Incremental Value of Left Ventricular Diastolic Function Reserve Index for Predicting Exercise Capacity in Patients with Hypertrophic Cardiomyopathy

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The changes of left ventricular diastolic function during exercise are heterogeneous in patients with hypertrophic cardiomyopathy (HCM). We sought to investigate whether exertional changes of mitral annular velocities and plasma N-terminal-pro-B-type natriuretic peptide (BNP) concentration are associated with exercise capacity in patients with HCM. After a comprehensive echocardiographic study, 32 patients with HCM performed symptom-limited graded supine bicycle exercise. Echocardiographic Doppler parameters were measured at each stage of exercise. Blood samples were collected at rest and immediately after exercise to determine the concentration of pro-BNP. Resting pro-BNP ($r = -0.620$, $P < .001$), E'_{base} ($r = 0.414$, $P = .018$), and $\Delta E'_{50W}$ (change of E' from base to 50 W of exercise) ($r = 0.367$, $P = .039$) were significantly correlated with exercise duration. Left ventricular longitudinal diastolic function reserve index, defined as $\Delta E' \times E'_{base}$, significantly correlated with exercise duration (at 50 W, $r = 0.540$, $P = .001$) independent of age, sex, body mass index, and resting pro-BNP level. When combining $\Delta E' \times E'_{50W}$ (<5.85 cm^2/s^2) and resting pro-BNP (>740 mg/dL), the predictive accuracy for exercise capacity could be improved (for <500 seconds, global $\chi^2 = 5.84$ in pro-BNP vs 8.10 in pro-BNP + $\Delta E' \times E'_{50W}$, $P = .023$). The assessment of left ventricular longitudinal diastolic function reserve can provide incremental information to pro-BNP for the prediction of exercise capacity in patients with HCM.

The most common symptom of patients with hypertrophic cardiomyopathy (HCM) is exercise intolerance.[1] Most patients with HCM fail to achieve normal oxygen consumption during exercise, mostly as a result of a failure of stroke volume augmentation because of diastolic dysfunction.[2-4] However, the changes of left ventricular (LV) diastolic function during exercise in patients with HCM are heterogeneous[5] and, therefore, it may have effects on exercise capacity (EC) in patients with HCM. Previously, resting plasma B-type natriuretic peptide (BNP) concentration, left atrial (LA) volume, and Doppler parameter representing LV relaxation have been shown as predictors of EC in patients with HCM.[4,6,7] However, the relationship between the changes of diastolic functional parameters during low-grade exercise and EC has not been evaluated. In this study, we hypothesized that the changes of diastolic functional indices during exercise have incremental information on EC in patients with HCM.

METHODS

Study Population

Between May 2004 and November 2005, patients with HCM were prospectively enrolled. The diagnosis of HCM was based on conventional echocardiographic demonstration of a nondilated, hypertrophic LV with maximal wall thickness greater than 15 mm and maximal wall thickness/posterior wall thickness ratio greater than 1.3 without other systemic or cardiac diseases that can induce LV hypertrophy other than mild to moderate hypertension. Patients who met the following criteria were excluded from participation: LV ejection fraction less than 50%; any other valvular heart disease including mitral regurgitation more than mild degree, atrial fibrillation, history of coronary artery disease, and newly developed wall-motion abnormality during the exercise testing; and inability to exercise. A total of 32 patients (26 male, mean age 55 years) met the criteria and comprised the study population. Eight patients had history of mild hypertension and blood pressure was well controlled in these patients. Patients underwent both resting and supine bicycle exercise echocardiography. Peripheral blood was collected for the measurement of the plasma N-terminal pro-BNP level at two time points: before exercise and immediately after exercise. All medications were withheld before exercise echocardiography. Study approval was obtained from the internal review board.

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Two-dimensional and Exercise Doppler Echocardiography[8]

Standard 2-dimensional measurements (LV diastolic and systolic dimensions, ventricular septum, posterior wall thickness, LV mass index) were obtained with M-mode quantification.[9] LV ejection fraction was calculated by the modified method of Quinones et al.[10] LA volume index (LAVI) was measured by prolated ellipsoidal method and LV outflow tract diameter measured at parasternal long-axis view.[9] After obtaining the rest images from the standard parasternal and apical views, multistage supine bicycle exercise testing was performed with a variable load bicycle ergometer (Medical Positioning Inc, Kansas City, MO). Patients pedaled at constant speed beginning at a workload of 25 W with an increment of 25 W every 3 minutes. Echocardiography was performed using an ultrasound system (Vingmed 7, GE, Horten, Norway) with 2.5-MHz transducer during rest, each stage of exercise, and recovery in the sequence described as follows. From the apical window, a 1- to 2-mm pulsed Doppler sample volume was placed at the mitral valve tip and mitral flow velocities from 5 to 10 cardiac cycles were recorded. The mitral inflow velocities were traced and the following variables were obtained: peak velocity of early (E) and late (A) filling, and deceleration time of the E wave velocity. Tricuspid regurgitant jet velocity was also obtained to estimate pulmonary artery systolic pressure using continuous wave Doppler, if measurable. Mitral annular velocity was measured by Doppler tissue imaging using the pulsed wave Doppler mode. The filter was set to exclude high-frequency signal, and the Nyquist limit was adjusted to a range of 15 to 20 cm/s. Gain and sample volume were minimized to allow for a clear tissue signal with minimal background noise. Early diastolic (E′) and systolic (S′) velocities of the mitral annulus were measured from the apical 4-chamber view with a 2- to 5-mm sample volume placed at the septal corner of the mitral annulus. These measurements were performed at baseline, at each stage of exercise, and at recovery in the same sequence. All data were stored digitally and measurements were made at completion of each study. Two-dimensional echocardiographic images from apical views at rest and during exercise were acquired, digitized, recorded, and analyzed for the wall-motion analysis. LV diastolic and systolic longitudinal function reserve were defined as $\Delta E'$ (change from E'_{base}, E'_{base} is the early diastolic mitral annular velocity at rest) and $\Delta S'$ (change from S'_{base}, S'_{base} is the systolic mitral annular velocity at rest) at each stage. As an index of EC, total exercise duration and calculated maximal workload (metabolic equivalent levels = [2 × workload {kg-m/min} + 300]/[3.5 × weight {kg}]) were used.[11]

Measurement of pro-BNP Concentration

An intravenous polyethylene cannula was inserted before resting echocardiography. After 20 minutes of supine rest peripheral blood was collected via venal puncture in an edetic acid tube; a second sample was obtained within 2 minutes after the termination of exercise while stress images were acquired. The blood was analyzed in triplicate by an electrochemiluminescence immunoassay method for the pro-BNP level (Elecsys proBNP, Roche Diagnostics, Basel, Switzerland).

Statistical Analysis

Continuous variables were summarized as mean ± SD. Categorical variables were summarized as percentages of the group total. Comparisons of clinical characteristics, echocardiographic Doppler indices, and parameters of EC between the two groups subdivided by median $\Delta E'_{50W}$ of 2 m/s were performed using the Mann-Whitney test for continuous variables and the Fisher's exact test for categorical variables. Comparison of log pro-BNP between rest and peak exercise was performed using the Wilcoxon signed rank test. Pearson's correlation coefficient was used to assess correlations between normally distributed variables; logarithmic transformation was used to adjust asymmetrically distributed variables. The relation between significant variables was investigated using stepwise multivariate linear regression. Receiver operating characteristic analysis was performed to obtain cut-off values for plasma pro-BNP concentration and $\Delta E'_{50W} \times E'_{base}$ for predicting exercise duration less than 500 seconds. Global χ^2 analysis was performed to assess whether (resting plasma pro-BNP) + ($\Delta E'_{50W} \times E'_{base}$) add incremental diagnostic information over individual value alone. A statistical software package (SPSS 13.0, SPSS Inc, Chicago, IL) was used and *P* values of less than .05 were considered significant.

Table 1 Baseline characteristics of study population

	Mean ± SD	Range
Age, y	55.0 ± 11.2	26-65
Male, n (%)	26 (81.2)	
History of smoking, n (%)	11 (29.7)	
History of hypertension, n (%)	13 (40.6)	
History of dyslipidemia, n (%)	6 (18.8)	
BMI, kg/m^2	23.7 ± 2.3	19.7-29.0
Plasma creatinine level, mmol/L	0.9 ± 0.1	0.6-1.3
Plasma proBNP, pg/mL	941.4 ± 877.2	18-3657
Systolic BP, mm Hg	122.7 ± 21.8	94-167
Diastolic BP, mm Hg	72.9 ± 10.2	59-106
Heart rate, beats/min	60.9 ± 8.3	49-82
LVEDD, mm	45.5 ± 4.0	34-53
LVEF, %	70.5 ± 6.8	60-86
IVS, mm	16.7 ± 3.7	9-26
PWT, mm	11.4 ± 3.3	7-24
LAVI, mL/m^2	36.6 ± 12.7	20.8-82.1
E, cm/s	58.9 ± 24.4	30.5-150.0
A, cm/s	55.0 ± 17.7	21.5-100.0
E/A ratio	1.2 ± 0.7	0.5-3.5
DT, ms	216.1 ± 51.1	104-340
E', cm/s	4.03 ± 1.23	2.0-6.5
A', cm/s	6.34 ± 2.10	3.0-11.8
E'/A'	0.68 ± 0.25	3.5-9.0
E/E'	15.71 ± 8.87	6.7-50.0
S', cm/s	6.01 ± 1.23	0.30-1.49
Peak TRV, m/s	2.4 ± 0.4	1.8-3.1

A, Late diastolic mitral inflow velocity; *A'*, late diastolic mitral annular velocity; *BMI*, body mass index; *BP*, blood pressure; *DT*, deceleration time of early mitral inflow; *E*, early diastolic mitral inflow velocity; *E'*, early diastolic mitral annular velocity; *IVS*, end-diastolic interventricular septal thickness; *LAVI*, left atrial volume index; *LVEDD*, left ventricular end-diastolic dimension; *LVEF*, left ventricular ejection fraction; *proBNP*, N-terminal pro-B-type natriuretic peptide; *PWT*, end-diastolic posterior wall thickness; *S'*, systolic mitral annular velocity; *TRV*, tricuspid regurgitant velocity.

RESULTS

Clinical and Echocardiographic Characteristics

Sixteen patients were taking calcium-channel blockers whereas 17 patients were taking β-blockers. Angiotensin-receptor blocker was administered in 9 patients, and 3 patients were taking an angiotensin-converting enzyme inhibitor. Diuretics were administered