Echocardiography for Cardiac Resynchronization Therapy: Recommendations for Performance and Reporting–A Report from the American Society of Echocardiography Dyssynchrony Writing Group *Endorsed by the Heart Rhythm Society*

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Echocardiography plays an evolving and important role in the care of heart failure patients treated with biventricular pacing, or cardiac resynchronization therapy (CRT). Numerous recent published reports have utilized echocardiographic techniques to potentially aide in patient selection for CRT prior to implantation and to optimized device settings afterwards. However, no ideal approach has yet been found. This consensus report evaluates the contemporary applications of echocardiography for CRT including relative strengths and technical limitations of several techniques and proposes guidelines regarding current and possible future clinical applications. Principal methods advised to qualify abnormalities in regional ventricular activation, known as dyssynchrony, include longitudinal velocities by color-coded tissue Doppler and the difference in left ventricular to right ventricular ejection using routine pulsed Doppler, or interventricular mechanical delay. Supplemental measures of radial dynamics which may be of additive value include septal-to-posterior wall delay using M-mode in patients with non-ischemic disease with technically high quality data, or using speckle tracking radial strain. A simplified post-CRT screening for atrioventricular optimization using Doppler mitral inflow velocities is also proposed. Since this is rapidly changing field with new information being added frequently, future modification and refinements in approach are anticipated to continue.

Keywords: Echocardiography, Doppler ultrasound, Congestive Heart Failure, Pacing Therapy

Echocardiography plays an important role in the care of patients with heart failure treated with cardiac resynchronization therapy (CRT). A large number of clinical reports have utilized echocardiography before CRT implantation to assess abnormalities of mechanical activation, known as dyssynchrony, to potentially improve patient selection or guide lead placement. In addition, echocardiography has been advocated to optimize the CRT device settings afterward. The purpose of this consensus report is to evaluate the contemporary state-of-the-art applications of echocardiography for CRT and to propose guidelines regarding current and potential future clinical applications. We acknowledge that this is a relatively young and rapidly changing field with new information being discovered continually. Because no optimal approach has yet been clearly defined, the strengths and limitations of the principal current techniques will be discussed along with practical recommendations.

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CLINICAL BENEFITS OF RESYNCHRONIZATION THERAPY

CRT has had a major favorable impact on the care of patients with heart failure, left ventricular (LV) systolic dysfunction, and mechanical dyssynchrony, routinely identified by electrocardiography (ECG) as abnormal electrical activation. CRT, also referred to as biventricular pacing, has been shown in several randomized clinical trials to improve heart failure functional class, exercise capacity, and quality of life, in addition to reducing hospitalizations and prolonging survival[1-7]

Table 1 Summary of important clinical trials of cardiac resynchronization therapy

	MUSTIC	PATH-CHF	MIRACLE	MIRACLE-ICD
Inclusion criteria	NYHA III LVEF < 35% EDD > 60 mm 6-min walk < 450 m QRS ≥ 150 ms	NYHA III, IV QRS ≥ 120 ms	NYHA III, IV LVEF ≤ 35% EDD ≥ 55 mm QRS ≥ 130 ms	NYHA III, IV LVEF ≤ 35% EDD ≥ 55 mm QRS ≥ 130 ms ICD indication
Sample	58	40	453	369
End points	QOL, 6-min walk, peak VO_2, HF hospitalization	Acute hemodynamics QOL, 6-min walk, HF hospitalization	QOL, NYHA class, 6-min walk, composite	QOL, NYHA class, 6-min walk
Study design	Single-blind, randomized, crossover	Single-blind, randomized, crossover	Double-blind, randomized, parallel-controlled	Double-blind, randomized, parallel-controlled
Treatment arms	CRT vs no pacing	CRT vs no pacing	CRT vs no pacing	CRT-D vs ICD
Major findings	CRT improved all end points, reduced hospitalization	CRT improved acute hemodynamics and chronic end points	CRT improved all end points; reduced HF hospitalization	CRT improved QOL and NYHA class only, and did not impair ICD function

	CONTAK	COMPANION	CARE-HF
Inclusion criteria	NYHA II-IV LVEF ≤ 35% QRS ≥ 120 ms ICD indication	NYHA III, IV LVEF ≤ 35% QRS ≥ 120 ms	NYHA III, IV LVEF ≤ 35% QRS > 150 ms or QRS = 120-150 with dyssynchrony
Sample	333	1520	819
End points	Composite of mortality, HF hospitalization and VT/VF	Primary: all-cause mortality or hospitalization; secondary: all-cause mortality	All-cause mortality or unplanned hospitalization
Study design	Double-blind, randomized, parallel-controlled	Randomized, parallel-controlled	Randomized, parallel-controlled
Treatment arms	CRT-D vs ICD	CRT vs CRT-D vs no pacing	CRT vs no pacing
Major findings	CRT improved secondary end points; primary end points did not improve	CRT and CRT-D improved primary end point; CRT-D; reduced mortality	CRT improved primary end point and reduced all cause mortality

CRT, Cardiac resynchronization therapy; *CRT-D*, cardiac resynchronization therapy-defibrillator; *EDD*, left ventricular end-diastolic diameter; *HF*, heart failure, *ICD*, implantable cardioverter defibrillator; *LVEF*, left ventricular ejection fraction; *NYHA*, New York Heart Association; *QOL*, quality of life score, *VF*, ventricular fibrillation; *VO_2*, maximal oxygen consumption; *VT*, ventricular tachycardia.

(Table 1). Furthermore, CRT is associated with reductions in mitral regurgitation (MR) and improvements in LV function.[2,8-12] Currently approved recommendations for CRT include patients with severe heart failure: New York Heart Association (NYHA) functional class III or IV, widened QRS greater than or equal to 120 milliseconds, and LV ejection fraction (EF) less than or equal to 35%.[13] Despite the great success of randomized clinical trails, approximately 25% to 35% of patients undergoing CRT do not respond favorably. Echocardiographic and Doppler imaging techniques have emerged to play a potential role in the care of the patient with CRT. Although there are several potential reasons for nonresponse to CRT, it has been suggested that the ECG widened QRS is a suboptimal marker for dyssynchrony, and that echocardiographic quantification of dyssynchrony may potentially play a role in improving patient selection for CRT.[12,14-16] The PROSPECT study (predictors of responders to CRT) was a recent observational multicenter study from Europe, the United States, and Hong Kong.[17,18] Although final data from this study are not yet available, the preliminary findings highlighted the complexity of technical factors that influence dyssynchrony analyses and the importance of training and expertise of individual laboratories to achieve reliable results. The PROSPECT study suggested that there are technical issues related to variability that are not yet resolved, and that future work is needed to improve reproducibility of dyssynchrony analysis.

OVERVIEW OF MECHANICAL DYSSYNCHRONY

Electrical activation in the normal heart typically occurs quickly within 40 milliseconds via conduction through the Purkinje network and is associated with synchronous regional mechanical contraction. A variety of myocardial diseases induce alterations in cardiac structure and function that result in regions of early and late contraction, known as dyssynchrony.[19] Although other authors have used the term "asynchrony" interchangeably, we will use the term "dyssyn-

chrony" in this report to describe this phenomenon. Mechanical dyssynchrony is usually associated with a prolonged QRS duration on the surface ECG, although it may also exist in a subset of patients with heart failure and depressed LV function and narrow QRS by ECG.[20,21] This report will focus on patients with wide QRS duration, because this is the current clinical practice for CRT.

Three types of cardiac dyssynchrony may occur: intraventricular, interventricular, and atrioventricular (AV). Abnormalities of timing of regional mechanical LV activation, known as intraventricular dyssynchrony, appear to be the principal factor associated with contractile impairment and affected by CRT. Accordingly, many echocardiographic Doppler parameters focus on intraventricular dyssynchrony, and we will use the term "dyssynchrony" throughout this report when referring to "intraventricular dyssynchrony," unless otherwise stated. The classic type of dyssynchrony resulting from abnormal electrical activation is seen with left bundle branch block. The typical pattern seen with left bundle branch block is early activation of the interventricular septum and late activation of the posterior and lateral LV walls.[19] The early septal contraction occurs before normal ejection when LV pressure is low and does not contribute to ejection. This process generates heterogeneous stress and strain in the LV, with one wall exerting forces on the contralateral wall. Typically early septal contraction causes posterior-lateral stretching or thinning, followed by late posterior-lateral contraction causing septal stretching or thinning.[22] Dyssynchrony results in inefficient LV systolic performance, increases in end-systolic volume and wall stress, and delayed relaxation that is thought to affect biological signaling processes involved in regulating perfusion and gene expression.[23] Improvements in LV synchrony are associated with LV functional improvements and reduction in MR.[8,24-28]

GENERAL APPROACH TO QUANTIFYING MECHANICAL DYSSYNCHRONY

Because the vast majority of patients with wide QRS appear to have mechanical dyssynchrony, an important goal of imaging is to improve patient selection for CRT by identifying the subset of patients with wide QRS but no mechanical dyssynchrony. The pathophysiologic reason for this scenario is unclear, but it appears that patients with minimal to no dyssynchrony have a lower probability of response to CRT and appear to have a poor prognosis after CRT.[15] There are other reasons for not responding to CRT, including ischemic disease with too much scar to reverse remodel, subsequent infarction after CRT, suboptimal lead placement, and other factors not yet defined.[24,29-33] Accordingly, the absence of dyssynchrony is only one factor for nonresponse, but one that potentially can be identified prospectively by echocardiographic Doppler methods.

Results from the PROSPECT study illustrated that technical factors of individual echocardiographic Doppler methods, such as feasibility and reproducibility, affect results in a multicenter setting.[17,18] Quantifying mechanical dyssynchrony in a series of patients with heart failure is complex, and no single ideal method currently exists. However, a practical approach that considers several factors is currently recommended to assist in determining that a patient has or does not have significant dyssynchrony. Ambiguities that may occur in analysis using different approaches must be adjudicated on a case-by-case basis. A reasonable starting point is to examine the routine 2-dimensional (2D) echocardiographic images. Trained observers can often assess dyssynchrony visually as an early septal in-and-out motion described as septal flash or bounce in typical left bundle branch block dyssynchrony. Because the presence or absence of dyssynchrony may be subtle in many patients with severe heart failure, visual assessment should not stand alone and the use of quantitative echocardiographic Doppler tools is advocated.

M-MODE

The technically simplest approach to quantify LV dyssynchrony is with conventional M-mode echocardiography that records septal-to-posterior wall-motion delay (Figure 1, *A*).

Step 1: Select either the parasternal long-axis or short-axis views.

Step 2: Position the M-mode cursor at the midventricular level (papillary muscle level).

Step 3: Set sweep speed to 50 to 100 mm/s.

Step 4: Identify the time delay from peak inward septal motion to peak inward posterior wall.

Pitzalis et al reported a cut-off value of greater than or equal to 130 milliseconds as a marker of LV dyssynchrony in a pilot series of 20 patients principally with nonischemic cardiomyopathy with a sensitivity of 100% and specificity of 63% to predict a greater than or equal to 15% decrease in LV end- systolic volume index, and improvements in clinical outcome.[34,35] Longer delays in septal to posterior wall-motion delay were associated with greater reverse remodeling. Measurement of the septal-to-posterior wall-motion delay by M-mode may be difficult in many patients because of complex septal motion that is both active and passive–wall-motion abnormalities involving the septum or posterior wall. Marcus et al highlighted these limitations in an analysis of M-mode data from 79 patients in the CONTAK-CD trial.[36] They found the reproducibility of M-mode measurements to be unsatisfactory, with responders (defined as ≥15% reduction in LV end-systolic volume) having septal-to-posterior wall-motion delays similar to nonresponders. The PROSPECT study also identified a high degree of variability in analysis.[17,18] Therefore, M-mode is not advocated to be used in isolation to quantify dyssynchrony, but may be considered as supplemental to other approaches, such as tissue Doppler (TD). In particular, the utility of M-mode in patients with ischemic cardiomyopathy has not been well demonstrated.

COLOR TD M-MODE

The addition of color TD M-mode is a useful adjunct to M-mode determination of LV dyssynchrony (Figure 1, *B*). Changes in direction are color coded, which may aid in identifying the transition from inward to outward motion in the septum and posterior wall. The same septal-to-posterior wall-motion delay greater than or equal to 130 milliseconds is considered to be significant dyssynchrony, although this method is affected by similar limitations with routine M-mode as described above.

LONGITUDINAL TD VELOCITY

The largest body of literature to quantify dyssynchrony is represented by the assessment of longitudinal LV shortening velocities using TD from the apical windows.[14-16,37-49] This is the principal method currently in clinical use, although it has limitations discussed subsequently. There are two basic approaches: color-coded or pulsed TD.

COLOR TD DATA ACQUISITION

Color TD data acquisition is simpler and more practical than pulsed TD and is the preferred method by consensus of this committee if

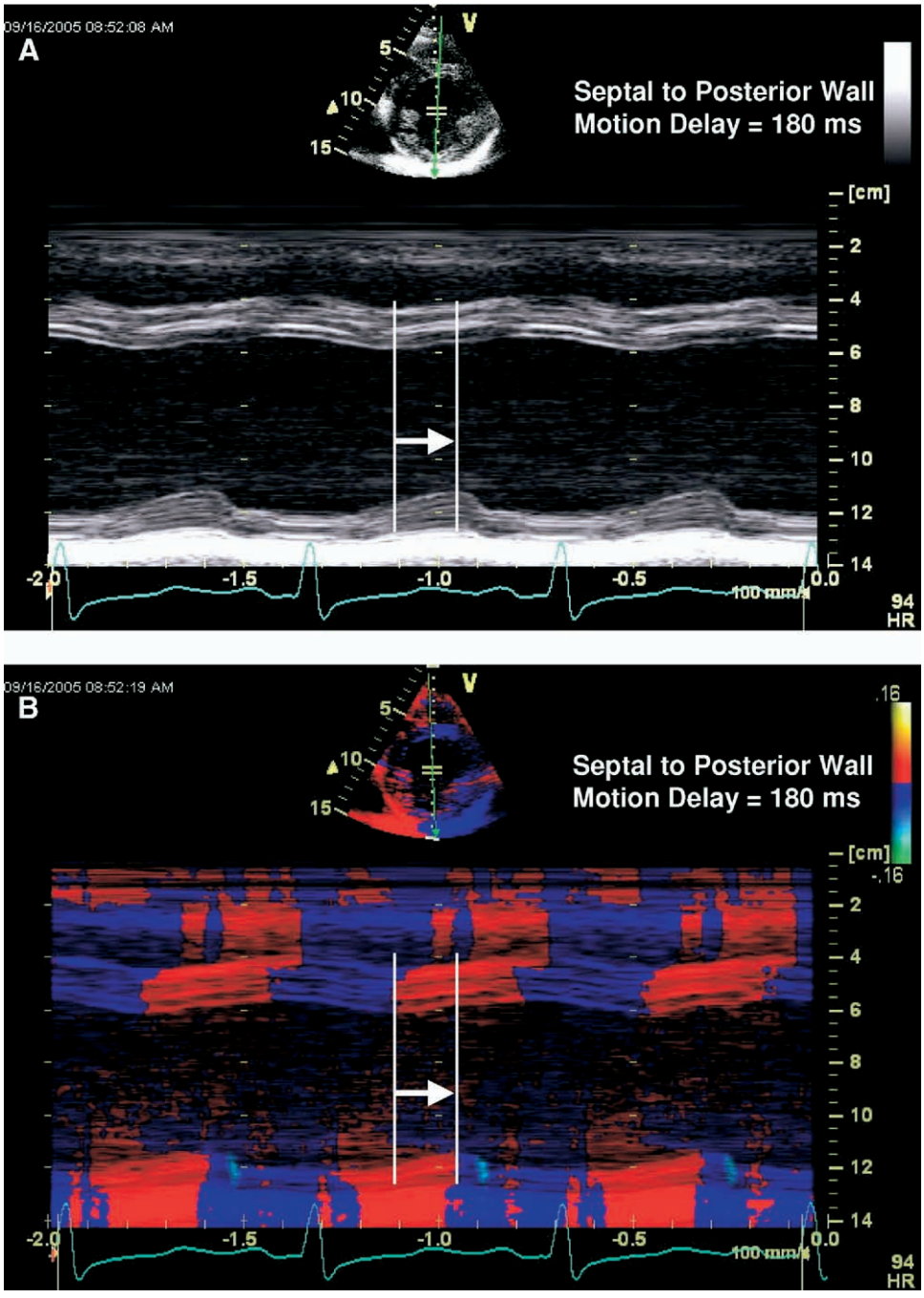

Figure 1 Routine M-mode (**A**) at midventricular level and color-coded tissue Doppler M-mode (**B**) demonstrating septal to posterior wall delay of 180 milliseconds, consistent with significant dyssynchrony (≥130 milliseconds).

high frame rate color TD echocardiographic equipment is available. High frame–rate color TD, usually greater than 90 frames/s, is available in several major equipment vendors with recent hardware and software. Individual variations in color TD between ultrasound systems may exist, but these details have not yet been elucidated.

Step 1: Adjust the ECG to be noise free with a delineated QRS waveform.

Step 2: Optimize 2D imaging to insure maximal apical-to-near field left atrial imaging, with overall gain and time gain control settings adjusted for clear myocardial definition.

Step 3: Position the LV cavity in the center of the sector and aligned as vertically as possible, to allow for the optimal Doppler angle of incidence with LV longitudinal motion.

Step 4: Set the depth to include the level of the mitral annulus.

Step 5: Activate color TD and adjust the sector to include the entire LV with a goal of achieving high frame rates (usually >90 frames/s). Decrease depth and sector width to focus on the LV to increase frame rates, as needed. Adjust overall color gain for clear delineation of the myocardium. If available, the online color coding of time to peak velocity data may be activated.

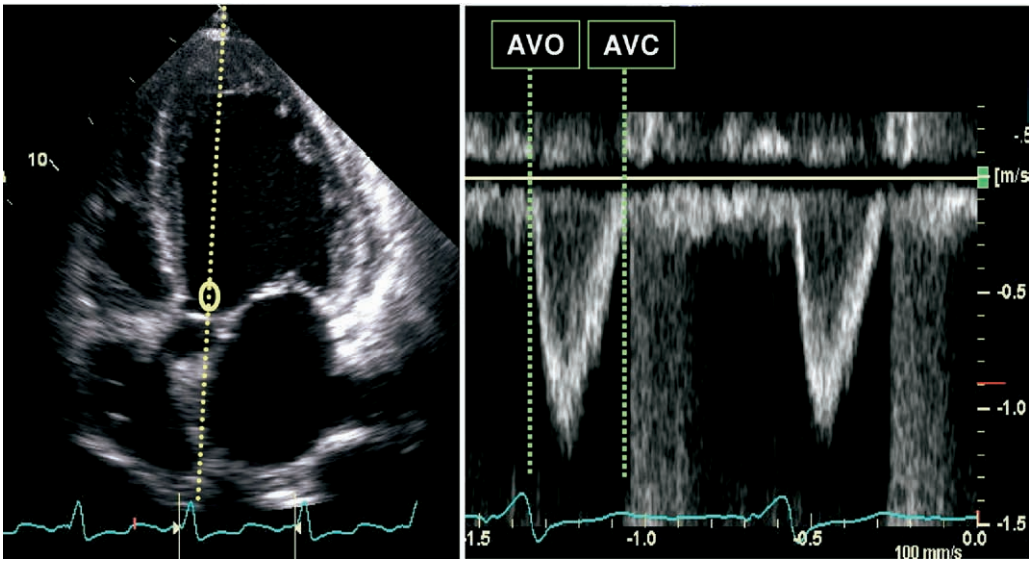

Figure 2 Determination of left ventricular ejection interval from pulsed Doppler of outflow tract. *AVC*, Aortic valve closure; *AVO*, aortic valve opening.

Step 6: Suspend patient breathing. Because low velocity TD data are affected by respiratory motion, we recommend that patients be instructed to hold their breath transiently if they are able, while a 3- to 5-beat digital capture is performed. This is usually at end expiration, but may be the phase with the optimal image quality. The number of beats captured should be increased if atrial or ventricular premature complexes are present.

Step 7: Record 3 standard imaging planes: apical 4-chamber view, apical 2-chamber view, and apical long-axis view.

Step 8: Determine the LV ejection interval. This is usually done using pulsed Doppler from an apical 5-chamber or apical long-axis view where the LV outflow tract is seen and velocity recorded (Figure 2).

COLOR TD DATA ANALYSIS

A major advantage of color DTI is the ability to analyze time-velocity data offline. The details for analysis vary by ultrasound vendor, but the general steps are similar.

Step 1: Determine the timing of LV ejection, usually from the beginning to the end of pulsed Doppler flow of the LV outflow tract. The details vary according to ultrasound system used, but timing usually is performed using the ECG as a time marker. The timing of beginning ejection to end ejection is then superimposed as the ejection interval on the subsequent time-velocity curve analysis.

Step 2: Size and place regions of interest (a minimum of 5 × 10 mm to 7 × 15 mm) in the basal and midregion of opposing LV walls (4 regions/view) to determine time-velocity plots.

Step 3: If possible, identify components of velocity curve, as a check for physiologic signal quality. These include isovolumic contraction velocity (usually <60 milliseconds from the onset of the QRS), the systolic wave, or S wave, moving toward the transducer and the early diastolic, or E wave, and late diastolic, or A wave, moving away from the transducer (Figures 3 and 4).

Step 4: Manually adjust the regions of interest within the segment both longitudinally and side-to-side within the LV wall to identify the site where the peak velocity during ejection is most reproducible. This is an important step to search for the most reproducible peak of greatest height, in particular where there is more than one peak or signal noise. If fine tuning of the region of interest fails to produce a single reproducible peak during ejection, the earlier peak is chosen if there are two or more peaks of the same height.

Step 5: Determine time from onset of the QRS complex to the peak systolic velocity for each region: 4 segments per view, for each of 3 views, for a total of 12 segments. An alternative is to determine the difference in the time to peak S wave from opposing walls, as described in the opposing wall delay method below. This is simply the time from the S wave of one wall to the S wave of the opposing wall on the same cineloops, and does not require measuring the onset from the QRS.

Step 6: Average the time to peak values in captured beats to improve reproducibility, because beat-to-beat variability may occur. A minimum of averaging 3 to 5 beats is recommended, with the number of averaged beats increased if beat-to-beat variability is encountered, excluding sequences with atrial or ventricular premature complexes. Analysis of TD data in atrial fibrillation is especially complex and problematic, and no data are currently available to support dyssynchrony analysis in this scenario.

POSTSYSTOLIC SHORTENING VELOCITIES

Some previous studies have included postsystolic shortening (positive myocardial velocity after aortic valve closure, which may be greater than the ejection peak) in their dyssynchrony analysis.[47] The greatest sensitivity and specificity for predicting response to CRT appears to be attained when limiting peak longitudinal velocities for dyssynchrony analysis to the interval from aortic valve opening to aortic valve closure.[37,43] Notabartolo et al[47] measured the maximal difference in the time to peak systolic velocity including postsystolic shortening from the 6 basal segments. An average cut-off value greater than 110 milliseconds has a high sensitivity at 97%, but decreased specificity at 55% to predict LV reverse remodeling. Although the optimal approach has not yet been completely clarified, the current weight of evidence favors analysis of peak velocities during the ejection interval.

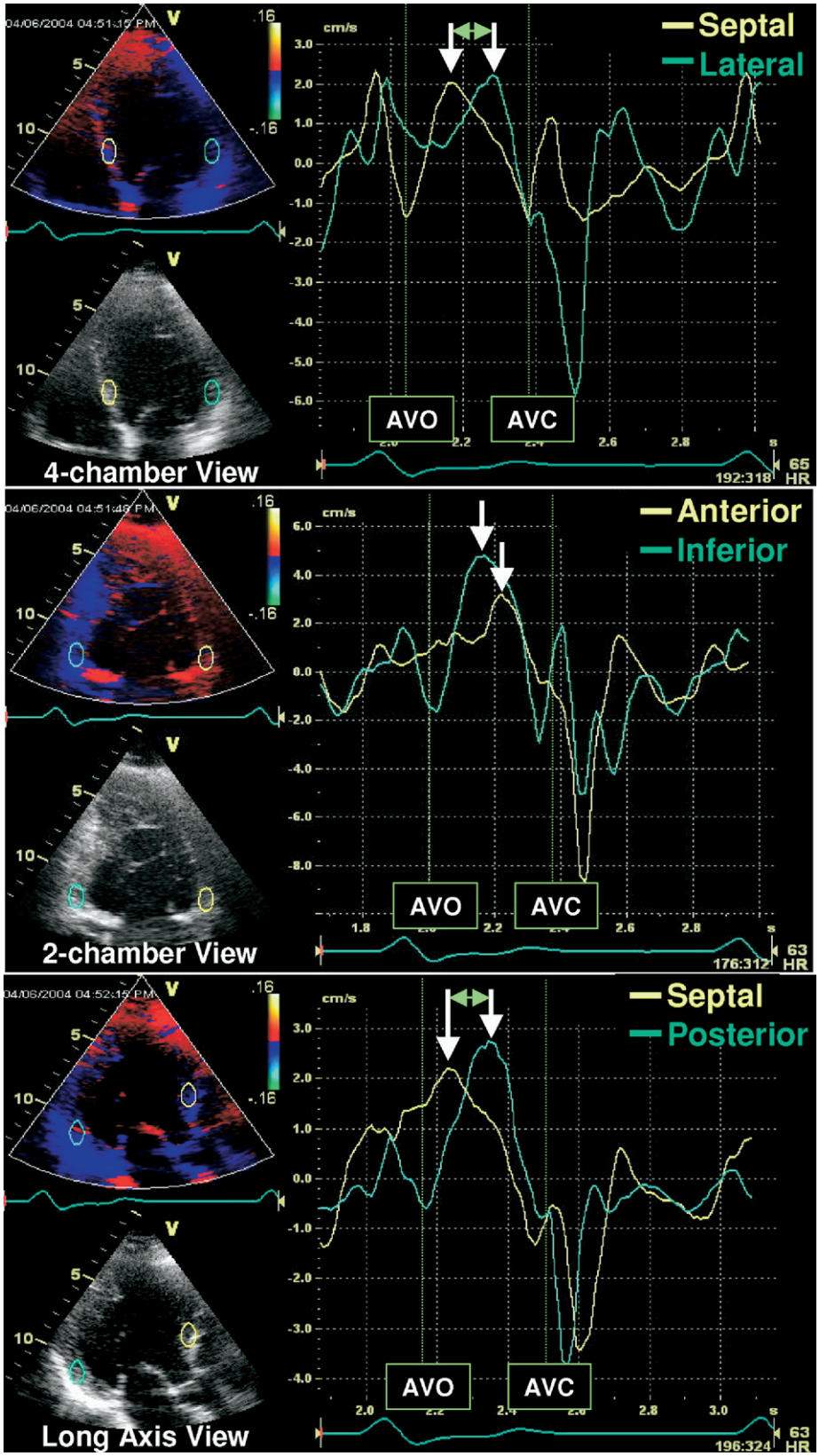

Figure 3 Color-coded tissue Doppler study from 3 standard apical views of patient who responded to resynchronization therapy. Time-velocity curves from representative basal or midlevels are shown. Maximum opposing wall delay was seen in apical long-axis view of 140 milliseconds between septum and posterior wall, consistent with significant dyssynchrony (≥65 milliseconds).

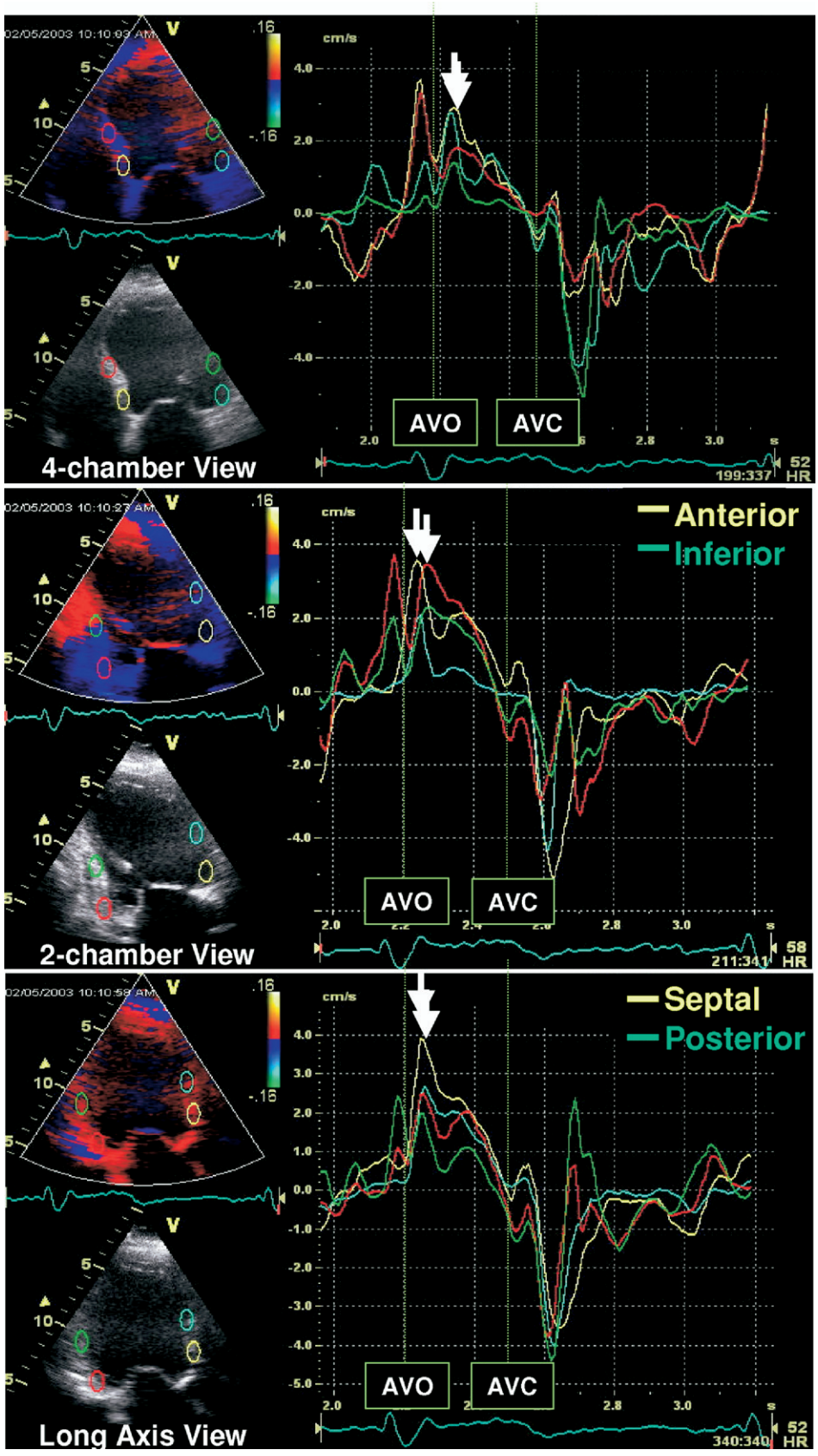

Figure 4 Color-coded tissue Doppler study from 3 standard apical views of patient who did not respond to resynchronization therapy. Time-velocity curves from both basal and midlevels show no significant opposing wall delay less than 65 milliseconds.

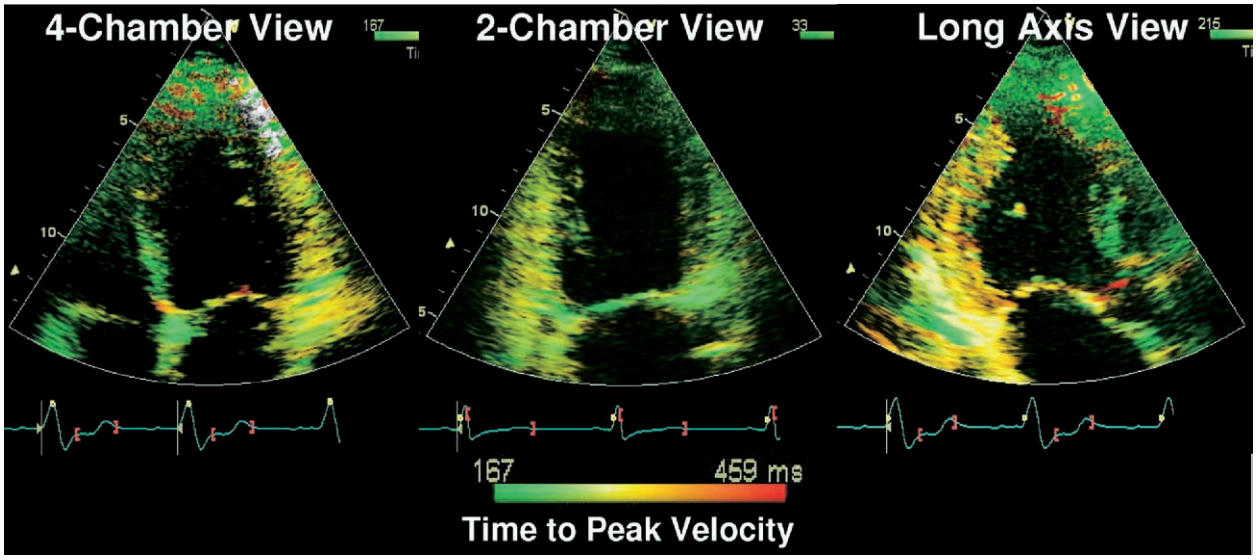

Figure 5 Tissue Doppler study from 3 standard apical views demonstrating color coding of time to peak velocity data from patient with dyssynchrony who responded to resynchronization therapy. Lateral wall (4-chamber view) and posterior wall (apical long-axis views) are color-coded *yellow-orange*, indicating delay in time to peak velocity.

CLINICAL STUDIES USING COLOR TD

The majority of studies have used color-coded TD to assess LV dyssynchrony and predict outcome, and it is the consensus of this writing group that this is currently the preferred approach. The simplest TD approach to identify LV dyssynchrony by color-coded TD uses the basal segments of the apical 4-chamber view to measure the septal-to-lateral delay, known as the two-site method.[15] Subsequently, a 4-segment model was applied that included 4 basal segments (septal, lateral, inferior, and anterior). An opposing wall delay greater than or equal to 65 milliseconds allowed prediction of both clinical response to CRT (defined by an improvement in NYHA class and 6-minute walking distance) and reverse remodeling (defined as a ≥15% reduction in LV end-systolic volume).[15] In addition, patients with LV dyssynchrony greater than or equal to 65 milliseconds had a favorable prognosis after CRT.[15,48] An extension of this opposing wall delay method has included data from the 3 standard apical views: 4-chamber, 2-chamber, and long-axis. The maximum difference in time-to-peak velocity values among the 4 sites from each of the 3 apical views is determined as the maximal opposing wall delay. An important feature of this 3-view model is that it includes the anterior-septum and posterior walls seen in the apical long-axis view, which often has dyssynchrony. Yu et al developed a 12-segment SD model using color TD that also integrates information from the same 3 apical views (4-chamber, 2-chamber, and long-axis).[31,43] The mechanical dyssynchrony index, also known as the Yu index, was derived from calculating the SD of the time-to-peak systolic velocity in the ejection phase 12-site standard deviation.[31,43,49] A 12-site standard deviation cut-off value of greater than or equal to 33 milliseconds was derived from the healthy population to signify mechanical dyssynchrony. To predict LV reverse remodeling (defined as a ≥15% reduction in LV end-systolic volume) in patients with a QRS duration greater than 150 milliseconds, this cut-off value has a sensitivity of 100% and specificity of 78%. For patients with a borderline prolongation of QRS duration of 120 to 150 milliseconds, the sensitivity is 83% and specificity is 86%.[49] An alternate method is to calculate the maximal difference in the time to peak systolic velocity among all segments, where a cut-off value of greater than or equal to 100 milliseconds predicts response to CRT.[31,43] The PROSPECT study reported that the 12-site time-to-peak SD had a lower yield and higher variability than more simple approaches, which illustrates its disadvantage as a more technically demanding approach.[18]

An extension of TD is automated color coding of time-to-peak velocity data. One method is known as tissue synchronization imaging (TSI) (Figure 5). This technology adds a color-coded overlay onto 2D images for a visual identification of regional mechanical delay. Timing should focus on the ejection period and exclude early isovolumic contraction and late postsystolic shortening. Gorcsan et al used TSI color coding to guide placement of regions of interest and assess an antero-septal-to-posterior wall delay greater than or equal to 65 milliseconds from time-velocity curves to predict acute improvement in stroke volume after CRT.[12] Yu et al also used TSI in 56 patients and found the Ts-SD derived by TSI from 12 LV segments had a highest receiver operating characteristic curve area of 0.90. Inclusion of postsystolic shortening in the model significantly reduced the receiver operating characteristic curve area to 0.69. Furthermore, all of the TSI parameters showed a slight, but consistently lower, predictive value than data derived directly from the time-velocity curves.[50] Thus, it is recommended that myocardial time-velocity curves be examined with adjustment of regions of interest as described above to ensure the accuracy of the true peak velocities when TSI is used.

PULSED TD

Pulsed TD has been described as a means to assess dyssynchrony and is available on most echocardiography systems (Figure 6). Briefly, pulsed TD presets must be optimized on the echocardiographic system as recommended by the individual manufacturers. The general approach is as described above in the step-by-step color TD data acquisition and analysis sections, with modifications. The pulsed sample volume is set to approximately 1-cm length, the velocity scale set to maximize the time-velocity curve, and the

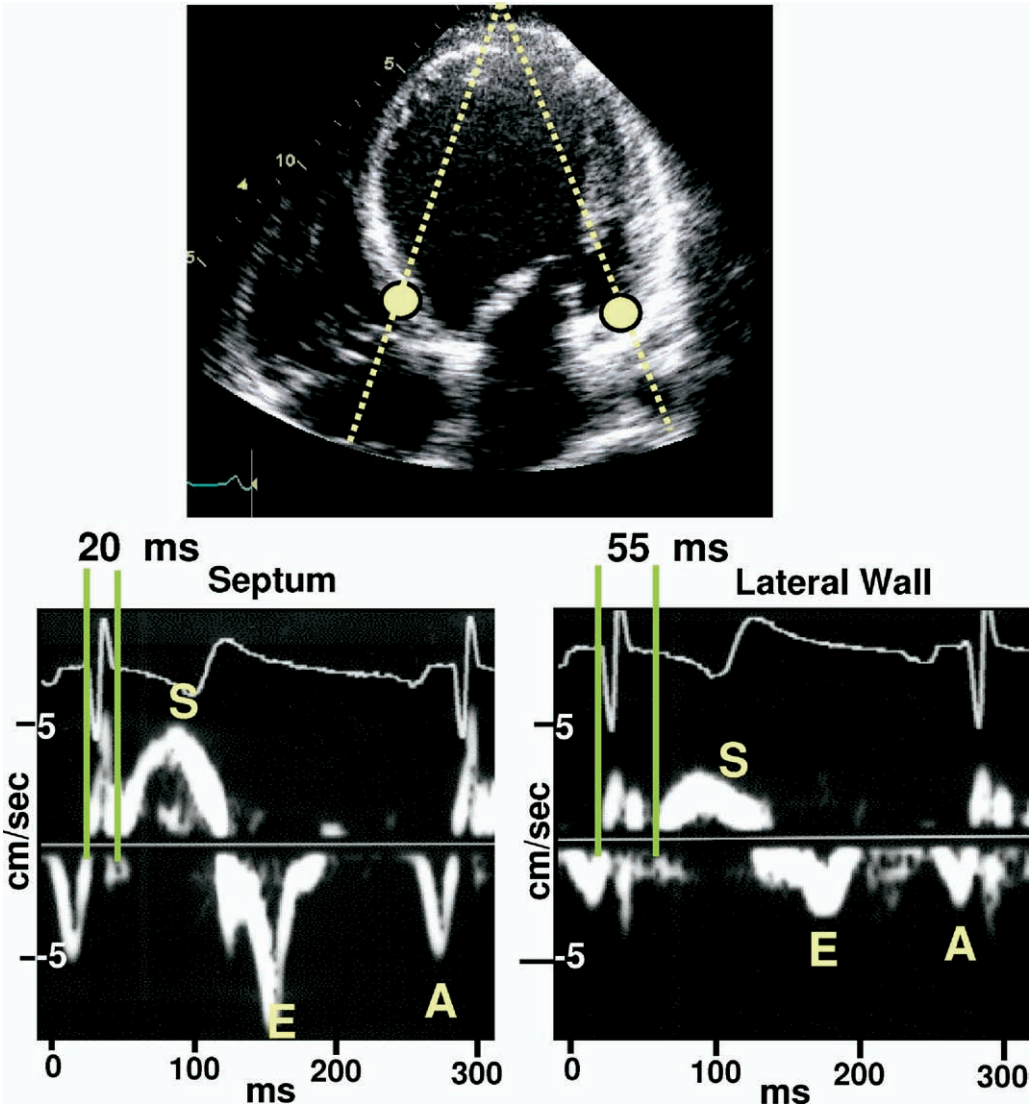

Figure 6 Pulsed tissue Doppler demonstrating dyssynchrony with delayed time to onset systolic velocity in lateral wall, as compared with septum in patient with left bundle branch block before resynchronization therapy.

sweep speed set to 50 to 100 mm/s. Unlike offline color TD data analysis, the step where the sample volume is moved within the segment to search for a reproducible time-velocity signal must be done online. This is a major disadvantage of pulsed TD because it is time-consuming and susceptible to influences of breathing, patient movement, and alterations in heart rate. In addition, the timing of the ejection interval must be transferred manually. Furthermore, the peak velocity may be difficult to identify because of a broad spectral display with a plateau during systole. Because of these technical limitations, color-coded TD is the approach preferred by this writing group. Currently, clinical studies of pulsed TD to predict response to CRT are less numerous than those using color TD. Penicka et al used pulsed wave TD to measure the time of onset of the systolic signal of basal segments from the apical 4-chamber and long-axis views and the lateral right ventricular (RV) wall.[51] Using a composite index of interventricular and intraventricular dyssynchrony longer than 100 milliseconds, they achieved 88% accuracy in identifying all but 6 patients who responded to CRT.

TD LONGITUDINAL STRAIN, STRAIN RATE, AND DISPLACEMENT

Strain and strain rate imaging have the theoretic advantage of differentiating active myocardial contraction or deformation from passive translational movement and have been utilized to identify dyssynchrony.[40,42,52] Longitudinal strain is calculated linearly from TD velocity data as percent shortening (Figure 7). However, TD longitudinal strain can be technically challenging because strain is calculated along scan lines, is Doppler angle dependent, and is difficult in patients with spherical LV geometry, often encountered in severe heart failure. Comparing myocardial velocities and strain rate, Breithardt et al found an association between regional myocardial motion (expressed by velocity parameters) and deformation (expressed by strain rate imaging parameters).[52] They concluded that the degree of dyssynchrony was not completely represented by the timing of myocardial velocity, particularly in ischemic heart disease, and that the timing of deformation should be the preferred modality. Sogaard et al found that the extent of delayed

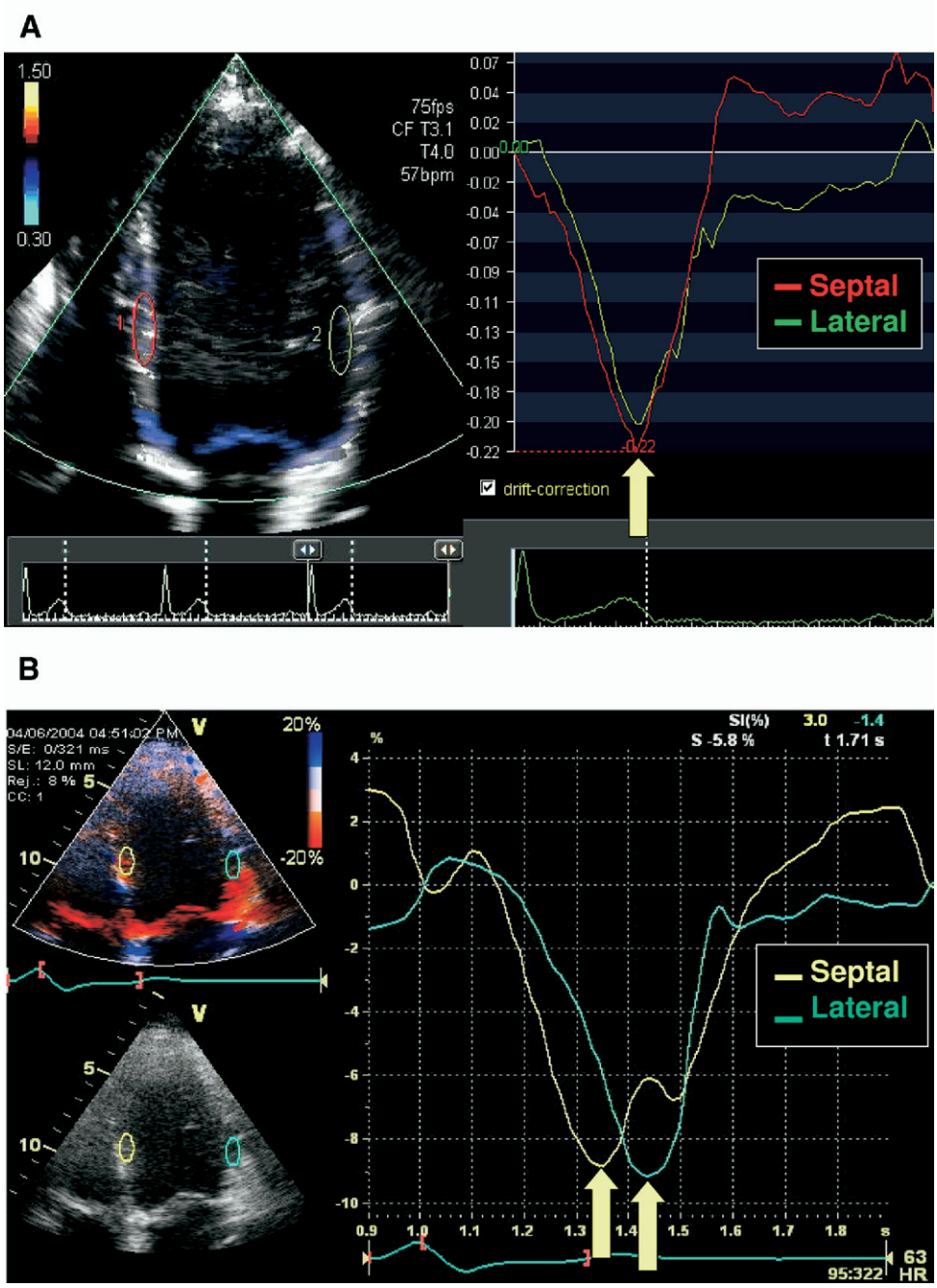

Figure 7 Doppler tissue images demonstrating longitudinal strain in healthy synchronous patient (**A**) and in patient with left bundle branch block before (**B**) resynchronization therapy.

longitudinal contraction at the base predicted improvement in EF after CRT.[41,42] However, Yu et al demonstrated that parameters of strain rate imaging are not useful to predict reverse remodeling response.[43,44,53] Currently, TD strain rate is restricted by a poor signal-to-noise ratio, which adversely affects reproducibility. On the other hand, improvements in strain analysis, including software developments such as strain determined by speckle tracking of routine gray-scale images, are promising as useful markers of systolic dyssynchrony.[54]

Displacement imaging uses TD data to calculate the distance of myocardial movement, and is typically color coded and overlaid onto 2D images. The signal-to-noise ratio is more favorable than strain or strain rate imaging, but displacement is also affected by passive motion, and the Doppler angle of incidence. Improvements in displacement or tissue tracking have been described after CRT, however, cut-off values for predicting response and clinical outcomes after CRT have not yet been established.[42]

RADIAL STRAIN

Because radial thickening is a major vector of LV contraction, and short-axis dynamics are important markers of dyssynchrony,[55] it is

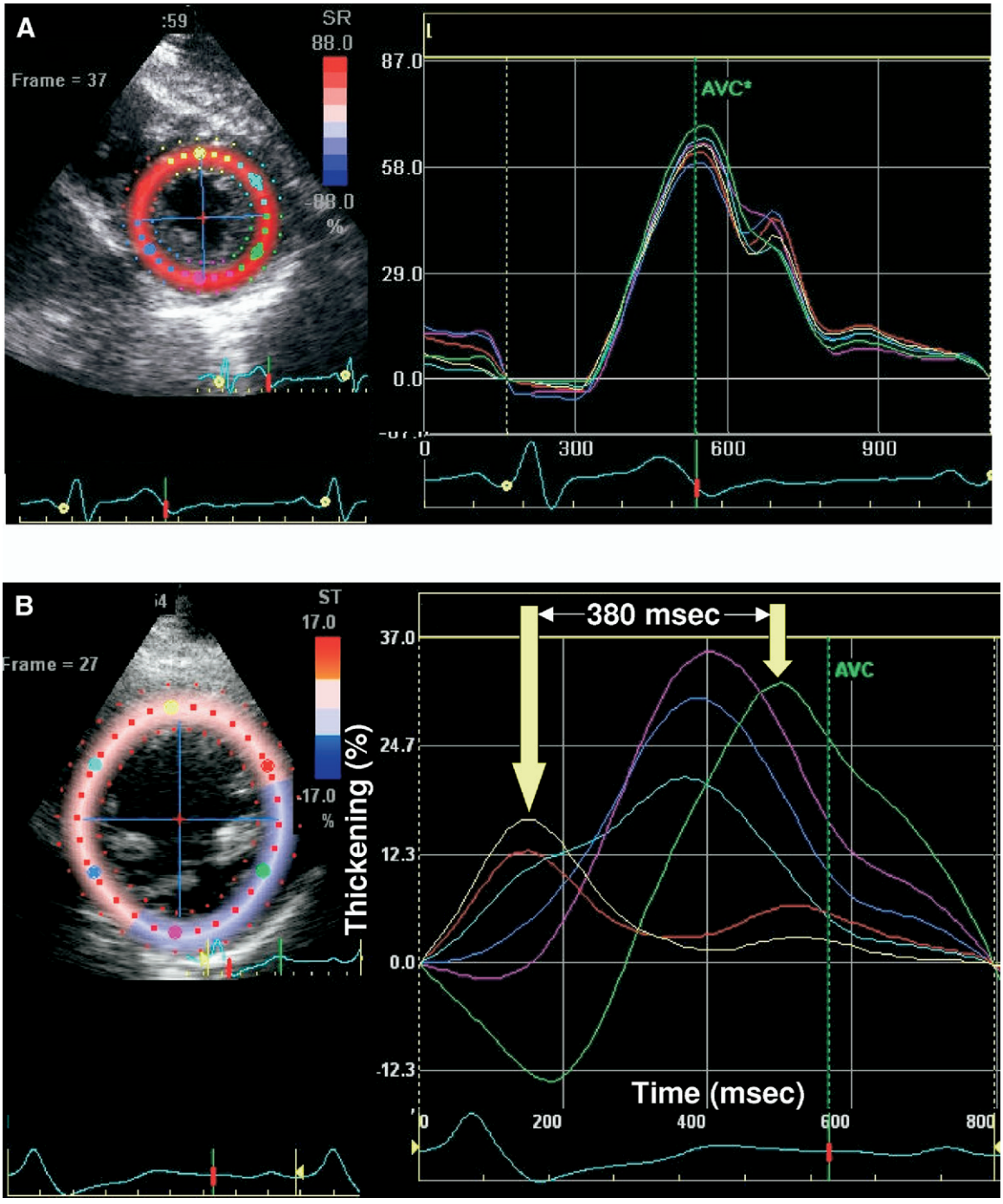

Figure 8 Speckle-tracking images demonstrating synchrony of peak segmental radial strain in healthy individual (**A**) and severe dyssynchrony in patient with heart failure and left bundle branch block (*LBBB*) referred for resynchronization therapy (**B**).

reasonable to utilize this information in a comprehensive examination. Strain has an advantage over M-mode of differentiating active from passive motion and identifying radial mechanical activation.[56] Dohi et al first used TD strain to quantify radial mechanical dyssynchrony in 38 patients who underwent CRT.[57] Radial strain was calculated from TD velocity data from the anteroseptum and posterior wall in the mid LV short-axis view.[58] Disadvantages of TD radial strain included signal noise without adequate image quality and the effect of the Doppler angle of incidence.

A more recent approach is application of a speckle-tracking program that is applied to routine gray-scale echocardiographic images, which is not limited by Doppler angle of incidence. Suffoletto et al studied 64 patients undergoing CRT.[54] Speckle tracking applied to routine midventricular short-axis images determines radial strain from multiple points averaged to 6 standard segments (Figure 8). Baseline speckle-tracking radial dyssynchrony (defined as a time difference in peak septal to posterior wall strain $\geq$ 130 milliseconds) predicted a significant increase in LV EF, with 89% sensitivity and 83% specific-

ity, in 50 patients followed up for 8 ± 5 months after CRT. An interesting subset of patients who did not have dyssynchrony by longitudinal TD velocities had a favorable response to CRT predicted by speckle-tracking radial dyssynchrony. These data suggest the additive value of assessing dyssynchrony from short-axis planes in addition to long-axis planes. A recent study of 176 patients combined longitudinal DTI velocity data with radial speckle-tracking strain data and found patients who had both positive longitudinal and radial dyssynchrony patterns had a high incidence of improvement in EF after CRT,[59] whereas patients with neither longitudinal nor radial dyssynchrony had a low incidence of EF improvement. Patients with heterogeneous patterns of dyssynchrony had intermediate responses. These data suggest that combining dyssynchrony data may be of additive value.[59]

THREE-DIMENSIONAL ECHOCARDIOGRAPHY

LV dyssynchrony in reality is a 3-dimensional phenomenon. Three-dimensional echocardiography provides a unique and powerful tool for the evaluation of LV dyssynchrony.[60] The advantage of real-time 3-dimensional echocardiography is that it allows for a comparison of synchrony between of the segments of the LV together in the same cardiac cycle (Figure 9). Regional wall-motion patterns can be visualized and quantified after segmentation of the LV chamber with semiautomatic contour tracing algorithms. Preliminary reports suggest that this approach enables a comprehensive analysis of LV wall motion before and during CRT with a direct comparison of endocardial wall motion between all LV segments. Kapetanakis et al calculated a systolic dyssynchrony index from the dispersion of time to minimum regional volume for all 16 LV segments and found this to be predictive of reverse remodeling after CRT in 26 patients.[61] This approach has the potential for a more comprehensive analysis of LV dyssynchrony.[62] However, disadvantages include lower spatial and temporal resolution, with frame rates for 3-dimensional wide-sector image acquisition at approximately 20 to 30 frames/s.

INTERVENTRICULAR DYSSYNCHRONY

Interventricular dyssynchrony, principally assessed as the interventricular mechanical delay (IVMD), is defined as the time difference between RV to LV ejection. This is determined as the time from the onset of the QRS to the onset of LV ejection versus RV ejection, usually measured as the onset of pulsed Doppler flow velocities in the LV and RV outflow tracts, respectively (Figure 10).[63-65] IVMD has been identified as a predictor of worsening symptom status and cardiac mortality in patients with heart failure, and has been shown to be of prognostic value in patients with CRT (usually >40-50 milliseconds).[65] Although IVMD is simple, reproducible, and possible with routine equipment,[15] it appears to be a nonspecific predictor of response to CRT. Bax et al demonstrated that IVMD was similar in 59 responders and 21 nonresponders to CRT: 47 ± 34 vs 49 ± 29 milliseconds, respectively (P = not significant).[16] Achilli et al reported results of the SCART study of 133 patients, where a positive response to CRT was predicted by IVMD longer than 44 milliseconds with a sensitivity of 66% and a specificity of 55%.[63] Richardson et al also showed that an IVMD longer than 50 milliseconds added prognostic information to patients undergoing CRT as part of the CARE-HF trial analysis.[65] The PROSPECT trial recently demonstrated that IVMD and other simple pulsed Doppler measures of dyssynchrony, such as the pre-ejection delay and the LV filling time to cardiac cycle length ratio, had the advantage of a high yield and high reproducibility in a multicenter setting.[18] However, most evidence suggests that interventricular dyssynchrony is not as useful in the prediction of response to CRT as LV intraventricular dyssynchrony, when a technically adequate study is possible. Comparisons of current principal measures of dyssynchrony appear in Table 2.

OTHER APPROACHES TO ASSESS DYSSYNCHRONY

Breithardt et al reported phase analysis using a semiautomatic method for endocardial border delineation.[66] The degree of LV dyssynchrony was quantified in 2D echocardiographic sequences from the apical 4-chamber view, focusing on the septal-lateral relationships. Computer-generated regional wall movement curves were compared by a mathematic phase analysis, based on Fourier transformation. The resulting septal-lateral phase angle difference is a quantitative measure for intraventricular dyssynchrony. Another method to determine dyssynchrony using conventional 2D echocardiography is velocity vector imaging. This method uses a series of unique B-mode pixel tracking algorithms to calculate regional myocardial velocities toward an operator-selected point of reference (Figure 11). A pilot study by Cannesson et al examined 23 patients with heart failure undergoing CRT using digital cineloops from standard apical views, with the user tracing the mid-LV wall from a single frame.[67] Dyssynchrony, defined as the greatest opposing wall peak longitudinal systolic velocity delay among the 3 views greater than or equal to 75 milliseconds, predicted EF response with 85% sensitivity and 80% specificity when patients were followed 8 ± 5 months after CRT.

EFFECTS ON LV REVERSE REMODELING AND MR

LV remodeling is a dynamic process characterized by progressive chamber dilatation, distortion of cavity shape, disruption of the mitral valve geometry with MR, and deterioration in contractile function that culminates in heart failure.[68,69] LV remodeling may be triggered by pressure or volume overload or loss of contracting myocytes from ischemic injury, or may be genetically programmed.[70] Although precise mechanisms and intracellular signaling pathways for LV remodeling are unknown, neurohormones and local trophic factors modulate the dynamic balance between distending forces that favor dilatation and the restraining forces imposed by the extracellular collagen matrix that may affect gene expression of myocyte function.[23] CRT often results in reverse remodeling where LV size and function progressively improve over time. This is a CRT-dependent, dynamic process where subsequent cessation of CRT results in progressive deterioration in LV function toward baseline values.[14] The extent of LV reverse remodeling varied according to cause of heart failure in the MIRACLE and other trials. Reduction in volume and severity of MR and the increase in EF were consistently 2- to 3-fold greater in nonischemic patients than in patients with ischemic heart failure in spite of significantly larger baseline volumes and lower EFs.[68] In an important study of 141 patients who received CRT, those who decreased LV end-systolic volume by at least 10% at 3 to 6 months had a more favorable long-term clinical outcome, including lower all-cause mortality (7% vs 31%), cardiovascular mortality (2% vs 24%), and heart failure events (12% vs 33%; all $P < .005$).[68,71]

CRT can reduce MR by improved temporal coordination of mechanical activation of the papillary muscles acutely and later

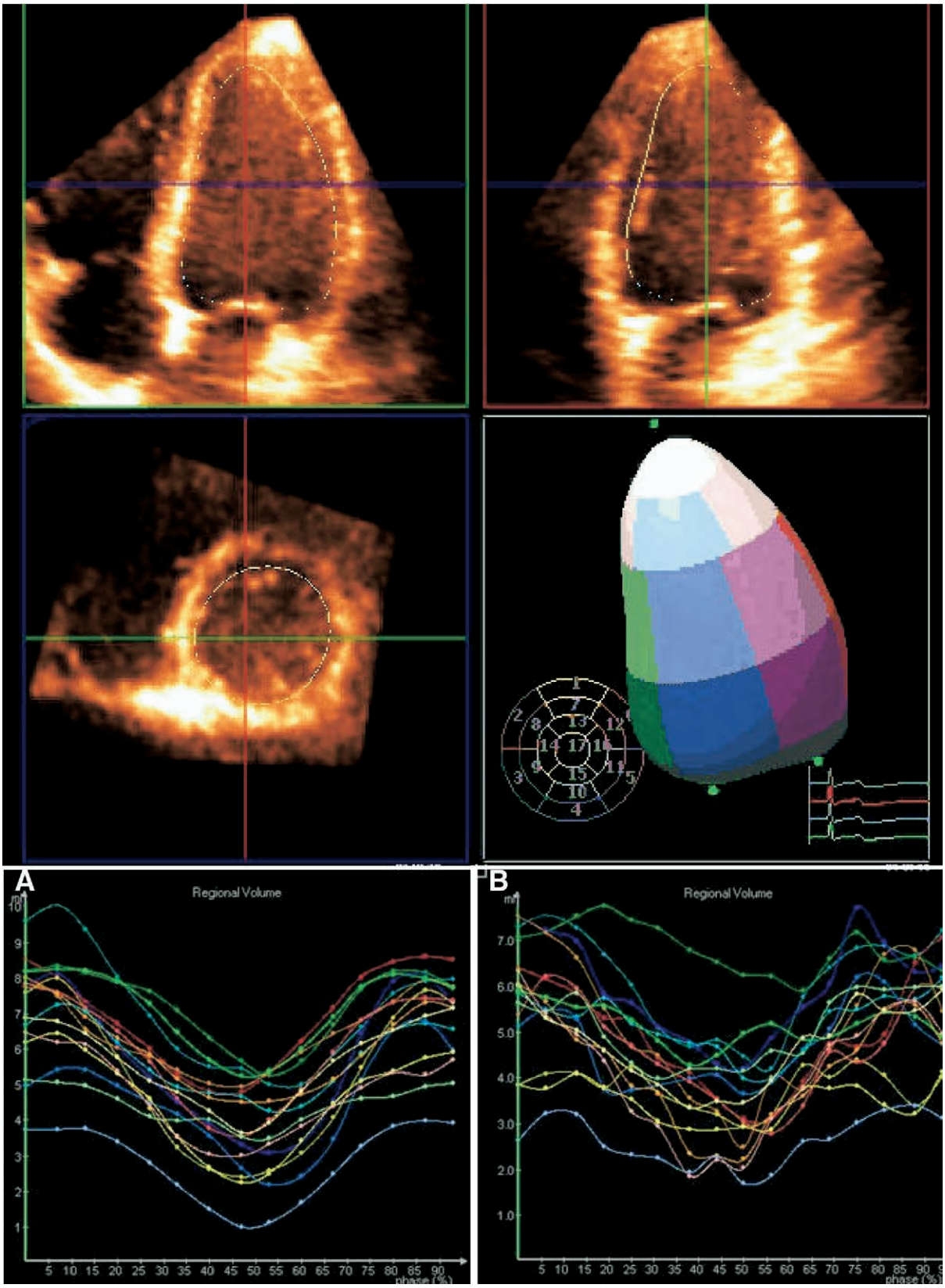

Figure 9 Three-dimensional echocardiographic assessment of segmental volume displacement in patient with normal synchrony (**A**) and with significant dyssynchrony (**B**).

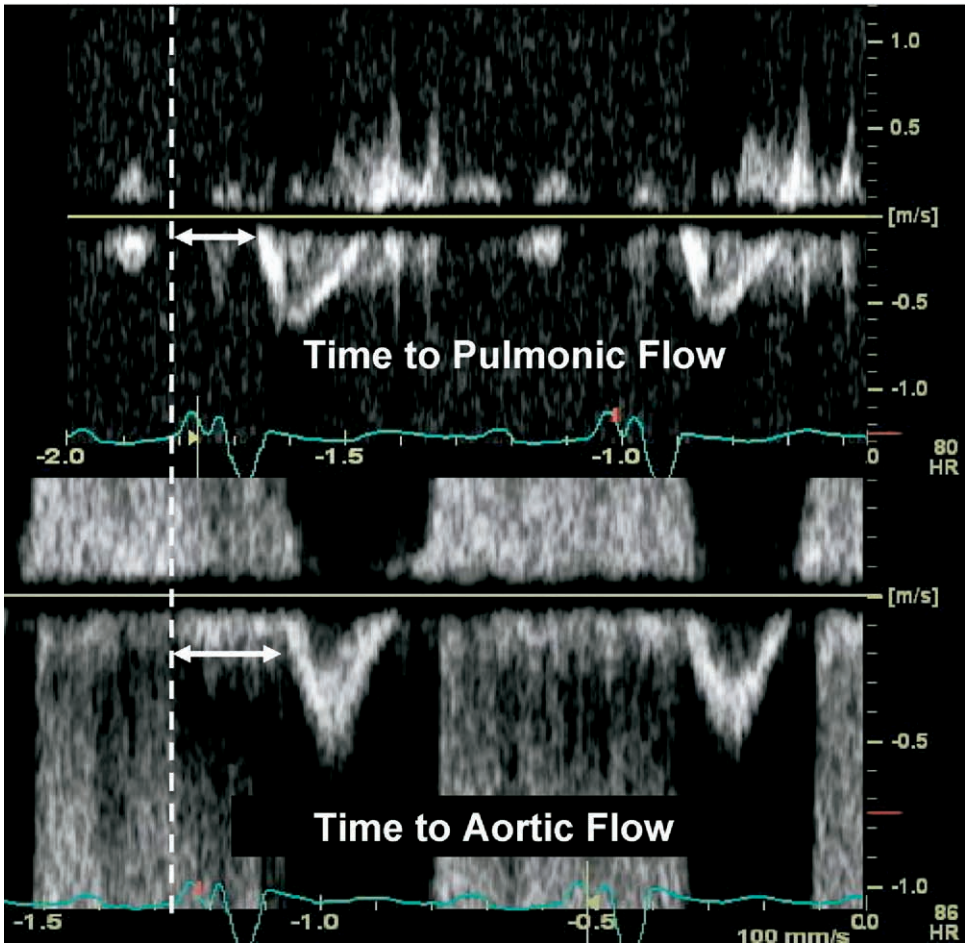

Figure 10 Pulsed Doppler from right ventricular outflow tract and left ventricular (LV) outflow tract demonstrating significant delay in LV ejection (>40 milliseconds).

improvements in LV size and geometry from reverse remodeling[28] (Figure 12). Breithardt et al used the proximal isovelocity surface area method during both pacing-off and CRT in the first week after CRT to report a significantly reduced regurgitant volume from 32 ± 19 to 19 ± 9 mL, and effective regurgitant orifice area from 25 ± 19 to 13 ± 8 mm^2, with CRT.[8] An important factor for acute reduction of MR after CRT appears to be improvement in the coordination of papillary muscle forces on the mitral chordae that increase the area of mitral leaflet coaptation. Kanzaki et al associated reductions in MR after CRT with acute improvements in the timing of mechanical activation of the papillary muscle sites, using mechanical strain activation mapping.[28]

PACING LEAD PLACEMENT

Several studies have suggested a potential role for echocardiographic Doppler methods to direct LV lead placement through identification of the anatomic site of latest mechanical activation. Ansalone et al were among the first to show that LV lead placement concordant with the site of latest velocity activation by TD was associated with a more favorable response to CRT.[30] They observed that the inferior or posterolateral wall was the location of latest mechanical activation in 75% of cases. Murphy et al demonstrated that the color-coded time-to-peak velocities approach described above could identify the site of latest systolic velocity and that lead placement at this site was associated with the greatest clinical and hemodynamic benefit of CRT.[72] There was a graduated response, such that LV pacing at a site one segment away from maximal delay was associated with a modest but more limited benefit, and patients paced at greater than one segment remote from the area of maximal delay had no significant reverse remodeling after a mean follow-up of more than 6 months. Suffoletto et al[54] utilized 2D speckle tracking to analyze LV radial strain to identify the site of latest mechanical activation before CRT and also observed that the patients with concordant LV lead placement had more favorable reverse remodeling. They found that 22 patients who had LV lead placement concordant with the site of latest activation had slightly greater improvements in LV EF (10 ± 5%), as compared with 24 patients who had discordant lead position (6 ± 5%; $P < .05$). Although these studies are encouraging, prospective studies will be needed to determine definitively the role of echocardiography in guiding LV lead placement.

RATIONALE FOR AV DELAY OPTIMIZATION

Because the ventricles are paced in CRT, the AV delay needs to be programmed. The optimal programmed AV delay for an electronic pacemaker has been defined as the AV delay that allows completion of the atrial contribution to diastolic filling resulting in most favorable

Table 2 Principal dyssynchrony indices associated with response to cardiac resynchronization therapy

Index	Method	Normal	Cutoff	Advantages	Disadvantages
Intraventricular longitudinal dyssynchrony					
Opposing wall delay, two sites[12,15,38]	Color tissue Doppler peak velocity (apical 4-chamber or long-axis views)	<50 ms	≥65 ms	Rapidly applied; offline analysis is possible	Requires color TD equipment; affected by passive motion tethering
Maximum wall delay, 12 sites[43,47]	Color tissue Doppler peak velocity (apical 4-chamber, 2-chamber, and long-axis views)	<90 ms	≥100 ms	More complete detection of longitudinal dyssynchrony; offline analysis is possible	Requires color TD equipment; affected by passive motion tethering
Yu index[14,31,43]	Color tissue Doppler, 12-segment SD (apical 4-chamber, 2-chamber, and long-axis views)	<30 ms	≥33 ms	More complete detection of longitudinal dyssynchrony; offline analysis is possible	Requires color TD equipment; more time-consuming; affected by passive motion tethering
Delay in onset of systolic velocity[51]	Pulsed tissue Doppler (apical 4-chamber, 2-chamber, and long-axis views; LV and RV)	<80 ms	≥100 ms	More widely available	Acquisition technically difficult; offline analysis is not possible; affected by passive motion tethering
Delayed longitudinal contraction[41,42]	Color tissue Doppler-strain-strain rate (apical views)	None	N/A	Less affected by passive motion or tethering; offline analysis is possible	Requires specialized color TD equipment; technically demanding
Intraventricular radial dyssynchrony					
Septal to posterior wall delay[34,35]	M-mode (parasternal mid-LV view)	<50 ms	≥130 ms	Widely available; rapidly applied; no advanced technical requirements	Largely affected by passive motion or tethering; difficulties with segmental akinesis
Septal to posterior wall delay[54,57]	Radial strain (parasternal mid-LV view)	<40 ms	≥130 ms	Less affected by passive motion or tethering; speckle tracking may be applied to routine images	Requires specialized instrumentation for analysis; assesses only radial dynamics
Interventricular dyssynchrony					
Interventricular mechanical delay[62-64]	Routine pulsed Doppler (RVOT and LVOT views)	<20 ms	≥40 ms	Widely available; no advanced technical requirements; highly reproducible	Nonspecific; affected by LV and RV function

LV, Left ventricular; *N/A*, not applicable; *OT*, outflow tract; *RV*, right ventricular; *TD*, tissue Doppler.

preload before ventricular contraction.[73] An AV delay programmed too short will result in absence or interruption of the atrial component (mitral A wave) by the premature ventricular contraction and closure of the mitral valve. An AV delay programmed too long can result in suboptimal LV preload or diastolic MR, or may even allow native LV conduction, which defeats the purpose of CRT.

Although the importance of AV synchrony is unquestioned, the need for routine echocardiographic Doppler AV timing optimization in all patients with CRT is controversial because an ideal approach has not yet been defined and there are often logistic challenges coordinating the echocardiography laboratory with electrophysiology technical staff for device programming. Auricchio et al concluded that although AV delay often positively impacts hemodynamics, LV resynchronization of intraventricular dyssynchrony is more important.[74] Many centers currently use empiric out-of-the-box AV delay device settings of approximately 100 to 130 milliseconds for CRT. Other centers rely on AV delay optimization algorithms based on ECG data to approximate the optimal AV delay optimal as [PR (ms) × 0.50], if QRS > 150 ms or [PR (ms) × 0.70], if QRS < 150 ms.[75] Sawhney et al recently conducted a prospective randomized trial of 40 patients comparing aortic Doppler optimized AV intervals to a fixed AV interval of 120 milliseconds after CRT.[76] AV optimized patients exhibited improved NYHA class and quality of life, but no significant improvement in 6-minute walk distance or EF at 3 months postimplant. A larger report of 215 patients undergoing Doppler-guided AV optimization found small differences between the baseline and post-AV optimization average AV delay (120 vs 135 milliseconds, respectively).[77] Furthermore, AV optimization enhanced LV hemodynamics in only a minority of patients with CRT, suggesting that a significant percentage of patients do not need to undergo formal AV optimization. Patients with intra-atrial conduction delay at baseline appeared to benefit greatest by prolonging the AV delays (150-250 milliseconds) during AV optimization (Figure 13).[77] These patients were identified by complete loss of the mitral inflow A wave

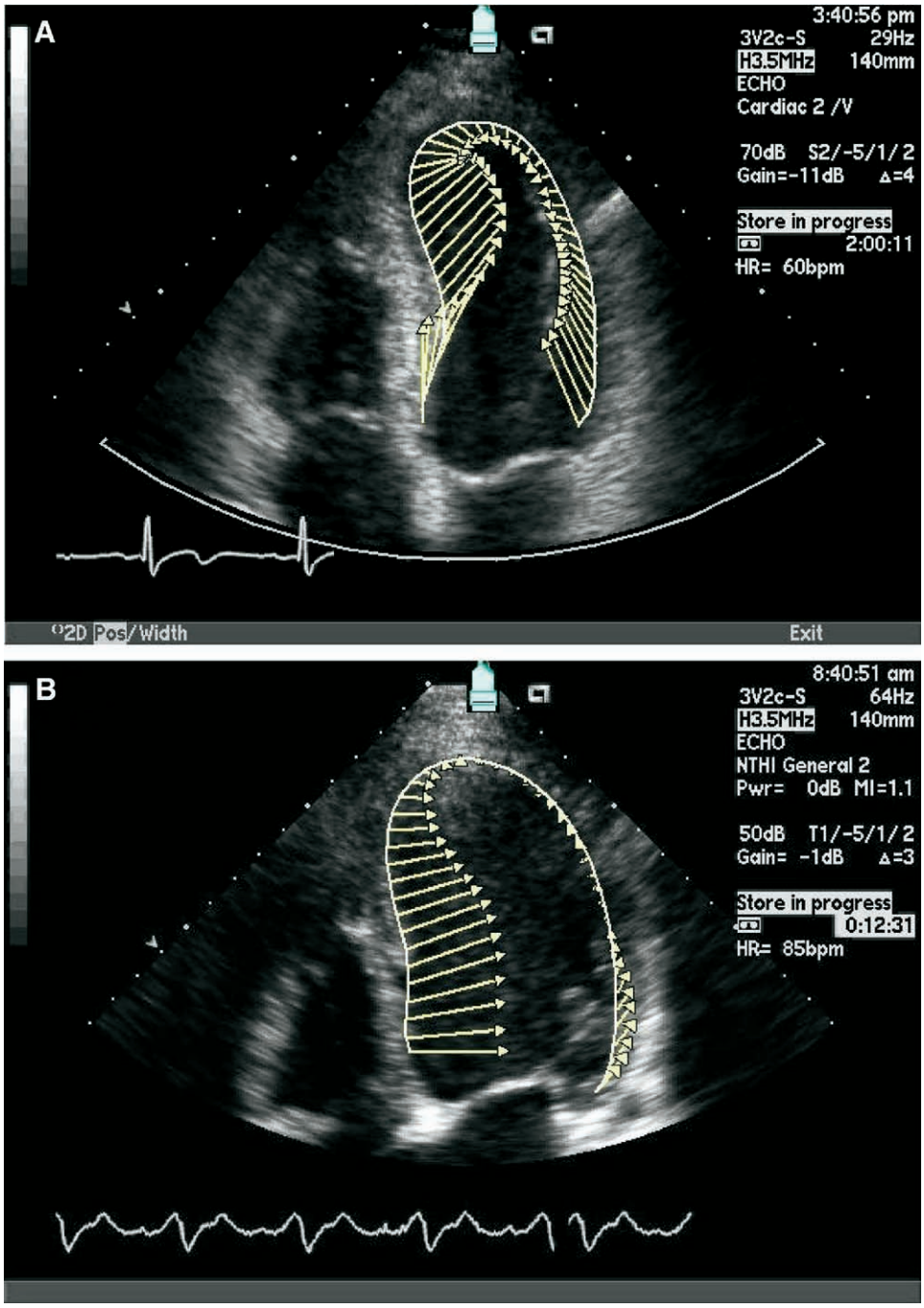

Figure 11 Velocity vector images demonstrating synchrony of velocity convergence toward center of left ventricle in healthy individual (**A**) and severe septal-lateral wall dyssynchrony in patient with heart failure and left bundle branch block (LBBB) referred for resynchronization therapy (**B**).

with an empiric setting that was too short. Although a recommendation for routine care has not been established, the following section provides guidelines for AV optimization after CRT.

RITTER AND ITERATIVE METHODS FOR AV DELAY OPTIMIZATION

Pulsed Doppler interrogation of mitral inflow to assess LV filling, and either pulsed Doppler or continuous wave Doppler sampling of the LV outflow tract to assess LV ejection, are utilized for the Ritter and iterative AV optimization protocols.[78,79] The method of Ritter et al attempted to optimally synchronize the termination of atrial contraction with the onset of ventricular systole.[79] This method requires programming the AV delay to a short (50 milliseconds) and then a long (200 or 250 milliseconds) interval while testing their impact on end-diastolic filling. The AV delay is then determined by correcting the long AV delay by the time shift from short and long Doppler tracings. The iterative method is simpler and begins by programming

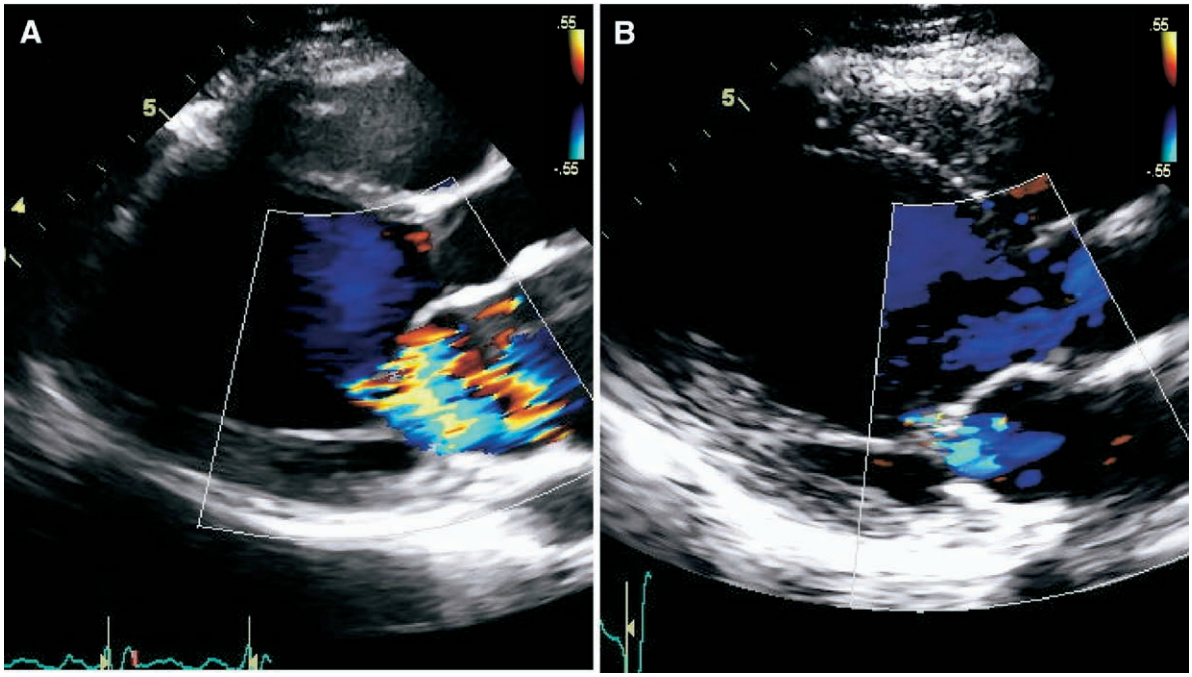

Figure 12 Parasternal long-axis view demonstrating reduction in mitral regurgitation in patient from before (**A**) to day after (**B**) resynchronization therapy.

the CRT device in atrial synchronous V pacing mode testing a series of AV intervals sequentially. This usually begins with an AV delay of 200 milliseconds, then decreases in increments of 20-millisecond intervals to a minimum AV delay as short as 60 milliseconds. The minimal AV delay that allows for adequate E and A wave separation and termination of the A wave at approximately 40 to 60 milliseconds before the onset of the QRS would be considered the optimal AV delay, and usually corresponds with a stage I diastolic filling pattern.[80] Technical features include positioning the pulsed wave sample volume deeper toward the left atrium (as opposed to the standard position at the mitral leaflet tips) to optimize detection of the mitral valve closure click, preparing settings of high sweep speeds and low filters, and inputting the ECG signal from the device directly to the ultrasound system, if possible. A variation on the iterative method for AV optimization uses transaortic Doppler velocities as a surrogate for stroke volume. The optimal sensed and paced AV delay is determined by the maximum aortic time-velocity integral value at 6 selected paced and sensed AV delays. A typical protocol will include measurements at AV delays of 60, 80, 100, 120, 140, and 160 milliseconds, with each paced and sensed AV delay setting separated by a rest period of at least 10 to 15 beats.

SIMPLIFIED DOPPLER SCREENING FOR AV OPTIMIZATION

A simplified Doppler screening protocol after CRT implantation is proposed using pulsed Doppler mitral inflow, because no consensus currently exists for the routine performance of AV optimization after CRT[77,81] (Figure 14).

Step 1: Optimize the ECG signal, including inverting the QRS complex if necessary.

Step 2: Optimize pulsed Doppler mitral inflow velocity using high sweep speeds, low filters, and the sample volume set at mitral annular level to determine closure clicks.

Step 3: Examine mitral inflow pattern. No AV optimization protocol is required if:

a. E and A waves are clearly identified and separated.
   and
b. Termination of the A wave occurs at least 40 milliseconds before QRS onset or mitral valve closure click.

Note that the mitral valve closure click should be aligned with the QRS complex as a surrogate for the beginning of LV systole. A pattern consistent with stage I diastolic filling (E wave lower than A wave) has not been shown to be improved on by AV alterations after CRT, and it is suggested by Kedia et al that formal AV optimization is not required in these patients.[77] AV optimization is recommended if any of the following are observed: A wave is not identified, E and A waves are merged, or A wave is truncated by mitral closure. AV optimization should be considered if stage II (pseudonormal) or stage III (restrictive) diastolic dysfunction is noted.[77,80] An absent A wave may be associated with intra-atrial conduction delay and often requires a longer AV pacing delay. On the other hand, E and A waves merge when the AV pacing delay is set too long. A truncated A wave requires lengthening of the AV delay. For these scenarios, either the iterative or Ritter methods described in detail above may be performed depending on the preference. Patients in atrial fibrillation or with frequent ventricular ectopy or tachycardia would not be appropriate candidates for AV optimization. Patients with mitral prosthetic valves may also be problematic.

BIVENTRICULAR (V-V) OPTIMIZATION

The recent generation of CRT devices allows for optimization of interventricular delays (V-V delays).[82-86] The first evidence of benefit from V-V optimization was reported by Sogaard et al.[87] The CRT settings were further optimized by V-V timing in 20 patients, resulting in an additional increase in LV EF (from 22 ± 6% at baseline to 30 ± 5% after CRT to 34 ± 6% after V-V optimization, $P < .01$). In

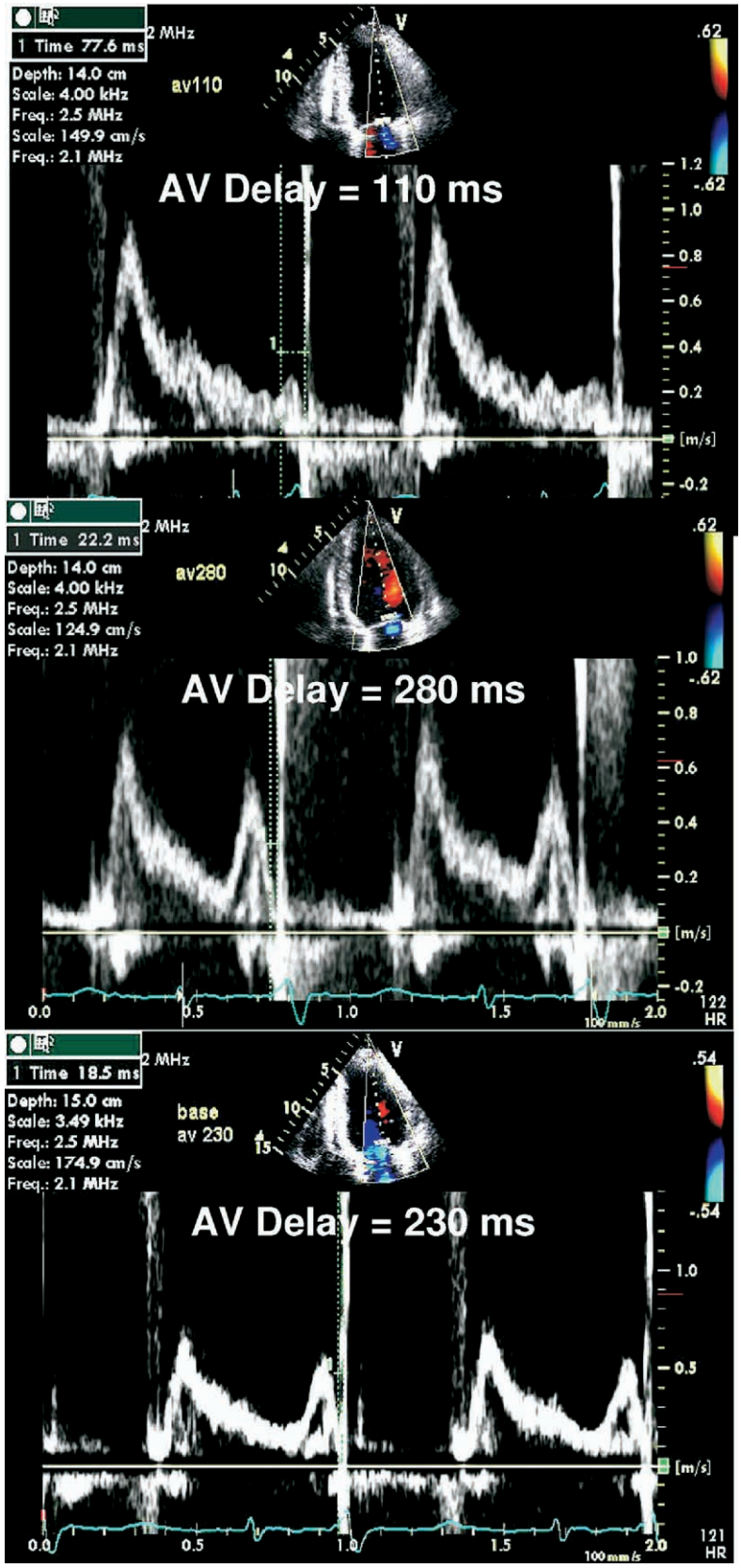

Figure 13 Atrioventricular optimization using mitral inflow velocities in patient with intra-atrial conduction delay. Default setting of 110 milliseconds resulted in loss of mitral inflow A wave (*top*). Delays of 280 milliseconds (*middle*) and 230 milliseconds (*bottom*) improved filling with contribution of atrial component. Alignment of mitral closure click with end of A wave was believed to be optimal with 230-millisecond delay.

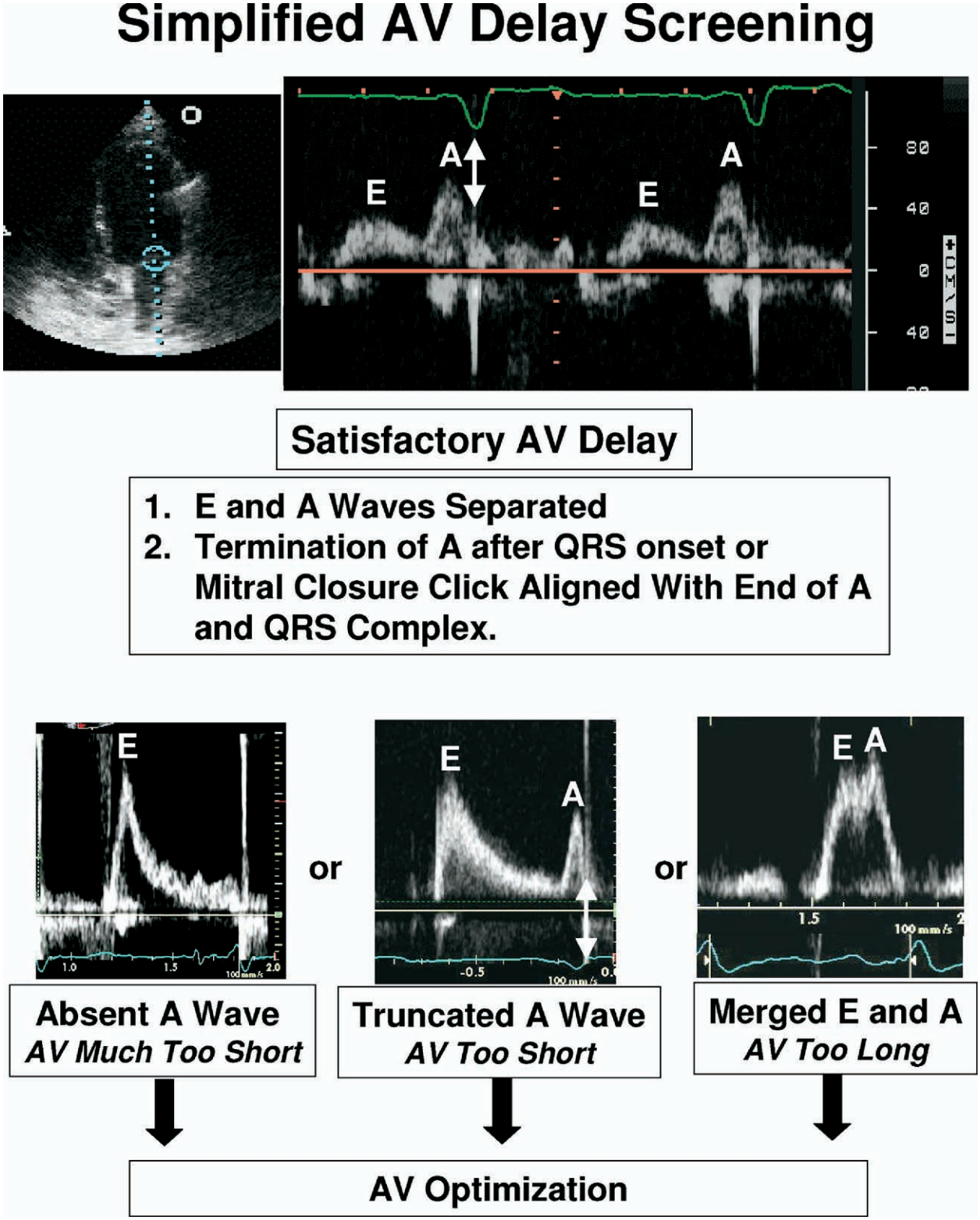

Figure 14 Simplified atrioventricular (AV) delay screening using mitral inflow Doppler velocities. Sample volume is placed within mitral valve to see closure click. AV optimization may not be necessary if E and A waves are separated, and termination of A wave is before QRS onset or mitral closure click aligned with end of A and QRS complex (usually type I diastolic dysfunction with E lower than A) (*top*). AV optimization is indicated if A wave is truncated, E and A waves are merged, or A wave is absent (*bottom*). Optimization may be considered if stage II (pseudonormal) or stage III (restrictive) diastolic filling patterns are present.

addition, Bordachar et al demonstrated that V-V optimization resulted in a significant reduction in MR.[88,89] V-V optimization is generally performed by changing the V-V sequence, starting with the LV being activated before the RV, and then stepwise lengthening or shortening of the V-V interval (eg, with intervals of 20 milliseconds) and measuring the highest aortic time-velocity integral. Current studies have shown that subsets of patients do acutely benefit from V-V optimization, but long-term benefit has yet to be determined.

DYSSYNCHRONY IN THE NARROW QRS PATIENT POPULATION

Mechanical dyssynchrony may exist in a subset of patients with heart failure who have narrow QRS duration (<120 milliseconds). If CRT can be shown to be of benefit to these patients, the application of echocardiographic assessment of dyssynchrony is potentially of great importance for patient selection for therapy.[20,21,64] Bleeker et al showed CRT to benefit 33 patients with NYHA class III/VI heart failure and EF less than or equal to 35%, but QRS less than 120 milliseconds, who had mechanical dyssynchrony defined as a septal-to-lateral wall time-to-peak systolic velocity delay of greater than or equal to 65 milliseconds by TD.[90] In a separate study, Yu et al reported results on 51 patients with heart failure with narrow QRS (<120 milliseconds) who had CRT based on TD measures of dyssynchrony. CRT resulted in significant reductions of LV end-systolic volume, and improvement of NYHA class, 6-minute hall-walk distance, and EF, similar to patients with wide QRS who underwent CRT.[91] The first randomized trial of CRT in patients with heart failure with narrow QRS complexes (<130 milliseconds), known as the RethinQ trial, was recently published by Beshai et al.[92] Dyssynchrony was defined as a TD septal-to-lateral wall cutoff of greater than or equal to 65 milliseconds from either apical 4-chamber views or apical long-axis views, or M-mode septal to posterior wall delay greater than or equal to 130 milliseconds. All patients who met inclusion criteria (96% by TD) had CRT devices implanted, and 172 were randomized to either CRT-off as a control or CRT-on. This trial failed to show a therapeutic effect of CRT on the primary end point of peak myocardial oxygen consumption. Although a positive effect of CRT was observed on the secondary end point of improvement in NYHA functional class, other parameters including quality-of-life score, 6-minute walk test, and LV reverse remodeling did not change. Benefit of CRT on 6-minute walk distance, however, was demonstrated in patients with nonischemic disease. A prespecified subgroup analysis of patients with borderline QRS duration between 120 and 130 milliseconds and dyssynchrony showed benefit of CRT by significantly improving their peak myocardial oxygen consumption and NYHA functional class.[92] In summary, the RethinQ randomized trial concluded as mostly negative, however, many unanswered questions remain. It is unclear whether the type or degree of dyssynchrony may be refined in this narrow QRS population to predict response to CRT, or whether other patient selection factors may impact results. Clearly, future larger randomized clinical trials are required to determine the role of CRT in patients with narrow QRS, and the potential pivotal role that echocardiographic Doppler will play in their selection for therapy.

APPLICATION OF DYSSYNCHRONY ANALYSIS IN CLINICAL PRACTICE AND REPORTING

Although a number of echocardiographic dyssynchrony methods discussed have suggested superiority to ECG QRS width for predicting response to CRT, evidence from large-scale clinical trials and current practice guidelines do not include an echocardiographic Doppler dyssynchrony study for patient selection.[13] **Accordingly, this writing group currently does not recommend that patients who meet accepted criteria for CRT should have therapy withheld because of results of an echocardiographic Doppler dyssynchrony study**.[13]

We acknowledge that many centers are currently applying these analyses as an adjunct to assist with clinical decision making for CRT for selected patients who may have borderline inclusion criteria, such as a borderline QRS duration. Although limited data are available from clinical trials, enrollment in the CARE-HF randomized CRT trial required patients with borderline QRS duration between 120 and 149 milliseconds to meet two of 3 additional criteria for dyssynchrony: an aortic pre-ejection delay longer than 140 milliseconds, an IVMD longer than 40 milliseconds, or delayed activation of the posterolateral LV wall.[6] In addition, the subgroup analysis of patients with QRS 120 to 129 milliseconds and evidence of mechanical dyssynchrony in RethinQ demonstrated benefit from CRT.[92] Other possible clinical settings where dyssynchrony analysis may potentially play a role is in patients with borderline EF or ambiguous clinical histories for NYHA functional class. If there is a clinical request for a dyssynchrony echocardiogram for these or other scenarios, it is the consensus of this group that it is reasonable for the following dyssynchrony measures to be performed and reported.

TD Opposing Wall Delay (the Maximum Time from S Wave Peak of One Wall to the S Wave Peak of the Opposing Wall) in Apical 4-chamber or Apical Long-axis Views

A cutoff of greater than or equal to 65 milliseconds is consistent with significant dyssynchrony, or Yu index (12-site SD) using longitudinal TD velocities from 3 standard apical views. A cutoff of greater than or equal to 33 milliseconds is consistent with significant dyssynchrony.

IVMD Using Pulsed Doppler from RV Outflow Tracts and LV Outflow Tracts

A cutoff of greater than or equal to 40 milliseconds is consistent with significant dyssynchrony.

Radial Dynamics, Which May be Additive Value, Include Septal-to-Posterior Wall Delay Using M-Mode in Patients With Non-Ischemic Disease With Technically High Quality Data, Or Using Speckle Tracking Radial Strain

A cutoff of greater than or equal to 130 milliseconds is consistent with significant dyssynchrony.

Other indices that appear in Table 2 may be included, if desired by individual laboratories. A conservative approach to carefully exclude mechanical dyssynchrony is advised, because an optimal approach has not yet been clearly defined. Agreement with more than one of these measures improves the confidence in the dyssynchrony analysis,[59] although a precise scheme to their collective additive value is currently unknown. **We advise that the dyssynchrony reporting should not include a recommendation whether a patient should undergo CRT, as this should be a clinical decision on a case-by-case basis for these borderline or**

challenging cases. Many other methods described in this report are promising, but may currently be too technically challenging or underdeveloped.

Echocardiography plays an exciting and evolving role in the care of the patient with CRT, from quantifying improvements in ventricular function and MR to optimizing the device after implantation. Although a great deal of work has been done to quantify mechanical dyssynchrony in hopes of refining patient selection and guiding lead placement, this is a complex and challenging field with future work needed and several promising studies ongoing. Technologic improvements in echocardiographic data acquisition and analysis as well as advances in our understanding of the pathophysiology of dyssynchrony and CRT have great potential to impact future clinical practice and improve patient outcome.

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REFERENCES

1. Abraham WT, Hayes DL. Cardiac resynchronization therapy for heart failure. Circulation 2003;108:2596-603.
2. Butter C, Auricchio A, Stellbrink C, et al. Effect of resynchronization therapy stimulation site on the systolic function of heart failure patients. Circulation 2001;104:3026-3029.
3. Young JB, Abraham WT, Smith AL, et al. Combined Cardiac Resynchronization and Implantable Cardioversion Defibrillation in Advanced Chronic Heart Failure: The MIRACLE ICD Trial. JAMA 2003;289:2685-2694.
4. Bradley DJ, Bradley EA, Baughman KL, et al. Cardiac Resynchronization and Death from Progressive Heart Failure: A Meta-analysis of Randomized Controlled Trials. JAMA 2003;289:730-740.
5. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-Resynchronization Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure. N Engl J Med 2004;350:2140-2150+2227.
6. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539-49.
7. McSwain RL, Schwartz RA, DeLurgio DB, Mera FV, Langberg JJ, Leon AR. The impact of cardiac resynchronization therapy on ventricular tachycardia/fibrillation: an analysis from the combined Contak-CD and InSync-ICD studies. J Cardiovasc Electrophysiol 2005;16:1168-71.
8. Breithardt OA, Sinha AM, Schwammenthal E, et al. Acute effects of cardiac resynchronization therapy on functional mitral regurgitation in advanced systolic heart failure. J Am Coll Cardiol 2003;41:765-770.
9. Lancellotti P, Melon P, Sakalihasan N, et al. Effect of cardiac resynchronization therapy on functional mitral regurgitation in heart failure. Am J Cardiol 2004;94:1462-5.
10. Porciani MC, Dondina C, Macioce R, et al. Echocardiographic examination of atrioventricular and interventricular delay optimization in cardiac resynchronization therapy. Am J Cardiol 2005;95:1108-1110.
11. Turner MS, Bleasdale RA, Vinereanu D, et al. Electrical and mechanical components of dyssynchrony in heart failure patients with normal QRS duration and left bundle-branch block: Impact of left and biventricular pacing. Circulation 2004;109:2544-2549.
12. Gorcsan J III, Kanzaki H, Bazaz R, Dohi K, Schwartzman D. Usefulness of echocardiographic tissue synchronization imaging to predict acute response to cardiac resynchronization therapy. Am J Cardiol 2004;93:1178-81.
13. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation 2005;112:e154-235.
14. Yu CM, Chau E, Sanderson JE, et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. Circulation 2002;105:438-45.
15. Bax JJ, Bleeker GB, Marwick TH, et al. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. J Am Coll Cardiol 2004;44:1834-1840.
16. Bax JJ, Abraham T, Barold SS, et al. Cardiac resynchronization therapy: Part 1–issues before device implantation. J Am Coll Cardiol 2005;46:2153-67.
17. Yu CM, Abraham WT, Bax J, et al. Predictors of response to cardiac resynchronization therapy (PROSPECT) - Study design. Am Heart J 2005;149:600-605.
18. Ghio S, Chung E, Leon A, et al. Predictors of Response to Resynchronization Therapy. Presented at the European Society of Cardiology Meeting. Vienna, Austria. September 4, 2007 [abstract] 2007.
19. Grines CL, Bashore TM, Boudoulas H, Olson S, Shafer P, Wooley CF. Functional abnormalities in isolated left bundle branch block. The effect of interventricular asynchrony. Circulation 1989;79:845-853.
20. Yu CM, Lin H, Zhang Q, Sanderson JE. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. Heart 2003;89:54-60.
21. Bleeker GB, Schalij MJ, Molhoek SG, et al. Frequency of left ventricular dyssynchrony in patients with heart failure and a narrow QRS complex. Am J Cardiol 2005;95:140-2.
22. Sade LE, Kanzaki H, Severyn D, Dohi K, Gorcsan J III. Quantification of radial mechanical dyssynchrony in patients with left bundle branch block and idiopathic dilated cardiomyopathy without conduction delay by tissue displacement imaging. Am J Cardiol 2004;94:514-518.
23. Spragg DD, Kass DA. Pathobiology of left ventricular dyssynchrony and resynchronization. Prog Cardiovasc Dis 2006;49:26-41.
24. Bilchick KC, Helm RH, Kass DA. Physiology of biventricular pacing. Curr Cardiol Rep 2007;9:358-65.
25. Kass DA. Ventricular resynchronization: pathophysiology and identification of responders. Rev Cardiovasc Med 2003;4 Suppl 2:S3-S13.
26. Leclercq C, Faris O, Tunin R, et al. Systolic improvement and mechanical resynchronization does not require electrical synchrony in the dilated failing heart with left bundle-branch block. Circulation 2002;106:1760-3.
27. Nelson GS, Berger RD, Fetics BJ, et al. Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. Circulation 2000;102:3053-9.
28. Kanzaki H, Bazaz R, Schwartzman D, Dohi K, Sade LE, Gorcsan J III. A mechanism for immediate reduction in mitral regurgitation after cardiac resynchronization therapy: insights from mechanical activation strain mapping. J Am Coll Cardiol 2004;44:1619-25.
29. Bashir JG, Frank G, Tyers O, Lampa M, Yamaoka R. Combined use of transesophageal ECHO and fluoroscopy for the placement of left ventricular pacing leads via the coronary sinus. Pacing Clin Electrophysiol 2003;26:1951-4.
30. Ansalone G, Giannantoni P, Ricci R, Trambaiolo P, Fedele F, Santini M. Doppler myocardial imaging to evaluate the effectiveness of pacing sites in patients receiving biventricular pacing. Journal of the American College of Cardiology 2002;39:489-499.
31. Yu CM, Fung WH, Lin H, Zhang Q, Sanderson JE, Lau CP. Predictors of left ventricular reverse remodeling after cardiac resynchronization therapy for heart failure secondary to idiopathic dilated or ischemic cardiomyopathy. Am J Cardiol 2003;91:684-8.

32. Bleeker GB, Kaandorp TA, Lamb HJ, et al. Effect of posterolateral scar tissue on clinical and echocardiographic improvement after cardiac resynchronization therapy. Circulation 2006;113:969-76.
33. Adelstein EC, Saba S. Scar burden by myocardial perfusion imaging predicts echocardiographic response to cardiac resynchronization therapy in ischemic cardiomyopathy. Am Heart J 2007;153:105-12.
34. Pitzalis MV, Iacoviello M, Romito R, et al. Cardiac resynchronization therapy tailored by echocardiographic evaluation of ventricular asynchrony. J Am Coll Cardiol 2002;40:1615-22.
35. Pitzalis MV, Iacoviello M, Romito R, et al. Ventricular asynchrony predicts a better outcome in patients with chronic heart failure receiving cardiac resynchronization therapy. J Am Coll Cardiol 2005;45:65-9.
36. Marcus GM, Rose E, Viloria EM, et al. Septal to posterior wall motion delay fails to predict reverse remodeling or clinical improvement in patients undergoing cardiac resynchronization therapy. J Am Coll Cardiol 2005;46:2208-14.
37. Bax JJ, Abraham T, Barold SS, et al. Cardiac resynchronization therapy: Part 2–issues during and after device implantation and unresolved questions. J Am Coll Cardiol 2005;46:2168-82.
38. Bax JJ, Marwick TH, Molhoek SG, et al. Left ventricular dyssynchrony predicts benefit of cardiac resynchronization therapy in patients with end-stage heart failure before pacemaker implantation. Am J Cardiol 2003;92:1238-40.
39. Bleeker GB, Bax JJ, Schalij MJ, van der Wall EE. Tissue Doppler imaging to assess left ventricular dyssynchrony and resynchronization therapy. Eur J Echocardiogr 2005;6:382-4.
40. Bortone A, Macia JC, Leclercq F, Pasquie JL. Monomorphic ventricular tachycardia induced by cardiac resynchronization therapy in patient with severe nonischemic dilated cardiomyopathy. Pacing Clin Electrophysiol 2006;29:327-30.
41. Sogaard P, Egeblad H, Kim WY, et al. Tissue Doppler imaging predicts improved systolic performance and reversed left ventricular remodeling during long-term cardiac resynchronization therapy. J Am Coll Cardiol 2002;40:723-30.
42. Sogaard P, Hassager C. Tissue Doppler imaging as a guide to resynchronization therapy in patients with congestive heart failure. Curr Opin Cardiol 2004;19:447-51.
43. Yu CM, Fung JW, Zhang Q, et al. Tissue Doppler imaging is superior to strain rate imaging and postsystolic shortening on the prediction of reverse remodeling in both ischemic and nonischemic heart failure after cardiac resynchronization therapy. Circulation 2004;110:66-73.
44. Yu CM, Gorcsan J III, Bleeker GB, et al. Usefulness of tissue Doppler velocity and strain dyssynchrony for predicting left ventricular reverse remodeling response after cardiac resynchronization therapy. Am J Cardiol 2007;100:1263-70.
45. Bax JJ, Molhoek SG, van Erven L, et al. Usefulness of myocardial tissue Doppler echocardiography to evaluate left ventricular dyssynchrony before and after biventricular pacing in patients with idiopathic dilated cardiomyopathy. Am J Cardiol 2003;91:94-7.
46. Sun JP, Chinchoy E, Donal E, et al. Evaluation of ventricular synchrony using novel Doppler echocardiographic indices in patients with heart failure receiving cardiac resynchronization therapy. J Am Soc Echocardiogr 2004;17:845-50.
47. Notabartolo D, Merlino JD, Smith AL, et al. Usefulness of the peak velocity difference by tissue Doppler imaging technique as an effective predictor of response to cardiac resynchronization therapy. Am J Cardiol 2004;94:817-820.
48. Bleeker GB, Bax JJ, Fung JW, et al. Clinical versus echocardiographic parameters to assess response to cardiac resynchronization therapy. Am J Cardiol 2006;97:260-3.
49. Yu CM, Fung JW, Chan CK, et al. Comparison of efficacy of reverse remodeling and clinical improvement for relatively narrow and wide QRS complexes after cardiac resynchronization therapy for heart failure. J Cardiovasc Electrophysiol 2004;15:1058-65.
50. Yu CM, Zhang Q, Fung JWH, et al. A novel tool to assess systolic asynchrony and identify responders of cardiac resynchronization therapy by tissue synchronization imaging. J Am Coll Cardiol 2005;45:677-684.
51. Penicka M, Bartunek J, De Bruyne B, et al. Improvement of left ventricular function after cardiac resynchronization therapy is predicted by tissue Doppler imaging echocardiography. Circulation 2004;109:978-83.
52. Breithardt OA, Stellbrink C, Herbots L, Claus P, Sinha AM, Bijnens B, Hanrath P, Sutherland GR. Cardiac resynchronization therapy can reverse abnormal myocardial strain distribution in patients with heart failure and left bundle branch block. J Am Coll Cardiol 2003;42:486-94.
53. Yu CM, Zhang Q, Chan YS, et al. Tissue Doppler velocity is superior to displacement and strain mapping in predicting left ventricular reverse remodelling response after cardiac resynchronisation therapy. Heart 2006;92:1452-6.
54. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J III. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. Circulation 2006;113:960-8.
55. Helm RH, Leclercq C, Faris OP, et al. Cardiac dyssynchrony analysis using circumferential versus longitudinal strain: implications for assessing cardiac resynchronization. Circulation 2005;111:2760-7.
56. D'Hooge J, Heimdal A, Jamal F, et al. Regional Strain and Strain Rate Measurements by Cardiac Ultrasound: Principles, Implementation and Limitations. Eur J Echocardiogr 2000;1:154-170.
57. Dohi K, Suffoletto MS, Schwartzman D, Ganz L, Pinsky MR, Gorcsan J III. Utility of echocardiographic radial strain imaging to quantify left ventricular dyssynchrony and predict acute response to cardiac resynchronization therapy. Am J Cardiol 2005;96:112-116.
58. Dohi K, Pinsky MR, Kanzaki H, Severyn D, Gorcsan J III. Effects of radial left ventricular dyssynchrony on cardiac performance using quantitative tissue Doppler radial strain imaging. J Am Soc Echocardiogr 2006;19:475-82.
59. Gorcsan J III, Tanabe M, Bleeker GB, et al. Combined longitudinal and radial dyssynchrony predicts ventricular response after resynchronization therapy. J Am Coll Cardiol 2007;50:1476-83.
60. Sugeng L, Weinert L, Lang RM. Left ventricular assessment using real time three dimensional echocardiography. Heart 2003;89 Suppl 3:iii29-36.
61. Kapetanakis S, Kearney MT, Siva A, Gall N, Cooklin M, Monaghan MJ. Real-time three-dimensional echocardiography: a novel technique to quantify global left ventricular mechanical dyssynchrony. Circulation 2005;112:992-1000.
62. Bordachar P, Lafitte S, Reuter S, et al. Echocardiographic parameters of ventricular dyssynchrony validation in patients with heart failure using sequential biventricular pacing. J Am Coll Cardiol 2004;44:2157-65.
63. Achilli A, Peraldo C, Sassara M, et al. Prediction of Response to Cardiac Resynchronization Therapy: The Selection of Candidates for CRT (SCART) Study. Pacing Clin Electrophysiol 2006;29 Suppl 2:S11-9.
64. Ghio S, Constantin C, Klersy C, et al. Interventricular and intraventricular dyssynchrony are common in heart failure patients, regardless of QRS duration. Eur Heart J 2004;25:571-578.
65. Richardson M, Freemantle N, Calvert MJ, Cleland JG, Tavazzi L. Predictors and treatment response with cardiac resynchronization therapy in patients with heart failure characterized by dyssynchrony: a pre-defined analysis from the CARE-HF trial. Eur Heart J 2007;28:1827-34.
66. Breithardt OA, Stellbrink C, Kramer AP, et al. Echocardiographic quantification of left ventricular asynchrony predicts an acute hemodynamic benefit of cardiac resynchronization therapy. J Am Coll Cardiol 2002;40:536-45.
67. Cannesson M, Tanabe M, Suffoletto MS, Schwartzman D, Gorcsan J III. Velocity vector imaging to quantify ventricular dyssynchrony and predict response to cardiac resynchronization therapy. Am J Cardiol 2006;98:949-53.
68. Sutton MG, Plappert T, Hilpisch KE, Abraham WT, Hayes DL, Chinchoy E. Sustained reverse left ventricular structural remodeling with cardiac resynchronization at one year is a function of etiology: quantitative Doppler echocardiographic evidence from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). Circulation 2006;113:266-72.
69. Sutton MS, Keane MG. Reverse remodeling in heart failure with cardiac resynchronisation therapy. Heart 2007;93:167-71.

70. Solomon SD, Skali H, Anavekar NS, et al. Changes in ventricular size and function in patients treated with valsartan, captopril, or both after myocardial infarction. Circulation 2005;111:3411-9.
71. Yu CM, Bleeker GB, Fung JW, et al. Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy. Circulation 2005;112:1580-6.
72. Murphy RT, Sigurdsson G, Mulamalla S, et al. Tissue synchronization imaging and optimal left ventricular pacing site in cardiac resynchronization therapy. Am J Cardiol 2006;97:1615-21.
73. Ronaszeki A. Hemodynamic Consequences of the Timing of Atrial Contraction During Complete AV Block. Acta Biomedica Lovaniensia 1989;15.
74. Auricchio A, Stellbrink C, Block M, et al. Effect of pacing chamber and atrio-ventricular delay on acute systolic function of paced patients with congestive heart failure: the Pacing Therapies for Congestive Heart Failure Study Group: the Guidant Congestive Heart Failure Research Group. Circulation. Circulation 1999;99:2993-3001.
75. Stelbrink C, Breithardt OA, Franke A. Impact of cardiac resychronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances. J Am Coll Cardiol 2001;38:1957-1965.
76. Sawhney NS, Waggoner AD, Garhwal S, Chawla MK, Osborn J, Faddis MN. Randomized prospective trial of atrioventricular delay programming for cardiac resynchronization therapy. Heart Rhythm 2004;1:562-7.
77. Kedia N, Ng K, Apperson-Hansen C, et al. Usefulness of atrioventricular delay optimization using Doppler assessment of mitral inflow in patients undergoing cardiac resynchronization therapy. Am J Cardiol 2006;98: 780-5.
78. Waggoner A, Faddis M, Osborn J, et al. AV delay programming and cardiac resynchronization therapy: left ventricular diastolic filling indices and relation to stroke volume. J Am Coll Cardiol 2005;45(3A):99A.
79. Ritter P, Padeletti L, Gillio-Meina L, et al. Determination of the optimal atrioventricular delay in DDD pacing: comparison between echo and peak endocardial acceleration measurements. Europace. 1999;1:126-130.
80. Oh JK, Hatle L, Tajik AJ, Little WC. Diastolic heart failure can be diagnosed by comprehensive two-dimensional and Doppler echocardiography. J Am Coll Cardiol 2006;47:500-6.
81. Harry M. Pacemaker Optimization. In: Harry M, ed. Essentials of Echocardiography: An Illustrative Guide. *Cardiac Ultrasound Consulting*: Cardiotext, 2006:256-257.
82. Porciani MC, Dondina C, Macioce R, et al. Temporal variation in optimal atrioventricular and interventricular delay during cardiac resynchronization therapy. J Card Fail 2006;12:715-9.
83. Naqvi TZ, Rafique AM, Peter CT. Echo-driven V-V optimization determines clinical improvement in non responders to cardiac resynchronization treatment. Cardiovasc Ultrasound 2006;4:39.
84. Vanderheyden M, De Backer T, Rivero-Ayerza M, et al. Tailored echocardiographic interventricular delay programming further optimizes left ventricular performance after cardiac resynchronization therapy. Heart Rhythm 2005;2:1066-72.
85. Perego GB, Chianca R, Facchini M, et al. Simultaneous vs. sequential biventricular pacing in dilated cardiomyopathy: an acute hemodynamic study. Eur J Heart Fail 2003;5:305-13.
86. Boriani G, Muller CP, Seidl KH, et al. Randomized comparison of simultaneous biventricular stimulation versus optimized interventricular delay in cardiac resynchronization therapy. The Resynchronization for the HemodYnamic Treatment for Heart Failure Management II implantable cardioverter defibrillator (RHYTHM II ICD) study. Am Heart J 2006;151:1050-8.
87. Sogaard P, Egeblad H, Pedersen AK, et al. Sequential versus simultaneous biventricular resynchronization for severe heart failure: Evaluation by tissue Doppler imaging. Circulation 2002;106:2078-2084.
88. Bordachar P, Garrigue S, Lafitte S, et al. Interventricular and intra-left ventricular electromechanical delays in right ventricular paced patients with heart failure: implications for upgrading to biventricular stimulation. Heart 2003;89:1401-5.
89. Bordachar P, Garrigue S, Reuter S, et al. Hemodynamic assessment of right, left, and biventricular pacing by peak endocardial acceleration and echocardiography in patients with end-stage heart failure. Pacing Clin Electrophysiol 2000;23:1726-30.
90. Bleeker GB, Holman ER, Steendijk P, et al. Cardiac resynchronization therapy in patients with a narrow QRS complex. J Am Coll Cardiol 2006;48:2243-50.
91. Yu CM, Chan YS, Zhang Q, et al. Benefits of cardiac resynchronization therapy for heart failure patients with narrow QRS complexes and coexisting systolic asynchrony by echocardiography. J Am Coll Cardiol 2006;48:2251-7.
92. Beshai JF, Grimm RA, Nagueh SF, et al. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. N Engl J Med 2007; 357:2461-71.