DEVICE THERAPY

REVIEW ARTICLE

Use of Echocardiography to Manage Cardiac Resynchronization Therapy

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ABSTRACT. Current guidelines recommend cardiac resynchronization therapy (CRT) for a subset of patients with systolic heart failure; however, the optimal settings for each patient and the characterization of the patient population most likely to benefit are still areas of active research and debate. New techniques in echocardiography may facilitate adjustment of pacer specifications to augment a positive response or enhance response in a minimal or non-responder. In addition, these new imaging strategies may allow clinicians to pre-select patients who may benefit from CRT despite not conforming to guideline-based recommendations. In this review we relate the current data regarding the use of echocardiography to guide the management of CRT.

KEYWORDS. cardiac resynchronization therapy, echocardiography, heart failure.

Introduction

Heart failure (HF) is the final common pathway for all serious cardiac disorders, including those having valvular, ischemic, myopathic, hypertensive, and arrhythmic etiology. American Heart Association (AHA) class IA recommendations for the treatment of HF encompass the use of angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, aldosterone antagonists, implantable cardioverter-defibrillators (ICDs), and cardiac resynchronization therapy (CRT). The problem of non-response to CRT in a persistently large proportion of recipients, taken together with the cost of CRT, necessitates development of tools to prospectively distinguish responders from non-responders, both within the population identified as candidates for CRT based on current clinical guidelines and outside this population, as a subset of patients with HF and mechanical dyssynchrony despite a narrow QRS complex may ultimately be shown to benefit from CRT. This problem also warrants efforts to find ways to optimize device settings to improve hemodynamic and clinical results in patients who demonstrate inadequate, absent, or negative response to CRT.

Current guidelines recommend that patients with New York heart Association (NYHA) class III or IV HF symptoms despite optimal medical management, left ventricular ejection fraction (LVEF) less than 35%, QRS duration greater than 120 ms, and sinus rhythm be considered for CRT. These guidelines are based on several well-designed clinical trials including COMPANION (Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure), a multicenter randomized controlled trial that demonstrated a 36% reduction in death for HF patients who received CRT. Initially, it appeared that patients with mild-to-moderate HF (NYHA class I or II) might not benefit from CRT. However, recent data suggest that even these less symptomatic patients may benefit. The REVERSE (REsynchronization reVErses Remodeling in Systolic Left vEntricular Dysfunction) trial randomized HF patients with NYHA class II and III symptoms to receive either ICD alone or ICD with CRT (CRT-D). The group receiving CRT-D displayed decreased mortality, decreased number of hospitalizations, increased time to death, and increased time to HF hospitalization. As in prior studies, patients deriving greatest benefit from CRT were those with very wide QRS complexes (>150 ms) and left bundle branch block (LBBB).

CRT is deemed to be ineffective in a relatively large proportion (30% in most studies) of recipients. Based on this statistic, Sanderson calculated a potential cost in Europe of 7.5 billion euros for CRT device implantation.
in non-responders, along with a potential for 22,500 deaths related to complications from CRT device implantation in this group. Thus, prospectively distinguishing responders from non-responders to CRT is a high priority for clinical and economic reasons, but the best method for accomplishing this is currently under debate. Echocardiography has been the most widely studied imaging modality to identify candidates for CRT, for primary (prospective) optimization (immediately after CRT initiation) as well as secondary optimization in non-responders. This review will discuss studies on the use of echocardiography for selection of HF patients for CRT and for optimization of device settings in patients with inadequate, absent, or negative response to CRT.

**Echocardiography to assess the effect of CRT on ventricular function and hemodynamics**

Echocardiography is used to assess and quantitate the effects of CRT on hemodynamics and function. (See Table 1) CRT can exert effects on interventricular, intraventricular, and atrioventricular synchrony. After CRT initiation, dyssynchrony is reduced both immediately post implantation and over a longer time period. In a study of 100 patients with left ventricular (LV) dyssynchrony assessed with tissue Doppler imaging (TDI), Bleeker et al demonstrated that immediately after CRT initiation stroke volume increased, as evidenced by decreased LV end-systolic volume (LVEDV) and stable LV end-diastolic volume (LVEDV) in those patients with echocardiographic evidence of reduced dyssynchrony. Furthermore, when CRT was turned off, these effects disappeared. Importantly, the 15 patients who did not have decreased LV dyssynchrony on TDI did not have echocardiographic evidence of reverse remodeling, a major indicator of response to CRT, after 6 months. The beneficial effects of CRT may extend beyond LV systolic function to improvements in diastolic function. Using pulsed Doppler analysis Waggoner et al demonstrated improvements in LV diastolic filling time and mitral E-wave velocity and duration immediately after CRT initiation. The beneficial effects were seen only in the subgroup of patients with E/A ratios greater than 1. A recent study suggested that CRT decreases diastolic dyssynchrony (defined as maximum time delay in peak early diastolic velocity measured using TDI), and that those patients who did not have echocardiographic evidence of remodeling (decreased LVEDV) at 6 months did not have diastolic dyssynchrony at baseline.9

**Echocardiography to predict clinical response to CRT**

Most studies estimate that 60–70% of patients will have a positive clinical response to CRT18 and predicting responsiveness to CRT is an area of active research. Refining the algorithms for prospective identification of patients who will respond to CRT could not only prevent patients without likelihood of benefit from undergoing an invasive procedure, but could also make available the benefits of CRT to those patients with HF who do not meet the established criteria (for example, QRS duration >120 ms) for CRT. The PROSPECT was designed to address the question of whether echocardiographic parameters provide incremental discriminatory power for selecting CRT recipients, above and beyond the established criterion of QRS duration. It was a prospective multicenter study involving 498 patients meeting AHA criteria for CRT. Prior to initiation of CRT, patients were evaluated for 12 different echocardiographic parameters including LV filling time
## Table 1: Summary of studies cite

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Data acquisition</th>
<th>Primary or secondary optimization</th>
<th>Echocardiographic parameters of dyssynchrony and/or response</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeker, 2007</td>
<td>100</td>
<td>TDI</td>
<td>Primary</td>
<td>LVEDV, LVESV</td>
<td>Responders displayed increased reverse remodeling at 6 months compared to non-responders</td>
</tr>
<tr>
<td>Waggoner, 2005</td>
<td>50</td>
<td>TDI</td>
<td>Primary</td>
<td>Systolic and diastolic mitral annular velocities</td>
<td>Responders displayed increased diastolic and systolic mitral annular velocities</td>
</tr>
<tr>
<td>Shanks, 2010</td>
<td>266</td>
<td>TDI</td>
<td>Primary</td>
<td>Time delay to peak systolic and early diastolic velocities at four basal LV segments</td>
<td>Reverse remodeling at 6 months was observed only in those with systolic or diastolic dyssynchrony at baseline</td>
</tr>
<tr>
<td>Chung, 2010 (PROSPECT Trial)</td>
<td>498</td>
<td>TDI M-mode SDA</td>
<td>Primary</td>
<td>12 Doppler parameters including: left ventricular filling time (in relation to cycle length), peak velocity difference, delayed longitudinal contraction and interventricular mechanical delay, QRS duration &gt;120 ms</td>
<td>NYHA class, hospitalizations and death decreased in 50%, increased in 16%. LVESV decreased in 35%. Doppler echocardiographic findings did NOT provide incremental predictive power beyond standard CRT selection criteria</td>
</tr>
<tr>
<td>Young, 2003 MIRACLE ICD Trial</td>
<td>328</td>
<td>SDA</td>
<td>Primary</td>
<td>Ritter’s technique for AV delay optimization, QRS duration</td>
<td>Improved quality of life with CRT without mortality reduction</td>
</tr>
<tr>
<td>Leon, 2005 InSYNC III Trial</td>
<td>422</td>
<td>SDA</td>
<td>Primary</td>
<td>Ritter’s technique for AV delay optimization, QRS duration</td>
<td>Optimization of AV delay improved stroke volume and exercise capacity but not quality of life</td>
</tr>
<tr>
<td>Kedia, 2006</td>
<td>215</td>
<td>TDI</td>
<td>Primary</td>
<td>Iterative technique for AV delay optimization</td>
<td>No difference in mortality in patients who underwent AV optimization</td>
</tr>
<tr>
<td>Bertini, 2010</td>
<td>30</td>
<td>2DST SDA</td>
<td>Primary</td>
<td>VV offset optimization to maximize LVOT VTI</td>
<td>Concordance in optimal VV offset among different optimization strategies</td>
</tr>
<tr>
<td>Valzania, 2007</td>
<td>37</td>
<td>SDA</td>
<td>Primary and secondary</td>
<td>AV delay optimization using iterative method, VV offset optimization to maximize LVOT VTI</td>
<td>Optimal VV offset and AV delay change over time</td>
</tr>
<tr>
<td>Mokrani, 2009</td>
<td>50</td>
<td>SDA</td>
<td>Secondary</td>
<td>AV delay optimization to maximize LVOT VTI</td>
<td>Optimal AV delay during exercise differs from optimal AV delay at rest</td>
</tr>
<tr>
<td>Valzania, 2008</td>
<td>24</td>
<td>IEGM SDA</td>
<td>Secondary</td>
<td>VV offset and AV delay optimization to maximize LVOT VTI</td>
<td>Optimal VV offset varied with exercise but AV delay did not; optimization of VV offset improved hemodynamics</td>
</tr>
<tr>
<td>Sawhney, 2004</td>
<td>40</td>
<td>SDA</td>
<td>Primary</td>
<td>AV delay optimization to maximize LVOT VTI</td>
<td>AV delay optimization improved NYHA class and quality of life at 3 months</td>
</tr>
<tr>
<td>Ellenbogen, 2010 SMART-AV Trial</td>
<td>980</td>
<td>SDA</td>
<td>Primary</td>
<td>AV delay optimization to maximize LVOT or mitral VTI</td>
<td>No difference among fixed AV delay, AV delay optimization with echocardiography, and AV delay optimization with ECG in combined endpoint of LVEF, quality of life, NYHA class, 6-min walk distance, LVEDV</td>
</tr>
<tr>
<td>Boriani, 2006 Rhythm-II Trial</td>
<td>130</td>
<td>SDA</td>
<td>Primary</td>
<td>AV delay optimization to maximize mitral VTI VV offset optimization to maximize LVOT VTI</td>
<td>No difference in composite endpoint of quality of life, NYHA class, and 6-min walk distance with or without VV offset optimization</td>
</tr>
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</table>
Echocardiographic evidence of reverse remodeling, proposed by some to be the definitive indication of CRT responsiveness, may or may not be clinically relevant. In PROSPECT, clinical response was quantitated using a score composed of NYHA class and hospitalizations or death from HF, but the clinical response rate was much higher than echocardiographic response rate, which has been confirmed in other studies.12,23 Moreover, patients were evaluated at 6 months and it is possible that the effects of CRT may not occur until after a longer time interval in some patients.

In our opinion, the most important shortcomings of PROSPECT were that 1) dyssynchrony was measured primarily by tissue and blood pool Doppler echocardiography, which by definition cannot differentiate when LV walls are not contracting synchronously due to dyssynchronous electrical activation (true dyssynchrony) from when they are not contracting synchronously due to imbalance of force generation between opposing walls, as occurs when dyssynchrony measurements are performed on a normally contracting wall opposite from an ischemic or infarcted wall, which may be akinetic or dyskinetic (two-dimensional speckle tracking strain analysis holds the potential to overcome this problem, and was not utilized in PROSPECT); and 2) dyssynchrony analysis was restricted exclusively to the ejection phase of the cardiac cycle, despite the well-established fact that the isovolumic contraction phase requires greater developed wall stress than does the ejection phase and therefore may be the more important determinant of cardiac efficiency. In other words, it takes more force generation within the myocardium to open the aortic valve than it does to eject a stroke volume once the valve is opened, so it might behoove investigators to pay closer attention to the intraventricular mechanical dyssynchrony which occurs when dyssynchrony measurements are performed

### Table 1: Continued

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<tr>
<td>Leon, 2005 InSync III Trial</td>
<td>422</td>
<td>SDA</td>
<td>Primary and secondary</td>
<td>AV delay optimization to maximize LV inflow using the Ritter method VV offset optimization to maximize LVOT VTI</td>
<td>VV offset optimization improved stroke volume and 6-minute walk distance</td>
</tr>
<tr>
<td>Rao, 2007 DECREASE-HF Trial</td>
<td>306</td>
<td>IEGM</td>
<td>Secondary</td>
<td>VV offset optimization to minimize dyssynchrony measured with IEGM</td>
<td>No difference between simultaneous and sequential biventricular pacing in LVEF and LVSV</td>
</tr>
<tr>
<td>Mullens, 2009</td>
<td>75</td>
<td>TDI SDA</td>
<td>Secondary</td>
<td>AV delay optimization based on separation of E and A waves without A wave truncation</td>
<td>Improvement in LV filling and ejection when changes to CRT settings were made according to a protocol</td>
</tr>
</tbody>
</table>

TDI: tissue Doppler imaging; LVSV: left ventricular stroke volume; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; LV: left ventricular; NYHA: New York Heart Association; SDA: spectral Doppler analysis; AV: atrioventricular; VTI: velocity time integral; LVOT: left ventricular outflow tract; IEGM: intracardiac electrogram; LVEDV: left ventricular end-diastolic volume; 2DST: two-dimensional speckle tracking (myocardial strain) analysis.
Echocardiographic evidence of dyssynchrony and may benefit from CRT. The RethinQ trial demonstrated that in patients with the standard indication for CRT, except with a narrow (<130 ms) QRS complex, and evidence of mechanical dyssynchrony by echocardiography, there was no significant difference between the CRT-on and CRT-off groups in exercise capacity, quality of life, and LV function. However, and consistent with multiple other studies, subgroup analysis demonstrated a significant increase in exercise capacity (the primary endpoint of this study) only in the cohort with the longest QRS duration (120–130 ms). Thus, on the basis of extant data, only QRS duration, and not any Doppler echocardiographic parameter, can be described as the single best predictor of response to CRT, although controversy exists regarding even this notion.

Ongoing multicenter trials, including ECHO-CRT, which incorporates two-dimensional strain/speckle tracking analysis of dyssynchrony, are evaluating echocardiographic modalities that are more advanced than the Doppler analysis employed in PROSPECT, to detect mechanical dyssynchrony and predict response to CRT in patients with both wide and narrow QRS complexes. To explain the variable responsiveness to CRT in patients with narrow QRS, it has been suggested that intraventricular (rather than interventricular) conduction delay leads to dyssynchrony in this group of patients. Echocardiography is the primary method of measurement for intraventricular dyssynchrony. In a recent review Pavlopoulos discussed 17 echocardiographic parameters of intraventricular dyssynchrony. These include M-mode-derived septal to posterior wall motion delay, which measures the time delay between maximal centripetal displacement of the anteroseptal and posterior walls of the LV; tissue Doppler imaging to measure time from the onset of the QRS complex to the time of peak long axis velocity of the basal segments of the left ventricle (a delay of >65 ms is considered significant); the peak velocity difference, which uses TDI to measure the time between the onset of the QRS to the highest peak longitudinal velocity during the ejection phase of the cardiac cycle; two-dimensional speckle tracking (myocardial strain analysis), and various other forms of advanced echocardiographic imaging. At this time there is no consensus on which of these modalities is the most useful, and further studies investigating this will be of benefit.

Echocardiography has been used immediately after CRT initiation to predict intermediate-term clinical response. Fifteen patients in whom interventricular dyssynchrony was not found to be reduced immediately after CRT implantation did not display LV reverse remodeling at 6 months. In contrast, those patients in whom interventricular dyssynchrony was reduced immediately after CRT implantation displayed greater reduction in QRS duration (at least 20 ms) and larger increases in LV outflow tract (LVOT) velocity time integral (a parameter used to estimate stroke volume) immediately after initiation. In addition, responders tended to have the widest QRS length at baseline and the most intraventricular dyssynchrony (measured by septal to lateral wall delay of greater than 60 ms).

Identifying predictors of non-response to CRT has become a priority given the costs to both the health-care system and the patient when CRT devices are implanted in non-responders. In separate studies Kronber an Ypenburg et al followed long-term outcomes in patients who are not responsive in the short term to CRT (response being measured by NYHA class and LV reverse remodeling, respectively) and found that patients who do not respond to CRT have higher mortality rates than patients who do respond.

Several studies have shown that patients with ischemic cardiomyopathy have lower response rates to CRT than do those with dilated cardiomyopathy of non-ischemic etiology, suggesting that the presence of scar tissue, particularly in the wall subtended by the LV lead, may limit the beneficial effect of resynchronization pacing in these patients. Thus, cardiac MRI, which is a sensitive tool for the mapping of ventricular fibrosis, might be helpful prior to device implantation in order to ascertain the optimal site for lead placement.

The site of optimal lead placement can be mapped with echocardiography as well. Using two-dimensional speckle tracking (radial strain analysis) Ypenburg et al assessed patients undergoing CRT device implantation for lead position with respect to the site of maximal LV activation delay. They found that the patients whose LV lead was at the point of latest mechanical activation were more likely to respond to CRT (measured by reverse remodeling of the LV at 6 months) than those with a discordant lead position. Moreover, in patients with optimal lead placement, mortality and HF hospitalizations decreased over 16–32 months.

Finally, recent retrospective data suggest that some patients may be “super-responders” to CRT, defined as improvement in LVEF to greater than or equal to 50% and reduction of LV systolic volume greater than or equal to 15%. Out of 186 patients who underwent CRT, 9.7% met these criteria of super-response. Global longitudinal strain was the strongest predictor of super-response, although left atrial volume was also an independent predictor.

Echocardiography to optimize CRT

Given the implications for patient outcome and healthcare expenditure, patient selection for CRT is a high priority. However, another area requiring further study is the potential for optimizing CRT in non-responders. Currently there is no gold standard parameter with which to optimize CRT and no standard imaging modality to guide optimization. The most widely used imaging modality, however, is echocardiography.

One technique for CRT optimization involves varying the AV (atrophicventricular) delay. The goal of this programming is to find the optimal timing of atrial and ventricular activation to maximize atrial systolic contribution to LV filling, maximize stroke volume, minimize isovolumic contraction time, and establish diastasis, without resulting in end-diastolic mitral regurgitation, and while preserving biventricular pacing. There are
several echocardiographic techniques to optimize AV delay, the most widely employed being Ritter’s technique. According to this method the mitral inflow pattern is assessed using pulsed Doppler analysis. The optimal AV delay results in MV closure at the end of the Doppler A wave, marking the completion of atrial systolic contribution to ventricular filling. Thus, optimal filling occurs only when four criteria are met: 1) absence of E and A wave fusion (which occurs at longer AV delays or when total diastolic filling time is reduced at higher heart rates), 2) absence of A wave truncation (which occurs at shorter AV delays when onset of ventricular systole and mitral valve closure prematurely terminates atrial systolic contribution to ventricular filling), 3) absence of end-diastolic mitral regurgitation (which occurs at longer AV delays when the atrial systolic contribution to ventricular filling leaks back into the atria prior to onset of ventricular systole and mitral valve closure), and 4) preservation of biventricular pacing (which requires that the programmed AV delay be shorter than native or intrinsic conduction time). In many cases it is not possible for all four criteria to be met simultaneously. There are limitations when using this method: measuring the A wave can be difficult in patients with high diastolic pressures or restrictive physiology because of A wave attenuation or abbreviation. Moreover, this method unlike others does not directly measure forward stroke volume (especially when mitral regurgitation is present) so may not actually be optimizing hemodynamic response.

A second technique employed to find the optimal AV delay is called the iterative technique. In this method the AV delay is set to a value just below intrinsic AV conduction time, and then sequentially shortened (in 20-ms increments) while spectral Doppler imaging of mitral inflow determines when A wave truncation occurs. The AV delay is then sequentially lengthened (in 10-ms increments) until A wave truncation is no longer present. This method was used in the CARE-HF trial and maximizes the period of diastasis between the E and the A waves.

Both Ritter’s method and the iterative technique aim to maximize atrial emptying and LV filling by avoiding the A wave truncation that occurs when the AV delay is too short. Implementation of these techniques should theoretically result in a reduction of mean left atrial pressure. However, whether either of these methods necessarily maximize stroke volume is not known, nor is it clear that there is any difference in the results of the two methods, as they are essentially identical when the constraint of preserving biventricular pacing is present. In contrast to the Ritter and iterative methods, which are designed to maximize diastolic transmitial flow, spectral Doppler tracings from the LVOT measure actual forward stroke volume. LVOT velocity time integral (VTI) is measured from the apical five-chamber window. Cross sectional area \((\pi r^2)\) of the LVOT is calculated by measuring its diameter in the parasternal long-axis window and assuming that the LVOT is geometrically cylindrical. The product of LVOT VTI and LVOT cross-sectional area equals stroke volume, and the AV delay providing the largest stroke volume can thus be identified. Other investigators have used the aortic valve VTI rather than the LVOT VTI, as the aortic valve VTI, which is obtained with continuous wave Doppler, is a more reproducible measurement and therefore may decrease interobserver variability, which has been estimated to be as high as 10% with the LVOT VTI method. However, a major caveat for the aortic valve VTI method is that changes in LV stroke volume (and stroke work) induced by varying the AV delay or VV offset may affect the aortic valve orifice area, which is assumed to be constant when calculating stroke volume, and this would reduce the accuracy of results, especially in patients with low-flow low-gradient aortic stenosis, in whom, by definition, aortic valve orifice area changes with changes in LV stroke work. In 30 patients undergoing AV delay optimization for CRT, Jansen et al compared diastolic transmitial VTI, diastolic filling time, LVOT VTI, and Ritter’s formula. They found that measurement of the VTI of diastolic transmitial flow correlated best with invasive measurement of LV dP/dT using a pulmonary artery catheter.

To illustrate the use of combined inflow and outflow Doppler echocardiography for CRT optimization, Figure 1 shows pulsed Doppler spectra of transmitral inflow (a–e) and LV outflow (f–j) in a patient with ischemic cardiomyopathy who displayed no clinical improvement after receiving CRT with preset paced AV delay of 150 ms and atrial pacing rate of 80 bpm (k). Owing to sick sinus syndrome, the cardiac rhythm was 100% A-biV paced at all time points. At these baseline settings, mitral inflow and LVOT VTI (stroke volume) were severely reduced (a and f, respectively). After increasing the paced AV delay to 200 ms, a slight increase in LVOT VTI was noted (b and g). There was a further slight increase in LVOT VTI when the pacing rate was reduced to 60 bpm; however, the A wave remained quite small (c and h). When reevaluated after 3 weeks (d and i) and 6 months (e and j), not only was the LVOT VTI markedly increased, but the A wave amplitude and VTI were as well, most likely as a result of a time-dependent reduction of LV end-diastolic pressure made possible by: 1) increased LV stroke volume, 2) increased diastolic filling time, and 3) mitigation of restrictive physiology over the 6-month period. During this time, the patient improved from NYHA class III symptoms to NYHA class I.

AV delay is one important determinant of the hemodynamic effect of CRT. The programmed delay between LV and RV lead firing, the VV delay (or offset), can also have a significant effect on hemodynamics. Just as with AV delay optimization, measuring the LVOT VTI at different VV delays is a method of determining the VV delay that results in maximal stroke volume. Other methods measure residual interventricular mechanical dyssynchrony during VV delay optimization. One such method employs pulsed Doppler spectra to measure the delay between onset of RV outflow and LV outflow. The difference between RV isovolumic contraction time (time from beginning of QRS complex to onset of RVOT pulsed Doppler spectrum) and LV isovolumic contraction time (time from beginning of QRS complex to onset of...
LVOT pulsed Doppler spectrum) equals interventricular delay. Interventricular mechanical delay can also be determined by comparing the timing of contraction of the basal lateral RV segment with that of the most delayed LV segment with respect to the onset of the QRS to ascertain which VV interval will result in the least residual dyssynchrony.28

Intraventricular dyssynchrony is assessed echocardiographically with several techniques. Dispersion of timing to peak velocity of opposite walls of the LV is measured using tissue Doppler imaging. When multiple walls and segments of the left ventricle are analyzed in this fashion, a global dyssynchrony index can be generated.41 This methodology has been employed in the successful repositioning of suboptimally positioned LV leads that were contributing to excess residual LV intraventricular dyssynchrony.28

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Other techniques to assess intraventricular dyssynchrony take advantage of newer technologies, such as two-dimensional speckle tracking to measure the timing and magnitude of myocardial strain (rather than just translation in space) and three-dimensional echocardiography. Seo et al42 evaluated intraventricular dyssynchrony in CRT patients using speckle tracking and showed that its ability to predict response to CRT was as good as invasive hemodynamic measurements of dP/dT. There appears to be good concordance among these advanced echocardiographic techniques for the optimization of hemodynamic response to CRT by VV offset adjustment.43 As indicated above, assessment of myocardial strain rather than tissue velocity partially overcomes a problem of tissue Doppler analysis of dyssynchrony highlighted by PROSPECT: when analysis is confined to measuring translation of myocardium in space (as is the case for tissue Doppler imaging), delayed centripetal displacement of a hypokinetic, akinetic, or dyskinetic wall or segment cannot be distinguished from a truly dysynchronous wall or segment, in which the delay is due primarily to late electrical activation (and not primarily to disparity of contractile function between opposing walls). Only under the latter circumstance

**Figure 1:** Spectral Doppler echocardiographic analysis of transmittal left ventricular inflow (a–e) and left ventricular outflow (f–j); (k) baseline electrocardiogram during atrial pacing at 80 bpm, AV delay 150 ms, and simultaneous biventricular pacing; (l) electrocardiogram during atrial pacing at 60 bpm, AV delay 200 ms, and simultaneous biventricular pacing. Left ventricular inflow (a) and outflow (f) during atrial pacing at 80 bpm and AV delay 150 ms; left ventricular inflow (b) and outflow (g) during atrial pacing at 80 bpm and AV delay 200 ms; left ventricular inflow (c) and outflow (h) during atrial pacing at 60 bpm and AV delay 200 ms; 3-week follow-up (d and i); 6-month follow-up (e and j).
would CRT be expected to provide hemodynamic or clinical benefit.

What constitutes optimal CRT programming for an individual patient can change over time. CRT patients in one study underwent VV offset optimization at initiation of CRT and again at 6 and 12 months. Forty-one percent of patients required readjustment of their VV offset at 6 months and 57% at 12 months. These adjustments resulted in a significant increase in LVOT VTI.44 Some attribute these changes to remodeling of the LV with CRT therapy, but further studies are needed to ascertain the exact mechanism behind these changes.

Optimal settings for CRT during physical exertion may be different from those obtained in the resting state due to changes in heart rate, loading conditions, and intrinsic atrioventricular conduction velocity with exercise. Mokrani et al45 measured LVOT VTI in 50 CRT patients at rest and during exercise, and varied the AV delay to maximize LVOT VTI. He found that the optimal AV delay during exercise was shorter in 37% and longer in 26% of patients. Optimization of AV delay during exercise resulted in increased LVOT VTI and LV filling time compared with setting a standard shortened AV delay during exercise or having just one AV delay for both exercise and rest. Moreover, Valzania et al46 found that 58% of patients with CRT required titration of their VV delay when exercising to maximize aortic VTI. This study, unlike that by Mokrani et al,45 did not find a difference in optimal AV delay during rest and exercise.

**Does echocardiography-based CRT optimization improve outcomes?**

At this time there is no evidence to support the routine use of echocardiographic techniques for the prospective optimization of CRT parameters. To justify using time-consuming and complicated echocardiographic techniques to optimize CRT settings rather than employing preset pacing parameters for all patients, studies that show improvement in outcomes with echocardiography are required, and thus far the evidence is mixed. Using echocardiography to evaluate prospective optimization of CRT settings has been investigated by several groups. Sawhney et al47 compared LVOT VTI-guided AV delay optimization to an empirically programmed AV delay (120 ms). In patients receiving echocardiography-guided optimization, LVEF increased 7.8% versus only 3.4% in the group receiving the preset AV delay (p<0.02). Moreover, after 3 months patients who had undergone optimization demonstrated greater improvement in NYHA functional class as well as quality of life.47 In the SMART-AV (SMARTdelay Determined AV-Optimization: a comparison to other AV delay methods used in cardiac resynchronization therapy) trial, 980 patients received either echocardiography-based AV delay optimization, ECG-based optimization, or a fixed AV delay of 120 ms. In contrast to the findings of Sawhney et al,47 no difference between groups was found in the primary endpoint of LVESV or in the secondary endpoints of LVEDV, NYHA class, 6-min walk distance, LVEF, or quality of life at 6 months.48

The Rhythm-IID (Resynchronization for the Hemodynamic Treatment for Heart Failure Management II Implantable Cardioverter Defibrillator) trial evaluated the utility of both AV and VV delay optimization. In this trial 90 patients were randomized to receive echocardiography-based VV delay optimization. They were compared to the control group at 3 and 6 months with respect to the primary outcomes of freedom from CRT-D-related complications and improvement in a composite clinical endpoint comprising 6-min walk distance, quality of life, and NYHA class. No difference was observed between patients who underwent VV offset optimization and those who received a preset VV offset.49 In a follow-up study the same investigators found no difference in LV end systolic dimension (LVESD), LVEF, LVEDV, or in the proportion of responders (42% vs 47%), but did find improvement in LA dimension, LVESV, and MV closure-to-opening time. They also found that the optimal AV and VV delay changed over time. Optimization of VV offset resulted in an increase in LVOT VTI and this result remained significant at 6 months.50 The InSync III trial suggested that VV offset optimization led to moderate improvement in stroke volume and 6-min walk distance, but not in other clinical parameters including quality of life or NYHA class.34

The DECREASE-HF (Device Evaluation of CONTAK RENEWAL 2 and EASYTRAK 2: Assessment of Safety and Effectiveness in Heart Failure) trial followed 306 patients over 6 months, comparing simultaneous, sequential, and LV resynchronization pacing, and found no difference between the three groups in LV stroke volume or ejection fraction.51

The FREEDOM (Frequent Optimization Study Using the QuickOpt Method) trial is currently underway to evaluate an automated device-dependent optimization procedure versus echocardiography-guided optimization. This trial will enroll more than 1,500 patients in 178 centers to ascertain whether serial optimization of AV and VV delays using standardized protocols will improve outcomes relative to approaches relying on physician preference. It is anticipated that results from this trial will shed light on whether device optimization improves outcomes and, if so, give rise to a standardized protocol for device optimization.52 If device-based optimization proves efficacious, it may save time and cost of echocardiography-based optimization in the future.

**CRT optimization for non-responders**

While the aggregate results of the aforementioned studies of prospective optimization of resynchronization pacing settings do not support the routine use of echocardiographic optimization at the time of device implantation, it is possible that the sizeable subpopulation (30%) of CRT recipients deemed to be non-responders might benefit from such attention after device implantation. A small randomized study of the efficacy of a multidisciplinary
secondary optimization clinic for non-responders evaluated 75 patients who had undergone CRT at least 6 months prior to the study date and had persistent NYHA class III or IV symptoms or persistence of adverse remodeling of the left ventricle. The staff of this clinic included specialists in electrophysiology, HF, and imaging. Doppler echocardiography was used to measure interventricular dyssynchrony, intraventricular dyssynchrony, and stroke volume. Multiple factors that may have been contributing to the lack of CRT response were identified, including AV timing, arrhythmias, medication, and changing of the LV lead position. In these 75 patients who were CRT non-responders the multidisciplinary team determined that 74% had room for improvement in some aspect of their therapy. Twenty-one percent had lead malposition, 24% were on suboptimal medical therapy, 9% had persistent intraventricular dyssynchrony, 11% had interventricular dyssynchrony, 32% had arrhythmias, and 46% had a suboptimal AV delay as measured by the Ritter technique. In patients who underwent evaluation according to the protocol of the multidisciplinary clinic and had a resultant adjustment of their CRT device settings, an increased time to first event was observed, and 88% of patients displayed increased LV filling and LV ejection fraction.

Conclusions

Echocardiography has the potential to guide cardiac resynchronization therapy in patients with advanced HF. The routine use of echocardiographic parameters (other than LVEF and end-diastolic dimension) to select patients for CRT or to optimize device settings at the time of implantation is not supported by currently available data. However, by virtue of its accessibility, portability, and ability to assess and quantitate cardiac structure and function in real time and to non-invasively measure ventricular filling and ejection, the judicious and selective use of various echocardiographic techniques, such as tissue and blood pool Doppler and two-dimensional speckle tracking (myocardial strain analysis), should result in salvage for some of the 30% of CRT recipients deemed to be non-responders. Given the economic implications of HF in general, and the expense of CRT in particular, this would represent a major advance in health-care cost containment. More importantly, it could improve quality of life and longevity in this growing population of patients.

References


52. Abraham WT, Gras D, Yu CM, Guzzo L, Gupta MS, FREEDOM Steering Committee. Rationale and design of a randomized clinical trial to assess the safety and efficacy of frequent optimization of cardiac resynchronization therapy: the Frequent Optimization Study Using the QuickOpt Method (FREEDOM) trial. *Am Heart J* 2010; 159:944–948.e1.