CARDIOLOGY Rounds®

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Echocardiographic Evaluation of Heart Failure Patients for Cardiac Resynchronization Therapy: A Practical Primer

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Despite major advances in medical therapy, morbidity and mortality remain high among patients diagnosed with heart failure (HF). In Canada, the average in-hospital mortality per index admission averaged 9.5 deaths/100 hospitalized cases between 1997 and 2000. The one-year HF readmission rate was 23.6% during that same period.[1] Cardiac resynchronization therapy (CRT) was introduced in the early 1990s and has undergone major developments since then.[2] The objectives of this issue of *Cardiology Rounds* are to:

- **discuss the different types of cardiac dyssynchrony encountered in HF patients**
- **review the different echocardiographic techniques in assessing and quantifying cardiac dyssynchrony prior to biventricular pacer implantation**
- **discuss the reference values and criteria of these echocardiographic techniques in predicting a favourable response to CRT**
- **review the value of echocardiography in optimizing left ventricular (LV) lead positioning during implantation**
- **evaluate the utility of echocardiography in optimizing the biventricular pacer settings and measuring the objective outcomes of CRT post-implantation.**

CRT requires pacing of the left and right ventricles simultaneously. The right atrial and right ventricular leads are inserted in a standard fashion. The left ventricle free wall is paced via a lead inserted into the coronary sinus.[3] The 2002-2003 Canadian Cardiovascular Society consensus guidelines for the diagnosis and management of heart failure recommends CRT for severely symptomatic HF patients despite optimal medical therapy, but who have reasonable rehabilitation potential, with a mean QRS duration >130 msec and left ventricular ejection fraction (LVEF) <35% (Grade B recommendation, Level II evidence).[4]

The Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial, published in 2002, was one of the first clinical trials to demonstrate the clinical benefits of CRT. The inclusion criteria included: moderate-to-severe HF symptoms (New York Heart Association [NYHA] class III/IV), despite optimal medical therapy; LVEF ≤35%; and a wide QRS complex (duration ≥130 msec). Over a follow-up period of 6 months, the MIRACLE trial demonstrated that CRT significantly improved symptoms, exercise tolerance, and quality of life in participants. However, the trial was not able to demonstrate a mortality benefit. In addition, 20% to 30% of the patients did not respond to CRT, emphasizing the need for additional criteria for selecting potential responders for the therapy.[5]

The Cardiac Resynchronization Heart Failure (CARE-HF) trial used similar inclusion criteria as the MIRACLE trial. In addition to electrocardiographic (ECG) inclusion criteria, if the QRS duration was between 120-149 msec, patients were required to meet 2 of 3 additional echocardiography criteria for dyssynchrony: an aortic pre-ejection delay >140 msec, an interventricular mechanical delay >40 msec, or delayed activation of the postero-lateral left ventricular wall.[6]

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In addition to significant symptomatic improvement, the CARE-HF trial was able to demonstrate a 36% reduction in all-cause mortality over a mean follow-up period of 29.4 months. In terms of absolute risk reduction, It was further estimated that for every 9 devices implanted, 1 death and 3 hospitalizations for major cardiovascular events were prevented.[6] The additional benefits of CRT observed in the CARE-HF trial may be due, in part, to the longer follow-up. Better patient selection with additional echocardiography criteria also likely played a role.

The presence of substantial LV dyssynchrony is a major predictor of CRT response. However, mechanical dyssynchrony is not necessarily related to electrical dyssynchrony. Many HF patients with increased QRS duration may not exhibit mechanical dyssynchrony and many patients with normal QRS duration may have ventricular dyssynchrony. A recent echocardiogram study among HF patients with normal QRS duration revealed that 51% had systolic dyssynchrony, while 46% had diastolic dyssynchrony noted by tissue Doppler imaging.[7] These considerations underscore that fact that surface ECG may not be a good marker for ventricular mechanical dyssynchrony. Alternative imaging modalities, such as echocardiography, can be used to assess and quantify the degree of underlying mechanical dyssynchrony.

Mechanical dyssynchrony in HF

There are 3 types of mechanical dyssynchrony encountered in HF patients. The association of each type of mechanical dyssynchrony with HF severity and symptoms is currently unclear. Various echocardiographic techniques have been used to assess different types of cardiac mechanical dyssynchrony in an effort to select potential responders for CRT.

Atrio-ventricular (AV) dyssynchrony

Abnormal conduction of the AV node results in a delay between atrial and ventricular contraction, resulting in shortened ventricular filling time and limiting net diastolic stroke volume.[8]

Interventricular dyssynchrony

The presence of left bundle branch block (LBBB) can lead to a delay in the onset of LV contraction and relaxation compared with the right ventricle. Earlier onset of right ventricular contraction can result in right ventricular ejection occurring during the LV end-diastolic period. The higher pressure within the right ventricle reverses the transseptal pressure gradient and displaces the septum into the LV. This abnormal septal motion can result in an altered regional ejection fraction with decreased septal contribution to global LV performance.[9]

Intraventricular dyssynchrony

Overall LV systolic function depends on the coordinated LV contraction that, in turn, depends on normal ventricular activation. When a portion of the LV is prematurely activated, regions of both early and delayed contraction are generated that contribute to altered myocardial perfusion and impaired LV performance.[10] Relatively early or late regional shortening also result in wasted work.[11]

Echocardiographic techniques to assess and quantify cardiac dyssynchrony pre-implantation

There are a number of echocardiography-based techniques for assessing cardiac dyssynchrony. Many require specialized software and proprietary equipment. This review is limited to a number of techniques that are relatively easy to perform and reproduce in most laboratories with contemporary echocardiography equipment.

AV dyssynchrony

AV dyssynchrony can be assessed by mitral inflow duration and LV filling time. However, there are no specific defined criteria for AV dyssynchrony in the literature.[12]

Interventricular dyssynchrony

Interventricular dyssynchrony can be assessed by calculating the interventricular mechanical delay (IVMD), which is defined as "the time difference between the aortic pre-ejection interval (APEI) and pulmonic pre-ejection interval (PPEI)," (ie, IVMD = APEI – PPEI). APEI is the time from Q-wave onset on the ECG to aortic valve opening, as measured by pulsed-wave Doppler at the LV outflow tract in the apical 5-chamber view (Figure 1). PPEI is the time from the Q-wave on the ECG to the pulmonic valve opening as measured by pulsed-wave Doppler at the right ventricular outflow tract in the basal parasternal short-axis view (Figure 2). Normal IVMD is approximately 8 msec.[9] An IVMD ≥40 msec is considered indicative of interventricular dyssynchrony.[13,14]

Figure 1: Aortic pre-ejection interval (APEI) is the time from Q-wave onset to the aortic valve opening, as measured by pulsed-wave Doppler at the LV outflow tract in the apical 5-chamber view.

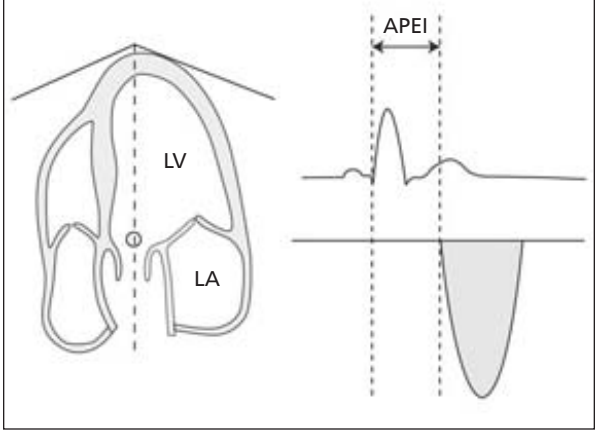
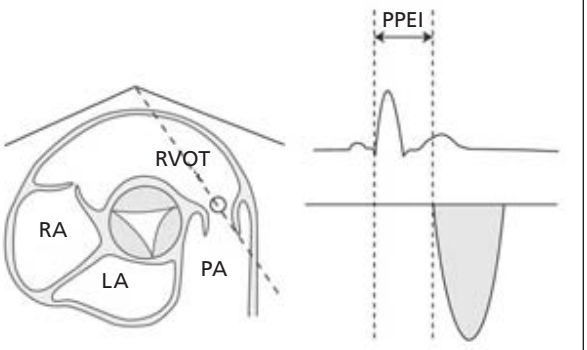


Figure 2: Pulmonic pre-ejection interval (PPEI) is the time from Q-wave onset to the pulmonic valve opening as measured by pulsed-wave Doppler at the right ventricular outflow tract in basal parasternal short-axis view.



Intraventricular dyssynchrony

Intraventricular dyssynchrony can be assessed by measuring the APEI (Figure 1). As mentioned above, APEI is the time from Q-wave onset on the ECG to the aortic valve opening as measured by pulsed-wave Doppler at the LV outflow tract in the apical 5-chamber view (Figure 2). Normal APEI is 93±14 msec.[9] An APEI ≥140 msec is considered indicative of intraventricular dyssynchrony.[15]

Septal-to-posterior wall motion delay (SPWMD) is measured by using an M-mode recording from either the parasternal long- or short-axis view (Figure 3). SPWMD is the difference in time from peak excursion of the septum and the posterior wall at the papillary muscle level. A SPWMD ≥130 msec was proposed as a marker of intraventricular dyssynchrony.[16] This method is sometimes limited by the inability to obtain a perpendicular M-mode section at the papillary level; extensive anterior septal infarction causing anterior septal akinesis; or difficulty in visualizing the maximal posterior wall excursion.

Figure 3: Septal-to-posterior wall motion delay (SPWMD) is measured by using an M-mode recording from either the parasternal long or short-axis view. SPWMD is the difference in times between peak excursion of the septum and the posterior wall at the papillary muscle level.

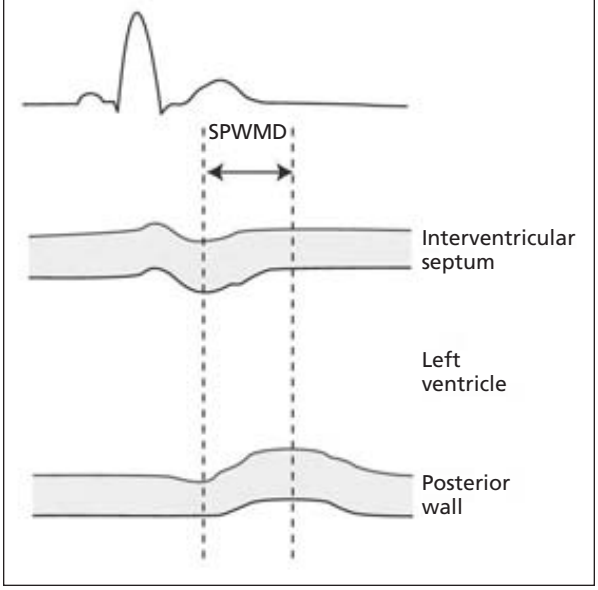
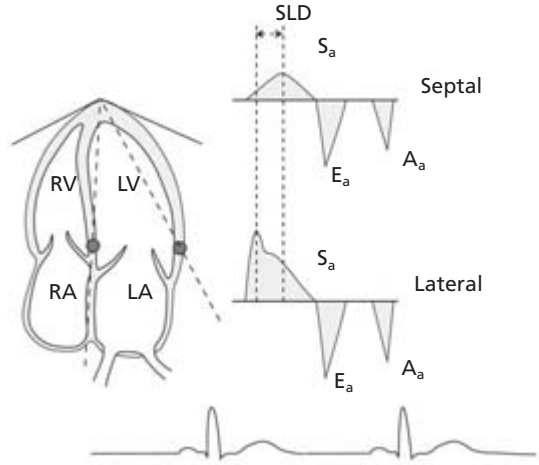


Figure 4: Septal-to-lateral (SLD) is measured by the time difference between the basal septum and lateral wall (apical 4-chamber view) in the timing from Q-wave onset to peak systolic velocity, as measured by tissue Doppler imaging (TDI).



Septal-to-lateral delay (SLD) by tissue Doppler imaging (TDI) allows measurement of peak systolic velocity of different regions of the myocardium and timing of the peak systolic velocity in relation to the onset of the Q-wave. Based on these variables, TDI can provide accurate information on intraventricular dyssynchrony. Bax et al demonstrated that a delay of ≥60 msec between basal septal and basal lateral wall in time-to-peak tissue velocity was an indicator of substantial intraventricular dyssynchrony (Figure 4).This parameter has shown to predict LVEF improvement after biventricular pacer implantation.[17]

Twelve-segment colour tissue Doppler imaging (TDI) was used by Yu et al to study 67 HF patients with narrow QRS complexes (≤120 ms) and 45 HF patients with wide QRS complexes (>120 ms); 88 patients served as normal controls. Altogether, 12 sample volumes were placed in the myocardium using a 6 basal, 6 mid-segmental model.[7] The authors concluded that the following 2 parameters were indicators for intraventricular dyssynchrony:

- the maximal difference between peak systolic velocities of any 2 of 12 segments >100 msec
- the standard deviation (SD) of all 12 time intervals measuring time-to-peak systolic velocity deviation of 33 msec, also referred to as the dyssynchrony index.

Strain, strain rate imaging,[18] and Tissue Synchronization Imaging (Vingmed, GE)[19] have been used in various

studies for assessing intraventricular dyssynchrony with favourable results. However, these echocardiographic techniques require specialized software and proprietary equipment to perform, and will not be discussed in this article.

Echocardiography in optimizing lead positioning during implantation

The goal of biventricular pacing is to actively pace the most delayed site(s) of the LV to reduce cardiac dyssynchrony. TDI studies reveal that the most frequently delayed site in patients with dyssynchrony is the lateral wall (35%), followed by the anterior (26%) and posterior (23%) walls.[20] The standard technique has always been to place the coronary sinus lead in the posterior and postero-lateral vein to pace the mid-lateral LV wall. Ansalone et al, using TDI during lead placement to assess the basal region, demonstrated that the greatest delayed activation improved LV ejection fraction, LV volumes, NYHA class, and 6-minute walk.[20]

Echocardiography in guiding optimization of device timing post-implantation

The biventricular pacer allows further fine-tuning post-implantation and the ability to optimize device timing. This includes the ability to adjust atrio-ventricular (AV) and interventricular (VV) delay. Doppler echocardiography is used to help select and monitor the optimal pacer settings.

AV delay

AV delay is the timing between left atrial and LV contraction sequence. It is adjusted to provide the longest LV filling time without truncating atrial contribution by mitral valve closure. When AV delay is too short, the "E" and "A" waves are separated, but the "A" wave is truncated. When AV delay is too long, the "E" and "A" waves are fused and the filling time is reduced.[21] The delay optimizes stroke volume and minimizes mitral regurgitation. AV delay optimization was used in the MUSTIC, MIRACLE, MIRACLE-ICD, and InSync trials. The transmitral flow duration is assessed by an iterative method, where filling patterns are recorded at various AV delays. The "Ritter" method is then used, which provides a formula to derive the optimal AV delay using a short and a long AV delay measurement by transmitral pulsed-wave (PW) Doppler.[22] Alternatively, the maximum transmitral velocity time integral (VTI) can be used to select the optimal AV delay by assessing the maximum transmitral flow volume, after going through a series of tested AV delays.

Interventricular (VV) delay

VV delay is the timing between the LV and RV contraction sequence. It is adjusted to optimize LV filling to produce the largest stroke volume. Stroke volume is the product of the LV outflow tract (LVOT) cross-sectional area (CSA) and the aortic velocity time integral (VTI), as measured by pulsed-wave (PW) Doppler at the apical 5-chamber view.[23] Since the CSA is assumed to be constant, the aortic VTI is used as a surrogate for stroke volume estimation. The optimal VV delay is set by selecting the setting that yields the largest VTI; this is obtained by running through a sequence of ventricular pacing intervals. VV delay optimization was used in the InSync III trial. Unfortunately, this method is limited by difficulties in maintaining the same alignment and position of the PW Doppler through many different pacer settings. In addition, the patient's respiratory efforts may add additional variation to the LVOT VTI measurements.

An alternative method has been proposed to identify the optimal VV setting by minimizing the septal-lateral delay in time-to-peak tissue velocity as measured by the colour TDI method at the basal septal and basal lateral segments in the apical 4-chamber view.[24] This method is still being tested and may provide a more reproducible method for optimizing VV delay settings.

Unresolved issues

A number of issues remain to be resolved in utilizing various echocardiographic-based techniques to assess patients undergoing CRT.

Different types of cardiac dyssynchrony exist in patients with HF. Once the biventricular pacer is implanted, it is unclear whether the goal of CRT optimization should focus on optimizing atrio-ventricular delay, interventricular, or intraventricular synchrony.

There are a number of echocardiographic methods for assessing patients for CRT (as discussed above). However, it is unclear which one or which set of parameters provides the most optimal information for selecting favourable responders to CRT. There have been no head-to-head comparisons of the diagnostic utility of the different echocardiographic methods or in their ability to predict favourable CRT response. Therefore, there is the need for a prospective trial to identify an optimal set of parameters that is easy to reproduce and simple to measure. Ideally, these measurements should not require proprietary hardware, specialized software, or extensive offline measurements. At present, the most reproducible set

of parameters from the various echocardiography labs include:

- interventricular mechanical delay (IVMD) by spectral Doppler ≥40 msec
- aortic pre-ejection interval (APEI) by spectral Doppler ≥140 msec
- septal-to-posterior wall motion delay (SPWMD) by M-mode ≥130 msec
- septal-lateral delay (SLD) by TDI ≥60 msec

An empirical scoring system can be used to rate the number of criteria fulfilled out of the 4 (ie, 1 of 4, 2 of 4, etc.) This scoring system will require testing retrospectively or in prospective clinical trials to assess its ability to predict favourable response to CRT and compare that to the more novel echocardiographic techniques.

Conclusions

Cardiac synchronization therapy (CRT) is now a recommended therapy for HF patients who are severely symptomatic (ie, with an LVEF <35% despite optimal medical therapy). When only ECG criteria (ie, prolonged QRS duration) are used, 20%-30% of the patients undergoing CRT will not improve. The assessment of atrio-ventricular, interventricular, and intraventricular dyssynchrony is possible, using various echocardiographic techniques. These echocardiographically-based techniques are useful in predicting a favourable response to CRT. Future patient selection for CRT should include a combination of ECG and echocardiographic criteria. The CARE-HF trial has employed such a combination selection strategy.[6] However, an optimal set of echocardiographic parameters remains to be determined. Moreover, echocardiography can aid in lead positioning during implantation, optimizing AV and VV settings of the biventricular pacers after implantation, and assessing outcomes of CRT.

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Abstract of Interest

Dyssynchrony Score – A New Method of Quantifying Cardiac Dyssynchrony by Three-Dimensional Echocardiography

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BACKGROUND: Cardiac resynchronization therapy (CRT) benefits about 70% of patients. Real-time three-dimensional echocardiography (RT3DE) may increase this response rate by improving patient selection. Compared to Doppler, RT3DE can assess global left ventricular (LV) dyssychrony and also provide complimentary information. We developed a scoring system of cardiac dyssychrony from measurement of segmental volume change over time.

METHODS: RT3DE was performed in 19 patients within 24 hours after biventricular pacing (16M, 3F; mean age 69.8Y; 9 ischemic and 10 non ischemic cardiomyopathy) with CRT off and then on. A full volume 3D-echo was also obtained in 7 patients with LV systolic dysfunction (5M, 2F mean age 64.6Y) who did not meet criteria for CRT and in 10 subjects with normal LV systolic function (7M, 3F; mean age 39.6Y). Using semi-automated endocardial contour tracing, volume versus time curves were constructed for the 17 LV segments. The time to minimum LV volume in each segment was computed and mean time ± 1 SD was determined for every patient. A dyssynchrony score (DS) was derived as the sum of time that segments exceeded the ± 1 SD range.

RESULTS: All normal subjects had a DS of < 150 msec. In 95% of CRT patients the pre CRT score was > 150 msec. With CRT the DS fell significantly (p = 0.015), approaching that of non CRT candidates with LV dysfunction. (Table: LVEDV = left ventricular end-diastolic volume and LVESV = left ventricular end-systolic volume).

CONCLUSIONS: Dyssychrony score by RT3DE integrates the entire LV function and distinguishes varying degrees of dyssynchrony by a semiautomated technique. The predictive value of this method in identifying normal LV synchrony is particularly high. This may be helpful in improving selection of candidates for CRT.

TABLE

Patient Population	LVEDV (ml) Mean	LVESV (ml) Mean	LVEF (%) Mean	DS in msec Mean (SD)
1. Normal controls (n = 10)	94.30	41.15	60.75	82.0 (30.1)
2. CRT patients (n = 19)				
– Pre CRT	202.50	146.65	29.45	343.3 (137.5)*
– Post CRT	191.04	133.11	32.90	257.2 (79.0)*
				*p = 0.015
3. LV Dysfunction (n = 7) (not CRT candidates)	171.50	120.09	31.00	248.6 (101.2)

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