Evaluation of left bundle branch block as a reversible cause of non-ischaemic dilated cardiomyopathy with severe heart failure. A new concept of left ventricular dyssynchrony-induced cardiomyopathy

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Keywords
dilated cardiomyopathy; congestive heart failure; resynchronization therapy; pacing; left bundle branch block; left ventricular dyssynchrony

Abstract

Objectives We sought to determine if amelioration of left bundle branch block (LBBB)-induced contraction disturbances achieved by left ventricular (LV)-based pacing could result in sustained reversal of severe LV dysfunction in certain patients with chronic heart failure due to non-ischaemic cardiomyopathy.

Background It has been shown that LBBB induces asynchronous contraction of LV. However, whether such a functional contraction disturbance, if present for an extended period of time, could account for a dilated cardiomyopathy remains unknown.

Methods The study population comprised 29 patients with dilated cardiomyopathy, sinus rhythm, LBBB and severe heart failure (14 patients in New York Heart Association (NYHA) class III and 15 in class IV). Patients were followed prospectively after resynchronization therapy. LV function was considered to be normalized when ejection fraction (EF) was >50% at 1 year.

Results Five among the 29 patients (17%; group 1) demonstrated both complete normalization of LV function following resynchronization therapy (EF: from 19 ± 6 to 55 ± 3%, P = 0.001) and clinical improvement (mean NYHA class: 3.4 ± 0.5 to 1.8 ± 0.4, P = 0.02; 6-min walk distance: 300 ± 136 to 444 ± 75 m, P = 0.12; peak VO2: 11.9 ± 4 to 15.8 ± 2 ml/min/kg, p = 0.03). Among the remaining 24 patients (83%; group 2) EF improved but did not normalize (from 21 ± 8 to 23 ± 11%, ns).

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Baseline clinical features could not predict which patients would exhibit the reversal of LV dysfunction.

**Conclusions**
Normalization of LV function 1 year after resynchronization therapy in a small but important number of patients suggests that long-standing LBBB may be a newly identified reversible cause of cardiomyopathy.

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In a great proportion of afflicted patients, non-ischaemic dilated cardiomyopathy (DCM) leads to congestive heart failure (CHF) and death within a limited period of time [1]. Pharmacological treatments have been shown to improve the prognosis of these patients statistically, but quality of life and survival remain poor [2]. Currently, long-term consequences of DCM can only be altered substantially by heart transplantation, a procedure limited to some few hundreds of patients per year worldwide, or by identifying a reversible cause of the DCM. At present these reversible causes are largely restricted to alcoholic cardiomyopathy, when total withdrawal from alcohol is obtained [3,4], and to tachycardiomyopathy after termination of the tachycardia [5,6]. Among the latter, the best example is reversed DCM associated with persistent atrioventricular reciprocating tachycardia in children [7,8].

Left bundle branch block (LBBB) is known to impair the mechanical function of the left ventricle (LV) [9,10]. Further LBBB is often associated with DCM, although it is generally assumed to be secondary to the underlying disease process. However, the possibility exists that in some patients the LBBB-induced abnormal LV contraction pattern could, over the long-term, induce DCM. The only way to confirm this hypothesis is to verify, as in tachycardiomyopathy, if LV function returns to normal after essential “reversal” of LBBB. With this concept in mind, LV pacing was utilized in this study to ameliorate the conduction disturbance, and the impact of this intervention on LV function was examined over time.

**Methods**

**Study population**

This prospective observational study was conducted on consecutive patients admitted to our department for evaluation and treatment of non-ischaemic DCM. All patients exhibited severe CHF (New York Heart Association class III or IV lasting for more than 6 months) in spite of optimal medical treatment, permanent LBBB (present on multiple electrocardiograms recorded at minimum within the preceding 1 year), and a successfully implanted LV-based pacing system in the absence of bradycardia indication for pacing.

Non-ischaemic DCM was diagnosed when all of the following conditions were fulfilled: (1) normal coronary angiography, (2) LV end-diastolic diameter > 60 mm, and (3) LV ejection fraction (LVEF) < 0.40 measured by radionuclide ventriculography. Only patients with permanent LBBB and a QRS duration > 140 ms were included. Patients with a potential reversible cause for their DCM were excluded, particularly those who had a chronic alcoholic consumption > 80 g/day, and those with permanent atrial fibrillation, thyroid dysfunction or suspected myocarditis. Patients previously implanted with pacemakers or defibrillators were also excluded.

**Objectives of the study**

The objective of the study was to ascertain whether DCM, responsible for severe CHF in patients with chronic LBBB, could be reversed at least in some cases when disappearance of LBBB was obtained by LV-based pacing. For the purposes of this report, normalization of LVEF was considered the most appropriate assessment of reversion of DCM [5,6,8]. The mean normal value of LVEF measured by radionuclide angiography in our hospital is 55 ± 3%, and “normal” is considered to be values within 2 standard deviations of the mean. Consequently, in the present study, patients who at the 12-month follow-up visit had a LVEF > 50% were considered to have had ‘normalization’ of LV function. The second goal of the study was to determine if certain clinical features would usefully predict which patients would exhibit normalization of LV function.

**Implantation procedure**

The transvenous approach for permanent LV resynchronization pacing used in our centre has been previously described in detail [11,12]. The LV lead
was placed in a lateral coronary vein where the latest local electrogram at an accessible site was recorded relative to the QRS onset and where the pacing threshold was considered adequate without diaphragmatic contraction. The atrial lead was positioned in the right atrial appendage. The atrio-ventricular delay was individually programmed before discharge using previously published echocardiographic criteria [13].

Examination protocol

After informed consent was obtained patients were examined at baseline (within 2 weeks before implantation) and the following data were collected: New York Heart Association functional class, QRS duration, 6-min hall walk distance, peak oxygen consumption during a morning cardiopulmonary exercise test when feasible (some patients in class IV were unable to perform this test), and LV ejection fraction (EF) measured by gated equilibrium radionuclide ventriculography.

A complete echocardiographic examination was performed but, for the purpose of this report, only measurements of end-diastolic and end-systolic diameters, fractional shortening and mitral regurgitation area are provided. Implantation of the device and follow-up of the patients including history, clinical and echocardiographic data were performed by two different groups of physicians in the cardiology department. Radionuclide ventriculography and cardiopulmonary exercise test were performed by physicians totally independent of the cardiology department and blinded to the status of the patients and the goals of the study. In order to exclude the possibility that altered LVEF was exclusively the effect of pacing and not genuine remodelling, echocardiography and radionuclide ventriculography were repeated 3–9 h after cessation of pacing in patients with EF > 50% at the 1-year follow-up.

Follow-up

Patients were discharged 5–6 days after device implantation. They were advised to take their pharmacological treatment carefully and not to modify this treatment without consulting a physician of the cardiology department (their general practitioners were similarly advised). Follow-up visits were scheduled at 1, 6, and 12 months after device implantation, and every 6 months thereafter. During these visits the appropriate functioning of the device was carefully verified. Further, the adequacy of LV capture was assessed by 24-h Holter monitoring, and the examinations performed at baseline were repeated.

Statistical analysis

Values are expressed as mean ± standard deviation. Comparison of parameters between baseline and the 12-month visit was made using Student’s paired t-test. Comparison of LVEF between each follow-up visit was performed using a one way analysis of variance. Comparison of baseline data between patients with and without normalization of LV function was made using an unpaired t-test. Differences were considered significant when the P value was <0.05.

Results

Population

Between 1996 and 2002, 29 patients (19 males; mean age 70 ± 7.7 years) who fulfilled the inclusion criteria were successfully implanted with a permanent LV-based pacing device (LV only: 24 patients; biventricular: five patients). Among the study group, five patients (17%; group 1), whose baseline characteristics are shown in Table 1, showed normalization of LV function during pacing.

<table>
<thead>
<tr>
<th>Patient (no.)</th>
<th>Age</th>
<th>Gender</th>
<th>NYHA class</th>
<th>Heart failure duration (months)</th>
<th>Left bundle branch block duration (ms)</th>
<th>QRS duration (months)</th>
<th>Left ventricular ejection fraction (%)</th>
<th>Peak oxygen consumption (ml/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59</td>
<td>F</td>
<td>IV</td>
<td>120</td>
<td>120</td>
<td>230</td>
<td>11</td>
<td>5.8</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>M</td>
<td>III</td>
<td>36</td>
<td>36</td>
<td>140</td>
<td>18</td>
<td>14.5</td>
</tr>
<tr>
<td>3</td>
<td>74</td>
<td>F</td>
<td>III</td>
<td>16</td>
<td>16</td>
<td>180</td>
<td>16</td>
<td>14.0</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>F</td>
<td>IV</td>
<td>36</td>
<td>36</td>
<td>175</td>
<td>26</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>76</td>
<td>M</td>
<td>III</td>
<td>42</td>
<td>42</td>
<td>180</td>
<td>26</td>
<td>16.2</td>
</tr>
<tr>
<td>Mean</td>
<td>69.6 ± 7</td>
<td></td>
<td>50 ± 40</td>
<td>50 ± 40</td>
<td>181 ± 32</td>
<td>19 ± 6</td>
<td>11.9 ± 4</td>
<td></td>
</tr>
</tbody>
</table>

PT = patient, NYHA = New York Heart Association.
showed normalization of their LVEF (from 19 ± 6 to 55 ± 3%, \( P = 0.001 \)) at the 12-month follow-up visit. These individuals had also exhibited progressive increase in LVEF at each intermediate visit (Fig. 1) and a parallel improvement in their clinical status, exercise tolerance and echocardiographic data (Table 2). On the other hand, despite a significant functional improvement (New York Heart Association class from 3.5 ± 0.5 to 2.8 ± 0.9, \( p < 0.001 \)), 24 patients (group 2) did not demonstrate any significant LV dysfunction reversal (LVEF from 21 ± 8 to 22.8 ± 11%, ns) at the 12-month visit or at the last intermediate follow-up visit for the patients who died during the first year. Seven patients (24%), all from group 2, died before the 12 months visit (six patients from intractable CHF and one patient from non-cardiac cause).

The five group 1 patients received conventional medical treatment before implantation: diuretics and angiotensin converting inhibitors or angiotensin receptor antagonists in all, digitalis in one patient, beta blockers in three patients. In one patient beta blockers were contraindicated due to chronic obstructive pulmonary disease. In another patient beta blockers were discontinued due to initial worsening of CHF; however, this drug was successfully prescribed 6 months after implantation of the LV-based pacing since LV function had already dramatically improved. This was the only significant change in medical treatment in this group during the 12-month follow-up period.

### Acute results after cessation of LV-based pacing

In the five patients with “normalization” of EF during LV-based pacing, echocardiographic and electrocardiographic parameters measured a few hours after cessation of pacing were unchanged compared with those observed during pacing. Furthermore, we observed that the intrinsic QRS duration tended to decrease in all group 1 patients between baseline and 1-year (182 ± 32 to 162 ± 19 ms, \( P = 0.07 \)).

### Table 2  Comparison of data between baseline and the 12 months follow-up visit in patients with normalization of LV function during pacing (group 1, \( n = 5 \)) and between baseline and the last follow-up visit in patients without normalization of LV function (group 2, \( n = 24 \)), and comparison of mean data between the two groups

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 5)</th>
<th></th>
<th></th>
<th></th>
<th>Group 2 (n = 24)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
<td>( P )</td>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
<td>( P )</td>
<td></td>
</tr>
<tr>
<td>NYHA class (mean)</td>
<td>3.4 ± 0.5</td>
<td>1.8 ± 0.4</td>
<td>0.016</td>
<td></td>
<td>3.5 ± 0.5</td>
<td>2.8 ± 0.9</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>6-min test distance (m)</td>
<td>300 ± 136</td>
<td>444 ± 75</td>
<td>0.12</td>
<td></td>
<td>342 ± 117</td>
<td>392 ± 123</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Peak oxygen (mL/min/kg)</td>
<td>11.9 ± 4.3</td>
<td>15.8 ± 2</td>
<td>0.03</td>
<td></td>
<td>111 ± 1.7</td>
<td>12 ± 2.6</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>181 ± 32</td>
<td>146 ± 21</td>
<td>0.09</td>
<td></td>
<td>176 ± 20</td>
<td>176 ± 18*</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>19 ± 6</td>
<td>55 ± 3</td>
<td>0.001</td>
<td></td>
<td>21 ± 8</td>
<td>22.8 ± 11</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Left ventricular diastolic diameter (mm)</td>
<td>78.0 ± 6.1</td>
<td>57.2 ± 5.2</td>
<td>0.002</td>
<td></td>
<td>76 ± 9</td>
<td>75 ± 8</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Left ventricular fractional shortening (%)</td>
<td>13.6 ± 2.7</td>
<td>31.0 ± 2.7</td>
<td>0.0001</td>
<td></td>
<td>11.9 ± 4</td>
<td>13.5 ± 5.3</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>Mitral regurgitation area (cm²)</td>
<td>9.1 ± 4.4</td>
<td>1.2 ± 1.8</td>
<td>0.001</td>
<td></td>
<td>8.3 ± 5.4</td>
<td>7.1 ± 1.4</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>PR interval (ms)</td>
<td>178 ± 23</td>
<td>226 ± 30*</td>
<td></td>
<td></td>
<td>21/3</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

\( *P < 0.01, \) NYHA = New York Heart Association.
Long-term follow-up of patients with LVEF > 50%

Among the group 1 patients, three were subsequently followed between 1 and 2 years without deterioration in their clinical and LVEF status. The two remaining patients were followed for longer periods and had a complete evaluation 3 and 7 years after implantation, both remained asymptomatic, and had LVEFs and end-diastolic diameters of 57% and 48 mm (patient no. 2), and 64% and 51 mm (patient no. 1), respectively.

Predictive factors of LV dysfunction reversal

Baseline features did not provide a precise means of identifying which LBBB DCM patients would exhibit an improved EF with LV-based pacing (Table 2). In essence all baseline parameters were identical in the two groups except for the PR interval which was significantly shorter (P = 0.002) in group 1 (178 ± 23 versus 226 ± 30 ms). Of note, however, despite identical baseline QRS duration and similar ventricular pacing configuration (uni-LV or biventricular), the paced QRS duration just after implantation was also shorter in group 1 than that was the case for group 2 (146 ± 21 versus 176 ± 18 ms, P = 0.003). Further, location of the LV leads in group 1 patients did not differ from group 2 patients.

Discussion

Usually LBBB is considered as a marker indicative of underlying structural cardiac disease, but may become evident before development of clinical manifestations of DCM [14]. This study suggests that in certain individuals LBBB per se may contribute to the development of DCM, giving rise to a new concept of LBBB-induced cardiomyopathy.

Did the study population exhibit idiopathic cardiomyopathy?

Our patient population had severe non-ischaemic DCM as demonstrated by baseline clinical characteristics (New York Heart Association class III or IV), mean LVEF and end-diastolic diameter of 21% and 78 mm, respectively, and normal coronary angiography. Further we carefully excluded the known reversible causes of cardiomyopathy, particularly patients with alcoholic abuse and thyroid dysfunction.

Some cases of clear improvement in idiopathic DCM have been reported [15,16]. However, “complete” recovery is rare and when it occurred the patients were usually young and had a short duration of symptoms, neither of these characteristics apply to our study population. In our cases the long-lasting (over several years) evolution of CHF symptoms essentially excludes the possibility of either “spontaneous” recovery, or of the DCM being of acute infectious or toxic myocarditis origin. Furthermore, modification of pharmacological treatment was avoided during follow-up except in one case in whom beta blockers previously not tolerated could be subsequently introduced after marked improvement in LVEF at 6 months follow-up. Consequently, it could be reasonably assumed that our patients indeed had exhibited severe idiopathic DCM upon entry into this study.

Was the procedure to validate the concept of LBBB-cardiomyopathy satisfactory?

From time to time certain definite causes of DCM have been identified and the procedure to validate the causal relationship has always been well defined: observation of “normalization” of a markedly depressed LVEF following the withdrawal of the presumed causative factor. For example, this procedure was followed to verify the concept of tachycardiomyopathy that emerged when young patients with permanent junctional tachycardia and DCM-induced CHF were cured by ablation of the reentrant tachycardia circuit [5,6,8]. The concept of alcoholic cardiomyopathy was verified using the same protocol [3,4]. Consequently it is not unreasonable to conclude that long-term reversal, during LV-based pacing, of a severely depressed LVEF in some patients with idiopathic DCM and LBBB suggests the concept of LBBB-induced cardiomyopathy.

Was the reversal of LV dysfunction real?

Our findings (Table 2 and Fig. 1) indicate that the reversal of LV dysfunction encompassed not only LVEF, but also end-diastolic diameter and mitral regurgitation. A remaining important question to consider is whether this reversal is complete or not. It seems complete, comparing baseline values of radionuclide angiography and echocardiography with those at the 12-month follow-up, supporting the view that the cardiac status of the group 1 patients could be considered “normal”.

Was the procedure to validate the concept of LBBB-cardiomyopathy satisfactory?
Possible mechanism of LV dysfunction reversal

It has long been known that LBBB induces an abnormal LV contraction pattern resulting in LV dysfunction with a decrease in EF and dP/dt [9,10]. Whether this abnormal contraction pattern could provoke, over time, DCM remains unknown, but the possibility is supported by Framingham data [14] in which LBBB was reported to precede appearance of CHF in a subset of individuals.

The findings observed in our patients strongly suggest that acquired LBBB may provoke, possibly in certain susceptible individuals, DCM. Amelioration of LBBB induced by LV-based cardiac resynchronization therapy may substantially diminish the mechanically deleterious effects of the intraventricular dyssynchrony. The outcome is progressive improvement in LV function. Further, the observation that after cessation of pacing the QRS duration tended to decrease in group 1 patients supports the notion that LBBB-induced dysynchrony leads to a form of LV dysfunction which aggravates intraventricular conduction disturbances. Presumably LV-based pacing interrupts this vicious circle and thereby tends to improve intraventricular conduction over time.

Predictive factors of LV dysfunction reversal

The small number of patients who normalized their LV function limits identification of predictors of reverse remodelling. It should be stressed that many potential discriminating factors have not been analyzed either because they were not included in the database or they are still undetermined. However, the shorter PR interval in group 1 is an observation that should be evaluated in subsequent studies.

Unresolved issues

There remain many unresolved issues with respect to the LBBB-induced DCM issue. Why some patients with long-term evolution of well-defined DCM and CHF had, after LV pacing, normalization of their LV function while others did not is unclear. What are the environmental or genetically-transmitted factors responsible for different outcomes? Should LBBB-dysynchrony be prevented by cardiac resynchronization therapy before appearance of overt signs of CHF?

Limitations

The small number of patients included in this report limits its interpretation. Nonetheless, our primary goal was just to assess, in a selected population with idiopathic DCM and LBBB, if some patients could normalize their LV function during LV-based pacing thereby giving rise to a new category of curable non-ischaemic DCM. Potentially, evaluation of LV dyssynchrony in every patient may have clarified the interpretation of the results. Future studies may use various cardiac imaging techniques to allow better assessment of the impact of particular LV pacing sites on overall LVEF.

Conclusion

The observation in this report of normalization of LV function after disappearance of LBBB by LV-based pacing in a significant subset of idiopathic DCM patients with long-term LBBB and severe CHF leads to the new concept of LBBB-induced cardiomyopathy. In this regard, many questions remain to be resolved. Nevertheless, the finding that disorganized intra-LV contraction may induce a totally reversible DCM in patients who previously were considered incurable is potentially important, and warrants further evaluation in prospective clinical trials.

References


