ECHOCARDIOGRAPHIC EVALUATION OF MECHANICAL DYSSYNCHRONY

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INTRODUCTION

Congestive heart failure (CHF) is the leading cause of hospitalization[1] and accounts for about 300,000 deaths in the United States.[2] Global left ventricular (LV) function can be compromised by either absolute decrease of myocardial contraction or discoordinate myocardial contraction of different segments, or both. In normal hearts, ventricular electric activation and contraction occur in a highly coordinated manner. However, among patients with systolic heart failure, the prevalence of intraventricular conduction delay is 30-50%. These patients have electrical and mechanical dyssynchrony.

In patients with left bundle branch block (LBBB), LV dyssynchrony results from delayed contraction of the LV free wall. Early septal contraction leads to stretching of the lateral wall during early systole; in turn, the delayed contraction of the LV lateral wall causes the septum to stretch during late systole. The early systolic stretch of the lateral wall and the late systolic stretch of the septum lead to delayed intraventricular pressure rise (dP/dt) and reduced cardiac output. LV dyssynchrony also induces pathological changes at the molecular, cellular, and tissue levels, contributing to the increased mortality and morbidity in patients with heart failure.[3]

Patients with heart failure and dyssynchrony may therefore benefit from therapies aimed at restoring synchrony. This can be achieved by atrial synchronized biventricular pacing or LV pacing only, i.e., cardiac resynchronization therapy (CRT). In this procedure, a pacing lead is inserted close to the LV free wall through the cardiac veins in addition to RV pacing lead implantation.[4] Early stimulation by LV pacing leads to earlier LV lateral wall contraction and an improvement in LV dyssynchrony.[4]

EFFECTS OF RESYNCHRONIZATION

Acute effects

As reported in animal and human studies, CRT causes an acute improvement of LV function, including increased +dP/dt, stroke volume, and cardiac output and decreased end-systolic wall stress.[4,5] CRT also has been reported to improve RV function and decrease the severity of mitral regurgitation as assessed by tissue Doppler (TD) imaging6 and Doppler echocardiography, respectively.[7]

Midterm and long-term effects

The acute improvement in LV function does not appear to be directly linked to the CRT response.[8] To date, at least eight large randomized clinical trials in CRT have been completed along with numerous retrospective and nonrandomized studies.[9-16] Varying effects on clinical and echocardiographic characteristics have been reported, including an improvement in NYHA functional class, six minute walk distance, exercise capacity (peak oxygen consumption), hospitalization for heart failure and cardiac mortality. Echocardiographic studies showed improvement in stroke volume, ejection fraction and reverse remodeling (reduction of LV dimensions, end-diastolic and end-systolic volumes). While a universal definition of responders to CRT is not present, the most frequently used indicator is LV reverse remodeling, i.e., reduction in LV end-systolic volume. Patients with a reduction of 15% or more after CRT are considered responders.

PREDICTION OF THE RESPONSE TO CRT BY QRS DURATION

The width of the QRS complex and/or presence of complete LBBB in surface electrocardiogram are important prognostic factors in CHF patients.[17,18] QRS width has also been shown to correlate with dyssynchrony.[19] Based on this, the following criteria for CRT are endorsed: 1) NYHA function class ≥3; 2) LVEF ≤ 35%; and 3) QRS ≥120 ms. This is well supported by clinical trials showing symptomatic improvement and LV reverse remodeling in patients with a prolonged QRS duration. In particular, patients with QRS duration >150 ms showed the most improvement; however, 20-30% of patients with a wide QRS duration do not show beneficial effects after CRT.[20,21] Furthermore, QRS duration was similar prior to biventricular pacing in responders and nonresponders, and studies demonstrated that QRS width does not correlate well with LV intraventricular dyssynchrony.[22] On the other hand, the identification of mechanical dyssynchrony by TD imaging can accurately predict CRT responses.[23]

EVALUATION OF LV (INTRAVENTRICULAR) DYSSYNCHRONY USING ECHOCARDIOGRAPHY

Echocardiography has become the imaging modality to assess LV dyssynchrony because of its wide availability,

low cost and flexibility. Numerous echocardiographic variables have been used to identify the presence of LV dyssynchrony and to predict CRT response.

M-mode echo

In the M-mode image of the parasternal long axis view, the maximal inward motion indicating maximal displacement of anterior septum and posterior wall can be identified from the endocardial borders. The time difference of the maximal inward motion of these two walls indicates the extent of mechanical delay. Pitzalis reported that a time delay of ≥130ms can predict LV reverse remodeling and event-free survival after CRT.[24-26] However, this approach has limitations. First, only wall motion of anterior septum and posterior wall can be evaluated. Other walls where the contraction is most frequently delayed (e.g., lateral wall) could not be reliably assessed in M-mode images. Second, the maximal inward motion of endocardium of these two walls can be flat in some cases (e.g., patients with depressed function), making it difficult to reliably identify the maximal movement of either or both walls.

Two-dimensional (2D) echo

Tracking the endocardial movement in 2D images provides more insights in myocardial contraction in multiple myocardial segments. Breithardt et al. tracked the endocardial movement using a special software and plotted the displacement of regional endocardium measured from echocardiography over time, then analyzed data in the frequency domain to quantify the phase relationship between the displacement curves of different regions.[27] Using this method, the synchrony between two regional displacement curves can be calculated by the difference between their respective phase angles. Phase differences near 0° indicate near-perfect synchrony, whereas a difference of 180° defines maximal dyssynchrony. In healthy individuals, septal-lateral phase angle difference is monophasic and <25°, indicating near synchrony. However, three different phase relationships between septal-lateral motion were defined in patients with advanced heart failure and LBBB: type I with monophasic displacement curve of both septal and lateral wall and phase angle differences <25°; type II with either monophasic or biphasic displacement curves in septal and lateral wall and angle difference >25°; and type III with triphasic or inverted monophasic septal displacement with phase angle difference significantly >25°.

The authors further examined the immediate and early effect of CRT on functional improvement. They found that in patients with type II displacement pattern, LV function and synchrony showed the best improvement with LV-only or biventricular pacing, and the improvement was associated with an increase of LVEF. This study demonstrated that only patients with significant mechanical delay experience functional improvement with CRT. It is also possible to use echo contrast agents to enhance endocardial contour tracing and then calculate the regional fractional area changes of 24 LV sectors. The coefficient of variation of the regional fractional area change in all sectors indicates the presence of spatial dyssynchrony, whereas the coefficient of variation in the time to maximal regional fractional area change is an index of temporal dyssynchrony.

Although these approaches appear promising, the methodologies are quite complex for routine clinical application unless special online processing software is integrated into the ultrasound system.

Tissue Doppler imaging (TDI)

TD imaging usually provides clear signals of velocities in different myocardial regions and has become by far the most frequently used echocardiographic method to quantify LV dyssynchrony. In either pulsed-wave Doppler spectrum or color-coded images, time to the onset of systolic velocity (Ts-onset), time to the peak systolic velocity (Ts) and time to the peak displacement (TT) can be measured to indicate different LV mechanical events. The absolute or maximal difference or standard deviation of these variables in myocardial segments may be calculated to identify the presence of LV dyssynchrony.

Pulse wave TD

Several studies have demonstrated the value of Ts-onset in pulse wave Doppler spectrum to assess LV dyssynchrony.[28-30] Penicka et al. recorded the pulse wave Doppler signals and measured Ts-onset in LV basal septum, lateral wall and posterior myocardial segments. The difference between the longest and shortest time interval of Ts-onset of these three segments was used as an indicator of LV intraventricular dyssynchrony. Meanwhile, the difference between the basal septum and RV free wall was considered an indicator of interventricular dyssynchrony.

The sum of LV intraventricular dyssynchrony and interventricular dyssynchrony at 102ms showed the highest accuracy in predicting the improvement of LVEF six months after CRT, with a sensitivity of 96% and specificity of 77%.[28] Bordachar et al. performed detailed analysis of LV dyssynchrony by measuring time intervals in pulse wave TD spectra.[31] They measured both Ts-onset and Ts in 12 LV basal and mid segments and then calculated the difference between the longest and shortest Ts-onset and Ts to indicate maximal LV mechanical delay. They also calculated the standard deviation of Ts-onset and Ts in 12 LV segments as an index of LV systolic dyssynchrony. In different pacing modes, changes in both LV mechanical delay and systolic dyssynchrony indices correlated significantly with changes of cardiac output and other hemodynamic parameters. Despite these promising results, using pulse wave TD to measure time intervals can be challenging when gain and filters are not carefully adjusted, as the onset and peak signals may appear blurred. In addition, the measurements in different myocardial segments are not simultaneous, and minor variations in heart rate can lead

to inaccuracies.

Color-coded TD

Color mapping of myocardial velocities in real-time 2D images provides a simultaneous display of color-coded velocities from all myocardial segments in a given view (e.g., apical 4-chamber view). Myocardial velocities can be displayed in a graphical format from these images, and their traces usually show clear onset and peak. When the imaging sector is narrowed just for imaging a single wall, the frame rate can reach 200 frames per second. More importantly, with the color sector widened to the full view, but with proper adjustment of depth, the frame rate is frequently >100 frames per second. The high temporal resolution is extremely important in timing mechanical delay. Therefore, color-coded TD is the recommended method to evaluate LV dyssynchrony. The three most frequently used indexes are: the time delay of Ts from basal septum to basal lateral wall and standard deviation of Ts in 12 basal and mid LV segments.

The time delay between basal septum and basal lateral wall was evaluated by Bax et al. in 85 patients before and six months after CRT. Seventy-four percent of these patients showed at least a one NYHA-class improvement and at least a 25% improvement in the six-minute walking distance. These patients had a better prognosis and were defined as CRT responders. They were identified at baseline by a Ts delay ≥65 ms between basal septum and lateral wall.[32] In another study, Notobartolo et al. measured Ts in six LV basal segments (septal, lateral, anterior, inferior, anteroseptal and posterior) and calculated maximal difference of Ts (in ejection and post-ejection phases) as an index of LV dyssynchrony.[33] Patients with a maximal difference in Ts ≥110ms had significantly better clinical and echocardiographic outcomes after CRT.

Perhaps the most frequently used LV dyssynchrony index is the standard deviation of the time to peak systolic velocities in 12 LV segments. Yu et al.

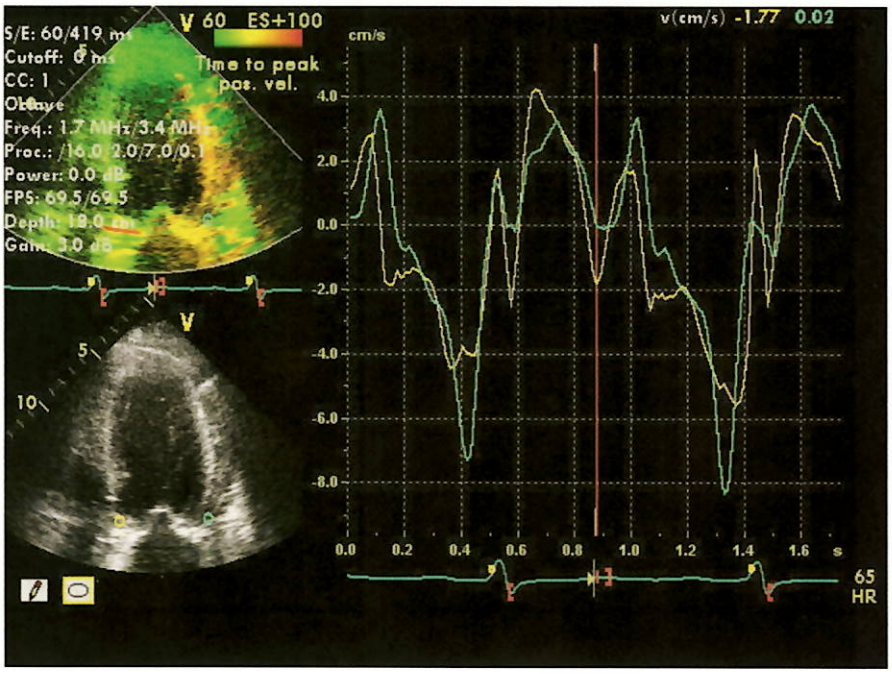

Figure 1. Example of tissue synchronization imaging (TSI) from a patient with mechanical dyssynchrony. Left upper panel shows the apical 4-chamber view with TSI color map superimposed on the different myocardial segments. Basal lateral wall appears orange, while basal segment of inferior septum appears green. This indicates a significant delay in lateral systolic velocity compared with septal contraction. Lower left panel shows the 4-chamber view in gray scale. Both images show the position of the sample volume used to derive the graphs on the right (septum in yellow, lateral wall in blue). Right panel displays the velocity curves — with the septum base in yellow and the lateral base in blue. The vertical red line in the middle marks the end of systole. The peak lateral ejection velocity in blue was delayed by 71 ms compared with the peak septal ejection velocity in yellow.

showed that this index (≥31ms) is the most powerful predictor of LV reverse remodeling in both ischemic and non-ischemic heart failure patients three months after CRT.[34]

In addition to time to onset and peak systolic velocity, tissue displacement can be calculated by integrating myocardial velocities over time. In some ultrasound systems, tissue displacement can be displayed in real-time color mapping as well. Patients with LBBB show early septal displacement compared with delayed radial systolic excursion of posterior, lateral and inferior walls.[35] Tissue displacement can also be used to detect postsystolic shortening (or delayed longitudinal contraction). The extent of postsystolic shortening, confirmed by strain rate imaging, can predict the long-term improvement of LVEF.[36]

Tissue synchronization imaging (TSI)

Although it is easy to measure time to the peak systolic velocity off-line from the stored color TDI images, measuring 12 segments can be very time consuming. It is easier to display the presence of dyssynchrony and the segments with latest contraction using 2D real-time images. In GE Vivid systems, a special signal processing algorithm is used for the automatic detection of peak contraction velocities, namely, tissue synchronization imaging (Figure 1). In TSI, time to peak velocities is color coded and superimposed on the 2D grayscale images.[5,37] Green is coded for normal timing, yellow-orange for moderate delay, and red for

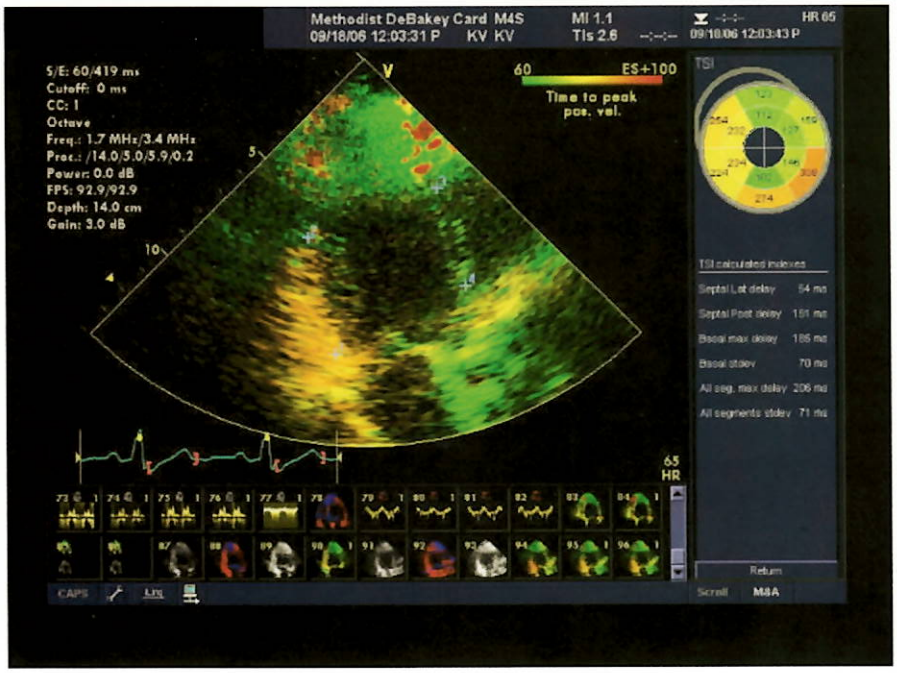

Figure 2. Bull's-eye map showing the time interval between QRS complex and peak systolic ejection velocity in the different myocardial segments, using the TSI color map. Shorter time intervals are shown in green, intermediate delays in yellow, and the longest delays in orange/red. This patient had a time delay of 151 ms between basal segment of anterior septum (green) and basal posterolateral wall (orange). The Ts-SD (Yu index) for the 12 segments was 71 ms. Both observations are indicative of significant mechanical dyssynchrony and a high likelihood of reverse LV remodeling with successful CRT.

severe delays in peak longitudinal velocity. The interval for displaying Ts can be manually adjusted, usually with the onset falling after aortic valve opening to avoid detecting the high isovolumic contraction velocities.

Myocardial velocity traces can be displayed and Ts calculated from TSI images. The time delay in posterior or lateral walls or Ts standard deviation in multiple segments is of similar predictive value to those derived from conventional TSI images.[5,37] In addition to color mapping of time to peak ejection velocities, a bull's-eye map of time to peak contraction in the 16 segments can be obtained along with an automatically derived Ts standard deviation (Figure 2). Furthermore, 3-D reconstruction of LV mechanical events can be achieved using TSI in multiple apical planes. However, there is limited data on whether such 3D reconstruction can improve the accuracy for selecting patients for CRT.

Strain and strain rate imaging

Strain and strain rate (SR) measure myocardial deformation and rate and eliminate the effects of tethering and translation on tissue velocity. However, the value of SR imaging in assessing CRT effect has been controversial. Yu et al. found that TDI is superior to SRI for predicting LV reverse remodeling.[34] However, other researchers argued that strain and strain rate measured in Yu's study were derived from noisy tissue Doppler signals that were acquired with a low frame rate. Thus, the errors could have been amplified and the results may be inaccurate, especially for timing events.[38] Yu et al. also questioned the value of postsystolic shortening phenomenon for assessing LV dyssynchrony. However, one may disagree with their findings due to their equivocal definition of postsystolic shortening.

Whether SRI has incremental value in evaluating inter- and intraventricular mechanical dyssynchrony and in selecting patients for CRT deserves additional studies. The angle dependency of Doppler derived SR is an important limitation to the above method. On the other hand, tissue speckle tracking does not have that limitation and can provide useful information for defining cardiac coordination. This was recently confirmed by Suffoletto et al. The investigators measured the time to peak radial strain in six segments in a mid-LV short-axis cross section and calculated the maximal difference of the time to peak radial strain.[39] A maximal difference of 130ms predicted a ≥ 15% increase in LVEF during follow up, with a sensitivity of 89% and a specificity of 83%.

Three-dimensional imaging

Regional fractional area change of LV segments can be calculated using border detection of the cavity with contrast enhancement. The variation in regional fractional area change among different LV sectors can be used as an index of dyssynchrony. Similarly, if regional volume can be calculated, variations of regional EF may be more sensitive in detecting LV dyssynchrony. Using currently available 3D transducers, calculation of LV volumes can be very quick and accurate. Kapetanakis et al. measured the time to minimal regional volume in the 16 myocardial segments and used the standard deviation from the 16 segments as a dyssynchrony index.[40] A cut-off value of 8.3% identified the CRT responders.

ASSESSMENT OF INTERVENTRICULAR DYSSYNCHRONY USING ECHOCARDIOGRAPHY

Although LV intraventricular dyssynchrony appears to be the main factor determining the response to CRT, interventricular dyssynchrony can be measured easily in patients undergoing CRT. Two parameters are usually

used. The first parameter is derived from pulse wave Doppler flow signals, namely the time between QRS complex to onset of flow in the right ventricular (RV) outflow tract and the time between QRS complex to onset of flow in the LV outflow tract. The difference between these two intervals is then calculated as an index of RV-LV interventricular dyssynchrony. A delay of ≥40ms suggests significant interventricular dyssynchrony.[23,41] However, this index could not predict the response to CRT.[31] The second parameter is derived from TD images. The time difference between time to peak systolic velocity in basal septum and basal RV free wall can be calculated as an index of RV-LV interventricular dyssynchrony. However, its role in predicting CRT response is controversial.[28,32,34]

CLINICAL APPLICATION TO ROUTINE ECHOCARDIOGRAPHIC EVALUATION

At the Methodist DeBakey Heart Center, we use TD imaging to evaluate patients with possible mechanical dyssynchrony. Apical views are acquired using TSI along with graphic displays for the contraction of the different myocardial segments. These are used to calculate the time delay and the Yu index. The time delay between the basal opposing segments in the apical 4 (inferior septum and lateral wall), 2 (anterior and inferior walls), and 3 (anterior septum and inferolateral walls) chamber views, as well as the Yu index, are noted. In addition, it is useful to identify the segment(s) with maximal delay.

PERSPECTIVE

Although significant mechanical LV dyssynchrony has been shown to be present in patients with narrow QRS,[42] selecting patients for CRT still depends on the presence of a wide QRS complex. There are ongoing clinical trials in patients with significant mechanical LV dyssynchrony but a narrow QRS. The results of these trials are important for the proper selection of patients for CRT. As recently reported, systolic and diastolic dyssynchrony are frequent in patients with heart failure, irrespective of LVEF.[43,44] Several studies are under way to determine the potential role of CRT in many other patient groups (e.g., NYHA class II, narrow QRS complex, EF >40%).

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