



Issues in Cardiac Resynchronization Treatment

a report by

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Congestive heart failure (CHF) is the number one hospital discharge diagnosis for older adults and the leading cause of hospital readmissions, reflecting poor quality of life for patients and increased healthcare resource use, and is the cause of 300,000 deaths annually.¹ Cardiac resynchronization therapy (CRT) has become a new effective treatment modality in those with drug-resistant advanced CHF. Recommendations for optimal patients eligible for CRT are based on trials that showed its benefit in patients with wide QRS (≤ 120 ms), advanced left ventricular (LV) systolic dysfunction with an ejection fraction of $\geq 35\%$, LV enlargement (end-diastolic diameter ≥ 5.5 cm) and class III or IV CHF symptoms despite optimum medical regimen.^{3,4} Evaluation of these studies shows that as many as 30–40% of patients do not respond to or even deteriorate after CRT despite tight selection criteria.³

Several potential mechanisms may be responsible for this lack of benefit in some patients post-CRT, discussed below.

Electrical versus Mechanical Dyssynchrony

Electrical dyssynchrony as determined by electrocardiogram (ECG) may not necessarily determine mechanical dyssynchrony—the real target for correction by CRT. In support of this argument, there are a number of studies that have compared electrical with mechanical dyssynchrony criteria and found that the response to CRT is better predicted by mechanical dyssynchrony rather than by electrical dyssynchrony.⁵ The problem with these mechanical dyssynchrony criteria is that these studies have evaluated different segments of the myocardium and vary in the extent of evaluation of the myocardium, as well as in the timing of evaluation within the cardiac cycle.^{6–10} This results in disparity among various dyssynchrony criteria when one compares one method with another. Intra-subject variability in these measurements of mechanical dyssynchrony is another confounder.

Mechanical dyssynchrony in the radial direction—particularly by speckle tracking—is a newer method that can improve patient selection;¹¹ however, radial dyssynchrony does not necessarily correlate with mechanical dyssynchrony in the longitudinal direction and the significance of one over the other is unclear. Other evidence in support of the importance of mechanical rather than electrical dyssynchrony is the finding of significant response to CRT in patients with narrow QRS who obviously do not have electrical synchrony—at least based on surface QRS—but nevertheless have significant mechanical dyssynchrony.^{12–14}

Technical Factors

Besides the presence of mechanical dyssynchrony itself, there are several technical reasons that may be responsible for lack of response from CRT.¹⁵

These include selection of inappropriate targets for resynchronization. In general, it has been shown that the placement of the LV lead in the posterolateral branch shows better improvement in cardiac function than the placement of the LV lead in the anterior great cardiac vein or the medial vein,^{16,17} others have shown no difference in long-term benefit of LV placing site.¹⁷ The issue of whether LV lead placement in the most delayed segment leads to maximum improvement from CRT remains unsettled. While studies have shown that concordance of LV position with the most delayed LV segment results in maximum improvement in cardiac output,^{14,18} no studies have placed LV leads intraprocedurally, guided by echocardiography. Other studies have shown lack of benefit of CRT if the anterior wall and anterior interventricular septum are the most delayed segments.¹⁹ Appropriate placement of LV lead in the coronary sinus branch may be hampered by lack of a branch vein in the appropriate territory, lack of suitable anatomy for lead placement including tortuosity of the branch, acute angulation at origin, narrow caliber, or diaphragmatic stimulation when the lead is placed in the appropriate vein. In addition, in at least 5% of patients there is dislodgement of the LV lead after initial successful placement. In an additional number, there is an increase in the lead thresholds or loss of capture that may lead to loss of biventricular pacing. In general, the larger the diameter of the target coronary sinus vein at implantation, the easier it is to be successfully cannulated, but the easier it is for the lead to dislodge; the more difficult it is to place the LV lead during implantation due to angulation, etc., the more stable the lead position after implantation. Assessment of coronary venous system by multi-slice computed tomography (CT) prior to CRT may improve



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selection of patients for percutaneous versus epicardial CRT.²⁰ Other methods being tested include magnetic wire navigation using stereotaxis and endoscopic and pericardial approaches.^{21,22}

Myocardial Viability

Presence of myocardial viability is another important predictor of response to CRT and has not been well evaluated. Limited studies have shown that detection of a significant amount of myocardial scar despite the presence of mechanical asynchrony predicts lack of response to cardiac resynchronization.²³

Pacemaker Programming

Atrioventricular and Interventricular Delays

Another important parameter that is often overlooked is whether or not the biventricular pacemaker is appropriately programmed.²⁴ Optimal atrioventricular (AV) delay was determined by earlier studies from diastolic filling time of mitral inflow. Nominal settings for pacemaker devices include typically short AV delays of 100–120ms. These data come from good biventricular capture at short AV delays, and also show that echo-derived diastolic mitral inflow filling time is the longest at short AV delays. However, short AV delays often lead to premature mitral valve closure. This reduces forward atrial contribution in late diastole and leads to pulmonary vein atrial flow reversal and, in turn, increased pulmonary venous pressure. Thus, longest diastolic mitral inflow filling time is not necessarily associated with best cardiac output. In the author's experience, patients have needed AV delays between 30ms and 290ms. Therefore, programming of AV delay needs to be performed on an individual basis.

Despite the availability of interventricular or sequential ventricular programming capability, the devices are often left in simultaneous pacing mode following implantation. While studies have shown that the majority of patients need LV pre-excitation for better cardiac output, at least one-third of patients have better hemodynamics with simultaneous LV and right ventricular (RV) pacing or even RV pre-excitation.²⁵ Unless tested, optimal interventricular timing in a patient cannot be predicted based on ECG.

Atrial Pacing versus Sensing

Some patients who might be better off with atrial sensing are often inappropriately atrially paced at relatively higher heart rates such as 70bpm. Programming a lower back-up atrial pacing rate down to, for example, 50bpm often allows intrinsic atrial rhythm and heart rate variability during exercise.

Pacemaker Response to Exercise

Although advantage is often taken of the capability of current generation pacemakers to increase heart rate in response to exercise in chronotropically incompetent patients, it is not uncommon that patients continue to have markedly limited heart rate variability and hence get symptomatic after minimal exercise. Except in truly sedentary patients, this often results from lack of device sensitivity to detect mechanical activity. In some patients referred for optimization who are chronotropically incompetent or atrially paced, exercise-induced increase in heart rate function is turned 'off.' Sometimes slope of activation timing depending on lower rate limit may delay increase in heart rate upon commencement

Table 1: Mechanical Dyssynchrony Criteria

Major Dyssynchrony Criteria

Standard deviation of time to peak velocity in basal and mid-myocardial segments >45ms
Ejection septolateral delay >65ms
Delayed longitudinal contraction (DLC) in three of four basal to mid-posterolateral segments without DLC elsewhere
Septoposterior wall delay on two-dimensional radial strain of >130ms
Peak negative strain of >12 ^s -1 in the basal to mid-lateral or basal to mid-posterior segments

Intermediate Dyssynchrony Criteria

Septoposterior wall delay on M-mode of >130ms
Standard deviation of time to peak velocity in basal and mid-myocardial segments 30–44ms
Inter and intra-ventricular dyssynchrony >100ms
Delayed longitudinal contraction in the basal to mid-inferior wall and basal to mid-inferior interventricular septum
Right ventricular paced rhythm

Minor Dyssynchrony Criteria

Aortic pre-ejection time of >140ms
Interventricular dyssynchrony of >40ms on PW Doppler
Maximum difference in 12 basal and mid-segments on TVI >110ms
Septoposterior wall delay >65ms (posterior more than interventricular septum) in the apical three-chamber view

of exercise and hence results in inappropriate early quitting of exercise. Simple adjustment of pacemaker sensitivity and/or slope may overcome this problem. Change in the exercise-induced change in AV delay is another area where little investigation has been carried out. Currently, all devices allow decrease in AV delay with increases in heart rate, however the magnitude of AV delay change for a given increase in heart rate is too little, hence the pacemaker algorithm of AV shortening in the current generation pacemakers may not be appropriate for all patients.

Sleep Apnea

Another ignored factor that leads to lack of response to CRT or worsening of symptoms after initial response is the presence of sleep apnea in a significant number of CHF patients post-CRT. It is known that sleep apnea leads to worsening of heart failure. Our evaluation has suggested potential mechanisms of worsening of heart failure symptoms with sleep apnea. These include marked tachycardia compromising diastolic filling, worsening of mitral regurgitation and exaggerated ventricular interdependence during the hyperpneic phase of the sleep apnea cycle,²⁶ and ventricular ectopy during the bradypneic phase.

Experience at the Author's Institution

At the author's center, potential patients for CRT are evaluated for the presence of mechanical dyssynchrony irrespective of presence of electrical asynchrony by means of tissue Doppler imaging echocardiography and two-dimensional strain imaging by speckle tracking. All published criteria that have evaluated mechanical dyssynchrony are used. There is often a lack of concordance between different parameters in the majority of patients except those with the most severe mechanical dyssynchrony. An algorithm has therefore been developed to report dyssynchrony based on the author's experience in evaluating over 600 tissue Doppler studies (see *Table 1*). Mechanical dyssynchrony is reported as present if there are three major, two

major and two intermediate; one major and three intermediate; four intermediate, two intermediate and two minor; or one intermediate and three minor positive criteria.

In addition, the majority of these patients, particularly those who remain symptomatic following CRT, undergo optimization of biventricular pacemaker. Unlike other reports that have looked at LV outflow velocity time integral (VTI) for improvement in cardiac output in response to various A to V and V to V changes, multiple parameters are evaluated, including mitral inflow filling time, premature mitral valve closure, mitral inflow atrial wave duration, pulmonary vein atrial reversal, and systolic/diastolic ratio, as well as pulmonary vein D wave deceleration time, mitral regurgitation severity, LV dP/dt when it can be evaluated by mitral regurgitation signal, and pulmonary artery pressure in response to changes in pacemaker settings, as well as inter-ventricular and intra-ventricular dyssynchrony by tissue velocity imaging during the interventricular changes. Strain imaging is used in some patients when tissue velocity imaging is not helpful.

In patients who are pacemaker-dependent, atrial pacing is performed at 90bpm to determine appropriately paced AV delay at higher heart rates. Finally, patients perform modest exercise in order to ensure appropriate increase in heart rate in those who are pacemaker-dependent and to determine chronotropic competence in those who are A sensing at baseline. This assists in determining upper rate limit and corresponding AV delay. Acute improvement in cardiac output has been found in patients in response to AV optimization and further improvement in response to inter-ventricular optimization.²² In the process of collecting data, it appears that most patients maintain this improvement in their daily lives for several weeks following optimization.

Other Issues in Biventricular Pacemaker Programming

While it is possible to perform biventricular pacemaker optimization activity at the author's center, this activity is demanding on resources. Personal interest, referring physician awareness of benefits of pacemaker optimization, and certain research protocols allow us to conduct this activity. However, pacemaker optimization is not routinely performed in many centers in the US, or it is performed only on a limited basis. Reasons for this include the need for advanced echo Doppler skills, the time needed to perform these procedures, a lack of protocols directing physicians on how to perform the procedure, and, most importantly, lack of reimbursement for the procedure. Even though pacemaker clinics are in place in various centers in the US, these are usually run by nurses who are limited to evaluating pacemaker thresholds, etc. These clinics could be an ideal platform for collaboration between electrophysiology and echo teams. Attention needs to be given not only to pacemaker thresholds, but also, importantly, to whether pacemaker programming is a leading maximum homodynamic benefit for a given patient.

There is also a need to develop methods that are less sophisticated but can still provide a reasonable guide to pacemaker programming with minimum expertise. A non-invasive device called SphygmoCor® system tonometer is currently being evaluated (Medical Inc., Lisle, Illinois) to see if it can track cardiac output in response to various A to V and V to V timings compared with echocardiography. Results indicate that there is concordance between echo Doppler ejection timing and SphygmoCor-derived radial artery systolic ejection in 80% of subjects.²³ Finally, many patients require repeat optimization because of cardiac remodeling. These results therefore suggest that clinics should evaluate and perform this optimization perhaps at about four- to six-monthly intervals on these subjects. ■

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