Prognostic Value of Coronary and Microvascular Flow Reserve in Patients with Nonischemic Dilated Cardiomyopathy

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Background: Coronary and microvascular blood flow reserve have been established as important predictors of prognosis in patients with cardiovascular disease. The aim of this study was to assess the value of coronary flow velocity reserve (CFVR) and real-time myocardial perfusion echocardiography (RTMPE) for predicting events in patients with nonischemic dilated cardiomyopathy.

Methods: One hundred ninety-five patients (mean age 54 ± 12 years; 66% men) with dilated cardiomyopathy (left ventricular ejection fraction < 35% and no obstructive coronary disease on invasive angiography or multidetector computed tomography) who underwent dipyridamole stress (0.84 mg/kg over 10 min) RTMPE were prospectively studied. CFVR was calculated as the ratio of hyperemic to baseline peak diastolic velocities in the distal left anterior coronary artery. The replenishment velocity (β), plateau of acoustic intensity (A_N), and myocardial blood flow reserve were obtained from RTMPE.

Results: Mean CFVR was 2.07 ± 0.52, mean A_N reserve was 1.05 ± 0.09, mean β reserve was 2.05 ± 0.39, and mean myocardial blood flow reserve ($A_N \times \beta$) was 2.15 ± 0.48. During a median follow-up period of 29 months, 45 patients had events (43 deaths and two urgent transplantations). Independent predictors of events were left atrial diameter (relative risk, 1.16; 95% confidence interval, 1.08–1.26; $P < .001$) and β reserve ≤ 2.0 (relative risk, 3.22; 95% confidence interval, 1.18–8.79; $P < .001$). After adjustment for β reserve, CFVR and myocardial blood flow reserve no longer had predictive value. Left atrial diameter added prognostic value over clinical factors and left ventricular ejection fraction ($\chi^2 = 36.8–58.5$, $P < .001$). Beta reserve added additional power to the model ($\chi^2 = 70.2$, $P < .001$).

Conclusions: Increased left atrial diameter and depressed β reserve were independent predictors of cardiac death and transplantation in patients with nonischemic dilated cardiomyopathy. Beta reserve by RTMPE provided incremental predictive value beyond that provided by current known prognostic clinical and echocardiographic factors. (J Am Soc Echocardiogr 2013;26:278-87.)

Keywords: Dilated cardiomyopathy, Contrast echocardiography, Myocardial perfusion, Prognostic value, Myocardial blood flow reserve

Dilated cardiomyopathy (DCM) is a prevalent cardiovascular condition associated with left ventricular dysfunction and poor prognosis. The reliable selection of patients at higher risk for hard events is of great importance for their management, especially considering current available therapeutic approaches, such as implantable cardioverter-defibrillators, and limited resources for health care.[1] Moreover, outcomes have been improved for most high-risk patients, which have resulted in a shift in the selection process for patients referred for heart transplantation.[2] Multivariate analysis of clinical and echocardiographic variables has helped identify significant predictors of survival, and prognostic models have been developed and validated.[3]

The incorporation of new advances in cardiovascular medicine may have a potential prognostic impact in patients with DCM. In this context, impairment of coronary flow velocity reserve (CFVR) by Doppler echocardiography in the left anterior descending coronary artery (LAD) has been associated with higher mortality and progression of heart failure.[4,5] Neglia *et al.*[6] also demonstrated that severely depressed myocardial blood flow analyzed by positron emission tomography is a predictor of poor prognosis in patients with idiopathic left ventricular

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This study was supported by a grant from Fundação de Amparo à Pesquisa do Estado de São Paulo (São Paulo, Brazil).

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0894-7317/$36.00

http://dx.doi.org/10.1016/j.echo.2012.12.009

Abbreviations

CFVR = Coronary flow velocity reserve

DCM = Dilated cardiomyopathy

LA = Left atrial

LAD = Left anterior descending coronary artery

LVEF = Left ventricular ejection fraction

MBFR = Myocardial blood flow reserve

NYHA = New York Heart Association

RTMPE = Real-time myocardial perfusion echocardiography

dysfunction, independent of the degree of left ventricular functional impairment and the presence of overt heart failure. Quantitative contrast echocardiography has been shown to be useful for assessing global and regional myocardial blood flow reserve (MBFR) using different pharmacologic stimuli.[7-11] This technique seems feasible for the assessment of mechanistic insights at a microvascular level and has been applied for evaluating the effects of therapy and predicting mortality in patients with heart failure.[12,13]

In this study, we sought to determine the value of CFVR and parameters of flow reserve obtained by quantitative myocardial contrast echocardiography for predicting cardiac death and heart transplantation in patients with nonischemic DCM. In addition, we investigated whether these parameters added incremental prognostic value over clinical and resting echocardiographic data in this specific group of patients.

METHODS

Patients

From October 2005 to July 2011, we prospectively studied 201 consecutive patients with nonischemic DCM who underwent dipyridamole stress with measurement of CFVR by Doppler echocardiography in the LAD and quantitative analysis of myocardial blood flow by real-time myocardial perfusion echocardiography (RTMPE). All patients were on standard medical treatment for ≥1 year, including angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, β-blockers, diuretics, and digoxin.[1] The doses of these medications were stable for ≥3 months. Inclusion criteria were age >18 years, left ventricular systolic dysfunction, defined as left ventricular ejection fraction (LVEF) < 35% by Simpson's rule, and no obstructive coronary artery disease by invasive angiography or multidetector computed tomography. Exclusion criteria were decompensated heart failure (defined as New York Heart Association [NYHA] functional class IV or need for intravenous inotropic drugs) within 2 weeks of stress testing, valvular heart disease, serious ventricular arrhythmias, atrial fibrillation, previous myocardial infarction, previous percutaneous coronary intervention, severe obstructive pulmonary disease, second-degree or third-degree atrioventricular block, allergy to echocardiographic contrast, presence of any intracavitary shunt, pregnancy, and breast feeding. Patients who did not complete ≥6 months of follow-up without events were also excluded. All clinical management decisions were taken by physicians who were unaware of the results of RTMPE. Patients who underwent cardiac resynchronization therapy during follow-up were censored at the time of the procedure. Informed consent was obtained from each patient, and the study protocol conformed to the ethical guidelines of the Declaration of Helsinki, as reflected in a priori approval by the ethics committee of the Heart Institute at the University of São Paulo Medical School.

Study Protocol

Before stress testing, patients were requested to abstain from xanthine-containing food and drinks for ≥24 hours. Patients underwent complete resting two-dimensional echocardiography, followed by measurement of LAD velocities and RTMPE using a commercially available ultrasound system equipped with myocardial contrast echocardiographic software (iE33; Philips Medical Systems, Bothell, WA).

Coronary blood flow in the distal LAD was detected using color Doppler, first obtaining a modified foreshortened two-chamber view or, if distal LAD flow was not feasible, using a low parasternal short-axis view of the base of the heart.[4,5,10] Pulsed-wave sample volume positioning in the distal LAD was guided by contrast-enhanced color Doppler imaging.

Myocardial perfusion imaging was performed using a low–mechanical index real-time pulse sequence scheme (power modulation) using a mechanical index of 0.2, a frame rate of 25 to 30 Hz, and continuous intravenous infusion of either lipid-encapsulated microbubbles (Definity; Lantheus Medical Imaging, North Billerica, MA) or perfluorocarbon-exposed sonicated dextrose albumin. The formulation of perfluorocarbon-exposed sonicated dextrose albumin has been described elsewhere.[14]

The contrast infusion rate was adjusted for complete left ventricular cavity opacification, and shadowing in the mid left atrial (LA) cavity was obtained. Once stable myocardial enhancement was reached, the contrast infusion rate was kept constant, Doppler recordings in the distal LAD were performed, and sequences of low-power perfusion images in the apical two-chamber, three-chamber, and four-chamber views were acquired at baseline. To assess the replenishment kinetics, microbubble destruction in the myocardium was induced by a manually delivered flash containing five consecutive high–mechanical index (1.4) impulses and acquired sequences contained ≥15 cardiac cycles. After the completion of resting perfusion sequences, contrast infusion was stopped, and hyperemia was induced by dipyridamole infusion through a parallel port at dose of 0.84 mg/kg over 10 min. At the end of dipyridamole infusion, contrast infusion was restarted at the same rate as in the baseline study, and Doppler recordings in the distal LAD and perfusion sequences were acquired for hyperemic measurements. Blood pressure and cardiac rhythm were continuously monitored before, during, and up to 20 min after dipyridamole infusion. Twelve-lead electrocardiograms were obtained at baseline and at 2-min intervals during dipyridamole infusion.

Quantitative Analysis of RTMPE

Cardiac measurements and hemodynamic evaluations were obtained as recommended by the American Society of Echocardiography.[14-17] End-diastolic and end-systolic volumes and LVEF were calculated using a modified Simpson's biplane method.[15] Mitral regurgitation was classified as absent, mild, moderate, or severe using qualitative analysis by Doppler color flow mapping and quantitative parameters, including vena contracta width, regurgitant volume and fraction, and effective regurgitant orifice area.[16] Diastolic dysfunction was classified as degree I (abnormal relaxation), II (pseudonormal pattern), III (reversible restrictive pattern), or IV (fixed restrictive pattern).[17] CFVR was calculated as the ratio of hyperemic to baseline peak diastolic velocities in the distal LAD. The average of three consecutive cardiac cycles with the best spectral curve was considered for analysis.[4,5,10]

Real-time myocardial perfusion echocardiographic quantification was performed using commercially available software (QLAB version 7.0; Philips Medical Systems). Only end-systolic frames were selected for analysis. The left ventricle was divided into 17 segments.[18] Basal