Cardiac Resynchronization Therapy for Heart Failure Shows Great Promise

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The prevalence of congestive heart failure continued to increase during the last decade, reaching epidemic proportions in the United States and Europe [1,2]. Despite recent advances in pharmacologic treatment, patients with advanced CHF have a limited capacity for exercise, have high rates of hospitalization and rehospitalization, and they die prematurely. In these patients the quality of life and the overall long-term prognosis are significantly compromised [1,2]. Moreover, many patients do not sufficiently improve on optimal drug treatment, or, after improvement for a short period they become refractory to medical therapy. Intolerant to most of the drugs currently considered optimal medical therapy is another group of CHF patients who require further treatment. In the past, these patients could only be offered heart transplantation, but even in the U.S. only 51% of patients received a donor organ [3]. Furthermore, a significant number of patients with advanced CHF have contraindications for heart transplantation.

In recent years, implantable devices for mechanical treatment of CHF have emerged as a promising approach among the therapeutic options for CHF. However, mechanical support with implantable left ventricular assisted devices is reserved for the minority of patients who have severely decompensated heart failure and many limitations [3]. Therefore, additional strategies are being developed.

A relatively new factor that plays an important role in CHF pathophysiology and is fast gaining recognition is abnormal electrical conduction, which can delay the timing of atria function and create discoordination in ventricular contraction. These electromechanical mechanisms result in decreasing systolic function of the heart. Recently, a widened QRS was firmly established as an independent risk factor for mortality from dilated cardiomyopathy [4] and, according to the MADIT II data, in patients with ischemic cardiomyopathy as well [5]. In approximately 30% of patients with dilated cardiomyopathy, the disease process not only depresses cardiac contractility but also affects the conduction pathways by causing a delay at the onset of the right or left ventricular systole [6]. This asynchronous pattern of ventricular contraction reduces the already diminished contractile reserve of the heart [7] and leads to mechano-energetic uncoupling [8]. This process is indicated by a widened QRS interval on electrocardiogram, and these patients have worse clinical outcomes than those with normal QRS intervals [4,5,9]. Therefore, the idea that restoration or resynchronization of impaired cardiac conduction by pacing might be used to improve ventricular contraction has been of special interest for pacing specialists in the last decade.

In this issue of *IMAJ*, Drs. Gurevitz and Glikson [10] present the current status of cardiac resynchronization therapy in patients with CHF. The authors conclude that CRT is beneficial in appropriately selected patients, as shown in clinical studies that clearly demonstrated a significant improvement in symptoms (New York Heart Association class, quality of life and exercise capacity), hemodynamic parameters (increased peak oxygen consumption, increased LV ejection fraction, reduction in severity of mitral regurgitation and reduction in QRS duration), and a reduced rate of hospitalizations for heart failure.

The body of evidence provided by several different studies has been so convincing that AHA/ACC/NASPE Task Force for Pacing, in their very recently updated guidelines, indicated CRT for patients with dilated cardiomyopathy at class IIa with a level of evidence A [11]. It is still unknown whether CRT will reduce mortality, and studies presently underway in the USA and Europe will provide the answer to this important question [3,9,10]. On the basis of the current findings, it is feasible to implant CRT devices in patients who have the following:

- Drug-refractory, symptomatic heart failure NYHA class $\geqslant$ III
- LV ejection fraction $\leqslant$ 0.35
- QRS duration $\geqslant$ 130 msec.

Although the guidelines [11] indicated a cutoff for LV end-diastolic diameter of more than 55 mm, this selection criterion has not been used in all prospective, concluded or ongoing studies. Of minor note is the discrepant labeling used in the chapter title and in the presented guidelines; indeed, the title of the chapter is: "Section I-H: Pacing in Specific Condition (continued) 2. Idiopathic Dilated

CHF = congestive heart failure

CRT = cardiac resynchronization therapy
LV = left ventricular
NYHA = New York Heart Association

Cardiomyopathy. Pacing Recommendations for Dilated Cardiomyopathy," but the guidelines refer both to patients with idiopathic and to those with ischemic cardiomyopathy.

Despite the symptomatic beneficial effect of CRT, which is undoubted and considerable in the vast majority of patients, additional information is required for this therapy to be more broadly applied. It has been reported by different authors that about 20–30% of the patients showed only minor changes in acutely measured hemodynamic parameters, quality of life, functional class or distance walked [9,10,12]. Those patients are usually referred to as "non-responders" to CRT. The definition of "non-responder" to CRT still lacks uniformity and there is no single parameter that can be used for best characterizing the chronic effect of CRT. Endpoints like changes in NYHA functional classification, distance walked in 6 minutes, or changes in quality of life score are very weak since they may be influenced by spontaneous changes or by the placebo effect. One possible endpoint for assessing the effect of CRT may be considered a combined endpoint – namely, the change of oxygen uptake at an anaerobic threshold during exercise testing and a reduction of LV end-diastolic and end-systolic diameter. It is well known that changes in volume have prognostic implication; it is also accepted that changes in oxygen uptake during physical activity are related to cardiac, pulmonary and system metabolism, and have a high prognostic value. Thus, if exercise tolerance can increase while the ventricle is getting smaller, it may be assumed that a new and improved cardiac and systemic hemodynamic has been achieved while lowering the chronic myocardial energy cost.

When discussing "non-responder" patients to CRT, the first question is whether the pacing site matches the delayed portion of the left and right ventricles, thus pre-excitating the electrical and mechanically delayed region. According to the most current pathophysiologic understanding of CRT, a more homogeneous, timely and adequate distribution of the regional loading than that present during intrinsic delay activation should be reached; thus, the appropriate selection of pacing site is crucial. Recent acute hemodynamic data [13] suggest that the largest increase in systolic function is achieved when pacing the lateral wall. Using a high resolution three-dimensional electro-anatomic mapping technique such as CARTO, NOGA and EnSite, an abnormal delayed region of activation mainly located at the posterolateral and lateral wall of the left ventricle was found in patients with dilated cardiomyopathy of any etiology and ventricular conduction. Thus, this finding substantiates that this part of LV may be considered the target region for pacing. However, a crucial and frequently underestimated issue in properly selecting the most optimal pacing site is that the coronary vein anatomy and the anatomic course of the phrenic nerve may be two major anatomic obstacles. A further limitation in lead placement regards the capability to adequately stimulate the left ventricle. According to personal experience (A.A.), such a target region cannot be reached because of anatomic obstacles or electrical problems in about 10–15% of patients.

The second question is whether QRS duration adequately represents ventricular electrical asynchrony. The baseline QRS duration is a gross descriptor of the quantity of electrical abnormality, which does not necessary correlate with mechanical abnormality. Acute hemodynamic data from the PATH-CHF study [14] showed that patients with a QRS duration of 120–150 msec had minor changes in contractility and stroke volume compared to patients with QRS duration >150 msec [15]. It has been debated whether acute hemodynamic changes predict chronic effects. From a pathophysiologic standpoint CRT acts primarily as a positive inotropic remedy, but at a macroscopic level it resynchronizes different ventricular regions, leading to lower myocardial oxygen consumption. Because of this, it may be expected that acute hemodynamic changes forecast chronic hemodynamic cardiac and system changes. The recently presented data from the PATH-CHF II study substantiate such an acute and chronic correlation. Noteworthy is the effect of CRT on symptoms, quality of life and exercise tolerance in patients prospectively stratified according to the QRS duration. In agreement with the previous hypothesis, patients with a relatively narrow QRS complex had fewer symptomatic and functional benefits at 3 months follow-up than patients with a large QRS complex. Indeed, about 40% of the patients with a baseline QRS duration of 120–150 msec, and more than 70% of the patients with a baseline QRS >150 msec showed a meaningful clinical increase in oxygen uptake at peak exercise >1 ml/kg/min. However, at 1 year follow-up the difference between the two groups was no longer evident; there was a large increase in all measured parameters in patients with both narrow and wide QRS. This indicates that the acute-to-chronic correlation may be different when considered in the short or long term. The findings strongly suggest that there is a time-dependency effect by CRT related to the baseline QRS complex – i.e., a marked and immediate effect for patients with a QRS complex >150 msec, and a marked but late-coming effect for patients with a narrow QRS complex. This concept of time-dependent effect based on baseline QRS duration is quite new and crucial for the definition of responder and non-responder patients to CRT.

Finally, the intriguing PATH-CHF II data [16] allow the question whether baseline QRS duration can still be considered a good marker of asynchrony, or should other techniques that exclusively explore mechanical function be considered adequate. One major limitation of most of the non-invasive imaging techniques is the large inter-observer variability and the lack of standardized parameters that best describe the mechanical asynchrony.

In addition to the above-mentioned points, several questions have not been fully addressed:

- What is the best ventricular pacing configuration: biventricular pacing or LV pacing alone?
- Does therapy with beta blockers have a synergistic effect on reverse remodeling achieved during CRT?

* In accordance with the MERIT-CHF study [17] sudden death is significantly more frequently observed in CHF patients who have NYHA class I-III, as opposed to patients who have class IV. Because CRT significantly improves the functional capacity of paced patients, and shifts patients from class IV to a higher location, it is expected that the amount of patients dying suddenly due to VT/VF will increase. This speculation could be verified during a InSync-ICD study.

- Does CRT have an anti-arrhythmic or, conversely, a pro-arrhythmic effect* (risk of ventricular tachycardia or ventricular fibrillation)?

In the long term, it is not known whether the device of choice for heart failure patients will be a "stand-alone" cardiac resynchronization device or one that also incorporates an ICD. The recently published MADIT II trial [18] questioned the feasibility of biventricular pacemaker implantation as the sole device, since virtually all patients with a severely damaged LV due to ischemic cardiomyopathy have an indication for an ICD. This logical postulation, and the question whether patients with non-ischemic cardiomyopathy should receive such devices are currently being addressed in ongoing randomized studies [19].

Several specific points regarding CRT should be emphasized. The ultimate applicability of CRT will have to account for a balance of risks and benefits in the eligible patient population. As with all forms of interventional cardiology with very specific techniques, it is reasonable to expect that only experienced operators and approved technology will lead to a greater safety profile for implantation of the device. Until now, about 20,000 biventricular devices (the vast majority being pacers alone, with about 25% combined with ICD) have been implanted worldwide [10]. In accordance with these data and the approximate number of patients with advanced CHF in Israel, about 400–500 patients may be candidates for CRT (to date about 150 CRT devices have been implanted in Israel, including pacers and ICD with biventricular pacing) [M. Glikson, 2 November 2002; personal communication]. In a recent market analysis of the projected implants of CRT devices in the U.S. [20], the approximate number of CRT devices to be implanted in Israel in 2003 was calculated to be in the order of 325 implants with the potential growth of 140% by the year 2004.

Expectations

CRT is a new and very effective therapy for a highly selected patient population. A very important landmark for CRT has been passed. The new prospective randomized trials and registries may now allow the development of carefully drawn recommendations for optimal patient selection for CRT, indications for implantation, and the follow-up of patients with these unique devices. Answers to the questions raised here should also guide the choice of implantable devices to be developed by priority: multisite pacemakers alone, or multifunction devices in conjunction with multisite pacing and automatic defibrillation?

Five ongoing clinical trials for evaluating CRT plan to enroll more than 4,000 CHF patients [19]. These trials include: COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in CHF), PACMAN (Pacing for Cardiomyopathy), CARE-HF (Cardiac Resynchronization in Heart Failure), VecToR (Ventricular Resynchronization Therapy Randomized trial), and PAVE (a trial involving LV post-atrioventricular nodal ablation evaluation). If these studies show a beneficial effect of resynchronization therapy on all-cause mortality, CRT should be recognized as a class I indication of therapy for CHF with level of evidence A [19].

ICD = implantable cardioverter defibrillator

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