Acute Effect of Nonsurgical Septal Reduction Therapy on Regional Left Ventricular Asynchrony in Patients With Hypertrophic Obstructive Cardiomyopathy

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Background—Patients with hypertrophic obstructive cardiomyopathy have left ventricular (LV) diastolic dysfunction due, in part, to temporal heterogeneity in regional function. The acute effect of the relief of LV outflow tract obstruction is unknown. Therefore, we investigated the effects of nonsurgical septal reduction therapy (NSRT) on regional function.

Methods and Results—Twenty-two patients (aged 56±17 years) underwent echocardiographic examination, including tissue Doppler imaging, simultaneously with left heart catheterization before and after NSRT. LV regional function was assessed in 12 segments from which myocardial strain was obtained. Asynchrony was calculated as the coefficient of variation of the time interval from the QRS complex to the onset of expansion and to early diastolic strain. After NSRT, a significant reduction in LV outflow tract obstruction (from 57±5 to 12±3 mm Hg) occurred with shortening of the time constant of LV relaxation (71±4 to 61±3 ms; both P<0.05). The coefficient of variation of the time interval to onset of regional expansion decreased significantly and related well to the changes in the time constant of LV relaxation (r=0.81, P<0.01).

Conclusions—NSRT has a favorable effect on LV regional asynchrony, which accounts for the acute changes in LV relaxation. (Circulation. 2002;106:412-415.)

Key Words: cardiomyopathy • diastole • echocardiography • hemodynamics

Left ventricular (LV) diastolic function is impaired in patients with hypertrophic obstructive cardiomyopathy due to impaired relaxation and increased chamber stiffness.1,2 In these patients, ventricular relaxation is related to systolic and diastolic hemodynamic loads and the extent of spatial and temporal heterogeneity of load and inactivation.1 Numerous studies have demonstrated the presence of nonuniform relaxation in patients with hypertrophic cardiomyopathy using several invasive and noninvasive techniques.2–4 Although regional fibrosis, hypertrophy, myocyte disarray, and ischemia can account for some of the regional heterogeneity, the presence of LV outflow tract (LVOT) obstruction results in a further imbalance of loads that can adversely affect regional function. In patients with subaortic obstruction, LV systolic pressure is elevated in all ventricular segments proximal to the obstruction but is much lower in the LVOT.1 Therefore, we hypothesized that nonsurgical septal reduction therapy (NSRT), which reduces LVOT obstruction (dynamic load) and results in regression of hypertrophy (structural change), could lead to a decrease in the heterogeneity of regional function. Because regression of LV hypertrophy is a long-term effect of NSRT and to study primarily the impact of dynamic loads, we examined the acute effects of NSRT on segmental function using tissue Doppler imaging.

Methods

Patient Population
The study population was composed of 22 consecutive patients (aged 56±17 years; 13 women) who underwent NSRT at our institution after providing informed consent. The group's mean NYHA class was 3.1±0.1, and the angina class was 2.5±0.2. All patients had a LVOT gradient ≥30 mm Hg, due to systolic anterior motion of the mitral valve, despite receiving ≥1 cardiac medication (15 on β-blockers, 11 on calcium antagonists, and 3 on disopyramide).

Left Heart Catheterization
All medications were withheld for 48 hours before NSRT. Patients were premedicated with midazolam and fentanyl immediately before catheterization. After cannulation of right and left femoral arteries and calibrating the transducers (Medex), LV and aortic pressures were acquired simultaneously using a pigtail catheter in the LV and a guiding catheter in the aorta. The following LV pressures were determined: peak, end-systolic (at aortic valve closure), preA (before A wave increase in LV pressure), and end-diastolic (EDP) pressures.

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Aortic systolic and diastolic pressures were also noted. The difference between aortic diastolic pressure and LV EDP was used as a measure of the diastolic perfusion pressure in the coronary circulation. The time constant of LV relaxation (τ) was calculated invasively using isovolumetric relaxation time (IVRT) and the natural logarithm (Ln) of LV systolic pressure at aortic valve closure (LVS) and pre-A pressures with a previously validated equation in which τ=IVRT/(Ln LVS−Ln preA). LVOT gradient was monitored both invasively and with Doppler echocardiography (Doppler versus catheter gradient: r=0.95, SEE=3 mm Hg, P<0.01).

Echocardiographic Studies
Patients were imaged simultaneously with left heart catheterization in a supine position with a System FIVE digital ultrasound machine (GE Vingmed Ultrasound) that was equipped with a tissue imaging and Doppler transducer. The standard apical (4, 2, and 5-chamber) views were acquired in all patients, except for 4 subjects in whom it was not feasible to obtain satisfactory apical 2-chamber views. During acquisition, a narrow sector angle was used, and image depth was adjusted to allow for maximal acquisition frame rate.

After obtaining baseline images, NSRT was performed as previously described. An intracoronary Omnipaque injection down the lumen of the inflated balloon (inside the septal perforator branch of the left anterior descending artery) resulted in a myocardial blush that was readily identified by transthoracic imaging and allowed for the accurate identification of the septal segments involved with systolic anterior motion. Tissue Doppler imaging was performed both before and after NSRT, and the recordings were stored digitally as 2D color cine-loops for later analysis using the Echopac GE Vingmed system.

Echocardiographic Analysis
All the analyses were performed by a single investigator who was blinded to clinical and hemodynamic data. Measurements were made using reconstructed curves from data stored digitally. The lateral, anterior, inferior, inferolateral, anterior septum, and inferior septum walls were each divided into 2 halves, basal and distal (n=12 segments). Strain measurements (Figure 1A) were assessed in the longitudinal direction from the basal and distal halves of each wall, with care taken to avoid angulation. The following parameters were measured: peak systolic strain and time intervals from the QRS complex to the compression/expansion crossover point and from the QRS complex to early diastolic strain (Figure 1B).

Assessment of Asynchrony
The index of regional asynchrony (spatial heterogeneity) for systolic strain was computed as the coefficient of variation (SD/mean) for all 12 myocardial segments. Likewise, the coefficient of variation was used to describe asynchrony (temporal heterogeneity) in the time interval from the QRS complex to the compression/expansion crossover point and to early diastolic strain.

Statistics
Data are presented as mean±SEM or as median (25th to 75th percentile) values, where appropriate. Paired t or Wilcoxon signed rank tests were used to compare the hemodynamic and strain data before and after NSRT, with regression analysis used to relate changes in LV hemodynamics to tissue Doppler indices of asynchrony. A r<0.05 defined statistical significance.

Results
Changes in LV Hemodynamics
After NSRT, the LVOT gradient decreased and aortic systolic, diastolic, and pulse pressures increased (all P<0.05), without a change in heart rate (Table). Overall, there were small group changes in LV diastolic pressures. However, the individual responses were more variable. The coronary diastolic perfusion pressure improved significantly after the procedure. NSRT also resulted in an improvement in indices of LV relaxation (IVRT and τ). The changes in LV EDP occurred in a similar direction and magnitude to those in τ (r=0.88, P<0.001), such that the patients who showed the largest improvement in LV relaxation exhibited a decrease in EDP, whereas when τ was prolonged, EDP increased.

None of the patients developed a left bundle branch block or total atrioventricular block, and peak creatine kinase averaged 964±100 U/L.

Changes in Regional Function
Peak systolic strain decreased in the anterior septum basal segment (-13.3±3.5% to -8±3.4%, P=0.01), otherwise, there were no significant changes. The spatial heterogeneity in peak systolic strain was unchanged (P>0.2).

The time interval from the QRS complex to the compression/expansion crossover point decreased significantly in 6 of
the 12 segments (distal segments of anterior septum, inferior lateral, inferior septum, and basal segments of anterior and inferior walls; \( P=0.009 \) to 0.02). In the remaining 6 segments, it did not reach statistical significance \( (P=0.06 \) to 0.26). Similarly, the time from the QRS complex to early diastolic strain became significantly shorter in 5 of the 12 segments (distal segments of anterior septum, inferior lateral, and anterior, inferior, and basal segment of the inferior wall; \( P=0.05 \). In the remaining 7 segments, the improvement varied between 4% and 28% but did not reach significance \( (P=0.1) \).

**Changes in Asynchrony of Regional Function**

A significant decrease was present after NSRT in the coefficient of variation in the time interval from QRS to the compression/expansion crossover point \( (23\pm2\% \) to \( 18\pm1\%; \ P=0.026 \) and to early diastolic strain \( (16\pm4\% \) to \( 13\pm2\%; \ P=0.03 \).

**Relation of the Changes in Regional Function to LV Hemodynamics**

A significant correlation was present between the acute reduction in LVOT gradient, but not creatine kinase leak, and the change in the coefficient of variation of the time interval to onset of regional expansion \( (r=0.6, \ P=0.03) \).

The changes in \( \tau \) were significantly related to the reduction in LVOT gradient \( (r=0.56, \ P=0.02) \) and the increase in coronary diastolic perfusion pressure \( (r=0.7, \ P<0.01) \). Importantly, a strong association was observed between the change in \( \tau \) and that in the coefficient of variation of the time to onset of regional expansion \( (r=0.81, \ P<0.01; \ Figure 2) \), whereby patients with the greatest improvement in LV asynchrony had the most shortening in \( \tau \). Likewise, a similar correlation was observed between the change in LV asynchrony and that in EDP \( (r=0.79, \ P=0.02) \).

**Discussion**

**Long-Term Effects of NSRT on LV Diastolic Function**

We and others have reported on the improvement in LV relaxation and filling pressures 3 to 6 months to a year after NSRT.\(^6,9\) The mechanisms were related to relief of the early systolic load that delays and slows relaxation, as well as to an increase in the early diastolic filling load, which aids fiber lengthening. In addition, LV stiffness decreases after NSRT due to a reduction in LV mass, an improvement in relaxation, and a reduction in interstitial collagen.\(^10\)

**Acute Effects of NSRT on Hemodynamics**

Acutely, NSRT results in a reduction in LVOT obstruction leading to an increase in aortic systolic and diastolic pressures, improvement in \( \tau \), and overall small changes in filling pressures. Theoretically, one would expect some deterioration in LV diastolic function acutely after NSRT due to the induction of myocardial infarction; however, it is possible that the improvement in LV asynchrony, the relief of LVOT obstruction, the increase in coronary filling load, and the reflex sympathetic stimulation could counteract the negative impact of infarction.

To investigate the mechanisms by which NSRT alters relaxation, we correlated the changes in \( \tau \) to those in LVOT gradient, coronary diastolic perfusion pressure, and regional asynchrony. The change in \( \tau \) related positively to the decrease in LVOT gradient as the early systolic load that slows relaxation decreased. Likewise, \( \tau \) improvement was significantly correlated with the increase in coronary perfusion pressure, which aids relaxation. The asynchrony in LV regional function showed an overall improvement after NSRT and had a strong correlation with the changes in \( \tau \). Because no acute changes would be expected to occur in LV structure (excluding the infarction area) with NSRT, our findings lend credence to the important influence of dynamic loads on regional function.

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