WM for prediction of hard events (lower specificity). Although some may object that the higher sensitivity/lower specificity of MP results in a higher number of normal coronary angiograms, this is not the case for prognostication, when expanding the identification of patients at risk for hard events may possibly reduce serious cardiac events through the simple extension of intensive medical

Table 4. Comparison Between Predictive Models Obtained Censoring Patients Who Underwent Revascularization as in the Main Analysis (n=184) or Including Those Patients and Their Following Events (n=10) Through the End of the Study, Stratifying Models on the Basis of the Performance of Coronary Revascularization

| | Revascularized Patients Censored | | | Revascularized Patients Included | | |
|-------------------------------|----------------------------------|------------------|-----------|----------------------------------|------------------|--------|
| | NRI | P for Difference | | NRI | P for Difference | |
| | | P | Harrell C | | χ ² | P |
| Clinical vs clinical+WM | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Clinical vs clinical+MP | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Clinical+WM vs clinical+WM+MP | 0.014 | 0.076 | 0.001 | 0.001 | 0.120 | 0.002 |

WM indicates wall motion; MP, myocardial perfusion; and NRI, net reclassification index.

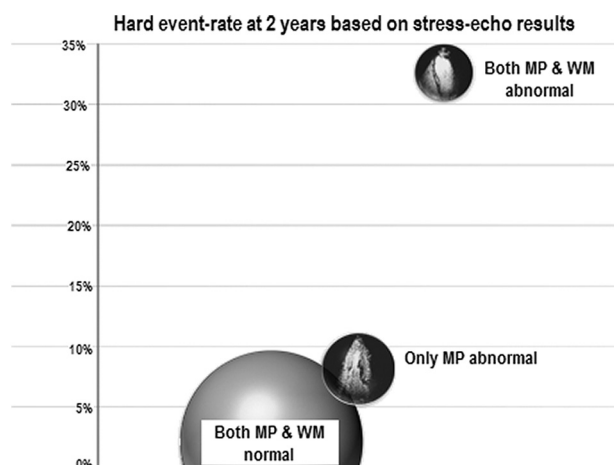


Figure 5. Risk of developing death or nonfatal myocardial infarction at 2 years, disregarding clinical data and based on imaging results only (y axis), in patients who were not revascularized during follow-up; different bubble dimensions represent patient numbers in each subgroup (normals=846 patients, isolated reversible MP defect=137 patients, both reversible MP and WM abnormal=85 patients). WM indicates wall motion; MP, myocardial perfusion.

therapy to patients not previously recognized as high risk by standard WM assessment.

Study Limitations

In the main analysis, we censored patients who underwent revascularization at any time after stress testing, because of the potential confounding effect of revascularization. This is considered a reasonable choice for prognostic studies, but by so doing we virtually excluded the highest-risk patients from the study, reducing the total number of events and possibly underestimating the discriminative power of the diagnostic test. This would be especially true for an inducible WM abnormality, because its presence and extension remains the main instrumental parameter currently used to indicate revascularization (whereas MP defect alone may not per se result in indication for revascularization). Still, the majority of revascularized patients (82%) had both a MP defect and WM abnormality, so that it is unlikely that censoring revascularized patients posed a differential bias in the assessment of the prognostic value of MP or WM. To better elucidate this effect, we conducted a second prognostic analysis including revascularized patients, which demonstrated that stratifying models by revascularization procedure did not alter the predictive value of perfusion or wall motion responses (Table 4).

Electrocardiographic and hemodynamic changes during stress were not analyzed in our study, but these parameters have never been clearly associated with prognosis during dipyridamole SE.^{6,7}

It is also unclear what role medications had on patient outcome, because these medications were not tracked during the follow-up period. Because lipid-lowering and antiplatelet agents have a significant impact on survival in CAD, their affect on the outcome of patients with abnormal perfusion during stress testing needs to be explored. The advantage of real-time perfusion echocardiography in this setting is that the effects of medications and other lifestyle modifications on

myocardial blood reserve can be serially assessed without the radiation risk incurred with serial radionuclide imaging.²²

Both bolus and continuous infusion contrast techniques were used for this study. Although continuous infusion would have been the ideal technique for analyzing contrast replenishment following a high mechanical index impulse, we found that the bolus technique resulted in much lower contrast utilization and produced equivalent results for visual analysis. Others have shown that the analysis of contrast replenishment from small bolus injections of contrast is effective for detecting CAD, with accuracy values that exceed the accuracy of single-photon emission computed tomography imaging.²³ In this study, we also found that the predictive value of DipRCE was equivalent when using bolus injections or continuous infusion.

Conclusions

MP analysis during DipRCE provides independent information for predicting mortality and nonfatal myocardial infarction in patients with known or suspected CAD after adjustment for clinical data, ejection fraction, and WM analysis. Patients with abnormal WM and MP are at higher risk for hard events. A normal MP study is associated with better survival than a normal WM study.

Disclosures

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CLINICAL PERSPECTIVE

Dipyridamole real-time contrast echocardiography (DipRCE) has considerable advantages over other imaging stress-tests, including no irradiation, spatial and temporal resolution, short test duration, immediate availability of results at the bedside, and the ability to perform stress and rest images in the same setting. The addition of myocardial perfusion (MP) imaging over standard wall motion (WM) analysis during DipRCE improves the sensitivity to detect coronary artery disease (CAD), but its risk reclassification potential to predict hard cardiac events in large numbers of patients with known or suspected CAD remains unknown. We studied 1252 patients with DipRCE and followed them for a median of 25 months. A total of 59 hard events (4.7%) occurred during the follow up (24 deaths, 35 myocardial infarctions). Reversible MP defects added incremental prognostic value and risk reclassification benefit to predict hard events, after adjustment for clinical data, ejection fraction, and WM analysis. A normal MP response during DipRCE identified a low-risk patient group (close to 1% yearly hard event rate) with a better outcome than patients with a normal WM but abnormal MP response. An ischemic WM response, which was always accompanied by MP defects, predicted the highest risk of hard events. Patients with a normal MP response can be reassured regarding their low risk of future 1 or 2-year hard events, regardless of their clinical risk factors or previous CAD history. MP should not simply substitute WM analysis during DipRCE, but the 2 variables are complementary and may have different clinical implications for the cardiologist.