

# İleri Kalp Yetmezliği Tedavisinde Kardiyak Resenkronizasyon: Alternatif Bir Tedavi mi?

## CARDIAC RESYNCHRONIZATION IN PATIENTS WITH SEVERE HEART FAILURE: IS AN ALTERNATIVE THERAPY?

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### Özet

Farmakolojik ve cerrahi tedavi seçeneklerindeki gelişmelere rağmen, ileri kalp yetmezlikli hastaların prognozu hala kötüdür. Bu tür hastaların bir kısmında sol dal bloğu ve intraventriküler ileti gecikmesi gibi her iki ventrikülün senkronize çalışmasını engelleyen kalp ileti bozuklukları bulunmaktadır. Her iki ventrikülün de senkronize çalışmasını sağlayan biventriküler uyarımlı kalp pili tedavisi, ileri kalp yetmezliği tedavisinde farmakolojik ve cerrahi tedaviye bir alternatif olarak araştırılmaktadır. Resenkronizasyonu sağlayan kalp pillerinde genellikle transvenöz yolla sağ atriyum, sağ ventrikül ve sol ventriküle (koroner sinüs vasitesiyle) yerleştirilen leadler ile senkronizasyon sağlanmaktadır. Erken sonuçlar gerek sinus ritmindeki, gerekse atriyal fibrillasyondaki hastaların hemodinamik parametrelerinde, yaşam kalitelerinde ve egzersiz kapasitelerinde önemli iyileşmeler sağlandığını göstermektedir. Bu iyileşmeye neden olan etkenlerin diyastolik doluşta iyileşme, mitral yetmezliğinde azalma ve daha efektif sistolik kasılma olduğu düşünülmektedir. Bu makale, günümüzde bu konu hakkında yapılmış çalışmalarını tarayarak, ventriküler senkronizasyon bozukluğunun patofizyolojisi, klinik çalışmaların derlenmesi ve kardiyak resenkronizasyonun kalp cerrahisindeki yeri ve geleceğine yönelik değerlendirmeleri içermektedir.

**Anahtar kelimeler:** Kardiyak resenkronizasyon, biventriküler kalp pili, konjestif kalp yetmezliği

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### Summary

Despite advances in pharmacological therapy, the prognosis of patients with advanced congestive heart failure (CHF) remains poor. Many of these patients have cardiac conduction abnormalities, such as left bundle-branch block or interventricular conduction delays, that can lead to ventricular dyssynchrony (abnormal ventricular activation that results in decreased ventricular filling and abnormal ventricular wall motion). Biventricular (BiV) pacing is an alternative, nonpharmacologic therapy under active investigation for the treatment of CHF. Resynchronization devices with transvenous leads in the right atrium, right ventricle, and left ventricle (via the coronary sinus) have been implanted in patients to provide atrial triggered biventricular pacing. Preliminary evidence indicates improvement in hemodynamics, quality of life, and exercise capacity in patients in sinus rhythm as well as in patients with atrial fibrillation. An improvement in diastolic filling, a decrease in mitral regurgitation, and more efficient systolic ejection are proposed as the mechanisms behind these benefits. This article reviews the pathophysiology of ventricular dyssynchrony and examine insights from clinical trials that are evaluating cardiac resynchronization therapy for CHF and cardiac surgery.

**Keywords:** Cardiac resynchronization, biventricular pacemaker, congestive heart failure

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### Introduction

In recent years there has been a growing interest in using cardiac pacing as additive treatment in severe congestive heart failure (CHF). Pharmacological treatment has made considerable progress in the treatment of severe CHF. Angiotensin converting enzyme (ACE) inhibitors, b blockers, and spironolactone have significantly reduced mortality and morbidity in New York Heart Association (NYHA) class II-IV patients, while improving their quality of life [1-3]. But the benefit is probably not permanent and will be limited in time. A variety of non pharmacological approaches are available to treat these refractory CHF patients. Heart transplant remains the best solution but it can only be applied to a restricted

number of patients. So, for more than 10 years now, permanent dual chamber pacing with short atrioventricular (AV) delay has been proposed as an adjuvant treatment of advanced CHF. It is estimated that 30% of patients with severe CHF have intraventricular conduction disturbances mechanically characterised by a discoordinate ventricular contraction pattern and wide QRS complexes [4]. Wilensky et al [5] thus demonstrated that atrioventricular and intraventricular conduction disorders, with 30% mean increase in PR interval and QRS duration, had been gradually occurring in more than 80% of patients who died from pathologically proven dilated cardiomyopathy (DCM), over a mean follow up period of 30 months. Other studies have revealed that intraventricular conduction block with or without prolonged AV delay

adversely influences ventricular function due to discoordinate contraction [5-10]. This is usually indicated on the surface electrocardiogram by widening of the QRS complex, a finding associated with increased morbidity and mortality in CHF patients [11].

Thirteen years ago, an Austrian group proposed implanting dual chamber pacemakers in advanced CHF patients who did not meet the usual criteria for a pacing indication [12]. Short term results were encouraging. A revolutionary idea was born: using cardiac pacing as an adjuvant therapy to medical and surgical treatment in drug refractory heart failure. This therapy is increasingly being termed cardiac resynchronization, and over the past year alone, more than 20 studies have reported short-or long term effects from the treatment. In this review, we aimed to summarize the underlying pathophysiologic mechanisms, clinical status, and future directions of this rapidly emerging and novel approach to CHF treatment.

### Pathophysiology

The left ventricle (LV) normally contracts synchronously with little more than 40 ms variation in the onset of electrical activation throughout the wall and very similar low-level variability in the timing of mechanical activation as well. Synchrony of contraction is important because it results in more effective and energetically efficient ejection. When a portion of the heart is prematurely stimulated, as for example with a left bundle branch block (LBBB) or single-site ventricular pacing, the activation sequence changes markedly, generating regions of both early and delayed contraction [13-15]. Early shortening at the stimulation site is wasted work because pressure is still low and no ejection is occurring. Late activation of the region remote to the stimulator occurs at higher stress because the paced territory has already developed tension, yet it is also characterized by wasted work because the early activated territory may now undergo paradoxical stretch [16]. The net result is a decline in systolic function of about 20% with reduced cardiac output and increased end-systolic volume and wall stress [17,18], delayed relaxation [19], and decline in efficiency [20]. Discoordination may also contribute to abnormal regional function and pro-arrhythmia [21]. Late-systolic stretch of the myocardium, which observed in the discoordinate septum [16,22], can lower force generation by rapidly disrupting cross-bridges. In addition such mechanical stretch can trigger calcium release to induce after-contractions and arrhythmia [21].

In addition to intraventricular conduction, the AV time delay also influences net chamber mechanics- with too short or too long an interval resulting in sub-optimal chamber filling and contributing to mitral regurgitation (MR) [23]. The latter occurs as the mitral valve re-attains an open midstream configuration during late diastole, which promotes regurgitation during the onset of ventricular systole [24].

### Mechanisms

The aim of multisite biventricular (BiV) pacing is to correct not only the atrioventricular asynchrony but also the non-uniformity of ventricular activation, contraction and relaxation sequences. It was proposed primarily to patients with drug refractory heart failure with LV systolic dysfunction and wide QRS complex. The first implantations in man were

simultaneously performed in 1994 by two teams, in a restricted number of patients, and results were rather encouraging [25,26]. Based on these preliminary experiments, several groups evaluated this concept in acute haemodynamic studies. BiV pacing has been shown markedly improve cardiac output, increase systolic pressure, lower pulmonary wedge pressure [27], enhance ventricular systolic function as assessed by maximal rate of pressure rise [28,29] and pressure-volume loops [27], and improve the magnitude and synchrony of wall contraction [30,31]. Furthermore both BiV and LV-only pacing can generate systolic improvement while concomitantly reducing myocardial energy consumption, resulting in improved chamber efficiency [32]. Short-term BiV pacing also reduces sympathetic activity, probably because of enhanced systolic function [33].

### Implantation Techniques

Initial lead placement was surgical, and although surgical mortality was low, the approach was abandoned by the time owing to attendant morbidity from surgery itself. A transvenous approach was introduced by Daubert et al [34] in 1998, and this approach has since become the mainstream method, employing specifically designed leads to assist in placement. The target location (i.e., a lateral or posterolateral vein in mid-cavity position) can be reached in a majority of patients (about 75%), and similar results have been reported by several groups using various technologies [35,36].

The question of precisely where on the LV optimal pacing is achieved remains incompletely resolved and is likely to vary somewhat from patient to patient. Butter et al [37] reported that short-term systolic response did depend on the LV pacing site, with the mid-part of the LV lateral wall generally providing the greatest improvement in most patients [28]. One potential explanation is that pre-excitation of the lateral wall optimally offsets the region with the greatest basal delay in activation and may also help ameliorate MR by pre-stimulating the papillary muscle [38].

Implantation of an LV lead via the coronary sinus poses some technical challenges, most often related to a dilated right heart anatomy and/or variable or suboptimal coronary venous anatomy. Both can render coronary sinus cannulation and lead placement more difficult. Although overall reported complication rates have been generally low, one must keep in mind that most of these data have come from centers with extensive experience. Furthermore, CHF patients ill-tolerate complication related arrhythmia or perforation. The major serious complications are dissections or perforations of the coronary sinus (or cardiac vein), which result in cardiac tamponade. In the series by Ricci et al [35], cardiac tamponade complication occurred in 0.9% of 190 patients treated. Pacing thresholds in the 1-1.5 V range are achieved in approximately 90% of patients and maintain such thresholds over the long term. Several alternative approaches such as transseptal [39] or pericardial-epicardial approaches may be useful in case with coronary sinus or venous anatomy failure. The surgical epicardial approach may still be considered useful in appropriate candidates in whom heart surgery is already indicated, or for those with failed transvenous lead implantation due to anatomic or technical difficulties.

### Clinical studies

There are some completed clinical studies involving long-term multisite BiV cardiac stimulation for the treatment of advanced dilated cardiomyopathy with underlying conduction delay (QRS > 120 to 150 msec). Early experience began in Europe with the work of Cazeau et al [26], Bakker et al [40]. To date, three placebo control studies have been completed: the MUSTIC trial [41], the PATH-CHF trial [42], and the MIRACLE trial [43].

In the MUSTIC study 67 patients with severe heart failure with normal sinus rhythm and a duration of the QRS interval of more than 150 msec, received transvenous atrioventricular pacemakers. This single-blind, randomized, controlled crossover study compared the responses of the patients during two periods: A three-month period of inactive pacing (ventricular inhibited pacing at a basic rate of 40 bpm) and a three-month period of active (atrioventricular) pacing. The primary end point was the distance walked in six minutes; the secondary end points were the quality of life as measured by questionnaire, peak oxygen consumption, hospitalizations related to heart failure, the patient's treatment preference (active vs. inactive pacing), and the mortality rate. Forty-eight patients completed both phases of the study. The 6-min walking distance was 23% greater with active pacing, the quality-of-life score improved by 32% ( $p < 0.001$ ), peak oxygen uptake increased by 8% ( $p < 0.03$ ), hospitalizations were decreased by two thirds ( $p < 0.05$ ), and active pacing was preferred by 85 percent of the patients ( $p < 0.001$ ). The significantly lower number of hospitalizations with atrioventricular pacing during the first crossover period is encouraging, but it involves only a short time. These results support the therapeutic value of ventricular resynchronization in patients who have severe CHF and major intraventricular conduction delay. Interestingly, this study did not observe a placebo effect.

In recently published the PATH-CHF study, 41 patients were randomized to four weeks of first treatment with biventricular or univentricular stimulation, followed by four weeks without treatment, and then four weeks of a second treatment with the opposite stimulation. The best cardiac resynchronization therapy (CRT) was continued for nine months. The primary end points were exercise capacity measures. Oxygen uptake increased at peak exercise ( $p < 0.001$ ) with the first treatment, and from at peak exercise ( $p = 0.002$ ) with the second treatment. The 6-min walking distance increased significantly after the first treatment ( $p < 0.001$ ) and second treatment ( $p = 0.03$ ). All improvements persisted after 12 months of therapy. CRT appears promising in terms of improving a patient's clinical symptoms, although the impact on mortality is unknown.

The recently completed MIRACLE trial is the largest study to date. Four hundred fifty-three patients with moderate-to-severe symptoms of heart failure associated with an ejection fraction of 35 percent or less and a QRS interval of 130 msec or more were randomly assigned to a cardiac-resynchronization group (228 patients) or to a control group (225 patients) for six months, while conventional therapy for heart failure was maintained. The primary end points of this study were the New York Heart Association functional class, quality of life, and the 6-min walking distance. As compared with the control group, patients assigned to cardiac resynchronization experienced an

improvement in the 6-min walking distance (+39 vs. +10 m,  $p = 0.005$ ), functional class ( $p < 0.001$ ), quality of life ( $p = 0.001$ ), time on the treadmill during exercise testing ( $p = 0.001$ ), and ejection fraction ( $p < 0.001$ ). In addition, fewer patients in the group assigned to cardiac resynchronization than control patients required hospitalization (8% vs. 15%) or intravenous medications (7% vs. 15%) for the treatment of heart failure ( $p < 0.05$  for both comparisons). Mortality was < 10% in both treatment arms at six months. The investigators reported a placebo effect with respect to quality of life but not for exercise or cardiac-function parameters.

Additional trials are currently underway in the US and Europe to address important unanswered issues. Several studies are evaluating the efficacy of combining internal defibrillation (ICD) with BiV resynchronization (MIRACLE ICD, CONTAK CD, INSYNC ICD, BELIEVE). Other studies are addressing whether resynchronization therapy improves mortality (COMPANION, CARE-HF, PACMAN). The COMPANION study is the largest, with a target recruitment of 2,200 patients [44], and it is powered to determine a mortality benefit of 25% in patients with dilated cardiomyopathy and a basal QRS duration > 120 ms. It includes a placebo group, a combined ICD and resynchronization therapy group, and a group receiving resynchronization therapy only. Finally, studies are planned to test the relative merits of single-site LV pacing versus BiV pacing for resynchronization (BELIEVE, PAVE and OPTSITE).

### Biventricular Pacing and Cardiac Surgery

Complete LBBB with impaired left ventricular function leads to interventricular septal wall motion abnormalities [45]. Weaning from extracorporeal circulation can be difficult in these high-risk patients. Conventional therapeutic strategies focus on maximizing cardiac output by administration of adrenergic drugs, and in severe cases implantation of intra-aortic balloon pumps. Several studies have demonstrated, that intra- and postoperative biventricular pacing as well as shortening of artoventricular delay can improve cardiac index and decrease wedge pressure [46,47]. Improvement of ventricular function following correction of underlying disease is often rapid and can usually be observed within the first 24 hours after the operation. Long-term multisite BiV pacing may not be necessary in this patient group. But some patients, having severely depressed ventricular function with wide QRS preoperatively may necessitate permanent pacing. But we need long-term prospective studies to see effect of BiV pacing on survival included this patient group.

Kaplinsky et al [48] used BiV resynchronization therapy as a bridge to transplantation. This new perspective may be alternative bridge techniques to transplantation.

### Unresolved Issues

Although much has been learned over past several years regarding CRT, many important questions remain unanswered. What is the proper stimulation site? How long will short term results last? If there is a long term effect, does biventricular pacing reduce mortality? In this regard, it is important that the ongoing trials such as COMPANION, which are addressing these key questions, proceed to completion so that the role of this therapy can be properly and fully evaluated. The mortality

impact of resynchronisation may ultimately be tied in with ICDs, particularly if the results of ongoing multicenter trials show survival benefits from such devices in CHF.

The optimal method of therapy itself is unresolved. Questions remain as to whether BiV stimulation is needed, whether multisite left-heart stimulation would enhance the efficacy, or, if an RV lead is to be placed, where the optimal location is and what the best timing delay is between RV and LV stimulation. A large unresolved question is whether this therapy is going to be useful in patients with atrial fibrillation. Some studies have suggested utility [49,50], although larger trial data remain inconclusive [51]

Another important questions remain should need clarification. Who are appropriate candidates for multisite biventricular pacing? What inclusion criteria should be used to assess ventricular dysynchronisation (electrical, mechanical, or both)? Another point also should be clarified for cardiac surgeons. When should BiV pacemakers use as adjunct to operative procedures? Which patients are good candidate for combined procedures? There is still no conclusive evidence yet. We need still some prospective studies to answer these questions.

## Results

CRT can improve cardiac function and efficiency in CHF patients with discoordinate contraction due to abnormal contraction. Several recent modest-sized placebo-controlled trials suggest that long-term benefits can be substantial. Its ultimate utility and acceptance into CHF management will depend on fully establishing its indications and long-term therapeutic value, refining the targeting of patients most likely to benefit and enhancing the treatment systems to achieve these goals. Much exciting studies has already been done, but much more studies has to be done to clear some unresolved points.

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