Mechanism of Acute Mechanical Benefit From VDD Pacing in Hypertrophied Heart
Similarity of Responses in Hypertrophic Cardiomyopathy and Hypertensive Heart Disease

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Background—Dual-chamber pacing can improve symptoms in hypertrophic cardiomyopathy (HCM), but the mechanism remains unclear. We hypothesized that pacing generates discoordinate contraction and a rightward shift of the end-systolic pressure-volume relation (ESPVR) and that benefits from this mechanism do not depend on the presence of resting outflow pressure gradients or obstruction.

Methods and Results—Eleven patients with NYHA class III symptoms, 5 with HCM, and 6 with hypertensive hypertrophy and cavity obliteration, were studied by invasive conductance catheter methods. No patient had coronary artery or primary valvular disease. Pressure-volume relations were recorded before and during VDD pacing by use of a short (75-millisecond) PR interval to achieve preexcitation. Left ventricular cavity pressure was simultaneously recorded at basal and apical sites, with pressure at the basal site used to generate the ESPVRs. VDD pacing shifted the ESPVR rightward, increasing end-systolic volume by 45% (range, 17% to 151%; \( P < 0.002 \)). Resting and provokable gradients declined by 20% (range, −56% to +3%) and 30% (range, −65% to −12%), respectively (\( P < 0.05 \)). Preload declined by 3% to 10% because of the short PR interval. Preload-corrected contractility indexes and myocardial workload declined by ≈10% (\( P < 0.001 \)). Diastolic compliance and relaxation time were unchanged. Pacing made apical pressure-volume loops discoordinate, limiting cavity obliteration and reducing distal systolic pressures. Results in both patient groups were similar.

Conclusions—VDD pacing shifts the ESPVR rightward in HCM patients with cavity obliteration with or without obstruction, increasing end-systolic volumes and reducing apical cavity compression and cardiac work. These effects likely contribute to reduced metabolic demand and improved symptoms.

Key Words: pacing ■ cardiomyopathy ■ hypertrophy ■ hemodynamics

Dual-chamber pacing may benefit HCM patients with intraventricular gradients having symptoms refractory to medical therapy.1–6 However, not all patients improve symptomatically, and the amount of pressure gradient decrease can be small.5,6 These facts have tempered the enthusiasm for pacing therapy and highlighted the need for better patient selection criteria and thus for a better understanding of its mechanical effects.7

Pacing is thought to generate mechanical benefits by limiting outflow tract narrowing and dynamic obstruction because of asynchronous septal activation.1–6 This hypothesis focuses on a critical site of discoordinate activation (ie, proximal septum) and thus predicts little benefit for patients without outflow tract obstruction or SAM.

An alternative but related explanation is that pacing-induced asynchrony results in net contractile depression and a rightward shift of the ESPVR as shown in experimental studies in normal animal hearts.5,9 The resulting increase in Ves can greatly influence cavity gradients and SAM. Because the effect on Ves would be present as long as a sufficient territory of muscle became dyskinetic, VDD pacing may also be effective in patients without outflow obstruction, such as those with HH-CO commonly seen in the elderly.10,11

The present study tested the hypothesis that VDD pacing has its primary mechanical effect on the systolic ventricle, shifting the ESPVR rightward and thereby reducing cavity obliteration, outflow gradients, and myocardial work. We reasoned that this mechanism would apply similarly to HCM ventricles with rest gradients and SAM as well as to HH-CO without obstruction and suggest a mechanism by which pacing may convey sustained relief of symptoms.

Methods

Patients
The study group consisted of 11 patients, 5 with HCM and 6 with HH-CO. All HCM patients had resting intraventricular pressure

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gradients >30 mm Hg and asymmetric ventricular hypertrophy. Patients with HH-CO had long-standing hypertension, concentric hypertrophy, and middistal systolic cavity obliteration. All 11 patients had NYHA class III heart failure symptoms despite maximum tolerated doses of calcium channel and β-adrenergic blockers. These drugs (but not other types of antihypertensive medicines) were withheld 24 to 48 hours before the study. No patient had significant coronary artery or valvular disease. All patients gave informed consent to this protocol, which was approved by the Joint Committee on Clinical Investigation of the Johns Hopkins Medical Institutions.

Procedure
Detailed methods for PV catheterization study in HCM patients have been previously reported.1–6,15,16 After routine right- and left-side catheterization, a multielectrode conductance catheter (Webster Labs or Sentron) was positioned inside the LV. The conductance catheter had an 8-cm hole and 2 distal side holes but no pigtails so that ventricular ectopy could be minimized after placement within the obliterating apex. Apical pressures were recorded through the side holes by use of a fluid-filled manometer. LV pressures used for PV analysis were measured by a 2F micromanometer (SPC-320, Millar Instruments) inside a pigtail catheter placed in the proximal half of the LV chamber. The volume was measured with the conductance catheter connected to a stimulator/microprocessor (Sigma V, CardioDynamics) and calibrated as previously reported.1–6,15 Although no complications occurred in this study, 2 instances of ventricular perforation occurred subsequently while the straight-tipped conductance catheter was used in hypertrophied LV. New catheter design should facilitate such studies.

ESPVs and EDPVrs were generated from data recorded during transient rapid preload reduction by balloon obstruction of inferior vena caval inflow (SP9516, Cordis). A 2.5F pacing wire (Baxter) advanced through this catheter was positioned in the right atrium for atrial sensing. Ventricular pacing was achieved with a steerable quadripolar catheter placed at the right ventricular apex. Pacing stimuli were provided by an external dual-chamber pulse generator (Medtronic 5311B) in VDD mode, with the AV delay set to the longest value that still yielded optimal ventricular preexcitation as judged by QRS duration (mean, 75 milliseconds).

Data Analysis
Blood pressure during the cardiac cycle was measured with a fluid-filled manometer. LV pressures used for PV analysis were measured by a 2F micromanometer (SPC-320, Millar Instruments) inside a pigtail catheter placed in the proximal half of the LV chamber. The volume was measured with the conductance catheter connected to a stimulator/microprocessor (Sigma V, CardioDynamics) and calibrated as previously reported.1–6,15 Although no complications occurred in this study, 2 instances of ventricular perforation occurred subsequently while the straight-tipped conductance catheter was used in hypertrophied LV. New catheter design should facilitate such studies.

The ESPVR was derived from the series of end-systolic PV points derived from multiple cardiac cycles during transient preload reduction. The time constant of isovolumic relaxation (τ) was the negative inverse slope of the pressure-dp/dt plot with the use of data between dP/dtmax and 2 mm Hg above end-diastolic pressure. EDPVrs were derived from end-diastolic PV points from the variably volume-loaded beats.12,13 These data were fit to the equation \( P = \frac{PVA}{Ves} + \frac{PESV}{SW} \) by nonlinear regression analysis, where \( P \) is the chamber stiffness and \( \alpha \) is a scaling factor. Finally, the total PVAV was determined from the sum of cardiac SW and the area bounded by the ESPVR and EDPVR between Ves and Ves.
TABLE 2. Hemodynamic Effects of VDD Pacing

<table>
<thead>
<tr>
<th></th>
<th>HCM (n=5)</th>
<th>VDD Pacing</th>
<th>P</th>
<th>HH-CO (n=6)</th>
<th>VDD Pacing</th>
<th>P</th>
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<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>68±6.5</td>
<td>70±5.6</td>
<td>0.2</td>
<td>71±18.7</td>
<td>72±18.1</td>
<td>0.2</td>
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<td>Rest gradient, mm Hg</td>
<td>67±33</td>
<td>52±34</td>
<td>0.005</td>
<td>17±19</td>
<td>15±17</td>
<td>0.32</td>
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<td>PESP gradient, mm Hg</td>
<td>152±47</td>
<td>104±51</td>
<td>0.04</td>
<td>113±44</td>
<td>75±36</td>
<td>0.04</td>
</tr>
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<td>RAP, mm Hg</td>
<td>7.8±4.3</td>
<td>8.1±3.4</td>
<td>0.50</td>
<td>8.2±3.3</td>
<td>7.4±2.5</td>
<td>0.96</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>20.8±7.7</td>
<td>18.6±7.0</td>
<td>0.04</td>
<td>13.7±7.6</td>
<td>12.7±6.4</td>
<td>0.40</td>
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<tr>
<td>Pes (mm Hg)</td>
<td>118±18.5</td>
<td>111±6.9</td>
<td>0.31</td>
<td>173±36.5</td>
<td>173±34.9</td>
<td>0.95</td>
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<td>Volumes</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>ESV,* mL</td>
<td>18±7.3</td>
<td>23±9.2</td>
<td>0.01</td>
<td>18±11.2</td>
<td>29±14.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Vess* mL</td>
<td>12±5.2</td>
<td>17±7.5</td>
<td>0.01</td>
<td>8.4±6.2</td>
<td>16.5±9.5</td>
<td>0.02</td>
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<tr>
<td>EDV, mL</td>
<td>91±10.9</td>
<td>80±15.1</td>
<td>0.03</td>
<td>90±26.4</td>
<td>87±26.3</td>
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<td>Stroke volume, mL</td>
<td>69±13.0</td>
<td>57±21</td>
<td>0.03</td>
<td>69±20.6</td>
<td>57±18</td>
<td>0.01</td>
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<td>Cardiac output, L/min</td>
<td>4.7±1.0</td>
<td>4.0±1.3</td>
<td>0.04</td>
<td>4.7±1.3</td>
<td>3.9±1.0</td>
<td>0.02</td>
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<td>Systolic indexes</td>
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<td>Ees, mm Hg/mL</td>
<td>8.1±6.2</td>
<td>6.1±5.3</td>
<td>0.58</td>
<td>10.7±11.8</td>
<td>7.25±5.3</td>
<td>0.33</td>
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<td>dP/dt*max, mm Hg/s</td>
<td>1304±200</td>
<td>1208±192</td>
<td>0.04</td>
<td>1767±526</td>
<td>1522±548</td>
<td>0.004</td>
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<td>Diastolic indexes</td>
<td></td>
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<td></td>
<td></td>
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<td>β, mL⁻¹</td>
<td>0.031±0.009</td>
<td>0.024±0.016</td>
<td>0.34</td>
<td>0.026±0.009</td>
<td>0.042±0.024</td>
<td>0.13</td>
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<td>τ, ms</td>
<td>48.3±10.6</td>
<td>50.2±12.4</td>
<td>0.54</td>
<td>62.4±28.9</td>
<td>56.0±21.8</td>
<td>0.47</td>
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<td>TTPFR, ms</td>
<td>163±51.7</td>
<td>174±53.6</td>
<td>0.41</td>
<td>169±83.6</td>
<td>187±92.6</td>
<td>0.16</td>
</tr>
<tr>
<td>PFR/EDV, s⁻¹</td>
<td>3.9±1.0</td>
<td>4.7±1.3</td>
<td>0.02</td>
<td>4.3±1.6</td>
<td>4.7±1.5</td>
<td>0.18</td>
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<tr>
<td>Energetics</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PVA,* mm Hg · mL/beat</td>
<td>8693±1413</td>
<td>7472±1551</td>
<td>0.04</td>
<td>12 432±5447</td>
<td>11 531±5292</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SW,* mm Hg · mL/beat</td>
<td>6427±1737</td>
<td>5530±1918</td>
<td>&lt;0.05</td>
<td>9606±4212</td>
<td>8044±3104</td>
<td>0.07</td>
</tr>
<tr>
<td>SW*/PVA*</td>
<td>0.75±0.18</td>
<td>0.73±0.15</td>
<td>0.73</td>
<td>0.77±0.11</td>
<td>0.73±0.14</td>
<td>0.44</td>
</tr>
</tbody>
</table>

*Parameter at a matched EDV (see "Methods").

Energetics

Total myocardial work indexed by PVA at a matched end-diastolic volume (PVA*) was reduced by VDD pacing. In HCM patients, this decline was somewhat greater (14%) than in HH-CO patients (7%), but changes were significant in both groups. The ratio of SW to PVA (mechanical work efficiency) remained unchanged.

Differences Between HCM and HH-CO

Although the 2 patient groups reflected different hypertrophic disease conditions, there were important similarities. For example, all ventricles had cavity obliteration and elevated baseline Ees, and their response to pacing was very similar. The only parameter with a significantly different response to pacing was EDV, which declined less in HH-CO patients (3% versus 12%, P<0.05). The contribution of atrial contraction to net chamber filling fell from 44±16% in HCM at baseline to 12±9% with VDD pacing (P=0.03), whereas it decreased from 33±19% to 23±15% (P=0.27) in HH-CO patients, consistent with the greater preload decline in HCM.

Diastolic Indexes

LV end-diastolic pressure decreased, along with preload volume (P=0.04 in HCM patients). Peak filling rate normalized to EDV rose slightly in HCM patients (P=0.02) even though neither τ nor chamber stiffness was altered.

hearts. Figure 3 shows data from the same 2 hypertrophy patients during VDD pacing. Control relations (Figure 2) are superimposed for comparison. Pacing induced a rightward ESPVR shift with little slope change.

Group data are provided in Table 2. The ESPVR shift was indexed by the end-systolic volume determined at a matched end-systolic pressure of 100 mm Hg. That pressure rose by 39% in HCM and by 96% in HH-CO patients (both P<0.05). Ves* (preload-adjusted Ves) increased similarly. Ees tended to decline in both groups, but this did not achieve statistical significance. Evidence for a net negative contractile effect was supported by dP/dt*max*, which declined by 7% in HCM and 14% in HH-CO patients (both P<0.05). By virtue of the need for a short AV delay, pacing reduced preload volume in both groups. This reduction, combined with the rightward ESPVR shift, led to an 18% decline in stroke volume (P<0.05).

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Regional Dyssynchrony and Pressure Gradient Reduction

Regional dyssynchrony at the site of apical pacing was examined from apex-segment PV loops. Figure 4A shows the time plot of this apical volume signal under normal sinus rhythm versus VDD conditions. The bent arrow indicates pacing stimulation and shows the consequent early onset of contraction in the apical territory. By midsystole, however, this region was stretched by the late-activated myocardium (arrowhead), increasing apical volume. This prevented the heart from contracting to a small Ves during VDD pacing. Figure 4B displays these data as regional PV loops. Whereas the control loop had a normal configuration, with positive external work, the loop with VDD pacing was a figure eight, with little early ejection and subsequent systolic bulging.

Figure 4C and 4D demonstrates the consequences of apical discoordinate motion on systolic cavity. In the control state, lowering preload led to a marked increase in late systolic apical pressure because of cavity obliteration, with substantial isovolumic work performed by the distal myocardium. In contrast, the discoordinate apex with VDD pacing did not develop late systolic pressure increases because the cavity no longer obliterated in midsystole.

Discussion

This study demonstrates for the first time in humans that dual-chamber pacing with preexcitation of the hypertrophied ventricle induces a rightward shift of the ESPVR resulting from discoordinate motion at the site of premature activation. This increases Ves at any given end-systolic pressure and thus significantly reduces intraventricular pressure gradients and myocardial work. PV analysis enabled us to adjust for load changes induced by pacing. As predicted by this model, the mechanical response is virtually the same in HCM as HH-CO patients, suggesting that obstruction is not a prerequisite for gradient reduction by pacing and that pacing may help HH-CO patients who do not have outflow tract obstruction.

VDD Pacing and ESPVR Shift

The rightward ESPVR shift observed in the present study is analogous to that reported in normal canine hearts. As shown in Figure 4 and reported by others, this shift results from dyssynergy in chamber mechanical contraction. As shown in Figure 2, both HCM and HH-CO ventricles undergo minimal Ves change over a broad physiological loading range, reflecting ESPVR steepness. Thus, only small changes in Ves are likely needed to influence SAM and distal cavity pressure. Although small, the rightward ESPVR shift from pacing reflected a substantial rise in Ves compared with baseline. Achieving a similar Ves without pacing would require a 30% increase in preload that would also raise LV end-diastolic pressures >40 mm Hg.

Prior short-term clinical studies of HCM have not observed an increase in Ves with pacing, but this may relate to methodological limitations. Because of chamber geometric

Figure 1. Effect of VDD pacing on rest and provokable pressure gradients. Pressure tracings from the LV base and apex are plotted along with the ECG. A, HCM patient with rest gradient. Note the sharp increase in the pressure gradients on cessation of pacing (arrow). B, HH-CO patient with a small rest gradient but a provokable gradient >100 mm Hg at baseline. The gradient was provoked by PESP (arrow). C, Same patient as in B. With VDD pacing, the provokable gradient (arrow) is much reduced. Note the similar coupling intervals before and after the extrasystole.

Figure 2. Baseline PV loops in normal sinus rhythm during transient preload reduction caused by inferior vena caval occlusion. A, Normal subject included for comparison purposes. B, HCM patient. C, HH-CO patient. Note the steep ESPVRs in these patients.
abnormalities, small volume changes, especially at the apex, are difficult to assess from echocardiographic images. The conductance catheter method is better suited to evaluating small relative changes in volume by use of multiple recording segments. This applies in HCM hearts with abnormal geometry.13

Effects on Pressure Gradient and Cardiac Work
The present study confirms prior reports showing VDD pacing reduces intraventricular pressure gradients in the short term in patients with HCM.1–4,6,15,16 Furthermore, the pressure gradient was similarly reduced even when generated by cavity obliteration rather than by outflow tract obstruction, suggesting that the mechanism did not depend on obstructive physiology.

VDD pacing increases Ves while reducing overall cardiac work as indexed by PVA*. Unlike negative inotropic drugs, this pacing effect on workload was more directly targeted to distal regions of the heart generating high systolic forces from midsystolic cavity compression. By limiting cavity obliteration, pacing may diminish isovolumic work in these regions, reducing energy consumption, and over time, resulting in ventricular remodeling.3,17,18 This concept is supported by PET scan data from HCM patients treated with long-term pacing, which has shown reduced oxygen uptake and higher metabolic reserve in the obliterating region.19,20

Diastolic Parameters
Diastolic abnormalities contribute prominently to the clinical course and symptoms of patients with LV hypertrophy, and Ca2+ channel blockers are thought to provide benefit in part by enhancing filling dynamics, relaxation, and chamber distensibility.21,22 However, these agents (and β-adrenergic blockers) do not alter chamber compliance in the short term.12 In this sense, they are no different from pacing, which also does not alter the diastolic PV relation in the short term. The present data provide the first direct analysis of such effects under variable loading conditions.

AV sequential pacing slows relaxation in normal canine hearts.23 However, the effect of pacing on active relaxation in human HCM has been less consistent. Betocchi et al16 reported that τ increases with pacing, whereas Nishimura et al15 found no change at the optimal AV delay. There were no significant τ changes in the present study as well. These disparities are likely the result of differences in the site of intraventricular pressure measurement, heterogeneity of the HCM substrate and load (gradient) reduction from pacing, and sample size. Although relaxation was unchanged, pacing increased the peak filling rate normalized for EDV. This pacing influence on filling was likely related to increases in the early filling gradient caused by the shortened PR interval as shown by Nishimura et al.15 This short-term change likely resolves with longer-term pacing as suggested in long-term studies.1

Similarities of VDD Pacing and Other Therapies
In contrast to filling indexes, which may return to prepacing levels with long-term pacing, systolic indexes with long-term VDD pacing often remain impaired. The dP/dtmax remains lower, and the end-systolic dimension by two-dimensional echocardiogram is greater than the baseline.3 These changes likely contribute to symptomatic improvement rather than cause symptom deterioration. The first line of therapy for symptomatic HCM patients with intraventricular gradients has been negative inotropic agents, such as β-adrenergic and

Figure 3. PV loops during VDD pacing for the same HCM and HH-CO patients as in Figure 2. The baseline ESPVRs and EDPVRs are reproduced in dashed lines for comparison. A, HCM patient. B, HH-CO patient. Note the rightward displacement of the ESPVRs caused by pacing without a significant change in the slope. The EDPVRs are superimposable with or without pacing.

Figure 4. Apical segment volume plots of an HH-CO patient. A, Signal-averaged, steady-state apical segment volumes at baseline and during pacing plotted against time. B, Apical dyskinesis shown in a PV plot. Apical segment PV loops at baseline (C) and during pacing (D) during transient inferior vena caval occlusion. See text for details.
calcium channel blockers or disopyramide. All these agents decrease contractility and thereby diminish intraventricular pressure gradients. However, because pacing at the right ventricular apex reduces contractility by causing temporal and spatial asynchrony in contraction, its effects on the pressure gradient are additive to the negative inotropic agents that act more globally. Ves also increases after septal myotomy-myectomy, and catheter-based septal reduction may also increase Ves. Thus, a common mechanism for relief of pressure gradients in HCM may be an increase in Ves with or without generalized contractile depression.

**Hypertensive Heart Disease**

Medical treatment for HH-CO patients shares many similarities with that for HCM patients. In particular, both types of patients are often helped by β-receptor and calcium channel blockers. The present study showed that VDD pacing could increase Ves for the short term and decrease provokable pressure gradients in HH-CO patients. If the increase in Ves is important in improving symptoms in HCM patients by reducing intraventricular gradients and myocardial workload, then VDD pacing should benefit HH-CO patients as well. Only 1 prior study has evaluated a group of HCM patients without resting pressure gradients, and it reported no improvement from dual-chamber pacing. However, these patients had reduced ejection fraction and likely did not have cavity obliteration, because there were no provokable pressure gradients. We would agree that pacing has little role in patients in whom Ves is already high enough to prevent cavity obliteration or outflow obstruction.

**Study Limitations**

This study examined short-term hemodynamic responses to VDD pacing in HCM and HH-CO patients in the catheterization laboratory at rest in the supine position. Therefore, it cannot predict the efficacy of long-term pacing in these patients on its own. However, existing published data on the long-term use of pacing in HCM do indicate that it can relieve symptoms and lower the intraventricular pressure difference. Nevertheless, gradient reduction cannot be used as the sole index of efficacy, because some HCM patients have significant reduction in the pressure gradient without symptomatic improvement, possibly because of the heterogeneity of HCM, labile nature of the pressure gradient, and simultaneous load changes with pacing. Long-term prospective, randomized, and double-blinded studies are currently underway to examine pacing effects in both HCM and HH-CO patients. Preliminary 6-month results suggest that long-term pacing in HH-CO patients increases exercise time and produces sustained symptomatic relief.

A catheter can be entrapped in the obliterating apex, causing artifactual pressure differences between the apex and the base. However, we used a straight-tipped catheter with several side holes to minimize the probability of entrapment. Furthermore, direct peak instantaneous pressure gradients (55±31 mm Hg; range, 28 to 100 mm Hg) were highly correlated to those obtained noninvasively by Doppler velocity (50±48 mm Hg; range, 0 to 120 mm Hg) by linear regression ($r^2=0.945$ and $P<0.0001$). The strength of the PESP contraction can vary with the premature interval, and ideally this is fixed by use of programmed electrical stimulation. Although this was not done in this study, we carefully matched coupling intervals for the PESP analysis so that valid comparisons of provokable gradients could be made.

**Conclusions**

VDD pacing increases Ves in the short term because of a rightward shift of the ESPVR, reduces intracavitary pressure gradients, and lowers total chamber workload in HCM patients. These effects likely underlie symptomatic improvement in select patients with HCM. Because similar mechanical effects are induced in patients with HH-CO, individuals with this disorder may also benefit from VDD pacing therapy. Current randomized trials are addressing this hypothesis.

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**References**


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