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## Left Ventricular Remodeling and Synchronized Biventricular Pacing in Advanced Heart Failure

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Ventricular remodeling describes the process of changes in heart size, geometry, and function that occur in response to a variety of stimuli. An increase in heart size requires the integrated disassembly and reassembly of the extracellular collagen matrix and realignment of the myofilaments to avoid sarcomeric disruption. Left ventricular (LV) hypertrophy (LVH) requires similar structural remodeling of chamber architecture and a uniform increase in wall thickness so that wall force is equally distributed throughout the ventricular walls. Ventricular remodeling may be physiologic or pathologic. Physiologic remodeling occurs with normal growth, pregnancy, and prolonged aerobic or isometric physical exercise. Pathologic remodeling occurs in chronic pressure or chronic volume overload states that usually develop over a period of years. A unique type of pathologic remodeling occurs within hours to days after the abrupt loss of contracting myocytes following an acute myocardial infarction (MI).<sup>1</sup> Physiologic and pathologic remodeling are both initiated by alterations in ventricular loading conditions, but the two types are distinguishable in that physiologic remodeling is adaptive and reversible, while pathologic remodeling is usually irreversible or only partially reversible. Pathologic remodeling is characterized by progressive dilatation, distortion of ventricular shape, and deteriorating contractile function, leading to the onset of heart failure.<sup>1</sup> Ventricular dilatation increases load and, in addition, disrupts the normal architecture of the mitral valve apparatus and annulus causing mitral regurgitation. Mitral regurgitation further increases LV loading conditions and may escalate the deterioration in contractile function. Thus, LV dilatation begets further LV dilatation, mitral regurgitation, heart failure, and sudden death from ventricular arrhythmias.

There are 5 million heart failure (HF) patients in the USA and approximately 500,000 new cases of HF are diagnosed each year at an annual cost of almost 30 billion dollars. HF is the most common hospital discharge diagnosis in patients >65 years. In more than two-thirds of patients, HF is the direct result of LV remodeling following MI due to epicardial coronary artery diseases. Progressive LV dilatation develops in 50% of survivors of acute MI with early contractile dysfunction and LV ejection fraction  $\leq 40\%$ .<sup>2</sup> In most of the remaining patients with HF, ventricular remodeling results from primary myocardial disease that is usually idiopathic dilated cardiomyopathy or, less frequently, hypertrophic or restrictive cardiomyopathy. Development of HF has grave clinical prognostic implications with regards to survival, need for recurrent hospital admissions, severe limitation of exercise capacity, and impaired quality of life.

Over the last two decades, it has become apparent that ventricular dilatation is triggered and then sustained by load-induced myocardial stretch/deformation, which may be regional or global, and activates and amplifies a number of specific intracellular signaling pathways that include induction of hypertrophy. When the hypertrophic response is sufficient to normalize LV load, progressive dilatation may be attenuated. Myocardial stretch/deformation also activates intracellular signaling that facilitates



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LV dilatation including stretch-induced activation of the family of matrix metallo-proteinases (MMPs) that degrade the extracellular collagen matrix.<sup>3</sup> The extracellular matrix provides the normal stretch-resistant collagen framework that counterbalances the distending forces, prevents dilatation, and maintains myocardial integrity and ventricular architecture.

### Therapeutic strategies

Therapeutic strategies have been developed specifically to prevent progressive dilatation and remodeling by reducing LV loading conditions with pharmaceutical agents that include vasodilators, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and  $\beta$ -adrenergic receptor blockers.<sup>4,6</sup> Appropriately timed interventions with these different classes of pharmacologic agents have been successful in attenuating, rather than reversing, ventricular remodeling and stabilizing myocardial contractile function. In patients with acute MI, early myocardial reperfusion with thrombolytic therapy or percutaneous coronary artery interventions have limited initial myocyte loss and, in so doing, preserved ejection fraction and reduced the stimulus for progressive dilatation with alterations in chamber geometry. Alternative strategies as potential therapeutic interventions that are currently under investigation in animal experiments include epicardial restraint and blockade of MMP activation to prevent degradation of the extracellular matrix. Both of these latter interventions have been shown to attenuate LV dilatation and preserve contractile function.<sup>7,8</sup>

### Cardiac resynchronization therapy

In multicenter clinical trials, a novel form of therapy for HF has recently been demonstrated to be efficacious in a special population of heart failure patients with prolonged intraventricular conduction and LV systolic dysfunction. This new device therapy is known as Cardiac Resynchronization Therapy (CRT) and employs atrial sensed synchronous biventricular pacing with optimization of the atrioventricular delay to trigger ventricular contraction immediately following atrial systole, prolong LV filling time, and particularly restore inter-ventricular and intraventricular activation and contraction towards normal. The impact of biventricular pacing therapy on ventricular remodeling and its role in the treatment of patients with HF is the main focus of this issue of *Cardiology Rounds*.

One-third of patients with clinical systolic HF have prolonged intraventricular conduction as evidenced by increased electrocardiographic QRS duration. Prolonged intraventricular conduction causes major changes in the cardiac periods within the cardiac cycle and is associated with decreased survival.<sup>9,10</sup> In HF patients with QRS duration >135 ms, there is increased isovolumic contraction time, increased isovolumic relaxation time with little change in ejection time and a resultant significant reduction in LV filling time partly due to fusion of the rapid filling phase with the atrial systolic contraction phase. In addition, prolonged QRS duration is associated with electrical and mechanical dyssynchrony that results in incoordinate ventricular contraction and regional differences in myocardial

stretch/deformation. The alterations in temporal electrical and mechanical synchrony during systolic contraction decrease dP/dt, stroke volume, and ejection fraction with concomitant increase in LV volumes and worsening mitral regurgitation.<sup>11</sup> The degree of intraventricular conduction duration and QRS prolongation beyond normal values correlates not only with decreased survival, but also increased prevalence of adverse clinical cardiovascular events such as HF.<sup>9,10</sup>

Initial small, uncontrolled studies demonstrated that synchronized biventricular pacing in patients with moderate to severe heart failure was associated with improvement in symptoms and enhanced exercise capacity. Some of these open-label studies indicated that biventricular pacing resulted in a reduction in LV volumes, a decrease in mitral regurgitation, and an increase in ejection fraction, so-called "reverse remodeling."<sup>12,13</sup> In addition, in one small trial in HF patients, when biventricular pacing was terminated after 3 months of continuous therapy, the previous symptomatic improvement and favorable effects on LV volumes, mitral regurgitation, and function attenuated by 1 week and reversed towards baseline values by 1 month.<sup>12</sup> These early promising results from small clinical unblinded studies, together with corroborative findings in canine models of HF and left bundle branch block, spawned subsequent multicenter controlled trials of CRT. These trials, including MUSTIC<sup>14</sup> and MIRACLE,<sup>15</sup> revealed improvements in New York Heart Association (NYHA) symptom class and favorable effects on exercise capacity and quality of life compared to placebo in patients with moderate and severe HF. Further trials – MIRACLE ICD<sup>16</sup> and COMPANION<sup>17</sup> – have compared the effects of combined biventricular pacing and internal cardiac defibrillators (ICD) versus biventricular pacing alone because the major causes of death in HF patients are sudden death from high-grade ventricular arrhythmias and progressive ventricular dysfunction.

### The MIRACLE Study

The Multicenter InSync Randomized Clinical Evaluation (MIRACLE) study was a prospective, double-blind, placebo-controlled trial of 453 patients already receiving optimized HF therapy randomized to CRT or no CRT. MIRACLE was designed to determine whether synchronized biventricular pacing was efficacious as compared to placebo (no CRT).<sup>15</sup> The primary endpoints of the trial were improvement in NYHA symptom class, 6-minute hall walk distance, and quality of life (assessed using the Minnesota Living with Heart Failure Questionnaire) after 6 months of biventricular pacing versus no pacing (placebo). A secondary endpoint in this optimally-treated population of HF patients was to investigate whether there was any objective evidence for attenuation or reverse LV remodeling evidenced by changes in LV structure and function to indicate that LV remodeling accompanied the beneficial impact on symptoms, exercise capacity, and quality of life versus the no pacing group.

In the MIRACLE study, all patients had InSync devices implanted with optimization of atrioventricular (AV) delay and were randomized to CRT "on" or CRT pacing "off." The

**Table 1: Baseline demographics for patients implanted, randomized, and completing echocardiographic follow-up visits<sup>19</sup>**

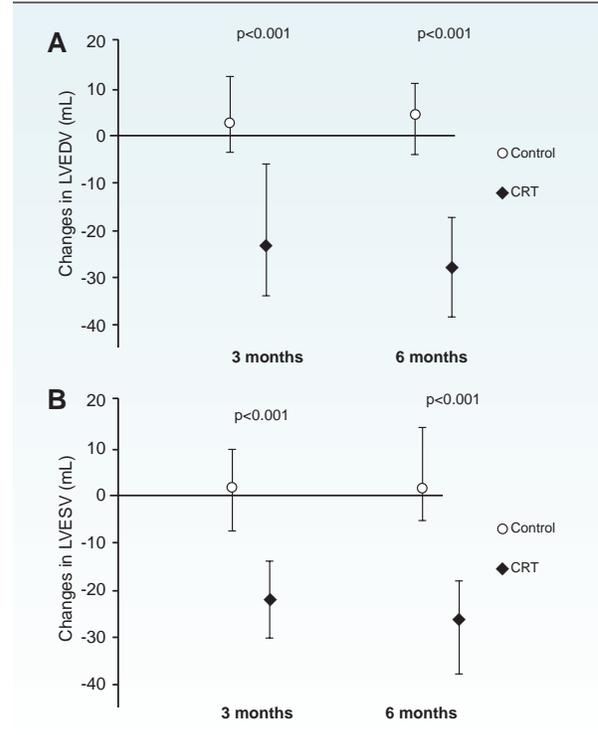
Parameter	Control Group (n = 151)	CRT Group (n = 172)
Age, y	64.8±11.4	63.9±11.0
Gender, % male	68.9	65.1
Ethnicity, % white	90.1	90.1
NYHA, % class III	94.7	90.1
QRS duration, ms	164.7±20.6	166.4±19.7
LVEF, %	24.3±6.8	24.5±6.8
LVEDD, mm	73.5±9.7	73.9±10.2
LVEDV, mL	293.9±105.1	295.6±102.6
LVESV, mL	227.5±98.6	227.7±93.7
6-minute hall walk, m	295.4±94.3	307.2±77.8
Heart rate, bpm	71.3±13.3	69.2±14.6
Systolic blood pressure, mm Hg	113.4±21.5	113.9±21.6
Diastolic blood pressure, mm Hg	68.8±12.4	69.8±13.0
Diuretic use, %	94.0	94.2
ACE-I or ARB use, %	92.1	94.8
β-Blocker use, %	56.3	62.2

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 Continuous parameters are expressed as mean ±SD.  
 ACE-I = ACE inhibitors, ARB = angiotensin-receptor blockers.

patient inclusion criteria were NYHA class III/IV, LV end-diastolic dimension ≥55 mm, ejection fraction ≤35%, a QRS duration ≥135 ms; these criteria were similar to other CRT studies in the United States. All patients had to be on an optimal conventional HF medical regimen that remained unchanged for a minimum period of 1 month. This medical treatment strategy had to include diuretics, ACE inhibitors or ARBs, digitalis and, if β-blockers were used, they had to be administered for at least 3 months. Doppler echocardiography was used to quantify the longitudinal structural changes in LV architecture and systolic and diastolic function from baseline to 3 and to 6 months of continuous synchronized biventricular pacing as compared to patients randomized to the non-paced group. The temporal changes in paired studies at 3 and 6 months provided the framework for assessing whether ventricular remodeling differed between the 2 patient groups randomized to biventricular pacing versus no pacing.

Baseline demographics for the patients in the echocardiographic analysis in the MIRACLE study who were implanted, then randomized to the 2 treatment strategies, and who completed the Doppler echocardiographic studies at baseline, 3 and 6 month follow-up visits were similar (Table 1). However, at variance with prior CRT studies, approximately 50% of the patients randomized in the MIRACLE study had HF due to ischemic heart disease, and a similar proportion had HF due to idiopathic non-ischemic dilated cardiomyopathy. LV end-diastolic and end-systolic volumes at baseline were markedly elevated and mean ejection fraction was low at 24%, but were not significantly different in the CRT “on” versus the CRT

**Figure 1: Median change (with 95% confidence intervals) in LV end-diastolic volume (LVEDV) (A) and LV end-systolic volume (LVESV) (B) at 3 and 6 months after randomization in the control group (circles) and the CRT group (diamonds).**



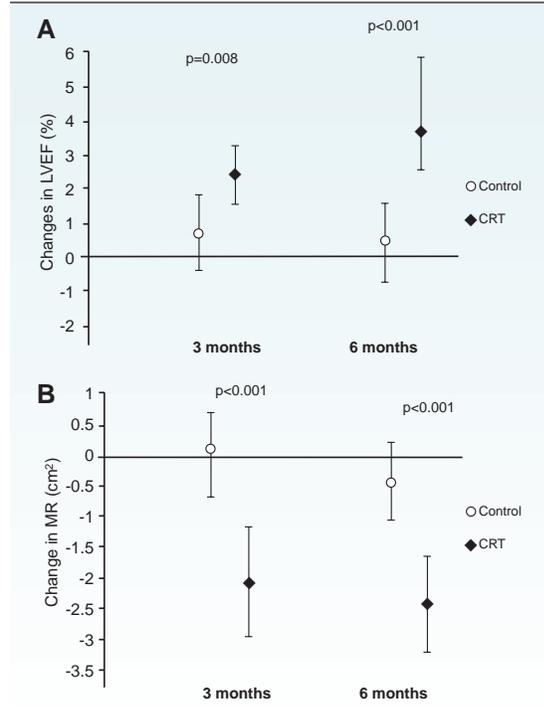
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“off” group. Use of diuretics, ACE inhibitors, and β-blockers were equivalently distributed across the biventricular paced and non-paced groups so that any differences in LV remodeling over the 6 months after randomization could not be ascribed to any differences in the use of these pharmacologic agents or a drug effect.

After 6 months of continuous synchronized biventricular pacing, LV end-diastolic and end-systolic volumes decreased significantly compared to the CRT “off” group. This reduction in LV volumes was already apparent at 3 months, which was the earliest time point evaluated, and decreased further between 3 and 6 months (Figures 1 and 2). This structural reverse remodeling did not occur in the CRT “off” patients. Importantly, CRT did not simply attenuate progressive LV dilatation such as that which occurs with ACE inhibitor or ARB therapy, but resulted in decreased ventricular volumes below baseline values, consistent with reverse remodeling. These changes in LV volumes in the CRT patients occurred in addition to continued optimal medical HF treatment.

Reduction in LV volume was not accompanied by any favorable alteration in LV chamber shape towards ellipsoidal geometry at 6 months, but it was associated with a decrease in the severity of mitral regurgitation that was apparent at 3 months, but was more pronounced at 6 months. Reduction in the severity of mitral regurgitation only occurred in the patients with biventricular pacing. Improvement in mitral regurgitation was most likely mediated by partial restoration

**Figure 2:** Median change (with 95% confidence intervals) in LV ejection fraction (LVEF) (A) and mitral regurgitation (MR) (B) at 3 and 6 months after randomization in the control group (circles) and the CRT group (diamonds).<sup>19</sup>

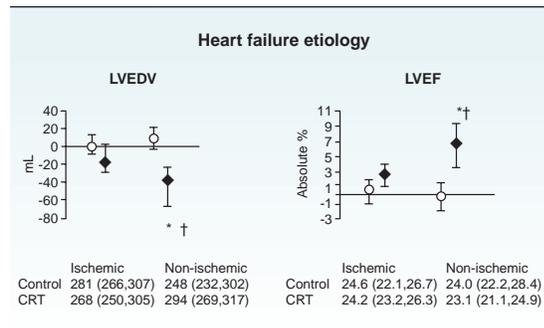


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of normal mitral subvalve geometry and decreases in mitral annular circumference as ventricular volume declined, but may also be due in part to restored coordination of the papillary muscle shortening.<sup>18</sup> The combination of the decrease in LV volume and the concomitant decline in severity of mitral regurgitation both reduced LV loading conditions, which in turn was associated with improved pump function because LV load and systolic contractile function are inversely correlated. As predicted from La Place's law, the decrease in ventricular volumes was associated with modest, but highly significant increases in LV ejection fraction at 3 months. Ejection fraction further improved between 3 and 6 months concordant with the temporal changes in chamber remodeling. There was no change in ejection fraction in the non-biventricular paced patients on optimal medical therapy over the same time period. These findings of reverse remodeling detected by serial echocardiograms in patients with continuous synchronized biventricular pacing in the MIRACLE study have been corroborated in other studies of biventricular pacing MUSTIC,<sup>14</sup> MIRACLE ICD,<sup>16</sup> and CONTAK CD.<sup>13</sup>

In the echocardiographic analysis of the MIRACLE study, biventricular pacing was associated with alterations in the cardiac periods such that isovolumic contraction time and intraventricular mechanical delay (time between the onset of antegrade blood flow in the aorta and the onset of antegrade blood flow in the pulmonary artery) both decreased (Figure 3). In addition, biventricular pacing was associated with increased LV filling time

**Figure 3:** Comparison of the median changes from baseline with 2-sided 95% confidence intervals by etiology of heart failure in the control group (circles) and the CRT group (diamonds) for LV end-diastolic volume (LVEDV) in the left panel and for LV ejection fraction (LVEF) in the right hand panel.<sup>19</sup>



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that may have also contributed to improvement in ejection function as compared to the non-biventricular paced patients. LV diastolic function that was assessed as deceleration time of the early diastolic transmitral flow velocity signal increased significantly after 6 months of biventricular pacing, while there were no corresponding changes in the non-paced group. The myocardial performance index/Tei index, which combines diastolic and systolic function as the sum of isovolumic contraction time and isovolumic relaxation time divided by ejection time, improved markedly in the biventricular paced group, but not in the non-paced patients at 6 months. These findings indicate that reverse structural remodeling induced by synchronized biventricular pacing improved both systolic and diastolic LV function but, of note, this structural and functional ventricular remodeling did not correlate with reductions in QRS duration.

Symptomatic benefits and increased exercise capacity have been described in a number of multicenter trials of biventricular pacing. In the MIRACLE study, significant improvements in NYHA symptom class, 6-minute hall walk distance, and quality of life occurred in approximately two-thirds of patients with biventricular pacing. Although there were no striking direct correlations between Doppler echocardiographic measures of changes in ventricular structure, function, and symptoms; symptomatic benefits and increased exercise capacity occurred predominantly in patients who exhibited the greatest degree of ventricular reverse remodeling.<sup>15</sup> The MIRACLE trial was similar to most trials of biventricular pacing in that it was not designed or powered to detect differences in mortality between CRT and non-paced patients, but the clinical implications of reverse remodeling and reduction in LV volume would predict a decrease in adverse cardiovascular events, including life-threatening ventricular arrhythmias over long-term follow-up if these volume changes are maintained.<sup>19,20</sup>

Reverse ventricular remodeling and associated symptomatic improvement occurred after 6 months of biventricular pacing independently of the etiology of HF,

that is, whether it was due to ischemic or to non-ischemic dilated cardiomyopathy. However, the changes in LV volumes and ejection fraction with biventricular pacing were 2- to 3-fold greater in patients with non-ischemic versus those with ischemic etiology of HF. These differences in LV size and function between the ischemic and non-ischemic patients with biventricular pacing were significant at 6 months. These changes were sustained at 1-year follow-up in spite of larger baseline volumes, lower ejection fractions, and more dyssynchrony as evidenced by greater interventricular mechanical delays.<sup>21</sup> These findings could not be explained by any discrepancies in the use of  $\beta$ -adrenergic receptor blocking agents in the 2 different etiologies of HF because the effects of CRT on ventricular remodeling occurred regardless of the use of  $\beta$ -adrenergic receptor blocking agents.

A plausible explanation for the significant, but less extensive reverse remodeling in the ischemic versus the non-ischemic ventricles (regardless of greater LV size, lower ejection fraction and greater dyssynchrony in the non-ischemic hearts) is the larger volume of viable versus non-viable myocardium available for rectification. In the proportion of patients who do not appear to respond to biventricular pacing by reverse remodeling, causes that have been implicated include sub-optimal LV electrode placement for LV activation or the placement of LV electrodes in or adjacent to non-viable scar tissue from prior infarction. In a number of such patients, repositioning of the left or right ventricular electrodes has resulted in reduced dyssynchrony with subsequent reverse remodeling.<sup>22</sup>

Precisely how synchronized biventricular pacing induces ventricular remodeling is not clearly understood, but there are several likely contributory mechanisms that deserve consideration. One mechanism is that by optimizing AV delay, LV filling is prolonged and initiation of ventricular contraction is timed to immediately follow atrial systole, thereby increasing end-diastolic volume and ejection function. Another mechanism involved in reverse remodeling that would be unique to biventricular pacing is the reduction in intraventricular conduction delay leading to a resynchronization of septal and lateral LV wall motion and a reduction in end-systolic volume. Resynchronized interventricular electrical activation improves right and LV interaction. How LV pacing alone elicits the same magnitude of mechanical benefit as synchronous biventricular pacing<sup>23</sup> with such a different temporal electrical activation, is difficult to reconcile, but indicates that improvements in mechanical synchrony and function do not require electrical synchrony.<sup>23</sup> In the MIRACLE study, biventricular pacing reduced intraventricular mechanical delay that was measured as the time period between the onset of right ventricular ejection and the onset of LV ejection, while this time period/interval remained unchanged in the non-paced group. These 3 factors: prolonged filling time, intraventricular, and interventricular synchronization in combination, decreased

the ventricular dyssynchrony and thereby improved regional and global myocardial mechanics at diminished energy costs,<sup>24</sup> and also possibly reversed the molecular polarization of myocardial stretch/deformation-induced expression gradients of calcium handling and gap junction proteins.<sup>25</sup>

Several important issues regarding biventricular pacing remain unresolved. Approximately 20%-25% of patients with advanced HF do not respond to CRT. Reliable identification of patients likely to exhibit reverse remodeling and derive symptomatic benefit is an important goal. A simple measure that has been investigated is the aortic pre-ejection interval (APEI), which is the time period measured from the onset of the QRS to the onset of antegrade blood flow in the LV outflow tract. In the MIRACLE echocardiographic sub-study, an APEI >160 ms, regardless of the etiology of HF, LV volume, or ejection fraction at baseline, was strongly associated with a greater likelihood of reverse remodeling.<sup>26</sup> Progress is also being made with respect to identifying patients with intractable HF who are the most likely to improve with biventricular pacing using Doppler echocardiography and, in particular, using Doppler tissue imaging (DTI) techniques for measuring the time to regional myocardial peak velocities and peak strain rates.<sup>22,27</sup>

Another issue in need of clarification is whether biventricular pacing should be coupled with internal defibrillator placement, particularly in patients with ischemic cardiomyopathy as the cause for HF with low ejection fraction (<35%) who do not meet the MADIT II study recommendations for internal cardiac defibrillator placement.<sup>28</sup> A further remaining and unresolved issue regarding biventricular pacing with, or without, automatic internal defibrillators, is how to rationalize the costs involved with appropriate placement of these devices during the current era of health care cost containment.

## Conclusion

Synchronized biventricular pacing is a new therapeutic development that has proved efficacious in several multicenter clinical trials in patients with chronic severe HF intractable to conventional medical therapy, including ACE inhibitors or ARBs,  $\beta$ -receptor blocking agents, and diuretics. Importantly, the objective structural and functional remodeling demonstrated primarily by echocardiography is associated with improvements in quality of life, exercise capacity, and NYHA symptom class. Thus, as data becomes available from completed and currently ongoing multicenter clinical trials of biventricular pacing, a role will be found for these devices in the therapeutic armamentarium for chronic severe HF that may be welcome in elderly patients not considered for surgical revascularization, heart transplantation, or destination therapy with LV assist device placement. CRT may also emerge as appropriate temporary or permanent rescue therapy for young patients before advancing to heart transplantation.

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