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Noninvasively-determined Diastolic Stiffness is Abnormal during Exercise, but not at Rest, in Patients with Apical Hypertrophic Cardiomyopathy

Jong-Won Ha, MD[1], Eui-Young Choi, MD[1], Jin-Mi Kim, RN[1], Jeong-Ah Ahn, RN[1], Se-Wha Lee, RN[1], Hye-Sun Seo, MD[1], Ji-Hyun Lee, MD[1], Se-Joong Rim, MD[1], Jae K. Oh, MD[2] and Namsik Chung, MD[1]

[1]Cardiology Division, Yonsei University College of Medicine, Seoul, Korea
[2]Division of Cardiovascular Diseases, Mayo Clinic College of Medicine, Rochester, Minnesota, USA

Background : The ratio of mitral inflow (E) and annular velocity (E') to stroke volume (E/E'/SV) has been used as an index of diastolic elastance (Ed). However, its change during exercise has not been evaluated. We hypothesized that Ed values obtained during exercise would be abnormal in patients with apical hypertrophic cardiomyopathy (ApHCM).

Methods : Ed was measured at rest and during graded supine bicycle exercise (25 Watts, 3 minute increments) in 15 patients with ApHCM (12 male; mean age, 57 years) and in 15 age- and gender-matched control subjects.

Results : Ed was not significantly different at rest and during 25 W of exercise. However, Ed was significantly higher at 50 W of exercise in patients with ApHCM compared to control subjects (0.21±0.05 vs. 0.15±0.04 cm/s, p=0.0059). There was significant positive correlation between the magnitude of change in proBNP levels during exercise and the change of Ed from rest to 50 W of exercise (r^2=0.69, p<0.0001).

Conclusion : Noninvasively-determined Ed was similar at rest and during mild exercise between patients with ApHCM and control subjects. However, Ed was significantly higher during moderate exercise in ApHCM patients, suggesting a dynamic change in LV stiffness during exercise in these patients.

KEY WORDS : Hypertrophic cardiomyopathy · Diastolic stiffness · Exercise.

Introduction

Apical hypertrophic cardiomyopathy (ApHCM) is a unique form of hypertrophic cardiomyopathy (HCM), in which the hypertrophy of myocardium predominantly involves the apex of the left ventricle (LV). Although studies have found that ApHCM has a benign prognosis in terms of cardiovascular mortality,[1)2)] one third of ApHCM patients may develop unfavorable clinical events and potentially life-threatening complications, such as myocardial infarction, atrial fibrillation, and stroke.[2)] Many of the clinical and pathophysiological features of HCM result from a complex disturbance of diastolic function.[3)4-9)] However, changes in diastolic function during exercise in patients with ApHCM are not well-known. Recently, the ratio of the mitral inflow and the annular velocity to stroke volume (E/E'/SV) was used as an index of diastolic elastance (Ed).[10)] However, in patients with ApHCM, the change of Ed during exercise has not been evaluated. We hypothesized that Ed during exercise would be abnormal in patients with ApHCM.

Methods

Study Population

Mitral inflow and septal mitral annular velocities were measured at rest and during graded supine bicycle exercise (25 W, 3-minute increments) in 15 patients with ApHCM

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• Address for Correspondence : Jong-Won Ha, Cardiology Division, Yonsei University College of Medicine, 250 Seongsan-no, Seodaemun-gu, Seoul 120-752, Korea Tel : +82-2-2228-8460, Fax : +82-2-393-2041, E-mail : jwha@yumc.yonsei.ac.kr

(12 males; mean age, 57 years) and in 15 age- and gender-matched control subjects. Of the patients with ApHCM, 6 patients were taking calcium channel blockers and 7 patients were taking beta-blockers. Angiotensin receptor blockers were being taken by 7 patients and 1 patient was taking diuretics. However, all medications were withheld before exercise echocardiography. Seven patients were in New York Heart Association class 2 symptom status at the time of evaluation. Study approval was obtained from the Institutional Review Board of Yonsei University College of Medicine.

TWO-DIMENSIONAL AND EXERCISE DOPPLER ECHOCARDIOGRAPHY (DIASTOLIC STRESS ECHOCARDIOGRAPHY)[11]

Standard two-dimensional measurements (LV diastolic and systolic dimensions, ventricular septum and posterior wall thickness, left atrial volume, and LV outflow tract diameter) were obtained with the patient in the left lateral position. The LV ejection fraction (EF) was calculated by the modified Quinones method.[12] Left atrial volume was measured by the prolate ellipsoid method.[13][14] After obtaining resting images from the standard parasternal and apical views, a multistage supine bicycle exercise test was performed with a variable load bicycle ergometer (Medical Positioning, Inc., Kansas City, Missouri). Patients pedaled at a constant speed, beginning at a workload of 25 Watts with a 25-Watt incremental increase every 3 minutes. Echocardiography was performed using a GE Vingmed System 7 ultrasound system with a 2.5-MHz transducer while the patient was at rest, each stage of exercise, and during recovery, as described in the following sequential steps. From the apical window, a 1-2 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) stage filling, and the E wave velocity deceleration time. If measurable, the tricuspid regurgitant jet velocity was also obtained to estimate pulmonary artery systolic pressure by using continuous-wave Doppler. Stroke volume (SV) was measured from the LV outflow tract diameter and the pulse wave Doppler signal as described previously.[15] Mitral annular velocity was measured by tissue Doppler 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. To provide a continuous variable that might estimate Ed, the ratio of E to E' was used as an estimation of mean left atrial pressure (E/E').[16-18] The operant Ed was then estimated as E/E' divided by the volume of filling during diastole, assuming the absence of significant aortic regurgitation (SV).[10] These measurements were performed in the same sequence at baseline, during each stage of exercise, and at recovery. All data were stored digitally, and measurements were made at the completion of each study. Two-dimensional echocardiographic images from apical views at rest and during exercise were acquired, digitized, recorded, and analyzed for the analysis of wall motion.

MEASUREMENT OF PROBNP LEVELS

Blood samples for proBNP analysis were drawn at rest and immediately after peak exercise. Samples were stored at 4 ℃ and analyzed within 4 hours of the blood draw. Prior to analysis, each tube was inverted several times to ensure homogeneity. The whole blood was then analyzed in triplicate by an electrochemiluminescence immunoassay method for proBNP levels (Elecsys proBNP, Roche Diagnostics, Basel, Switzerland).

STATISTICAL ANALYSIS

Continuous variables were summarized as a mean±standard deviation. Categorical variables were summarized as a percentage of the group total. The relationship between proBNP level and Ed was evaluated with linear regression analysis. In this analysis, log-transformed proBNP values were used because the proBNP distribution was positively skewed. The change in proBNP levels during exercise were also compared with the change in Ed values during exercise by linear regression analysis. Statistical significance was defined as <0.05.

RESULTS

BASELINE ECHOCARDIOGRAPHIC FINDINGS

Patients with ApHCM had thicker interventricular septums and posterior walls. The left atrial volume index was significantly larger in ApHCM patients compared to the control subjects. Although LVEF at rest was higher in ApHCM patients compared to control subjects with a borderline significance (72±5 vs. 68±5, p=0.051), S' at rest was significantly lower in patients with ApHCM (6.2±0.9 vs. 7.0±1.0 cm/s, p=0.028), suggesting abnormal LV longitudinal contractions. There were no significant differences in mitral inflow velocities (E, A, E/A, DT) between the two groups. SV and tricuspid regurgitation velocity at rest were also similar between two groups (Table 1).

Table 1. Baseline echocardiographic results

	ApHCM (n=15)	Control (n=15)	*p* value
LVEDD (mm)	50±3	49±4	0.78
LVESD (mm)	30±3	32±4	0.15
Ejection fraction (%)	72±5	68±5	0.051
IVS (mm)	11±1	9±1	0.0002
PW (mm)	11±1	9±2	0.021
LV mass index (g/m^2)	107.4±19.6	91.5±18.5	0.064
LAVI (ml/m^2)	25±6	19±5	0.013
E (m/sec)	0.64±0.20	0.61±0.14	0.57
A (m/sec)	0.61±0.11	0.71±0.15	0.053
E/A	1.1±0.3	0.9±0.3	0.17
DT (msec)	191±28	203±35	0.31
TR velocity (m/sec)	2.2±0.2	2.2±0.1	0.91
Stroke volume (ml)	68±14	61±16	0.23
E' (cm/sec)	5.2±1.1	6.5±1.7	0.019
E/E'	12.7±4.4	9.6±1.9	0.021
S' (cm/sec)	6.2±0.9	7.0±1.0	0.028

LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; IVS, interventricular septal thickness; PW, posterior wall thickness; LAVI, left atrial volume index; E, peak velocity of early diastolic filling; A, peak velocity of diastolic filling during atrial contraction; DT, deceleration time; TR, tricuspid regurgitation; E' early diastolic mitral annular velocity; S', systolic mitral annular velocity

Table 2. Hemodynamic response to exercise

	ApHCM (n=15)	Control (n=15)	*p* value
HR at rest (beats/min)	60±6	63±9	0.25
HR at 25W (beats/min)	90±13	93±10	0.42
HR at 50W (beats/min)	100±12	104±10	0.39
Systolic BP (mmHg) at rest	121±21	127±11	0.38
Systolic BP (mmHg) at 25W	145±25	142±15	0.67
Systolic BP (mmHg) at 50W	155±22	154±19	0.91
Diastolic BP (mmHg) at rest	74±11	78±7	0.30
Diastolic BP (mmHg) at 25W	86±15	87±7	0.89
Diastolic BP (mmHg) at 50W	85±11	92±10	0.083

HR, heart rate; BP, blood pressure

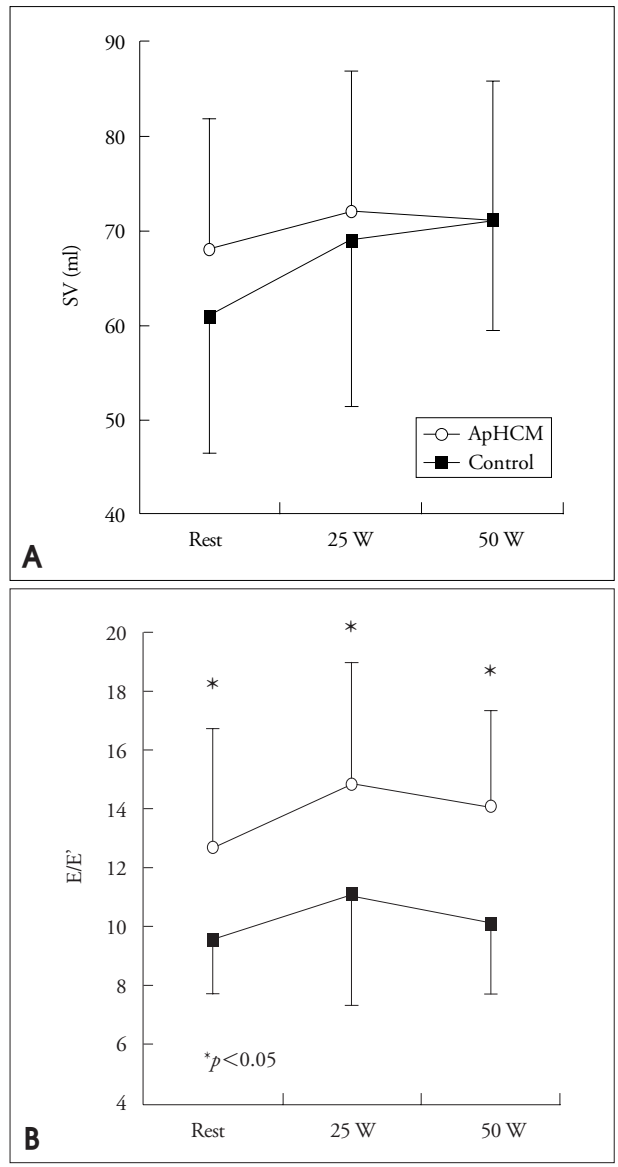

Fig. 1. A: Change of SV in subjects when at rest to when exercising. Note the similar SV values at rest and during exercise between the groups. B: Change of E/E' values in subjects when at rest to when exercising. Higher E/E' values at rest and during exercise were found in ApHCM patients compared to control subjects.

Hemodynamic response to exercise

The effect of supine bicycle exercise on heart rate and blood pressure is shown in Table 2. In both groups, heart rate, systolic blood pressure, and diastolic blood pressure were increased after exercise compared to when at rest. We found no significant differences between the groups with regard to changes in either the heart rate or the systolic and diastolic blood pressures when at rest or during exercise (Table 2).

LV diastolic elastance at rest and with exercise

E/E' was significantly higher both at rest and during exercise in patients with ApHCM compared to control subjects (rest, 12.7±4.4 vs. 9.6±1.9 cm/s, p=0.021; 25 W, 14.8±4.3 vs. 11.1±2.4 cm/s, p=0.011; 50W, 14.1±3.6 vs. 10.1±1.8 cm/s, p=0.02) (Fig. 1). However, the magnitude of change in E/E' from rest to exercise did not differ significantly between the groups (from rest to 25 W, 1.9±2.8 vs. 1.3±2.4 cm/s, p=0.58; from rest to 50 W, 1.2±2.8 vs. 0.6±1.2 cm/s, p=0.43). SV during 25 W and 50 W of exercise, as well as the SV increments during exercise, were similar between the groups (Fig. 1). Furthermore, Ed was not significantly different between groups at either rest or during mild exertion (rest, 0.19±0.05 vs. 0.17±0.05 cm/s, p=0.27; 25 W, 0.21±0.06 vs. 0.18±0.09 cm/s, p=0.31). However, during 50 W of exercise, Ed became significantly higher in patients with ApHCM when compared to control subjects (0.20±0.05 vs. 0.15±0.04 cm/s, p=0.006) (Fig. 2) (Table 3).

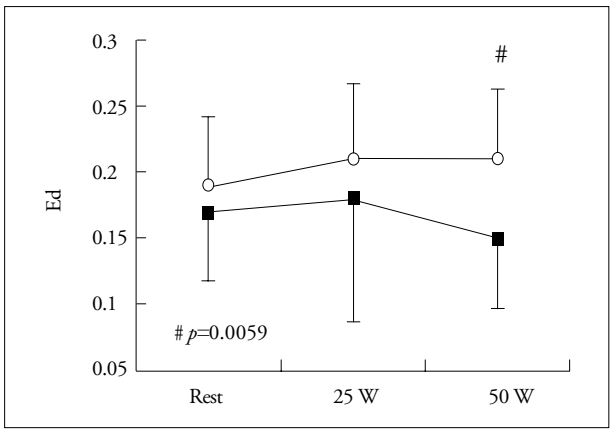

Fig. 2. Ed value changes when at rest and during exercise. Similar Ed values were measured when the subjects were at rest and during 25 W of exercise, but were significantly higher in ApHCM patients during 50 W of exercise.

Table 3. Diastolic elastance measurements and proBNP levels at rest and during exercise

	ApHCM (n=15)	Control (n=15)	*p* value
Ed at rest	0.19±0.05	0.17±0.05	0.27
Ed at 25 W	0.21±0.06	0.18±0.09	0.31
Ed at 50 W	0.20±0.05	0.15±0.04	0.006
ProBNP at rest (pg/ml)	363±221	96±217	0.016
ProBNP at peak exercise (pg/ml)	392±246	92±199	0.012

Ed, diastolic elastance; proBNP, N-terminal pro-brain natriuretic peptide

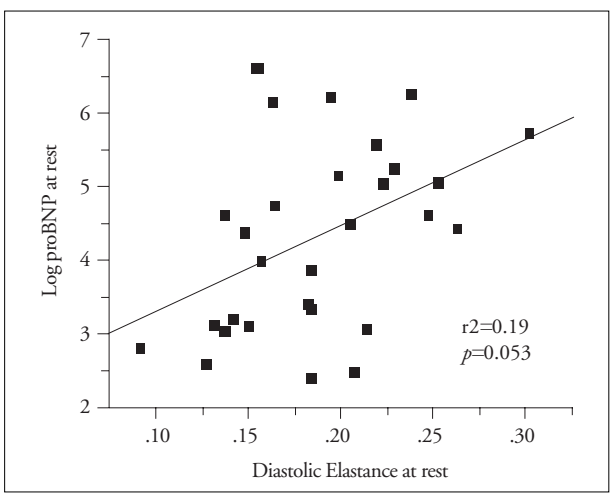

Fig. 3. Plot showing the relationship between the log proBNP levels and Ed while the patients were at rest. ProBNP levels correlated with Ed at the resting state (r^2=0.19, p=0.053).

PROBNP AND DIASTOLIC ELASTANCE

Pro BNP levels at rest (363±221 vs. 96±217 pg/ml, p=0.016) and at peak exercise (392±246 vs. 92±199 pg/ml, p=0.012) were significantly higher in patients with ApHCM compared to control subjects. Only minor changes in ProBNP levels were found in the control group during exercise. In contrast, proBNP levels were significantly elevated in ApHCM patients during exercise (⊿proBNP with exercise, 29±30 vs. -4±19 pg/ml, p=0.018). The log-transformed proBNP levels at rest showed a weak correlation with Ed at rest (r^2=0.19, p=0.053) (Fig. 3). However, there was a stronger positive correlation between the magnitude of proBNP change during exercise and the change in Ed values from rest to 50 W of exercise (r^2=0.69, p<0.0001) (Fig. 4).

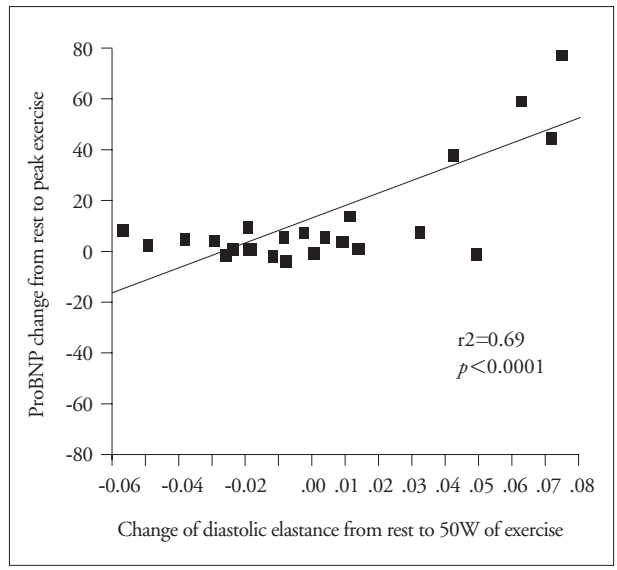

Fig. 4. The relationship between the change of proBNP levels as well as the change of Ed in subjects going from the resting state to peak exercise. A significant positive correlation between the magnitude of change in proBNP levels during exercise and the change of diastolic elastance from a resting state to 50 W of exercise (r^2=0.69, p<0.0001).

DISCUSSION

The present study is, to our knowledge, the first to demonstrate the dynamic change of ventricular stiffness in patients with ApHCM using non-invasively-determined LV elastance. Interestingly, LV elastance at rest and during mild exertion did not differ between ApHCM patients and control subjects, but LV elastance became abnormal in ApHCM patients during moderate exertion. Additionally, the magnitude of the increase in proBNP levels during exercise was significantly correlated with the increase in ventricular stiffness during exercise in ApHCM patients.

DIASTOLIC FUNCTION IN APHCM

Although extensive investigations have been made regarding diastolic function in patients with HCM, few studies evaluated diastolic function in patients with ApHCM. In a previous study, we showed the presence of chronic diastolic dysfunction in patients with ApHCM.[19] In patients with diastolic heart failure, exercise testing revealed the failure of SV increase with exercise despite markedly elevated filling pressures.[20]

Since Ed is the parameter that combines SV with LV filling pressures, it can be speculated that patients with ApHCM will have an abnormal Ed during exercise. This hypothesis was supported by our finding that Ed became abnormal with exercise. Abnormal Ed values during exercise in ApHCM patients were driven by higher E/E' values. Since SV responses to exercise were similar between the groups, elevated filling pressure was the primary factor responsible for increased Ed in ApHCM patients. In severe diastolic dysfunction, SV can not be increased in response to stress factors such as exercise, and LV filling pressures are inevitably elevated during exercise. We speculate that the diastolic function of ApHCM is abnormal but not severe enough to compromise the SV response to exercise. Therefore, the augmentation of SV during exercise was maintained but was accompanied by an elevation in LV filling pressure.

Change of proBNP and diastolic elastance in ApHCM patients

BNP is released in direct proportion to the ventricular volume expansion and pressure overload, as well as the ventricular wall stress in patients with systolic heart failure.[9)14)21)] Plasma proBNP levels have been well correlated with the LV diastolic pressures in patients with a normal LV systolic function.[22)] About 40% of the patients with ApHCM had an elevated plasma level of proBNP, suggesting the presence of elevated filling pressures at rest in some of the ApHCM patients.[19)] However, the relationship between the concen-tration of proBNP and ventricular stiffness in patients with ApHCM has not been investigated. In our study, the log-transformed proBNP levels at rest showed a borderline significant positive correlation with the Ed values. The result of our study is consistent with a previous study showing subjects with higher Ed values had higher plasma BNP concentrations.[10)] However, our study further demonstrates that the magnitude of proBNP increase during exercise was significantly correlated with the increase in ventricular stiffness during exercise.

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