Echocardiographic Assessment of Ventricular Dyssynchrony

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Although cardiac resynchronization therapy (CRT) has been of unquestioned therapeutic benefit to many patients with heart failure identified by a widened QRS complex on an electrocardiogram, many patients do not respond favorably. Several studies using echocardiographic methods to measure abnormalities of mechanical activation, known as dyssynchrony, have been proposed to improve patient selection for CRT. Many single-center studies from institutions with special expertise have demonstrated the feasibility of echocardiographic dyssynchrony to potentially assist with patient selection. However, the PROSPECT trial, a recent large multicenter study, highlighted the technical challenges in echocardiographic dyssynchrony analysis in mainstream clinical practice. Accordingly, a uniform clinical approach has not been established, and refinements of echocardiographic approaches and methods are constantly evolving. This article reviews current echocardiographic methods to quantify ventricular dyssynchrony, their strengths and limitations, and the proposed and potential expanding clinical applications.

Introduction

Currently accepted clinical criteria for cardiac resynchronization therapy (CRT) for patients with symptomatic heart failure include New York Heart Association functional class III-IV, widened QRS duration (> 120 ms on an electrocardiogram), and low left ventricular (LV) ejection fraction (≤ 35%) [1,2]. The widened QRS complex of the patient's electrocardiogram, which is a marker of delayed electrical activation, is thought to be a surrogate for delayed mechanical activation, known as dyssynchrony. CRT typically consists of multisite pacing of the left ventricle from septal and free-wall lead sites. It has been shown to correct mechanical dyssynchrony, result in immediate improvements in LV function, and have favorable biologic effects known as reverse remodeling [2,3]. Wide clinical experience with CRT has shown that not all patients respond favorably clinically or by measures of LV function. The nonresponder rate appears to be 25% to 30%, depending on the definition of response used [4–8]. Several clinical studies have demonstrated that some patients do not have significant degrees of mechanical dyssychrony despite having a widened QRS [9–13]. Accordingly, these patients without mechanical dyssynchrony do not appear to benefit from CRT, and echocardiographic methods designed to quantify dyssynchrony have been proposed as a way to more accurately identify patients likely to respond to CRT. More recent studies, however, have highlighted the complexity of echocardiographic dyssynchrony analysis [14••]. This article reviews the current and most promising echocardiographic approaches, explores their limitations, and discusses potential applications.

Overview of Echocardiographic Dyssynchrony

Dyssynchrony may be manifested as delays in atrioventricular activation, right ventricular (RV) to LV activation, or intraventricular activation within the segments of the left ventricle [4,6,15–18]. Several echocardiographic methods to measure mechanical dyssynchrony have been suggested. These can be grouped into the principal echocardiographic formats of M-mode echocardiography, pulsed Doppler, and tissue Doppler imaging (TDI). TDI may be further used as a post-processing approach to calculate displacement and strain. Studies of a more recent method, speckle tracking, are just beginning to emerge. The PROSPECT study is a recent observational multicenter, prospective study from Europe, the United States, and Hong Kong that attempted to examine the relative predictive value of a large series of echocardiographic variables [19,20••]. Clinical outcome and reduction of LV end-systolic volume were used as determinants of response to CRT. Although only preliminary results of this study have been presented, PROSPECT represents a test of the implementation of echocardiographic measures of dyssynchrony in a large patient population.

It showed that no single echocardiographic means to determine dyssynchrony is ideal, and it highlighted the importance of technical factors such as feasibility and reproducibility in dyssynchrony analysis. Accordingly, this article addresses specific measures of dyssynchrony in light of the strengths and limitations of each.

Global Measures of Dyssynchrony: Pulsed Doppler

Cazeau et al. [21–23] proposed several measures of dyssynchrony using routine pulsed Doppler echocardiography. These include the pre-ejection delay, interventricular mechanical delay (IVMD), and the LV filling time as a percentage of the R-R interval. The pre-ejection delay is recorded from the apical five-chamber or apical long-axis views where the pulsed Doppler sample volume is placed in the LV outflow tract, proximal to the aortic valve. Time-velocity recordings of LV ejections are made, and the pre-ejection delay is determined as the time from the onset of the electrocardiographic QRS to the onset of LV ejection velocity. A delay in LV ejection is thought to result from the summation of regional segmental delays. In a normal left ventricle, this interval is short and reflects the sum of electrical depolarization and isovolumic contraction. A pre-ejection delay of more than 140 ms is usually considered as consistent with significant dyssynchrony. A limitation is that a delayed pre-ejection interval is a nonspecific marker for global poor LV function and may not reflect segmental LV dyssynchrony.

A related measure, IVMD, requires an additional measure of the RV ejection interval (Fig. 1). Accordingly, IVMD is the difference between the LV pre-ejection delay and the RV ejection delay. The RV ejection interval is determined from the parasternal window at the level of the base of the heart and in short axis. The transducer is positioned so that the pulmonic valve and RV outflow tract are imaged. The pulsed Doppler sample volume is placed in the RV outflow tract immediately proximal to the pulmonic valve. Time-velocity analysis is similarly determined from the onset of the QRS complex to the onset of RV flow velocity. An IVMD of more than 40 ms is usually considered as resulting from significant dyssynchrony. It is important that similar heart rates occur for the LV and RV ejection intervals, and variations in heart rate represent a limitation. Another limitation of IVMD is that RV ejection is affected by global RV function, which may be a confounding variable in dyssynchrony analysis. Achilli et al. [24] tested IVMD prospectively in the SCART study. They followed 133 patients after CRT and found that an IVMD of longer than 44 ms predicted a response, with a sensitivity of 66% and a specificity of 55%. This study illustrated the positive predictive value but suggested that other factors may influence the response to CRT. Richardson et al. [25] recently showed the predictive value of IVMD in the CARE-HF study, which randomized patients to receive CRT or to a control group.

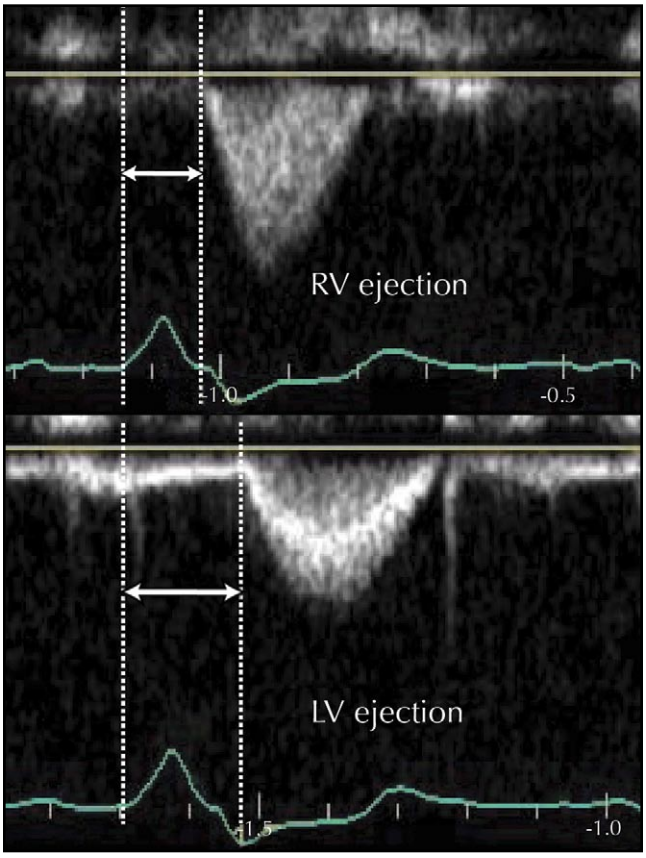

Figure 1. An example of pulsed Doppler interventricular mechanical delay (IVMD) before cardiac resynchronization therapy. The *top panel* demonstrates the time to onset of right ventricular (RV) ejection *(arrow),* taken from the parasternal short-axis view proximal to the pulmonic valve. The *bottom panel* demonstrates the time to onset of left ventricular (LV) ejection *(arrow),* taken from an apical five-chamber view proximal to the aortic valve. The difference in time from RV to LV ejection (IVMD) is usually considered to represent significant dyssynchrony if it is 40 ms or longer.

Another pulsed Doppler measure of dyssynchrony can be assessed using mitral inflow velocities [22]. This index is determined using pulsed Doppler from the apical four-chamber view with the sample volume placed at the tips of the mitral leaflets. The duration of LV filling from the onset of the mitral inflow E wave to the end of the mitral inflow A wave is first measured. This duration is then corrected for heart rate by dividing by the R-R interval and is expressed as a percentage. Cazeau et al. [21,22] also demonstrated that an LV filling time that is 40% or less of the R-R interval is consistent with significant dyssynchrony and predicts response to CRT. In general, pre-ejection delay, IVMD, and the ratio of filling time to R-R have high yield and high reproducibility. The preliminary results of PROSPECT suggested that these simple, routine pulsed Doppler means are useful because of their technical ease. However, they have overall modest predictive value. Because these indices have been well tested, it appears that their true value and limitations are known.

Regional Measures of Dyssynchrony: M-mode and Tissue Doppler

Most of the studies of echocardiography that examine LV dyssynchrony have focused on determining the delay in regional segments. This is because the principal cause of a widened QRS complex in CRT candidates is the left bundle branch block (LBBB) pattern [26,27]. The classic mechanical activation of LBBB is that of early septal activation and delayed posterior and lateral segmental activation. One of the first methods to determine LV dyssynchrony was by M-mode echocardiography. This can be achieved by placing the M-mode cursor through the septum and the posterior wall. Pitzalis et al. [28] demonstrated in patients with nonischemic cardiomyopathy that a delay of peak inward motion from the septum to the posterior wall of 130 ms or longer predicted a favorable response to CRT, as defined by a reduction in LV end-systolic volume. The M-mode approach becomes problematic, however, when applied to a large series of CRT patients, most of whom have ischemic heart disease and wall motion abnormalities. This is because the low amplitude of wall motion often makes it difficult to confidently determine peak inward motion. Furthermore, M mode cannot differentiate between active and passive motion, which is an important confounding variable. Marcus et al. [29] illustrated these limitations in a substudy from the Contak-CD trial. They found the reproducibility of M-mode measurements and their predictive value to be unsatisfactory. The M-mode approach has a physiologically sound basis and may be potentially useful in some patients, particularly those with nonischemic disease, to complement other approaches, such as TDI. However, technical limitations are often encountered, and M mode is currently not advocated as reliable means to assess LV dyssynchrony in isolation.

Most studies of echocardiographic assessment of LV dyssynchrony have involved TDI and its related post-processing methods [4,10,15,16,30–33]. TDI has been attractive because it provides the ability to determine the mechanical timing of an event within a specified region of the left ventricle. Although a pulsed TDI approach has been described as useful [34], most investigators have favored the color-coded TDI for dyssynchrony analysis. Color-coded TDI is preferred principally because the analysis may be done offline, whereas the adjustment of the pulsed TDI must be done online, requiring a lengthy process that may be difficult to execute in a patient with a complex pattern of dyssynchrony. The principal TDI format is velocity data, and the post-processing formats, displacement and strain, are derived from the velocity data. The advantage of velocity data is the strong signal-to-noise ratio and its application to many patients. A principal disadvantage of velocity is that it cannot differentiate active motion from passive motion. Strain imaging has the advantage of isolating the important active motion information; however, strain and strain rate by TDI are often affected by signal noise and appear more difficult to master [33].

TDI data usually are acquired from the apical views, principally the apical four-chamber view, the apical two-chamber view, and the apical long-axis view. The simplest approach is to determine the time difference between the peak TDI velocities of the two basal sites using the apical four-chamber view (Fig. 2). Bax et al. [6] introduced this method, which has been shown to predict response to CRT. An opposing wall delay of 65 ms or longer has been most widely used as a cutoff value [6,14••,15]. In general, the peak systolic velocity waves, or S waves, are determined during the LV ejection interval. Accordingly, the time from the beginning of ejection to the end of ejection is marked on the TDI time-velocity tracing using pulsed Doppler from the LV outflow as a guide for ejection. The advantage of limiting analysis to the ejection interval is that it will exclude post-systolic velocities, which may be confounding variables that decrease sensitivity [17]. Furthermore, the early isovolumic contraction velocity is excluded by marking the ejection interval. A disadvantage of using the Doppler markers of ejection from a different beat than the TDI velocity data is that variations in heart rate may interfere with the accuracy of analysis. Accordingly, special attention must be paid to the cardiac cycle length for these comparative measurements. The Yu index, a more complete and highly sensitive means of TDI velocity analysis, involves calculating the SD from 12 different sites [8,11,12,16,17,32]. This is done by recording color-coded TDI data from apical four-chamber, apical two-chamber, and apical long-axis views and measuring the time to peak S waves from the onset of the QRS complex in basal and mid segments. For each time-to-peak measurement, it is important to move the region of interest within the segment along the longitudinal axis and in the endocardial to epicardial plane to determine the most reproducible peak velocity. This form of manual spatial averaging enhances reproducibility of peak velocity data. A cutoff of more than 33 ms of SD units has been shown to be associated with response to CRT [32]. Other regional TDI methods, such as strain imaging or displacement, have been successful in some laboratories but less successful in others. Although the advantage of strain is to separate active mechanical activation from passive motion, difficulties with signal noise using TDI strain may be encountered [11,32]. Currently, the robust signal-to-noise ratio of the TDI velocity data appears to favor its application.

Promising Future Applications: Speckle Tracking and Three-dimensional Imaging

Recent data have emerged using speckle-tracking echocardiographic analysis to determine regional strain. This method can be applied to routine gray-scale echocardiogram images and can determine strain as myocardial thickening and thinning vectors independent of the Doppler angle of incidence. Suffoletto et al. [35] have described the initial approach as applied to the mid-LV short-axis

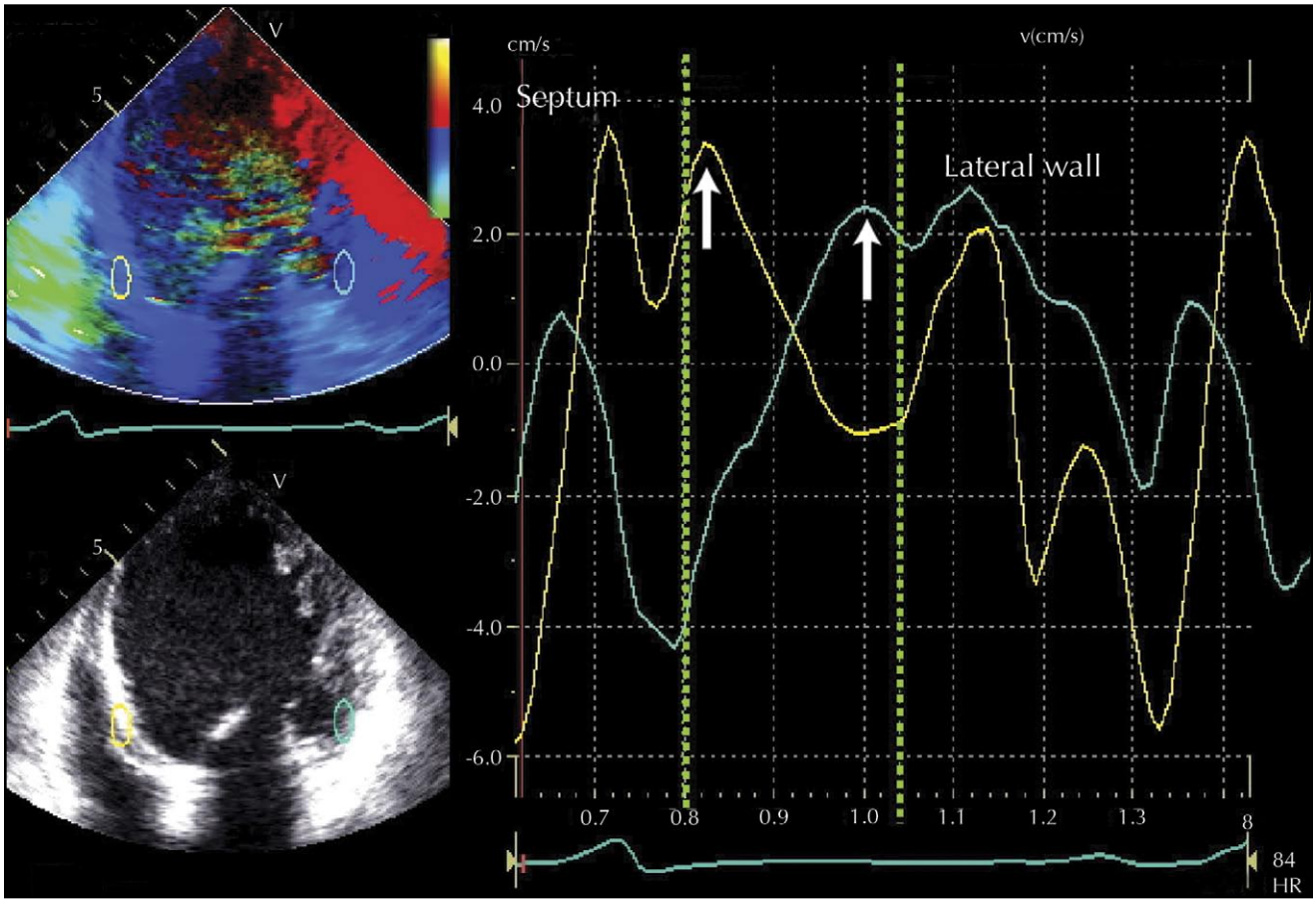

Figure 2. Tissue Doppler image of the apical four-chamber view prior to resynchronization therapy. Regions of interest (7 × 15 mm) were placed on the basal septum and basal lateral wall. The *vertical lines* indicate the timing of aortic valve opening (AVO) and aortic valve closure (AVC) and demarcate the ejection interval. The *vertical arrows* demonstrate the respective peak velocities during ejection, and their time difference is the opposing wall delay. An opposing wall delay is usually considered to represent significant dyssynchrony if it is 65 ms or longer.

image. This method can determine LV segmental strain toward the center of the LV cavity. This allows for calculation of radial septal and posterior wall time to peak thickening, which appears to be an important marker of mechanical dyssynchrony. In an initial experience, the septal to posterior wall delay, with a similar cutoff as M mode of at least 130 ms, was associated with response to CRT. More recently, a combined approach using longitudinal TDI velocities to assess longitudinal dyssynchrony and speckle-tracking radial strain to assess radial dyssynchrony has been shown to be of additive value [14]. Specifically, if both methods were in agreement on longitudinal and radial dyssynchrony, an ejection fraction response could more confidently be anticipated following CRT. On the other hand, a heterogeneous pattern in which longitudinal or radial dyssynchrony (but not both) was present was associated with a mixed response. This study illustrated the complexity of dyssynchrony patterns in patients referred for CRT and demonstrated the potential pitfalls of singular dyssynchrony approaches. The advantages of speckle tracking are that the data do not depend on Doppler angle of incidence and that no activation of TDI is required. In other words, offline analysis may be done on routine images, which enhances applicability. The disadvantages are that adequate image quality is needed; the speckle-tracking algorithm will not work on suboptimal images. In addition, the performance of speckle tracking appears to be related to frame rate. The optimal frame rates appear to be 30 to 90 Hz with a mean of 65 Hz in the initial experience.

Another promising approach is three-dimensional echocardiographic analysis. Kapetanakis et al. [36] and Horstman et al. [37] have presented data using an approach of segmental volume displacement in a model of real-time three-dimensional echocardiography for dyssynchrony analysis. They demonstrated the feasibility of extracting mechanical activation information from the whole left ventricle rather than a single tomographic plane, as in two-dimensional echocardiography. They measured the time to maximum displacement of each segment and calculated the SD as a marker of dyssynchrony. The advantage of this method is that a more complete analysis of LV dyssynchrony may be made in the individual patient, particularly because dyssynchrony patterns may be complex. The disadvantages include the inability to differentiate active from passive motion,

frame rates that are still relatively slow, and the need for adequate image quality for proper operation of the analysis software. However, continued advances in computer technology make this approach particularly promising.

CRT in Patients with a Narrow QRS

In an effort to refine patient selection, the studies discussed in this article focused on using imaging techniques to identify the subset of patients with a wide QRS who do not have significant mechanical dyssynchrony and who may not benefit from CRT. Several authors have demonstrated that mechanical dyssynchrony may exist in patients with heart failure who have a narrow QRS complex [38,39]. The precise reason for this dissociation of electrical from mechanical activation remains unknown, but it provides a potential opportunity for echocardiography to identify patients with mechanical dyssynchrony who would not be identified otherwise. Two observational pilot studies showed the benefit of CRT to patients with a narrow QRS who have mechanical dyssynchrony identified by TDI [40,41]. These studies have provided proof of the concept that CRT has potential to benefit this group of patients with heart failure. More recently, the RethinQ study, the first randomized trial of CRT in patients with a narrow QRS population, showed mixed results [42••]. This study randomized 172 patients who met inclusion criteria for mechanical dyssynchrony (a low ejection fraction and a narrow QRS complex) to a control group or to receive CRT. The primary end point of peak myocardial oxygen consumption was not different between groups, and this study was considered negative in this respect. However, all results were not negative; significant improvements were observed in New York Heart Association functional class and 6-minute walking distance in a subgroup of patients with nonischemic disease. In addition, only 14 heart failure events (16%) occurred in the group receiving CRT, versus 41 heart failure events (22%) in controls. This event rate difference did not reach statistical significance, perhaps due to a small sample size. Accordingly, whether CRT is beneficial to patients with echocardiographic dyssynchrony and a narrow QRS complex remains unclear. Limitations of the RethinQ study included using myocardial oxygen consumption as a primary end point because of its variability, a sample size that was underpowered to show therapeutic benefit, and perhaps patient selection factors. Future randomized trials are needed to clearly define whether patients with a narrow QRS and mechanical dyssynchrony can benefit from CRT with refined patient selection.

Conclusions

The echocardiographic evaluation of mechanical dyssynchrony is an evolving field in which new data are being released often. Although an enormous amount of data supports the hypothesis that mechanical dyssynchrony is the principal pathophysiologic feature that is corrected by CRT, the optimal means to quantify it remain uncertain. The more complex echocardiographic methods, such as TDI, which have shown the most promise for predicting response in single-center studies, have performed less well in a multicenter setting. It appears that difficulties with technical factors play a major role. On the other hand, the technically simpler pulsed Doppler methods, such as IVMD, have performed well in a multicenter setting but have a lesser predictive value. Furthermore, factors others than lack of dyssynchrony, such as global scar burden, scar location, or too advanced disease, are associated with nonresponse to CRT [18,43–45]. In summary, no single echocardiographic method has replaced the current clinical selection criteria for CRT using the wide QRS. Furthermore, the benefit of CRT to patients with a narrow QRS who were selected for CRT by echocardiographic dyssynchrony is controversial and unclear. Current efforts to improve dyssynchrony analysis continue to intensify, and future refinements for clinical applications are likely to be forthcoming.

Clinical Trial Acronyms

CARE-HF—Cardiac Resynchronization in Heart Failure; Contak-CD—Contak–Cardiac Defibrillator; PROSPECT—Predictors of Response to Cardiac Resynchronization Therapy; RethinQ—Resynchronization Therapy in Patients with Narrow QRS; SCART—Selection of Candidates for CRT.

Disclosure

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References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Hunt SA, Abraham WT, Chin MH, et al.: **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): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society.** *Circulation* 2005, **112:**e154–e235.
2. Cleland JG, Daubert JC, Erdmann E, et al.: **The effect of cardiac resynchronization on morbidity and mortality in heart failure.** *N Engl J Med* 2005, **352:**1539–1549.
3. Abraham WT, Fisher WG, Smith AL, et al.: **Cardiac resynchronization in chronic heart failure.** *N Engl J Med* 2002, **346:**1845–1853.

4. Bax JJ, Abraham T, Barold SS, et al.: **Cardiac resynchronization therapy: part 1--issues before device implantation.** *J Am Coll Cardiol* 2005, **46:**2153–2167.
5. Bax JJ, Ansalone G, Breithardt OA, et al.: **Echocardiographic evaluation of cardiac resynchronization therapy: ready for routine clinical use? A critical appraisal.** *J Am Coll Card* 2004, **44:**1–9.
6. Bax JJ, Bleeker GB, Marwick TH, et al.: **Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy.** *J Am Coll Cardiol* 2004, **44:**1834–1840.
7. Yu CM, Wing-Hong Fung J, et al.: **Understanding nonresponders of cardiac resynchronization therapy--current and future perspectives.** *J Cardiovasc Electrophysiol* 2005, **16:**1117–1124.
8. Yu CM, Bleeker GB, Fung JW, et al.: **Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy.** *Circulation* 2005, **112:**1580–1586.
9. Bax JJ, Marwick TH, Molhoek SG, 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:**1238–1240.
10. Bax JJ, Molhoek SG, van Erven L, et al.: **Usefulness of myocardial tissue Doppler echocardiography to evaluate left ventricular dyssynchrony before and after biventricular pacing in patients with idiopathic dilated cardiomyopathy.** *Am J Cardiol* 2003, **91:**94–97.
11. Yu CM, Zhang Q, Chan YS, et al.: **Tissue Doppler velocity is superior to displacement and strain mapping in predicting left ventricular reverse remodeling response after cardiac resynchronization therapy.** *Heart* 2006, **92:**1452–1456.
12. Yu CM, Zhang Q, Fung JWH, et al.: **A novel tool to assess systolic asynchrony and identify responders of cardiac resynchronization therapy by tissue synchronization imaging.** *J Am Coll Cardiol* 2005, **45:**677–684.
13. Yu Y, Kramer A, Spinelli J, et al.: **Biventricular mechanical asynchrony predicts hemodynamic effect of uni- and biventricular pacing.** *Am J Physiol Heart Circ Physiol* 2003, **285:**H2788–H2796.
14.•• Gorcsan J, Tanabe M, Bleeker GB, et al.: **Combined longitudinal and radial dyssynchrony predicts ventricular response after resynchronization therapy.** *J Am Coll Cardiol* 2007, **50:**1476–1483.

This paper illustrates the complexity of dyssynchrony patterns that may exist and the potential of a combined approach using more than one index to improve predictive value.

15. Gorcsan J, 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:**1178–1181.
16. Yu CM, Chau E, Sanderson JE, et al.: **Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure.** *Circulation* 2002, **105:**438–445.
17. Yu CM, Fung JW, 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:**66–73.
18. Tournoux FB, Alabiad C, Fan D, et al.: **Echocardiographic measures of acute haemodynamic response after cardiac resynchronization therapy predict long-term clinical outcome.** *Eur Heart J* 2007, **28:**1143–1148.
19. Yu CM, Abraham WT, Bax J, et al.: **Predictors of response to cardiac resynchronization therapy (PROSPECT)--study design.** *Am Heart J* 2005, **149:**600–605.
20.•• Ghio S, Chung E, Leon A, et al.: **Predictors of response to resynchronization therapy** [abstract]. *Presented at the European Society of Cardiology Congress 2007.* Vienna; September 4, 2007.

These preliminary results of the multicenter PROSPECT study highlight the technical factors and limitations that influence results of echocardiographic dyssynchrony analysis and the need for training, experience, and further refinements for mainstream clinical practice.

21. Cazeau S, Alonso C, Jauvert G, et al.: **Cardiac resynchronization therapy.** *Europace* 2004, **5(Suppl 1):**S42–S48.
22. Cazeau S, Bordachar P, Jauvert G, et al.: **Echocardiographic modeling of cardiac dyssynchrony before and during multisite stimulation: a prospective study.** *Pacing Clin Electrophysiol* 2003, **26:**137–143.
23. Cazeau S, Gras D, Lazarus A, et al.: **Multisite stimulation for correction of cardiac asynchrony.** *Heart* 2000, **84:**579–581.
24. Achilli A, Peraldo C, Sassara M, et al.: **Prediction of response to cardiac resynchronization therapy: the selection of candidates for CRT (SCART) study.** *Pacing Clin Electrophysiol* 2006, **29(Suppl 2):**S11–S19.
25. Richardson M, Freemantle N, Calvert MJ, et al.: **Predictors and treatment response with cardiac resynchronization therapy in patients with heart failure characterized by dyssynchrony: a pre-defined analysis from the CARE-HF trial.** *Eur Heart J* 2007, **28:**1827–1834.
26. Kass D: **Left ventricular versus biventricular pacing in cardiac resynchronization therapy: the plot in this tale of two modes.** *J Cardiovasc Electrophysiol* 2004, **15:**1348–1349.
27. Kass DA: **Ventricular resynchronization: pathophysiology and identification of responders.** *Rev Cardiovasc Med* 2003, **4(Suppl 2):**S3–S13.
28. Pitzalis MV, Iacoviello M, Romito R, et al.: **Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony.** *J Am Coll Cardiol* 2002, **40:**1615–1622.
29. Marcus GM, Rose E, Viloria EM, et al.: **Septal to posterior wall motion delay fails to predict reverse remodeling or clinical improvement in patients undergoing cardiac resynchronization therapy.** *J Am Coll Cardiol* 2005, **46:**2208–2214.
30. Bax JJ, Abraham T, Barold SS, et al.: **Cardiac resynchronization therapy: part 2--issues during and after device implantation and unresolved questions.** *J Am Coll Cardiol* 2005, **46:**2168–2182.
31. Yu CM, Fung WH, 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:**684–688.
32. Yu CM, Gorcsan J 3rd, Bleeker GB, et al.: **Usefulness of tissue Doppler velocity and strain dyssynchrony for predicting left ventricular reverse remodeling response after cardiac resynchronization therapy.** *Am J Cardiol* 2007, **100:**1263–1270.
33. Sogaard P, Egeblad H, Kim WY, et al.: **Tissue Doppler imaging predicts improved systolic performance and reversed left ventricular remodeling during long-term cardiac resynchronization therapy.** *J Am Coll Cardiol* 2002, **40:**723–730.
34. Penicka M, Bartunek J, De Bruyne B, et al.: **Improvement of left ventricular function after cardiac resynchronization therapy is predicted by tissue Doppler imaging echocardiography.** *Circulation* 2004, **109:**978–983.
35. Suffoletto MS, 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* 2006, **113:**960–968.

36. Kapetanakis S, Kearney MT, Siva A, et al.: **Real-time three-dimensional echocardiography: a novel technique to quantify global left ventricular mechanical dyssynchrony.** *Circulation* 2005, **112:**992–1000.
37. Horstman JA, Monaghan MJ, Gill EA: **Intraventricular dyssynchrony assessment by real-time three-dimensional echocardiography.** *Cardiol Clin* 2007, **25:**253–260.
38. Bleeker GB, Schalij MJ, Molhoek SG, et al.: **Frequency of left ventricular dyssynchrony in patients with heart failure and a narrow QRS complex.** *Am J Cardiol* 2005, **95:**140–142.
39. Yu CM, Lin H, Zhang Q, Sanderson JE: **High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration.** *Heart* 2003, **89:**54–60.
40. Yu CM, Chan YS, Zhang Q, et al.: **Benefits of cardiac resynchronization therapy for heart failure patients with narrow QRS complexes and coexisting systolic asynchrony by echocardiography.** *J Am Coll Cardiol* 2006, **48:**2251–2257.
41. Bleeker GB, Holman ER, Steendijk P, et al.: **Cardiac resynchronization therapy in patients with a narrow QRS complex.** *J Am Coll Cardiol* 2006, **48:**2243–2250.
42.•• Beshai JF, Grimm RA, Nagueh SF, et al.: **Cardiac-resynchronization therapy in heart failure with narrow QRS complexes.** *N Engl J Med* 2007, **357:**2461–2471.
The first randomized trial of resynchronization therapy in patients with a narrow QRS and dyssynchrony by echocardiographic Doppler methods.
43. Adelstein EC, Saba S: **Scar burden by myocardial perfusion imaging predicts echocardiographic response to cardiac resynchronization therapy in ischemic cardiomyopathy.** *Am Heart J* 2007, **153:**105–112.
44. Bleeker GB, Kaandorp TA, Lamb HJ, et al.: **Effect of posterolateral scar tissue on clinical and echocardiographic improvement after cardiac resynchronization therapy.** *Circulation* 2006, **113:**969–976.
45. Gradaus R, Stuckenborg V, Loher A, et al.: **Diastolic filling pattern and left ventricular diameter predict response and prognosis after cardiac resynchronization therapy.** *Heart* 2007 [Epub ahead of print].