# Survival in cardiac resynchronization therapy. What do we know?

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## ABSTRACT

Patients with moderate or severe heart failure often have some form of intraventricular conduction abnormality and increased QRS duration on the routine electrocardiogram. The most common pattern is the left bundle branch block, when the electrical activation of both ventricles is disturbed and the lateral wall of the left ventricle is significantly delayed. The use of cardiac pacing to coordinate the impaired electrical activation and myocardial contraction is called cardiac resynchronization therapy (CRT). Randomized trials of cardiac resynchronization were demonstrated to improve left ventricular systolic function, exercise tolerance, quality of life, and reduction in rehospitalization frequency of the patients. Resynchronization also prolongs survival in patients with NYHA Class III or IV heart failure and left ventricular ejection fraction ≤35%. Recent developments using electro-anatomic mapping, contact and noncontact endocardial mapping have demonstrated that the correct positioning of the pacing electrodes provides better resynchronization and better response to CRT. Body surface potential mapping and noninvasive electrocardiographic imaging provide also a deeper insight into the mechanism of cardiac electrical depolarization and contributing to develop the selection method of best pacing sites for patients referred for CRT. *(Anadolu Kardiyol Derg 2007: 7 Suppl 1; 57-9)*

**Key words:** chronic heart failure, cardiac resynchronization therapy, cardiac activation, body surface potential mapping, noninvasive electrocardiographic imaging

## Introduction

Chronic heart failure (CHF) is a growing health challenge throughout the whole World. About two percent of the whole population has heart failure, although the syndrome mainly affects the elderly that is about 6-10% of the people over the age of 65 years (1). In Europe and North America the lifetime risk of developing CHF is approximately one in five for a 40-year old (2), and interestingly, the age-adjusted incidence of CHF remained stable over the past 20 years (3, 4). Despite the latest achievements of medical therapy in advanced stages of CHF, mortality remained high and quality of life severely impaired (5). In respecting the major advances in pharmacological treatment of CHF, many heart failure patients are relapsing into advanced heart failure, being in poor condition in terms of quality of life and disease prognosis (6).

Heart transplantation has decreased mortality in patients who do not respond to drug therapy and also improved quality of life, but finding donors is still a major difficulty. Surgical techniques to treat CHF like cardiomyoplasty, left partial ventriculectomy, and reconstruction of mitral valve complex did not bring substantial benefit. Among the other non-pharmacological approaches, electrical therapies including cardiac pacing and /or implantable cardiac defibrillators (ICD-s), have been developed over the last 10 years. After an initial, but disappointing experience with dual-chamber pacing (7), a new treatment, cardiac resynchronization therapy (CRT) was developed, introduced by Caseau et al. (8) and Bakker et al. (9). They described the first cases of atrio-biventricular pacemaker implantations in patients with severe and drug-refractory CHF without conventional pacemaker indications. Their concept was based on the fact that in CHF, left ventricular systolic dysfunction, high-grade intraventricular conduction delays are frequently observed: 25-50% of the patients have QRS duration>120 ms and 17-25% of patients shows left bundle branch block (LBBB). Moreover in such patients with advanced heart failure atrio- ventricular (AV) dyssynchrony, with a prolonged PR interval is also a common finding (13).

### Haemodynamic studies

Biventricular or left ventricular pacing improves hemodynamics in patients with CHF and LBBB, increasing cardiac output, and reducing ventricular filling pressures. The haemodynamic improvements due to CRT may begin almost immediately after pacing is initiated. Cardiac resynchronization therapy also reduces sympathetic nervous activity as well as brain natriuretic peptide release, thus having a beneficial neurohormonal effect (11). Importantly, CRT improves systolic function without increasing cardiac oxygen consumption, unlike inotropic drugs (10, 11). Taking into account these facts, CRT contributes to reversing mechanical - energetic uncoupling, the characteristic event of CHF.

### Procedural problems

In most of the patients, CRT has been provided by biventricular pacing with a lead inserted transvenously in a tributary vein or

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the coronary sinus for the epicardial pacing of the left ventricle. This sophisticated technology is still evolving, improving specific catheters and left ventricular leads guarantees the better implantation success, which is now greater than 90% (14). In the MIRACLE study (15) among the 453 patients, the major complications of left ventricular lead implantation were death, complete AV block, coronary sinus dissection (16), or perforation (17).The pacing leads had to be repositioned in 20 patients (4.1%), replaced in 10 patients (2.04%) and removed only in seven patients (18).

**Electroanatomic mapping of cardiac activation and proper lead positioning**

The use of CRT to treat patients with CHF and left bundle branch block lead to methods of quantifying the amount of intraventricular and/or interventricular asynchrony. Echocardiographic studies reveled (19, 20) that the haemodynamic consequences of abnormal conduction patterns in patients with dilated cardiomyopathy are in close correlation with QRS complex enlargement and apparently may result from interventricular dyssynchrony and loss of septal contraction. Kass (21) highlighted the importance of identifying the patients who are to respond to CRT. Given the expensive, invasive and complex nature of the procedure, and the nearly 30% of patients who do not derive proven benefit, it is a special task to define the cohort of optimal candidates to undergo CRT. From the other hand, the procedure itself is invasive, and may also have well defined complications.

Recent developments using electroanatomic mapping (22) as well as contact and noncontact mapping (23, 24) have demonstrated the importance of correct positioning of pacing electrodes to get better resynchronization and good response to CRT. New methods of assessing multisite stimulation, like the BSPM (25) and noninvasive electrocardiographic imaging (ECGI) (26), provide a deeper insight into the mechanism of cardiac electrical activation of both ventricles, and thereby they are contributing to develop the selection method of the best pacing sites for patients referred for CRT.

**Clinical effects of CRT**

The first non-randomized trials on the clinical effects of CRT demonstrated a significant benefit of patients implanted with biventricular pacemaker. Later, controlled, randomized and prospective trials have been completed and have demonstrated the clinical income of CRT in patients with advanced heart failure, like MUSTIC, MIRACLE, PATH CHF, MIRACLE-ICD, CONTAK-CD and COMPANION studies (13, 27). All these trials, except CONTAK-CD and MIRACLE-ICD included patients with severe heart failure (NYHA Class III or IV) on optimal drug therapy with left ventricular systolic dysfunction, dilated left ventricle and wide (>120-150 ms) QRS.

The results of first non-controlled and controlled trials on mortality were also encouraging, but they have to be interpreted very carefully because the primary outcome was not mortality (10, 11). Two prospective, randomized trials with morbidity and mortality as primary endpoints were also initiated; the CARE-HF and the COMPANION trials, and both of their CRT arms demonstrated a significant reduction in primary outcome (all-cause mortality and hospitalization) (p=0.01). Similar results were given in the two secondary end-points of the trials; death and cardiovascular hospitalizations, and death and heart failure hospitalizations (13). However, only CRT plus ICD therapy was associated with a significant, 36% reduction in total mortality (p=0.003) at 1 year, and 24% reduction in mortality observed in he CRT arm, but not statistically significant (p=0.059). Unfortunately, this trial was not designed to compare CRT and CRT plus ICD treatment modules.

The recently published Cardiac Resynchronization-Heart Failure trial, reported by Cleland et al. (28) demonstrated that cardiac resynchronization therapy alone prolongs survival in patients with class III or IV heart failure and left ventricular ejection fraction less than 35%. Mortality from all causes was significantly reduced, from 30% in the conventional medical-therapy group to 20% in the cardiac resynchronization group (p<0.002). According to the results of this study it is also important, that the beneficial effect of CRT on mortality took place gradually in time, and therefore it may be associated with the effects of reverse ventricular remodeling. The results provide support for the implantation of a biventricular pacing device alone on patients with NYHA class IV who do not desire an implantable cardioverter defibrillator.

**Potential new indications for CRT**

Current European Society of Cardiology guidelines recommend CRT (with Class I strength and evidence level A) in patients with medically refractory, symptomatic NYHA Class III and IV heart failure with idiopathic or ischaemic cardiomyopathy, prolonged QRS interval (≥120 ms), left ventricular end diastolic diameter ≥55 mm and left ventricular ejection fraction (LVEF) 35% (5). However, we may expect that in the near future new indications will be validated which could be the followings:

a. Previously right ventricular paced patients. Right ventricular apical pacing induces ventricular dyssynchrony and may cause deterioration of cardiac performance and clinical outcome. The RD-CHF trial (29) suggests that pacemaker upgrading from uni-right ventricular pacing to biventricular pacing significantly improved clinical outcome.

b. Patients with conventional pacemaker indications. The DAVID trial (30) showed that in an ICD population without pacemaker indication, right ventricular apical pacing increased morbidity and mortality compared with no pacing.

c. CRT in asymptomatic patients or those with mild heart failure. Cardiac resynchronization therapy significantly decreased left ventricular end-systolic and left ventricular end-diastolic volumes and mitral regurgitation in NYHA Class II patients, with decreased LVEF (31, 32), and thus, might be beneficial in NYHA Class II patients with a left ventricular reverse remodeling target.

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