Cardiac Resynchronization Therapy…

and Beyond

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Disclosures

Dr. Kowal has been the local principal investigator for the following multi-center studies:

Medtronic
ACED Trial
InSYNC Registry
WAVE Study
MAVRC Registry
IDEA-VF study

St. Jude Medical
PAVE Trial
RHYTHM-ICD Trial
RHYTHM-ICD V-V Timing Trial
QuickSite Lead Registry

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Congestive heart failure (CHF) is one of the leading causes of morbidity and mortality in the United, impacting nearly 1 in 5 individuals during the course of their lifetime. In addition to the well established understanding of the role of myocyte contractile dysfunction and neurohormonal dysregulation in the pathogenesis of CHF, abnormalities of cardiac electrical activation have recently been recognized as contributing to the progression of CHF. Multisite, biventricular pacing has emerged as an effective therapy for CHF complicated by electromechanical dyssynchrony in combination with traditional pharmacologic therapy. This Grand Rounds will review the principles underlying cardiac dyssynchrony, the importance of biventricular pacing in correcting this abnormality (termed cardiac resynchronization therapy, or CRT), predictors of success with CRT and future directions for biventricular pacing.

Conduction Abnormalities and Electro-mechanical Dyssynchrony

Arrhythmias are more prevalent in the setting of CHF and are an important cause of morbidity and mortality. In addition, it has become apparent that electrical conduction abnormalities, in the absence of discrete arrhythmia, can directly impact on CHF severity and prognosis. Altered or delayed conduction can lead to dyssynchronous myocardial contraction, manifest on multiple levels, including: 1) atrioventricular (AV) dyssynchrony involving excessive delay between atrial and ventricular systole; 2) interventricular dyssynchrony involving discordant onset of right and left ventricular systole; and/or 3) intraventricular dyssynchrony characterized by delayed between peak contraction of the various segments of the left ventricular myocardium. These various types of electromechanical dyssynchrony may be manifest on the surface electrocardiogram as a prolonged PR interval as well as interventricular conduction delay (IVCD), typically left bundle branch block (LBBB).[2]

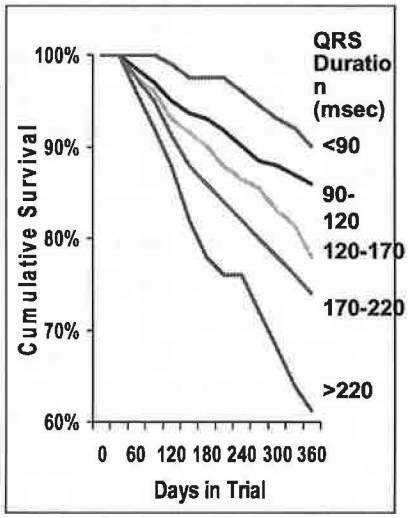

Figure 1: Survival as a function of QRS duration . from Gottipaty, et al.

Prolongation of the QRS duration regardless of morphology correlates total mortality as well as arrhythmic death in subjects with CHF (Fig. 1).[3,4] In addition, the altered ventricular mechanics caused by IVCD have profound effects on hemodynamics. LBBB is associated with significant delay in electrical and mechanical activation of the lateral left ventricular wall relative to the left ventricular septum. As a result, septal and lateral LV segments contract sequentially rather than simultaneously, delaying and diminishing LV force generation, since a component of septal contraction is expended displacing the lateral wall. In addition, since intracavitary pressure rise prior to the onset of lateral wall activation, these segments experience increase wall stress and myocardial oxygen demand. These factors combine to delay the time between QRS onset and the generation of sufficient pressure to open the aortic valve, known as the pre-systolic time

interval (LVPSI).[2, 5-8] If dyssynchrony is severe, lateral wall contraction may actually occur after aortic valve closure, significantly reducing ejection fraction and developed pressure.[9] The net result is a reduction in stroke volume, ejection fraction (EF), developed force (dP/dt) and cardiac output. Interestingly, even in the setting of RBBB, significant LV electrical dyssynchrony has may be present. The increased wall stress in the segments of delayed activation elevates myocardial oxygen consumption and reduces regional myocardial blood flow reserve.[10, 11]

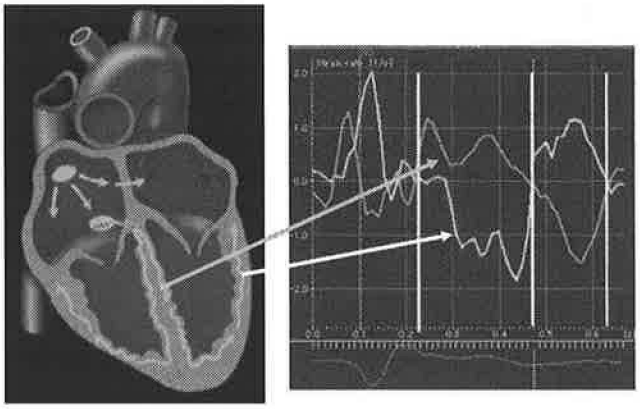

Figure 2: Tissue Doppler imaging comparing septal to lateral contraction velocity. Note the delay in lateral activation until after closure of the aortic valve (middle white line. From Sogaard.

These alterations are evident both in traditional echocardiography as well as in newer tissue Doppler modalities. LBBB is associated with an increased LVPSI as well as the interventricular delay (IVD; the difference in the RV and LV pre-systolic time intervals). In addition, significant delay between contraction of the left ventricular septum and lateral walls may be noted by M mode imaging (the septal/posterior wall motion delay; SPWMD). Tissue Doppler imaging is a modality that measures the regional longitudinal contraction of individual LV segments may also illustrate significant regional delays (Fig. 2).[2, 9, 12-15]

Ventricular dyssynchrony is manifest on a sub cellular level as well.[16] In dog models of CHF with LBBB, regions of delayed contraction show elevations of stress induced kinases, such as *p-erk,* compared with earlier-activated segments. These delayed regions also show reductions in the calcium-handling proteins, Phospholamban and SERCA2a, as well as down regulation of the gap junction subunit, connexin-43 (CX43). These changes may reflect a genetic program activated in response to elevated wall stress and provide further evidence of the regional effect of myocardial dyssynchrony. In addition, the regional down regulation of CX43 may lead to

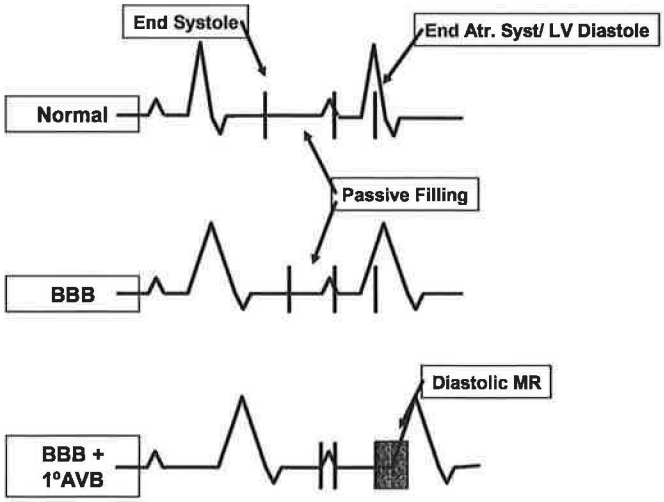

Figure 3: The reduction of passive LV filling time due to BBB and PR prolongation.

dispersion of conduction properties and may underlie or contribute to the heightened arrhythmogenesis associated with the QRS prolongation.

Electromechanical dyssynchrony also alters LV diastolic function. Prolonged systolic activation times due to IVCD shorten available time for passive left ventricular filing prior to the onset of atrial contraction. In the combined setting of IVCD and PR prolongation (AV dyssynchrony), the delay between atrial contraction and the onset of ventricular activation further limits the time for passive LV filling. Atrial contraction may complete prior to the onset of ventricular contraction resulting in a short segment during which the mitral valves may displace passively into the atrial tissue with resultant mitral regurgitation during diastole (Fig. 3).[6]

Recent reports of CHF exacerbation in the setting of RV pacing further highlights the significance of ventricular dyssynchrony. RV apical pacing delays LV mechanical activation in a manner similar to LBBB. Several clinical studies demonstrate a direct correlation between the extent of RV apical pacing and the development of clinical CHF. The DAVID trial, a study designed to explore the utility of dual chamber pacing at 70 bpm (DDDR-70) to facilitate up-titration of β-blockers in heart failure patients, demonstrated an increase in heart failure hospitalization and a trend towards increased mortality among those randomized to DDDR-70 compared with those with low-rate, backup pacing (VVI-40).[17] Subjects assigned to DDDR-70 had 56% ventricular pacing compared with a 2% pacing in the VVI group (Fig.4).

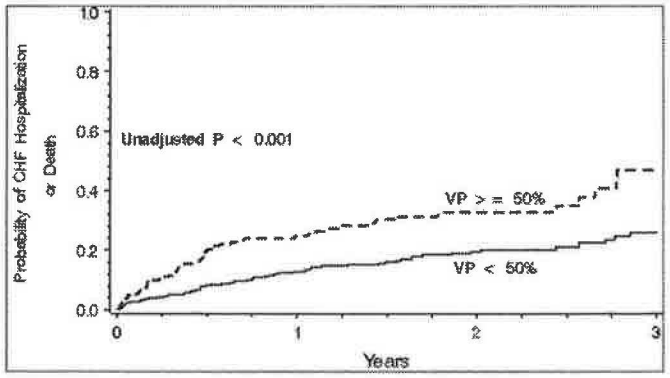

Figure 4: CHF Hospitalization or Death in MADIT-II as a function of percentage RV pacing.

Likewise, in the MADIT-II study, comparing ICD to conventional medical therapy in patients with depressed LV function due to prior myocardial infarction, the ICD arm was associated with a 23% increased risk of heart failure hospitalizations, likely due to the presence of intermittent right ventricular pacing. In fact, obligate RV pacing in those patients with complete heart block negated the mortality benefit from an ICD.[18]

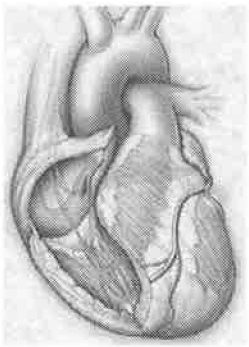

Figure 5: Leads in CRT. From Jacho[1]

Cardiac Resynchronization with Biventricular Pacing

The recognition of the detrimental role of ventricular dyssynchrony on myocardial performance has led to the development of pacing modalities designed to "resynchronize" myocardial contraction, termed cardiac resynchronization therapy (CRT). CRT is accomplished by simultaneous pacing the RV apex (or septum) with the area of LV late activation (typically on the lateral LV wall). Initially mediated by surgical placement of an epicardial LV lead in

conjunction with a standard pacing system, CRT is now implanted percutaneously; the LV lead is placed in an epicardial LV vein via the coronary sinus in conjunction with a conventional pacemaker or ICD system (Fig.5).

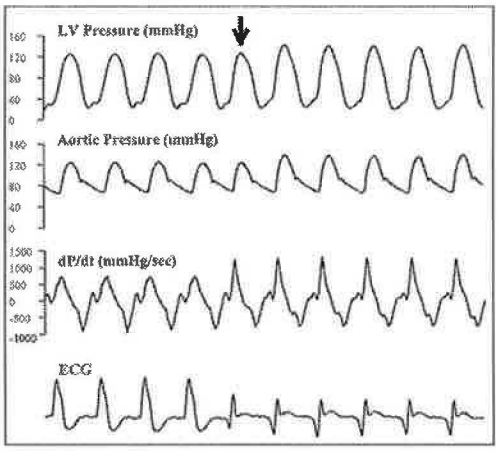

Figure 6: Hemodynamic changes due to acute biventricular pacing (arrow).

Multiple studies have demonstrated the acute benefit of CRT.[10, 19, 20] Initiation of CRT increases in systolic pressure, and dP/dt while decreasing in left ventricular end-diastolic pressure, and mitral regurgitation (Fig 6). Unlike inotropic therapy, however, the improvement in dP/dt is accompanied by a reduction in myocardial O_2 consumption (Fig. 7). In addition, a significant reduction in sympathetic neural activity has been observed with biventricular pacing compared with RV pacing or intrinsic conduction in patients with IVCD. Echocardiography also reveals acute re-establishment of near simultaneous septal and lateral wall contraction; this finding may also be observed in M-mode echocardiography as in normalization the SPWMD.[13]

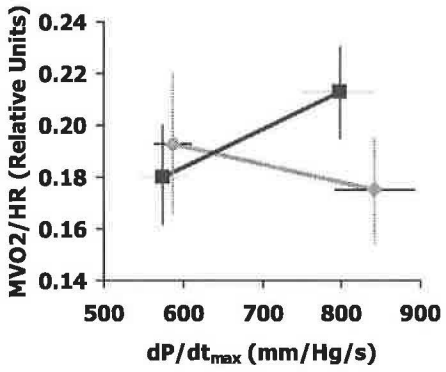

Figure 7: Change in MVO2 due to CRT (diamonds) or dobutamine (squares). From Nelson.

Studies of Chronic CRT

Several multi-center, randomized clinical trials have demonstrated the chronic benefits of CRT. Despite subtle differences in enrollment criteria, these studies generally enrolled subjects with NYHA Class III and IV CHF, an LVEF of $\leq 35\%$, an LV end-diastolic dimension > 55 mm, and a QRS duration >120-130 msec and optimal medical therapy with a β-blockers and ACE-I. When assigned to CRT, patients in the MUSTIC study demonstrated statistically significant improvements in NYHA class, exercise capacity and quality of life compared to periods during which they were crossed over to intrinsic ventricular activation (Fig. 8).[21] Non-blinded, non-randomized extensions of this study continue to demonstrate the long-term benefit of CRT therapy.[22]

The larger MIRACLE trial enrolled patients in a parallel manner comparing CRT to optimal medical therapy without an implanted device. Again, patients assigned to CRT demonstrated a statistically significant improvement in NYHA class, exercise capacity and quality of life. In addition, this study demonstrated a statistically significant 50% reduction in hospitalization for CHF due to CRT. The subsequent RHYTHM-ICD study demonstrated similar results when comparing patients receiving ICD therapy with and without CRT.[23]

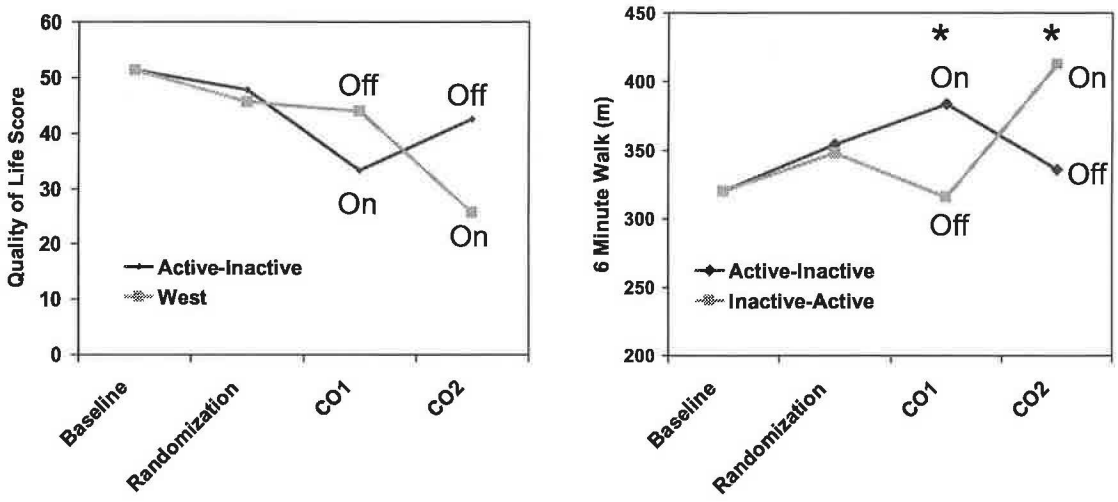

Figure 8: Results of the MUSTIC Study. Changes in quality of life (left) and 6-minute walk distance at baseline and during active and inactive period of CRT. From Cazeau.

The COMPANION study was a mortality trial comparing patients on optimal medical therapy for CHF with both CRT-pacing and CRT-ICD therapy. Both CRT arms demonstrated statistically significantly reductions in heart failure hospitalization (25% and 27%, respectively). In addition the CRT-ICD arm demonstrated a statistically significant reduction in all-cause mortality (36%). A clinical reduction in mortality was associated with the CRT-pacing (24%); however this did not reach statistical significance in-part due to the premature cessation of the study. A 32% reduction in CHF mortality did reach significance.[24] A recent meta-analysis of over 6,000 patients enrolled in these and other smaller CRT trials confirmed both the functional improvements as well as a 21% all-cause mortality reduction associated with CRT driven largely by reduction in CHF mortality.[25] The recently reported CARE-HF trial not only mirrored the results of the prior studies but also demonstrated a clear statistically-significant 36% relative, 10% absolute reduction in all cause mortality associated with CRT-pacing even in the absence of ICD therapy (Fig. 9).[2, 26]

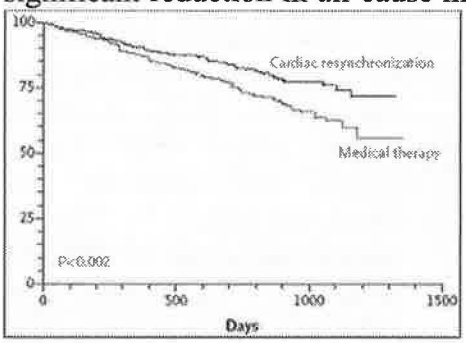

Figure 9: All-cause mortality in the CARE-HF study. From Cleland.

CRT and Reverse Remodeling

The clinical benefits associated with chronic CRT are mirrored by objective metrics of improved myocardial performance. The above studies have consistently demonstrated improvements in LVEF, with decreases in LV volumes and mitral regurgitation due to changes in cardiac sphericity. Yu, *et al* found that following three months of CRT, a significant component of improved LV performance was maintained when biventricular pacing was immediately withheld, and gradually deteriorated towards pre-pacing levels over time (Fig. 10).[14] These data indicate that CRT acutely improves LV synchrony and

chronically stimulates a reversal of the detrimental remodeling associated with CHF. More efficient myocardial oxygen metabolism has been reported along with improvements in myocardial blood flow reserve.[27] In addition, CARE-HF and other studies demonstrated a reduction in BNP suggesting that the improvement in myocardial performance impact the neurohormonal axis.[12, 26] Similarly, reductions in HRV have been reported. At present, it remains unclear how CRT impacts the genetic program in the failing myocyte.

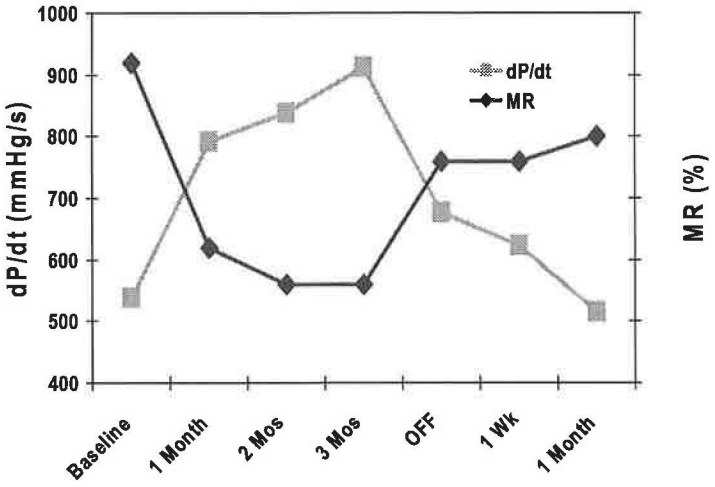

Figure 10: Evidence of reverse remodeling due to CRT. Changes in dP/dt and MR before,during and after cessation of CRT. From Yu.

The mechanism underlying CRT-mediated reverse remodeling is complex. Perhaps counterintuitive, LV-based pacing does not markedly reduce the time to peak contraction of delayed LV segments (Fig. 11). Rather, CRT delays early-activated segments to create a more uniform pattern of contraction. The resultant reduction in intraventricular dyssynchrony facilitates recruitment of segments of post-systolic contraction thus increasing dP/dt, LVEF and cardiac output, and reducing wall stress and MR.[14, 28] The RV pacing component of CRT also delays RV activation, thus reducing interventricular delay. Finally, the timing of ventricular activation during CRT diminishes AV delay; in conjunction with the reduction in ventricular activation time, this reduction in AV dyssynchrony increases diastolic filling time. Chronically, the beneficial effects of CRT on all three aspects of dyssynchrony facilitate reverse LV remodeling.

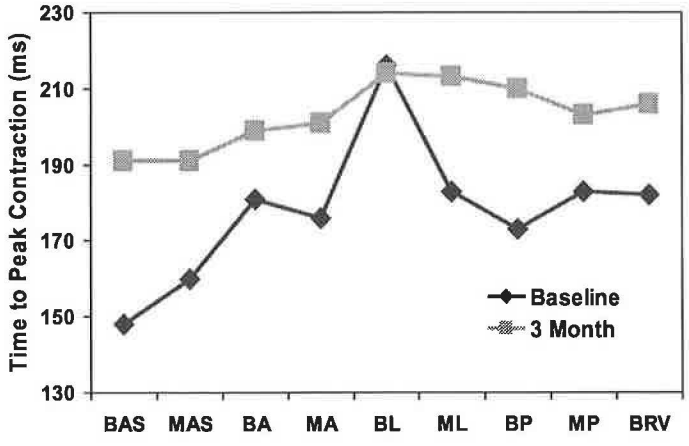

Figure 11: Time to peak systolic contraction at various LV segments before and after CRT. B, basal; M, mid; AS, anterior-septal; A, anterior; L, lateral; P, posterior;

The Dark Side of CRT

Despite the robust clinical data supporting CRT, several pitfalls have been identified. LV lead placement may be hindered by anomalous CS and LV venous anatomy as well as the proximity of appropriate target sites to the phrenic nerve. The rate of successful LV lead delivery ranges from 88%-95% with a 2% post-procedure incidence of lead dislodgement.

Study	Non-responders (%)	Measure
Pitzalis, et al.	40%	↓ LVESVI ≥ 15%
Penicka, et al.	45%	↑ EF ≥ 25%
Yu, et al.	43%	↓ LVESV ≥ 15%

More importantly, a common feature of CRT trials has been the observation that approximately one-third of patients do not seem to respond to therapy (Table). Poor response to CRT likely stems from inadequate delivery of therapy due to poor LV lead position and an absence of baseline dyssynchrony. Several acute and chronic studies have examined optimal LV lead position. The site of greatest electrical and mechanical delay may differ making it difficult to individualize appropriate LV lead positioning. This is further complication in patients with prior MI and nonviable myocardium in the lateral wall. Unlike laterally positioned leads, anterior and anterior lateral LV leads do not render a significant chronic improvement in NYHA class or EF (Fig. 12).[29] Acutely, up to 33% of patients demonstrate worsened hemodynamics with LV leads in the anterior LV vein.[30]

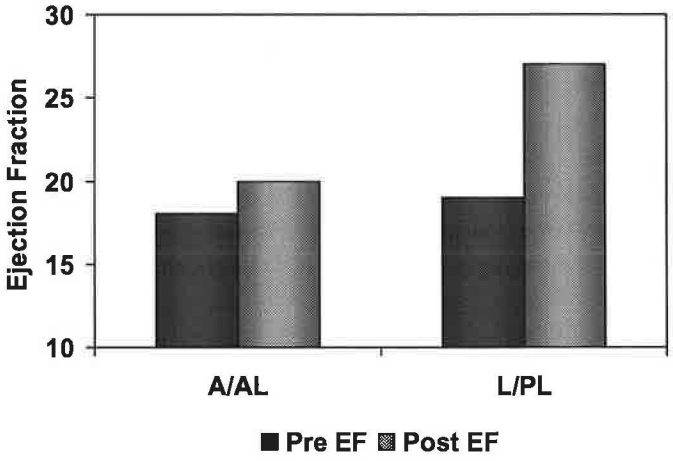

Figure 12: The role of LV lead position in the success of CRT. A/AL, anterior/anteriorlateral; L/PL, lateral/posteriorlateral. From Rossieri.

The principle reason for the presence of nonresponders to CRT likely relates to the inaccuracy of QRS to predict significant ventricular dyssynchrony. QRS duration (particularly >150 msec) correlates with clinical response to CRT. However, when echocardiography is used to evaluate for LV dyssynchrony, up to 30% of patients with QRS duration > 150 show no significant electromechanical delay.[12, 13, 28, 31] Among patient with QRS duration of 120-150 msec dyssynchrony was evident

in only 50%. Conversely, 25-20% of patients with LV systolic dysfunction and a normal QRS duration have echocardiographic evidence of dyssynchrony suggesting that a subpopulation of "normal QRS" patients may benefit from CRT.[32, 33]

Multiple echocardiographic modalities, including M-mode, tissue Doppler, tissue tracking and strain rate imaging have used to evaluate non-responders to CRT.[6, 9, 12, 13, 15, 29, 31, 34-38] Uniformly, echocardiographic measures of dyssynchrony correlate well with response. Using a 15% reduction in LV end-systolic volume as a metric for response, two measures have emerged as robust markers: 1) the standard deviation of the time to peak systolic contraction of 12 LV segments (Ts-SD), and 2) the septal-posterior wall motion delay (SPWMD).[13, 28] When prospectively assessed, a SPWMD effectively distinguished subjects with improvement in LVEF (92% sensitivity, 78% specificity) and clinical CHF exacerbations. Unfortunately, measurements such as Ts-SD currently require complex off-line analysis and SPWMD is hampered in the setting of septal wall-motion abnormalities. Simpler thresholds, such as a LV pre-systolic interval or the IVD may be adequate. Two groups demonstrated an 85% response to CRT (measured by a 15% reduction in LV end-systolic volume).[6, 34] Furthermore, the requirement that subjects enrolled in CARE-HF with a QRS duration between 120-150 msec also have a LVPSI >140 msec, an IVD >40 msec or a diastolic interval of <40% may account for the impressive reduction in morbidity and mortality in this study.

Future Roles for CRT

Functional mitral regurgitation is common with LV systolic dysfunction. Remodeling that leads to a more spherical left ventricular shape, altered activation of the posterior papillary muscle, and restriction to leaflet movement due to both elevated LA pressure and dilated LV dimension, combine to increase the mitral/atrial valve orifice area with resultant mitral regurgitation. Resynchronization therapy has been associated with a decrease in functional MR due principally to the re-coordination of papillary muscle contraction and reverse remodeling. In fact some studies suggest that CRT's success is due principally to the reduction of mitral regurgitation, although the mere presence of MR does not distinguish responders. A potential role for CRT in the treatment of functional MR, even in the absence of significant QRS prolongation, is being explored.

CRT may also suppress ventricular arrhythmia. PVCs and appropriate ICD therapy are less common during CRT. A case of suppression of sustained VT in a patient with prior MI using CRT has been reported. In addition, we demonstrated biventricular pacing reduces the induction of ventricular arrhythmias in patients with LV dysfunction and a prior MI.[39, 40] CRT may become as an alternate therapy for arrhythmia suppression in ischemic patients with recurrent VT.

Summary

In summary, cardiac resynchronization therapy by means of biventricular pacing has emerged as an effective therapy for moderate and severe heart failure in patient with left ventricular dysfunction and electromechanical delay, when delivered in conjunction with optimal medical therapy. While a significant proportion of patients fail to respond to CRT, echocardiography may provide the necessary incremental information to identify patients who will derive benefit. Future studies will likely reveal the promise of other scenarios in which CRT renders favorable outcomes.

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