Cardiac resynchronization therapy (CRT) has been proposed as an alternative treatment in patients with severe, drug-refractory heart failure. The clinical results are promising, and improvement in symptoms, exercise capacity, and systolic left ventricular (LV) function have been demonstrated after CRT, accompanied by a reduction in hospitalization and a superior survival as compared with optimized medical therapy alone. However, 20% to 30% of patients do not respond to CRT. Currently, patients are selected mainly on electrocardiogram criteria (wide QRS complex, left bundle branch block configuration). In view of the 20% to 30% of nonresponders, additional selection criteria are needed. Echocardiography (and, in particular, tissue Doppler imaging) may allow further identification of potential responders to CRT, based on assessment of inter- and intraventricular dyssynchrony. In addition, echocardiography may allow optimal LV lead positioning and follow-up after CRT. In the current review, the different echocardiographic approaches to predict response to CRT are discussed. In addition, the use of echocardiography to guide LV lead positioning and follow-up after CRT are addressed. (J Am Coll Cardiol 2004;44:1–9) © 2004 by the American College of Cardiology Foundation

Heart failure is the major cause of mortality, morbidity, and hospitalization in patients age ≥60 years, and its costs represent 1% to 2% of the global health expenses ($20 billion in the U.S.) (1,2). Despite major advances in medical therapy, morbidity and mortality remain high (3). Cardiac resynchronization therapy (CRT) was introduced in the early 1990s, and developed dramatically over time (4). Cardiac resynchronization therapy was approved by the Food and Drug Administration in 2001 and was classified in the American College of Cardiology/American Heart Association/North American Society of Pacing and Electrophysiology Heart Rhythm Society 2002 guideline update for implantation of pacemakers and antiarrhythmic devices with the level of evidence IIA (5). These guidelines were based on two controlled trials: Multisite Stimulation in Cardiomyopathy (MUSTIC) with a crossover design (6), and Multicenter InSync Randomized Clinical Evaluation (MIRACLE) a parallel placebo trial (7). In these trials, the inclusion criteria were very similar: 1) severe heart failure despite optimized medical therapy; 2) depressed left ventricular ejection fraction (LVEF); and 3) wide QRS complex (duration >120 ms) with left bundle branch block morphology. Both trials demonstrated that CRT significantly improved symptoms, exercise tolerance, and quality of life (6,7). Still, 20% to 30% of patients did not respond to CRT (8), emphasizing the need for additional selection criteria to identify potential responders.

Recent data have demonstrated that mechanical dyssynchrony is not necessarily related to electrical dyssynchrony (9,10), and that the presence of substantial left ventricular (LV) dyssynchrony is a major predictor of response to CRT. Indeed, some patients with a wide QRS complex do not exhibit LV dyssynchrony, whereas some patients with a narrow QRS complex may demonstrate LV dyssynchrony (11–13). These considerations suggest that the surface electrocardiogram may not be the optimal marker to select candidates for CRT. New imaging techniques, in particular various echocardiographic approaches, may be superior to select potential responders to CRT. In this manuscript, the published echocardiographic approaches to evaluate mechanical dyssynchrony will be discussed. In addition, the value of echocardiography for evaluation of benefit from CRT and to optimize LV lead positioning will be addressed. However, before discussing the various echocardio-
graphic approaches, the different forms of dyssynchrony are defined briefly.

MECHANICAL DYSSYNCHRONY (ELECTROMECHANICAL DELAY): DEFINITIONS

Atrioventricular (AV) dyssynchrony. Atrioventricular dyssynchrony may be related to the dysfunction of both the sinus node and the AV node. While sinus node dysfunction induces chronotropic incompetence, abnormal conduction of the AV node results in:

- a delay between atrial and ventricular contraction (“AV dyssynchrony”);
- mitral valve incompetence with occurrence of late diastolic regurgitation;
- shortened ventricular filling time, limiting net diastolic stroke volume (14);
- atrial systole often occurs simultaneously with early passive filling, hence reducing LV filling (15).

Interventricular dyssynchrony. Dyssynchronous electrical activation of the ventricles, as during left bundle branch block, is associated with the right ventricular events preceding those of the LV, locally different contraction patterns, abnormal distribution of mechanical work in the LV, deficiencies in regional perfusion, and, therefore, decreased mechanical performance. The delay in onset of LV contraction and relaxation produces interventricular dyssynchrony and affects mainly the interventricular septal motion and its contribution to LV ejection. Earlier onset of right ventricular contraction results in right ventricular ejection occurring during LV end-diastolic period. The higher pressure within the right ventricle reverses the transseptal pressure gradient and, therefore, displaces the septum into the LV (16).

Intraventricular dyssynchrony. Coordinate LV contraction depends on normal ventricular activation. When a portion of the LV is prematurely activated, it generates regions of both early and delayed contraction that will contribute to altered LV performance (17). Early shortening or late shortening results in wasted work (18). The early contraction occurs when pressure is low and does not lead to ejection. The late contraction occurs at higher stress and results in paradoxical stretch of early contracting segments. The net result is a decline in systolic performance, an increase in end-systolic volume and wall stress, a delayed relaxation, and a decline in efficiency (19,20).

It is currently unclear to what extent each of these different forms of dyssynchrony contributes to the severity of heart failure. Crucial, however, is that all different dys-synchronies are assessed to identify patients with a high likelihood of response to CRT. As stated earlier, the traditional selection parameters are insufficient, and additional measurements are needed. Echocardiography may permit the assessment of all forms of dyssynchrony. In the following paragraphs, the conventional and more advanced echocardiographic measurements are summarized.

ECHOCARDIOGRAPHIC ASSESSMENT AND QUANTIFICATION OF DYSSYNCHRONY

Conventional echocardiography. The AV dyssynchrony can be assessed from conventional echocardiography by evaluating the mitral inflow duration; to date, there are no specific criteria for AV dyssynchrony in the literature.

Interventricular dyssynchrony can be evaluated by assessing the extent of interventricular mechanical delay (IVMD), defined as the time difference between left and right ventricular pre-ejection intervals (Fig. 1). An IVMD $\leq 40$ ms is considered indicative of interventricular dyssynchrony (21,22).

M-mode echocardiography may be useful for assessing intraventricular dyssynchrony (23). Using an M-mode recording from the parasternal short-axis view (at the papillary muscle level), the septal-to-posterior wall motion delay (SPWMD) can be obtained (Fig. 2), and a cut-off value $\geq 130$ ms was proposed as a marker of intraventricular dyssynchrony. However, frequently the SPWMD cannot be obtained, either because the septum is akinetic after extensive anterior infarction or because the maximal posterior motion is ill-defined. In addition, it is often not possible to obtain perpendicular M-mode sections of the proximal LV.

Newer echocardiographic methods. Two newer methods have been described, both addressing intraventricular dys-synchrony. Breithardt et al. (24) evaluated 34 patients undergoing CRT using a semiautomatic method for endocardial border delineation. The degree of LV dyssynchrony was quantified in two-dimensional echocardiographic sequences from the apical four-chamber view, focusing on the septal-lateral relationships. Computer-generated regional wall movement curves were compared by a mathematical phase analysis, based on Fourier transformation (Fig. 3). The resulting septal-lateral phase angle difference is a quantitative measure for intraventricular (dys)synchrony.

Kawaguchi et al. (25) studied 10 patients with and without CRT, and, to optimize endocardial LV border detection, echocardiography contrast (Optison, Mallinckrodt, Hazelwood, Missouri) was used; the contrast-enhanced images were processed using a technique referred to as cardiac variability imaging (26). On the four-chamber images, the endocardial border was outlined manually and
regional fractional area changes were determined and plotted versus time, yielding displacement maps. From these maps, the dyssynchrony between the septum and lateral wall was determined.

Both methods are restricted by the use of a single imaging plane. Any dyssynchrony in other walls will be overlooked, and, thus, the precise extent of dyssynchrony cannot be measured. Three-dimensional echocardiography, with the better spatial resolution, may potentially overcome this limitation. An example of this approach is shown in Figure 4. However, the clinical feasibility of real-time three-dimensional echocardiography still has to be proven.

Tissue Doppler imaging (TDI), strain and strain rate, tissue tracking (TT). Tissue Doppler imaging allows measurement of peak systolic velocity of different regions of the myocardium, and timing of peak systolic velocity in relation to electrical activity (QRS complex) (27,28). Based on these variables, TDI can provide accurate information on electromechanical coupling, and also assess interventricular and intraventricular dyssynchrony (Fig. 5). In addition, information on diastolic function can be obtained. Different groups have subsequently used TDI to assess dyssynchrony before CRT. Interventricular dyssynchrony was evaluated by Rouleau et al. (22) who studied 35 patients with dilated cardiomyopathy. Using TDI, the authors demonstrated an excellent agreement between QRS duration and interventricular dyssynchrony. Yu et al. (11) used TDI to assess intraventricular dyssynchrony in 88 normal individuals, 67 patients with heart failure and a narrow QRS complex (<120 ms), and 45 with a wide QRS complex (>120 ms). In this study, 12 sample volumes were placed in the myocardium, and for each sample the time from onset of QRS complex to peak systolic velocity was measured. From these data, two parameters indicating intraventricular dyssynchrony were derived:

1. The maximal difference between peak systolic velocities of any 2 of the 12 segments (interventricular dyssynchrony defined as a difference >100 ms); and
2. The SD of all 12 time intervals measuring time to peak systolic velocity (interventricular dyssynchrony defined as a standard deviation of 33 ms, also referred to as dyssynchrony index).

The authors demonstrated absence of substantial intraventricular dyssynchrony in normal individuals, whereas 73% of the patients with a wide QRS complex had substantial intraventricular dyssynchrony. Of interest, 51% of the
patients with a narrow QRS complex also exhibited substantial intraventricular dyssynchrony.

In other studies, intraventricular dyssynchrony was measured by placing two sample volumes (on the basal parts of the septum and lateral wall), and a delay of 60 ms between peak systolic velocities of the septum versus lateral wall (referred to as “septal-to-lateral delay”) was used as an indicator of the substantial intraventricular dyssynchrony (27,29).

All these studies used color TDI images, and TDI tracings were derived by postprocessing of the data. Other studies have used pulsed-wave TDI and demonstrated comparable results (30,31). Single point measurements of myocardial velocities using pulsed-wave TDI can only be performed once in the same heartbeat, and information obtained is, thus, influenced by heart rate differences, changes in loading conditions, and breathing. Due to this, collection of sufficient data information covering multiple myocardial segments becomes time consuming.

Using the digitally stored color-coded tissue Doppler images, further extended off-line analysis can be performed (i.e., strain and strain-rate analysis). Strain analysis allows direct assessment of the degree of myocardial deformation during systole and is expressed as the percentage of segmental shortening or lengthening in relation to its original length (32,33); it provides important information on the timing of onset and peak of myocardial contraction, permitting measurement of (dys)synchrony (Fig. 6). Compared with TDI, the main advantage of strain rate imaging resides in the better differentiation between active systolic contraction and passive displacement, which is of particular importance in ischemic patients with scar tissue (34).

The degree of systolic segmental shortening can be obtained with color-coded TDI by calculating the instantaneous regional velocity gradient (i.e., the strain rate, $s^1/s$) and integrating this information over time (strain, %) (32). Recent studies (35–37) have focused on the application of strain and TT for the detection of mechanical intraventricular dyssynchrony in patients considered for CRT, and particular attention was paid to events that occurred late in systole extending into the isovolumetric relaxation phase and diastole. In a typical patient with left bundle branch block and delayed lateral wall activation, a delay in the onset of lateral wall shortening (as compared with the septum) can be observed (Fig. 6). However, the clinical applicability of strain rate imaging is still limited by artefacts and a poor signal-to-clutter ratio, which renders the image acquisition and analysis process time-consuming and tedious. Moreover, the technique is operator-dependent, which limits reproducibility and widespread use.

Similar information about LV contractile synchrony can be obtained more easily with the use of a color-coded
display of myocardial displacement (Tissue Tracking, GE Vingmed, Horten, Norway) (38). Regional and global systolic performance can be quickly visualized, and rough information on regional strain distribution can be derived from the width of the LV color bands. Applying TT in patients with failing LV function allows rapid assessment of regional differences in both myocardial performance and timing (Fig. 7). Tissue tracking is a parametric imaging modality that requires correct timing of LV mechanical events, such as LV ejection, filling, and isovolumic contraction and relaxation. This information can be derived from the timing of valvular opening and closure, identified either by Doppler echocardiography or by M-mode techniques.

**ECHOCARDIOGRAPHIC MARKERS TO ASSESS BENEFIT FROM CRT**

In the following section, the echocardiographic approaches and markers used to demonstrate benefit from CRT will be discussed.

**Improvement in LV function, mitral regurgitation, and reverse remodeling.** Most studies have used the biplane Simpson’s approach to determine LVEF and volumes. In addition, three-dimensional approaches have also been used to assess these parameters (39). Various studies have demonstrated improvement in LVEF after CRT. Yu et al. (38) showed an improvement in LVEF from 28 ± 10% to 34 ± 13% directly after CRT, with a further improvement (to 40 ± 15%) during three months of CRT. Interestingly, when the pacemaker was turned off, LVEF deteriorated immediately to 34 ± 13% with a further reduction to 30 ± 12% (nonsignificant vs. baseline) after four weeks without pacing. Large clinical trials have suggested a more modest improvement in LVEF (e.g., in the MIRACLE trial, the median increase in LVEF was 4.6%) (7).

Systolic and diastolic parameters can also be obtained with conventional Doppler echocardiography and include: aortic velocity-time-integral, diastolic filling time, myocardial performance index (Tei), E/A ratio, E-deceleration time, isovolumetric relaxation, and pulmonary vein flow. Some of these parameters showed improvement after CRT (40,41), although interpretation is hampered by AV delay optimization (see the following text), as frequently performed with CRT.

Several studies using color Doppler imaging have shown a reduction in mitral regurgitation after CRT (7,40,41). In particular, Breithardt et al. (42) have elegantly demonstrated that the effective regurgitant orifice area decreased immediately after CRT.

Additional studies demonstrated significant reverse remodeling after CRT (35,40,41,43). Data from the MIRACLE trial (172 patients) showed a 30% reduction in LV end-diastolic volume and end-diastolic volume after six months of CRT (41). Data on improvement in geometry (sphericity index) and reduction in LV mass are contradictory (40,41).
Improvement of AV dyssynchrony (or optimization of AV delay). Restoration of optimal AV timing may improve systolic performance by optimizing LV preload. The acute hemodynamic benefits can be monitored noninvasively by Doppler echocardiography. An increase in the aortic velocity time integral (=stroke volume) and a prolongation of the diastolic filling time at the mitral valve by at least 10% to 20% from baseline documents systolic improvement. In 1995, an echocardiographic algorithm was proposed for the optimization of AV delay in patients with high degree AV block who underwent pacemaker implantation (44). The authors proposed that the optimal AV delay should provide the longest LV filling time without premature truncation of the A-wave by mitral valve closure. This approach is widely

Figure 5. (A) The typical tissue Doppler imaging tracings (peak systolic velocity [PSV], diastolic velocities [E’ and A’]) obtained in the septum of a normal individual. (B) Illustration of assessment of timing from onset of QRS to peak systolic velocity. (C) Evaluation of intraventricular (dys)synchrony by placing sample volumes on the septum (yellow curve) and lateral wall (green curve). Data from a normal individual showing complete intraventricular synchrony. (D) Severe intraventricular dyssynchrony between the septum (yellow curve) and lateral wall (green curve).

Figure 6. Myocardial deformation as assessed by strain rate imaging. Negative strain indicates shortening and is expressed as the percentage from its initial end-diastolic length (%). Strain curves obtained from six segments show synchronous onset of shortening and peak shortening in a normal individual (left panel). In contrast, a delay in the onset and the peak of lateral wall shortening (yellow curve) is observed in a patient with heart failure and left bundle branch block (right panel). Postsystolic shortening is present in the late activated lateral wall, as indicated by the late negative peak (arrow).
accepted as an easy method for AV optimization, although it has not yet been validated in patients with left-ventricular-based pacing. It is currently not clear whether AV delay optimization is needed, or whether an AV delay of 100 to 120 ms would be sufficient for all patients.

**Interventricular resynchronization.** Interventricular dysynchrony, as measured by IVMD, was reduced by 19% after CRT in the MIRACLE trial (41). Tissue Doppler imaging was also used to demonstrate interventricular resynchronization; Yu et al. (28) showed a large mechanical delay between the free right ventricular wall and the lateral wall of the LV, which was completely reversed after CRT.

**Intraventricular resynchronization.** Pitzalis et al. (23) demonstrated substantial intraventricular resynchronization, with a reduction in SPWMD from 192 ± 92 ms to 14 ± 67 ms (p < 0.001); moreover, using a cutoff value ≥130 ms, a QRS duration ≥150 ms, and a PQ interval ≥180 ms, reverse remodeling could be predicted with an accuracy of 85%.

Using the phase analysis (see the preceding text regarding advanced echocardiographic methods) as described by Breithardt et al. (24), intraventricular resynchronization was demonstrated acutely after CRT and was associated with an acute improvement in systolic function. In addition, the extent of dysynchrony before CRT was related to the extent of improvement of systolic function (Fig. 8). Using the contrast-enhanced echocardiographic approach from Kawaguchi et al. (25), a reduction of 40% in intraventricular dyssynchrony was shown immediately after CRT.

Using pulsed-wave TDI (and a five-segment model), Ansalone et al. (30) have demonstrated intraventricular resynchronization after CRT accompanied by reverse remodeling and improvement in clinical parameters (New York Heart Association [NYHA] functional class, 6-min walking distance). The magnitude of benefit was related to the pre-CRT intraventricular dysynchrony. Similarly, Garrigue et al. (31) demonstrated intraventricular resynchronization using pulsed-wave TDI, even in patients with right bundle branch block. Two studies using color TDI images demonstrated substantial resynchronization after CRT (27,28). The observed resynchronization was accompanied by an improvement in systolic function, NYHA functional class, and 6-min walking distance. Using the 12-segment model proposed by Yu et al. (45), prediction of reverse remodeling after CRT was demonstrated. Multivariate regression analysis demonstrated that the extent of intraventricular dysynchrony was the only predictor of reverse remodeling, and a dyssynchrony index <33 ms (see the preceding text) allowed complete separation of patients with and without reverse remodeling after CRT; only patients with an index >33 ms demonstrated reverse remodeling.

Tissue tracking and strain rate imaging (35,36) have also proved useful in assessing longitudinal resynchronization. When the latter is interpreted as a decrease in percentage of

![Figure 7. Tissue tracking (TT) in a patient with heart failure and left bundle branch block. An irregular distribution of color-bands is seen during systole (left panel), indicating poor systolic performance of the lateral wall. Systolic apical displacement occurs only in the basal part of the lateral wall, whereas the remaining parts of the lateral wall show no net apical displacement during systole (gray color). After adjusting the TT time interval to left ventricular diastole (right panel).](image)

![Figure 8. Relationship between the septal-lateral phase angle (ΦLS) at baseline and the best achievable hemodynamic improvement, measured as the percent increase in left ventricular (LV) peak positive dP/dt. Type I: near synchronous wall motion; Type II: delayed lateral wall movement; Type III: biphasic septal motion (based on reference 24).](image)
the extent of LV basal segments displaying delayed longitudinal contraction (an active contraction after closure of the aortic valve), it has been documented that CRT immediately reduced the extent of such diastolic contraction from 49 ± 16% to 23 ± 13% (p < 0.01) (35). Another study used strain rate imaging to quantify the acute effects of CRT on myocardial deformation (37). In this study, CRT reversed the pathologic septal-lateral strain relationships and reduced the incidence of early systolic prestretch in the late activated wall and of postsystolic shortening.

**ECHOCARDIOGRAPHY TO OPTIMIZE LEAD POSITIONING**

Studies using TDI have shown that the latest mechanical activity is frequently located in the lateral wall (35%), followed by the anterior and posterior regions (26% and 23%), whereas the inferior wall/ septum infrequently show the latest mechanical activity (16%) (46). Because the aim of resynchronization is to actively pace the most delayed site(s) of the LV, the selection of the pacing site(s) is needed to maximize the effect of CRT. Accordingly, Ansalone et al. (46) have demonstrated that optimal resynchronization was obtained when the (echocardiographically determined) region with the latest activity was paced; in addition, clinical response was superior in these patients. From this perspective, three-dimensional echocardiography may potentially allow optimal identification of the location with the latest activity.

**UNRESOLVED ISSUES**

A number of issues need to be resolved, as summarized below.

1. At present, several echocardiographic methods to assess dyssynchrony have been proposed, varying from conventional to advanced approaches, primarily involving TDI, strain, strain rate, and TT. It is currently unclear which of these provides optimal information on dyssynchrony and which parameters may actually allow prospective identification of responders to CRT. Furthermore, various forms of dyssynchrony are present, and it is unclear which form contributes most to heart failure. Accordingly, it is uncertain whether optimization of AV delay, interventricular or intraventricular resynchronization should be the principal goal of CRT.

2. The underlying etiology of heart failure may be important. Patients with ischemic cardiomyopathy frequently have large areas of scar tissue, and not infrequently these are the areas of latest activity. It is unclear whether pacing of nonviable (scar) tissue results in clinical improvement.

3. The new generation of biventricular pacemakers has the possibility of sequential ventricular pacing. Sogaard et al. (36) have recently proposed that echocardiographic optimization (using TT) of the V-V delay may further enhance benefit from CRT. The authors demonstrated that V-V optimization resulted in a further reduction in the active diastolic contraction from 23 ± 13% to 11 ± 7% (p < 0.01) with a simultaneous increase in LVEF from 30 ± 5% to 34 ± 6% (p < 0.01). More studies are needed to clarify this issue.

**Conclusions.** Cardiac resynchronization therapy is now considered an established therapy for patients with severe heart failure, with good clinical results, although 20% to 30% of patients do not respond to CRT. At present, patient selection is mainly based on QRS duration. Evidence is accumulating that echocardiography may be the ideal technique to identify responders to CRT. Based on assessment of AV dyssynchrony, interventricular and intraventricular dyssynchrony, accurate prediction of response to CRT will be feasible. In particular, TDI may allow precise assessment of interventricular and intraventricular dyssynchrony. In this respect, we suggest expanding the current guidelines on selection of candidates for CRT by including assessment of dyssynchrony by echocardiography.

Moreover, based on assessment of the site of latest activation in the LV, echocardiography can guide LV lead positioning and may be used to optimize AV delay and V-V delay. Finally, echocardiography allows assessment of resynchronization and follow-up after CRT.

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