The Role of Echocardiography in Cardiac Resynchronization Therapy

Wojciech Mazur, MD, and Eugene S. Chung, MD

Corresponding author
Eugene S. Chung, MD
The Heart and Vascular Center, Christ Hospital, 2123 Auburn Avenue, Suite 100, Cincinnati, OH 45219, USA.
E-mail: chunge@ohioheart.org

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Echocardiography is the most important imaging tool for managing heart failure patients. With the advent of cardiac resynchronization therapy (CRT), its role has been broadened by data pertaining to patient selection, optimization of device settings, and outcome assessment. Beyond ejection fraction determination, echocardiographic methods that measure tissue velocity and strain may have the capability to determine degree of mechanical dyssynchrony and possibly predict likelihood of benefit with CRT. After implantation (as the ventricles are fully paced, adjusting the atrioventricular delay [atrioventricular optimization]), the timing of the right ventricular and left ventricular lead stimulation (ventricular–ventricular optimization) to achieve maximal cardiac filling or ejection may be clinically important. Atrioventricular and ventricular–ventricular optimization rely on echocardiography to determine optimal values. In long-term follow-up, serial measurement of left ventricular volume has significant correlation with mortality and is a reasonable measure of successful CRT; echocardiography is uniquely suited for this purpose.

Introduction

Cardiac resynchronization therapy (CRT) is recommended by consensus treatment guidelines for heart failure (HF) patients with low left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) functional class III to IV, QRS ≥ 120 ms, and an optimal medical regimen [1]. The main role of echocardiography in CRT has been as the most common method for determining LVEF due to its wide availability, ease of application, low patient risk, and extensive, generalized clinical experience. However, echocardiography has begun to play a more significant role in CRT in the past several years, involving patient selection [2], implementation, and follow-up [3]. In this article, we review the expanding role of echocardiography in CRT by examining dyssynchrony detection, atrioventricular (AV) and ventricular–ventricular (VV) optimization, and evaluating clinical outcomes.

Detecting Mechanical Dyssynchrony

The American College of Cardiology (ACC), American Heart Association (AHA) [1], and European Society of Cardiology [4] guidelines recommend assessment of ejection fraction (EF), functional class, and QRS duration when considering a patient for CRT without mention of echocardiographic measures of dyssynchrony. In contrast, in patient selection, the UK National Institute for Health and Clinical Excellence (NICE) [5] recommends inclusion of echocardiographic measures of mechanical dyssynchrony for patients with QRS duration between 120 and 150 ms. However, this document does not provide guidance regarding specific methods or cut-off values.

For the purpose of this review, the term *dyssynchrony* refers to the mechanical phenomenon of differences in systolic timing between segments of the left ventricle (LV). Dyssynchrony should not be viewed as an "all or none" phenomenon but as a continuum with varying grades of severity. Nonetheless, for tests aiming to detect dyssynchrony (as with other screening methods, such as stress testing), selection of a cut-off value is clinically important. The presumed mechanism of CRT effect is correction of ventricular mechanical dyssynchrony for which the QRS duration is used as a surrogate. However, this relationship between QRS and mechanical dyssynchrony should not be assumed because there are patients with a prolonged QRS but no significant dyssynchrony on tissue Doppler testing [6]; conversely, there are those with a narrow QRS and clear evidence of mechanical dyssynchrony detected using similar methods [7]. There appears to be poor correlation between QRS and dyssynchrony in the variety measured using longitudinal tissue Doppler velocity [6]. Given these observations and the fact that approximately 30% of patients undergoing CRT using prolonged QRS as a criterion do not derive notable benefit from CRT [8], more sophisticated methods of detecting dyssynchrony based on echocardiography have been developed and tested by multiple investigators. There are more than 400 original and

Table 1. Summary of echocardiographic predictors of response to CRT

Echocardiographic predictor	Description of method	Echocardiographic method	Cut-off
SPWMD	M-mode measured by parasternal short-axis view	M-mode	> 130 ms
IVMD	Defined as the difference between LV and RV preejection intervals	Pulse Doppler	> 40 ms
LVFT/RR	Percentage change in LVFT in relation to cardiac cycle length as measured by transmitral Doppler echocardiography	Doppler	< 40%
LPEI	Defined as the time interval between the beginning of QRS and beginning of LV ejection by Doppler	Doppler	> 140 ms
Intraventricular dyssynchrony LLWC	Defined as the presence of overlap between the end of lateral wall contraction (by way of M-mode echocardiography) and onset of LV filling (by Doppler echocardiography)	M-mode and pulse Doppler	Any overlap
Ts (lateral-septal)	Delay between Ts at basal-septal and basal-lateral segments	TDI	> 60 ms
Ts-SD	Standard deviation of time from QRS to peak systolic velocity in ejection phase for 12 LV segments (6 basal and 6 middle)	TDI	> 32 ms
Ts-peak (medial)	Maximum difference of Ts for 6 segments at medial level	TDI	> Median
Ts-onset (medial)	Maximum difference of time to onset of systolic velocity for 6 segments at medial level	TDI	> Median
Ts-peak (basal)	Maximum difference of Ts for 6 segments at basal level	TDI	> Median
Ts-onset (basal)	Maximum difference of time to onset of systolic velocity for 6 segments at basal level	TDI	> Median
PVG	Derived from subtracting the maximal to the minimal difference of Ts for 6 segments at basal level	TDI	> 110 ms
DLC	Measured in the 6 basal LV segments with a systolic contraction component in TDI and confirmed by negative strain rate	TDI and SRI	> 2 basal segments

CRT—cardiac resynchronization therapy; DLC—delayed longitudinal contraction; IVMD—interventricular mechanical delay; LLWC—left lateral wall contraction; LPEI—left ventricular preejection interval; LV—left ventricular; LVFT—left ventricular filling time; PVG—peak velocity gradient; RR—cardiac cycle length; RV—right ventricular; SPWMD—septal-posterior wall motion delay; SRI—strain rate imaging; TDI—tissue Doppler imaging; Ts—time to peak systolic velocity; Ts-SD—standard deviation of time to peak myocardial systolic velocity of the 12 left ventricular segments.

review articles published in the field of echocardiographic predictors of CRT response, with many of these parameters achieving high sensitivity and specificity in pilot studies. A partial list of these articles is presented in Table 1.

Echocardiographic assessment of dyssynchrony:

M-mode echocardiography

Septal-to-posterior wall motion delay is obtained from M-mode recording of the parasternal short-axis view at the level of papillary muscles. A cut-off value of more than 130 ms was proposed as a marker of clinically significant intraventricular dyssynchrony [9,10]. However, this parameter has proven difficult to obtain because of frequent lack of clear septal deflection, particularly with ischemic cardiomyopathy. Subsequent larger studies have failed to confirm initial findings [11,12••], and this method does not have a clinically relevant role in patient selection.

Tissue Doppler imaging

Tissue Doppler imaging (TDI) measures the velocity of cardiac tissue in relationship to the cardiac cycle, from which the following parameters can be derived: peak systolic velocity, time to onset of systolic velocity, and time to peak systolic velocity [13]. With pulsed-wave TDI, only one region can be interrogated at a time, which increases procedure time and precludes simultaneous comparison of segments. A more effective method for assessing dyssynchrony is color-coded TDI, which acquires velocity data from the entire sector and allows multiple simultaneous interrogations. One well-studied example of this tech-

nique was developed by Bax et al. [14] and compares the time to peak velocity of basal, septal, and basal lateral segments. Septal-to-lateral delay ≥ 60 ms was demonstrated to predict acute response to CRT. An alternative analysis introduced by Yu et al. [15] measures time to peak velocity of 12 basal and mid segments in apical two-chamber, four-chamber, and parasternal long-axis views. Standard deviation (SD) of these 12 time intervals of time to peak myocardial systolic velocity (Ts-SD) represents a measure of dyssynchrony. Ts-SD ≥ 33 ms resulted in sensitivity and specificity of 96% and 75% in predicting left ventricular (LV) reverse remodeling.

Many early echocardiographic parameters were subsequently evaluated in a large nonrandomized, prospective, multicenter (53 centers in Europe, Hong Kong, and United States) trial for their ability to predict response or nonresponse to CRT. Predictors of Response to CRT (PROSPECT) [12••] enrolled 498 patients with standard CRT indications (EF ≤ 35%, QRS ≥ 130 ms, NYHA class III–IV) and measured 12 echocardiographic parameters of dyssynchrony based on conventional (septal-posterior wall motion delay, interventricular mechanical delay, LV filling time in relation to cardiac cycle length, LV preejection time, and intraventricular dyssynchrony of lateral wall contraction) and tissue Doppler–based methods (septal-to-lateral delay, SD of 12 segments, delayed longitudinal contraction, maximum difference of time to peak systolic displacement for four segments, maximum difference of time to peak systolic velocity for six basal segments, and maximum difference of time to onset of systolic velocity for six basal segments) were evaluated after site training in acquisition methods and blinded core laboratory analysis. Clinical composite score improved in 69% of patients, whereas LV end-systolic volume (LVESV) decreased ≥ 15% in 56% of patients. The ability of the 12 parameters to predict clinical response varied widely, with sensitivity ranging from 6% to 74% and specificity ranging from 35% to 91%. For predicting LVESV response, sensitivity ranged from 9% to 77% and specificity from 31% to 93%. Although several parameters were able to distinguish responders and nonresponders with clinical significance, none were able to distinguish responders from nonresponders to a degree that should affect clinical decision making. Factors that may have contributed to this finding include several potential sources of variability: use of different vendors, echocardiographic image acquisition across many clinical sites of different experience, and inherent difficulties of dyssynchrony measurements.

Strain and strain rate analysis

Strain is defined as the change in length divided by baseline (diastolic) length, and strain rate is the rate of this change [16]; these measures represent tissue deformation and are able to distinguish between passive motion and active contraction. This characteristic of strain and strain rate measures is of particular importance in ischemic cardiomyopathy with areas of infarcted myocardium. To compare the accuracy of TDI and strain methods for dyssynchrony detection, Miyazaki et al. [17••] studied patients with normal hearts, those with EFs less than 35%, and those with left bundle branch block. As expected, by both methods, dyssynchrony was greater in the abnormal group. However, significant overlap was found using TDI methods, whereas strain methods demonstrated better discriminatory strength between these groups. Importantly, almost 50% of healthy subjects had TDI values above the proposed cut-off for predicting responders to CRT.

Tissue synchrony imaging

Tissue synchrony imaging (GE Vingmed Vid 7 [GPS Medical Inc., Indianapolis, IN]) is a signal processing algorithm that uses TDI data to automatically detect peak positive velocity and then color code the time to peak velocity (green for normal timing, yellow-orange for moderate delay, and red for severe delay). This methodology allows for quick visual estimation of variation of timing during systole. Using quantitative data derived from tissue synchrony studies, Yu et al. [18] demonstrated high sensitivity and specificity in distinguishing CRT responders versus nonresponders (defined by LVESV reduction by 15% at 3 months). Recent, similar dyssynchrony assessment packages have become available from Siemens, Philips, Toshiba, and Tomtec Inc.

Direction of dyssynchrony

In attempting to study timing differences between LV segments in systole, one must be mindful that myocardial contraction does not occur in one plane. Rather, each segment undergoes motion that can be reduced to three vectors: longitudinal, circumferential, and radial. The degree to which motion in each direction contributes to the overall vector and the relative significance of dyssynchrony in each direction has not been well characterized.

Delgado et al. [19] attempted to answer these questions by studying strain-based dyssynchrony in all three directions (longitudinal, circumferential, and radial) for the ability to predict response to CRT in 161 patients. Speckle tracking strain analysis was performed in apical two- and four-chamber views and the parasternal short-axis view at the level of papillary muscles. In each direction, two parameters for dyssynchrony were measured: maximal time delay between peak systolic strain of any two segments and asynchrony index of the LV (SD of time to peak systolic strain of 6 or 12 segments, depending on the type of strain). In this study, 55% of patients were classified as responders using LVESV reduction ≥ 15% at 6 months. At baseline, only dyssynchrony measured using radial strain was different between subsequent responders and nonresponders. A cut-off value of radial dyssynchrony ≥ 130 ms predicted response to CRT, with sensitivity and specificity of 83% and 80%, respectively. Gorcsan et al. [20•] evaluated combined longitudinal and radial dyssynchrony in 190 HF patients in predicting response to CRT. Longitudinal dyssynchrony was assessed by color TDI methods, whereas

radial dyssynchrony was measured using speckle tracking methods. Longitudinal dyssynchrony was defined as time to peak velocity difference ≥ 60 ms and radial dyssynchrony ≥ 130 ms. When longitudinal and radial dyssynchrony were present, 95% of patients had an improvement in EF ≥ 15%; when both were absent, only 21% had an EF response. When longitudinal or radial dyssynchrony was positive (but not both), 59% of patients had an improved EF ≥ 15%. Combining both indices predicted EF response with sensitivity and specificity of 88% and 80%, respectively.

Real-time three-dimensional echocardiography

Real-time three-dimensional echocardiography allows for more precise measurements of LV volume and EF than conventional two-dimensional methods. For dyssynchrony assessment, volume of each segment is measured over time. With normal synchronous contraction, each segment will achieve minimum volume at nearly the same time after onset of systole. However, times will be dispersed with dyssynchrony. Further, rather than sampling only 16 or 17 segments, approximately 3000 points of endocardial surface can be tracked with three-dimensional imaging. To facilitate visual assessment of results, polar data maps of color-coded times to peak volume reduction have been developed; the ability to quickly and accurately visualize patterns of time to peak contraction may be helpful in optimal LV lead placement. In a study of 89 patients, three-dimensional echocardiography-derived systolic dyssynchrony index (SD of time to peak volume reduction of 16 segments) was found to be reproducible, correlated with worsening LV function (regardless of QRS duration), and predictive of CRT response [21].

Myocardial scar: predictor of nonresponse to CRT

Despite the fact that the majority of patients treated with CRT based on current criteria appear to benefit from its use, the potential risks of implanting an LV lead (complications, diaphragmatic stimulation, cost, nonresponse) make the ability to prospectively identify those who are not likely to respond clinically useful. Accordingly, in a small study with 40 patients, Bleeker et al. [22•] demonstrated that in the presence of a transmural (> 50% wall thickness) posterolateral scar (detected using cardiac MRI), CRT response rate was only 14% compared with 81% in those without a scar in that location. They noted that degree of dyssynchrony was not corrected by CRT in patients with a posterolateral scar. Scar detection using echocardiography (although perhaps not as accurate as with MRI) may serve a similar role in distinguishing responders from nonresponders. Accordingly, Ascione et al. [23] investigated 74 patients with ischemic cardiomyopathy. Using end-diastolic wall thickness less than 6 mm as scarred myocardium, a percent global scar area (GSA) was calculated by dividing the number of scarred LV segments by 16. As expected, based on previous cardiac MRI studies, a significant inverse relationship was found between percent GSA and response rate. Mean percent GSA was significantly higher in nonresponders than in responders (31.6% ± 18% vs 6.4% ± 11%). Applying the cut-off value of GSA ≤ 18% resulted in sensitivity and specificity of 94.7% and 77.8%, respectively, for CRT response. However, there are no published echocardiographic data regarding scar location and response to CRT.

Importantly, poor cardiac status may be associated with poor CRT response and may have a place in clinical discussions. Gradaus et al. [24] evaluated 122 consecutive patients with HF with an average QRS duration of 170 ± 32 ms and dyssynchrony demonstrated by TDI. Multivariate analysis revealed that restrictive filling pattern, LVESV, and pulmonary capillary wedge pressure were significant predictors of poor response to CRT.

Are we missing dyssynchrony by rest echocardiography?

Most patients evaluated for CRT are in NYHA functional class III and are asymptomatic at rest but symptomatic with exertion. All dyssynchrony indices derived have been measured at rest. To evaluate the dynamic nature of dyssynchrony in some patients, Wang et al. [25] reported a series of 433 HF patients with no evidence of dyssynchrony at rest (QRS < 120 ms; Ts-SD < 33 ms). After 6 minutes of treadmill exercise, 33% of patients developed dyssynchrony denoted by increased Ts-SD. Interestingly, an E/Ea ratio of more than 10 at rest predicted exercise-induced dyssynchrony in multivariate analysis. It remains to be seen if exercise-induced dyssynchrony will lead to a strategy of dynamic dyssynchrony therapy in which different pacer settings at exercise attempt to account for changes in dyssynchrony.

Where do we go from here?

For now, echocardiography does not have a clear role in patient selection beyond conventional study, a fact that is reflected in ACC/AHA practice guidelines for HF. Post hoc analyses of the PROSPECT database may shed light on fundamental questions regarding the nature of mechanical dyssynchrony (eg, should it be measured in radial, longitudinal, or circumferential direction, and is speckle tracking–based strain measurement more robust than TDI methods?) It is possible that multimodality imaging will be necessary to achieve high sensitivity and specificity for CRT response. These modalities may include cardiac CT (coronary sinus venogram), cardiac MRI (for ischemic cardiomyopathy, total scar burden, and scar location), and echocardiography (strain derived from speckle tracking). This combined approach would improve concordance between LV pacing site and area of latest activation and avoid areas of scarred myocardium. The ability to assess the likelihood of benefit as low, moderate, or high will aid in preimplant conversation in weighing the attendant risks, benefits, and setting expectations.

AV and VV Optimization

All CRT devices have the capability to adjust AV delays and VV timing. The goal of AV optimization is to ensure LV contraction does not occur before complete filling, whereas

with VV optimization, the goal is to minimize LV mechanical dyssynchrony. From dual-chamber pacemaker studies, adjustment of AV delay in HF patients has been shown to improve hemodynamic measures in some patients [26,27] but not in others [28]. In a single-center study of CRT patients, varying the AV interval appeared to significantly impact hemodynamic parameters at a patient-specific value rather than a "one-size-fits-all" setting, supporting the concept of AV interval optimization on a case-by-case basis [29]. Stockburger et al. [30] reported acute improvement in LV and right ventricular (RV) preejection intervals, interventricular mechanical delay, and myocardial performance index by optimizing AV delays. Hardt et al. [31] assessed immediate and chronic effects of AV optimization in CRT patients: E/E′ ratio and TDI of mitral annulus improved acutely at 6-week follow-up. There was a slight increase in EF compared with baseline (three percentage units), modest improvement in 6-minute walk test, and significant decrease in N-terminal pro-brain natriuretic peptide.

LV filling in relation to AV delay is typically measured by pulsed Doppler interrogation of the mitral valve, in which excessively short AV delay results in truncation of the A wave, and a long AV delay results in E- and A-wave overlap. AV delay can be empirically adjusted so that LV ejection begins after A-wave completion and the time velocity integral of the E and A waves is maximized. Alternatively, the time velocity integral of the LV outflow tract Doppler may be used as a surrogate for stroke volume with various AV delay settings. However, a larger, prospective, randomized study evaluating the effect of AV optimization on clinical outcomes is needed to definitively aid in clinical management.

When considering VV optimization, the primary aim is to minimize ventricular dyssynchrony by adjusting the timing of the RV and LV leads. However, it is unclear which measures of dyssynchrony would be most appropriate, easy to obtain, reproducible, and correlated with acute hemodynamic improvement. Accordingly, Bordachar et al. [32] performed a small study in 41 CRT patients evaluating a number of dyssynchrony parameters under different VV settings. Dyssynchrony changes produced by different VV settings were associated with significant hemodynamic changes to varying degrees, highlighting the clinical relevance of this process. Furthermore, simultaneous RV/LV settings were found to be optimal in only 15% of patients. However, the challenge of identifying a relatively quick, easy, and reproducible method of measuring dyssynchrony and the effect of VV optimization on long-term clinical outcomes remains unanswered.

InSync III Marquis was a multicenter, prospective, double-blind study of 241 patients undergoing CRT who were randomly assigned to receive simultaneous VV stimulation or VV timing optimized by way of M-mode dyssynchrony measurement. The primary aim was to test equivalence of VV optimization and simultaneous VV timing for safety and clinical outcomes [33]. This study (presented but not yet published) achieved the primary end point of noninferiority for clinical response. Furthermore, there were trends toward further benefit with VV optimization versus simultaneous stimulation in terms of clinical response and NYHA classification. There were no differences observed in 6-minute walk or cardiopulmonary exercise testing and in cardiac structure (LVEF, mitral regurgitation, LV volumes). Once these data are published, it may become more reasonable to consider VV timing as a routine part of device optimization after implantation.

Defining Responders

Response to CRT can be measured in two categories: clinical and cardiac structure. Clinical parameters of response such as NYHA classification and quality of life are clearly important; however, change in LV volumes after HF interventions are reliably correlated with mortality and have been suggested as a potential surrogate end point in HF trials [34,35]. In following a post-CRT patient's LV volumes for evidence of improvement, echocardiography has several advantages over gated pool nuclear ventriculography, angiography, CT, and MRI. There is no radiation, no routine use of contrast material, wide availability, and no conflict with implanted metallic device. Potential disadvantages include variability in measurements arising from difficulties in image acquisition, inadequate endocardial definition, and lack of generalized experience with volume measurements. However, using Simpson's method in the apical four- and two-chamber views, an experienced echocardiographer should achieve acceptable reproducibility, particularly when using sophisticated digital reading and analysis equipment. The generally accepted threshold for significant end-systolic volume reduction is 15%.

It is interesting to note that concordance of clinical and volume improvement after CRT is not perfect [36•]. In the PROSPECT study, approximately 60% of patients showed agreement between the two measures of response, clinical composite score, and LVESV reduction. Approximately 45% were improved by both measures, and 15% were not improved by either. In the remaining 40%, only one of the outcome measures was improved (data on file at Medtronic, Inc.). Without a consensus on whether clinical or LV structural changes should assume greater weight, assessment of patient status on follow-up should include a clinical measure and LVESV evaluation at 6 months.

Conclusions

With the advent of CRT, echocardiography has assumed a far-reaching role in HF research and patient management: determining EF as a patient selection criterion for CRT, further stratifying the likelihood of therapeutic effect by dyssynchrony and scar detection, optimization of AV and VV timing intervals after implantation, and following changes in LV volumes long term as a measure of response to CRT. Some of these roles, particularly dyssynchrony measurements and optimization techniques, require further refinement before incorporation into guidelines.

Disclosures

Dr. Mazur serves as a consultant for Medtronic, Inc. Dr. Chung serves as a consultant for Medtronic, Inc. and Boston Scientific Corp. and receives research support from CHF Solutions Inc., Medtronic Inc., and Boston Scientific Corp.

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