Mechanism of Benefit of Negative Inotropes in Obstructive Hypertrophic Cardiomyopathy

Mark V. Sherrid, MD; Gretchen Pearle, RDCS; David Z. Gunsburg, MD

Background—Drugs with negative inotropic effect are widely used to decrease obstruction in hypertrophic cardiomyopathy (HCM). However, the mechanism of therapeutic benefit has not been studied.

Methods and Results—We used M-mode, two-dimensional, and pulsed Doppler echocardiography to study 11 patients with obstructive HCM before and after medical elimination of left ventricular outflow tract obstruction. We measured 148 digitized pulsed Doppler tracings recorded in the left ventricular cavity 2.5 cm apical of the mitral valve. Successful treatment slowed average acceleration of left ventricular ejection by 34% (P=.001). Mean time to peak velocity in the left ventricle was prolonged 31% (P=.001). Mean time to an ejection velocity of 60 cm/s was prolonged 91% (P=.001). Before treatment, left ventricular ejection velocity peaked in the first half of systole; after successful treatment, it peaked in the second half (P=.001). In contrast, after treatment, we found no change in peak left ventricular ejection velocity. We also found no change in the distance between the mitral coaptation point and the septum, as measured in two planes, indicating no treatment-induced alteration of this anatomic relationship.

Conclusions—Medical treatment eliminates mitral-septal contact and obstruction by decreasing left ventricular ejection acceleration. By slowing acceleration, treatment reduces the hydrodynamic force on the protruding mitral leaflet and delays mitral-septal contact. This, in turn, results in a lower final pressure gradient. (Circulation. 1998;97:41-47.)

Key Words: cardiomyopathy ■ hypertrophy ■ drugs ■ echocardiography

The observation that drugs with negative inotropic effect reduce or eliminate obstruction in hypertrophic cardiomyopathy (HCM) has led to their widespread use.1-4 Such treatment may improve symptoms and exercise tolerance.5-7 Yet little is known about the actual mechanism of such improvement. Do negative inotropes eliminate obstruction by altering the anatomic relationship between the mitral valve and the ventricular septum, or is their beneficial effect related to changes in left ventricular (LV) flow?

Echocardiography is ideally suited for such investigation because it is easily repeated after gradient reduction and allows analysis of both anatomy and flow.8-10 In this context, we studied patients with obstructive HCM before and after successful medical treatment to determine the mechanism of benefit of such drugs.

Methods

Patients
We prospectively studied 11 patients with symptomatic obstructive HCM and mitral-septal apposition whose treatment resulted in elimination of obstruction. All patients had septal thickness >15 mm with no apparent cause of hypertrophy.11 The peak pressure gradient across the LV outflow tract was determined by use of continuous-wave Doppler in the apical five-chamber view.12 The initial mean pressure difference was 76 mm Hg (range, 45 to 125 mm Hg). All patients met three additional criteria: (1) pretreatment pressure difference ≥45 mm, (2) successful medical elimination of the pressure difference, and (3) good-quality echocardiograms. Patients were treated with a clinical protocol of drug testing with the goal of rapid gradient elimination on sequential Doppler echocardiography. Intravenous metoprolol to a dose of 15 mg was used first unless contraindicated. If the Doppler gradient was reduced within 30 minutes to <30 mm Hg, oral β-blockers were continued as sole therapy. If a >30 mm Hg gradient persisted, oral disopyramide was administered.13,14 In patients with a contraindication to disopyramide, oral verapamil was begun 240 to 360 mg/d in divided doses.15 Treatment failures (defined as persistent gradient >30 mm Hg) were identified by Doppler within 48 hours, and combination regimens were begun. Clinical characteristics and medical treatment of the 11 patients are shown in Table 1. All were in normal sinus rhythm. The average time interval between the echocardiograms was 6 days.

For comparison purposes, we also performed echocardiograms on 10 normal control subjects whose mean age was 59 years. Informed written consent, approved by our institution’s research committee, was obtained before echocardiography.

Echocardiographic Data Acquisition and Measurements
Echocardiograms were performed on a Hewlett-Packard Sonos 1000 system.

Pulsed Doppler
Because there is evidence that LV flow acting on the protruding leaflet of the mitral valve is the trigger of obstruction,6,16,17 we carefully examined this flow for changes in velocity and acceleration after treatment.8,18 In the
The apical five-chamber view, the pulsed Doppler sample volume was placed in the LV, 2.5 cm apical of the coaptation point of the mitral valve and 1 cm from the interventricular septum, near the centerline of color flow. We refer to this point as the apical of the mitral valve point (AMV point). This location is shown in Fig 1.

The two-dimensional image in the area apical of the mitral valve was magnified to ensure proper placement of the sample volume. Two minutes of flow velocity tracings were recorded on videotape at 100-mm/s sweep speed before and after treatment. In this area, we recorded beats that had high peak velocities and minimal spectral dispersion. Small sample volume and low filter settings were used. A modified ECG lead I was continuously recorded.

Selection of Recorded Pulsed Doppler Tracings for Analysis

Peak flow velocity and acceleration in the LV vary, depending on sample volume position, in both the axial and transverse directions. For example, beats recorded 1 cm from the mitral valve have higher velocities and acceleration than those recorded at the AMV point, and flow close to the septum has a different flow-velocity contour than flow further from the septum. Similar spatial heterogeneity has been reported in other locations in the LV.

To ensure a representative sampling of Doppler tracings, we chose many beats, all recorded at the AMV point, for analysis. To avoid selection bias, we blinded the trace selection process with regard to both treatment status and appearance of the Doppler tracing. When choosing recorded beats for analysis, the research technologist was not aware of the patient’s treatment status, nor was she able to see the Doppler tracings, because the lower part of the video monitor was covered with opaque paper. Consequently, traces at the AMV point were selected for analysis only on the basis of the location of the sample volume seen on the simultaneous two-dimensional image without visualization of the Doppler tracing. All selected traces were then digitized into a Nova-Microsonics analysis computer for subsequent measurement. Beats were excluded if they did not show laminar flow or if they showed a truncated envelope.

The digitized Doppler images were then measured by tracing the modal velocities on the Nova-Microsonics system. We measured peak and mean systolic LV ejection velocity, acceleration time (the time from onset of ejection until peak velocity), and mean acceleration (peak velocity/acceleration time). Because systolic anterior motion often begins at leaflet coaptation, we assessed acceleration in early ejection by measuring the elapsed time from ejection onset to a velocity of 40 and 60 cm/s, as shown in Fig 2.

We measured the prejection period as the time from the beginning of the ECG Q wave to the onset of ejection and the ejection time as

---

**TABLE 1. Clinical Characteristics of 11 Treated Patients**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y</th>
<th>Sex</th>
<th>Symptoms</th>
<th>Gradient, mm Hg</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>M</td>
<td>Dysp</td>
<td>47</td>
<td>Diso 400</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>M</td>
<td>Dysp, Ang</td>
<td>96</td>
<td>Diso 900*</td>
</tr>
<tr>
<td>3</td>
<td>57</td>
<td>F</td>
<td>Dysp</td>
<td>68</td>
<td>Aten 50</td>
</tr>
<tr>
<td>4</td>
<td>74</td>
<td>F</td>
<td>Dysp, Ang</td>
<td>65</td>
<td>Diso 800</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>M</td>
<td>Dysp</td>
<td>68</td>
<td>Diso 600</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>F</td>
<td>Dysp</td>
<td>125</td>
<td>Diso</td>
</tr>
<tr>
<td>7</td>
<td>78</td>
<td>M</td>
<td>Dysp</td>
<td>120</td>
<td>Diso</td>
</tr>
<tr>
<td>8</td>
<td>69</td>
<td>M</td>
<td>Dysp</td>
<td>58</td>
<td>Verap 180</td>
</tr>
<tr>
<td>9</td>
<td>77</td>
<td>M</td>
<td>Dysp</td>
<td>45</td>
<td>Aten 50</td>
</tr>
<tr>
<td>10</td>
<td>58</td>
<td>F</td>
<td>Dysp, Sync</td>
<td>73</td>
<td>Verap 240</td>
</tr>
<tr>
<td>11</td>
<td>75</td>
<td>F</td>
<td>Dysp, Sync</td>
<td>70</td>
<td>Diso 600</td>
</tr>
</tbody>
</table>

Dysp indicates dyspnea; Diso, disopyramide; Ang, angina; Aten, atenolol; Meto, metoprolol; Verap, verapamil; Sync, syncope; and Ind, indenal.

*Disopyramide level, 2.5 µg/mL; therapeutic range, 2 to 5 µg/mL.
the time from onset of ventricular ejection until the end of ejection. The RR interval was determined for each measured beat, and systolic time intervals were corrected for heart rate by use of Weissler’s formulas.

**Continuous-Wave Doppler**
Continuous-wave Doppler was performed from the apex, through the area of mitral-septal contact. We avoided contamination of this signal by flow from mitral regurgitation and by flow from the aortic valve or aorta. We examined early acceleration by measuring acceleration from the onset of ejection until a velocity of 1/m second. We were interested in this early portion of systole because we wanted to detect any change in acceleration before the onset of mitral-septal contact and development of a narrowed orifice and obstruction. (Mitral-septal contact occurred later, 244 ms after Q-wave onset.)

**M-mode Echocardiogram**
M-mode recordings were made during the same examination and within 5 minutes of the two-dimensional ones. The purpose of these recordings was to analyze the anatomic relationship between the mitral valve and the ventricular septum, as well as to analyze the overall LV dimension, both before and after treatment. The LV area of interest was magnified. Tracings were recorded from the parasternal window at 100 mm/s paper speed on a strip chart. Views that showed the mitral coaptation point and the most systolic anterior motion of the mitral valve were recorded. M-mode views were correlated with the two-dimensional view to avoid mistakenly recording chordal systolic anterior motion.

Complexes with a clear coaptation point in continuity with early mitral-septal contact were subsequently measured from the strip-chart recordings with a Dextra D-200 analysis system. We measured the distance between the mitral valve coaptation point and the interventricular septum and the distance between the septum and the posterior wall (which is the short axis of the LV cavity at this level). The duration of mitral-septal contact was measured, as well as the RR interval for each M-mode beat selected. Fig 3 illustrates the M-mode measurements.

**Two-Dimensional Echocardiogram**
To further examine the anatomic relationship between the mitral valve and the ventricular septum, apical five-chamber views of the LV outflow tract that clearly showed the position of the coapted mitral valve early in systole were magnified and recorded before and after treatment. We selected beats that showed the coapted mitral valve leaflets at the moment of coaptation and the interventricular septum. These beats were digitized and saved in a split-screen format that allowed comparison of images before and after treatment. The shortest distance between the coapted mitral valve leaflets and the interventricular septum was determined.

**Color-Flow Doppler**
Mitral regurgitation was assessed by color-flow Doppler in the parasternal and apical views. Regurgitation was qualitatively scored from 0 to 3 on the basis of the area of the color-flow regurgitant jet compared with the area of the left atrium: 0=no or trivial mitral regurgitation, 1=mild, 2=moderate, and 3=severe. In one patient, an eccentric jet was scored one grade higher than its apparent area.

**Statistical Analysis**
The statistical analyses were performed by use of SPSS (version 4.0.3) software (SPSS Inc) on a Macintosh SE/30 computer. Results are presented as mean±SEM. Student’s paired t tests were calculated for comparison of means before and after treatment of patients. Student’s group t tests were calculated for comparison of means between control subjects and patients. Relations between different variables were assessed by means of Pearson’s correlation coefficient. Significance level was based on a two-tailed test. A value of P≤.05 was considered significant.

**Results**
Medical treatment reduced the mean Doppler outflow tract pressure gradient from 76±8 to 0 mm Hg. The average time interval between the echocardiograms was 6 days.

**Pulsed Doppler**
We measured a total of 148 digitized pulsed Doppler flow velocity tracings recorded at the AMV point in the LV. The average number of tracings from each patient was seven before treatment and seven after treatment.

Comparison of average LV Doppler measurements before and after treatment is presented in Table 2. Despite the negative inotropic nature of the medications used, peak and mean ejection velocities at the LV AMV point were not significantly changed after treatment. In contrast, medication caused a significant slowing of mean acceleration to peak ejection velocity of 557±61 compared with 839±97 cm·s⁻¹·
TABLE 2. Comparison of Left Ventricular Pulsed Doppler Measurements Before and After Treatment in 11 Patients With OHCM

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gradient, mm Hg</td>
<td>76±8</td>
<td>0±0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Peak velocity, cm/s</td>
<td>105±8</td>
<td>93±8</td>
<td>.21</td>
</tr>
<tr>
<td>Mean velocity, cm/s</td>
<td>74±5</td>
<td>66±5</td>
<td>.14</td>
</tr>
<tr>
<td>Acceleration time, ms</td>
<td>137±10</td>
<td>179±12</td>
<td>.001</td>
</tr>
<tr>
<td>Mean acceleration, cm·s⁻¹·s⁻¹</td>
<td>839±97</td>
<td>557±61</td>
<td>.001</td>
</tr>
<tr>
<td>TT40, ms</td>
<td>19±3</td>
<td>32±5</td>
<td>.004</td>
</tr>
<tr>
<td>TT60, ms</td>
<td>35±7</td>
<td>67±10</td>
<td>.001</td>
</tr>
<tr>
<td>RR interval, ms</td>
<td>877±45</td>
<td>974±49</td>
<td>.01</td>
</tr>
<tr>
<td>Ejection time, ms</td>
<td>318±17</td>
<td>305±10</td>
<td>.31</td>
</tr>
<tr>
<td>Corrected ejection time, ms</td>
<td>434±19</td>
<td>409±10</td>
<td>.05</td>
</tr>
<tr>
<td>PEP, ms</td>
<td>87±6</td>
<td>102±7</td>
<td>.03</td>
</tr>
<tr>
<td>PEPC, ms</td>
<td>115±5</td>
<td>127±7</td>
<td>.07</td>
</tr>
<tr>
<td>Acceleration time/ejection time</td>
<td>0.44±0.03</td>
<td>0.59±0.03</td>
<td>.001</td>
</tr>
<tr>
<td>Early LVOT acceleration,*</td>
<td>5520±851</td>
<td>2736±156</td>
<td>&lt;.02</td>
</tr>
</tbody>
</table>

OHCM indicates obstructive hypertrophic cardiomyopathy; TT40, time interval from the onset of ejection to pulsed Doppler velocity of 40 cm/s; TT60, time interval from the onset of ejection to pulsed Doppler velocity of 60 cm/s; PEP, pre-ejection period; PEPC, corrected pre-ejection period; and LVOT, left ventricular outflow tract. Comparisons were made by use of Student’s paired t test. Data are presented as mean±SEM.

*Measured with continuous-wave Doppler through left ventricular outflow tract from onset of ejection to velocity of 1 m/s.

s⁻¹ before treatment (P=.001). Similarly, mean acceleration time was longer after treatment, 179±12 ms (P=.001). Time from ejection onset to 60 cm/s velocity was longer after treatment, 67±10 compared with 35±7 ms (P=.001). Individually, in this blinded study, acceleration was slowed after treatment in 10 of 11 patients; acceleration time was longer after treatment in 10 of 11 patients. Time to 60 cm/s velocity was longer after treatment in all 11 patients.

Before treatment, flow velocity peaked in the first half of ejection; acceleration time/ejection time was 0.44±0.03. After treatment, with slowed acceleration, velocity peaked in the second half of ejection; acceleration time/ejection time was 0.59±0.03 (P=.001). An example of pulsed Doppler tracings before and after gradient elimination is shown in Fig 4, demonstrating slowing of ejection acceleration after treatment.

Average heart rate decreased after treatment from 70 to 63 bpm (P=.02). To exclude the possibility that the decrease in heart rate was the cause of the observed acceleration changes, six patients who had no significant change in heart rate were examined separately. The results are shown in Table 3. There was still a significant difference in mean acceleration, mean acceleration time, time to 60 cm/s velocity, and the ratio of acceleration time to ejection time.

Continuous-Wave Doppler in the Outflow Tract
This measures a different location than the LV AMV point evaluated with pulsed Doppler and described above. Acceleration from the onset of ejection to a velocity of 1 ms/s was slower after treatment, 2736±156 compared with 5520±851 cm·s⁻¹·s⁻¹ (P<.02).

M-Mode Echocardiogram
We studied 68 M-mode tracings of the mitral valve that clearly showed the coaptation point, systolic anterior motion, and mitral-septal contact. The average number of tracings from each patient was four before treatment and three after treatment. After treatment, there was no significant change in the mean distance from the coaptation point of the mitral valve to the anterior septum (22 mm) or in the mean LV end diastolic diameter (44 mm). Mean end systolic diameter was larger after treatment, 27±0.2 compared with 25±0.2 mm. (P<.01). The average duration of mitral-septal contact was 134.6 ms. This was an average of 45% of the systolic ejection period. After treatment, there was no mitral-septal contact.

Two-Dimensional Echocardiogram
After treatment, there also was no change in the mean distance from the mitral coaptation point to the posterior septum at the moment of coaptation, 15 mm both before and after treatment.

Systolic Time Intervals
Mean corrected ejection time was shorter after treatment, 409±10 compared with 434±19 ms, reflecting the elimination of obstruction (P=.05). In the obstructed patients, there was a positive correlation between the continuous-wave Doppler pressure difference across the obstruction and the corrected LV ejection time (r=.61, P<.05).
TABLE 3. Comparison of Left Ventricular Pulsed Doppler Measurements Before and After Treatment in Six Patients With No Change in Heart Rate

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gradient, mm Hg</td>
<td>89 ± 13</td>
<td>0 ± 0</td>
<td>.001</td>
</tr>
<tr>
<td>Peak velocity, cm/s</td>
<td>109 ± 14</td>
<td>91 ± 9</td>
<td>.28</td>
</tr>
<tr>
<td>Mean velocity, cm/s</td>
<td>74 ± 8</td>
<td>63 ± 5</td>
<td>.28</td>
</tr>
<tr>
<td>Acceleration time, ms</td>
<td>133 ± 16</td>
<td>172 ± 19</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Mean acceleration, cm·s⁻¹·s⁻¹</td>
<td>890 ± 150</td>
<td>569 ± 84</td>
<td>.01</td>
</tr>
<tr>
<td>TT40, ms</td>
<td>19 ± 4</td>
<td>33 ± 5</td>
<td>.007</td>
</tr>
<tr>
<td>TT60, ms</td>
<td>38 ± 12</td>
<td>77 ± 15</td>
<td>.01</td>
</tr>
<tr>
<td>RR interval, ms</td>
<td>916 ± 75</td>
<td>944 ± 77</td>
<td>.25</td>
</tr>
<tr>
<td>Ejection time, ms</td>
<td>339 ± 20</td>
<td>303 ± 16</td>
<td>.008</td>
</tr>
<tr>
<td>PEP, ms</td>
<td>92 ± 8</td>
<td>108 ± 11</td>
<td>&lt;.03</td>
</tr>
<tr>
<td>Acceleration time/ejection time</td>
<td>0.39 ± 0.03</td>
<td>0.56 ± 0.04</td>
<td>.03</td>
</tr>
<tr>
<td>Early LVOT acceleration,*</td>
<td>6202 ± 1324</td>
<td>2508 ± 211</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

*Measured with continuous-wave Doppler through left ventricular outflow tract from onset of ejection to velocity of 1 m/s.

**Mechanism of Systolic Anterior Motion**

Systolic anterior motion is the trigger of obstruction. There is agreement that it is caused by the action of LV flow on the protruding mitral valve leaflet. The character of the hemodynamic force on the leaflet is a subject of ongoing debate. Initially, investigators hypothesized that anterior motion is caused by a Venturi mechanism whereby high velocity flow in the LV outflow tract lifts the mitral valve toward the septum. More recent data indicate that drag, the pushing force of flow, initiates the anterior motion by pushing the protruding mitral leaflet into the septum. After mitral-septal contact, the pressure difference is the force on the obstructing mitral leaflet. Once mitral-septal contact occurs and a narrowed orifice develops, a pressure difference occurs across the orifice. There is a predictable temporal relationship between the onset and end of mitral-septal apposition and the onset and end of the pressure gradient. This occurs not only because mitral-septal contact causes the gradient but also because the pressure difference maintains the mitral-septal apposition.

**Time and the Pressure Gradient**

The magnitude of the pressure gradient is time dependent. There is evidence that after mitral-septal contact, the orifice in obstructive HCM continues to narrow over time. Pollick et al. observed that the earlier in systole that mitral-septal contact occurs and the longer that the leaflet is in apposition with the septum, the higher the peak outflow pressure gradient is. That is, the pressure difference is time dependent. This occurs because after mitral-septal contact the pressure difference, the new hydrodynamic force on the obstructing leaflet, forces it further against the septum. This further decreases the orifice size, which further increases the pressure difference. An amplifying feedback loop is established in which obstruction begets further obstruction over time.

Progressive orifice narrowing explains two Doppler abnormalities that are observed in this condition, one after the stenosis in the LV outflow tract and the other before the stenosis in the body of the LV. First, after the stenosis in the outflow tract, progressive narrowing explains the increasing acceleration pattern of the outflow continuous-wave high-velocity jet (the contour is concave to the left). The concave contour of the jet occurs because the orifice continues to narrow in systole because the pressure difference continues to push the mitral valve into the septum. This explains why the outflow jet peaks late in systole. The jet in obstructive HCM is compared with the jet of aortic stenosis in Fig 5. The concave contour can be mathematically modeled if one assumes that the orifice size continuously decreases over time as a function of the increasing pressure difference. Second, before the stenosis in the LV cavity, progressive narrowing explains the unusual pattern seen on pulsed Doppler tracings. Here, a sudden midystolic drop in LV ejection velocity is observed. This pattern occurs because of obstruction. The deceleration of flow velocity in the body of the LV occurs at the same time as acceleration in the LV outflow tract; this can be explained only if the orifice is progressively narrowing over time.

**Color-Flow Doppler**

Before treatment, 6 of 11 patients had no or trivial mitral regurgitation. Only 2 patients had severe regurgitation. After treatment, there was less mitral regurgitation; average regurgitation score was 0.6 ± 0.2 after treatment compared with 1.4 ± 0.3 before treatment (P = .02).

**Comparison With Control Subjects**

Mean ejection acceleration was higher in patients with obstruction than in normal control subjects, 839 ± 97 compared with 382 ± 46 cm·s⁻¹·s⁻¹, P = .001. Peak ejection velocity was higher in patients with obstruction than in control subjects, 105 ± 8 compared with 63 ± 10 cm/s, P = .003. Even after the gradient was eliminated in HCM patients, mean acceleration was higher than in control subjects, 557 ± 61 compared with 382 ± 46 cm·s⁻¹·s⁻¹, P < .04. Peak velocity was higher as well, 93 ± 8 compared with 63 ± 10 cm/s, P < .03.

**Discussion**

The principal finding in this study is that successful medical treatment of obstruction slows the acceleration of LV ejection flow measured at a point 2.5 cm apical of the mitral valve. Mean acceleration to peak velocity in the left ventricle at the AMV point was decreased 34%. Mean time from ejection onset to peak velocity, the acceleration time, was prolonged 31%. The acceleration time from ejection onset to a velocity of 60 cm/s (ie, very early in ejection) was prolonged 91%. Before treatment, velocity peaked in the first half of the systolic ejection period; after treatment, it peaked in the second half. In contrast, the anatomic position of the mitral valve relative to the interventricular septum, as seen in two planes, was unchanged after treatment, as measured with both M-mode and two-dimensional echocardiography.
In summary, observations suggest that in obstructive HCM, the orifice narrows over time because of the rising pressure difference; the pressure difference rises over time because of the narrowing orifice.

**Effect of Pharmacological Decrease in LV Acceleration**

The following working hypothesis explains how the measured decrease in ejection acceleration may lead to a decrease in obstruction. The force of flow is directly related to the square of velocity, so even small decreases in initial LV velocity lead to larger decreases in the initial force on the leaflet. The decrease in force on the leaflet may delay systolic anterior motion, the trigger of obstruction, causing the mitral valve to contact the septum later in the systolic ejection period. This would leave less time in systole for the feedback loop to narrow the orifice, reducing the final pressure difference. Thus, a delay in systolic anterior motion would lead to delay of the feedback loop, leaving it less time to act and ultimately yielding a lower pressure gradient. In addition, delaying the trigger to systolic anterior motion may allow more time for papillary muscle shortening to provide countertraction. In the figure, for clarity, the “before” arrow is positioned above the “after” arrow, although at the beginning of systole they both actually begin with a pressure gradient of 0 mm Hg.

In obstructed patients, both the ejection acceleration and the peak ejection velocities were considerably higher than in normal control subjects. Consequently, the acceleration difference measured this early in ejection cannot be due to relief of obstruction.

Could the observed decrease in acceleration be a drug-induced epiphenomenon, associated with improvement but not its cause? We cannot exclude this idea. But given the flow-triggered nature of obstruction and the exponential relationship between velocity and force, it is likely that the observed decrease in acceleration is the therapeutic action. In addition, we have observed that suboptimal doses of medication that leave a residual gradient decrease acceleration to an intermediate degree.

**Comparison With Control Subjects**

In obstructed patients, both the ejection acceleration and the peak ejection velocities were considerably higher than in control subjects. This was true even after successful elimination of the pressure difference. A markedly increased rate of early systolic LV emptying has previously been shown in obstructive HCM. Because of this rapid emptying, the brachial artery dp/dt and the dp/dt are higher in patients with obstructive HCM than in normal controls. α-Blocker prevention of the B-agonist–induced rise in dp/dt has been shown.

---

**Figure 5.** Comparison of the Doppler velocity tracings of the high-velocity jets of aortic stenosis and obstructive hypertrophic cardiomyopathy (HCM). In aortic stenosis, as velocity increases, acceleration decreases. In contrast, in obstructive HCM, as velocity increases, acceleration also increases. In obstructive HCM, the rising pressure difference forces the mitral leaflet against the septum, which decreases the orifice size and further increases the pressure difference. This amplifying feedback loop explains the concave contour seen in obstructive HCM. The orifice size changes as an inverse function of the pressure difference across the stenosis, with the pressure difference itself causing an increase in narrowing. In aortic stenosis this does not occur. Progressive orifice narrowing also explains why the jet peaks late in systole in obstructive HCM. (From Reference 30, J Am Soc Echocardiogr, by permission of Mosby-Year Book, Inc.)

**Figure 6.** Proposed explanation of pressure gradient development before and after treatment of obstruction. Before treatment (top tracing), rapid left ventricular acceleration apical of the mitral valve, shown as a horizontal thick arrow, triggers early systolic anterior motion (SAM) and early mitral-septal (M-S) contact. Once mitral-septal contact occurs, a narrowed orifice develops, and a pressure difference results. The pressure difference forces the leaflet against the septum, which decreases the orifice size and further increases the pressure difference. An amplifying feedback loop is established, shown as a rising spiral. The longer the leaflet is in contact with the septum, the higher the pressure gradient. After treatment (bottom tracing), negative inotropes slow early systolic acceleration (shown as a horizontal wavy arrow) and may thereby decrease the force on the mitral leaflet, delaying SAM. Mitral-septal contact would occur later, leaving less time in systole for the feedback loop to narrow the orifice. This would reduce the final pressure difference. Delaying SAM may also allow more time for papillary muscle shortening to provide countertraction. In the figure, for clarity, the “before” arrow is positioned above the “after” arrow, although at the beginning of systole they both actually begin with a pressure gradient of 0 mm Hg.
Study Limitations

The observation that medications result in a decrease in flow acceleration and thereby eliminate mitral-valve contact and obstruction. Before treatment, velocity peaks in the first half of the ejection period; after successful treatment, it peaks in the second half. This finding can be observed easily by visual inspection of pulsed Doppler tracings in the left ventricle at the AMV point 2.5 cm apical of the mitral valve. An avenue of future research, suggested by these observations, pertains to patients who are medical failures, patients who remain obstructed and symptomatic despite medication. In these patients, if acceleration in the LV has slowed but there is still significant obstruction, medication alone may not be adequate to eliminate obstruction because of adverse anatomy. Study may show that these patients are the ones who will require further measures.

In summary, we believe that our data indicate that negative inotropes work by decreasing ejection acceleration and the hydrodynamic force on the protruding mitral leaflet, resulting in a lower final pressure gradient.

Acknowledgment

We would like to thank Edward Dwyer, MD; Tian-Yi Jing; Vijay Kohil, MD; Frank Miele; and Venice Polynice for their assistance.

References


Mechanism of Benefit of Negative Inotropes in Obstructive Hypertrophic Cardiomyopathy
Mark V. Sherrid, Gretchen Pearle and David Z. Gunsburg

Circulation. 1998;97:41-47
doi: 10.1161/01.CIR.97.1.41

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/97/1/41

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at: http://circ.ahajournals.org//subscriptions/