Changes in Left Ventricular Diastolic Function 6 Months After Nonsurgical Septal Reduction Therapy for Hypertrophic Obstructive Cardiomyopathy

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Background—Nonsurgical septal reduction therapy (NSRT) decreases left ventricular outflow tract (LVOT) gradient and improves symptoms in patients with hypertrophic obstructive cardiomyopathy (HOCM). NSRT effects on LV/left ventricular diastolic function are currently unknown.

Methods and Results—HOCM patients (n=29) had Doppler echocardiography at baseline and 6 months after NSRT to evaluate changes in LV volume, pre–A-wave pressure, early diastolic mitral annulus velocity (Ea) by tissue Doppler, and τ. At 6 months, a significant reduction in LVOT gradient (from 53.6±15 to 6±5 mm Hg; P<0.001) was accompanied by improvement in exercise duration (from 284±147 to 408±178 seconds; P=0.04) and New York Health Association class (from III to I; P<0.001). Pre-A pressure (18±6 to 14±5 mm Hg; P<0.01) and τ (62±8 to 51±8 ms; P<0.01) decreased, whereas Ea (5.8±1.8 to 8±1.8 cm/s; P<0.01) and LV end-diastolic volume (117±16 to 130±22 mL; P<0.01) increased.

Conclusions—NSRT improves LV relaxation and compliance, which contributes to the symptomatic relief seen at 6 months. (Circulation. 1999;99;344–347.)

Key Words: diastole ■ cardiomyopathy ■ hypertrophy ■ echocardiography

Patients with hypertrophic obstructive cardiomyopathy (HOCM) usually have increased LV/left ventricular filling pressures and dyspnea secondary to impaired relaxation and compliance. This is related to the contraction load imposed by LVOT obstruction, reduced diastolic filling loads, and asynchrony in the load distribution and (in)activation.1 Nonsurgical septal reduction therapy (NSRT) successfully relieves the obstruction and improves symptoms in HOCM patients.2–5 However, its effects on LV diastolic function are unknown. We therefore evaluated LV global and regional diastolic function 6 months after NSRT.

Methods
Our institutional review board approved the protocol, and all patients gave written informed consent before participation. Subjects had a basal septal thickness ≥1.5 cm, with LVOT dynamic gradient (anterior mitral leaflet septal contact) ≥40 mm Hg at rest or ≥60 mm Hg during dobutamine (to 40 μg·kg⁻¹·min⁻¹).

Twenty nine consecutive HOCM patients who were symptomatic despite maximal medical therapy underwent NSRT (some patients were included in a previous report5). Before NSRT, 2-dimensional and Doppler echocardiography were performed simultaneously with LV catheterization. LV pre-A pressure was measured before the A-wave increase in LV pressure. This pressure relates well to pulmonary capillary wedge pressure6 and thus was used in lieu of it. LV systolic pressures (LVS; peak [LVSp] and at aortic valve closure) and LVOT gradient were measured with Medex transducers (0 at midaxillary line). After angiography, an 8F guiding catheter was engaged in the left main artery, then a 2×10-mm balloon was advanced over a 0.014 standard wire into the septal perforator branch of the left anterior descending artery and inflated. Albunex was next injected into the balloon central lumen with simultaneous echocardiographic imaging to target ethanol delivery to the culprit septal segments. Subsequently, ethanol (2 to 5 mL) was injected into the inflated balloon lumen and left for 5 minutes. With a residual gradient ≥16 mm Hg, other septal branches were injected similarly. Echocardiography and treadmill testing (n=23, Bruce protocol) were repeated 6 months later.

Echocardiographic Studies
Parasternal and apical views were obtained by use of an Acuson or Hewlett-Packard ultrasound system. With pulse Doppler, 5 cardiac cycles were recorded at the mitral annulus and tips in the 4-chamber view. Isovolumic relaxation time (IVRT: between mitral valve tips and LVOT) (Figure 1) and LVOT peak velocity were recorded by continuous-wave Doppler. The velocities at the mitral annulus lateral corner and septal base (5 cycles) were recorded6 with tissue Doppler (TD) (Figure 1).

Echocardiographic Analysis
A single observer blinded to all data performed the analysis off-line using a Digisonics station (with 2-dimensional and Doppler software). Measurements included LV volume,7 septal base thickness (parasternal views), and septal area opacified by Albunex during
NSRT. Mitral inflow was analyzed for peak early diastolic (E) and late diastolic (A) velocities, acceleration time of E (AT-E: onset to peak E), and deceleration time of E and A (DT-E, DT-A, by linear extrapolation to baseline). IVRT (aortic valve closure to mitral flow onset) was derived as previously described.6,8 We noted in this HOCM population that early diastolic mitral annulus velocity at (Ea) the lateral corner has a weak inverse relation to filling pressures and is not influenced by pressure changes. Septal base septic, early diastolic, and late diastolic velocities were measured. LVOT peak gradient was derived by the modified Bernoulli equation10: maximal gradient was derived by the modified Bernoulli equation10: maximal gradient = 4v², where v (m/s) is peak LVOT velocity. The time constant of LV relaxation was derived as: τ = IVRT/(Ln LV–Ln pre-A).11 Pressures were obtained at baseline invasively. At 6 months, they were estimated noninvasively. LVSP was derived as systolic blood pressure−LVOT gradient. We previously noted E/Ea to relate well to pre-A pressure (r=0.76; pre-A pressure = 3.3+1.1(E/Ea); P<0.01) and to adequately detect LV filling pressure changes (r=0.8; SEE=3 mm Hg; P<0.01) in HOCM patients. This equation was validated in 17 additional patients with HOCM: when it performed equally well (r=0.82; P<0.01; SEE=3 mm Hg). Accordingly, we used it for pre-A pressure estimation at 6 months. τ Was also calculated at baseline noninvasively (see above). Furthermore, it was calculated assuming no change in pre-A pressure at 6 months.

Statistics
Baseline and 6-month Doppler data were compared by paired t test, and functional class changes were evaluated with Wilcoxon signed rank test. Regression analysis correlated τ changes with changes in LV volumes, LVOT gradient, septal thickness, New York Heart Association (NYHA) class, and exercise duration. Significance was set at P<0.05.

Results
Mean age was 53.6±15 years (range 29 to 83) (15 women). Four patients were in NYHA class IV, with 25 in class III; 23 had angina; and 18 had presyncope or syncope despite maximal therapy with β-blockers, verapamil, disopyramide, and amiodarone, or sotalol. All but 4 had a resting LVOT gradient (56±29 mm Hg; range 15 to 120 mm Hg), and 4 had dobutamine-provocable gradients. Patients had hyperdynamic ventricles without severe mitral regurgitation. Satisfactory mitral inflow and TD of mitral annulus and septal base were obtained in all. At baseline, inversely derived τ (62±8 ms) correlated well with noninvasive τ (r=0.8; SEE=9 ms).

Changes in Functional Status and Hemodynamics
AT 6 months, 24 patients were in NYHA class I, 4 were in class II, and 1 was in class III (this patient had no change in gradient, pre-A pressure, and τ), with 14 taking β-blockers or verapamil (lower doses). NYHA class decreased significantly (III to I; P<0.001). Five patients still had angina (P<0.001 versus baseline). In those who were able or agreed to exercise at baseline, exercise duration increased (from 284±147 to 408±179 seconds; P<0.04). There were no malignant ventricular arrhythmias or deaths in the 29 patients, and 6 were AV sequentially paced at 6 months. LVOT gradient was significantly reduced (6.5± mm Hg; P<0.001) as were LVS and pre-A (18±6 to 14±5 mm Hg) pressures (both P<0.01). τ Was shorter at 6 months (Figure 2A) (62±8 to 51±8 ms, P<0.01; for baseline noninvasive τ, P=0.03), with similar results observed using an unchanged pre-A pressure at 6 months (P=0.035). Shortening of τ related to LVOT gradient reduction (r=0.53; P=0.05). The changes in functional class and exercise duration were related to τ shortening (r=0.54 and −0.67, respectively; both P=0.03) and pre-A pressure reduction (r=0.48 and −0.58, respectively; both P=0.04).

Changes in LV Structure and Filling
LV end-diastolic volume increased (from 117±16 to 130±22 mL; P<0.01), and septal base thickness decreased (from 2.06±0.4 to 1.5±0.4 cm; P<0.001) at 6 months. IVRT (Figure 2B) and AT-E (Figure 2C) were significantly shorter, whereas E, A, E/A, and DT-E were relatively unchanged (Table). DT-A (Figure 2D) was significantly longer at 6 months. Late mitral annular Ea increased (P=0.001), and E/Ea decreased (from 12.9±5.2 to 9.8±4.7; P<0.01) (Figure 2E). τ Shortening was also related to septal thickness reduction (r=0.58; P=0.01) and LV volume increase (r=−0.57; P=0.05).

Changes in Septal Base Function
The systolic velocity was lower after NSRT (6.5±1 to 4.5±1 cm/s; P<0.01) and was related to LVOT gradient reduction (r=0.35; P=0.05). Early (5.3±1.4 to 5.2±1.5 cm/s; P=0.2) and late (7.8±2 to 8±2.5 cm/s; P=0.8) diastolic velocities...
were unchanged. Septal Ea change was directly related to risk area ($r=0.57; P=0.05$).

**Discussion**

HOCM patients frequently have dyspnea, largely resulting from diastolic dysfunction (a nearly universal feature), with myocardial ischemia contributing some to the diastolic dysfunction and dyspnea.1 Symptomatic HOCM patients are usually treated first with verapamil or β-blockers. These drugs may favorably modify LV diastolic function through their anti-ischemic actions. However, their benefit is present only in a select group of patients, with verapamil prolonging $\tau$ and increasing filling pressures in some patients. Accordingly, some patients remain symptomatic despite maximal medical therapy, with the only options left being pacemaker therapy or septal myectomy with its attendant morbidity and mortality. NSRT was recently introduced as an alternative therapy for such patients, and as shown by us and others,2–5 it significantly reduces the LVOT gradient and improves cardiac symptoms. This improvement is probably related to the diastolic function changes, LVOT gradient reduction, decrease in severity of mitral regurgitation, and a decrease in the frequency or severity of ischemia. The present study explores the effects of NSRT on LV diastolic function. NSRT favorably influences a number of factors that impair relaxation in HOCM. First is the systolic contraction load incurred with obstruction, which delays and slow relaxation.1 By relieving the obstruction, NSRT results in an improvement in relaxation. In fact, the shortening of $\tau$ in our patients was directly related to the LVOT gradient reduction. The shorter IVRT and AT-E and the higher lateral annular Ea reflect this improved relaxation, given the shorter $\tau$ and the lower pre-A pressure. The lengthening load that operates in early diastole is another factor. It enhances filling by promoting myocardial fiber lengthening. In HOCM patients, this load (and tension, where tension = pressure×radius/2×thickness) is reduced because of LV hypertrophy and the small ventricular dimensions that are frequently present.1 After NSRT, septal thick-
ness decreases and LV end-diastolic volume increases. Accordingly, wall tension increases, promoting LV filling. Furthermore, outflow obstruction relief results in a higher aortic diastolic pressure along with a lower LV end-diastolic pressure. Both changes increase coronary perfusion pressure and blood flow, thus possibly minimizing ischemia and increasing the coronary filling load, a load that aids relaxation during IVRT. DT-A is a measure of LV end-diastolic pressure and shortens with higher pressure; this parameter became significantly longer after NSRT, suggesting lower end-diastolic pressures after the procedure. Interestingly, lower filling pressures were observed after surgical myectomy, a procedure that reduces septal thickness and increases LV dimensions. NSRT also appears to alter the regional inflow territory, minimizing the inflow and outflow tract asynchrony and possibly contributing to the improvement in global LV relaxation. This occurs at the expense of reduced systolic function (and diastolic function) of the septal base afterward. In addition, NSRT increases LV compliance. This conclusion is supported by lower filling pressures in the face of the end-diastolic volume increase and may be the result of the mass volume ratio decrease and improvement in LV relaxation after NSRT. 

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