Is echocardiographic assessment of dyssynchrony useful to select candidates for cardiac resynchronization therapy?

**Echocardiography Is Not Useful Before Cardiac Resynchronization Therapy if QRS Duration Is Available**

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Several multicenter prospective randomized trials have shown that cardiac resynchronization therapy (CRT) improves functional capacity and quality of life in \( \approx 70\% \) of symptomatic heart failure (HF) patients.\(^1\) A smaller proportion of these selected patients shows a \( \geq 5\% \) increase in left ventricular (LV) ejection fraction and a \( >15\% \) reduction of LV end-systolic volume, indicating reverse remodeling of the LV.\(^2\) Finally, CRT reduces morbidity and mortality rates by \( \approx 30\% \) to \( 40\% .\)\(^3\) These data are comparable to those of established pharmacological therapies for HF, including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, and aldosterone antagonists. Of note, CRT is indicated in HF patients who remained symptomatic despite medical therapy; thus, they could be considered nonresponders to medical therapy. However, the precise proportion of nonresponders to medical therapy has not yet been quantified.

Response by Abraham and Abraham

Notwithstanding CRT being a very efficacious and cost-effective treatment, several efforts have been made to reduce the number of nonresponder patients. The issue of patients not responding to CRT is rather complex. There is lack of agreement on the definition of nonresponder (volumetric, functional, or exercise response), the cause of CRT nonresponse is likely multifactorial, and some patients may be too sick to show a meaningful and measurable benefit (“beyond repair”). Currently, we do not know which factors are predicting response to therapy and the relative weight of each of these factors. Therefore, the proportion of patients who are not amenable to CRT remains undefined. Among the factors predicting response to CRT, the presence of mechanical dyssynchrony has been indicated to play a determinant role.\(^4\)–\(^7\) The putative lack of responsiveness to CRT in the absence of mechanical dyssynchrony, together with evidence that mechanical dyssynchrony may exist even when QRS duration is within the normal range, has encouraged investigators to intensively study the hidden link between mechanical dyssynchrony and QRS duration (the latter being frequently but inappropriately indicated as electrical dyssynchrony).

Our task is to address the benefits of the use of the standard criteria for selection of patients for CRT as opposed to the (additional) use of imaging-derived indices of mechanical dyssynchrony. Arguments to adhere to currently available guidelines range from theoretical views on the mechanism of...
CRT to practical limitations of the techniques assessing mechanical dyssynchrony.

The Mechanism of CRT

In the current clinical practice of CRT, 2 pacing electrodes (or a single LV electrode in combination with intrinsic activation) create 2 wavefronts of activation. This activation modality is not physiological but is considerably better than the activation during a left bundle-branch block (LBBB) (Figure 1). This simple concept is supported by data from electrical mapping and hemodynamics in canine hearts with LBBB and hemodynamic measurements in patients. Figure 1 also shows that biventricular pacing makes activation more asynchronous than with normal physiological activation. This is also the case in ventricles with an infarction or diffuse slow conduction, conditions that may show mechanical dyssynchrony (Figure 1). However, the latter derangements are likely not amenable to CRT. Moreover, from the desynchronization of normally activated ventricles by biventricular pacing, it can be recognized that “nonresponse” in these cases of mechanical dyssynchrony does not mean a neutral effect but rather worsening cardiac pump function. Indeed, worsening pump function and increasing LV hypertrophy and sphericity have been reported in nonresponders. Therefore, proper prediction of CRT response is important. Moreover, when poorly validated diagnostic tools are used, there is a risk of creating more nonresponders, which could lead to greater reservations against CRT and ultimately even the withholding of this therapy from the patients who really need and “deserve” it.

QRS Duration, a Gross but Reliable Marker for CRT Patients

The most recent guidelines on cardiac pacing and CRT issued by the European Society of Cardiology/European Heart Rhythm Association have confirmed previous guidelines issued by other scientific organizations and do not recommend the use of mechanical dyssynchrony as selection criteria for HF patients. Only a QRS duration ≤120 ms is considered, among other criteria, an indication for CRT. The European Society of Cardiology/European Heart Rhythm Association Guidelines Writing Group, consisting of 12 scientists, and the document reviewers, including 16 European experts in the field of cardiac pacing and HF, stated in their recommendations that “in spite of positive results from observational studies of the benefit from CRT using mechanical dyssynchrony criteria to select patients, the real value of the mechanical dyssynchrony criteria for patient selection remains to be determined in randomized studies.” A similar conclusion was drawn for CRT indication in HF patients with QRS duration <120 ms. The rather conservative view seems, however, to be reinforced by the recent results of the Predictors of Response to CRT (PROSPECT) study and the CRT in Patients With Heart Failure and Narrow QRS (ReThinQ) trial. In analogy to LV ejection fraction, which is considered a gross yet imperfect stratification risk marker for sudden cardiac death but the best available thus far, QRS duration represents a gross description of electrical and probably mechanical (see below) ventricular asynchrony.

Electrical Mapping

We acknowledge the imperfect prediction of CRT response from QRS duration. However, rather than being disappointed, one should be surprised that such a simple and easy-to-measure index predicts so well. Actually, it may be this easy assessment that makes it such a strong tool in daily practice. A QRS prolongation, even modest, indicates abnormal and inhomogeneous activation. Increasing evidence suggests that LBBB, the most common ventricular conduction disturbance in HF patients, is a heterogeneous conduction disorder. High-resolution 3-dimensional mapping procedures showed...
that the transseptal conduction time, ie, the time between the earliest right ventricular (RV) and LV septal breakthrough point, is bimodally distributed and has a large range in the group of patients with transseptal conduction times >40 ms (Figures 2 and 3). This indicates a large heterogeneity in the RV to LV activation time. Furthermore, in patients with LBBB, the total LV endocardial activation time ranges from 60 to 160 ms (Figures 2 and 3). Etiology does not seem to have a major impact on the total endocardial activation time. Finally, the sum of transseptal and total endocardial activation time does not account for the maximum duration of the QRS; QRS duration is 20 to 60 ms longer, probably because of LV endocardial to epicardial conduction time (Figure 3). These data also show that QRS duration provides a quite good estimate of total electrical asynchrony.

Figure 2. Left, Three-dimensional electroanatomic mapping of the RV and LV (left). A color-coded activation sequence indicates the earliest (red) and the latest (blue) endocardial activation region. The earliest activated region is the anterolateral region of the RV, and the latest part is the posterobasal region of the LV. TV indicates tricuspid valve. Right, Distribution of transseptal time and total endocardial activation time as measured by contact (CARTO) and noncontact (EnSite) mapping in 24 patients. Adapted from Auricchio et al.18 with permission from the American Heart Association. Copyright 2004 American Heart Association.

Figure 3. Distribution of transseptal time, total endocardial activation time, and total QRS duration in 140 HF patients with a QRS duration ≥120 ms. Patients are ordered according to QRS duration (A) and transseptal time (B).
In addition, there is evidence that in LBBB the electrical activation of the LV follows a “U-shaped” path, starting at the septum and turning around the apex and subsequently toward the inferior wall of the LV. This activation pattern is generated by a functional line of block that is oriented from the base toward the apex of the LV. The location and length of the lines of block are highly variable but related to the site and time of LV breakthrough. The U-shaped activation pattern has been confirmed by several investigators using invasive noncontact mapping and noninvasive body surface mapping techniques (Figure 4). The line of block is predictably located in the anterior region of the LV when the QRS duration is >150 ms. Thus, there is a large area of delayed electrical activation over the LV free wall, where a lateral or posterolateral vein is usually found. This fits the clinical observation that in this subset of CRT patients the response is close to 90%. In contrast, patients with QRS duration <150 ms demonstrate a smaller line of block, more frequently located in the lateral region of the LV. Therefore, more precise characterization of the conduction patterns and block regions in candidates for CRT may improve the response rate to CRT. Such better characterization may help in choosing the best site and mode of pacing (Figure 5).

Conflicting Evidence on the Relevance of Mechanical Dyssynchrony

The aforementioned considerations in favor of the use of electrical criteria for selecting CRT patients have been questioned by a considerable number of relatively small, single-center studies, which show a better response to CRT in the presence of mechanical dyssynchrony. However, these studies are opposed by other studies showing no relation between mechanical dyssynchrony and CRT response. Moreover, preliminary data from a recent prospective multicenter trial (PROSPECT) indicate that, although some indices of dyssynchrony correlated with CRT response, their sensitivity and specificity were fairly poor. It was concluded that no single measure of mechanical dyssynchrony could be recommended to further improve patient selection beyond the current guidelines. These disappointing results were achieved despite specific training on imaging methods for each of the 30 participating centers, with a clear effort to enhance uniformity of approach. Furthermore, there was marked variability in the analysis derived from the identical images among the 3 blinded core centers. A few single-center studies also indicated a predictive value for mechanical dyssynchrony in patients with narrow QRS complex. However, these results are contradicted...
by a multicenter, prospective randomized trial, the ReThinQ study. In the 172 enrolled patients with QRS duration <130 ms and mechanical dyssynchrony, 6 months of CRT did not provide significant improvement in peak oxygen consumption or ejection fraction or a reduction in LV volumes compared with a control group. Several factors, including prospective randomized design and the inclusion of a control group, may account for the difference with the small observational trials.

Collectively, these results showed that the use of mechanical dyssynchrony measured according to current criteria does not add significant value to QRS duration. This opinion is in agreement with a recent statement of an expert group of the American Society of Echocardiography.

Theoretically, a proper mechanical index is relevant to the patient because ultimately it is pump function that matters. However, after concluding that the primary purpose of CRT is to correct conduction abnormalities, one should wonder what added value mechanical dyssynchrony can provide in addition to a good electrical index of intraventricular conduction block. Two points are of importance in this respect: (1) To what extent does mechanical behavior reflect electrical abnormalities? (2) What factors can confound the assessment of conduction abnormalities?

What Additional Information Could Mechanical Dyssynchrony Provide?

Electrical activation of myocytes is followed by their contraction, the electromechanical delay being typically 30 to 50 ms. For the LV as a whole, the electromechanical delay equals the delay between the R wave on the ECG and the rise in LV pressure. Detailed measurements in paced canine hearts have shown a close relationship between electrical activation times and the time to onset of fiber shortening.

In paced hearts, some regional differences in electromechanical delay have been observed, but these differences were 10 to 20 ms. Such local differences in electromechanical delay are an order of magnitude smaller than required to explain significant mechanical dyssynchrony in the presence of a narrow QRS complex or the absence of mechanical dyssynchrony in the presence of a wide QRS complex. Even when one accounts for the well-known abnormalities in excitation–contraction coupling in failing hearts, it is highly questionable whether regional differences in electromechanical delay on the order of 100 ms can occur. Therefore, one should consider that discrepancies between electrical and mechanical dyssynchrony are due to confounding factors. One such factor could be myocardial ischemia or infarction. Ischemic, stunned, hibernating, and infarcted tissue is almost entirely passive. Accordingly, it is being stretched by adjacent contracting fibers and the rise in LV cavity pressure (Figure 1). This region subsequently “shortens” during late systole, when LV pressure is falling again. Indeed, in some of the earliest reports on mechanical dyssynchrony in patients with narrow QRS complex, such dyssynchrony is reported in patients with ischemic cardiomyopathy. Such mechanical behavior provides the impression of a “late contracting” region, but in reality this is simply reversal of the LV pressure–induced ballooning of the passive tissue. As discussed in more detail elsewhere, such tissue is clearly not amenable to CRT. A similar impression of mechanical dyssynchrony can arise as a consequence of specific events like cardiac surgery.

Another confounding factor for mechanical dyssynchrony may be the increased inhomogeneity of regional contraction in failing ventricles, as observed with the conductance catheter technique and magnetic resonance imaging–derived radial wall motion analysis, even in ventricles with narrow QRS complexes. Valve surgery resolved these abnormalities in cases of valvular disease, suggesting that in these failing hearts mechanical overload generates dispersion of contraction. It is unlikely that such dispersedly distributed contraction is amenable to CRT (Figure 1). Therefore, when a good electrical index of dyssynchrony is available, the additive value of assessment of mechanical dyssynchrony is highly questionable.
Issues With Regard to Measurement of Mechanical Dyssynchrony

In addition to the aforementioned factors, imperfect measurement techniques and analyses may contribute to the inconsistent relation between mechanical dyssynchrony and CRT response. Extensive review of imaging techniques is beyond the scope of this article and can be found elsewhere.\textsuperscript{5,30,38} Briefly, measures of mechanical dyssynchrony may be based on timing of valve opening or on displacement, velocity, or deformation (strain) of tissue (Figure 6). Indices correlating best with local tissue behavior are those derived from local strain because motion or velocity with respect to an external reference point is confounded by factors like rigid body motion and behavior of adjacent regions (Figure 6).

It should be realized that deformations in the asynchronous heart are characterized by the most complicated patterns known\textsuperscript{32,39} (Figure 7); a simplified and partly flawed analysis of such complex motion pattern can easily lead to inconsistent data (Figure 6). Inappropriate alignment of the ultrasound beam with respect to the LV wall, as is frequently the case when velocities in the basal LV segments are analyzed, causes major deviations of the timing of onset and peak shortening.\textsuperscript{27} In that respect, it is surprising that it is advised to measure velocities at the most basal part of the LV wall because in that area the wall bends inward, and consequently the ultrasound beam is at a large angle with the wall. Velocity tracings can also change considerably by even slight changes in the position of the sample volume.\textsuperscript{27} The latter can be understood if one considers that myocardial deformation is a complex 3-dimensional process with different amounts and timing of shortening in different directions.\textsuperscript{40}

The observation that the degree of ventricular dyssynchrony obtained by measuring the septal-to-lateral delay was similar in patients with and without scars\textsuperscript{41} emphasizes the

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**Figure 6.** Principles of measurement of myocardial displacement, velocity, strain rate, and strain with the use of ultrasound (US) techniques. TDI measures velocities of the tissue with respect to the ultrasound probe. Local velocity depends on rigid body motion and rotation of the ventricle (gray arrows) and local shortening (black arrows), whereas only the latter reflects local mechanical behavior of the tissue. Adapted from http://folk.ntnu.no/stoylen/strainrate/Ultrasound/index.html#section_index with permission from Dr Asbjørn Støylen, ©2008.

**Figure 7.** Example of TDI and 2-dimensional (2D) strain measurements (speckle tracking) in a patient with dilated cardiomyopathy. TDI measurement indicated no mechanical dyssynchrony, whereas strain measurement showed dyssynchrony between the septum (upper) and lateral wall (lower trace). MVC indicates mitral valve closure; AVO, aortic valve opening; MVO, mitral valve opening; AVC, aortic valve closure. Courtesy of Dr DeBoeck, Department of Cardiology, University Medical Center, Utrecht, The Netherlands.
intrinsic limitation of tissue Doppler imaging (TDI) in distinguishing whether a segment is actively contracting or whether it moves passively as a result of active contraction in neighboring segments. An additional limitation of this method is indicated by the fact that a delayed contraction of the lateral wall was found in only $\approx66\%$ of the patients with LBBB and that CRT did not show a significant decrease in mechanical dyssynchrony. Finally, multiple peaks during TDI examinations are frequently observed and may create inconsistent choices for which peak in the TDI signal should be chosen as peak systolic velocity even by experienced operators; this may explain the considerable interobserver and intraobserver variability in the PROSPECT trial. Therefore, it seems that many mechanical dyssynchrony measures suffer from technical limitations of the technology and from difficult interpretation of the complex signals.

The technical limitations may, however, not be the only reason for the poor relation between CRT response and mechanical dyssynchrony. Two studies using MRI tagging, the gold standard on local deformation measurements, also showed a poor relation between indices of mechanical dyssynchrony and CRT response. In one of the studies, QRS duration was even a better predictor of CRT response. However, the use of indices related to discoordination (amount of stretch during systole) improved the prediction of CRT response. Therefore, it is possible that we need to focus more on discoordination, which is facilitated by the recent availability of speckle-tracking analysis.

**Conclusions**

Strong evidence indicates that QRS duration reflects conduction abnormalities, the details of which could be even better assessed with novel electrical mapping techniques. The “epidemic of mechanical dyssynchrony” in HF patients, as recently discussed by Kass, clearly suggests that current conventional echocardiographic assessment techniques are imperfect, inaccurate, or not used properly. Alternatively, apparent mechanical dyssynchrony may be due to abnormalities other than those that can be treated with CRT. In either case, we deeply appreciate and share a recent expert consensus statement of the American Society of Echocardiography, as follows: “Although a number of echocardiographic dyssynchrony methods have suggested superiority to ECG QRS width for predicting response to CRT, this writing group currently does not recommend that patients who meet accepted criteria for CRT should have therapy withheld because of results of echocardiographic Doppler dyssynchrony study.”

Dr Theodore P. Abraham is one of the authors of this statement.

Thus, there is very strong evidence for continued application of the current guidelines, with the use of simple ECG criteria, for selection of CRT patients. We acknowledge that additional information on structural and mechanical information may be of great value for increasing the proportion of clinical and/or volumetric response to CRT, but a reliable measure for this purpose has yet to be developed. Novel electroanatomic methods may be of help as much as novel mechanical measures.

**Disclosures**

Dr Prinzen has received research grants from Medtronic, Boston Scientific, and EBR Systems and served as a consultant for Medtronic Inc and Boston Scientific. Dr Auricchio received research grants from Medtronic, Boston Scientific, and St Jude Medical; received honoraria from Biotronik, Sorin, and Medtronic; and served as a consultant for Sorin.

**References**


Drs Prinzen and Aurrichio “acknowledge the imperfect prediction of CRT response from QRS duration,” and we enthusiastically concur with their opinion. Evidence at the experimental and clinical level suggests an electrical–mechanical disconnect. Therefore, it is reasonable to assume that QRS alone is not an accurate indicator of mechanical dyssynchrony. We submit that a necessary component for response to chronic resynchronization therapy (CRT) is mechanical and not electrical dyssynchrony. Indeed, it is not the electrical conduction delay per se but the associated mechanical dyssynchrony that results in inefficient ventricular contraction and reduced stroke volume. Consequently it makes sense that correcting the mechanical dyssynchrony via CRT leads to morphological, functional, and clinical improvements. Furthermore, we would like to offer our thoughts on some of the opinions expressed by Drs Prinzen and Aurrichio. First, their concern that significant regional differences in electromechanical delay cannot exist with a narrow QRS should be allayed by data showing quantitatively similar delays in LV free wall activation between patients with narrow QRS and left bundle-branch block heart failure, albeit in a minority of the patients with narrow QRS.¹ Second, they imply that discordance between mechanical and electrical dyssynchrony indices can be explained away by “confounding factors.” Evidence to the contrary comes from a canine dyssynchronous heart failure model in which preexcitation of the LV free wall can bring about improvement in hemodynamics and mechanical coordination despite worsening of electrical dispersion.² Third, they conclude that there is a poor correlation between indices of mechanical dyssynchrony and CRT response. We suggest that the issue of poor correlation pertains more to the particular technique rather than the concept. We agree that current tissue Doppler and similar echocardiographic techniques may not be well developed for dyssynchrony analysis at the current time. Moreover, it is our opinion that all echocardiography-based dyssynchrony analysis should be revisited with thoughtful and rigorous protocols. We contend that positive publication bias and general unawareness of the shortfalls of the echo-based techniques have led to the current uncertainty of their potential role in CRT. However, we maintain that the fundamental concept proposed by these echo-based techniques is valid and has been corroborated by other techniques. For example, magnetic resonance demonstrates a strong correlation between mechanical dyssynchrony and improvements in both systolic and diastolic function.³ Finally, it is our opinion that mechanical dyssynchrony will be one of multiple factors, including etiology, that will determine response to CRT. We submit that not offering CRT to a patient on the basis of the absence of mechanical dyssynchrony by echocardiography may not be optimal given the variability and conflicting data. However, corroboration of mechanical dyssynchrony by any technique, especially in borderline cases, may help with making a clinical decision. However, technical challenges persist and should be duly acknowledged and taken into account while adjudicating on individual cases.

References


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Echocardiography Is Useful Before Cardiac Resynchronization Therapy if QRS Duration Is Available

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Cardiac resynchronization therapy (CRT) has emerged as one of the few therapies available for patients with advanced heart failure (HF) that favorably affects symptoms, functional status, hospitalization rates, and mortality rate.1,2 It is thought that CRT achieves these benefits by coordinating contraction between ventricular segments that at baseline are dyssynchronous.3 Synchronized electrical excitation of the ventricles leads to near-simultaneous mechanical activation of the normal and delayed segments, resulting in greater stroke volume and reduction of mitral regurgitation with improved neurohormonal profile and reversal of adverse ventricular remodeling. The early large-scale clinical trials that established these benefits of CRT were limited to patients with prolonged QRS duration, a simple and convenient marker of delayed electrical activation. On the basis of these data, current guidelines recommend CRT for patients with ejection fraction <35%, moderate to severe symptoms (New York Heart Association class III to IV), and QRS >120 ms.

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A consistent finding from all trials of CRT, however, is a lack of clinical or echocardiographic benefit in approximately one third of patients (“nonresponders”).4 Unlike pharmacological therapy, CRT is complex, invasive, and costly; therefore, improved identification of patients likely to benefit is a clinical imperative. One factor among many underlying this high rate of nonresponse is that QRS duration is an imperfect surrogate for the disorder actually targeted by CRT: mechanical dyssynchrony. Mechanical dyssynchrony may involve delay in mechanical activation of the left ventricle (LV) relative to the right ventricle (RV) (interventricular dyssynchrony) or of one LV region relative to another (intraventricular dyssynchrony).

Several lines of evidence suggest that QRS duration may not always be concordant with mechanical dyssynchrony. Leclercq et al5 used an experimental model of tachypacing-induced HF with left bundle-branch block to demonstrate improvement in invasive indices of ventricular contractility after CRT with no change in electrical dyssynchrony. These findings suggest a disconnect between electrical and mechanical activity. Furthermore, small studies using tissue Doppler imaging (TDI)–based evaluation of mechanical activity demonstrate a low concordance between QRS duration and mechanical dyssynchrony. Up to 30% of HF patients with normal QRS duration may have significant mechanical dyssynchrony; conversely, 20% to 30% of HF patients with wide QRS duration may not have mechanical dyssynchrony.6 Taken together, these lines of evidence suggest that QRS...
duration is not closely related to mechanical dyssynchrony, and therefore it is not surprising that baseline QRS duration is not the best predictor of response to CRT.

Several reports have examined the significance of demonstrating mechanical dyssynchrony and its possible use in predicting response to CRT. Almost all of these studies used TDI-based criteria to evaluate dyssynchrony and have generated a number of potential dyssynchrony indices. In general, these indices demonstrate either a time delay in mechanical activation between segments of the LV (septal to lateral wall delay in time to peak systolic tissue velocity) or substantial dispersion of mechanical activation (standard deviation of time to peak systolic tissue velocity). Because of space constraints, we will not delve into details of individual parameters or cover the technical details of the manner in which individual measurements are performed. These topics have been well described in other recent reviews and the original articles.

A number of small, mostly single-center studies have suggested that a septal to lateral or opposing segment delay of 65 ms predicts response to CRT. Similarly, a standard deviation of time to peak tissue velocity $>32$ ms appears to predict response. Response in most studies was defined by clinical improvement and/or presence of reverse remodeling as demonstrated by echocardiography. In these small, nonrandomized, nonblinded, and retrospective studies, the reported cutoff values appear to be superior to QRS duration and several other conventional echocardiographic parameters in predicting response to CRT. These findings suggest that echo-derived parameters may be an efficient method of selecting patients for CRT. More recently, however, 2 recent large, multicenter, prospective studies—Predictors of Response to CRT (PROSPECT) and Resynchronization Therapy in Narrow QRS Study (ReThinQ) used echocardiographic criteria to select patients for CRT and found no correlation between echo-based indices of mechanical dyssynchrony and CRT benefit, raising questions about the need for echocardiography in selecting patients for CRT.

In this perspective, we present arguments for the continued use of techniques to demonstrate mechanical dyssynchrony before referring patients to CRT. At the outset, we emphasize that in the absence of rigorous, adequately powered, controlled studies using echo-based dyssynchrony to randomize patients to CRT versus no CRT, patients fulfilling the original clinical criteria for CRT should not be refused CRT. Even so, clinicians applying these clinical criteria should be prepared for $3$ of $10$ patients to show no response to CRT.

We will address the controversy by discussing 3 issues: (1) the rationale for evaluating mechanical dyssynchrony in HF; (2) the limitations and challenges of dyssynchrony analysis by echo, and (3) moving forward after PROSPECT and ReThinQ?

**Rationale for Evaluating Mechanical Dyssynchrony in HF**

As mentioned earlier, QRS duration correlates only weakly with mechanical dyssynchrony. The duration of the QRS complex on the surface ECG reflects the duration of total ventricular (RV and LV) electrical activation. On the one hand, rapid RV depolarization can offset delays in LV activation, resulting in normal QRS width. In addition, distal conduction disease may not manifest on the surface ECG. In both situations, significant mechanical dyssynchrony could be present despite a normal QRS. On the other hand, widening of the QRS complex might be a reflection of diffuse conduction disturbance or primarily RV delay with little LV mechanical dyssynchrony. Using TDI to measure temporal delay between septal and lateral wall peak systolic velocity, Bleeker et al$^6$ found that $70\%$ of patients with QRS duration $>150$ ms had severe mechanical dyssynchrony compared with $27\%$ of patients with a normal QRS width. When QRS duration was analyzed as a continuous variable in this study, however, there was no relationship between QRS duration and extent of LV dyssynchrony. Yu et al$^{12}$ confirmed a similar rate of mechanical dyssynchrony in a group of patients with HF and wide QRS yet found a $51\%$ prevalence of mechanical dyssynchrony in a narrow-QRS patient cohort. These observations suggest that although a particularly wide QRS complex ($>150$ ms) confers a greater likelihood of CRT response, patient selection based solely on QRS duration could result in significant overtreatment of one group of patients (QRS $>120$ ms) with simultaneous undertreatment of another group (QRS $\leq 120$ ms).

Does the presence of mechanical dyssynchrony predict response to CRT better than baseline QRS duration? Nelson et al$^{13}$ studied the acute response to multisite pacing using invasive pressure measurements in $22$ patients with dilated cardiomyopathy and QRS $>140$ ms. The extent of mechanical dyssynchrony, indexed by circumferential strain derived from tagged MRI, was a stronger predictor of systolic augmentation than basal QRS width ($r=0.88$ versus $r=0.55$). The chronic response to CRT was compared in a nonrandomized trial between comparable groups of patients with dilated cardiomyopathy and either wide ($>120$ ms) or narrow QRS ($\leq 120$ ms). Despite this difference in QRS duration, both groups had similar degrees of interventricular and intraventricular dyssynchrony by Doppler/M-mode echocardiography, and at $6$ months they achieved similar clinical and echocardiographic improvements.$^{14}$ Similarly, data from a multitude of TDI-based studies support the general concept.$^{7,11,15,16}$ Among the numerous indices of mechanical dyssynchrony that have been proposed, the criteria commonly used are septal to lateral wall delay $>65$ ms and standard deviation of time to peak systolic velocity of $12$ segments $>33$ ms. The relative value of TDI versus strain/strain rate in predicting response to resynchronization has not been fully resolved. Although these studies are limited by small numbers of patients, they provide convincing evidence supporting the hypothesis that mechanical dyssynchrony predicts response to CRT.

Moreover, analysis of myocardial mechanics after CRT suggests that the primary mechanism of improved LV performance is mechanical synchrony. Takemoto et al$^{17}$ showed that improvements in LV function in patients with HF and...
narrow QRS duration were related to reduced dyssynchrony rather than improved regional function. We have recently corroborated these data in an animal model of tachypacing-induced HF with a wide QRS duration, demonstrating improved LV performance coincident with improvements in mechanical dyssynchrony by echocardiography despite negligible if any change in regional contractility. Thus, the available data appear to strongly support a cause-and-effect relationship between mechanical dyssynchrony and CRT. Restoration of mechanical synchrony is associated closely with improvement in LV function. Therefore, the presence of mechanical dyssynchrony is necessary for patients to derive the best results from CRT. Limited studies suggest that CRT may be detrimental in the absence of dyssynchrony, and therefore it may not be prudent to treat all patients on the basis of QRS width. In a small, retrospective study, patients without dyssynchrony subjected to CRT had more adverse events than did those with dyssynchrony.

Limitations and Challenges of Dyssynchrony Analysis by Echo

In view of ReThinQ and PROSPECT, we are faced with a paradox. On one hand, substantial and convincing data indicate that TDI-derived dyssynchrony indices predict response to CRT. On the other hand, the only randomized and blinded studies suggest otherwise. Mechanical dyssynchrony is a necessary substrate for CRT. However, there are several reasons that the proposed criteria for diagnosing mechanical dyssynchrony may not be valid. Most relate to a number of technical and interpretative challenges routinely encountered in dyssynchrony analysis. These difficulties have been detailed elsewhere previously. With either tissue velocity or strain, there is considerable sensitivity of the signal amplitude and phase (timing) to the position of the sample region. Small changes in position often result in significant changes in peak velocity, number of peaks, signal fidelity, and timing of the peak. Similarly, tissue Doppler velocities and strain demonstrate dependence on the angle of insonation when full-sector images are used. Tissue velocity tracings often yield multiple systolic peaks within a single cardiac cycle (Figure, A and B). Determining which of these peaks is physiological versus noise is challenging and requires that the operator integrate information from deformation/velocity/strain/strain rate curves. In some difficult cases, it may not be possible to adjudicate the “physiological” peak. There is a general lack of consensus within the field about how best to resolve this problem. Additionally, TDI tracings may lack a distinct peak (domed peak), making it difficult to measure timing accurately (Figure, C). As a consequence, considerable intraobserver and interobserver variability exists, even within the context of clinical trials by experienced echocardiographers. Differences and the relative incremental value of tissue velocity versus strain rate or strain have not been thoroughly and rigorously examined.

Figure. A, Tissue velocity tracings from a normal subject show near-simultaneous mechanical activation of the septum (yellow) and lateral wall (green). Vertical dashed lines indicate aortic valve opening (AVO) and aortic valve closure (AVC). B, Example of multiple systolic peaks in the lateral wall (white arrows) compared with the single midsystolic septal peak (yellow arrow). Depending on which peak is picked, the time delay will be normal or dyssynchronous. C, Example of a “domed” peak (white arrow). Again, it is challenging to adjudicate the true peak, and this can cause substantial variability in timing measurement.
In addition to all of these challenges, it is our opinion that due diligence has not been performed on certain conceptual issues. We have resorted to using tissue velocity for dyssynchrony analysis without first establishing whether tissue velocity is indeed the best metric for mechanical activity. After all, tissue velocity merely tracks motion, whereas the heart does not just move—it deforms. Strain rate and strain track deformation and have been shown to be superior to TDI in evaluating regional mechanics. Strain by magnetic resonance has been used as the primary measure of dyssynchrony in experimental models. A recent article suggests that strain-derived dyssynchrony indices may be superior to chrony in experimental models.

These questions include how to assess regional mechanics before and after CRT, and how best to adjudicate multiple systolic peaks. We cannot condemn TDI if we cannot implement it appropriately, yet we cannot implement TDI appropriately without a better understanding of its application in HF.

**Moving Forward After PROSPECT and ReThinQ**

The ReThinQ study enrolled 172 patients who had a standard indication for an implantable cardioverter-defibrillator and randomly assigned them to CRT or no CRT for 6 months. The primary end point was the proportion of patients with an increase in peak oxygen consumption of ≥1.0 mL/kg body wt per minute during cardiopulmonary exercise testing at 6 months. Both groups did not differ significantly in the proportion of patients with the primary end point (46% and 41%, respectively). The peak oxygen consumption increased in a subset of patients with QRS duration ≥120 ms (P = 0.02) but was unchanged in the group with QRS duration <120 ms (P = 0.45). The authors concluded that patients with HF and narrow QRS intervals may not benefit from CRT.

The PROSPECT trial was a much larger study that enrolled 498 patients with standard CRT indications from 53 centers in Europe, Hong Kong, and the United States. Twelve echocardiographic parameters of dyssynchrony, based on both conventional echocardiography and TDI-based methods, were evaluated. The end points were an improved clinical composite score and ≥15% reduction in LV end-systolic volume at 6 months. Clinical composite score was improved in 69% of 426 patients, whereas LV end-systolic volume decreased ≥15% in 56% of 286 patients with paired data. The sensitivity ranged from 6% to 74% and specificity from 35% to 91% to predict clinical composite score. The sensitivity ranged from 9% to 77% and specificity from 31% to 93% for prediction of a ≥15% decrease in LV end-systolic volume. There was wide variability in the performance characteristics of each dyssynchrony parameter.

Superficially, there are 2 potential conclusions from these data: (1) CRT is not an effective therapy in patients with narrow QRS duration–related HF; and (2) echocardiographic measures of dyssynchrony are not efficient predictors of CRT response. However, given all we have presented in the preceding paragraphs, we submit that either of these conclusions would be imprecise. Indeed, for those of us who have practiced and endured the art of TDI and strain imaging for some time, these results are not at all surprising. We have already presented our views on the myriad challenges with TDI or strain imaging. However, it would be inaccurate to conclude that TDI- and strain-derived dyssynchrony analysis is not feasible in clinical practice. Instead, we believe that echocardiographic evaluation of dyssynchrony and, more precisely, its application to dyssynchrony analysis are not mature at present. Indeed, it would be shortsighted and unwise to abandon assessment of mechanical dyssynchrony. As stated before, dyssynchrony appears to be a necessary substrate for CRT with quantifiable resynchronization associated with improvements in LV function.

So how do we proceed at this time? Many basic questions need to be addressed with the use of more robust techniques, including strain analysis, before additional clinical trials are begun. These include the assessment of changes in regional mechanics before and after CRT and how to best adjudicate multiple systolic peaks. We cannot condemn the technique if we cannot implement it appropriately, and we cannot implement it appropriately if we do not understand the fundamental mechanics in HF using these techniques and their evolution with CRT. Ongoing and extensive experience with these techniques will enable a wider audience to develop expertise in these novel methods. Technological advances leading to less operator-dependent analysis of regional mechanics will substantially improve the reproducibility and clinical application of TDI and strain.

Finally, it is overly simplistic to assume that a single echocardiographic parameter will best predict response to CRT. The patient substrate in CRT is complex, and multiple factors influence the final response to CRT. All of these factors must be considered to decide the best course of action for a particular patient. Some of these factors include the following: (1) etiology of HF; (2) location of LV lead; (3) presence of scar and myocardial viability; and (4) timing and method of pacemaker optimization. Ischemic etiology, anterior locations of the LV lead, presence of scar in the implant area, and suboptimal pacemaker settings have all been associated with a poor response to CRT. There is also an effort to evaluate for presence of myocardial viability before CRT.

We foresee that a multifactor dyssynchrony score will likely emerge as the best predictor of response to CRT. This score will incorporate clinical factors, QRS duration, and multiple imaging parameters. Imaging parameters may not be restricted to intraventricular dyssynchrony alone and may include flow Doppler and TDI measurements of interventricular dyssynchrony. Such an approach will likely reveal that the presence of myocardial dyssynchrony is a heavily weighted component in this score and a required substrate. Post-CRT optimization may emerge as another important factor because it is not reasonable to draw conclusions on response to CRT without assessing whether the electrical therapy is being applied appropriately.
In conclusion, CRT is an important therapeutic advance in the treatment of patients with HF. As with all therapies, particularly invasive and expensive ones, accurate patient selection leads to maximal clinical benefits, optimal risk/benefit profile, and a cost-effective implementation of the technology. Ample data suggest that mechanical dyssynchrony is likely a critical substrate for CRT efficacy. An accurate, reliable, and routinely feasible assessment of mechanical dyssynchrony is needed to bridge the gap between theory and practice. Technological and methodological issues currently limit the use of dyssynchrony analysis routine use of dyssynchrony analysis. However, advances in engineering, analysis software, and our understanding of regional myocardial deformation should take dyssynchrony assessment beyond the surface ECG. In the meantime, judicious and thoughtful use of dyssynchrony analysis is warranted.

Acknowledgments
We thank Veronica L. Dimaano, MD, and Aurelio C. Pinheiro, MD, PhD, for their assistance with this manuscript.

Sources of Funding
This work was supported in part by grants from the National Institutes of Health (AG22554 and HL076513).

Disclosures
None.

References
We depart from opposite sides, but it appears that we and Drs Abraham and Abraham draw the same conclusions: QRS duration is not a perfect predictor of chronic resynchronization therapy (CRT) response, but echocardiographic techniques are not yet suitable to provide an improvement in this area. Although we agree on headlines, we would like to make a few additional comments. First, with recent studies showing the weakness of many mechanical variables, the poor correlation between QRS duration and mechanical dyssynchrony could well be due to the inaccuracy of determination of mechanical dyssynchrony measures. Indeed, several studies showed significant mechanical dyssynchrony even in healthy volunteers, which makes a proper definition of mechanical dyssynchrony questionable. Drs Abraham and Abraham also mentioned that reduction of QRS duration is not needed to achieve benefit of CRT. We agree with this opinion, but this observation cannot be used as an argument against baseline QRS duration as a selection criterion for CRT because the pathophysiology of this phenomenon is probably different. Second, speckle tracking–derived strain estimates appear to be more reliable measures (both theoretically and practically) than tissue Doppler imaging measures, but again, this approach also will require large-scale multicenter testing before it can be widely adopted. Furthermore, several studies indicate that even mechanical timing differences, determined with the use of magnetic resonance imaging tagging, do not provide a good prediction of CRT responders. Rather, indices containing the amount of strain appear to provide better predictions. Therefore, the novel techniques to measure strain offer interesting opportunities but by no means are ready for prime time. That is why we still recommend the use of QRS duration. Third, part of the argument for using mechanical dyssynchrony has come from single-center studies on CRT in patients with narrow QRS. After publication of the data on the Cardiac Resynchronization Therapy in Patients With Heart Failure and Narrow QRS (ReThinQ) study and presentation of data from the Evaluation of Screening Technologies in Electrically-Normal Mechanically-Dysynchronous Heart Failure Patients Receiving Cardiac Resynchronization Therapy (ESTEEM-CRT) study (Heart Rhythm Society, 2008), it is clear that at best only a subgroup of these patients may respond to CRT. However, another single-center study on CRT in patients with narrow QRS, not selected on the basis of echocardiographic criteria, reported good results similar to those observed in other studies using echocardiographic criteria. As stated by Drs Abraham and Abraham, we clearly need to better understand the mechanism of CRT. It may well be that some patients with narrow QRS respond to CRT but potentially through mechanisms other than dyssynchrony.

References

Response to Abraham and Abraham
Frits W. Prinzen, PhD; Angelo Auricchio, MD, PhD

We depart from opposite sides, but it appears that we and Drs Abraham and Abraham draw the same conclusions: QRS duration is not a perfect predictor of chronic resynchronization therapy (CRT) response, but echocardiographic techniques are not yet suitable to provide an improvement in this area. Although we agree on headlines, we would like to make a few additional comments. First, with recent studies showing the weakness of many mechanical variables, the poor correlation between QRS duration and mechanical dyssynchrony could well be due to the inaccuracy of determination of mechanical dyssynchrony measures. Indeed, several studies showed significant mechanical dyssynchrony even in healthy volunteers, which makes a proper definition of mechanical dyssynchrony questionable. Drs Abraham and Abraham also mentioned that reduction of QRS duration is not needed to achieve benefit of CRT. We agree with this opinion, but this observation cannot be used as an argument against baseline QRS duration as a selection criterion for CRT because the pathophysiology of this phenomenon is probably different. Second, speckle tracking–derived strain estimates appear to be more reliable measures (both theoretically and practically) than tissue Doppler imaging measures, but again, this approach also will require large-scale multicenter testing before it can be widely adopted. Furthermore, several studies indicate that even mechanical timing differences, determined with the use of magnetic resonance imaging tagging, do not provide a good prediction of CRT responders. Rather, indices containing the amount of strain appear to provide better predictions. Therefore, the novel techniques to measure strain offer interesting opportunities but by no means are ready for prime time. That is why we still recommend the use of QRS duration. Third, part of the argument for using mechanical dyssynchrony has come from single-center studies on CRT in patients with narrow QRS. After publication of the data on the Cardiac Resynchronization Therapy in Patients With Heart Failure and Narrow QRS (ReThinQ) study and presentation of data from the Evaluation of Screening Technologies in Electrically-Normal Mechanically-Dysynchronous Heart Failure Patients Receiving Cardiac Resynchronization Therapy (ESTEEM-CRT) study (Heart Rhythm Society, 2008), it is clear that at best only a subgroup of these patients may respond to CRT. However, another single-center study on CRT in patients with narrow QRS, not selected on the basis of echocardiographic criteria, reported good results similar to those observed in other studies using echocardiographic criteria. As stated by Drs Abraham and Abraham, we clearly need to better understand the mechanism of CRT. It may well be that some patients with narrow QRS respond to CRT but potentially through mechanisms other than dyssynchrony.

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Circ Cardiovasc Imaging. 2008;1:70-78
doi: 10.1161/CIRCIMAGING.108.791772

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