Acute Hemodynamic Effects of Biventricular DDD Pacing in Patients With End-Stage Heart Failure

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Despite advances made in drug treatment and the introduction of angiotensin-converting enzyme (ACE) inhibitors in particular, the prognosis of New York Heart Association (NYHA) class III and IV chronic congestive heart failure (CHF) is still pejorative (1) and quality of life is very poor. Various nonpharmacological therapies have been evaluated but are restricted in their effectiveness and applications. In the early 1990s, dual chamber pacing (DDD) pacing was proposed as primary treatment of refractory CHF but results were controversial. Recently, tests to evaluate the effect of simultaneous pacing of both ventricles have elicited a significant improvement of cardiac performance.

Methods. Acute hemodynamic study was conducted in 18 patients with severe CHF (New York Heart Association class III and IV) and major intraventricular conduction block (IVCB) (QRS duration = 170 ± 37 ms). Using a Swan-Ganz catheter, pulmonary artery pressure, pulmonary capillary wedge pressure (PCWP) and cardiac index (CI) were measured in different pacing configurations: atrial pacing (AAI) mode, used as reference, single-site right ventricular DDD pacing and biventricular pacing with the right ventricular lead placed either at the apex or at the outflow tract.

Results. The CI was significantly increased by biventricular pacing in comparison with AAI or right ventricular (RV). DDD pacing (2.7 ± 0.7 vs. 2 ± 0.5 and 2.4 ± 0.6 l/min/m², p < 0.001). The PCWP also decreased significantly during biventricular pacing, compared with AAI (22 ± 8 vs. 27 ± 9 mm Hg; p < 0.001).

Conclusions. This acute hemodynamic study demonstrated that biventricular DDD pacing may significantly improve cardiac performance in patients with IVCB and with severe heart failure, in comparison with intrinsic conduction and single-site RV DDD pacing.

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Methods

Inclusion criteria. The following criteria were required for inclusion in the study:

Age >18 and <80 years
Stable sinus rhythm
Severe CHF, as defined by:
   NYHA class III or IV, in stable condition for at least 4
   weeks despite medical treatment including at least di-
   uretics and ACE inhibitors at doses individually opti-
   mized for each patient
Left ventricular ejection fraction (LVEF) as assessed by
   echocardiography, or radionuclide angiography ≤35%
Left ventricular dilatation defined by an echocardiographic
   end-diastole diameter ≥60 mm
Intraventricular conduction blocks defined by QRS duration
   ≥120 ms, as measured from three leads at least on
   surface ECG in spontaneous sinus rhythm
Ischemic or idiopathic cardiomyopathy according the re-
   sults of previous coronary angiography
Written informed consent approved by our institutional
   Ethics Committee.

Exclusion criteria. The following criteria were required for exclusion in the study:

High degree (2nd or 3rd) AV block
Suspected acute myocarditis
Significant and correctable valvular heart disease
Acute coronary syndrome less than 3 months before
Percutaneous coronary angioplasty or coronary artery by-
   pass grafts within the preceding 12 months

Study protocol. Temporary cardiac pacing. Four 6F quad-
   ripolar electrode catheters (Bard Electrophysiology, CR Bard,
   Billerica, Massachusetts) were inserted through the femoral or
   the subclavian vein and placed at (Fig. 1):
   
   the right atrial appendage to pace the right atrium (RA)
   the mid or distal part of the coronary sinus (CS) to pace the
      left atrium (LA)
   the RV apex (RVA) and the RV outflow tract (RVOT) alter-
      natively to pace the right ventricle
   a lateral or posterolateral vein over the LV free wall
      through the CS to pace the left ventricle.

Electrode catheters were connected to an external DDD
   pacemaker (Biotronik GmbH and Co., Berlin, Germany). To
   eliminate any potential influence of individual intra- and
   interatrial conduction time on left atrial systole and on left AV
   synchrony, the two atria were paced simultaneously by con-
   necting the distal electrode of the coronary sinus lead to the
   negative pole of the atrial entry of the external pacemaker
   and the distal electrode of the right atrial lead to the positive pole.
   The energy delivered was programmed as twice the biatrial
   pacing threshold.

   To eliminate any variation of heart rate, we permanently
   overdrive the intrinsic atrial rate with a pacing rate (which was
   kept constant all along the study) of 10 beats per minute above
   spontaneous sinus rate in each patient. During DDD pacing,
   AV delay in each patient was set to the longest programmable
   value, ensuring complete and permanent ventricular (or biven-
   tricular) capture.

   Biventricular pacing was obtained by connecting the distal
   electrode of the LV lead to the negative pole of the ventricular
   entry and the distal electrode of the RV lead (placed alterna-
   tively at RVA and RVOT) to the positive pole. The energy
delivered was programmed to be twice the biventricular pacing
threshold.
Capture of both atria and both ventricles was confirmed by a significant shortening in paced P/QRS duration with typical modifications of morphology and axis on the surface ECG.

Three different pacing modes were compared in random order in each patient:

- Biatrial pacing in the atrial pacing (AAI) mode, serving as the reference
- Optimal single RV DDD pacing: after assessing the two different RV pacing sites, RV apex (RVA) and RVOT, the optimal RV DDD mode was defined as the one providing the highest value of cardiac index (CI) in each patient
- Optimal biventricular RV DDD pacing: after assessing two different combinations of simultaneous biventricular pacing, RV apex + LV and RVOT + LV, the optimal biventricular DDD mode was defined as the one producing the shortest duration of the paced QRS complex on surface ECG, in each patient.

**Hemodynamic study.** Patients were examined while in a supine, nonedematous, postabsorptive state. A thermodilution Swan-Ganz catheter (Baxter Healthcare, Edwards Critical-Care Division, Irvine, California) was inserted via the jugular vein and positioned in the pulmonary artery so that pulmonary capillary wedge pressure (PCWP) recordings were obtained upon balloon inflation. Cardiac output was recorded in triplicate or until three recordings within 10% of each other were obtained. Blood pressure was measured by cuff sphygmomanometer.

Pressures and CO were measured 10 min after the initiation of each new pacing mode. Pressure curves were analyzed by two blinded independent observers.

**Statistical analysis.** Each patient was his or her own control. Data are presented as means ± SD. A repeated measures analysis of variance (ANOVA) was used to compare hemodynamic data at baseline (AAI mode) and during single-site DDD pacing and during biventricular DDD pacing mode. The Wilks’ lambda statistic test was used to determine whether the modes differed and the method of contrasts with the resulting F-ratio to compare the modes pairwise. To adjust for the fact that we make three comparisons, a nominal p value of 0.05/3 (=0.0167) was used (Bonferroni method).

### Results

**Patients’ data (Table 1).** Eighteen patients, mean age 65 years, were included in the study. Most of them (14/18 = 78%) were in NYHA class IV; the 4 others were in class III. All patients were treated by ACE inhibitors and diuretics at the maximal tolerated doses. Digoxin was also prescribed in 60% of cases. Mean LVEF was 19 ± 4.5%. The LV systolic dysfunction was of ischemic origin in only 2 cases, 14 patients had an idiopathic dilated cardiomyopathy (DCM) with normal or coronary angiograms, 1 patient had a corrected valvular heart disease and the remaining patient had a sarcoidosis.

During normal sinus rhythm, the average PR interval was slightly prolonged (221 ± 51 ms). The mean QRS duration was 170 ± 37 ms with left bundle branch block morphology in all cases and left axis deviation (≥−30°) in 14 patients. The severity of heart failure was confirmed by hemodynamics in baseline conditions (AAI pacing mode). Cardiac index (CI) on average was 2 ± 0.4 l/mn/m². Mean pulmonary arterial pressure (PAP), PCWP, and V-wave values were 40 ± 11, 27 ± 9 and 33 ± 11 mm Hg, respectively.

**Influence of the pacing mode on QRS duration (Table 2).** Single-site RV-DDD pacing significantly increased QRS duration by comparison with AAI pacing (p < .01). Conversely, biventricular DDD significantly decreased QRS duration by comparison with either the reference mode (p < .01) or RV-DDD pacing modes (Fig. 2).

**Hemodynamic results.** In the 15 patients in whom both RV pacing sites were evaluated, the “optimal” performance in single-site RV-DDD pacing was observed in 9 cases when the RV lead was placed at the outflow tract and in 6 cases when the lead was placed at the apex. In three patients, only one site was tested (RVA in one and RVOT in two [patients 6, 9 and 16]). The AV delay did not significantly differ between these two configurations. With DDD biventricular pacing, the “optimal” configuration was LV + RVOT in 11 patients and LV + RVA in the other 7 patients. In nine patients, the location of the RV lead was different when comparing single-site RV DDD pacing and biventricular DDD pacing.

**RV-DDD pacing versus baseline (AAI mode) (Tables 2 and 3).** The RV-DDD pacing mode induced a statistically significant increase in CI (p < 0.01), on average +18.5% in comparison with baseline (2.4 ± 0.6 and 2 ± 0.4 l/mn/m², respectively).

Mean pulmonary capillary wedge pressure (PCWP) was significantly decreased in RV-DDD pacing mode, with a mean reduction of 11% (24 ± 8 vs. 27 ± 9 mm Hg, respectively).

The same observation was found concerning the V-wave, with a mean reduction of 7% (p < 0.01).
Biventricular-DDD pacing versus baseline (AAI mode) (Tables 2 and 3). Comparing the “optimal” biventricular DDD pacing mode with baseline (AAI pacing) in each patient revealed a highly significant benefit in terms of cardiac output increase (2.7 ± 0.7 vs. 2 ± 0.4 l/min/m², +35%; p < 0.001) and of mean PCWP, with a mean decrease of 18.5% (22 ± 8 vs. 27 ± 9 mm Hg; p < 0.001). The V-wave was also significantly reduced in biventricular pacing mode with a mean value of 21% (26 ± 10 vs. 33 ± 11 mm Hg; p < 0.001) (Fig. 3).

Biventricular DDD pacing versus conventional RV DDD pacing (Tables 2 and 3). Comparing the hemodynamic effects of “conventional” DDD RV single-site and biventricular DDD pacing modes elicited interesting results, including a slight but statistically significant (p < 0.01) improvement of CI (+12.5%), mean PCWP (−9%) and V-wave (−9%).

Responders versus nonresponders. Responders were defined as patients in which CI increased by 10% or more and PCWP decreased by 10% or more with biventricular DDD pacing compared to baseline (AAI mode). According to this definition, 12 patients were responder and 6 were nonresponders. From the different parameters studied (Table 4), univariate analysis showed that the only predictive factor of hemodynamic improvement was baseline LV ejection fraction. The LVEF was significantly lower in responder as compared to nonresponder patients (17 ± 27% vs. 21.6 ± 5.8%; p = 0.036). In contrast, PR interval, QRS duration and the presence of left axis deviation had no predictive value.

Discussion

Our study was aimed at assessing the acute hemodynamic effects of the best mode of DDD pacing therapy in patients with chronic CHF. Simultaneous biaatrial pacing and simultaneous biventricular pacing with an “optimal” AV delay in each patient were expected to optimize AV synchrony in the left heart as well as the ventricular activation sequence. The results of that method appeared to be positive because under the best pacing configuration for each individual patient, biventricular DDD pacing increased cardiac output by 35% (p < 0.001) on average, relative to AAI pacing, and by 12.5% relative to “optimal” RV single-site DDD pacing (p < 0.01). Mean and peak PCWP decreased on average by 18.5% (p < 0.001) and 21% (p < 0.001), respectively, relative to AAI pacing. However, response to pacing still varies much between patients. Twelve of the 18 patients can be considered as good responders when defined as an increase in cardiac output and PCWP reduction by more than 10%. Six patients—one-third of the population studied—were not improved. Thus, this preliminary study did not identify any predictive criteria of the type of response to biventricular DDD pacing, except that the LVEF was significantly lower (p < 0.04) in responders than in nonresponders.
nonresponders. There was a trend toward a longer mean PR interval and QRS duration in responders, although the difference was not statistically significant.

**Previous experience with conventional DDD pacing in CHF.** Short-term studies conducted in the early 1990s suggested that patients in normal sinus rhythm with severe CHF related to chronic LV systolic dysfunction and without any conventional indication for permanent cardiac pacing could benefit from DDD pacing with short AV delay programming (2,7), their symptoms and LVEF being significantly improved. The ventricular lead was conventionally placed at the RV apex (RVA). This beneficial effect was primarily attributed to the optimization of LV filling by significant prolongation of the ventricular filling time and reduction of presystolic mitral regurgitation (8). The study by Nishimura et al. (6), however, showed that DDD pacing could significantly improve cardiac performance only in patients with a long PR interval on surface ECG and evidence of major AV dysynchrony in the left heart. Responder patients were also characterized by a very short LV filling time and a long duration of mitral regurgitation in spontaneous rhythm. These preliminary data were only focused on the effect of DDD pacing on AV synchrony. At that time the general view was that the potential detrimental effects of ventricular pacing at the RVA on LV function (9,10) were largely counterbalanced by the benefits of extended filling time (8). However, the interest for conventional short AV delay DDD pacing was quickly damped by results from prospective studies, either controlled or uncontrolled, showing no improvement or even deterioration with pacing (4,5).

**Figure 3.** Acute hemodynamic effects of temporary biventricular DDD pacing in a class III patient with ischemic cardiomyopathy. Switching from AAI to biventricular DDD pacing at the same pacing rate produces an instantaneous decrease in pulmonary capillary wedge pressure (PCWP) (mean and systolic peak) and a 32% increase in cardiac output, while the QRS duration is decreased by 35% (200 to 130 ms).

**Table 3. Individual Hemodynamic Data in the Different Pacing Modes (AAI, DDD RVA, DDD RVOT, DDD Biventricular)**

<table>
<thead>
<tr>
<th>Patient</th>
<th>AAI</th>
<th>DDD RVA</th>
<th>DDD RVOT</th>
<th>BIV</th>
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<tr>
<td>CI (l/min/m²)</td>
<td>mPCWP (mm Hg)</td>
<td>V-Wave (mm Hg)</td>
<td>CI (l/min/m²)</td>
<td>mPCWP (mm Hg)</td>
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<td>2.9</td>
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CI = Cardiac index; mPCWP = mean pulmonary capillary wedge pressure; RVA = right ventricular apex; RVOT = right ventricular outflow tract; BIV = biventricular.

**Table 4. Comparison of Responder and Nonresponder Patients**

<table>
<thead>
<tr>
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<th>Responders (n = 12)</th>
<th>Nonresponders (n = 6)</th>
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<tr>
<td>QRS ms</td>
<td>175 ± 33</td>
<td>163 ± 44</td>
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<tr>
<td>PR ms</td>
<td>234 ± 44</td>
<td>220 ± 38</td>
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<tr>
<td>Axis°</td>
<td>−20 ± 36</td>
<td>−30 ± 56</td>
<td>0.6</td>
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<tr>
<td>LVEF %</td>
<td>17 ± 2.7</td>
<td>21.6 ± 5.8</td>
<td>0.036</td>
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LVEF = Left ventricular ejection fraction.
Alternative ventricular pacing sites. Further studies assessed the potential interest of improving both the AV synchrony and the activation sequence of the paced ventricle. A first attempt in this direction consisted in pacing the right ventricle at alternative sites, especially the RV outflow tract (RVOT) or the septal wall. Cowell et al. (11) studied the acute hemodynamic effects of (DDD) pacing at two different sites in RV, the apex and the septum close to the His bundle area in 15 patients with normal sinus rhythm and chronic CHF associated with poor LV function. Cardiac output increased significantly with RV septal DDD pacing in comparison to no pacing (4.9 ± 8 l/min vs. 4.1 ± 7 l/min; p < 0.04), but the difference was not statistically significant when compared with RV apical DDD pacing (4.4 ± 7 l/min; p = NS). This trend toward better cardiac performance with RV septal DDD pacing was not confirmed by a recently published cross-over randomized study by Gold et al. (12), who compared the hemodynamic effects of temporary RV septal (or RVOT) DDD pacing with spontaneous sinus rhythm in 13 CHF patients. Overall, pacing did not significantly improve cardiac output and right heart pressures. Subgroup analysis did not reveal any influence of the etiology of LV dysfunction, either idiopathic or ischemic, nor of the presence of a long PR interval on results.

Rationale for multisite pacing in CHF. In our study we deliberately selected patients with major intraventricular conduction block in spontaneous sinus rhythm. This type of abnormality is common in patients with dilated cardiomyopathy, either idiopathic or of ischemic origin. In Wilensky’s study (13), 82% of patients had significant intraventricular conduction disturbances on the last ECG recorded within 60 days before death. Among the patients who presented with conduction abnormalities at baseline, 68% had progressive disturbances in the time period studied. The mean QRS duration increased from 100 ± 20 ms at the first examination to 130 ± 30 ms at the end of follow-up. But very long QRS duration can occur, as in our series. Complete bundle branch block (BBB) was seen in 38% of patients, principally left BBB (29%). Right BBB was rare (9%) but was associated with left axis deviation in two-third of cases, indicating a probable association with left anterior fascicular block. Overall, left QRS axis deviation greater than −30° was observed in 65% of patients in the group.

The hemodynamic consequences of abnormal ventricular activation in DCM patients were extensively studied by Xiao et al. (14–16), who analyzed, using continuous-wave Doppler, the characteristics of the LV pressure pulse derived from the time course of functional mitral regurgitation. In 50 DCM patients with QRS duration between normal and extremely long (190 ms) and averaging 110 ms, a positive correlation was found between the QRS duration and the overall duration of mitral regurgitation LV contraction time (the time interval from Q to peak pressure), and to peak +dp/dt, and negatively with the peak rate of rise in LV pressure. These data show that the wider is the QRS complex, the longer are the LV contraction and relaxation times and poorer the LV systolic performance. Furthermore, prolonged isovolumic contraction and relaxation times induced a proportionate decrease in LV filling time to a critical value of 200 ms or less in patients with the longest QRS duration. The morphology (right or left BBB, or indefinite intraventricular conduction block) and axis of the QRS complex seem to have no direct influence on the magnitude of the abnormalities observed. However, Xiao et al. (14) noted that left axis deviation was associated with the longest QRS duration and thus with more severe electromechanical alterations. All these observations account for the presence of major delay and uneven contraction and relaxation in patients with poor LV function and a high degree conduction block within the ventricle.

Right ventricular pacing enhances such asynchrony and thus delays LV activation. These effects are all the more important as cardiac function is altered. Endocardial mapping studies (17,18) have shown that the earliest local activation time, the total LV endocardial activation time and the total duration of LV electrical activity were significantly longer in patients with structural heart disease than those with a normal heart and that the greater values were noted in patients with coronary artery disease with previous infarction scars. These studies have also shown that except in the patient subgroup with previous septal scars, the site of the latest LV activation during RV apical pacing was the LV posterior or posteroinferior base in the vast majority of patients with chronic LV dysfunction (Fig. 4). This explains why we chose to pace the left ventricle at its posterior base by placing the lead at the ostium of a lateral or posterolateral vein of the left ventricle in our series, which included a vast majority of idiopathic dilated cardiomyopathies. The aim was to simultaneously pace the two ventricles at the sites of the earliest activation in the right ventricle and of the latest activation in the left ventricle, thus expecting to best correct the activation and contraction asynchrony. This objective of optimal ventricular resynchronization is the rationale for treating heart failure by simultaneous biventricular pacing in patients with major
intraventricular conduction block. The significant reduction of QRS duration observed in this study under both biventricular DDD pacing modes, as compared with the two single-site RV-DDD and AAI pacing, bolstered the hypothesis that LV activity was resynchronized. The issue is to establish whether this partial correction of ventricular activation asynchrony is accompanied by an improvement of cardiac performance or not.

Acute hemodynamic effects of biventricular pacing. The first hemodynamic study on the acute effects of biventricular pacing did not address heart failure but rather the immediate postoperative consequences of aortocoronary bypass graft (19). In the study by Foster (19), four different pacing modes were randomly tested in 18 patients with LVEF >40%: AAI, RV-DDD, LV-DDD and biventricular DDD. Epicardial leads were set on the anterior face of both ventricles either side of the septum. Results showed a significant increase in cardiac output and a significant decrease in systemic vascular resistances under biventricular DDD pacing in comparison to other pacing modes.

These results are in agreement with those of our own study in CHF patients, but they partially differ from the recent report by Blanc et al. (20), who compared the acute hemodynamic effects of single-site RV pacing at the apex, of single site LV pacing, of simultaneous biventricular pacing and of intrinsic conduction in 23 patients with severe heart failure. Both LV pacing and biventricular pacing produced a significant decrease in PAP and PCWP, and a significant increase in arterial pressure. Cardiac output was not monitored in this study. Blanc et al. (20) did not find any significant difference between LV pacing alone and biventricular pacing. We can note that in the Blanc study, the LV was paced endocardially, whereas in our study the LV was paced epicardially at the posterolateral base corresponding to the site of latest LV activation. We can presume that these two approaches may result in different electrophysiologic and hemodynamic effects.

Study limitations. One of the limitations of our study is that biventricular pacing was acutely tested and we cannot predict the long-term response of chronic biventricular pacing. Furthermore, this study did not provide answers to a number of other questions: What are the underlying mechanisms of that beneficial hemodynamic effect? What is the optimal configuration to pace both ventricles? Additional studies using the most adequate imaging techniques are needed.

Conclusions. This acute study demonstrated that, compared with intrinsic rhythm and single-site RVDD pacing, biventricular DDD pacing may significantly improve cardiac performance in patients with major intraventricular conduction block and severe CHF related to chronic LV dysfunction. Such encouraging results, adding to those of the first attempts at permanent pacing (21,22) in patients with chronic heart failure, are an encouragement to initiate controlled studies to validate that novel therapeutic method.

References