Acute Effects of Diltiazem on Regional Left Ventricular Diastolic Filling Dynamics in Patients With Hypertrophic Cardiomyopathy as Assessed by Color Kinesis

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Background  The effect of calcium antagonists on regional left ventricular (LV) filling dynamics in patients with hypertrophic cardiomyopathy (HCM) is not well known, so the present study evaluated the results of echocardiography with color kinesis (CK) analysis during diltiazem infusion.

Methods and Results  Nineteen patients (16 men, 3 women; mean age 55±15 years) underwent echocardiography with CK analysis during intravenous diltiazem (10mg/2 min). Using the quantitative CK software the LV short-axis image was divided into 6 segments and the percent endocardial expansion at the early, mid- and late-diastolic filling time was averaged for all segments, with the standard deviation of the mean used as an index of diastolic asynchrony (asynchrony index). The regional mean filling time was also measured for the corresponding segments. As global diastolic parameters, the global filling time, peak filling rate, and the time-to-peak filling were calculated. After the administration of diltiazem, the asynchrony index was decreased for all three diastolic filling times. Diltiazem shortened the mean filling time overall, especially in the posterior and lateral wall segments. These findings were associated with significant improvement in the CK-derived global diastolic parameters.

Conclusions  Diltiazem has a favorable effect on LV diastolic asynchrony, which may account for the acute changes in global LV relaxation. (Circ J 2004; 68: 1035–1040)

Key Words: Diastolic function; Echocardiography; Hypertrophic cardiomyopathy

Left ventricular (LV) diastolic function is impaired in patients with hypertrophic cardiomyopathy (HCM) because of impaired relaxation and increased chamber stiffness and is related to the extent of spatial and temporal heterogeneity during diastole. Studies using invasive and noninvasive techniques have demonstrated a non-uniform filling process in patients with HCM. One such study showed that the calcium antagonist, verapamil, improved the heterogeneity of LV filling in HCM patients. There are no data regarding the effect on the regional filling dynamics in these patients of another calcium antagonist, diltiazem, which depresses the heart less than verapamil and therefore has a lower incidence of adverse effects. Color kinesis (CK) is a real-time echocardiographic technique that is useful for assessing regional LV systolic and diastolic function and was used in the present study to examine the acute effects of diltiazem on the regional LV filling dynamics in patients with HCM.

Methods

Study Population

Nineteen patients with HCM (13 men, 6 women; age 55±15 years, range: 27–75) were enrolled in this study. None had LV outflow obstruction nor had any been taking cardiac medications. The diagnosis of HCM was made chiefly on the basis of echocardiographic findings; that is, a ventricular septum and/or posterior wall >12 mm thick and asymmetrical septal hypertrophy defined as septal thickening at least 1.3-fold the thickness of the posterior wall. Patients who had systemic hypertension or other pathologic conditions causing cardiac hypertrophy, and those in the dilated stage were excluded. We also excluded patients who had any type of arrhythmia or conduction disturbance, or who had heart rate <55 or >100 beats/min. All patients were suitable for the CK studies; that is, they had satisfactory echo windows for tracking the endocardial border.

Protocol

All patients gave informed consent to participate in this study. After M-mode, Doppler, and CK echocardiographic variables were obtained, 10 mg of diltiazem was administered intravenously over 2 min and 10 min later the same variables were re-tested. Heart rate and blood pressure were monitored throughout the study.

M-Mode and Doppler Echocardiography

A complete transthoracic echocardiographic study, including M-mode, 2-dimensional, and pulsed-Doppler methods, was performed with a 4s transducer equipped with a commercially available apparatus (SONOS 5500, Phillips Medical Systems Co Bothell, WA, USA). According to the criteria of the American Society of Echocardiography, the M-mode echocardiographic variables of the LV dimension and wall thickness were calculated (Table I).

Using the pulsed-Doppler method, mitral and pulmonary flow velocity profiles were recorded, with the sample
volume placed at the tip of mitral valves and 1–2 cm into the pulmonary vein, respectively. The early filling velocity, atrial filling velocity and their ratio (E/A), E-wave deceleration time, systolic and diastolic forward velocities, and the velocity of the atrial reversal wave were calculated. We also obtained the isovolumic relaxation time and the duration of the atrial reversal wave, as described previously. All the Doppler tracings were acquired during a breath-hold and recorded at a paper speed of 100 mm/s.

**CK Data Acquisition and Analysis**

Systolic and diastolic CK images of the LV short-axis view at the papillary muscle level were obtained for each patient. As previously described, the acoustic quantification system was activated and the gain controls (lateral gain control and time gain compensation) were adjusted to optimally track the endocardial border. The accuracy of the endocardial tracking was assured by toggling on and off the color overlays. Particular care was taken to keep the transducer in the same position until the second set of CK data was acquired. The 2 consecutive beats of the CK images were acquired as cineloop memory and stored on an optic disc for the subsequent off-line analysis.

CK diastolic images were analyzed by quantitative CK software (EchoSoft Co Wilmington, DE, USA). Using this software, the end-diastolic color-encoded image was automatically divided into 6 segments, and the regional filling curves corresponding to each segment (ie, anterior wall, anteroseptal wall, ventricular septum, inferior wall, lateral wall, and posterior wall) were constructed (Fig 1). These regional filling curves reflected the percent endocardial expansion of each segment at any specific percent filling time. The percent endocardial expansion at the early (25%), mid- (50%), and late diastolic (75%) filling time was averaged for all segments, and the standard deviation of the mean was used as an index of diastolic asynchrony (asynchrony index). The regional mean filling time during diastole representing the average time for a pixel to change from tissue to blood for each segment was also calculated. As the parameters of global LV diastolic function...
The global mean filling time, peak filling rate, and the time-to-peak filling were measured by the same software. Changes in systolic function associated with intravenous diltiazem were also assessed by percent area change, which was derived from the systolic CK images. We described the CK-derived diastolic parameters in normal subjects in a previous report.9

### Statistical Analysis

Changes in echocardiographic variables were assessed by the paired t test and the data are expressed as mean ± SD. A p-value <0.05 was considered significant.

### Results

All of the patients completed the study protocol without any complications. Diltiazem decreased both systolic (123±20 mmHg to 106±16 mmHg, p<0.001) and diastolic (67±13 mmHg to 58±12 mmHg, p<0.001) blood pressures significantly, but no change was observed with regard to heart rate (67±8 beats/min to 68±12 beats/min, p=0.567).

### Changes in the Doppler Echocardiographic Parameters

Table 1 shows the Doppler echocardiographic parameters before and after the administration of diltiazem. There were modest, but significant changes in the mitral flow velocity.
profile: E velocity increased, A velocity decreased, and the E/A ratio increased. The deceleration time and the duration of the A velocity were also changed but not significantly. As with the pulmonary flow velocity profile, there were no significant changes in the systolic and diastolic forward flow velocities or the atrial reversal flow velocity; however, the duration of the atrial reversal wave shortened significantly with intravenous diltiazem.

Changes in the CK-Derived Parameters

Table 2 shows the regional and global CK-derived parameters before and after the administration of diltiazem. After diltiazem infusion, the asynchrony index was decreased for the 3 specific filling times and the mean filling time overall was shortened, especially in the posterior and lateral wall segments (Fig 2). These findings were associated with significant improvement in the CK-derived global diastolic parameters. However, no significant change was
observed in the systolic fractional area change. Representative cases are shown in Figs 3 and 4.

Discussion

There have been very few studies of the acute effects of calcium antagonists on the regional filling dynamics in patients with HCM.15-17 This probably because of the lack of easily obtainable diagnostic modalities that can assess the regional filling process. Bonow et al used radionucleotide angiography to assess changes in the heterogeneity of ventricular filling after the administration of verapamil1 but that method is somewhat expensive and time-consuming. More recently, Liu et al developed an automated segmental analysis system based on an automatic border detection technique and evaluated the effect of dobutamine on LV systolic and diastolic asynchrony in patients with LV hypertrophy caused by systemic hypertension.18 CK is also based on acoustic border detection and allows real-time assessment of endocardial contraction or expansion on a regional basis.6-9 In the present study, asynchronous ventricular filling was improved after intravenous diltiazem, as expressed by the decrease in the asynchrony index through-out diastole, which is consistent with the findings of the study using verapamil.2 We have also observed that diltiazem shortened overall the regional mean filling time, especially in the posterior and lateral wall segments, a finding that is partly supported by a previous study using M-mode echocardiography in which it was found that after acute verapamil treatment, the thinning rate of the posterior wall was increased to a greater extent than that in the ventricular septum.1 We speculate that the posterior and lateral wall segments, being less frequently hypertrophied in HCM, might be more amenable to changes in loading conditions that accelerate the inactivation process. On the other hand, Bonow et al observed that there was no relationship between the site of hypertrophy and the extent of changes in the regional filling process.3 This discrepancy in the observations could be explained by differences in the methods used to assess regional filling, the drugs used, or patient characteristics.

Previous studies have demonstrated that calcium antagonists, including diltiazem, improved ventricular relaxation in patients with HCM.19,20 However, Betocchi et al11 and Nishimura et al21 cautioned about empiric use of these agents because they can potentially increase the LV filling pressure,1,2 which raises the possibility that the improvement in the global CK-derived parameters observed in this study reflects the harmful effects of diltiazem. However, this study, as well as our previous one, using CK has shown that the CK-derived parameters are less dependent on the loading conditions,22 which suggests that the direct effect of diltiazem may contribute to the improvement in LV filling, presumably because of a favorable effect on myocardial ischemia. We have also observed that the duration of atrial reversal wave is shortened after intravenous diltiazem, indicative of a decline in the LV filling pressure.14 Nishimura et al21 used verapamil and Betocchi et al11 included patients with LV outflow obstruction; in the latter case there might be a detrimental effect that aggravates outflow obstruction, lowering coronary perfusion pressure and inducing myocardial ischemia. A simultaneous CK and hemodynamic study is needed to define exactly how diltiazem influences LV diastolic function in patients with a nonobstructive form of HCM.

Study Limitations

As described previously, CK has several limitations, the greatest of which is its dependence upon image quality and operator dependent gain-settings, although the reproducibility of this technique has been established.7 Second, we obtained only one short-axis view for each patient, whereas data from multiple views might have been more informative. However, we prioritized the accuracy of data acquisition by fixing the transducer at the same echo window. Finally, the relatively low frame rate (33 ms) of the currently available CK mode would be an inherent technical limitation that prevents examination of the changes in area during isovolumic relaxation time, which might reflect ‘relaxation’ in the strict sense. Future development of an ultrasonic machine with a higher frame-rate and more extended color encoding is required.

References


