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FROM PICTURES TO PRACTICE PARADIGMS

Imaging Cardiac Resynchronization Therapy

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Although a prognostic benefit has been shown from cardiac resynchronization therapy, questions are often directed toward the prediction of symptomatic or functional benefit. Recent multicenter trials have shown the pitfalls of current mechanical markers of left ventricular synchrony, but these negative trial results have not marked the conclusion of efforts to predict outcome. Potential new contributors to the assessment of mechanical synchrony include echocardiographic and magnetic resonance techniques for the assessment of myocardial deformation. Nonsynchrony markers that seem promising include assessment of the location and extent of myocardial scar and imaging of the coronary venous and phrenic nerve anatomy. (J Am Coll Cardiol Img 2009;2:486–97) © 2009 by the American College of Cardiology Foundation

In the last 2 years, 2 important multicenter trials involving 172 (1) and nearly 500 (2) patients showed failure of mechanical markers of left ventricular (LV) synchrony to predict outcome after cardiac resynchronization therapy (CRT). These findings contradicted a number of single center studies, reviewed elsewhere (3), suggesting that mechanical markers of LV synchrony could predict outcome after CRT. The negative trial results have not marked the conclusion of efforts to predict outcome from CRT, and indeed, a less well publicized multicenter study of 161 patients (4) showed that imaging of both synchrony and nonsynchrony markers could predict response. The goal of this review is to evaluate the role of imaging (not just of dyssynchrony) to the evaluation of potential candidates for CRT.

Defining the Benefits of CRT in Populations and Individuals

The use of CRT began with a series of acute studies in patients with depressed LV function,

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showing improvement in invasive hemodynamic parameters (5) and echocardiographic manifestations of LV dyssynchrony and stroke volume (6). After encouraging studies of acute and longer-term clinical effects (7–9), several randomized controlled trials involving >4,000 patients established the role for CRT in heart failure (10–16). These results have given a strong mandate for the routine use of CRT in eligible heart failure patients (Table 1).

In the context of this evidence base, the need to use imaging for the identification of mechanical synchrony might reasonably be questioned. However, the therapeutic expectations of patients in advanced heart failure are not restricted to survival but also functional status, which leads to the rather controversial definition as to whether an individual is a responder to CRT. Clinical end points (New York Heart Association functional class, quality of life score, exercise capacity expressed as 6-min walking distance), hemodynamic response, and echocardiographic end points (improved LV systolic function or reverse LV remodeling) have been used to evaluate response to CRT. Clinical assessment is subjective and unreliable given the placebo effect of CRT; 40% of patients randomized to no CRT experienced a significant reduction in symptoms. Acute hemodynamic response may not be predictive of long-term response. Changes in ejection fraction are modest, with most studies reporting an average improvement of 4% to 5%. Evidence of reverse remodeling provides an objective means of assessment of response to CRT—a 15% decrease in LV end-systolic volume (ESV) index with CRT has emerged as a consistent parameter of reverse remodeling and predictive of long-term clinical outcomes (17)—this is attained in about 60% of patients, in contrast with a clinical response rate in around 70%.

The CRT-responder concept should be applied with caution. First, there is little evidence to justify its application to considerations of survival. Although reverse remodeling is an important mediator of improved survival in heart failure, and seems to be associated with the response to CRT (17,18), a 9.5% reduction of ESV has a sensitivity and specificity of only 70% for prediction of mortality, and survival benefit from myocardial revascularization has been documented in the absence of reverse remodeling (19). Second, there are problems with trying to make this distinction on the basis of mechanical markers of LV synchrony. Third, although changes in synchrony has been proposed as the sine qua non of CRT response (20), the effect of therapy could be mediated in other ways (21).

Definition of Dyssynchrony

Electrical dyssynchrony. The measurement of electrical dyssynchrony has ranged from the simple lumped QRS duration, used in all of the large multicenter trials of biventricular pacing therapy, to more complex electrical activation maps. The latter show early right heart stimulation that rapidly moves to the lateral free wall (this delay is about 70 ms in the canine heart). The mechanical map shows a slower spread of contraction but follows a similar pattern.

Electrical dyssynchrony involves the primary activation delay typically manifested by a widened QRS complex. The transformation of electrical into mechanical dyssynchrony is complex because the latter is not solely

ABBREVIATIONS AND ACRONYMS

2D = 2-dimensional
3D = 3-dimensional
CMR = cardiac magnetic resonance
CRT = cardiac resynchronization therapy
CS = coronary sinus
ICE = intracardiac echocardiography
LV = left ventricle/ventricular
RV = right ventricle/ventricular
TDE = tissue Doppler echocardiography

Table 1. Landmark Trials in CRT

Study (Ref. #)	NYHA Functional Class	QRS (ms)	Follow-Up (Months)	End Points
MIRACLE (16)*	III, IV	≥130	6	NYHA, QoL, 6MHW
MUSTIC SR (14)	III	>150	3	QoL, 6MHW, VO_2
MUSTIC AF (15)	III	>200†	3	QoL, 6MHW, VO_2
CONTAK CD (18)‡	III to IV	≥120	6	Composite
MIRACLE ICD (17)§	III to IV	≥130	6	NYHA, QoL, 6MHW, VO_2
COMPANION (20)	III, IV	≥120	12	Morbidity + mortality
CARE HF (19)	III, IV	≥120‖	29¶	Morbidity + mortality

Left ventricular ejection fraction ≤35% for all trials. *Includes 71 patients enrolled in 3-month pilot study. †RV-paced QRS. ‡Includes 248 patients enrolled in 3-month crossover phase. §Excludes class II patients. ‖Echo-based criteria for QRS <150 ms. ¶Average.
CARE-HF = Cardiac Resynchronization-Heart Failure; COMPANION = Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; CONTAK CD = CONTAK-Cardiac Defibrillator; CRT = cardiac resynchronization therapy; MIRACLE = Multicenter InSync Randomized Clinical Evaluation; MIRACLE ICD = Multicenter InSync Randomized Clinical Evaluation Implantable Cardioverter Defibrillator trial; MUSTIC AF = Multisite Stimulation in Cardiomyopathies–Atrial Fibrillation; MUSTIC SR = Multisite Stimulation in Cardiomyopathies–Sinus Rhythm; NYHA = New York Heart Association; 6 MHW = 6-min hall walking test; QoL = quality of life; VO_2 = maximum oxygen uptake.

JACC: CARDIOVASCULAR IMAGING, VOL. 2, NO. 4, 2009
APRIL 2009:486–97

determined by when the tissue is excited. Rather, mechanical events require the cellular process of excitation–contraction coupling to generate myocyte force, and are thus influenced by processes that control calcium cycling, myofilament calcium interactions, regional loading, fibrosis, and other factors (22). Indeed, disparities in the timing of regional mechanical function may not be coupled to electrical stimulation delay. This might be caused by regional loading differences, fibrosis, and contractile strength of one part of the wall versus another. Mechanical imaging methods detect motion of the muscle but not its activation process, and so cannot necessarily delineate mechanisms for apparent dyssynchrony. This is important because dyssynchrony caused by electrical delay can be targeted by CRT, whereas that caused by regional properties and/or loading disparities may not be.

Mechanical dyssynchrony. In left bundle branch block or right ventricular (RV) pacing, septal activation occurs first, and results in pre-stretch of the still-quiescent lateral wall, which consequently reduces the peak rate of pressure increase (dP/dt_{max}). The delayed lateral wall contraction generates systolic forces that are also partly dissipated by re-stretching the now-early-relaxing septal region, lowering net cardiac output. Discoordinate papillary muscle activation can further compromise overall LV function by exacerbating mitral regurgitation (23) (Fig. 1). Disparities in wall stiffening that generate discoordinate motion are most marked in early systole (isovolumic contraction, lowering dP/dt_{max}), and late systole as one territory enters relaxation ahead of the other (24).

Mechanical dyssynchrony has been measured by a range of imaging modalities, with the largest evidence base being accumulated with echocardiography (3). Respectively, 30% and 40% of patients who fulfill eligibility criteria for CRT do not show a symptomatic response or reverse remodeling (18). Thus, electrical dyssynchrony alone, as detected by electrocardiography, may not be the optimal predictor of CRT response. The concept of disconcordance between electrical and mechanical dyssynchrony was supported by an experimental study that showed improvement in ventricular hemodynamics with CRT despite no change in electrical dyssynchrony (25).

Imaging Approaches to Mechanical Dyssynchrony

Echocardiography. Standard echocardiographic markers of LV mechanical synchrony have been recently reviewed (3). The primary source of variation between these markers relates to how timing is assessed: the simplest are maximal time delays between early and late contracting or electrically stimulated regions, total number of regional areas that show delay, and variance in timing of motion around the heart. However, this can miss critical information regarding the geographic distribution of delays that ultimately generate functional dyssynchrony, and conversely, hearts with scattered heterogeneity of activation or contraction may not necessarily have much functional dyssynchrony. The alternative to these segmental approaches are various approaches to index dyssynchrony, including vector mapping that amplifies the index if the delayed regions are clustered together, as well as the so-called CURE (circumferential uniformity ratio

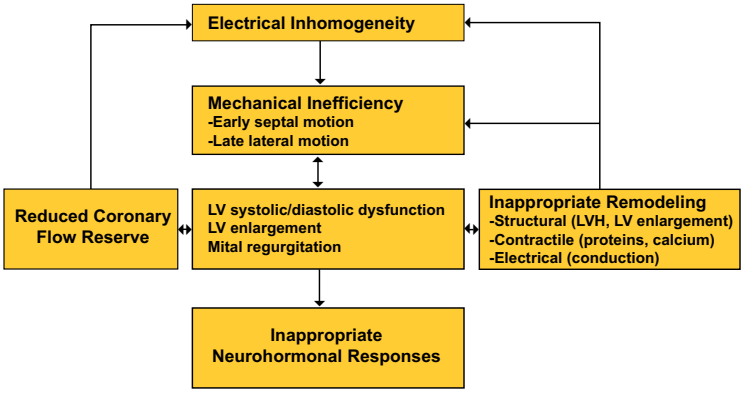

Figure 1. Contributors to Electrical and Mechanical Dyssynchrony

The contributors to mechanical delays include left ventricular (LV) remodelling, LV systolic and diastolic dysfunction, mitral regurgitation, coronary flow reserve, and neurohormonal changes. LVH = left ventricular hypertrophy.

estimate) index (26). These approaches can be applied to virtually any way of assessing electrical or mechanical dyssynchrony, and have the potential to enhance its specificity for therapeutic responsiveness. The second important variation relates to the orientation of the dyssynchrony measurements. Most tissue Doppler echocardiography (TDE) techniques provide data in the longitudinal orientation of the myocardium. However, most fibers are circumferentially oriented, and deformation in this dimension seems to provide a more reliable and stronger signal.

Despite a large evidence base with TDE, this form of analysis poses several problems. Signal noise is common, and variability between observers, often caused by the presence of multiple systolic peaks, seems to be a major problem (2). Second, the measurement of TDE time delays is time consuming, especially if multiple segments are interrogated. The development of parametric imaging techniques that color-code the segments based on time delay (27) may reduce spatial variation as well as save time (Fig. 2). Third, TDE examines the timing of contraction in a longitudinal direction, which may not be the optimal orientation for discerning both dyssynchrony and the impact of CRT (28). Recent data obtained using angle-corrected TDE show that radial velocities can also detect dyssynchrony and predict acute response to CRT (29).

Tissue velocity measures tissue motion relative to the transducer and is therefore susceptible to cardiac translational motion and tethering artifacts. Strain measurements are based on movement of tissue relative to its neighbor and are therefore site specific (30). Unfortunately, TDE-based strain analysis has not been shown to be superior to tissue velocity (31), likely reflecting the angle dependence of TDE analysis as well as signal-noise related problems. In contrast, speckle-tracking-based measurements of radial, circumferential, and longitudinal strain (32,33) seem to be both feasible and reliable (Fig. 3).

Quantitative analysis of dyssynchrony with 3-dimensional (3D) echocardiography requires border detection in a number of 2-dimensional (2D) slices, and creation of a 3D model from which time-volume data are obtained (34). The systolic dyssynchrony index, derived from the dispersion of time to minimum regional volume (Fig. 4), decreases after CRT. Unfortunately, the ability to compare timing of all myocardial segments with a 3D echocardiography approach is probably outweighed by limitations in edge detection and frame rates. This technique, speckle strain, and contrast variability imaging (35) are all the focus of current research.

Cardiac magnetic resonance (CMR). Potential advantages of CMR-based techniques for dyssynchrony assessment include high reproducibility, high spatial resolution, and the ability to obtain 3D information including circumferential mechanics (36), which may be superior to that obtained in the longitudinal direction (28). Myocardial tagging allows assessment of radial, longitudinal, and circum-

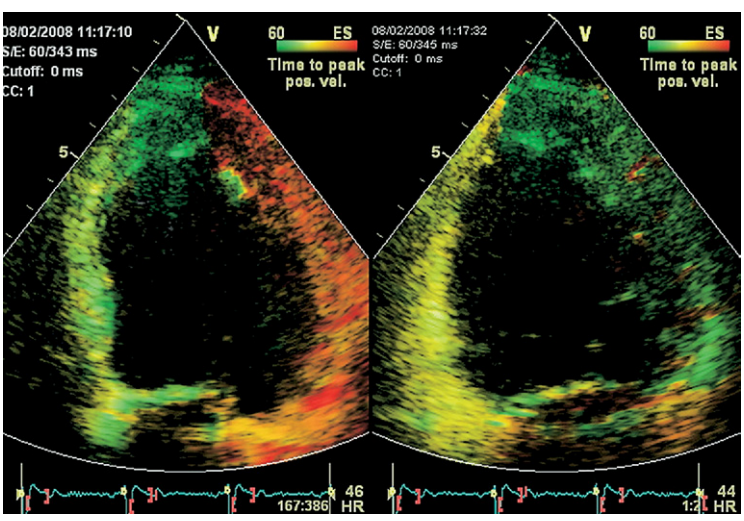

Figure 2. Parametric Display of Tissue Velocity

In this parametric display (often known by its proprietary name, tissue synchronization imaging), delayed activation of the posterolateral wall is evidenced by **red** coloration of the lateral and **yellow** coloration of the posterior walls.

JACC: CARDIOVASCULAR IMAGING, VOL. 2, NO. 4, 2009
APRIL 2009:486–97

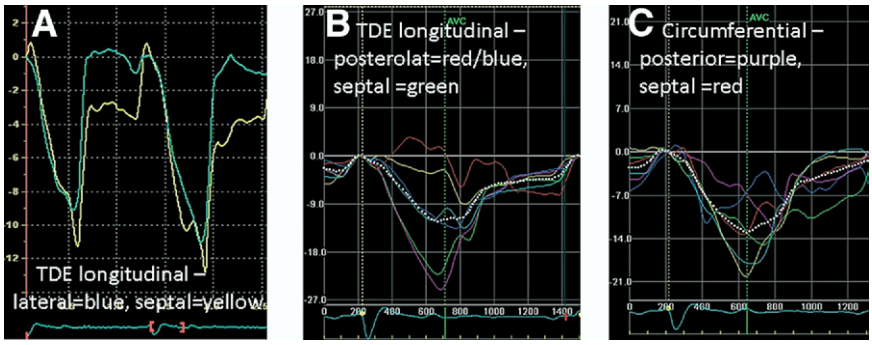

Figure 3. Assessment of Synchrony Using Tissue Doppler and Speckle Strain

Panel A shows synchronous septal **(yellow)** and lateral **(blue)** wall motion with tissue Doppler. **Panel B** shows delay between the septal **(green)** and posterolateral walls **(red and blue)** using longitudinal speckle strain, confirmed also with circumferential strain **(C)**. TDE = tissue Doppler echocardiography.

ferential strain by measurements between dark lines (markers or tags) left in the myocardium by special encoding pulses (Fig. 5). Recent advances that have drastically reduced analysis time include harmonic phase analysis of tagged CMR and strain-encoded CMR (37).

Three CMR indices have been used for measuring dyssynchrony. Regional variance is determined from the variance of strain magnitude in 28 radially displaced segments for each short-axis section (similar to the indices used in TDE), or the number of segments with delayed shortening as a percent of total regions examined (38) (Fig. 6). The regional variance vector is based on the product of a radial magnitude vector with a scalar representing time to maximal shortening (Fig. 6B). The resulting vector sum will only have significant magnitude if delayed versus early regions are geographically clustered (Fig. 6A, upper panel) (28). Lastly, regional strain uniformity is based on regional strain differences at a given moment in time. Time plots of strain (shortening/stretching) are generated at each of 28 evenly distributed segments around a short-axis slice (28). If segments shorten simultaneously (perfectly synchronous contraction), the plot appears as a straight line, whereas regionally clustered dyssynchrony generates an undulating plot. The relative ratio of first/zero-order magnitudes derived by Fourier analysis (Fig. 6C) generates an index known as the circumferential uniformity ratio estimate (28).

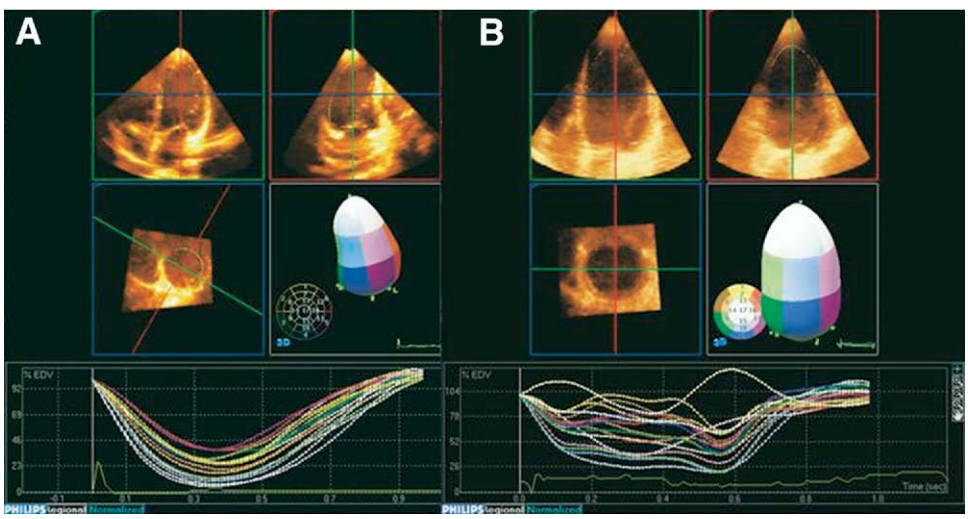

Figure 4. Evaluation of Synchrony Using 3-Dimensional Echocardiography

Uniform times to minimum volume indicate synchrony **(A)**. The dyssynchronous left ventricle is characterized by variation in times to minimum volume **(B)**.

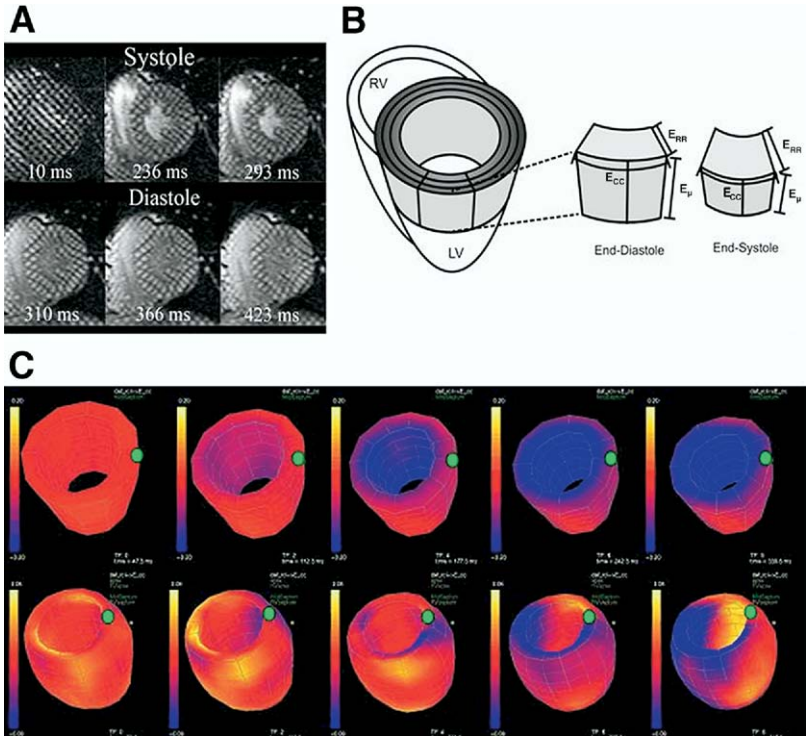

Figure 5. Use of Tagged Cardiac Magnetic Resonance for the Assessment of Synchrony

The progressive deformation of the grid **(A)** allows measurement of the time course of deformation in the principal axes of each segment **(B)**. The parametric display **(C)** shows the time course of contraction, which can be shown to be synchronous **(upper row)** or dyssynchronous **(lower row)**. RV = right ventricle; other abbreviation as in Figure 1.

Potential disadvantages of CMR include cost, long imaging time, availability, complex and long analysis times, and incompatibility with implanted devices. These technical problems will likely be solved, and CMR may become safe in patients with implanted devices.

Nuclear medicine techniques. When phase imaging is performed on perfusion scan data, segmental

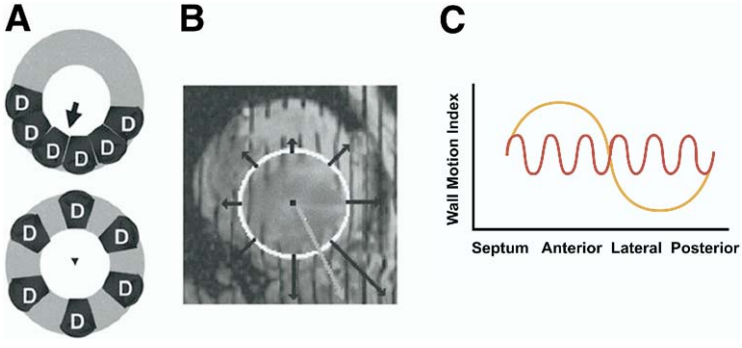

Figure 6. Cardiac Magnetic Resonance Techniques for Strain Measurement

The regional variance of strain **(A)** cannot differentiate identical variance of time to peak contraction between segments with delayed contraction clustered in 1 portion of the left ventricular wall **(A, top)**, versus dispersion of delay through the heart **(A, bottom)**; only the former displays dyssynchrony. The regional variance vector of principal strain **(B)** is based on the product of unit vectors with a scalar representing time at maximal shortening or instantaneous magnitude of shortening. Regional strain uniformity **(C)** provides a relative ratio of first/zero-order magnitudes derived by Fourier analysis. The heart with clustered regions **(A, top)** shows delays in 1 territory versus the other so this plot appears sinusoidal. Hearts with more variability **(A, bottom)** yield a higher frequency waveform.

JACC: CARDIOVASCULAR IMAGING, VOL. 2, NO. 4, 2009
APRIL 2009:486–97

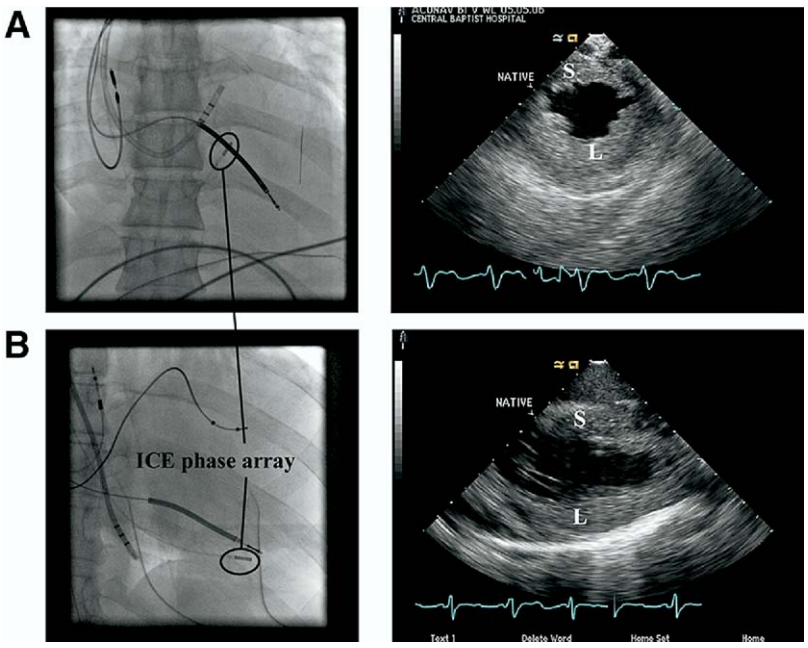

Figure 7. ICE

These typical intracardiac echocardiography (ICE) windows from catheter positions at the right ventricular base and apex show representative B-mode images in 2 different patients for short-axis **(A)** and long-axis **(B)** imaging. L = lateral wall, S = septum.

counts are proportionate to thickening. Although acquisitions are obtained at 8 frames/s, Fourier transformation of the data is believed to provide an effective temporal resolution of 75 frames/s. The results of nuclear imaging seem to correspond with those obtained with TDE (39), although the limited published data on CRT effectiveness indicate a sensitivity and specificity <80% (40).

The Role of Imaging in the EP Laboratory

Standard imaging approaches offer limited value during CRT implantation. Transthoracic echocardiography may disturb the sterile field, and poor acoustic windows are likely when optimal positioning is not possible. Transesophageal echocardiography requires a second operator.

Intracardiac echocardiography (ICE) is useful during implantation of biventricular devices, allows procedural sterility (the catheter is positioned in the right heart via a subclavian venous sheath), eliminates the need for a second operator, and provides excellent target resolution because of its close proximity (Fig. 7). Intraoperative ICE can facilitate cannulation of the coronary sinus (CS) by identifying the ostium, quantify the degree of mechanical dyssynchrony at the time of the procedure, and assess the acute response to CRT.

3D rotational angiography is an alternative that allows 3D chamber reconstruction at the time of intervention (Fig. 8) (41). This technique can serve

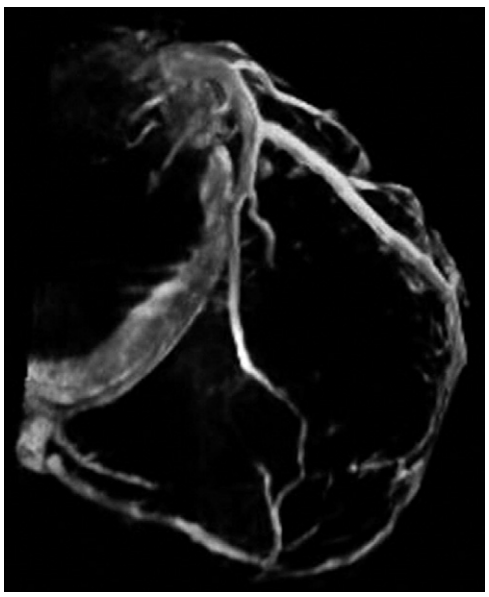

Figure 8. 3-Dimensional Rotational Angiography

This representative image from an electrocardiograph gated 3-dimensional rotational angiography show the coronary sinus and venous vasculature.

as a helpful tool during the implant by providing: 1) accurate 3D CS reconstruction; 2) multiangle visualization of the entire CS; 3) an endocardial view to evaluate branch take-off and valvular anatomy; and 4) accurate final LV lead tip position in relation to LV anatomy.

Nonresponse to CRT may be multifactorial, but incorrect positioning of the LV lead appears to be important; a lateral LV lead position may not be optimal for all patients. Intraoperative ICE can quantify the degree of mechanical dyssynchrony present at the time of the procedure, and with the use of additional echocardiographic parameters such as tissue Doppler velocity or strain measurements, can provide real-time physiologic information regarding CRT response (42) (Fig. 9).

Anatomical visualization and 3D reconstruction of cardiac chambers during implantation of CRT devices may be useful for facilitating lead localization and assess response. As technology continues to advance, cardiac imaging during EP interventions will contribute to better procedural success, reduce complications, and aid in the understanding of the interaction between electrical activation and anatomical substrates.

Post-Implantation Assessment in the CRT Patient

Echocardiography is a useful tool for the evaluation of therapeutic success during follow-up. Patients who do not show LV resynchronization do not show reverse remodeling after CRT (20). However, reverse remodeling needs time to occur, and more immediate effects of successful CRT include an improvement in LV ejection fraction and a reduction in mitral regurgitation, related to both increased closing force and improvement in interpapillary muscle synchrony (43). Late follow-up studies can be expected to show improved LV ejection fraction and reduced LVESV and LV end-diastolic volume, however, follow-up is usually at 6 months post-implantation and improvement may take up to 12 months, particularly in ischemic cardiomyopathy. Reverse remodeling is associated with a reduction in LV annular size and normalization of LV geometry, resulting in a further reduction in mitral regurgitation (44). Other changes include a reduction in RV size and decreases in tricuspid regurgitation and pulmonary artery pressure.

Echocardiographic atrioventricular optimization improves LV dP/dt_{max} and stroke volume acutely, and was performed in many effectiveness studies (45). The iterative method uses pulsed-wave Dopp-

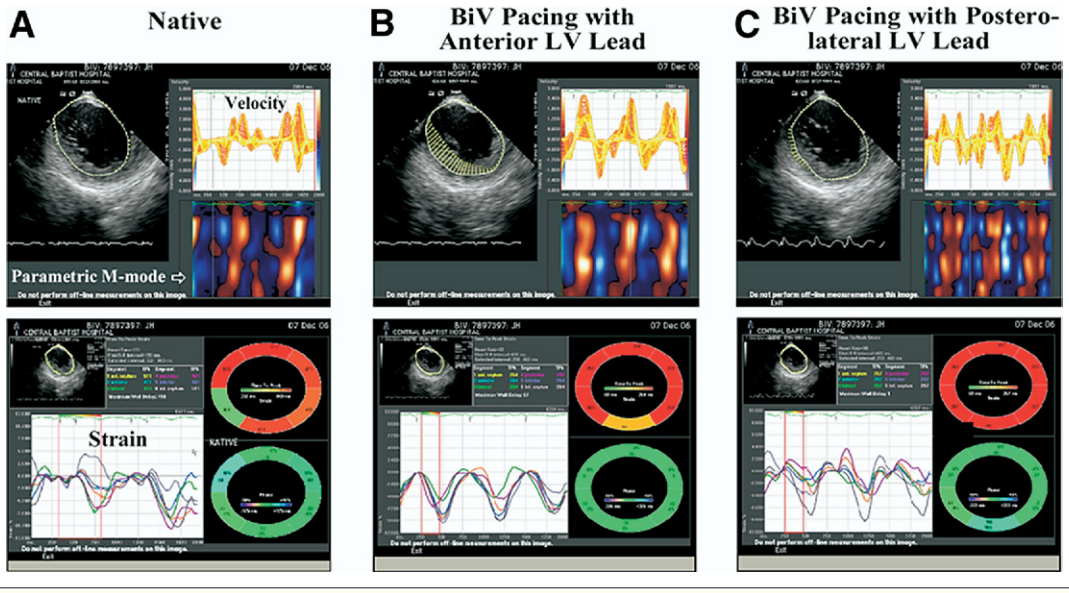

Figure 9. Use of On-Line Vector Velocity Imaging Analysis to Examine Synchrony in Short-Axis Images in Native and Paced States

In each state, velocity vectors are graphically represented in time and magnitude in **yellow/red** in the upper right, a parametric M-mode plot of systole **(red)** and diastole **(blue)** is seen below this, and B-mode image is broken into 6 segments automatically and a strain curve plotted for each **(bottom)**. The left ventricular (LV) dyssynchrony **(A)** is evidenced by nonalignment of strain and velocity vectors and a lack of clear separation of contracting and relaxing elements on the parametric M-mode plot. The biventricular (BiV) pacing with the LV lead in the anterior interventricular vein results to a significant reduction of dyssynchrony **(B)**. During BiV pacing with the LV lead in a posterolateral vein **(C)**, dyssynchrony does not seem to be improved.

JACC: CARDIOVASCULAR IMAGING, VOL. 2, NO. 4, 2009
APRIL 2009:486–97

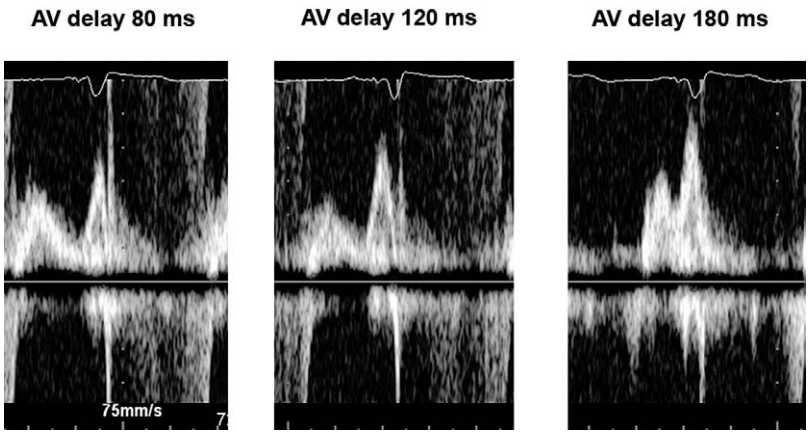

Figure 10. The Iterative Method for Atrioventricular Optimization

The sequence starts at a long atrioventricular (AV) delay (180 ms, shorter than intrinsic PR interval to ensure capture) and then shortening by 20-ms increments, until A-wave truncation appears (80 ms). Then atrioventricular delay is lengthened by 10-ms increments until A-wave truncation disappears and maximum E- and A-wave separation is provided.

ler imaging of mitral inflow (Fig. 10). Contemporary CRT devices permit programming of the ventricular-ventricular (VV) interval, but the contribution of VV optimization to improved systolic performance is controversial (45) (Fig. 11).

Patient Selection for CRT: Clinical Versus Imaging Criteria

Current criteria for CRT implantation include drug-refractory heart failure (New York Heart Association functional class III to IV), LV ejection fraction <35%, and a wide QRS complex (46). In the large CRT trials, Mollema et al. (47) showed that QRS duration alone yielded only a sensitivity and specificity of 53%, with an optimized cutoff value of 163 ms. Conversely, echocardiographic studies have shown that approximately 30% of patients with a wide QRS complex do not have evidence of LV dyssynchrony (as assessed by tissue Doppler imaging). As noted above, although single-center studies have shown a high accuracy of a variety

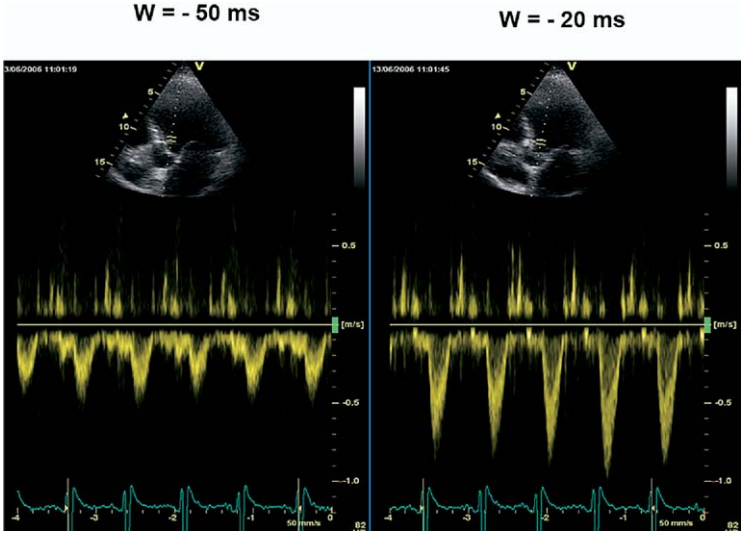

Figure 11. LV Stroke Volume During VV Optimization

Using 20-ms increments (starting at the left ventricle [LV] activated 80 ms before the right ventricle [RV], and ending at the RV activated 80 ms before the LV), the optimal ventricular-ventricular (VV) delay is the delay associated with the largest LV outflow tract velocity time integral.

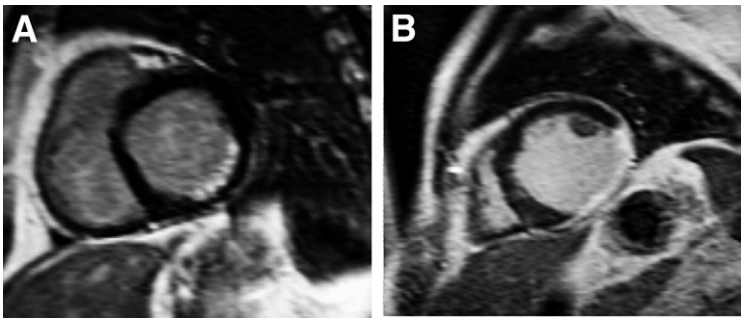

Figure 12. Contrast-Enhanced Cardiac Magnetic Resonance to Identify the Location and Thickness of Myocardial Scar

These examples of lateral scar show nontransmural **(A)** and transmural **(B)** scar thickness.

of parameters to predict CRT response, reliable measurement of LV dyssynchrony remains a work in progress. None of these different techniques was definitively superior in the PROSPECT (Predictors of Response to CRT) trial (2). Indeed, the message of this trial was that the reproducibility for these parameters was limited, and that both the sensitivity and the specificity of the echocardiographic techniques were modest.

How should these observations be incorporated into decision making? Patients with heart failure and a wide left bundle branch block but no mechanical dyssynchrony should not be denied CRT (3), although it is reasonable to have a dialog with the patient regarding the possibility of symptomatic or functional nonresponse. In the patient with congestive heart failure, systolic dysfunction, mechanical dyssynchrony and a narrow QRS, trial data do not currently justify the use of CRT (1).

Perhaps the focus on mechanical synchrony has been a distraction from more important contributions of imaging: the detection of scar, correspondence of pacing site and maximum VV delay, and RV and LV status. The presence of scar tissue in the target zone of the LV lead may limit response to CRT (48), and the total scar burden is also important (18). Contrast-enhanced CMR may provide delineation of scar tissue with the highest spatial resolution (Fig. 12). The LV lead is frequently not positioned in the site of latest mechanical activation, and patients with this lead position show a worse outcome (49–51). Provision of information on venous anatomy (Fig. 13) (52) or the cardiophrenic bundle (e.g., with multislice computed tomography) is important before CRT implantation.

Conclusions

Problems with the reproducibility of the current generation of imaging techniques has led to a degree of nihilism about imaging in resynchronization therapy. In fact, imaging has important

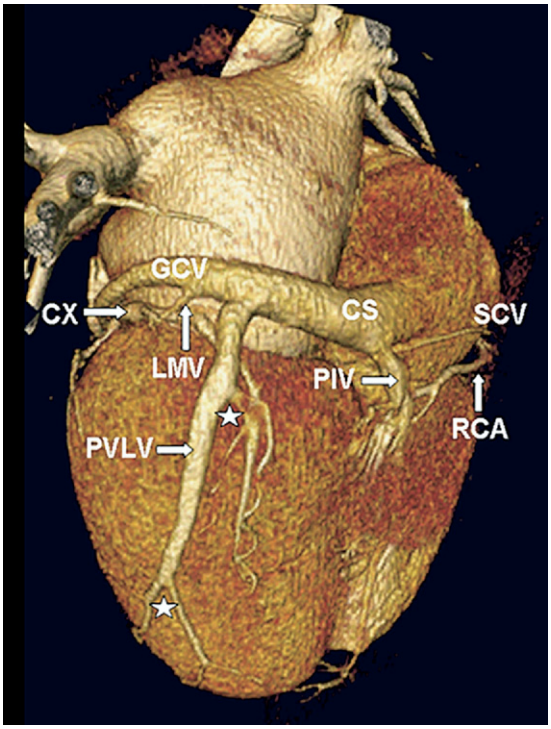

Figure 13. Use of Computed Tomographic Coronary Venography to Plan Lead Localization

This electrocardiograph-gated image shows the relationship of the right coronary artery (RCA) and left circumflex artery (CX) to the coronary sinus (CS), great cardiac vein (GCV) and superior cardiac vein (SCV), posterior interventricular vein (PIV) and left marginal veins (LMV), and posterior vein of the left ventricle (PVLV) and side branches (☆). Reprinted with permission from Van de Veire et al. (52).

JACC: CARDIOVASCULAR IMAGING, VOL. 2, NO. 4, 2009
APRIL 2009:486–97

contributions such as the characterization of LV and RV function and the assessment of myocardial viability and atrioventricular delay. Robust techniques of high temporal resolution are needed for the assessment of LV synchrony. At present, multiple imaging modalities contribute components of the decision matrix to proceed with this useful but not uniformly effective treatment modality.

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