Evaluation of Acute Dual-Chamber Pacing With a Range of Atrioventricular Delays on Cardiac Performance in Refractory Heart Failure

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Objectives. This study evaluated how variations in atrioventricular (AV) delay affect hemodynamic function in patients with refractory heart failure being supported with intravenous inotropic and intravenous or oral inodilating agents.

Background. Although preliminary data have suggested that dual-chamber pacing with short AV delays may improve cardiac function in patients with heart failure, detailed Doppler and invasive hemodynamic assessment of patients with refractory New York Heart Association class IV heart failure has not been performed.

Methods. Nine patients with functional class IV clinical heart failure had Doppler assessment of transvalvular flow and right heart catheterization performed during pacing at AV delays of 200, 150, 100 and 50 to 75 ms.

Results. Systemic arterial, pulmonary artery, right atrial and pulmonary capillary wedge pressures, cardiac index, systemic and pulmonary vascular resistances, stroke volume index, left ventricular stroke work index (SWI) and arteriovenous oxygen content difference demonstrated no significant changes during dual-chamber pacing with AV delays of 200 to 50 to 75 ms. There were also no changes in the Doppler echocardiographic indexes of systolic or diastolic ventricular function. The study was designed with SWI as the outcome variable. Assuming a clinically significant change in the SWI of 5 g/min per m², a type I error of 0.05 and the observed standard deviation from our study, the observed power of our study is 85% (type II error of 15%).

Conclusions. Changes in AV delay between 200 and 50 ms during dual-chamber pacing do not significantly affect acute central hemodynamic data, including cardiac output and systolic or diastolic ventricular function in patients with severe refractory heart failure due to dilated cardiomyopathy.

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The increasing incidence of congestive heart failure, as well as the limited supply of donor hearts available for transplantation, reinforces the need to find therapeutic modalities to improve cardiac function in patients with advanced heart failure (1,2). Patients with refractory heart failure have worsening symptoms or hemodynamic data despite optimal therapy with digoxin, diuretic agents and angiotensin-converting enzyme inhibitors or hydralazine/nitrates. They have a particularly poor prognosis and frequently require immediate pharmacologic or nonpharmacologic interventions for stabilization (3). Preliminary data have suggested that dual-chamber pacing with short atrioventricular (AV) delays may improve cardiac function in patients with heart failure, especially those with a long PR interval or diastolic AV valve regurgitation (4–8). We designed this study to determine how variations in AV delay affect hemodynamic data and ventricular systolic and diastolic function in patients with refractory heart failure due to dilated cardiomyopathy.

Methods

Study patients. The study included 9 patients (5 men and 4 women, mean age 69 ± 7 years) with refractory congestive heart failure (New York Heart Association functional class IV). Five patients had ischemic heart disease and four patients had idiopathic dilated cardiomyopathy. All patients had symptoms of fatigue and dyspnea with radiologic evidence of pulmonary venous congestion and cardiomegaly. All patients were in the cardiac intensive care unit for treatment of congestive heart failure at the time of the study. Long-term medications included digoxin (n = 7), diuretic drugs (n = 8), angiotensin-converting enzyme inhibitors (n = 4), hydralazine/
nitrates (n = 5) and amiodarone (n = 8). Short-term medications used for cardiac decompensation included dobutamine/dopamine/norepinephrine/milrinone (n = 2), dobutamine/dopamine/norepinephrine (n = 1), dobutamine/norepinephrine/milrinone (n = 1), dobutamine plus oral enoximone (n = 1) and oral enoximone (n = 1).

Five of the patients had permanent dual-chamber pacemakers at the time of the study, and four patients had temporary right atrial and right ventricular atrial pacing catheters placed for the study. The baseline cardiac rhythm at the time of study was sinus rhythm in one patient (PR interval 188 ms), sinus rhythm with first-degree heart block in one patient (PR interval 440 ms), bigeminy in one patient, third-degree heart block in two patients and dual-chamber pacing in four patients (AV delays of 110, 120, 200 and 200 ms, respectively). Of the two patients in third-degree heart block, one had a stable escape rate with temporary pacing leads in place while awaiting permanent pacemaker placement, and one had a permanent dual-chamber system with a stable junctional escape as an underlying rhythm. The indications for pacing in the five patients with preexisting permanent dual-chamber pacing systems at the time of study were complete heart block in three patients, symptomatic sinus bradycardia in one patient and AV junction ablation for paroxysmal atrial fibrillation in one patient.

**Study protocol.** The study was approved by the Committee on Human Research, and written, informed consent was obtained from each patient. Patients were studied in a nonfasted, postabsorptive state in a supine position. Each patient underwent a 10-min equilibration period. Pacing was performed at a minimum of 10 beats/min above the rest rate, with further increases in pacing rate only in patients in whom consistent capture was not achieved. This rate was maintained at all AV delay settings in each individual patient.

**Measurements.** *Invasive hemodynamic data.* Hemodynamic measures included heart rate, systemic systolic and diastolic blood pressures, right atrial pressure (RAP), pulmonary artery systolic and diastolic blood pressures, PCWP, cardiac output and arterial and venous oxygen saturations. Derived systemic hemodynamic data were calculated as follows: stroke volume index (SVI, ml/m²) = CI/HR, where CI = cardiac index and HR = heart rate; stroke work index (SWI, g/m per m²) = SVI × (MSP - PCWP) × 0.0136, where MSP = mean systolic arterial pressure; systemic vascular resistance (SVR, dynes-s-cm⁻²) = (MAP - RAP)/CO × 80, where MAP = mean arterial pressure and CO = cardiac output; pulmonary vascular resistance (PVR, dynes-s-cm⁻⁵) = (MPAP - PCWP)/CO × 80, where MPAP = mean pulmonary artery pressure; arterial venous oxygen difference (AVDO₂ [vol%]) = Arterial oxygen content - Venous oxygen content, where oxygen content = percent oxygen saturation × hemoglobin (g/dl) × 1.34.

**Doppler variables.** An average 6 to 10 high quality Doppler signals were used for analysis. The left ventricular and right ventricular systolic flow variables were measured using pulsed wave Doppler recordings as described previously (11), and included left ventricular outflow tract (LVOT) acceleration time, LVOT ejection time, LVOT velocity–time integral (VTI) (total area under the LVOT velocity curve as an estimate of the LVOT stroke volume), pulmonary artery acceleration time, pulmonary artery ejection time and pulmonary artery VTI. The severity of the mitral valve regurgitation was graded using the color Doppler mode as previously described (11).
The peak velocity of the mitral regurgitation was measured in the continuous wave Doppler mode as an index of the left ventricular–left atrial systolic pressure gradient. The mitral valve regurgitation acceleration time was measured as the interval from the beginning to the peak of the mitral regurgitation jet. The presence of diastolic mitral regurgitation was noted. The change in the systolic right ventricular–right atrial peak pressure gradient was estimated by the measurement of the peak tricuspid valve regurgitation velocity.

To estimate the left ventricular and right ventricular diastolic variables, the mitral and tricuspid flow curves were recorded in the pulsed wave Doppler mode. Both peak E and A wave flow velocities were measured for the mitral flow, and the mean peak E wave on the tricuspid diastolic flow curve was measured for the right ventricular flow. The mitral valve deceleration time was not able to be measured because of near fusion of the mitral valve E and A waves. The left and right ventricular filling times were measured as the interval from the beginning to the end of the diastolic flow on the mitral and tricuspid diastolic Doppler curves.

**Statistical analysis.** Data are expressed as the mean value ± SD. A p value <0.05 was considered significant. Statistical analysis was performed using repeated measures analysis of variance for hemodynamic variables and Doppler variables at AV delay settings of 50 to 75, 100, 150 and 200 ms.

**Results**

Baseline hemodynamic data included a mean heart rate of 71 ± 16 beats/min, MAP 79 ± 15 mm Hg, MRAP 11 ± 9 mm Hg, MPAP 36 ± 8 mm Hg, PCWP 22 ± 6 mm Hg, cardiac index 2.5 ± 0.7 liters/min per m², systemic vascular resistance 1,363 ± 535 dynes·sec·cm⁻⁵, and pulmonary vascular resistance 292 ± 214 dynes·sec·cm⁻⁵. The mean baseline echocardiographic left ventricular ejection fraction was 28 ± 8% (range 18% to 40%). Diastolic mitral regurgitation was present in two patients with complete heart block. Semiquantitative mitral regurgitation grades by echocardiography at baseline were mild (n = 1), mild to moderate (n = 5) and moderate (n = 3).

The patients’ hemodynamic variables at AV delays between 200 and 50 ms are shown in Table 1. There were no significant changes in measured or derived invasive hemodynamic variables between AV delay settings of 50 to 75, 100, 150 and 200 ms. Doppler assessment of left and right ventricular systolic function failed to reveal any differences in these patients at the various AV delays evaluated (Table 2). With the exception of mitral valve peak A wave velocity, there were no differences in left and right ventricular diastolic function at the various AV delays evaluated by Doppler echocardiography (Table 2). The mitral valve peak A wave velocity was significantly better at longer AV delays (p = 0.03). The diastolic mitral regurgitation present in two patients with complete heart block at baseline did not appear at any AV sequential pacing settings. Assessment of semiquantitative mitral regurgitation grade revealed no changes in grade at the studied AV delay settings.

**Discussion**

In our study of patients with refractory congestive heart failure due to dilated cardiomyopathy, dual-chamber pacing at AV delays of 50 to 200 ms did not immediately change hemodynamic variables as evaluated by invasive right heart catheterization. Whether AV delays were short or long, there were no differences in the SVI, SWI, PCWP or RAP, suggesting that there was no hemodynamic evidence for improvement in ventricular function with shorter AV delays compared with...
longer AV delays. The variable that we a priori considered to be of greatest importance was the SWI. This variable was chosen because it incorporates information on both pressure work and volume work and therefore assesses overall ventricu-
lar performance. The additional hemodynamic and Doppler data were analyzed to assess the effect of variable AV delays specifically on systolic and diastolic ventricular function. A clinically significant change in SWI was arbitrarily chosen as ≥5 g/min per m². As in our clinical experience, smaller changes can be seen with a spontaneous variation in this variable. Assuming a clinically significant change in SWI of 5 g/min per m² and a type I error of 0.05 as well as the observed standard deviation from our study, the observed power of our study is 85% (PASS Version 6.0, NCSS). This study had negative results with a type II error of 15%.

In our study, Doppler echocardiographic studies confirmed that AV delays do not influence ventricular performance in these patients with severe clinical heart failure with marked hemodynamic abnormalities resulting from dilated cardiomyopathy. There were no changes in the indexes of systolic or diastolic function during pacing with shorter or longer AV delays. Earlier studies by Hochleitner et al. (4,5) suggested that dual-chamber pacing at an AV delay of 100 ms improved the functional class, cardiac dimensions and congestive heart failure symptoms of 17 patients with advanced heart failure. One-half of these patients were taking intravenous inotropic agents at the time of initiating dual-chamber pacing. Of the paced patients who survived 1 year, the ejection fraction was significantly improved by pacing (19 ± 3% to 30 ± 4%), and there was an unexpectedly long median survival time of the entire group (22 months). In the first 2 years of pacing, the ejection fraction fell by 5% to 11% with early withdrawal of pacing. No invasive hemodynamic studies were performed to determine the mechanism of improved cardiac performance.

Further evidence to support the use of dual-chamber pacing in patients with congestive heart failure was provided by Brecker et al. (6). In 12 otherwise uncharacterized patients with an unreported severity of heart failure, all of whom had mitral and/or tricuspid diastolic regurgitation and left or right ventricular filling times of <200 ms, Doppler echocardiography was used early to assess the physiologic effects of dual-chamber pacing. Five patients had a prolonged PR interval and four patients had permanent pacemakers for complete heart block. At AV delays <50 ms, all patients had a significant reduction in mitral and tricuspid regurgitation times and a significant increase in left ventricular filling times. The group as a whole had an increase in cardiac output (3.9 to 5.0 liters/min by Doppler analysis) and improved exercise tolerance. Invasive hemodynamic studies were not performed. The investigators concluded that in patients with congestive heart failure and AV valve diastolic regurgitation, especially with a prolonged PR interval, dual-chamber pacing with a short AV delay improves the relation between atrial and ventricular systole, improves ventricular diastolic filling and leads to improved forward cardiac output. Guardigli et al. (7) also demonstrated progressive improvement in transmural flow in

### Table 2. Doppler Assessment of Cardiac and Valvular Function

<table>
<thead>
<tr>
<th>Doppler Variables</th>
<th>Atrioventricular Delay (ms)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50–75</td>
<td>100</td>
</tr>
<tr>
<td><strong>Left heart</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic variables</td>
<td>LVOT acceleration (s)</td>
<td>0.06 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>LVOT ejection (s)</td>
<td>0.21 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>LVOT VTI (m)</td>
<td>0.17 ± 0.07</td>
</tr>
<tr>
<td></td>
<td>MR peak velocity (m/s)</td>
<td>4.2 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>MR acceleration (s)</td>
<td>0.15 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>MR VTI (m/s)</td>
<td>1.2 ± 0.2</td>
</tr>
<tr>
<td><strong>Diastolic variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MV peak E wave velocity (m/s)</td>
<td>1.0 ± 0.3</td>
<td>1.1 ± 0.3</td>
</tr>
<tr>
<td>MV peak A wave velocity (m/s)</td>
<td>0.6 ± 0.4</td>
<td>0.7 ± 0.5</td>
</tr>
<tr>
<td>MV peak E/A ratio</td>
<td>2.9 ± 1.7</td>
<td>6.2 ± 8.6</td>
</tr>
<tr>
<td>MV filling time (s)</td>
<td>0.28 ± 0.06</td>
<td>0.28 ± 0.07</td>
</tr>
<tr>
<td><strong>Right heart</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic variables</td>
<td>PA acceleration (s)</td>
<td>0.06 ± 0.02</td>
</tr>
<tr>
<td></td>
<td>PA ejection (s)</td>
<td>0.21 ± 0.03</td>
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<tr>
<td></td>
<td>PA VTI (m)</td>
<td>0.12 ± 0.04</td>
</tr>
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<td></td>
<td>TR peak velocity (m/s)</td>
<td>3.2 ± 0.4</td>
</tr>
<tr>
<td><strong>Diastolic variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TV peak E wave velocity (m/s)</td>
<td>0.6 ± 0.2</td>
<td>0.7 ± 0.3</td>
</tr>
<tr>
<td>TV filling time (s)</td>
<td>0.25 ± 0.07</td>
<td>0.26 ± 0.08</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. E/A = early transmural flow velocity to atrial flow velocity; LVOT = left ventricular outflow tract; MR = mitral regurgitation; MV = mitral valve; PA = pulmonary artery; TR = tricuspid regurgitation; TV = tricuspid valve; VTI = velocity-time integral.
patients with dilated cardiomyopathy as AV delays were shortened to 80 ms during dual-chamber pacing.

In contrast to these favorable results, Nishimura et al. (8) evaluated the early hemodynamic effects of dual-chamber pacing with AV delays ranging from 61 to 240 ms in patients with moderate congestive heart failure as assessed by catheterization and Doppler echocardiography and reported no improvement in the systolic or diastolic ventricular function in the group as a whole with varying AV delays. Furthermore, there was an increase in tau (time constant of relaxation) from 64 to 73 ms at the 60-ms AV delay (p < 0.01), suggesting that a very short AV delay may impair left ventricular relaxation. With retrospective subgroup analysis in eight patients with a long PR interval (mean 283 ± 51 ms), pacing with a shorter AV interval significantly improved cardiac output (38% increase). Seven of these patients had a baseline short ventricular filling time and five had a baseline mitral diastolic regurgitation that was abolished by dual-chamber pacing. However, in the subgroup of seven patients with a normal or short PR interval, dual-chamber pacing with a shorter AV interval resulted in a significant decrease in cardiac output (4.2 to 3.4 liters/min, p < 0.01). In the present study also, the SVI, SWI and cardiac index tended to be lower and the AVDO₂ widest during pacing with an AV delay of 50 to 75 ms, although the differences were not statistically significant.

Gold et al. (12) assessed acute and chronic dual-chamber pacing in 12 patients with predominantly functional class III heart failure with no other indication for cardiac pacing. In the short term, there were no significant differences in the mean MAP, RAP, PAP, PCWP or cardiac index, even with analysis of patients with prolonged PR intervals (mean 242 ± 42 ms). In the chronic pacing portion of the study, a double-blind, randomized, crossover of 4 to 6 weeks of pacing with an AV delay of 100 ms compared with VVI pacing at 40 beats/min demonstrated no significant differences in ejection and clinical heart failure status.

In another study by Linde et al. (13), 10 patients with predominantly class III heart failure on a stable medical regimen underwent pacemaker placement and noninvasive long-term follow-up after determination of an “optimized” AV delay based on the acute highest aortic valve VTI. Over a 6-month follow-up period, there was no significant change in stroke volume, cardiac output, functional class or ejection fraction. In this study, however, hemodynamic assessments by catheterization were not performed.

In the present study, the effects of variations in AV delay on ventricular function were assessed by concurrent right heart catheterization and Doppler echocardiography in patients with more severe, truly refractory chronic heart failure. Our study addressed the issue of whether variations in AV delay between 200 and 50 ms would immediately influence hemodynamic data in patients with decompensated heart failure. The results demonstrated that there was no hemodynamic benefit with shorter or longer AV delays during dual-chamber pacing. Doppler echocardiography also failed to reveal any improvement in ventricular systolic or diastolic function. In an earlier study, a shorter AV delay was reported to improve hemodynamic data, particularly in patients with diastolic AV valve regurgitation. In this study, in the two patients with diastolic mitral regurgitation with complete heart block at baseline, diastolic regurgitation was abolished by all AV delay settings and shorter versus longer AV delays did not change hemodynamic data or ventricular function.

In this study, all patients had severe heart failure associated with not only markedly decreased ejection fraction, but also with markedly dilated left ventricles and markedly elevated PCWP. In patients with elevated PCWP, atrial contribution does not appear to influence left ventricular function (14). The failing left ventricle is unable to improve its systolic performance in response to an increase in preload because of a lack of a Frank-Starling reserve (15). Furthermore, because the failing ventricle functions on the steep portion of the ventricular diastolic pressure–volume curve, possible early changes in diastolic ventricular pressure caused by even effective atrial systole would not be expected to significantly change ventricular diastolic volume, even though pressures may increase. In addition, the presence of coexisting right-sided failure and pulmonary hypertension may have overshadowed any benefits to left-sided performance resulting from short AV delay pacing, as a substantial proportion of measured rest left ventricular diastolic pressure stems from forces extrinsic to the left ventricle (right ventricular filling) rather than from diastolic stiffness of the left ventricle itself (16). In the present study, changes in left or right ventricular volume were not measured directly during pacing with varying AV delays. Nevertheless, there were no changes in RAP or PCWP or in the Doppler echocardiographic filling variables, suggesting that there were no significant changes in left or right ventricular filling characteristics during pacing in our patients and possibly explaining the lack of change in systolic function.

**Study limitations.** The limitations of this study include the small sample size and the heterogeneity of baseline heart rhythm, which precluded comparison of baseline hemodynamic data and Doppler echocardiographic data with those during pacing with variable AV delays. The scope of our results therefore pertains specifically to AV delays between 200 and 50 ms in refractory heart failure. Assessment of changes from extremely prolonged baseline PR intervals to AV delays <200 ms, as studied by Nishimura et al., was not possible; therefore, the effect of improved AV synchrony provided by correcting extremely prolonged PR intervals in this refractory group of patients could not be assessed. In addition, analysis of group hemodynamic data and Doppler data at specific AV delays may not reveal changes, as optimal AV delay may vary between individual patients. It should be noted that the hemodynamic data at the average heart rate of 71 beats/min at baseline were almost identical to those during pacing at ~90 beats/min during variable AV delays, suggesting that it is unlikely that dual-chamber pacing at any rate with any AV interval will produce beneficial effects on ventricular systolic or diastolic function.
Conclusions. Early changes in AV delay between 200 and 50 ms do not significantly affect cardiac performance as evaluated by invasive hemodynamic data and detailed Doppler echocardiographic study in patients with severe heart failure due to dilated cardiomyopathy. Dual-chamber pacing with short AV delay pacing cannot be recommended for short-term treatment of refractory heart failure. Further investigation is required to assess the long-term hemodynamic effects of altering AV delay during dual-chamber pacing in patients with severe heart failure due to dilated cardiomyopathy.

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References