

Editorial

Multisite Biventricular Pacing

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Congestive heart failure (CHF) is a condition causing a poor quality of life for patients in NYHA class III or IV and has a dismal prognosis on the medium to short term [1]. Patient hospitalizations and treatment of the disease are also responsible for a large proportion of health care expenditures. Heart transplantation is the solution of choice at later stage of the disease, but it remains only available to a small number of patients [1]. Despite important therapeutic advances (ACE inhibitors [2], angiotensin II receptor blockers [3], the latter with diuretics prescribed at the maximal tolerated dose in 98% of patients, beta-blockers [4], and spironolactone [5], these prescribed to fewer patients as their effectiveness as treatment for severe heart failure is still under study), current medical therapy does not significantly improve prognosis [6]. New non-pharmacological alternatives like cellular cardiomyoplasty or left-ventricular (LV) implantable assist devices are still under evaluation.

Cardiac resynchronization therapy (CRT) with simultaneous right-ventricular (RV) and LV pacing is a promising therapeutic option in patients with severe heart failure and conduction defects. It has been shown to improve patients' functional, hemodynamic, and health-related quality of life [7]. Enormous advances have been made in this field within a short period of time. Indeed, CRT was only introduced in France in 1994 [8] and has been recently (2002) approved by the Food and Drug Administration. In the initial setup [8], the right-atrial and ventricular leads were placed in the conventional way. The left atrium was paced with a coronary sinus lead, and the epicardial lead was placed on the LV free wall. A conventional DDD pacemaker

was used. After 6 weeks of four-chamber pacing, the functional class of the patient, initially NYHA IV, was reduced to NYHA II.

Intraventricular conduction delay and left bundle branch block cause asynchronous RV and LV contraction and worsen LV dysfunction in cardiomyopathies, which in turn enhances the hemodynamic consequences of the baseline LV systolic dysfunction. Both LV and biventricular cardiac pacing are thought to improve cardiac function by effecting a more coordinated and efficient ventricular contraction [9]. CRT requires simultaneous pacing of both ventricles in synchrony with atrial pacing. The main technical difficulty is ensuring reliable LV pacing. Initially, epicardial leads were implanted, and in some cases also transseptally [10]. Nowadays, a transvenous approach is used, with insertion of the lead into an epicardial vein over the LV free wall. The thrust and bending of a lead while inside a blood vessel are substantially lower than those of freely moving leads. Growing experience with the procedure and improvements in lead technology have increased the success of implantation.

Many controlled studies have been conducted and published recently, proving a general improvement in condition and providing insight into the effectiveness of CRT. End points of the studies usually include subjective parameters, such as quality of life assessed with a questionnaire, and objective parameters, such as maximal distance walked in 6 min and peak oxygen uptake (VO_2). Results are available for the following studies: Multisite Stimulation in Cardiomyopathies (MUSTIC), the Multicenter InSync Randomized Clinical

Evaluation (MIRACLE), the Pacing Therapy for Congestive Heart Failure (PATH-CHF) multicenter trial, the Medtronic InSync study, the Ventak CHF/Contak CD study, Vigor CHF, and others still being conducted. Conclusions from these studies are listed below. CRT improves subjective parameters, such as patient quality of life (based on questionnaires) and also improves the objective measurements, such as: it increases the distance walked in 6 min, LV ejection fraction, heart rate variability [11], and peak oxygen consumption; it improves oxygen uptake; it lowers NYHA classification; and it decreases QRS duration. The rehospitalization rate was also significantly reduced with CRT. A recent study [12] proved that the clinical benefits of biventricular pacing appeared to be significantly maintained over a 12-month follow-up period. In another recent study on 125 patients implanted with a dedicated device and after a mean follow-up of 22 months, the mortality was 44% [13]. The causes of death were: sudden death in 42% of patients, progression of cardiac failure in 34%, and non-cardiac origin in 24%. The survivors showed a significant improvement in NYHA class from 3.3 ± 0.5 before implantation to 2.3 ± 0.5 at the end of follow-up, and a significant increase of 40% of peak VO_2 and of maximal exercise duration.

Despite all these interesting findings, and in view of the rather disappointing results from previous studies, some questions remain unanswered, among them the impact on all-cause mortality and sudden cardiac death. Two studies have been conducted (and are ongoing) to try to answer this question: CARE-HF in Europe and COMPANION in the USA. Further questions are: Which type of implantable device should be developed, multisite pacemakers or multisite pacemaker devices with defibrillation capabilities? Can novel delivery systems be developed, which will make implantation of these devices more accessible to clinicians? Is there a need for extended or restricted programming possibilities? Could CRT induce LV reverse remodelling and thus help prevent heart failure progression? What is the cost-effectiveness ratio for heart failure management? How to select potential responders? Studies are underway to validate these aspects of CRT and should be completed in the following years.

Patient selection is another problem: How many patients with LV dysfunction may potentially benefit

from CRT? In a recent study [14], it was shown that cardiac biventricular pacing serves only as a therapeutic option for a relatively small subgroup of patients (6%) with LV dysfunction. There is still room for improvement, especially concerning the optimal position of the RV and LV leads [15]. The best positions would be those that induce the greatest shortening of QRS duration [16]. Optimization of AV delay is another parameter still to be improved. Since the early nineties, the employment of DDD pacing from a RV site with a short AV delay in patients with severe heart failure has led to considerably conflicting results [17]. Similar to defibrillation shocks, even the pacing burst waveform might influence the outcome of CRT. Individual optimization is necessary to achieve optimal hemodynamic benefit [18]. The method of choice to show this is echocardiography [19]. It is a non-invasive method, and it has the potential to provide hemodynamic data by Doppler techniques and combine these with geometric information about ventricular volumes, ejection fraction, and contraction patterns. Another tool for long-term hemodynamic monitoring has recently been proposed with a new pacemaker sensor: the peak endocardial acceleration [20]. Its variations have been shown to highly correlate with those of dp/dt . An advantage of this sensor is that it can be used to adjust pacing modalities without any further examinations and could even be included in an automatic loop optimization algorithm.

Data from CRT studies suggest that chronic biventricular based therapy may offer new hope in clinical cases with severe end-stage heart failure. This mode of stimulation can be seen as another tool in the management of patients with end-stage heart failure. In some cases, it might even be used to bridge the time to transplantation. However, more long-term studies are needed to establish its chronic value. CRT remains a medical and technical challenge in the near future. As in other fields of cardiology, CRT has benefited from a close interaction between medicine, science, technology, and device manufacturers for the improvement of the condition of heart failure patients.

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