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STATE OF-THE-ART PAPER

Imaging for Planning of Cardiac Resynchronization Therapy

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CME Objective for This Article: At the end of this activity the reader should be able to: discuss the strengths and limitations of echocardiography in the assessment of dyssynchrony and measuring response to cardiac resynchronization therapy; discuss the current and potential role of cardiovascular magnetic resonance imaging techniques both from a technical and physiologic standpoint in evaluating mechanical dyssynchrony; discuss the role of radionuclide imaging techniques both from a technical and physiologic standpoint in evaluating cardiac dyssynchrony; and discuss the role of cardiac computed tomographic imaging in dyssynchrony assessment.

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Imaging for Planning of Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT) is a novel therapy for patients with refractory heart failure (HF). Large clinical trials evaluating CRT have demonstrated significant improvements in cardiac survival, decreases in recurrent HF hospitalization, and improvements in indexes of quality of life. Although numerous mechanisms are involved in CRT's therapeutic effects, correction of both interventricular and intraventricular mechanical dyssynchrony has been postulated as the key mechanism. To date, most large randomized controlled trials evaluating CRT have identified dyssynchronous patients on the basis of prolongation of the QRS complex from the baseline electrocardiogram. Concerns have been raised regarding the use of this measure for patient selection, stemming from a significant 30% to 40% non-response rate to CRT. Because of the cost and invasive nature of CRT, optimal patient selection for this therapy has become a priority for HF specialists and electrophysiologists. Cardiac imaging modalities have attempted to fulfill this need to improve patient selection by identifying mechanical dyssynchrony. Although early echocardiographic studies reported promising results, more recent larger scale studies have curtailed this enthusiasm, with a lack of established selection criteria for CRT in the current practice guidelines. This review summarizes the evidence to date and the potential role of imaging modalities in the selection and care of patients with HF referred for CRT. (J Am Coll Cardiol Img 2012;5:93–110) © 2012 by the American College of Cardiology Foundation

The emergence of cardiac resynchronization therapy (CRT) has provided cardiac caregivers with a novel therapeutic option for patients with refractory heart failure (HF). Large, prospective clinical studies have demonstrated that CRT can provide significant improvement of both cardiac mortality and morbidity (Table 1 [1–6]). However, up to 30% to 40% of patients do not respond to CRT (1,2). CRT is invasive and carries considerable costs related to implantation, serial device monitoring, and requirement for multiple device exchanges over a patient's lifetime. The recently published Resynchronization/Defibrillation for Ambulatory Heart Failure Trial found the incidence of serious complications in the CRT-defibrillator arm, such as ventricular perforation or device-related infection, to be 13%, which was considerably higher than in the implantable cardioverter-defibrillator arm (7). Furthermore, recent clinical trials have found that even patients with mildly symptomatic HF receive mortality benefit with CRT (7,8) (Table 2 [6–10]).

Cumulatively, these factors underscore a need for improved patient selection of this novel therapy to achieve optimal therapeutic cost-effectiveness. Current evidence indicates that cardiac imaging can identify and quantify the severity of mechanical dyssynchrony in patients beyond the presence of a widened QRS complex on electrocardiography.

Although novel echocardiographic parameters were reported to be promising in detecting mechanical dyssynchrony in single-center studies, such enthusiasm has been curbed by the negative results from the recent prospective multicenter PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) study. We anticipate that new echocardiographic parameters will continue to emerge. However, novel imaging modalities, such as cardiac magnetic resonance (CMR) can assess mechanical dyssynchrony differently from echocardiography from a technical perspective. CMR can also provide the location of myocardial scar and coronary venous anatomy, which influence the likelihood for success of CRT. In this report, we aim to review the evidence in assessing mechanical dyssynchrony by various noninvasive imaging modalities and their clinical relevance.

Mechanism

The main rationale for CRT stems from resynchronization of left ventricular (LV) contraction. Dyssynchronous contraction of the left ventricle over time may contribute to progressive negative remodeling and worsen patient symptoms and has been associated with increased mortality and adverse cardiovascular outcomes.

Patients with a left bundle branch block can have atrioventricular, interventricular, and intraventricular dyssynchrony, each with respective adverse ramifications on ventricular function. Interventricular dyssynchrony results from septal depolarization from the right ventricular bundle, as opposed to physiologic left-sided activation, leading to asynchronous right and LV contraction. Intraventricular dyssynchrony within the left ventricle itself results from septal and anteroseptal activation before the lateral and inferolateral segments, resulting in regional load disparities that can produce increased wall tension. Discoordinated papillary muscle activation during systole leads to abnormal mitral valve closure, with the development or worsening of pre-existing mitral regurgitation (11).

CRT may confer benefits by coordinating right ventricular and LV contraction, synchronizing the LV segments, prolonging the diastolic filling period with improvements of both coronary and LV filling, and restoring atrioventricular synchrony. The Cardiac Resynchronization–Heart Failure trial revealed that CRT can provide up to a 30% improvement in stroke volume and a significant reduction in mitral regurgitation within 3 months of initiating therapy (3). These beneficial effects on cardiac hemodynamic parameters are associated with reduced myocardial energy cost and may indirectly attenuate maladaptive neurohormonal activation and autonomic dysfunction. Recent studies have indicated that correction of intraventricular dyssynchrony, compared with interventricular dyssynchrony, plays a more significant role in the efficacy of CRT (12).

Beyond the Electrocardiogram

Electrocardiography has numerous limitations for identifying patients suitable for CRT. The threshold criteria of a QRS duration of ≥ 120 ms was not derived from prospective evaluation but rather from inclusion criteria of landmark clinical trials (1,3,4). In fact, the mean and median values of QRS durations of patients enrolled in the largest CRT trials were substantially higher than 120 ms (ranging from 155 to 160 ms) (Table 1). Echocardiographic studies have revealed a significant discordance between electrical and mechanical delay, with up to 30% of patients with QRS durations >150 ms and 50% of those with QRS durations >120 ms demonstrating no evidence of septal to lateral dyssynchrony (13). The QRS pattern may also further complicate patient selection. More than 73% of patients in the CRT arm of the Resynchronization/

Defibrillation for Ambulatory Heart Failure Trial had interventricular conduction delays with left bundle branch block patterns (7). Whether patients with right bundle branch block or nonspecific interventricular conduction delays would derive the same benefit from CRT remains unclear. Retrospective examination of landmark CRT trials demonstrated no benefit of CRT in patients with right bundle branch block for any hard clinical end point (14).

Echocardiographic data suggest that up to 30% to 50% of patients with symptomatic HF with compromised LV ejection fractions (LVEFs) and narrow QRS complexes (<120 ms) have evidence of mechanical dyssynchrony (15). The utility of CRT in this patient population was evaluated in the Cardiac Resynchronization Therapy in Patients With Heart Failure and Narrow QRS study, which included patients with QRS durations < 130 ms and echocardiographic evidence of mechanical dyssynchrony. The study demonstrated no difference for the primary end point of peak oxygen uptake at 6 months but found improvement in functional class (16). Although other studies also failed to demonstrate any difference in secondary outcome measures, such as LVEF, no study to date has evaluated hard clinical end points in this population (Table 3 [17–19]).

These data underscore the importance of other diagnostic modalities that may more precisely identify potential responders of CRT, including patients who not meet current clinical selection criteria.

Echocardiography

Over the past decade, echocardiography has emerged as a potentially useful tool to assess mechanical dyssynchrony. There are numerous advantages of echocardiography, including noninvasiveness, portability, and widespread availability. Numerous echocardiographic techniques have been devised to assess for dyssynchrony, including M mode, pulsed-wave Doppler imaging, tissue Doppler imaging (TDI), speckle tracking, and real-time 3-dimensional (RT3D) imaging (Tables 3 and 4 [12,20–38]).

Interventricular dyssynchrony could be identified by traditional 2-dimensional echocardiographic parameters, but intraventricular dyssynchrony is pri-

ABBREVIATIONS AND ACRONYMS

CCT	= cardiac computed tomography
CMR	= cardiac magnetic resonance
CRT	= cardiac resynchronization therapy
DENSE	= displacement encoding with stimulated echoes
GMPS	= gated myocardial perfusion single-photon emission computed tomography
HF	= heart failure
LV	= left ventricular
LVEF	= left ventricular ejection fraction
MRI	= magnetic resonance imaging
RT3D	= real-time 3-dimensional
SENC	= strain-encoded magnetic resonance imaging
TDI	= tissue Doppler imaging

Table 1. Landmark CRT Trials

Study	n	Inclusion Criteria	QRS (ms)	Design	Blinding	Control	Intervention	Follow-Up (months)	Primary End Point	Results
MIRACLE (4)	453	NYHA functional class III or IV, LVEF \leq 35%, LVEDD \geq 55 mm, SR	\geq 130	Parallel	Double blind	CRT-Off	CRT-On	6	6MWD, NYHA functional class, MLHFQ score	\uparrow 6MWD ($p = 0.005$), improved NYHA functional class ($p < 0.001$), \downarrow MLHFQ score ($p = 0.001$)
MIRACLE-ICD (5)	369	NYHA functional class III or IV, LVEF \leq 35%, LVEDD \geq 55 mm, ICD indicated, SR	\geq 130	Parallel	Double blind	CRT-D (CRT-Off)	CRT-D (CRT-On)	6	Peak Vo_2 , NYHA class, MLHFQ score	\uparrow 6MWD ($p = 0.36$), improved NYHA functional class ($p = 0.007$), \downarrow MLHFQ score ($p = 0.02$)
Contak CD (6)	490	NYHA functional class II–IV, LVEF \leq 35%, ICD indicated, SR	\geq 120	Parallel	Double blind	CRT-D (CRT-Off)	CRT-D (CRT-On)	6	Composite: all-cause mortality, HF hospitalization, VT/VF requiring intervention	RRR 15% ($p = 0.35$)
COMPANION (1)	1,520	NYHA functional class III or IV, LVEF \leq 35%, LVEDD \geq 60 mm, SR	\geq 120	1:2:2	—	Medical therapy	CRT-P, CRT-D	16.2 (median)	All-cause mortality or hospitalization	CRT-P HR: 0.81 (95% CI: 0.69–0.96; $p = 0.014$); CRT-D HR: 0.80 (95% CI: 0.68–0.95; $p = 0.010$)
CARE-HF (3)	813	NYHA functional class III or IV, LVEF \leq 35%, SR	\geq 150, 120–150 + echocardiographic dyssynchrony	Parallel	—	Medical therapy	CRT-P	29.4 (mean)	All-cause mortality or CV hospitalization	HR: 0.63 (95% CI: 0.51–0.77; $p < 0.001$)
CARE-HF Extended (2)								37.4	All-cause mortality	HR: 0.60 (95% CI: 0.47–0.77; $p < 0.0001$)

CARE-HF = Cardiac Resynchronization–Heart Failure; CI = confidence interval; COMPANION = Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy only; HF = heart failure; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricular ejection fraction; MIRACLE = Multicenter InSync Randomized Clinical Evaluation; MIRACLE-ICD = Multicenter InSync ICD Randomized Clinical Evaluation; MLHFQ = Minnesota Living With Heart Failure Questionnaire; NYHA = New York Heart Association; RRR = relative risk ratio; 6MWD = 6-minute walk distance; SR = sinus rhythm; VF = ventricular fibrillation; Vo_2 = oxygen consumption; VT = ventricular tachycardia; \uparrow = increased; \downarrow = decreased.

Table 2. CRT Trials in Mildly Symptomatic Heart Failure (NYHA Functional Classes I and II)

Study	n	Inclusion Criteria	Design	Blinding	Control	Intervention	Follow-Up	Primary End Point	Response
Contak CD (6)						See Table 1			
MIRACLE-ICD 2 (9)	186	NYHA functional class II, LVEF \leq 35%, QRS \geq 130 ms, LVEDD \geq 55 mm, ICD indicated, SR	Parallel	Double blind	CRT-D (CRT-Off)	CRT-D (CRT-On)	6 months	Change in peak Vo_2	\uparrow Peak Vo_2 ($p = 0.87$)
REVERSE (10)	610	NYHA functional class I or II, QRS \geq 120 ms, LVEF \leq 40%, LVEDD \geq 55 mm, SR	Parallel	Double blind	CRT-D (CRT-Off)	CRT-D (CRT-On)	24 months	HF clinical composite score (worsening)	19% vs. 34% ($p = 0.01$)
MADIT-CRT (8)	1,820	NYHA functional class I or II, LVEF \leq 30%, QRS \geq 130 ms, SR	3:2	Single blind	ICD	CRT-D	2.4 yr (mean)	All-cause mortality or nonfatal HF	HR: 0.66 (95% CI: 0.52–0.84; $p = 0.001$)
RAFT (7)	1,798	NYHA functional class II (80%) or III (20%), LVEF \leq 30%, QRS \geq 120 ms	Parallel	Double blind	CRT-D (CRT-Off)	CRT-D (CRT-On)	40 months (mean)	All-cause mortality or HF hospitalization	HR: 0.75 (95% CI: 0.64–0.87; $p < 0.001$)

MADIT-CRT = Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy; RAFT = Resynchronization/Defibrillation for Ambulatory Heart Failure Trial; REVERSE = Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction; other abbreviations as in Table 1.

Table 3. CRT Trials With Narrow QRS Complex (≤ 120 ms)

Study	n	Inclusion Criteria	Dyssynchrony	Blinding	Control/Intervention	Follow-Up (months)	Primary End Point	Secondary End Point Response
Yu et al (18)	51	NYHA functional class III or IV, LVEF $< 40\%$, QRS < 120 ms	Yu index ≥ 32.6 ms	Single blind	QRS > 120 ms/QRS < 120 ms	3	NYHA functional class, 6MWD, LVESV, LVEF, MR (p = significant for all)	
ESTEEM-CRT (19)	67	NYHA functional class III, LVEF $\leq 35\%$, QRS < 120 ms	Yu index > 28.7 ms	Single blind	Nil/CRT-D	12	NYHA functional class + MLHFQ	LVEDV, LVESV p < 0.0001 p < 0.0001
RethinQ (17)	172	NYHA functional class III, LVEF $\leq 35\%$, QRS < 120 ms	M-mode echocardiography, pulsed-wave Doppler, color TDI	Double blind	CRT-Off/CRT-On	6	Peak Vo_2	NYHA functional class 29% vs. 54% (p = 0.006) p = NS
ESTEEM-CRT = Evaluation of CRT in Narrow QRS Patients With Mechanical Dyssynchrony From a Multicenter Study; LVEF = left ventricular end-systolic volume; MR = mitral regurgitation; RethinQ = Cardiac Resynchronization Therapy in Patients With Heart Failure and Narrow QRS; TDI = tissue Doppler imaging; other abbreviations as in Table 1.								MLHFQ p = NS

marily assessed by quantitative echocardiographic methods. The difference of the pre-systolic period, measured from the onset of the QRS complex on the electrocardiogram to the initiation of Doppler flow in the pulmonary artery and the aorta, respectively, may be used to measure interventricular dyssynchrony. A difference of the pre-systolic period of 49 ms, as a marker of interventricular dyssynchrony, has been shown in retrospective analysis of the CARE-HF (Cardiac Resynchronization-Heart Failure) trial to correlate with event-free survival (20), as well as an independent predictor of response in the SCART (Selection of Candidates for Cardiac Resynchronization Therapy) trial (21). Another method of assessing interventricular dyssynchrony uses pulsed-wave tissue Doppler to measure the difference in time to contraction of the right ventricle and the lateral wall of the left ventricle visualized with the apical 4-chamber view. This parameter, however, has not shown any association with CRT outcomes. Other pulsed-wave Doppler techniques for dyssynchrony assessment include quantitation of the physiological intervals of the cardiac cycle, such as filling and isovolumetric contraction times.

M-mode echocardiography. M-mode echocardiography can assess septal to posterior wall motion delay obtained from the short-axis parasternal view of the left ventricle (Fig. 1). More recent color M-mode imaging makes use of TDI (see the following discussion) for quantification of septal to posterior wall motion delay (Fig. 2). Although M-mode echocardiography provides extremely high temporal resolution, there are several limitations, including the depth of ultrasound penetration, angulation issues across acoustic windows of the chest wall, and the requirement for myocardial walls to be as perpendicular to the transducer as possible. Assessment by M-mode imaging is especially challenging if the myocardial segments are akinetic because of prior myocardial infarction or scar, as inward excursion cannot be readily identified relative to the opposing wall. Additionally, this method of interrogation cannot differentiate between passive and active motion, which is a crucial aspect of mechanical dyssynchrony assessment. Early studies demonstrated a correlation of septal to posterior wall motion delay ≥ 130 ms with reverse remodeling (22), but recent studies have failed to demonstrate any association of septal to posterior wall motion delay with clinical outcomes after CRT implantation (23).

TDI. TDI may be used to assess tissue velocity or strain by myocardial deformation. TDI by pulsed-

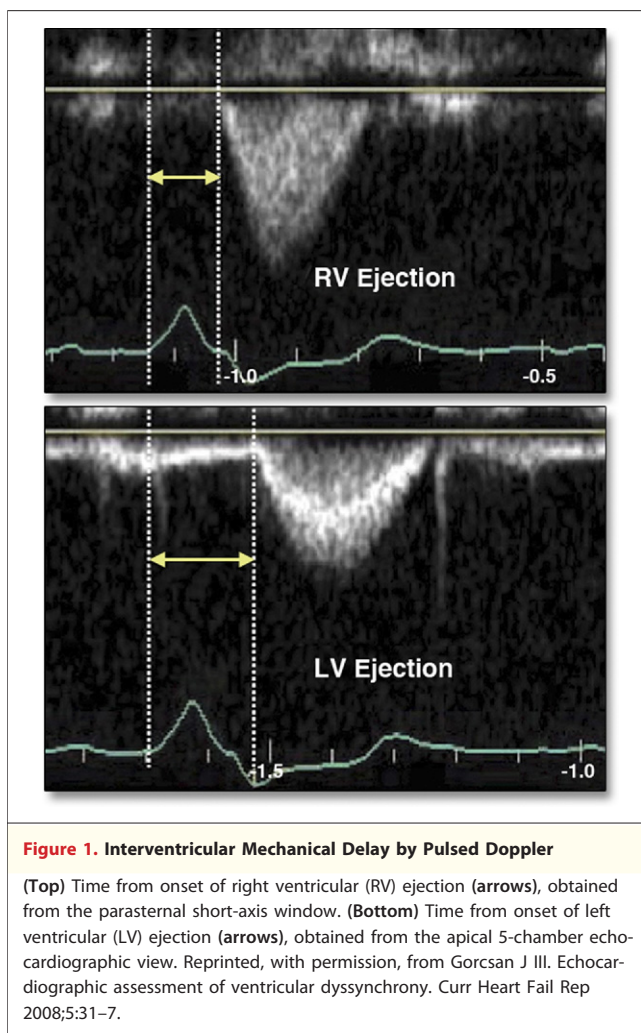
Table 4. Echocardiographic Dyssynchrony Assessment

Method	Threshold (ms)	Studies	Limitations	Attributes
Pulsed-wave Doppler				
IVMD	>44	Achilli <i>et al.</i> (21): \uparrow LVEF \geq 5% + NYHA functional class	Requires stable heart rate intervals Affected by RV function	Highly reproducible
LV filling time/R-R interval	<40%		Requires nearly parallel interrogation of MV inflow	Highly reproducible
M-mode echocardiography				
SPWD	>130	Pitzalis <i>et al.</i> (22): \uparrow LVEF \geq 5% Marcus <i>et al.</i> (23): not predictive	Difficult in patients with wall motion abnormalities (prior MI or scar) Cannot differentiate active + passive motion	High temporal resolution Highly reproducible Easily trained No specialized software required
TDI: pulsed wave				
LVDYS	>102	Penicka <i>et al.</i> (24): \uparrow LVEF \geq 25% Achilli <i>et al.</i> (21): not predictive	Cannot differentiate active + passive motion Technically challenging Requires optimal image quality Angle dependent Cannot assess multiple segments in 1 view	High temporal resolution No special probe required
TPSV-SD (6 segments)	>31.3	Jansen <i>et al.</i> (31): \downarrow LVESV \geq 15%		
TOSV-DF	>60	Soliman <i>et al.</i> (32): not predictive		
Color TDI				
TPSV-DF (2 segments)	>60–65	Bax <i>et al.</i> (12): \downarrow LVESV \geq 15%	Cannot differentiate active + passive motion Requires technical expertise	High temporal resolution Multiple segments may be assessed in 1 view
TPSV-DF (6 segments)	>105–110	Knebel <i>et al.</i> (20): \downarrow LVESV \geq 15%		
SPWD	>130	Bleeker <i>et al.</i> (33): \downarrow LVESV \geq 10%		
Yu index	>31.4–33	Yu <i>et al.</i> (25,26): \downarrow LVESV \geq 15% Gorcsan <i>et al.</i> (34): death/transplantation/LVAD implantation		
TSI				
TPSV-DF	>65	Van de Veire <i>et al.</i> (35): \downarrow LVESV \geq 15% + NYHA, 6MWD		
Yu index	>34.4	Yu <i>et al.</i> (36): \downarrow LVESV \geq 15%		
TDI strain				
TPSS-DF (radial)	>130	Dohi <i>et al.</i> (37): \uparrow SV \geq 15%	Highly angle dependent Requires technical expertise Requires optimal image quality	May differentiate between passive + active motion High temporal resolution
TPSS-SD (12 segments)	60	Mele <i>et al.</i> (38): \downarrow LVESV \geq 15%		
Speckle tracking				
SPWD (radial)	>130	Suffoletto <i>et al.</i> (27): \uparrow SV \geq 15% Gorcsan <i>et al.</i> (34): death/transplantation/LVAD implantation STAR study (28): death/transplantation/LVAD implantation Delgado <i>et al.</i> (29): mortality + HF hospitalization	Requires optimal image quality with high frame rate Requires technical expertise Speckles must remain in imaging plane	Angle independent May perform offline analysis on routine images May assess radial, longitudinal, and circumferential strain
RT3D echocardiography				
LVDYS index (16 segments)	>5.6%	Marsan <i>et al.</i> (30): \downarrow LVESV \geq 15%	Slower frame rates Requires optimal image quality Inability to differentiate active + passive motion Lower temporal + spatial resolution Requires regular rhythm Requires special ultrasound probe	More complete 3D analysis Angle independent Assess radial, longitudinal, and circumferential contraction Accurate LVEF assessment

DF = difference; IVMD = interventricular mechanical delay; LV = left ventricular; LVAD = left ventricular assist device; LVDYS = left ventricular dyssynchrony; LVEF = left ventricular ejection fraction; MV = mitral valve; NYHA = New York Heart Association; RT3D = real-time 3-dimensional; RV = right ventricular; SPWD = septal to posterior wall delay; STAR = Speckle Tracking and Resynchronization; 3D = 3-dimensional; TPSS = time to peak systolic strain; TPSV = time to peak systolic velocity; TSI = tissue synchronization imaging; other abbreviations as in Tables 1 and 3.

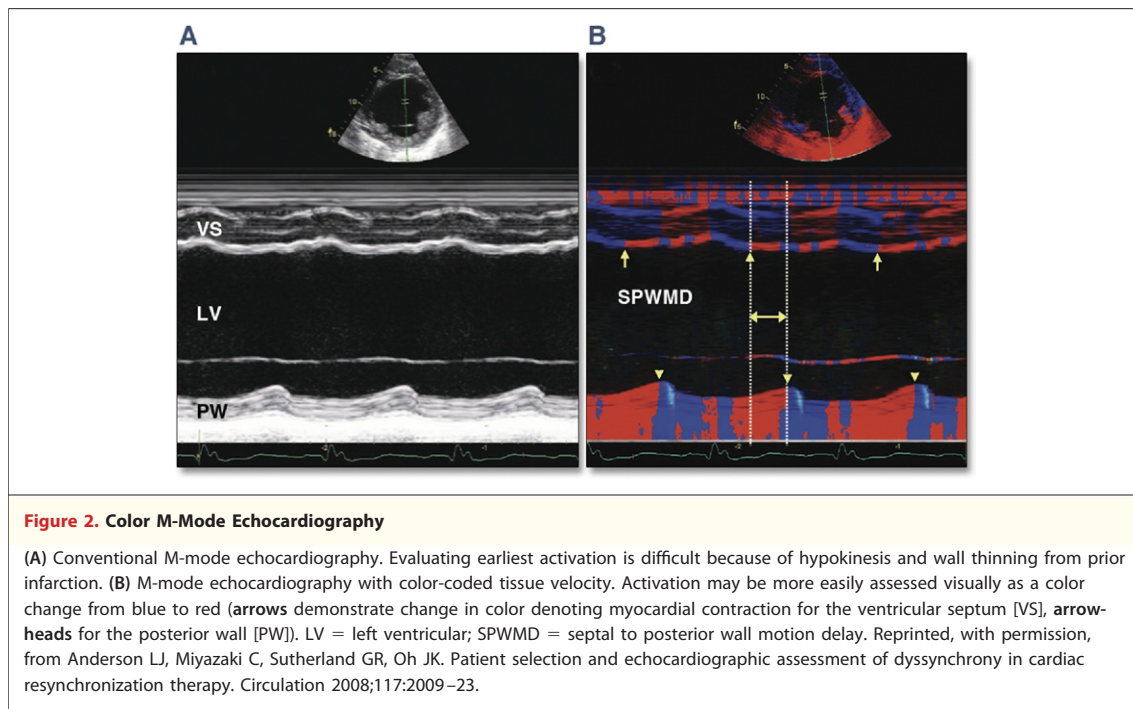
wave Doppler allows the assessment of longitudinal myocardial tissue velocity relative to the ultrasound transducer and has been the most investigated echocardiographic modality for dyssynchrony evaluation. Indexes of dyssynchrony may be generated from differences in the peak velocity, time to peak systolic velocity, or time to onset of peak systolic velocity of the LV walls as assessed in either single or multiple views (2, 4, or 12 segments). Although TDI also enjoys high temporal resolution similar to that of M-mode echocardiography, limitations include the requirement for interrogation of Doppler velocity data perpendicular to the ultrasound beam, limited tissue penetration, the need for adequate acoustic windows, and the inability to simultaneously assess more than 2 LV segments at once. Because of the nature of assessment relative to the ultrasound transducer, measurements are prone to error related to tethering of myocardium to surrounding tissues and translational motion of the heart. Pulsed-wave TDI must be performed online, with preclusion of further offline analysis. Numerous studies have evaluated TDI by pulsed-wave Doppler indexes of dyssynchrony for response to CRT, some demonstrating improvements in echocardiographic parameters (24) and others finding no association with reverse remodeling or clinical outcomes (21).

Color-coded TDI (Fig. 3) and color tissue synchronization imaging provide expansion over pulsed-wave Doppler for regional LV assessment by allowing the simultaneous interrogation of time to peak velocity for multiple myocardial segments in 1 view (13). Tissue synchronization imaging involves the identification of regional mechanical delay by overlaying color-coded temporal velocity data onto 2-dimensional or 3-dimensional images of the left ventricle. This assessment requires proficiency with involved post-processing software, as well as optimal image quality during acquisition of the study. Indexes that incorporate the standard deviation of time to peak systolic velocity for multiple myocardial segments have been proposed and shown to have higher correlation with reverse remodeling over standard color TDI parameters (25). Experienced centers have reported low intraobserver and interobserver variability for color TDI parameters of dyssynchrony (25), whereas other studies, including the PROSPECT trial, have found poor reproducibility (39). Studies evaluating color TDI have demonstrated an association with improved LVEF and reverse remodeling (25). Other parameters may be derived from tissue velocity data, such as myo-



cardial displacement, strain, and strain rate, but these measures have been shown to be inferior in comparison with TDI velocity (26).

Strain and strain rate. Myocardial strain, the percentage change of myocardial length from end-diastole to end-systole, and its time derivative, strain rate, may be assessed using TDI (see the previous discussion) or speckle tracking. Speckle tracking involves a post-processing computer algorithm that applies specific acoustic markers to the myocardium, termed “speckles,” to conventional 2-dimensional or 3-dimensional digital echocardiographic images (Fig. 4). Movements of these markers are tracked during the cardiac cycle, frame by frame, to determine regional myocardial strain. Strain is advantageous over the assessment of motion because it measures myocardial deformation and may therefore differentiate between passive translational motion of the myocardium and active systolic contraction.



Despite lower temporal resolution, speckle tracking has numerous advantages over TDI, including the ability to assess circumferential and radial strain in addition to longitudinal strain, relatively angle independent image acquisition, and significantly faster post-processing and image analysis. Despite these attributes, speckle tracking is limited by inferior temporal resolution compared with TDI, and similar to TDI, it requires technical expertise with post-processing software and is highly dependent on image quality. Single-center studies that evaluated delays to peak radial strain with speckle tracking have reported a significant association with response to CRT (2,27). The prospective, multi-center STAR (Speckle Tracking and Resynchronization) trial evaluated speckle-tracking assessment of strain in 132 patients referred for conventional CRT indications. Both radial and longitudinal strain were associated with favorable LVEF response and long-term freedom from death, LV assist device implantation, or transplantation over 3.5 years of follow-up (28). A more recent study of 397 patients with ischemic cardiomyopathy evaluated with speckle tracking before CRT found that discordant LV lead position and myocardial scar in the region of the LV pacing lead were independent determinants of all-cause mortality and HF hospitalization, while the extent of baseline LV radial dyssynchrony was associated with improved survival (29).

RT3D echocardiography. RT3D echocardiography can simultaneously assess 3-dimensional ventricular volumes and systolic contraction of all LV segments during the cardiac cycle (Fig. 5). Dyssynchrony indexes may be generated by calculating the standard deviation of the timing of inward systolic excursion of the various LV segments. The acquired data may be post-processed to generate color maps, which can localize regional dyssynchrony in real time as well as in 3 dimensions. This provides advantages over 2-dimensional methods, including angle-independent assessment of strain in all directions during the cardiac cycle. Additional parameters for LV assessment, including function, and volumes may be quantified with high accuracy without the need for any geometric assumptions. Despite these multiple attributes, a number of challenges presently exist for RT3D echocardiography. Data acquisition is more challenging than with 2-dimensional methods, with a high degree of reliance on excellent acoustic windows and stable cardiac rhythms. RT3D imaging has limited temporal and spatial resolution compared with 2-dimensional methods; requires time-consuming, technically challenging post-processing; and suffers from limited reproducibility of time-volume curves for akinetic segments. One study of 60 consecutive patients demonstrated correlation of RT3D findings with LV reverse remodeling (30). Presently, there has not been any clinical study evaluating the role of

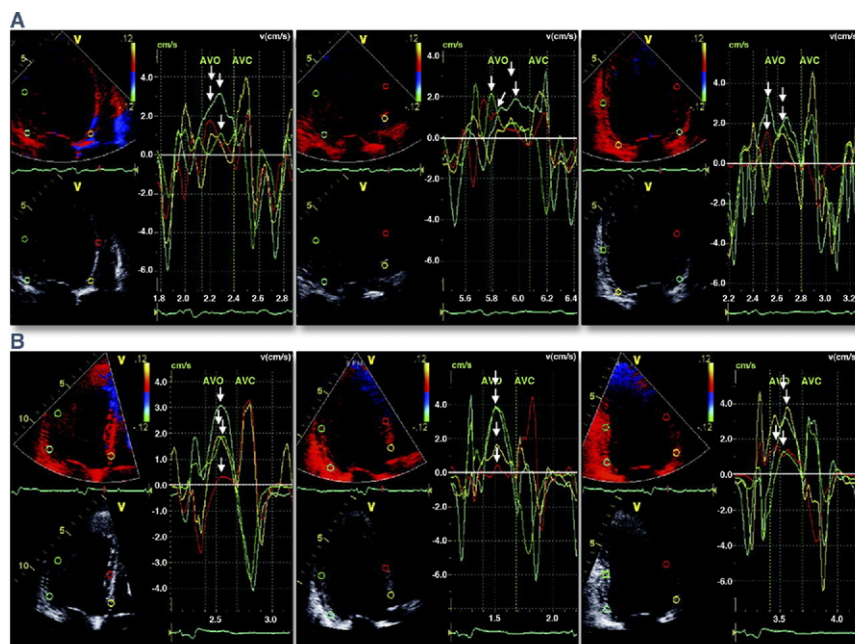


Figure 3. Color-Coded Tissue Velocity

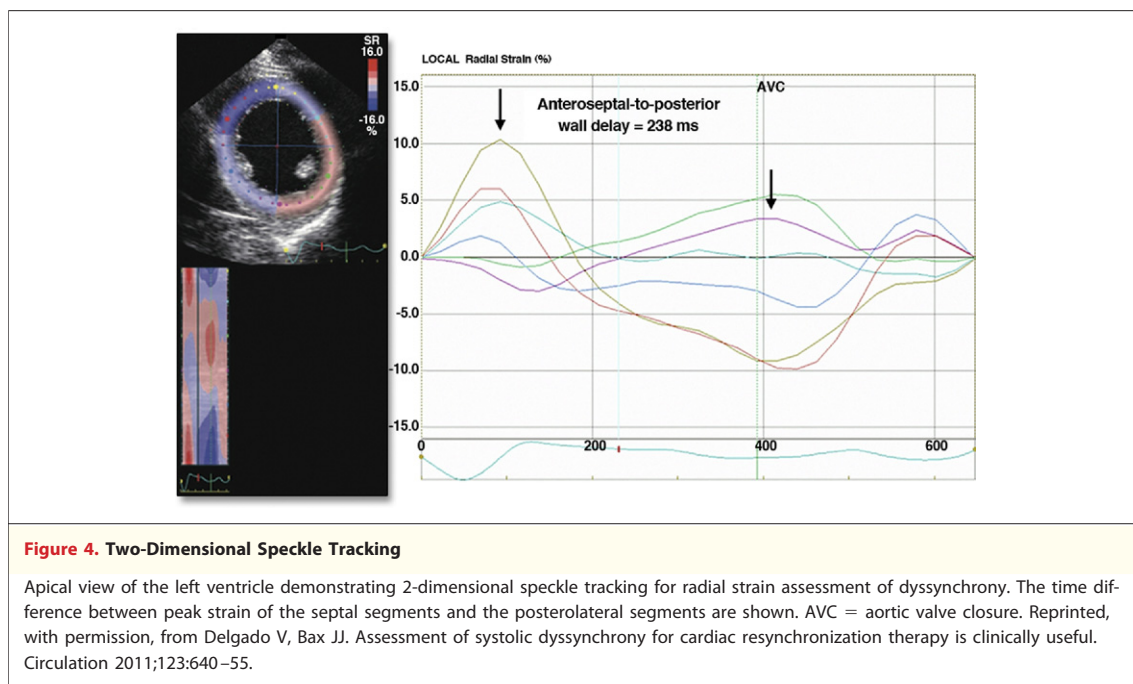
(A) Color-coded tissue velocity data from 12 left ventricular segments in a patient with dyssynchrony. (Left) Apical 4-chamber view, (middle) apical 3-chamber view, and (right) apical 2-chamber view. Arrows mark differences in time to peak velocity during systole for the various segments. (B) The same study after cardiac resynchronization therapy, with reduction in the disparity of time to peak activation. AVC = aortic valve closure; AVO = aortic valve opening. Reprinted, with permission, from Anderson LJ, Miyazaki C, Sutherland GR, Oh JK. Patient selection and echocardiographic assessment of dyssynchrony in cardiac resynchronization therapy. *Circulation* 2008;117:2009–23.

RT3D echocardiography in guiding CRT or its association with cardiac outcomes.

The PROSPECT trial. Despite the development of numerous echocardiographic methods to assess dyssynchrony in the past decade, many of the studies evaluating these techniques have fallen under scrutiny for reasons including single-center experience with limited study populations, absence of control arms, and controversial end points with surrogate markers of outcomes. Furthermore, most studies included largely retrospective data from echocardiographic registries, different threshold cutoffs for the same technique, short follow-up, and lack of randomization, blinding, or reporting of intraobserver and interobserver variability. Numerous studies have used the surrogate outcome measure of reverse remodeling, defined as a reduction in LV end-systolic volume of $\geq 10\%$ to 15% , as opposed to hard clinical end points. Although some studies have correlated reverse remodeling to clinical outcomes, other studies have demonstrated clinical response in patients without reverse remodeling (40). Post hoc analysis of the Cardiac Resynchronization–Heart Failure study failed to demonstrate

an independent association of reverse remodeling at 3 months after CRT with mortality (2). Another concern includes different threshold cutoffs among different studies for the same echocardiographic parameter, some of which have also been shown in asymptomatic, normal subjects (41). Finally, many single-center studies have not reported 95% confidence intervals, suggesting wide boundaries that may limit clinical utility.

To obtain a more comprehensive evaluation of echocardiographic parameters for dyssynchrony, a large, nonrandomized, multicenter trial (PROSPECT) was performed in 498 patients with HF with standard indications for CRT (39). Twelve different echocardiographic measures of dyssynchrony were evaluated. The study included blinded analysis performed by international core laboratories for the outcome measures of clinical composite score and LV reverse remodeling. None of the 12 echocardiographic methods proved to be sensitive or specific enough to be clinically useful for predicting response to CRT. The PROSPECT study demonstrated a high variance of TDI measurements owing to a number of factors inherent to the



determination of these values, including operator dependence, angle of interrogation, and acoustic windows. Even the same patient with repeated studies over time had significant variation in the echocardiographic dyssynchrony parameters. Although the PROSPECT study has been criticized for a number of design issues, at the time of the trial, many of the echocardiographic parameters being evaluated were still novel, and most centers did not have extensive experience with their evaluation. More recent analysis of the PROSPECT study revealed an association between the extent of LV dyssynchrony at baseline and the extent of reverse remodeling at 6-month follow-up (40). Whether the results of the PROSPECT trial are generalizable to today's standard of dyssynchrony assessment remains in contention.

Echocardiography may also play a significant role in serial follow-up of patients for optimization of CRT. In addition to continued noninvasive assessment of remodeling and ventricular function, optimization of pacemaker atrioventricular delay and right ventricular–LV lead intervals may avoid residual dyssynchrony after CRT implantation. Despite early promising data suggesting benefit, the multicenter, prospective SMART-AV (SmartDelay Determined AV Optimization) trial demonstrated no difference in the primary end point of HF-related adverse events at 6 months (42). A second study, which compared an electronic algorithm to echocardiographic optimization of CRT, also found no difference for HF composite score in

more than 1,600 patients (43). Although proponents of echocardiographic optimization argue that these studies did not target nonresponders, who may have the greatest potential for benefit, further evaluation is clearly required.

Magnetic Resonance Imaging

Recently, CMR has gained increasing attention for dyssynchrony assessment because of its high tissue and spatial contrast, coupled with highly accurate and reproducible assessment of LV volume and functional indexes. CMR techniques to assess dyssynchrony are rapidly expanding and are presently under evaluation in a number of studies.

MRI dyssynchrony. The advantages of contrast medium-enhanced CMR include high spatial resolution and tissue characterization, in addition to highly accurate quantification of chamber size and ventricular function and 3-dimensional assessment of myocardial strain. Compared with echocardiography, CMR has high reproducibility owing largely to tomographic imaging with less operator dependency. Disadvantages of CMR include long acquisition times, implanted cardiac devices as magnetic resonance hazards, and complex post-processing techniques. In recent years, newer methods have improved the efficiency and standardization of post-processing.

The most basic assessment of dyssynchrony by CMR is achieved with cine MRI, which produces a

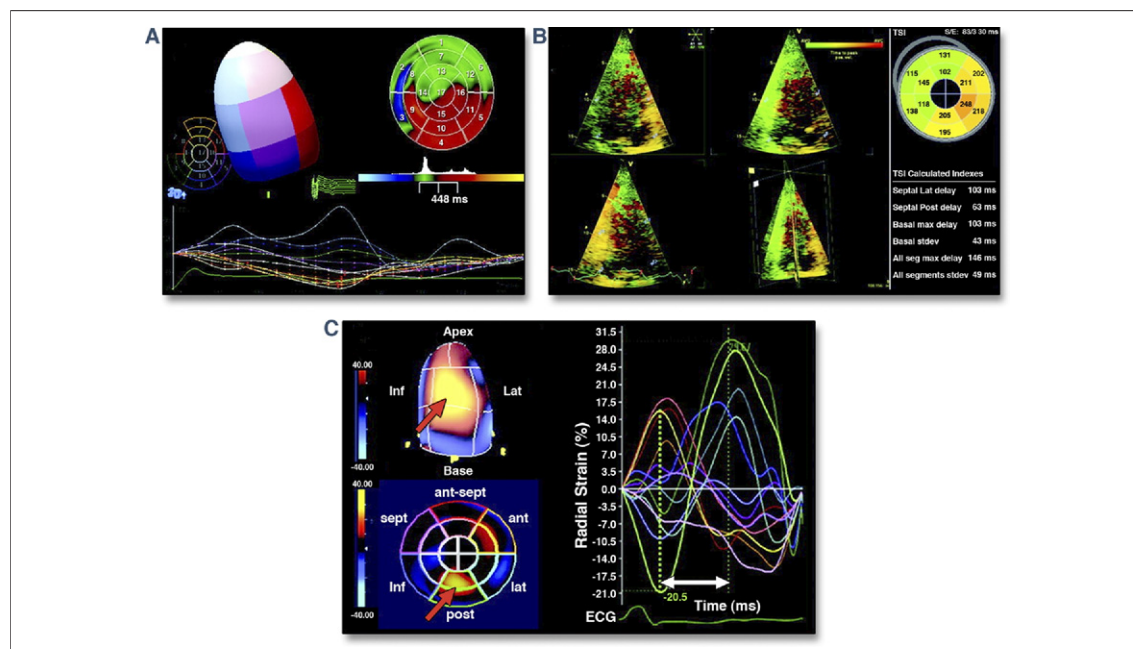


Figure 5. Three-Dimensional Echocardiographic Evaluation of Dyssynchrony

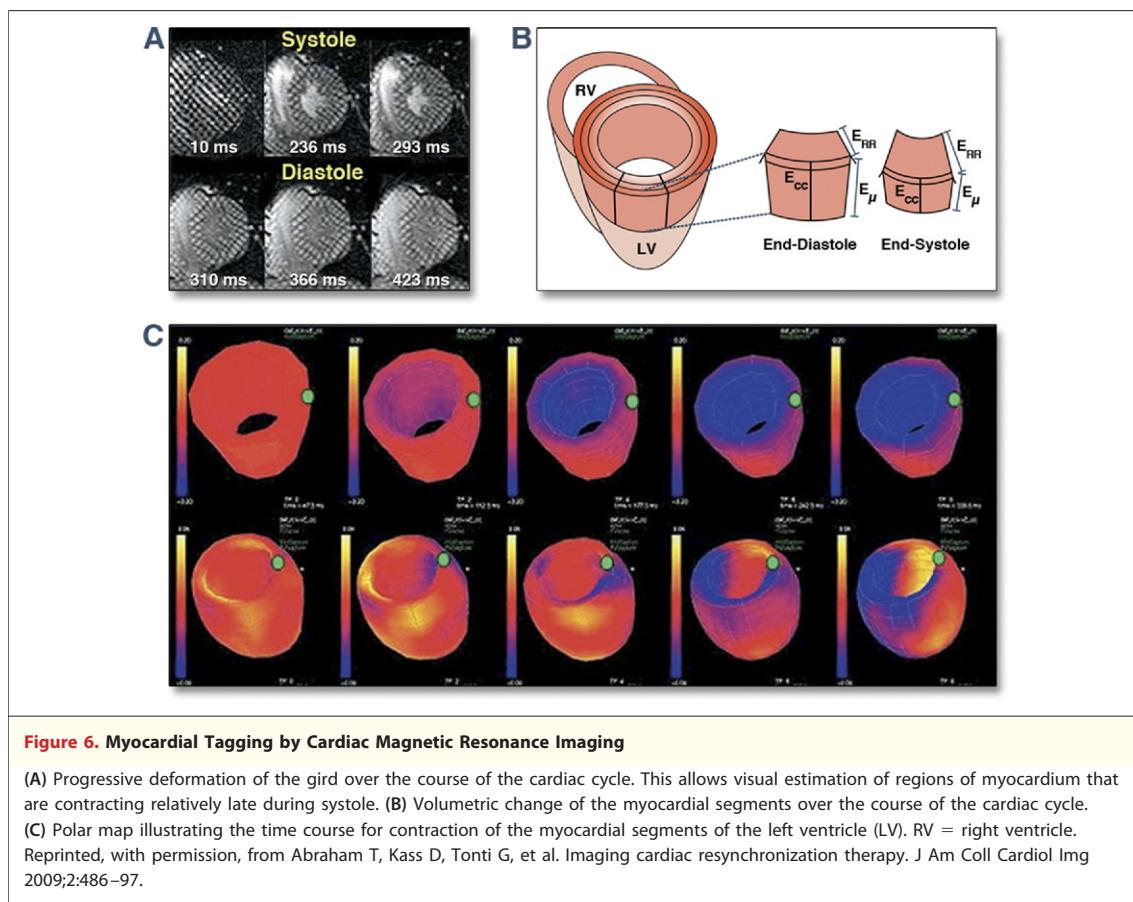
(A) Systolic dyssynchrony index used to evaluate left ventricular (LV) mechanical dyssynchrony calculated from the standard deviation (stdev) of time to minimal systolic regional volume of the 17-segment LV model. (B) Time dispersion map relating relative regional delay to contraction of the left ventricle. The green regions represent earliest myocardial contraction, while orange and red regions are the latest to contract. (C) Three-dimensional speckle tracking for assessment of strain. The time dispersion to peak strain may be calculated (radial strain is shown). A polar map denoting relative regional delay (blue earliest, yellow latest) also provides visual assessment of dyssynchrony. ant = anterior; ECG = electrocardiogram; inf = inferior; lat = lateral; max = maximal; post = posterior; seg = segments; sept = septal; TSI = tissue synchronization index. Reprinted, with permission, from Delgado V, Bax JJ. Assessment of systolic dyssynchrony for cardiac resynchronization therapy is clinically useful. *Circulation* 2011;123:640–55.

continuous series of oblique, short-axis slices from the ventricular apex to the base. This allows accurate volumetric assessment of chamber sizes and ventricular function indexes, such as stroke volume and LVEF. Interventricular and intraventricular dyssynchrony may be assessed qualitatively or quantitatively with software that tracks the myocardium during the cardiac cycle (44). Although cine MRI is acquired routinely, it is not particularly optimized for evaluation of regional dyssynchrony. More direct methods have been developed that provide more accurate and direct assessment of intramyocardial deformation, including myocardial tagging, strain-encoded MRI (SENC), phase-contrast MRI, and displacement encoding with stimulated echoes (DENSE), amongst others.

Myocardial tagging. Myocardial tagging is analogous to speckle tracking by echocardiography but with higher spatial resolution and reproducibility. Myocardial tagging is achieved by creating dark tagged lines or a grid over the myocardium through saturation of the magnetization in planes perpendicular to the imaged slice (Fig. 6). Tag lines enable an accurate analysis of myocardial motion and dis-

placement, which has been shown to be a robust method for assessment of both intraventricular and interventricular dyssynchrony (45). Newer methods of tagging, such as spatial modulation of magnetization, have resulted in shorter acquisition times and improved image quality of the myocardial tags (46).

Most echocardiographic techniques, apart from speckle tracking and RT3D imaging, are limited to the assessment of longitudinal strain. Data from animal models, in addition to more recent echocardiographic studies using speckle tracking, suggest that circumferential and radial strain more accurately predict response to CRT (27). Although 2-dimensional myocardial tagging can assess both circumferential and radial strain, the ability to track myocardial motion in 3 dimensions by inclusion of tagged long-axis cine imaging is an attractive extension that would also permit the assessment of longitudinal strain (47). Recently, 3-dimensional tagging with CMR has become more straightforward to analyze with the use of a post-processing technique termed harmonic phase imaging. The significant advantage of harmonic phase imaging relates to almost observer-independent estimation



of myocardial strains that permits quick and accurate post-processing of tagged cine images. Data from myocardial tagging may be used to produce myocardial strain-versus-time plots for the various ventricular walls that may be displayed and read similarly to a 12-lead electrocardiogram (48).

By directly tracking intramyocardial motion across the cardiac cycle, myocardial tagging may provide more specific assessment of myocardial deformation than TDI by differentiating regional strain abnormalities due to intrinsic abnormalities of myocardial contraction from passive tethering. TDI is more susceptible to errors from rotational motion of the heart and passive tethering as a result of determining myocardial velocity with respect to the mitral valve annulus or ultrasound transducer as opposed to the myocardium itself. Comparison with TDI has demonstrated higher specificity for dyssynchrony by myocardial tagging (17). Circumferential strain as assessed by tagging has also shown high correlation with LV volume curves assessed by RT3D echocardiography (49). A further advantage of myocardial tagging relates to the derivation of circumferential strain through assess-

ment of the entire myocardium, as opposed to using specific myocardial segments. True 3-dimensional assessment for regional dyssynchrony, in addition to determination of the extent of dyssynchronous myocardium, may be performed to differentiate those patients with diffusely dyssynchronous segments from those with clustered dyssynchronous segments within a particular wall, who may have a very different response to CRT. Use of a dyssynchrony index derived from myocardial tagging with CMR in a single-center study was highly predictive of improved functional class after CRT (50). Accuracy was further improved by the addition of late gadolinium enhancement imaging for the identification of myocardial scar.

SENC. SENC is another method for the assessment of dyssynchrony that involves using sinusoidal “tagged” surfaces that modulate longitudinal magnetization perpendicular to the imaging plane. Myocardial deformation during the cardiac cycle alters the local tag frequency in both the longitudinal and circumferential directions, which may be automatically detected and represented by a color scale as myocardial strain (51). This markedly

reduces any required post-processing, as with myocardial tagging, and has further advantages of high temporal and spatial resolution, in addition to extremely short acquisition time. SENC may be used to simultaneously assess regional strain of the right ventricle in addition to the left ventricle. SENC is limited by a requirement for sinusoidal magnetization modulation perpendicular to the image plane, which effectively precludes the assessment of radial strains. Both myocardial viability and regional strain may be simultaneously acquired with composite SENC, correlating regional strain with the extent of scar, which is highly desirable for CRT assessment (52). SENC and a method of performing fast SENC with an acquisition duration of only 1 heartbeat have shown excellent correlation with myocardial tagging (53). However, to date, no clinical outcome studies for CRT have been performed evaluating SENC or any of its derivatives.

Phase-contrast MRI. Phase-contrast velocity mapping uses the shift in phase of the myocardium between 2 opposing pulse gradients, which is proportional to the velocity of the myocardium. A color or gray scale is used to represent the magnitude and direction of tissue displacement in 3 dimensions. This method provides high temporal (2 ms) and spatial resolution and does not require the use of “tags” or segmentation of the myocardium. This is the CMR technique most similar in terms of imaging concept to TDI and has shown high correlation with the echocardiographic method (54). To date, there is a relative paucity of data assessing clinical response to CRT using phase-contrast MRI.

DENSE. DENSE encodes positional information into the phase of each image pixel. Therefore, the spatial resolution of DENSE is limited to only a single pixel (55). Using DENSE imaging, myocardial deformation may be tracked in 3 dimensions over the course of the cardiac cycle and is amenable to automated post-processing. DENSE imaging has been shown to have high correlation with myocardial tagging for regional wall motion abnormalities (56). However, similar to other CMR techniques, DENSE imaging has not been studied in relation to clinical response to CRT.

Presently, the above CMR methods provide a wealth of 3-dimensional data over the entire cardiac cycle. Future directions include a method of integrating this data into a simplified and standardized dyssynchrony index that may be used to efficiently screen and follow patients with CRT over time. One such index proposed by Leclercq *et al.* (57) uses strain data from the entire myocardium to derive a global dys-

synchrony score graded from 0 (pure dyssynchrony) to 1 (pure synchrony). This index has been used both to determine optimal LV lead placement (58) as well as for predicting clinical response to CRT.

Late gadolinium enhancement. One particular attribute of CMR is the potential to provide an integrated assessment for CRT. CMR can delineate chamber size and function with high accuracy, assess prognosis, determine myocardial perfusion, and help guide lead placement through assessment of the extent and location of myocardial scar and coronary venous anatomy, all in addition to dyssynchrony. This holistic evaluation may more accurately and cost-effectively screen patients for CRT. However, the relative contraindication of performing CMR in patients with a device pre-

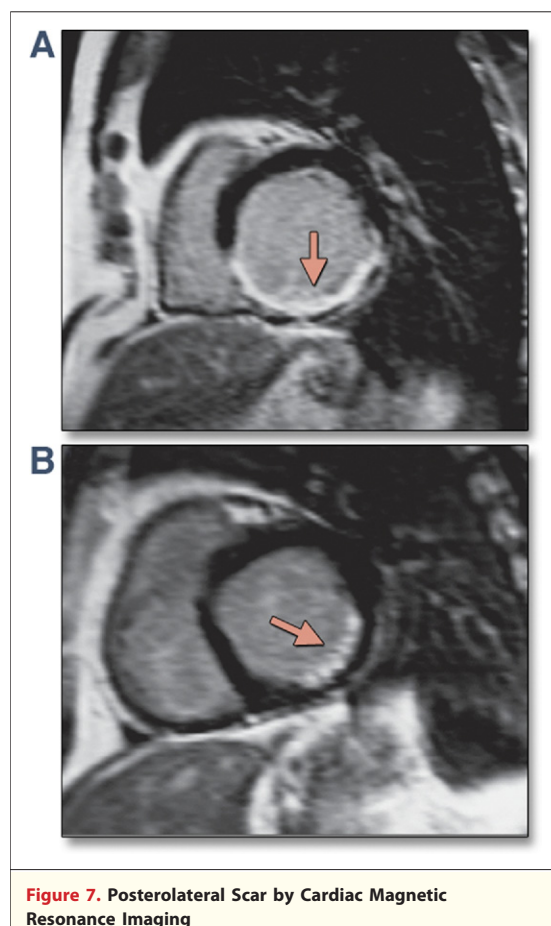


Figure 7. Posterolateral Scar by Cardiac Magnetic Resonance Imaging

(A,B) Late gadolinium enhancement images by cardiac magnetic resonance imaging demonstrating dense posterolateral scar in the left ventricle. Reprinted, with permission, from Bax JJ, Gorgsan J III. Echocardiography and noninvasive imaging in cardiac resynchronization therapy: results of the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) study in perspective. *J Am Coll Cardiol* 2009;53:1933–43.

cludes using CMR to evaluate device therapy for serial follow-up.

Multiple observational studies have suggested that the extent of myocardial scar is predictive of response to CRT (59–61). Furthermore, scar in the location of LV lead placement may reduce the effectiveness of CRT (60) (Fig. 7). One study of 40 patients with ischemic cardiomyopathy found lower response rates to CRT and no change in dyssynchrony for those with posterolateral scar (14% vs. 81%, $p < 0.05$) compared with those without (60). Another study of 23 patients reported that a cutoff value of 15% total LV myocardial scar provided sensitivity and specificity of 85% and 90%, respectively, for clinical response to CRT (59). Other studies have shown that pacing in a site with $<50\%$ scar transmural was associated with response to CRT (61).

Radionuclide Imaging

Similar to CMR, radionuclide imaging represents an attractive option for the selection of CRT in patients with HF because of its potential for comprehensive evaluation of LVEF and degree of myo-

cardial scar, in addition to mechanical dyssynchrony. Abnormalities of resting perfusion assessed by single-photon emission computed tomographic imaging have been associated with reduced improvement of functional and ventricular parameters after CRT (62). In addition to these parameters, phase analysis imaging from routine gated myocardial perfusion single-photon emission computed tomography (GMPS) may be used for dyssynchrony assessment (63). GMPS evaluates the pattern of ventricular activation through determination of regional LV counts during the cardiac cycle. An increase in counts is believed to correlate with regional LV wall thickening and may be used to assess the pattern of systolic contraction. Data from the entire myocardium are used to generate a phase distribution map that may be displayed as a histogram or polar map (Fig. 8).

Phase imaging analysis with GMPS for the identification of dyssynchrony has been validated in studies using TDI by echocardiography (63). The degree of LV dyssynchrony as assessed by GMPS was also shown to correlate with response to CRT in a study of 42 patients with severe LV dysfunction

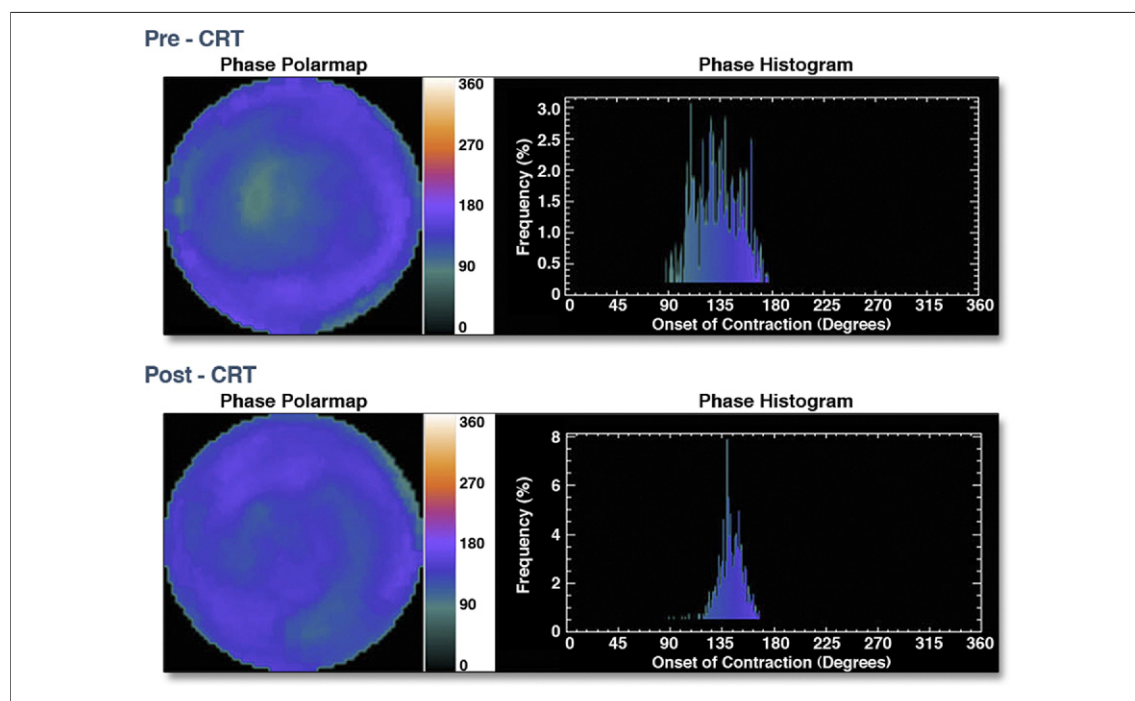


Figure 8. GMPS Phase Polar Map and Phase Histogram

Gated myocardial perfusion single-photon emission computed tomography (GMPS) phase polar map before (top left) and after (bottom left) cardiac resynchronization therapy (CRT). The colored phase polar map demonstrates delayed contraction of the lateral wall compared with the septum before CRT, which corrects after CRT. The phase histogram before CRT (top right) demonstrates a wide bandwidth consistent with delayed contraction of the lateral wall compared with the septum. The phase histogram narrows after CRT (bottom right), consistent with more synchronized contraction. Reprinted, with permission, from Friehling M, Soman P. Newer applications of nuclear cardiology in systolic heart failure: detecting coronary artery disease and guiding device therapy. *Curr Heart Fail Rep* 2011;8:106–12.

(64). A recent study evaluated the use of GMPS to determine the site of latest LV activation for LV lead placement and found a significantly higher response rate for patients with GMPS-guided LV lead placement, defined as a decrease of $\geq 15\%$ in LV end-systolic volume (65).

Another method of phase imaging analysis from gated blood-pool ventriculography may also evaluate mechanical dyssynchrony. This method was evaluated in a study of 103 patients with idiopathic dilated cardiomyopathy and was shown to be a significant predictor of adverse clinical outcomes in multivariate analysis (66). However, this technique requires sophisticated post-processing to carefully identify ventricular regions while excluding extra-cardiac structures and remains largely investigational.

A number of limitations of nuclear dyssynchrony assessment, including sophisticated post-processing techniques, potentially hazardous radiation exposure, and limited spatial resolution, have limited more widespread use. Limited spatial resolution not only affects dyssynchrony assessment but may also lead to overestimation of scar and concomitant underestimation of myocardial viability, particularly in this patient population with dilated cardiomyopathies and thin myocardial walls. Finally, studies to date evaluating GMPS have been small, single-center experiences, which have mostly evaluated secondary outcome measures.

Cardiac Computed Tomography

Mechanical dyssynchrony assessment by cardiac computed tomography (CCT) has previously been limited by poor temporal resolution. However, since the advent of dual-source multidetector computed tomography, both temporal and spatial resolution have significantly improved, redefining the role of CCT for the assessment of patients with HF.

CCT may be especially useful to help guide endocardial LV lead placement for CRT. Apart from prolonged procedure times with resultant increased risk for periprocedural complications and radiation exposure, inadequate LV lead position may lead to poor response to CRT. Pre-procedural use of CCT to characterize venous anatomy may substantially aid in LV lead placement (Fig. 9). One prospective, single-center study of 22 patients (9 with pre-procedural CCT and 13 without) reported decreased procedural times, use of contrast media, and radiation exposure (67).

Truong *et al.* (68) recently evaluated the utility of CCT for dyssynchrony assessment in a study of 38

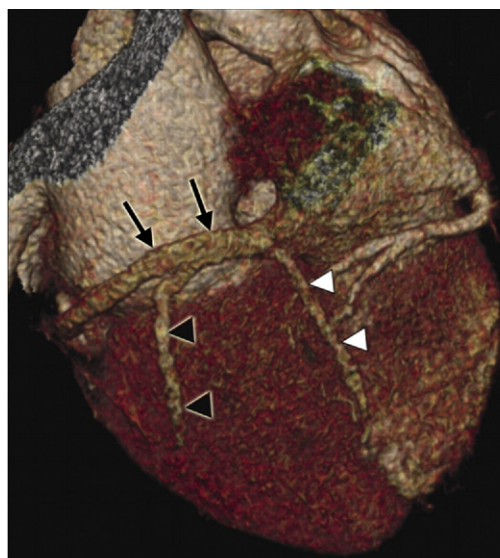


Figure 9. Volume-Rendered Image of the Coronary Sinus

Volume-rendered cardiac computed tomographic image of the coronary sinus (black arrows). The posterior vein of the left ventricle (black arrowheads) and posterior interventricular vein (white arrowheads) may also be visualized. Reprinted, with permission, from Gopalan D, Raj V, Hoey ETD. Cardiac CT: non-coronary applications. *Postgrad Med J* 2010;86:165–73.

patients with HF and normal controls. They devised an index of dyssynchrony on the basis of the standard deviation of time from the R-wave of the electrocardiogram to maximal wall thickness as assessed by CCT. Although they found a significant difference for the dyssynchrony index in patients with HF compared with the normal controls, comparison with echocardiographic measures of dyssynchrony demonstrated only a moderate correlation ($r = 0.65$, $p = 0.012$). LV structure and function assessment by CCT has also improved, although CCT has not performed as well in patients with LV dysfunction, with a tendency to overestimate LVEF (69). The use of dual-source multidetector computed tomography may identify and quantitate scar burden within the myocardium. This technique has been validated against CMR, although contrast-to-noise ratio is inferior with CCT (70). To date, no clinical studies evaluating CRT response with CCT localization of scar or dyssynchrony have been conducted.

CCT represents a promising tool for the investigation of patients with HF. Similar to radionuclide assessment, CCT is associated with ionizing radiation exposure, particularly in cases in which retrospective electrocardiographic gating is required for acquisition of the entire cardiac cycle.

Conclusions

CRT has demonstrated significant clinical benefits for patients with HF refractory to medical therapy. Despite advances in cardiac imaging over the past decade, there are still no imaging parameters that are routinely indicated to guide CRT therapy. To date, the major modality investigated for dyssynchrony assessment and measuring response to CRT has been echocardiography. Despite the large body of evidence that has quickly accrued, none of the numerous quantitative variables from echocardiography have been shown to achieve adequate robustness to be recommended for guidance of CRT. However, with increasing experience and technical expertise, many echocardiographic laboratories are demonstrating higher reproducibility and accuracy for

mechanical dyssynchrony. This has been coupled with studies examining harder clinical end points for outcome measures after CRT. Furthermore, novel imaging methods have shown great promise from both a technical and a physiological standpoint in assessing mechanical dyssynchrony. Future randomized control trials are required to determine whether imaging studies can provide more targeted CRT selection to reduce nonresponsiveness and complications related to CRT and ultimately provide more efficient health care expenditure.

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