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REVIEW PAPER

Tissue Doppler Imaging in the assessment of selection and response from cardiac resynchronization therapy

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Abstract Mechanistic studies, observational evaluations, and randomized trials have consistently demonstrated the beneficial effects of cardiac resynchronization therapy (CRT) in patients with moderate-to-severe chronic systolic heart failure and ventricular dyssynchrony who have failed optimal medical treatment. However, despite the promising results, in some patients undergoing CRT, the symptoms of heart failure do not improve or even worse. One of the most important reasons for this failure is probably the lack of distinct mechanical dyssynchrony before implantation. This review discusses the actual and potential role of Tissue Doppler Imaging in selection of patients and optimisation of CRT.

Introduction

Cardiac resynchronization therapy (CRT) with simultaneous right ventricular (RV) and left (LV) ventricular stimulation is a promising therapeutic option in patients with severe heart failure and left bundle branch block. Recently updated ACC/AHA/NASPE pacemaker and ICD guidelines included CRT as a class IIA recommendation for pacing.[1] Several trials[2] have demonstrated that CRT significantly improved acute hemodynamics, symptoms, exercise tolerance, and quality of life in patients with dilated cardiomyopathy. Still, since some patients do not respond to CRT, the need for additional selection criteria to identify potential responders has been suggested besides electrical dyssynchrony and new imaging modalities, in particular various echocardiographic approaches, have been described.

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Non-responder patients

Optimal hemodynamic response from resynchronization will depend on several factors such as the mode of implant (LV stimulation, optimisation of the AV interval, RV/LV timing, chronotropic incompetence), the etiology of heart failure (presence or absence of non-viable scar tissue), or the accurate information on ventricular dyssynchrony. Clinical predictors of lack of improvement in patients receiving CRT have been identified. In logistic regression analysis, independent predictors of lack of response to treatment were ischemic heart disease, severe mitral regurgitation, and left ventricular end-diastolic diameter $\geq$75 mm. If the patient obtains subjective and objective clinical improvement after implantation of a resynchronization device, worsening of the patient's heart failure symptoms suggests worsening of the primary pathologic process or loss of resynchronization, or both.

Non-responder patients have been defined as those who died of heart failure, underwent heart transplantation, did not increase the distance walked in 6 min $\geq$10%, or did not increase LVEF $\geq$25% having lack of reverse left ventricular remodeling (decrease in volumes). The percentage of non-responding patients to CRT as indexed by clinical symptoms or objective evidence of the absence of reverse chamber remodeling is 25% to 30% of recipients. The major entry criteria to date have been the presence of severe dilated heart failure (LVEF $\leq$0.35, NYHA class III or IV symptoms despite pharmacological therapy), sinus rhythm, and evidence of a conduction delay on the electrocardiogram as reflected by widening of the QRS complex ($\geq$120 ms). However, the correlation between QRS duration and acute mechanical response to CRT is modest, and in many chronic studies QRS duration has been a poor predictor of the CRT response. Since narrow QRS complex patients exist who benefit from CRT so long as they have dyssynchronous LV contraction, it appears that analysis of mechanical dyssynchrony is a better predictor of outcome than electrical dyssynchrony (QRS duration).

TDI technique

Although the cardiac mechanics related to multisite stimulation are only partially understood, echocardiography has emerged as a test of choice in the selection of candidates for this new treatment. There are several ways of assessing ventricular dyssynchrony using echocardiography. Tissue Doppler Imaging (TDI) allows the assessment of peak systolic velocity of different regions of the myocardium.[3–8] Precise timing of peak systolic velocity is possible when the TDI tracings are related to the electrical activity (QRS complex). Integration of this information allows accurate assessment of electromechanical coupling, and evaluation of inter- and intraventricular dyssynchrony.

Interventricular dyssyncrony refers to a prolonged delay between the onset of RV and LV activation. Pulmonary pre-ejection delay can be measured as the time from QRS onset to the start of pulmonary blood flow. The difference between aortic and pulmonary pre-ejection times provides a measure of interventricular mechanical delay and is considered abnormal with values greater than 40 ms.[3] TDI can also be used to evaluate interventricular dyssyncrony by placing sample volumes in RV basal free wall and LV basal septal and lateral walls and determining the time difference in the onset of RV–LV walls mechanical activation.[4–6] However, whether assessment of interventricular dyssynchrony is an effective tool to predict a positive response to CRT remains to be determined.

Intraventricular dyssynchrony is the predominant defect to be corrected by CRT. Tissue Doppler velocities may be displayed either as a spectral pulse or in color encoded two-dimensional or M-mode. Regional electromechanical delays can be measured (Fig. 1) from QRS onset to either the

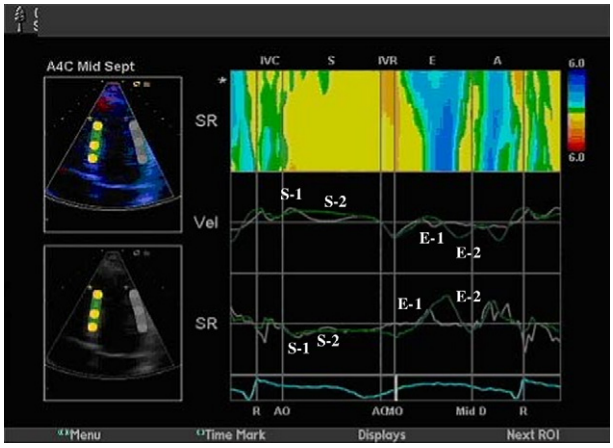

Figure 1 Poliparametric modality (velocity, strain rate, color strain rate) showing asynchrony between interventricular septum and left ventricular lateral wall. The delay of septal (green curve) versus lateral wall (white curve) is shown both in systole (S-2 vs S-1) and early diastole (E-2 vs E-1). A = atrial systole; AC = aortic valve opening; AO = aortic valve opening; E = early diastole; IVC = isovolumic contraction; IVR = isovolumic relaxation; MidD = mid-diastole; MO = mitral valve opening; S = systole; SR = strain rate; vel = velocity.

start or peak systolic shortening (S wave). It can be simply used to measure the delay between septal and either the posterior or lateral wall as a guide to intraventricular dyssynchrony, but this assumes the septum to be the earliest site of contraction and the posterior or lateral wall the latest. A more accurate assessment of the dispersion of intraventricular contraction can be calculated by analysing differences between all the different regions (intraventricular dyssynchrony by multiple segmental models) since LV models which assess more segments are more powerful than those that assess a smaller number of segments.[9]

Early diastolic (E) velocities can also be measured (Fig. 1). The time intervals of Q wave to peak S and Q to peak E at each site may be determined and the maximal difference of Q–S or Q–E between sites measures LV systolic and diastolic dyssynchrony, respectively. Despite significant improvement in LV systolic dyssynchrony, significant improvements in LV diastolic function have been observed after CRT only in patients with non-ischemic cardiomyopathy.[10]

A novel approach, known as tissue synchronization imaging (TSI), extends the concept of time-to-peak velocity as a marker for dyssynchrony by adding color coding (Fig. 2). TSI can characterize the baseline dyssynchrony that is predictive of an acute response to CRT. A $\geq$65 ms difference in time-to-peak velocity from the anteroseptal to the posterior wall using the apical long-axis view was greatly associated with immediate improvement in LV stroke volume.[11] These data are consistent with previous reports of the anteroseptal region being the earliest and the posterior wall being the latest activated site with typical left bundle branch block. This study dealt with Doppler stroke volume to assess acute response to CRT; however, the degree of long-term response supported by long-term data with a larger patient population needs to be addressed.

A high predictive value for a positive response to CRT by TSI has been recently reported[12] when the time to peak tissue velocity (Ts) was measured in ejection phase only, in particular when 12 (rather than 6) LV segments were analysed. The pre-installation of equations to compare various parameters of asynchrony and the advancement of computer hardware may allow to measure Ts of 12 segments from apical views within a few minutes and calculate Ts-12 automatically.

One limitation of TDI is that it does not distinguish between active and passive wall motion. This has led to the development of the TDI derived modalities of strain rate imaging (SRI), strain (ϵ) and tissue tracking (TT) analysis (Fig. 3).

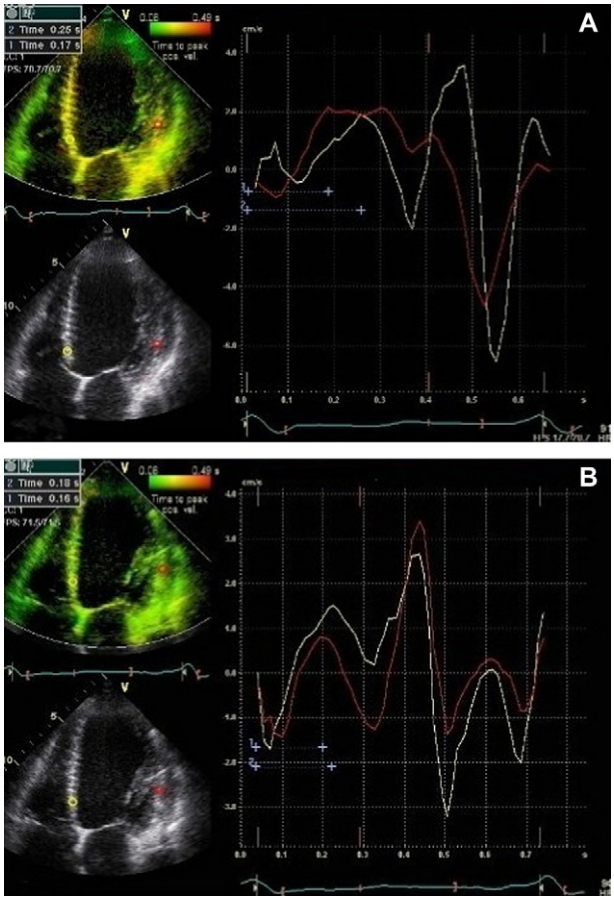

Figure 2 Echocardiographic tissue synchronization imaging (TSI) of LV segments before and after CRT. Before CRT (A) in a patient with LBBB and systolic paradoxical septal motion there was delay in the onset and peak sustained systolic contraction in the septal (red curve) compared with the lateral wall (yellow curve; [delay = 80 ms]). After CRT (B), there was marked improvement in the synchronicity, as reflected by the nearly overlapping of the myocardial velocity curves (delay = 20 ms) and the uniformity of green color in the 2D picture.

SRI[13–17] measures the rate of regional myocardial deformation, and integration of the regional strain rate curve enables the computation of myocardial shortening and lengthening (i.e., estimation of myocardial strain). Bundle branch block can lead to a significant redistribution of abnormal myocardial fiber strains, and these abnormal changes in the extent and timing of septal-lateral strain relationships can be reversed by CRT.[13] SRI has also been used before CRT to confirm true shortening in regions showing delayed longitudinal contraction (better known as post-systolic shortening), although strain rate based shortening/elongation information does not necessarily imply viability but can reflect passive phenomena.[14,15] It has

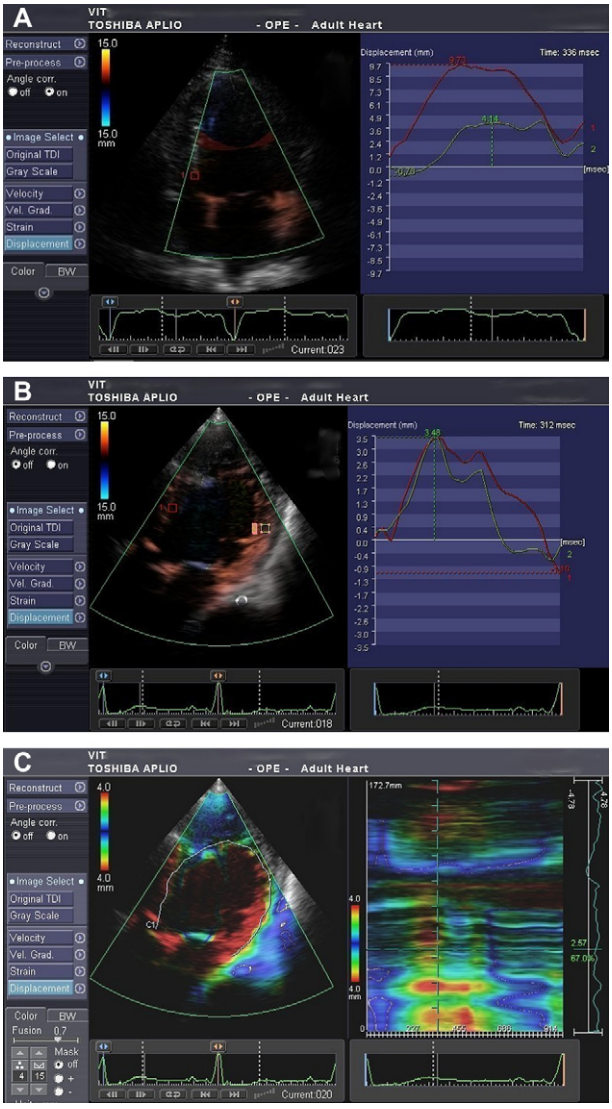

Figure 3 Tissue tracking (TT) or displacement before and after cardiac resynchronization therapy (CRT). A. Asynchrony of septal and lateral wall before CRT. B. Synchronicity of septal and lateral wall after CRT (same systolic peak). C. Color encoded tissue tracking showing walls synchronicity (straight vertical color line).

been shown[16] that the greater the number of segments displaying post-systolic shortening, the more severe the degree of dyssynchrony, and this was found to be predictive of short term efficacy of CRT. TT[18] visualises the longitudinal motion amplitude in each myocardial segment during systole in a color coded format and can be used in addition to SRI to determine the extent of myocardium with delayed longitudinal contraction. However, myocardial motion velocities and deformation parameters are low in patients with advanced systolic heart failure, which complicates the identification of peak systolic motion and deformation and makes the results susceptible to artifacts and errors. Furthermore, the benefit of not being affected by translational movement may be offset by the relatively large interobserver and intraobserver variability. Technical improvements are required to make SRI data analysis easier and applicable for routine clinical use.

Clinical applications

Cardiac resynchronization therapy has been shown to improve hemodynamics, quality of life, and VO_2 max in both acute and chronic studies of patients with ischemic or idiopathic dilated cardiomyopathy, low ejection fraction and prolonged QRS duration.[19–21] Various clinical trials have addressed these issues.[2] Resynchronization of systole can also be achieved for patients with conduction abnormalities other than left bundle branch block or patients with normal QRS duration who present with dyssynchronous contraction.[3]

CRT acts to limit disease progression even in patients with mild heart failure symptoms.[22] In optimally treated patients with mildly symptomatic NYHA class II heart failure, a wide QRS complex, and an ICD indication, CRT significantly improved cardiac structure and function and a composite clinical response measure over a 6-month period of follow-up. CRT produced significant improvement in LV systolic and diastolic volumes and LVEF, even if these effects did not translate into improved exercise capacity. However, these observations must be confirmed by future randomised controlled trials of mildly symptomatic heart failure patients before the indication for resynchronization therapy is extended to this population.

As opposed to population with ischemic chronic heart failure and LBBB, patients with congenital heart disease often demonstrate right ventricular conduction delay or RBBB, especially after ventricular surgery. This electrical disturbance is often associated with acute postoperative reduction of RV performance or chronic RV dysfunction due to residual defects such as pulmonary regurgitation as a result of previous surgeries or multiple previous procedures. Thus, RV dysfunction such as assessed by Tissue Doppler Imaging appears to be a reasonable therapeutic target in post-operative congenital heart disease. Issues specific to congenital heart disease include right bundle branch block, right (pulmonary) ventricular dysfunction, systemic right ventricular dysfunction, and single ventricle dysfunction.[23,24]

The use of multisite pacing as adjunctive therapy during weaning from cardiopulmonary by-pass has been reported in adults and children. This

practice in the immediate postoperative period is appealing because may avoid some of the unwanted side effects of increasing doses of inotropic agents used to support cardiac function. It has been described[25] an improved cardiac index and systolic blood pressure in postoperative patients with univentricular or biventricular anatomy and bundle branch block or interventricular conduction delay. Hemodynamic benefit of multisite RV pacing was similar to what has been reported in CAD or DCM patients with low ejection fraction. Cardiac index was calculated either with Fick equation or Doppler aortic data. Similar hemodynamic results using electrical resynchronization have been reported in patients with tetralogy of Fallot and RV dysfunction determined by echocardiography or angiocardiography.

Beneficial changes in systolic and diastolic RV function using TDI and strain Doppler have been documented after biventricular pacing in patients with post-operative transposition of the great arteries and either spontaneous or pacing-induced RV desynchronization.[26] CRT was associated with improved RV $+dP/dt$, fractional area change, and NYHA functional classification in the mid-term. Interventricular mechanical delay decreased and RV contraction synchrony improved. However, tricuspid valve regurgitation did not decrease following CRT in a similar way as functional mitral regurgitation. Thus, concurrent tricuspid valve interventions may be a necessary adjunct to CRT in patients with severe regurgitation but may be facilitated by the improvement in RV function achieved by resynchronization. A criticism was raised by the same authors regarding the inclusion in the resynchronization therapy of some patients with marginally decreased RV function who underwent ''preventive'' CRT at the occasion of other necessary cardiac surgery.

In congenital heart disease the heterogeneous patient population, technical limitations in pediatric patients, vascular access issues, and unique forms of ventricular asynchrony often obscure the selection of potential CRT beneficiaries. Despite these limitations, initial results are optimistic and experience thus far has been favorable.

Patients selection and management

Tissue Doppler Imaging is one of the most promising techniques for guiding patient selection. Ventricular asynchrony has a high prevalence in patients with LV dysfunction but there is poor agreement among the different methods available for detecting asynchrony.[27] Various echocardiographic and TDI parameters have been reported in the recent literature. A recently developed ''St Mary's protocol''[28] provides a high probability of dyssynchrony and identifies patients likely to benefit from CRT. By applying this protocol, it was found that 88% of patients had benefited symptomatically with a reduction in New York Heart Association (NYHA) functional class. Selection for biventricular pacing required the presence of two major criteria (TDI intraventricular dyssynchrony >55 ms, intraventricular + interventricular dyssynchrony >100 ms), or one major and three minor criteria, or four minor criteria (TDI intraventricular dyssynchrony >40 ms, interventricular dyssynchrony >40 ms, DFT <40% cardiac cycle, LVPEP >140 ms, QRS >130 ms).

TDI can be used to guide the management of patients with systolic heart failure (Fig. 4). Patients with drug-refractory HF should undergo a TDI study to quantitate LV ejection fraction and dyssynchrony. In the presence of LVEF <35%, an ICD should be implanted (no dyssynchrony) or CRT + ICD should be performed (significant dyssynchrony). Non-responder patients could have a TDI pacemaker optimisation study to check possible hemodynamic improvements after changes in PM settings.

Site optimisation

Echo-Doppler methods can also be used in optimising biventricular pacing. Preliminary evidence suggests that optimal improvements in LV performance may be achieved when pacing at the most

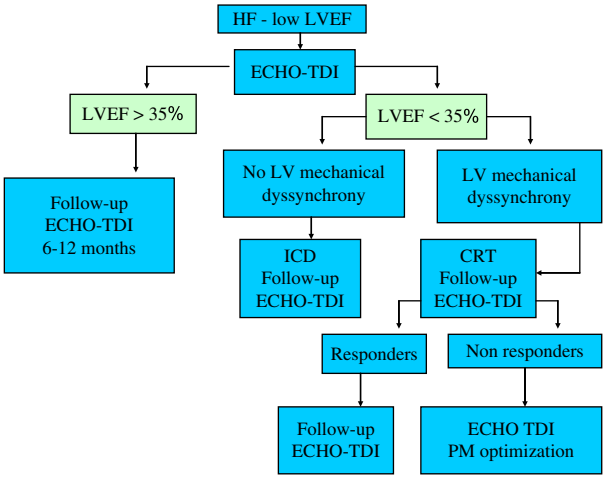

Figure 4 Management of patients with severe heart failure using TDI-guided CRT (see text for details). HF = heart failure; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; PM = pacemaker; TDI = Tissue Doppler Imaging.

delayed site.[29,30] TDI enables identification of the site of delayed LV contraction and may be useful in guiding LV lead placement at implantation,[31] even if the site of LV pacing is often limited by individual coronary venous anatomy.

The optimisation of AV delay following pacemaker implantation has traditionally been achieved using Doppler echocardiography. Alternatively, the AV delay can be programmed, guided by the aortic velocity time integral (VTI) with the maximum VTI recorded being defined as the optimal AV delay.

In more advanced biventricular pacemakers it is now possible to alter the interventricular pacing interval (IVPI), to allow either LV or RV preactivation. The IVPI can be adjusted to provide the maximal forward stroke volume as measured by the aortic VTI; however, more research is required in this area.

Assessment of benefits

It has been shown that biventricular pacing can result in reverse remodeling in patients with advanced heart failure,[32–34] and these changes are associated with improvement in systolic function, increase in LVEF, decrease in LV volumes, reduction of mitral regurgitation, and increase in diastolic filling time. The benefits are attributable to an improvement in intraventricular and interventricular synchrony as well as to a shortening of isovolumic contraction time.

Although these beneficial findings may be associated with a reduction in mitral regurgitation (MR) after CRT, a clear distinction has not been defined between immediate MR reduction and remote decreases secondary to reverse remodelling of the LV, which takes from weeks to months to occur. The immediate reduction in MR after CRT has been quantified and associated with the coordinated mechanical activation of papillary muscle insertion sites.[35] A delay in peak strain at the mid lateral segment adjacent to the anterolateral papillary muscle has been observed, implying tethering of the mitral leaflet, which was improved immediately after CRT. CRT appeared to coordinate the tethering forces on the papillary muscles and increase the leaflet coaptational surface to reduce MR.

Other mechanisms of decreased MR after CRT as assessed by color jet area have previously been attributed to decreases in LV size from reverse remodelling.[2,36] However, color jets are considerably affected by numerous factors: transducer frequency, gain, Nyquist limit, frame rate, jet eccentricity, and flow momentum, which is the product of flow rate and velocity. The degree of MR has also been assessed using the proximal isovelocity surface area method,[16] which uses both color and spectral Doppler data, during both pacing-off and CRT in the first week after CRT and a correlation has been shown with the reduction in isovolumic contraction time.

Promising data suggest the possibility of effective quantification of papillary muscle contractile function using maximum strain (ϵ_{max}) measurements derived from TDI, which theoretically are not affected by the tethering effect and contractile function of adjacent myocardial wall.[37–39] It has been shown that, in addition to increased closing force and papillary muscles recoordinated contraction described as main determinants of attenuation of functional MR, CRT may acutely reduce MR severity by improving systolic deformation of the papillary muscles or adjacent myocardial wall.[39] The overall improved strain in more spherical ventricles, together with an increased mean negative strain in the basal segments initiated by CRT, may relieve apical tenting of the mitral leaflets by reducing tethering of papillary muscles.

Sustained effects at longer follow-up after CRT in patients with both symptomatic and mildly symptomatic heart failure need to be confirmed in future studies.

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