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ORIGINAL RESEARCH

Coronary Flow Reserve During Dipyridamole Stress Echocardiography Predicts Mortality

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OBJECTIVES The goal of this study was to evaluate the ability of coronary flow reserve (CFR) over regional wall motion to predict mortality in patients with known or suspected coronary artery disease (CAD).

BACKGROUND CFR evaluated using pulsed Doppler echocardiography testing on left anterior descending artery is the state-of-the-art method during vasodilatory stress echocardiography.

METHODS In a prospective, multicenter, observational study, we evaluated 4,313 patients (2,532 men; mean age 65 ± 11 years) with known (n = 1,547) or suspected (n = 2,766) CAD who underwent high-dose dipyridamole (0.84 mg/kg over 6 min) stress echocardiography with CFR evaluation of left coronary descending artery (LAD) by Doppler. Overall mortality was the only endpoint analyzed.

RESULTS Stress echocardiography was positive for ischemia in 765 (18%) patients. Mean CFR was 2.35 ± 0.68. At individual patient analysis, 1,419 (33%) individuals had CFR ≤2. During a median follow-up of 19 months (1st quartile 8; 3rd quartile 36), 146 patients died. The 4-year mortality was markedly higher in subjects with CFR ≤2 than in those with CFR >2, both considering the group with ischemia (39% vs. 7%; $p < 0.0001$) and the group without ischemia at stress echocardiography (12% vs. 3%; $p < 0.0001$). At multivariable analysis, CFR on LAD ≤2 (hazard ratio [HR]: 3.31; 95% confidence interval [CI]: 2.29 to 4.78; $p < 0.0001$), ischemia at stress echocardiography (HR: 2.40, 95% CI: 1.65 to 3.48, $p < 0.0001$), left bundle branch block (HR: 2.26, 95% CI: 1.50 to 3.41; $p < 0.0001$), age (HR: 1.08, 95% CI: 1.06–1.10; $p < 0.0001$), resting wall motion score index (HR: 3.52, 95% CI: 2.38 to 5.21; $p < 0.0001$), male sex (HR: 1.74, 95% CI: 1.12 to 2.52; $p = 0.003$), and diabetes mellitus (HR: 1.47, 95% CI: 1.03 to 2.08; $p = 0.03$) were independent predictors of mortality.

CONCLUSIONS CFR on LAD is a strong and independent indicator of mortality, conferring additional prognostic value over wall motion analysis in patients with known or suspected CAD. A negative result on stress echocardiography with a normal CFR confers an annual risk of death <1% in both patient groups. (J Am Coll Cardiol Img 2012;5:1079–85) © 2012 by the American College of Cardiology Foundation

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The combination of conventional wall motion analysis with 2-dimensional echocardiography and coronary flow reserve (CFR) with pulsed Doppler flowmetry of mid-distal left anterior descending artery (LAD) is the recommended technique during vasodilator stress echocardiography (1). CFR has the proven ability to exert a powerful and additive prognostic value in several subsets of patients in large-scale multicenter studies: those with known or suspected coronary artery disease (CAD) (2), diabetes mellitus (3), normal or near-normal coronary arteries (4), and hypertension (5). It is equally effective for risk stratification both in men and women with chest pain and in those with normal results of dipyridamole stress echocardiography according to wall motion criteria (6). In addition, CFR is not modulated by concomitant medical therapy (5), allowing an excellent risk stratification even in the presence of negative result by wall motion analysis on medical therapy (7,8). However, all previous studies have analyzed composite endpoints whereas mortality is the most clinically meaningful prognostic endpoint (9,10). It has already been demonstrated that in patients with known or suspected CAD pharmacological or exercise stress echocardiography is an independent predictor of death, incremental to other clinical and echocardiography parameters (11–13). The purpose of this study was to assess the long-term value of dipyridamole stress echocardiography with the combined assessment of CFR on LAD for predicting mortality in patients with known or suspected CAD in a large-scale, multicenter, observational and prospective study.

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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CFR = coronary flow reserve

LAD = left anterior descending artery

METHODS

Patients. The initial population was represented by 4,416 patients evaluated at 4 Italian Cardiology Institutions (Lucca, Mestre, Cesena, and Pisa) from August 2003 to June 2011 for enrollment in a study focused on assessing the prognostic value of CFR in the setting of known or suspected CAD. The study design was observational, not randomized, and prospective; patient data were entered into the databank at the time of initial assessment. All patients underwent stress echocardiography with wall motion and CFR assessment of LAD by using transthoracic Doppler ultrasound. Of the 4,416 patients initially selected, 103 (2%) were lost to follow-up. Thus, 4,313 (2,532 men; mean ± SD age 65 ± 11 years) formed the study group. Indications for stress echocardiography were suspected CAD in 2,766 (64%) subjects and risk stratification of known CAD (i.e., history of myocardial infarction, coronary revascularization, and/or angiographic evidence of >50% diameter coronary stenosis) in the remaining 1,547 (36%). According to individual needs and physician's choices, 2,515 (58%) patients were evaluated after anti-ischemic drugs had been discontinued, and 1,798 (42%) patients were evaluated during anti-ischemic treatment (Table 1). All patients gave their written

Table 1. Clinical and Echocardiographic Characteristics for Patients With CFR on LAD >2 and ≤2

	CFR >2 (n = 2,894)	CFR ≤2 (n = 1,419)	p Value
Age, yrs	64 ± 11	68 ± 10	<0.0001
Male	1,615 (56)	917 (65)	<0.0001
Clinical history			
Family history of CAD	743 (26)	365 (26)	0.97
Diabetes mellitus	550 (19)	429 (30)	<0.0001
Arterial hypertension	1,865 (64)	1,026 (72)	<0.0001
Hypercholesterolemia	1,519 (52)	845 (60)	<0.0001
Smoking habit	867 (30)	444 (31)	0.37
Left bundle branch block	177 (6)	133 (9)	<0.0001
Prior myocardial infarction	665 (23)	449 (32)	<0.0001
Prior CABG	166 (6)	104 (7)	0.04
Prior PCI	626 (22)	364 (26)	0.003
Known CAD	949 (33)	598 (42)	<0.0001
Anti-ischemic therapy at the time of test			
Beta-blockers	775 (27)	578 (41)	<0.0001
Calcium antagonists	423 (15)	332 (23)	<0.0001
Nitrates	229 (8)	236 (17)	<0.0001
At least 1 medication	1,038 (36)	760 (54)	<0.0001
Resting echocardiogram			
WMA at rest	724 (25)	655 (46)	<0.0001
WMSI at rest	1.10 ± 0.24	1.26 ± 0.37	<0.0001
Left ventricular ejection fraction %	57 ± 7	53 ± 10	<0.0001
Stress echocardiography			
Ischemic result	249 (9)	516 (36)	<0.0001
WMSI at peak stress	1.11 ± 0.30	1.34 ± 0.39	<0.0001
Resting velocity on LAD, cm/s	31 ± 9	40 ± 22	<0.0001
CFR on LAD	2.68 ± 0.58	1.69 ± 0.25	<0.0001

Values are mean ± SD or n (%).
CABG = coronary artery bypass graft; CAD = coronary artery disease; CFR = coronary flow reserve; LAD = left anterior descending artery; PCI = percutaneous coronary intervention; WMA = wall motion abnormality; WMSI = wall motion score index.

informed consent before they underwent stress echocardiography. When patients signed the written informed consent form, they also authorized physicians to use their clinical data. Stress echocardiography data were collected and analyzed by stress echocardiographers not involved in patient care.

Stress echocardiography. Transthoracic stress echocardiographic studies were performed with commercially available ultrasound machines (Sonos 7500 or iE 33, Philips Ultrasound, Andover, Massachusetts; Vivid System 7, GE/Vingmed, Milwaukee, Wisconsin; Sequoia C256 Acuson Siemens Mountain View, California) equipped with multifrequency, phased-array sector scan probe (S3–S8 or V3–V7) and with second harmonic technology. Two-dimensional echocardiography and 12-lead electrocardiographic monitoring were performed in combination with high-dose dipyridamole administration (up to 0.84 mg over 6 min) (1). Echocardiographic images were semiquantitatively assessed using a 17-segment, 4-point scale model of the left ventricle (14). A wall motion score index was derived by dividing the sum of individual segment scores by the number of interpretable segments. Ischemia was defined as stress-induced new and/or worsening of pre-existing wall motion abnormality. Rest wall motion abnormality was akinetic or dyskinetic myocardium with no thickening during stress. CFR was assessed during the standard stress echocardiography examination by an intermittent imaging of both wall motion and LAD flow (1). Coronary flow in the mid-distal portion of LAD was searched in the low parasternal long-axis section under the guidance of color Doppler flow mapping (1). All studies were digitally stored to simplify off-line reviewing and measurements. Coronary flow parameters were analyzed off-line using the built-in calculation package of the ultrasound unit. Flow velocities were measured ≥2 times for each study; namely, at baseline and at peak stress (before aminophylline injection). At each time point, 3 optimal profiles of peak diastolic Doppler flow velocities were measured, and the results were averaged. CFR was defined as the ratio between hyperemic peak and basal peak diastolic coronary flow velocities. A CFR value ≤2.0 was considered abnormal (3). All investigators of contributing centers passed quality control criteria for regional wall motion and Doppler interpretation before entering the study as previously described (15). The previously assessed intraobserver and interobserver variability for measurements of Doppler recordings and regional wall motion analysis assessment were <10% (16).

Follow-up data. Follow-up data were obtained from review of the patient's hospital record, personal communication with the patient's physician and review of the patient's chart, a telephone interview with the patient or a patient's close relative conducted by trained personnel, or a staff physician visiting the patients at regular intervals in the outpatient clinic. Mortality was the only endpoint. To avoid misclassification of the cause of death (9), overall mortality was considered. Coronary revascularization (surgery or angioplasty) was also registered; however, it was not identified as a clinical event, and patients were censored.

Statistical analysis. Continuous variables are expressed as mean ± SD. Differences between groups were compared using the Student *t* test and the chi-square test, as appropriate. Mortality rates were estimated with Kaplan-Meier curves and compared using the log-rank test. Patients undergoing coronary revascularization were censored at the time of the procedure. Annual mortality was obtained from Kaplan-Meier estimates to take censoring of the data into account. The association of selected variables with outcome were assessed with the Cox proportional hazards model using univariate and stepwise multivariate procedures. In the Cox model, the time-dependent revascularization effect was estimated. A significance of 0.05 was required for a variable to be included in the multivariate model, and 0.1 was the cutoff value for exclusion. Hazard ratios (HRs) with the corresponding 95% confidence intervals (CIs) were estimated. The following covariates were analyzed: age, sex, left bundle branch block, family history of CAD, diabetes mellitus, arterial hypertension, hypercholesterolemia, smoking habit, previous myocardial infarction, previous coronary artery bypass graft, previous percutaneous revascularization, ongoing anti-ischemic therapy, resting wall motion abnormality, resting wall motion score index, ischemia at stress echocardiography, wall motion score index at peak stress, test positivity, and CFR on LAD.

Statistical significance was set at $p < 0.05$. SPSS version 20 (SPSS Inc., Chicago, Illinois) was used for analysis.

RESULTS

Stress echocardiographic findings. No complication occurred during the test. Mean CFR on LAD was

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2.35 ± 0.68. At individual patient analysis, 1,419 (33%) subjects had CFR ≤2 and 2,894 (67%) had CFR >2. Stress echocardiography was positive for ischemia in 765 (18%) individuals. Ischemia was assessed in 516 patients with CFR ≤2 and in 249 patients with CFR >2 (36% vs. 9%; $p < 0.0001$) (Table 1).

Patients with CFR ≤2 were older, more frequently men, and had a higher incidence of diabetes mellitus, arterial hypertension, hypercholesterolemia, left bundle branch block, previous myocardial infarction, and coronary revascularization (Table 1); in addition, they were more frequently tested under anti-ischemic medication than patients with CFR >2.

Survival analysis. During a median follow-up of 19 months (interquartile range: 8 to 36 months), 146 (3.4%) patients died.

According to the physician's judgment, 907 (21%) underwent myocardial revascularization (205 surgery and 702 percutaneous intervention) after a median of 111 days (1st quartile 30 days; 3rd quartile 250 days) from the index stress echocardiography. There were 470 revascularizations in patients with ischemia and 437 in those without ischemia at stress echocardiography (61% vs. 12%; $p < 0.0001$). In addition, there were 635 revascularizations in patients with CFR ≤2 and 272 revascularizations in those with CFR >2 (45% vs. 9%; $p < 0.0001$).

The 4-year mortality was significantly higher in patients with CFR ≤2 than in patients with CFR >2, both considering the group with ischemia (39% vs. 7%; $p < 0.0001$) and the group without ischemia at stress echocardiography (12% vs. 3%; $p < 0.0001$) (Fig. 1). Interestingly, in both patient groups, CFR ≤2 was associated with markedly greater annual mortality in subjects with known CAD as well as in subjects with suspected CAD (Fig. 2). Considering patients without ischemia and CFR >2, annual mortality was only 0.8% in those with known CAD and 0.6% in those with suspected CAD. In the subset of patients with suspected CAD and not undergoing medical therapy at the time of testing, the annual mortality was 0.6% in those with CFR >2 and 7.2% in those with CFR ≤2 ($p < 0.001$).

Univariate indicators of mortality are listed in Table 2. At multivariable analysis, CFR on LAD ≤2 (HR: 3.31 [95% CI: 2.29 to 4.78]; $p < 0.0001$), ischemia at stress echocardiography (HR: 2.40 [95% CI: 1.65 to 3.48]; $p < 0.0001$), left bundle branch block (HR: 2.26 [95% CI: 1.50 to 3.41]; $p < 0.0001$), age (HR: 1.08 [95% CI: 1.06 to 1.10]; $p < 0.0001$), resting wall motion score index (HR: 3.52 [95% CI: 2.38 to 5.21]; $p < 0.0001$), male sex (HR: 1.74 [95% CI: 1.12 to 2.52]; $p = 0.003$), and diabetes mellitus (HR: 1.47 [95% CI: 1.03 to 2.08]; $p = 0.03$) were independent predictors of mortality. Revascularization procedure did not exert any significant effect (HR: 0.586 [95% CI: 0.80 to 4,284]) when considered as a time-dependent covariate in the Cox model.

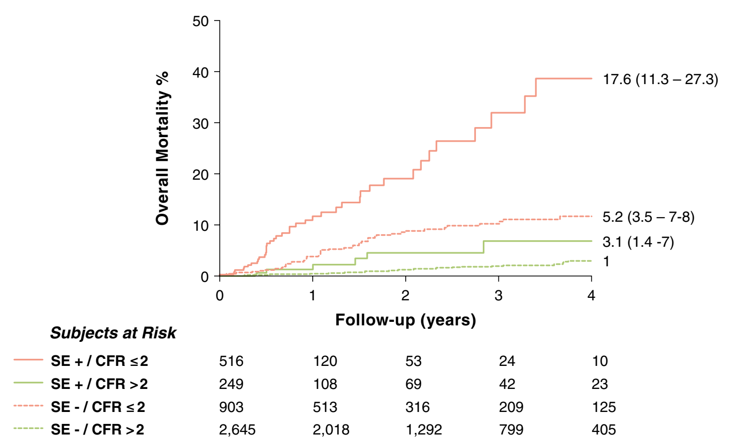

Figure 1. Wall Motion, CFR, and Risk

The study population separated on the basis of presence (+) or absence (−) of ischemia at stress echocardiography (SE) and coronary flow reserve (CFR) on left anterior descending artery ≤2 or >2. Assuming a hazard ratio of 1 for the lowest mortality rate subset (SE−/CFR), the hazard ratio with relative 95% confidence intervals are reported in the graphic. The number of patients per year is shown.

DISCUSSION

Dual-imaging vasodilator stress echocardiography is an independent predictor of death in an unselected cohort of patients, conferring useful prognostic information in subjects with known CAD as well as in those with suspected CAD. In particular, test positivity by wall motion criteria with impaired CFR on LAD identifies a particularly malignant test response with a risk >10% for annual mortality. On the opposite side of the spectrum of risk stratification, patients with no inducible ischemia and normal CFR have an annual rate of death <1%. At intermediate risk are those patients who have ischemia and preserved CFR and those who have nonischemic test results and reduced CFR.

Comparison with previous studies. The value of stress-induced wall motion abnormalities to predict mortality has been extensively documented in patients with known or suspected CAD (11–13). Our findings confirm and expand those previous expe-

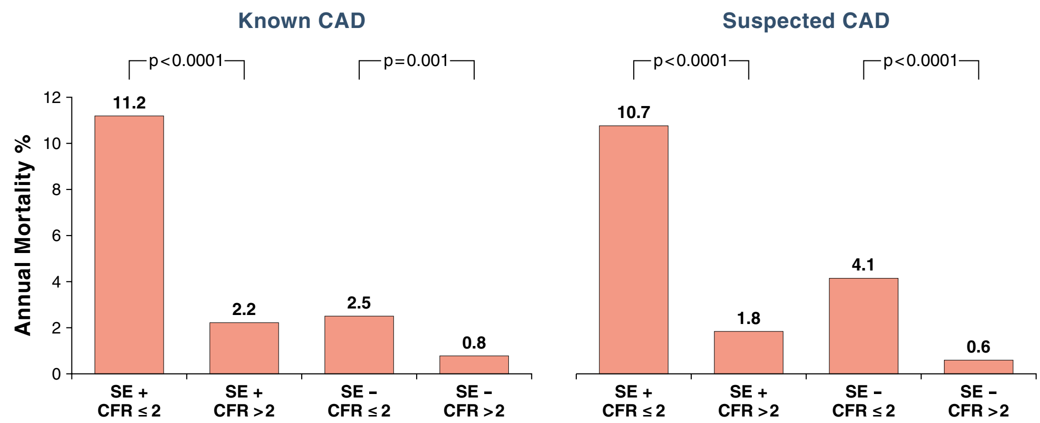

Figure 2. Annual Mortality Rate

Annual mortality in the group of patients with known coronary artery disease (CAD) and suspected CAD separated on the basis of presence (+) or absence (−) of ischemia at SE and CFR on left anterior descending artery ≤2 or >2. Abbreviations as in Figure 1.

riences, demonstrating an additive prognostic value of CFR assessment on LAD over wall motion analysis. In fact, a CFR ≤2 identified a subset of patients at increased risk of mortality both in the presence and in the absence of ischemia at stress echocardiography.

The current study has major relevant differences when compared with prior studies addressing the issue of prediction of future events with stress echocardiography. First, the study design is large-scale and multicenter, which provides a realistic picture of stress echocardiographic results obtained from heterogeneous nonacademic cardiologic institutions with on-site stress echocardiography interpretation; this setting is able to evaluate the effectiveness of pharmacological stress echocardiography in prognosis. Second, the sample size consisted of 4,313 patients, which is the largest population studied to date with combined CFR assessment, large enough to provide prognostic information only analyzing hard endpoints such as total mortality with no need to include surrogate or composite endpoints (2–7) to increase the power of prognostication. Third, the type of population analyzed (i.e., low risk) was ideal to test the performance of stress tests in identifying only those patients at

Table 2. Univariable and Multivariable Predictors of Mortality

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age	1.10 (1.08–1.12)	<0.0001	1.08 (1.06–1.10)	<0.0001
Male	1.86 (1.31–2.65)	0.001	1.74 (1.21–2.52)	0.003
Family history of CAD	0.59 (0.37–0.93)	0.02		
Diabetes mellitus	2.09 (1.48–2.95)	<0.0001	1.47 (1.03–2.08)	0.031
Arterial hypertension	1.35 (0.94–1.93)	0.10		
Hypercholesterolemia	0.91 (0.66–1.26)	0.57		
Smoking habit	1.09 (0.77–1.56)	0.62		
Left bundle branch block	4.70 (3.24–6.83)	<0.0001	2.26 (1.50–3.41)	<0.0001
Prior myocardial infarction	1.60 (1.13–2.25)	0.007		
Prior CABG	1.05 (0.55–2.00)	0.88		
Prior PCI	1.02 (0.69–1.50)	0.93		
Ongoing anti-ischemic therapy	1.65 (1.19–2.28)	0.002		
WMSI at rest	8.41 (6.08–11.63)	<0.0001	3.52 (2.38–5.21)	<0.0001
Ischemia at stress echocardiography	5.56 (3.93–7.87)	<0.0001	2.40 (1.65–3.48)	<0.0001
Resting velocity on LAD	1.03 (1.02–1.04)	<0.0001		
CFR on LAD	6.70 (4.74–9.47)	<0.0001	3.31 (2.29–4.78)	<0.0001

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

higher risk for mortality. Still, the high rate of revascularizations, especially in the ischemic result subset, may have lowered the power of stratification of stress testing.

Clinical implications. There are several tests and strategies for the evaluation of patients with known or suspected CAD, but no single strategy has been demonstrated to be superior overall. Nonetheless, the approach to these patients with physiological testing is sound, rational, and effective. Nowadays, the availability of high-tech imaging and its increasing and unrestricted use (17) is shadowing simpler and less expensive technologies such as ultrasounds. In most cases, the new technologies are deployed into clinical practice before their incremental and additive value has been demonstrated through the conventional process of health technology assessment (18,19). However, in a new environment of healthcare cost-containment, minimization of risks related to imaging such as ionizing radiations (20), stress echocardiography with dual imaging seems to be the appropriate tool to be implemented in the everyday clinical practice due to its high negative predictive value, low cost, lack of ionizing radiations, and wide availability. In fact, in large series of unselected patients referred to high-volume stress echocardiography laboratories, stress test results should influence clinical management. The benign prognostic implications of a nonischemic stress echocardiography with normal CFR on LAD should reduce the need for coronary angiography, representing the essential step for coronary revascularization only in case of extensive test positivity or markedly reduced CFR. The presence of a severely reduced CFR with no inducible ischemia by wall motion criteria may identify a group with relevant microvascular impairment that is not prognostically neutral as also shown in patients with hypertension (5), diabetes (3), and normal or near-normal coronary arteries (4). Dual-imaging stress echocardiography with dipyridamole has reached the status of an established technique that needs to be implemented in clinical echocardiography laboratories with appropriate training and technology upgrading. All these echocardiography parameters are entwined to provide an accurate and powerful risk stratification with the perfect tailoring of the test to the individual patient's needs.

Study limitations. In this study, there was no central reading. Stress echocardiography and CFR measurement were interpreted in the peripheral centers, and data were entered directly into the databank. This system allowed substantial sparing of human and technological resources, but it was also the logical prerequisite for a large-scale study, designed to represent the realistic performance of the test rather than the results of a single laboratory or even a single person working in a highly dedicated echocardiography laboratory. Because the assessment of the echocardiograms was qualitative and subjective, variability in reading the echocardiograms might have modulated the results of individual centers (21). However, all our readers in individual centers had a long-lasting experience in echocardiography, passed the quality control in stress echocardiography reading as previously described (15). The CFR was sampled only on LAD. There is no doubt that the 3 coronaries approach would be more fruitful, but at present it remains too technically challenging for a large-scale assessment. Forty-two percent of the patient population underwent dipyridamole stress echocardiography while receiving anti-ischemic medical therapy, which may have offset myocardial ischemia. Nevertheless, therapy exerts a negligible effect on the diagnostic (5) and prognostic (7) value of CFR. In the current study, follow-up was censored at the time of revascularization, and no data are available on the effect of treatments (surgery or angioplasty).

CONCLUSIONS

Mortality is the most relevant endpoint in risk stratification, and stress echocardiography with the combined approach of wall motion analysis and CFR on LAD is able to independently predict such a catastrophic event. Patients with a negative stress echocardiography and normal CFR are at very low risk for death (<1%/year). It is very difficult to demonstrate that even the most aggressive treatments might lower this rate of death.

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