Echocardiographic Assessment of Dyssynchrony for Predicting a Favorable Response to Cardiac Resynchronization Therapy

a report by

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Numerous clinical trials involving patients with severe, symptomatic heart failure (HF) and a wide QRS complex have shown benefits from cardiac resynchronization therapy (CRT). CRT can increase left ventricular ejection fraction (LVEF), decrease LV volume and mitral regurgitation, improve symptoms caused by HF,[1–3] and may also improve mortality.[4,5] The current guidelines from American College of Cardiology (ACC)/American Heart Association (AHA) suggest CRT implantation for patients with LVEF <35%, New York Heart Association (NYHA) class III or ambulatory IV HF, and dyssynchrony defined by a QRS >120ms.[6] However, among patients who receive CRT based on this criteria, one-third of patients will fail to respond to therapy. This may be due to inadequate placement of the coronary sinus lead, or the absence of mechanical LV dyssynchrony prior to implantation. Many non-responders do not exhibit intra-ventricular mechanical dyssynchrony at baseline, and it may be that CRT most benefits those with underlying dyssynchrony.

Owing to its ease of use and wide availability, echocardiography has emerged as the preferred modality to assess dyssynchrony. There are several echocardiographic techniques under investigation including, tissue Doppler imaging (TDI), realtime three-dimensional (3-D) echocardiography, and speckle tracking, although, currently, there is no clearly accepted standard.

What is Dyssynchrony?

Patients who have LV systolic dysfunction (LVSD) and dilatation frequently have a prolonged QRS complex, often in a left bundle-branch block (LBBB) pattern. QRS prolongation is generally associated with delayed electrical activation of the left ventricle, leading to uncoordinated ventricular motion, decreased stroke volume, and mitral regurgitation. Because of this association, QRS duration has been used as a surrogate marker for ventricular dyssynchrony. However, several studies have demonstrated that not all patients with a wide QRS complex exhibit evidence of mechanical dyssynchrony.[7] Furthermore, up to 30–50% of patients with a narrow QRS complex may have mechanical dyssynchrony measured by echocardiography. Some of these patients with narrow QRS may benefit from CRT.[8,9]

1. *Yu C M, Wing-Hong Fung J, Zhang Q, et al., "Understanding nonresponders of cardiac resynchronization therapy—current and future perspectives",* J Cardiovasc Electrophysiol *(2005);16(10): pp. 1,117–1,124.*
2. *Yu C M, Abraham W T, Bax J, et al., "PROSPECT Investigators. Predictors of response to cardiac resynchronization therapy (PROSPECT)—study design",* Am Heart J *(Apr 2005);149(4):pp. 600–605.*
3. *Sogaard P, Egeblad H, Pedersen A K, et al., "Sequential versus simultaneous biventricular resynchronization for severe heart failure: Evaluation by tissue Doppler imaging",* Circulation *(2002);106:pp. 2,078–2,084.*
4. *Bristow M R, Saxon L A, Boehmer J, et al., "Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure",* N Engl J Med *(2004);350:pp. 2,140–2,150.*
5. *Cleland J, Daubert J C, Erdmann E, et al., "The effect of cardiac resynchronization on morbidity and mortality in heart failure."* N Engl J Med *(2005);352:pp. 1,539–1,549.*
6. *Hunt S A, Abraham W T, Chin M H, et al., "CW. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure)",* Circulation *(2005);112: pp. 1,825–1,852.*
7. *Fung J W, Yu C M, Yip G, et al., "Variable left ventricular activation pattern in patients with heart failure and left bundle branch block",* Heart *(2004);90: pp. 17–19.*
8. *Bleeker G B, Schalij M J, Molhoek S G, et al., "Frequency of left ventricular dyssynchrony in patients with heart failure and a narrow QRS complex",* Am J Cardiol *(2005);95(1): pp. 140–142.*

Figure 1: Identifying Landmarks for Measurement of Time to Peak Systolic Velocity (TPSV), from QRS onset to the S2 Peak

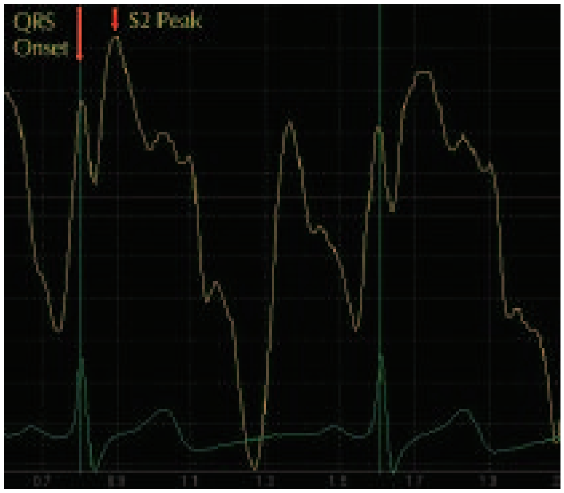
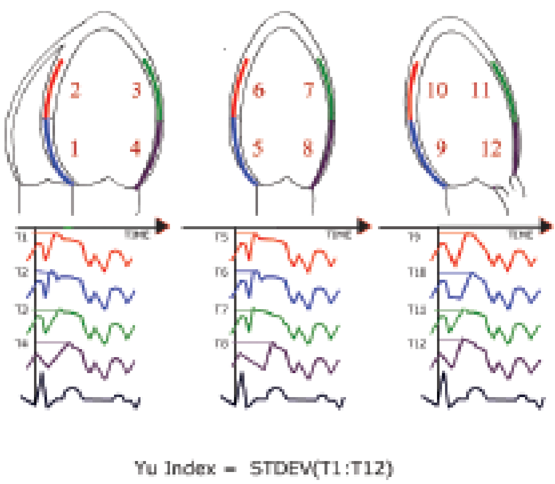


Figure 2: The Yu Index, or the Standard Deviation of the Time to Peak Systolic Values (TPSV) of all the Basal and Mid Segments from the Apical 4-, 2-, and 3-Chamber Views



The goal of CRT is to synchronize LV contraction. This is accomplished by pre-emptively pacing the latest activated segment in the LV resulting in improved coordination of each region of the LV's contribution to systole. This results in an increase in stroke volume, improvement in myocardial efficiency, an increase in the diastolic filling time and reduction of mitral regurgitation by synchronizing papillary muscle activation. CRT may also improve atrioventricular (AV) timing, which may improve diastolic filling and reduce mitral regurgitation. Inter-ventricular timing may also be enhanced through CRT, though the significance of this is currently not known.[1] In addition to the positive hemodynamic effects, CRT exerts a favorable effect on cardiac autonomic control that results in less dependence on sympathetic activation.[10] This can lead to smaller ventricular size and improved cardiac function in patients with severely symptomatic HF, known as 'reverse remodelling'.

Specific Echocardiography Methods to Evaluate Cardiac Dyssynchrony

Septal to Posterior Wall Motion Delay

The first developed and simplest method for evaluating dyssynchrony is the analysis of the activation of the posterior wall compared with the septum using M-mode. This is performed in the parasternal short axis view at the level of the papillary muscles. Delayed activation of the posterior wall versus the septum is consistent with dyssynchrony. A maximum septal to posterior wall motion delay (SPWMD) of 130ms was found to be predictive of reverse remodelling and improve HF status,[11] though this has not been seen in all studies.[12] SPWMD may be inaccurate in those who have had prior septal myocardial infarctions (MIs); however, it does not include assessment of the lateral wall, which is often the latest activated site.

Tissue Doppler Imaging

TDI works by evaluating the direction and velocity of the myocardium, using either pulsed-wave or color-coded Doppler. Pulsed-wave Doppler is generally considered to be more difficult and time-consuming, and has, therefore, been used less frequently. Assessment of delayed contraction using color-coded TDI is usually based on the time from onset of the QRS complex to the peak of the S2 component of the velocity trace, often referred to as

9. *Yu C M, Lin H, Zhang Q, et al., "High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration",* Heart *(2003);89: pp. 54–60.*
10. *Adamson P B, Kleckner K J, VanHout W L, et al., "Cardiac resynchronization therapy improves heart rate variability in patients with symptomatic heart failure",* Circulation *(22 Jul 2003);108(3): pp. 266–269.*
11. *Pitzalis M V, Iacoviello M, Romito R, et al., "Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony",* J Am Coll Cardiol *(2002); 40: pp. 1,615–1,622.*
12. *Marcus G M, Rose E, Biloria E M, et al., "VENTAK CHF/CONTAK-CD Biventricular Pacing Study Investigators. Septal to posterior wall motion delay fails to predict reverse remodeling or clinical improvement in patients undergoing cardiac resynchronization therapy",* J Am Coll Cardiol *(20 Dec 2005);46(12): pp. 2,208–2,214.*

time to peak systolic velocity (TPSV) (see *Figure 1*), though time to onset of velocity has also been studied.

Comparison of TPSV for any two basal segments (e.g. septal and lateral wall) using M-mode can provide a quick assessment of dyssynchrony. A delay of ≥60ms between the septal and lateral wall[13] or ≥65ms between the anteroseptum and posterior wall[14] has been found to predict increased ejection fraction after CRT implantation.

Bax et al. defined dyssynchrony as the maximum difference in TPSV between the basal anterior, inferior, septal, or lateral ventricular walls.[15] A value of 65ms was used as a cut-off with a sensitivity and specificity of 80% for predicting an improvement in NYHA classification and ≥25% increase in six-minute walking distance with CRT. In addition, a cut-off of 65ms was also predictive cardiac death or hospitalization for decompensated HF.

This method was expanded to include all six basal walls (inferoseptal, anteroseptal, anterior, lateral, posterior, and inferior) and measuring the TPSV, excluding isovolumic contraction.[16] The peak velocity difference (PVD) was then determined by subtracting the smallest from the largest TPSV. A PVD >110ms at baseline predicted reverse remodelling of the LV, increased ejection fraction, and decreased PVD at three months following the initiation of CRT. In addition, those with PVD ≤110ms at baseline had increased PVD and LV end diastolic volume, as well as a trend toward increased LV end systolic volume after CRT implantation. This suggests that device implantation may actually be deleterious in those with no dyssynchrony at baseline.

LV dyssynchrony may be better evaluated by recording all basal and mid segments from the apical 4-, 2- and 3-chamber views and deriving the standard deviation between all 12 resulting in TPSV measurements from all basal and mid segments, creating a dyssynchrony index (see *Figure 2*), also known as the Yu index.[17] In normal hearts, all walls move relatively simultaneously and, therefore, there is low variance of wall motion. When dyssynchrony is present, the distribution of TPSV values is much wider and there is a higher standard deviation. Yu et al. determined that ≥32ms indicated mechanical dyssynchrony and values in excess of this are correlated with a favorable CRT response.[17–19] Other investigators have not been successful in reproducing these findings, suggesting that obtaining the measurements is technically difficult.[20]

TDI acquisition and data reproduction is subject to numerous technical challenges. Good technique and patient compliance is needed to minimize translational motion caused by respiration or transducer motion. Analysis of a moving structure requires careful tracking of the region of interest sample for consistent results. Color scale and Doppler gain settings are important to achieve adequate colorization. This can be particularly difficult in cases with impaired contractile performance, requiring low-pulse repetition frequency settings to detect motion throughout the heart cycle. To minimize error and improve reproduction, acquisition should only be performed at appropriate Doppler angles, which can be difficult to achieve in dilated hearts. In addition, it is important to discriminate between genuine contraction and non-contributing segments that move passively, due to tethering with adjoining segments.

Realtime 3-D Echocardiography

Another approach for investigating dyssynchrony is by using 3-D echocardiography. Images are obtained

13. *Bax J J, Marwick T H, Molhoek S G, et al., "Left ventricular dyssynchrony predicts benefit of cardiac resynchronization therapy in patients with end-stage heart failure before pacemaker implantation",* Am J Cardiol *(2003);92: pp. 1,238–1,240.*
14. *Gorcsan J III, Kanzaki H, Bazaz R, et al., "Usefulness of echocardiographic tissue synchronization imaging to predict acute response to cardiac resynchronization therapy",* Am J Cardiol *(2004);93: pp. 1,178–1,181.*
15. *Bax J J, Bleeker G B, Marwick T H, et al., "Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy",* J Am Coll Cardiol *(2004); 44: pp. 1,834–1,840.*
16. *Notabartolo D, Merlino J D, Smith A L, et al., "Usefulness of the peak velocity difference by tissue Doppler imaging technique as an effective predictor of response to cardiac resynchronization therapy",* Am J Cardiol *(2004);94: pp. 817–820.*
17. *Yu C M, Zhang Q, Fung J W, et al., "A novel tool to assess systolic dyssynchrony and identify responders of cardiac resynchronization therapy by tissue synchronization imaging",* J Am Coll Cardiol *(2005);45:pp. 677–684.*
18. *Yu C M, Fung J W, Zhang Q, et al., "Tissue Doppler imaging is superior to strain rate imaging and postsystolic shortening on the prediction of reverse remodeling in both ischemic and nonischemic heart failure after cardiac resynchronization therapy",* Circulation *(2004);110: pp. 66–73.*
19. *Yu C M, Fung W H, Lin H, et al., "Predictors of left ventricular reverse remodeling after cardiac resynchronization therapy for heart failure secondary to idiopathic dilated or ischemic cardiomyopathy",* Am J Cardiol *(2003);91: pp. 684–688.*
20. *El Chami M F, Notabartolo D, Leon A, et al., "Assessment of dyssynchrony index as a predictor of response to resynchronization therapy (abstr)",* Circulation *(2004);110:pp. III-724–III-725.*

realtime with a special transducer and can then be analyzed offline (QLab, Philips). Semi-automated edge detection algorithms trace the endocardial border and create a 3-D 'cast' of the LV cavity. Changes in total cavity size and in each of the 16 standard American Society of Echocardiography (ASE) segments can then be analyzed throughout the cardiac cycle. As opposed to TPSV, real-time 3-D echocardiography (RT3DE) examines the time to minimum systolic volume (TMSV) measured from onset of QRS to minimum value of each segments' regional volume-time curve. Comparison of TMSV for any two basal segments, e.g. septal and lateral wall, provides a basic assessment of dyssynchrony. Similar to the dyssynchrony index of TDI, by recording the TMSV of all 16 segments and deriving the standard deviation, a systolic dyssynchrony index (SDI) can be created. Given variation in heart rate, this value may be expressed as a percentage of the cardiac cycle.

Kapetanakis et al. used RT3DE to evaluate dyssynchrony using the SDI in normal subjects, those with normal LVSF, and those with various degrees of HF.[21] This study suggested that normal subjects and those with normal LVSF had normally synchronized segmental function, whereas those with mild, moderate, and severe LV dysfunction had progressively higher values for the SDI. Interestingly, there was only a weak correlation between QRS duration and SDI (r=0.264, p=0.0005). A wide QRS duration was only able to predict 46% of patients with significant mechanical dyssynchrony. They also examined the SDI in those before and after CRT implantation. Those who were responders to CRT, defined as symptomatic improvement, had higher baseline SDI values compared with non-responders and had a decrease in SDI after device implantation. This is consistent with the notion that those who are most dyssynchronous at baseline respond best to CRT.

Kapetanakis et al., showed quite low inter-observer or intra-observer variability in obtained SDI, though this needs to be reproduced in other studies. Only one other small study has used SDI in those undergoing CRT and showed that SDI could be reduced with CRT implantation.[22]

Because the TMSV values are typically longer than the TPSV values used with TDI, as they represent the end-point of contraction rather than the point of fastest wall motion, TMSV (or SDI) cannot be compared directly with TPSV (or Yu index) on an absolute basis. It would be expected, though, that there should be correlation between the two if they both can predict dyssynchrony. In the study by Kapetanakis et al., there was only a weak non-significant correlation between the SDI and TDI dyssynchrony index (r=0.264, p=0.064), which suggests that the reproduction of any of the dyssynchrony methods may be difficult. It is also interesting to note that the correlation was better for narrow QRS patients than wide QRS patients. Finally, for a cut-off for 33ms for the TDI dyssynchrony index, as suggested by Yu, and arbitrary cut-off of 8.3% for SDI, there was an agreement in 56.5% of patients with broad QRS complex for the presence of dyssynchrony and 41.2% of patients with narrow QRS.

When compared with TDI, RT3DE provides better, though still imperfect, imaging of the apical segments owing to a lack of Doppler angle constraints associated with apical segments. Software editing tools for RT3DE are available to address difficulties associated with automatic border detection caused by sub-optimal image quality. Up to 20% of patients may have images that cannot be analyzed due to poor quality.[21] RT3DE evaluates wall motion regardless of whether it is circumferential, radial, or tangential. Unlike the TDI approach it is possible to obtain all segmental data from a single acquisition. Moreover, the volume data is 'true' volume data, i.e. it does not use geometric assumptions but uses actual voxel data contained within a dynamic surface mesh of the beating left ventricle.

Speckle-tracking Radial Strain

A novel method has recently been proposed to assess dyssynchrony called speckle tracking.[23] This is a type of strain imaging in which speckles, (by-products of ultrasound scattering and reflection) can be followed from frame-to-frame and used to assess radial motion in the parasternal short axis view. This may be especially useful because strain imaging can differentiate active motion from passive tethering of infarcted myocardium. Suffoleto et al.[23] examined

21. *Kapetanakis S, Kearney M T, Siva A, et al., "Real-Time Three-Dimensional Echocardiography—A Novel Technique to Quantify Global Left Ventricular Mechanical Dyssynchrony",* Circulation *(2005);112(7): pp. 992–1,000.*

22. *Zhang Q, Yu C M, Fung J W, et al., "Assessment of the effect of cardiac resynchronization therapy on intraventricular mechanical synchronicity by regional volumetric changes",* Am J Cardiol *(1 Jan 2005);95(1): pp. 126–129.*

23. *Suffoletto M S, Dohi K, Cannesson M, et al., "Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy",* Circulation *(21 Feb 2006);113(7): pp. 960–968.*

radial strain at the six basal wall segments and determined that a ≥130ms difference between the first and last segments time to peak strain had a 89% sensitivity and 83% specificity in predicting a ≥15% increase in ejection fraction at >3 months. The advantage of this method is that it is not dependent on the Doppler angle and may be more able to determine the site of the latest mechanical activation, resulting in a more precise target for placement of the coronary sinus lead.

This method can be technically difficult, however, and relies on adequate parasternal windows. Images must be acquired with a high frame rate so that speckles can be tracked appropriately, but this increased frame rate can lead to loss of image quality. This method is new and awaits validation by other investigators before its wider use can be expected.

Conclusion

Various echocardiographic techniques have been used to assess dyssynchrony in those with HF, in the presence or absence of a wide QRS complex. All studies to date, however, have either been retrospective or small prospective studies. The Predictors of Response to Cardiac Re-synchronization Therapy (PROSPECT) trial is an on-going multinational study to assess >300 patients undergoing CRT implantation to monitor which, of several echocardiographic dyssynchrony techniques, is best able to predict a clinical response and LV reverse remodelling.[2] Thirteen echocardiographic predictors of response are being measured, including SPWMD, TPSV of basal septal and basal lateral segments, and the standard deviation of the TPSV for the 12 basal and mid segments, among others. Unfortunately, the protocol does not call for either RT3DE or speckle tracking.

Recent studies have suggested that echocardiographic assessment of mechanical dyssynchrony is an important tool that can be used to help identify potential responders to CRT. At this time it is unclear which echocardiographic method is the most useful in assessing dyssynchrony or predicting who will benefit from CRT. The ideal echo parameters would be easy to acquire, reproducible, accurately predict responders to CRT, and could be obtained quickly with little or no post-processing. On-going and future studies will define which echo parameters are most useful in the identification of patients who may benefit from this important therapy. ■