Biventricular pacing in patients with heart failure and intraventricular conduction delay: state of the art and perspectives. The European view

Cardiac resynchronization through biventricular pacing has been recently introduced to treat patients with heart failure and intraventricular conduction delay, similar to complete left bundle branch block[1,2]. The prevalence of intraventricular conduction delay among patients with heart failure has been estimated to be as high as 30–50% and has been associated with poor survival[3–5]. Ventricular dysynchrony, due to interventricular and intraventricular conduction delays, is associated with paradoxical septal wall motion, pre-systolic mitral regurgitation, reduced diastolic filling times and delayed activation of free wall segments which may contract after aortic valve closure[6–9]. Acute studies demonstrated that biventricular pacing, and maybe left ventricular pacing alone, may improve both systolic and diastolic function[10–17]. Results from early studies of permanent biventricular pacing consistently showed acute improvement in symptoms of dyspnoea, fatigue, fluid retention and general well being as well as long-term reduction of NYHA functional class and number of hospitalization days[18–24]. Biventricular pacing was associated with shortening of QRS duration, and improvement of left ventricular ejection fraction, exercise tolerance on a 6-min walking test, maximal oxygen uptake and quality of life indexes, which persisted after 1-year follow-up.

The MUltisite STimulation In Cardiomyopathies (MUSTIC) Study[25]

The MUSTIC study is the first randomized study comparing biventricular pacing with no pacing in which a transvenous implant was performed in all patients. The study was conducted under the auspices of the European Society of Cardiology and supported by ELA Recherche, Medtronic and the Swedish Heart and Lung Association and by a grant from the Swedish Medical Research Council. Sixty-seven patients in sinus rhythm (group I) were enrolled. They were in stable class III, in spite of optimal medical therapy, with left ventricular ejection fraction lower than 35%, left ventricular diastolic diameter greater than 60 mm, QRS duration larger than 150 ms and exercise tolerance lower than 450 mt on a 6-min walking test. The study included a 6-month single-blind randomized cross-over phase, during which atrioventricular (active) pacing was compared with ventricular inhibited (inactive) pacing at a basic rate of 40 beats, min−1, each for a 3-month period in random order. The primary end-point was the distance walked in 6 min. The secondary end-points were quality of life, peak oxygen uptake, hospital admissions because of heart failure, patient preference, with regard to active or inactive pacing at the end of cross-over, and death. During the active phase, when compared with the inactive phase, the mean distance walked in 6 min increased by 23% (P<0.001), the quality of life Minnesota score decreased by a mean of 32% (P<0.001) and the peak oxygen uptake increased by a mean of 8% (P<0.03).

No significant carryover effect was observed. During the first period, three hospitalizations for heart failure occurred during active pacing as compared with nine during inactive pacing (P<0.05). At the end of the crossover period, 85% patients preferred the active mode (P<0.001), 4% the inactive mode and 10% had no preference. In Table 1, the main results of the study are summarized.

Fifty-eight patients in chronic atrial fibrillation were enrolled in the group II. Enrolment criteria were the same as in group I, but QRS duration during right ventricular pacing had to be larger than 200 ms. Complete heart block was induced at the time of pacemaker implantation to ensure complete and permanent ventricular paced capture. Biventricular pacing and right ventricular pacing were compared in a randomized 3-month crossover period. The main results have been published only as an abstract[26], but did not substantially differ from those of group I, although with a less significant improvement during
biventricular pacing. In fact, the mean distance walked in 6 min increased by 10%, the Minnesota score decreased by a mean of 16% and the peak oxygen uptake increased by a mean of 21%.

Where are we going from here?

It is claimed that cardiac resynchronization therapy by means of endocardial or epicardial biventricular stimulation is achievable and that it may improve functional class, exercise tolerance and quality of life in selected patients with advanced heart failure; however, several open issues still need to be clarified. They include technical aspects, patient selection, benefits of overall survival and sudden death, costs and organizational problems.

Technical aspects

Left ventricular-based pacing is a difficult technique. It may be performed transvenously by inserting the third lead into the coronary sinus and by positioning it in the cardiac veins which are in contact with the epicardium of the left ventricle. Enlargement of the right atrium, dilatation of the coronary sinus and anatomical variability of the cardiac veins are the most common difficulties to be overcome. In spite of using dedicated leads, in the published studies implantation success rate ranged from 82% to 92% and procedure duration was time consuming with long X-ray exposures[18,27–31]. Posterior and lateral veins have been identified as the optimal pacing site [32], but target positions could not be always obtained at implantation, due to anatomical obstacles, high pacing threshold, phrenic stimulation or lead instability. Optimal positioning has been reported in 64–79% of patients[28,30]. Epicardial stimulation may be an alternative approach, but it requires lateral minitoracotomy and general anaesthesia[33]. In contrast, the thoracoscopy approach has been abandoned because of major arrhythmic complications at implant and poor long-term lead performance[34].

Optimal pacing configuration has not been defined yet. Acute studies showed that left ventricular pacing alone may be as effective or even more effective than biventricular pacing[13,15]. Furthermore, it is not known if the right and left ventricle should be paced simultaneously or with some interventricular delay[35]. Recent introduction of new devices with separate channels for right and left ventricular pacing will allow investigations in this field.

Patient selection

Impaired functional class, low left ventricular ejection fraction and wide QRS have been the major criteria used to identify the patients who may benefit from cardiac resynchronization. However, almost 25% of patients are not responders to pacing therapy. It has been suggested that poor functional class, a wide basal QRS and larger QRS shortening during biventricular pacing identifies responder patients from non-responders[36]. A combination of a wide basal QRS and impaired basal left ventricular dP/dt max may increase sensitivity and specificity in predicting responders to biventricular pacing[37]. In the Insync Italian Registry[22] responder patients could not be predicted according to QRS duration, left ventricular ejection fraction impairment, exercise tolerance, left ventricular lead positioning, and the presence of sinus rhythm or chronic atrial fibrillation. Only actual cardiac dysynchrony, as documented by echo techniques aimed at evaluating interventricular mechanical delay, prolonged left ventricular pre-ejection delay and activation of left ventricular segments after aortic valve closure were effective in identifying responder patients.

Total mortality and sudden death

In spite of a large amount of data on the benefits of cardiac resynchronization on functional status and

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**Table 1 MUSTIC trial: main results (modified from Cazeau S et al.)[25]**

<table>
<thead>
<tr>
<th>Group</th>
<th>Parameter</th>
<th>Active pacing</th>
<th>Inactive pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First 6 min walk test</td>
<td>384 ± 79 m</td>
<td>336 ± 128 m</td>
</tr>
<tr>
<td></td>
<td>Peak oxygen uptake</td>
<td>15·9 ± 5·8 ml . kg·min⁻¹</td>
<td>15·3 ± 5·9 ml . kg·min⁻¹</td>
</tr>
<tr>
<td></td>
<td>Quality of life</td>
<td>33 ± 22</td>
<td>43 ± 21</td>
</tr>
<tr>
<td></td>
<td>Second 6 min walk test</td>
<td>413 ± 117 m</td>
<td>316 ± 142 m</td>
</tr>
<tr>
<td></td>
<td>Peak oxygen uptake</td>
<td>16·4 ± 3·6 ml . kg·min⁻¹</td>
<td>14·8 ± 3·9 ml . kg·min⁻¹</td>
</tr>
<tr>
<td></td>
<td>Quality of life</td>
<td>26 ± 20</td>
<td>44 ± 25</td>
</tr>
<tr>
<td>Both</td>
<td>6 min walk test</td>
<td>399 ± 100 m</td>
<td>326 ± 134 m</td>
</tr>
<tr>
<td></td>
<td>Peak oxygen uptake</td>
<td>16·2 ± 4·7 ml . kg·min⁻¹</td>
<td>15·0 ± 4·9 ml . kg·min⁻¹</td>
</tr>
<tr>
<td></td>
<td>Quality of life</td>
<td>30 ± 21</td>
<td>43 ± 23</td>
</tr>
</tbody>
</table>

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quality of life, data on the impact of cardiac resynchronization on patient survival are totally lacking. Only a few observational data have been reported from the patients enrolled in the InSync Study, who showed a 1-year mortality rate of 22% (48% sudden)\(^{[19]}\), and in the InSync Italian Registry, in whom 10-month mortality was 7% (38% sudden)\(^{[22]}\). In the MUSTIC study\(^{[25]}\) 6-month mortality was 6.2% (75% sudden); three patients died during the active phase (two suddenly) and one patient during the inactive phase.

A specific issue of cardiac pacing in heart failure is the relationship between biventricular pacing and spontaneous ventricular tachyarrhythmias. Theoretically, simultaneous pacing from the right and left ventricular chamber could prevent reentry by reducing ventricular activation time and avoiding very late activation of the postero-lateral wall of the left ventricle. On the other hand, epicardial pacing of the left ventricular wall through the coronary veins could be proarrhythmic by increasing electrical instability of myocardial cells. It has been reported that in a population with heart failure biventricular pacing significantly decreased ventricular ectopic counts, when compared with both sinus rhythm and right ventricular pacing\(^{[30]}\). Furthermore, in patients with standard indications to cardioverter defibrillator, enrolled in the Ventak CHF trial, in which a 6-month single-blind randomized crossover phase of biventricular pacing compared with no pacing was planned, appropriate therapy for ventricular tachyarrhythmias was significantly less common during biventricular pacing\(^{[39]}\). Two major trials are ongoing to deal with the impact of biventricular pacing on mortality, the CArdiac REsynchronization in Heart Failure (Care-HF) and the COMparison of Medical therapy, Pacing ANd Defibrillation In cONgestive heart failure (COMPANION). In the Care-HF trial, 800 patients with chronic heart failure, in II or IV NYHA functional class, on optimal drug treatment, with left ventricular ejection fraction \( \leq 35\% \), dilated left ventricle, enlarged QRS and echo dysynchrony, with no indications to pacemaker or defibrillator implantation, will be randomized to optimal pharmacological therapy or to optimal pharmacological therapy and biventricular pacing with a defibrillator. The main end-points of the study will be 1-year all-cause mortality and 1-year hospitalizations.

### Costs

Heart failure overall prevalence has been estimated as high as 1–2% with significant health care expenditure\(^{[40]}\). Biventricular pacing may enhance health care costs for equipment, implantation procedure, follow-up and pacemaker-related complication treatment. Due to the complexity of the technology and implantation, procedure costs may be higher than with conventional pacemakers. On the other hand, several studies\(^{[21,25]}\) demonstrated that clinical improvement by biventricular pacing was associated with a major reduction in the need for hospitalization and hospital days. Balancing extra costs by saving hospital days makes the cost-benefit ratio of pacing therapy look favourable. Larger controlled studies will add more information to this issue.

### Organizational problems

The high prevalence of heart failure and the high prevalence of intraventricular conduction delays among patients with heart failure may suggest that a huge number of patients will be candidates for cardiac resynchronization therapy in Europe in the coming years. This requires a careful analysis of health care resource selection and a new organizational model with which to implement the relationship between the heart failure specialist and electrophysiologists. A new integrated database for multidisciplinary patient management should be implemented.

### Conclusion

Preliminary results of cardiac resynchronization therapy for heart failure are very challenging as far as patient functional status and quality of life are concerned. However, hard end-points and several open issues should result from large randomized trials. Organizational issues will have to be faced both from...
References


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