Coronary Flow Velocity Reserve during Pharmacologic Stress Echocardiography with Normal Contractility Adds Important Prognostic Value in Diabetic and Nondiabetic Patients

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Background: Coronary flow velocity reserve (CFVR) increases the diagnostic sensitivity of stress echocardiography. The aim of this study was to evaluate the prognostic value of CFVR in patients without new wall motion abnormalities during pharmacologic stress echocardiography.

Methods: The outcomes of 651 patients with normal wall motion response during stress echocardiography with dobutamine up to 50 μg/kg/min (n = 351) or dipyridamole up to 0.84 mg/kg over 4 min (n = 300) were evaluated. CFVR was calculated simultaneously in the distal territory of the left anterior descending coronary artery. CFVR $\geq$ 2 was defined as normal. Major events considered during follow-up were cardiovascular death, myocardial infarction, and late myocardial revascularization.

Results: Normal CFVR was recorded in 523 patients and reduced CFVR in 128. During a mean follow-up period of 34.6 $\pm$ 18 months, 48 major events occurred, in 25 patients (4.8%) with normal and 23 patients (18%) with reduced CFVR; event-free survival was significantly different between patients with normal versus abnormal CFVR (P < .0001). Diabetes increased risk only in patients with abnormal CFVR (P = .05). In the multivariate analysis, CFVR and history of smoking were the only independent predictors of combined morbidity and mortality. Abnormal CFVR was associated with a higher event rate, independently of the pharmacologic stress technique used. The event hazard ratio was inversely proportional to CFVR.

Conclusions: CFVR was an independent predictor of mortality after pharmacologic stress echocardiography with normal wall motion, and the degree of decrease was associated with increased risk. Diabetes worsened prognosis only with abnormal CFVR. (J Am Soc Echocardiogr 2014;27:1113-9.)

Keywords: Stress echocardiography, Stress echocardiographic prognosis, Risk assessment, Coronary flow velocity reserve

It is accepted that a normal contractile response on stress echocardiography has a much better prognosis than in the presence of transient wall motion abnormalities. However, it does not completely rule out the possibility of significant coronary artery disease (CAD), or an event-free prognosis, especially in patients with complete left bundle branch block, in elderly patients or those assessed under anti-ischemic treatment, in patients with left ventricular hypertrophy or single-vessel disease, in incomplete studies (e.g., deficient tests with atropine contraindications), and in the diabetic population.[1–5] In this last group, there is great concern about the prevention of cardiovascular complications. Hence, it is highly important to identify patients at greater risk for developing coronary disease to adopt special surveillance, treat them more aggressively, and ultimately attempt to reduce morbidity and mortality.

In the past 15 years, the potential of stress echocardiography has expanded dramatically, with the possibility of assessing noninvasively coronary flow velocity at rest and its relation with peak pharmacologic stress. The simultaneous recording of wall motion and coronary flow velocity reserve (CFVR) images is today the state of the art for drug-induced stress studies in some laboratories.[6–11]

It is established that left anterior descending coronary artery (LAD) CFVR < 2 with dobutamine or dipyridamole increases the diagnostic sensitivity of stress echocardiography,[11–14] and recent evidence has shown that dipyridamole can also provide additional prognostic information to contractile analysis in patients with known or suspected CAD.[15–19]

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Abbreviations

AMI = Acute myocardial infarction

CAD = Coronary artery disease

CFVR = Coronary flow velocity reserve

CI = Confidence interval

HR = Hazard ratio

LAD = Left anterior descending coronary artery

In this observational study, we investigated the mid- and long-term prognostic information derived from the transthoracic Doppler echocardiographic analysis of CFVR and its degree of LAD restriction in patients with and those without diabetes with known or suspected CAD who underwent stress echocardiography with normal wall motion performed with dobutamine or dipyridamole.

MATERIAL AND METHODS

Patients

The initial population involved 2,455 patients included at two institutions (Investigaciones Médicas, Buenos Aires, Argentina, and Polimedic, Santa Rosa, Argentina) from June 2001 to November 2011. All patients underwent pharmacologic stress echocardiography with dobutamine or dipyridamole (according to the treating physician) with CFVR assessments by transthoracic Doppler echocardiography at the LAD level. Patients with baseline abnormal wall motion in the LAD territory ($n = 256$), positive transient contractile abnormalities ($n = 678$), cardiac disease, valve disease or different congenital diseases ($n = 357$), ejection fraction $< 35\%$ ($n = 184$), suboptimal ultrasound windows ($n = 97$), impossibility of finding the LAD ($n = 90$), and no information on poststudy outcomes ($n = 142$) were excluded from the study.

Thus, 651 patients were ultimately analyzed; 329 (50.53%) were men, and the mean age was 66.45 ± 11.82 years. Stress echocardiography was indicated for suspected CAD and/or its risk stratification (history of acute myocardial infarction [AMI], myocardial revascularization, and/or angiographic evidence of significant coronary stenoses). All patients provided written informed consent before undergoing stress echocardiography.

Stress Echocardiography

Transthoracic stress echocardiographic studies were performed with commercially available echocardiographs (Vivid 9, Vivid 7, and System 5 [GE Medical Systems, Milwaukee, WI] and, from 2001 to 2006, HDI 5000 [Philips Medical Systems, Andover, MA]), equipped with multifrequency probes and second-harmonic technology. All patients were simultaneously monitored with 12-lead electrocardiography.[9] Two-dimensional images were obtained at rest and with doses of up to 50 μg/kg/min dobutamine ($n = 351$) or 0.84 mg/kg dipyridamole over 4 min ($n = 300$). Sensitization with atropine was done in patients without contraindications to its use and with handgrip maneuvers.

In all patients, distal LAD CFVR was obtained with pulsed Doppler echocardiography under color Doppler guidance. Coronary flow velocity was continuously acquired from baseline until the first minute after ending dipyridamole infusion and intermittently at baseline and at peak maximal dobutamine dose. CFVR was defined as the ratio between maximum diastolic flow velocity at peak stress and baseline flow velocity, considering as abnormal a value <2.[7,20,21] It was categorized in 4 groups according to its absolute value: >2, 1.99 to 1.75, 1.74 to 1.5, and <1.49.

Wall motion was analyzed under baseline conditions and up to 8 min after ending dipyridamole infusion (hand grip and eventually atropine) and also at each stage of dobutamine. Echocardiographic images were assessed by using a 16-segment model of the left ventricle and a four-point semiqualitative scale.[22] The wall motion score was visually calculated by dividing the score obtained from the sum of each individual segment evaluation during stress by the number of interpretable segments. Ischemia was defined as a new abnormality in wall motion or worsening of a preexisting one. Akinesia or dyskinesia was defined as resting wall motion alteration with absence of systolic thickening during stress echocardiography. Studies were digitally stored. Diastolic coronary flow velocities were calculated from the average of 3 baseline recordings and at peak stress (Figure 1). All operators were trained by the same investigator.

Follow-Up

Follow-up was provided by the treating physicians on the basis of the information recorded in the medical history at each visit and by telephone interviews with the patients or relatives. Major events were cardiovascular death, AMI, or need for myocardial revascularization (angioplasty or coronary artery bypass grafting) >90 days after study performance.

Statistical Analysis

Results for continuous variables are expressed as mean ± SD or median (interquartile range) according to normal or non-normal distribution. Qualitative variables are expressed as frequencies and percentages. Quantitative variables were compared by using Student *t* tests or nonparametric tests. Categorical variables were compared by using χ^2 or Fisher's exact tests. Event-free survival was determined by using the Kaplan-Meier method for patients with normal and reduced CFVR. Survival times were compared by using the log-rank test. A Cox regression model was used to evaluate the association between independent variables and the presence of events, introducing significant variables in univariate analysis and calculating the hazard ratios (HRs) and their 95% confidence intervals (CIs). Statistical significance was set at a value of $P < .05$. SPSS version 16 (SPSS, Inc, Chicago, IL) was used to perform statistical analyses.

RESULTS

Stress Echocardiography

No major complications were registered during study performance.

Baseline Population Characteristics

Patients with normal and reduced CFVR had statistically significant differences in age (65.62 ± 12.13 vs 69.61 ± 9.91 years, $P = .001$); the rate of patients presenting with mild to moderate left ventricular systolic functional impairment secondary to inferior, lateral, or posterior wall motion abnormal contractility (8.8% vs 21%, $P = .01$); the presence of previous AMI (12.7% vs 19.5%, $P = .047$), and histories of diabetes (10.8% vs 24.6%, $P = .0001$) and active smoking (10.2% vs 17.2%, $P = .031$) (Table 1).

Events during Follow-Up

Preserved CFVR was registered in 523 patients and reduced CFVR in 128. The mean follow-up duration was 34.6 ± 18 months. During this