

KAN EKKOKARDIOGRAFI BRUKES I FORBINDELSE MED UTVELGELSE TIL CRT?

Ekkokardiografiske teknikker ble raskt svært viktige for utvelgelse av pasienter etter introduksjonen av kardial resynkroniseringsterapi (CRT) rundt milleniumskiftet. Mye av luften gikk imidlertid ut av ekko-ballongen etter at studier som PROSPECT (Circulation 2008) og EchoCRT (New England Journal of Medicine 2013) ble publisert.

Hjerteforum inviterte derfor professor John Gorcsan 3rd til å skrive om hvilken rolle ekkokardiografi har nå i CRT-problematikken. Gorcsan er en av verdens absolutt mest anerkjente kardiologer innen dette feltet og var blant annet «kjernelaboratorium» for ekkokardiografi i EchoCRT. Han har publisert utallige artikler om emnet i Journal of the American College of Cardiology, Circulation, European Heart Journal og New England Journal of Medicine.

God lesing!

Thor Edvardsen, medredaktør

THE CURRENT ROLE OF ECHOCARDIOGRAPHY IN CARDIAC RESYNCHRONIZATION THERAPY

John Gorcsan III and Antonia Delgado-Montero

Cardiac resynchronization therapy (CRT) has become a major therapeutic advance for heart failure (HF) patients with depressed left ventricular (LV) ejection fraction (EF) and electrocardiographic (ECG) QRS widening. Randomized clinical trials have shown CRT to improve morbidity and mortality in both severely symptomatic HF patients with advanced disease [1, 2] and those who are less symptomatic [3-5]. A challenge has been that patients selected for CRT using clinical criteria have had a non-responder rate of approximately one-

third [6-9]. Accordingly, there has been great interest in improving CRT response and patient outcomes using echocardiographic imaging of regional mechanics, known as dyssynchrony, as an adjunct to patient selection. Although there have been many supportive publications, the role of echocardiographic dyssynchrony in patient selection is presently unclear. Recent randomized clinical trials of low EF HF patients with narrow QRS width showed that they cannot be successfully selected for CRT by echocardiographic dyssynchrony alone, and it appears that some element of QRS widening is required for benefit [10, 11]. Revised patient selection guidelines focused on ECG criteria specifically more clearly favoring patients with left bundle branch block (LBBB) ≥ 150 ms [12, 13]. There is some element of uncertainty of CRT benefit in patients with intermediate ECG criteria (QRS width 120-149 ms or non-LBBB).

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Improvements in using echocardiographic imaging to guide LV lead placement have also emerged recently as means to improve CRT response. This article will review the current and future role of echocardiography in CRT beyond simple EF determination to improve understanding of the pathophysiological basis of dyssynchrony as it relates to a potential contemporary role in patient selection, discuss risk for ventricular arrhythmias and to guide CRT lead placement to improve patient outcomes.

Dyssynchrony and electromechanical substrates for resynchronization

An early observation was that abnormal timing of regional LV mechanics, termed dyssynchrony, when measured by imaging in patients with QRS widening before CRT was associated with a more favorable response. Several studies from international centers demonstrated that patients with QRS widening but no measurable evidence of mechanical dyssynchrony had a much lower response rate to CRT and less favorable clinical outcomes [14-16]. This important observation that patients with significant dyssynchrony before CRT have a more favorable response has supported imaging dyssynchrony as a means to improve patient selection. The reason for QRS widening without mechanical dyssynchrony remains unclear with hypotheses including discrete scar of the conduction system, or other disease process that is not understood. None the less, the lack of mechanical dyssynchrony before CRT has been well supported as a prognostic marker for less favorable outcome after CRT.

The hypothesis that CRT could help HF patients with mechanical dyssynchrony by echocardiography in patients with narrow QRS (<130 ms) was tested by two randomized clinical trials. RethinQ was first to show that CRT was not beneficial to patients with narrow QRS width in patients with dyssynchrony by tissue Doppler imaging (TDI) [11]. Most definitively, the EchoCRT trail, a larger multicenter randomized cohort of 809 New York Heart Association III-IV

HF patients with narrow QRS <130 ms, EF ≤35 %, LV end-diastolic diameter ≥55 mm, and mechanical dyssynchrony concluded that these patients do not benefit from CRT [10]. EchoCRT used either a peak-to-peak time delay in tissue Doppler LV opposing wall velocities or a peak-to-peak septal to posterior wall radial strain timing as selection criteria for the trial. All patients were implanted and then randomized to CRT-On or CRT-Off. The primary end-point was death or HF hospitalization. EchoCRT was stopped prematurely because of futility in demonstrating a difference in the primary end point and because of a worrisome increased mortality rate in the CRT-On group, which suggested a higher arrhythmic death rate. Accordingly, it appears that the combination of both electrical dyssynchrony (QRS widening) and mechanical dyssynchrony by cardiac imaging results in the most favorable CRT response (figure 1).

Dyssynchrony as a marker for prognosis

Response to CRT is affected by multiple factors including location and extent of myocardial scar, LV lead position, right ventricular function and in addition to lack of baseline dyssynchrony [17-22]. The existence and grade of mechanical dyssynchrony has consistently been associated with short and long term prognosis [7, 8, 23]. The PROSPECT study revealed that there is variability in echo-Doppler measu-

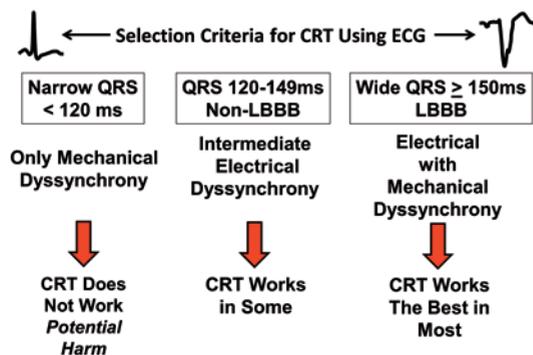


Figure 1. The current understanding of the relationship of electrocardiographic QRS width and morphology and response to cardiac resynchronization therapy (CRT). LBBB = Left bundle branch block

res of dyssynchrony among many published measures [24]. Accordingly, we have selected the measures that are best represented in the literature with the most evidence for their prognostic value. The most widely available and simple routine measure is pulsed Doppler echocardiography to measure interventricular mechanical delay (IVMD) (figure 2). The LV pre-ejection time is measured from the QRS onset of pulsed Doppler flow, with the sample volume placed proximal to the aortic valve in the apical long axis or five-chamber view. Similarly, the RV pre-ejection time is measured from the QRS onset of pulsed Doppler flow, with the sample volume placed proximal to the pulmonic valve in the parasternal short axis view. IVMD is the RV ejection time subtracted from the LV ejection time. An IVMD >40 ms is considered significant and associated with prognosis [25, 26]. In CARE-HF study, where 813 patients were randomized to CRT or control group, a larger baseline IVMD was related to better outcome regarding all-cause mortality (HR 0.47, 95 % CI 0.34 - 0.66; $p < 0.0001$) [27]. Color coded tissue Doppler imaging (TDI) has been widely used to detect the velocity of regional motion and can be easily applied to the apical views. The most widely used peak-to-peak velocity cut-off from the apical 4 chamber view was ≥ 65 ms and the Yu index calculated as the standard deviation of the time to systolic velocity peak from 12 segments (basal and mid) in the 3 conventional apical views with a value ≥ 33 ms associated with CRT response [16, 28-30]. More recently, cross-correlation of the opposing wall tissue Doppler velocity curves to determine phase of acceleration have been useful to predict prognosis.

Olsen et al have used cross-correlation analysis of the acceleration curves derived from tissue Doppler velocity curves to detect CRT response [31]. Subsequently Risum et al showed in 131 CRT patients from two different centers that dyssynchrony by maximal activation delay by cross-correlation was independently associated with survival hazard ratio (HR) 0.35, 95 % CI 0.16-0.77, $p = 0.01$ [27].

The echocardiographic method most well represented in the literature to determine dyssynchrony is speckle tracking strain [32]. This is applied to routine grayscale echocardiographic images and can determine regional myocardial deformation parameters: thickening and thinning, or shortening and lengthening dependent on the vector of contraction. Speckle tracking analysis has the advantage of using routine 2D images with no angle dependency, it can also combine the ability of the strain analysis to detect scarred areas; although it requires an adequate image quality and relatively high frame rate (60-90 Hz). Radial strain from the parasternal mid wall view, although associated with variability in amplitude has been reported as a sensitive indicator of timing of regional contraction (figure 3). In particular, radial strain is sensitive for determining the timing of

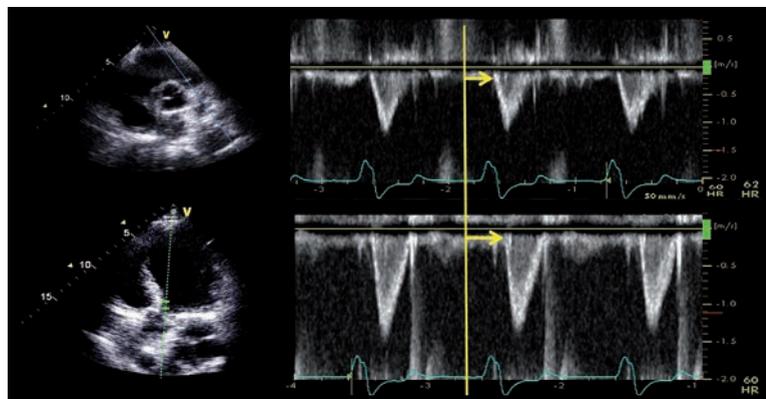


Figure 2. An example of intraventricular mechanical delay (IVMD) using pulsed Doppler echocardiography, which has been associated with response to cardiac resynchronization therapy. The top panel is the time from the QRS to onset of pulmonic flow (arrow) using the parasternal short axis view (top left) and the spectral display (top right). The bottom panel is the time from the QRS to the onset of left ventricular outflow tract flow (arrow) using the modified apical 4 chamber view (bottom left) and spectral display (bottom right). IVMD is the difference between time to left ventricular flow and pulmonic flow, which is 45 ms in this example.

low-amplitude septal deformation, which may be difficult to detect by other strain approaches. Delgado et al compared dyssynchrony measured by radial, longitudinal and circumferential strain in 161 patients, where only radial strain was able to predict CRT response with a sensitivity of 83 % and a specificity of 80 % [33]. A peak-to-peak radial strain approach most widely used has been the time difference between the anterior septum to the posterior wall of ≥ 130 ms, which has been associated with important outcome variables including HF hospitalization and long term survival [26]. Lim et al. reported longitudinal strain as an important alternative and has the advantage of potentially providing scar information in addition to dyssynchrony information [34]. Lim et al. used the longitudinal deformation to describe the longitudinal strain delay index (SDI) as a marker of dyssynchrony and segmental viability. SDI is calculated as the sum of difference between end-systolic and peak strain across the longitudinal 16 segments, indicating less viable segment when lower longitudinal shortening [34]. In the prospective MUSIC study, a SDI $>25\%$ predicted CRT response with a sensitivity and specificity of 95 and 83 % respectively [35]. A promising approach described by De Boeck et al is the systolic rebound

stretch in the septum calculated as the sum of the septal systolic stretch that occurs after the initial shortening [36, 37]. In 62 HF patients septal rebound stretch of 4.7 % was an independent predictor of CRT response with a sensitivity and specificity of 81 %.

Potential opportunities to influence patient selection: intermediate QRS and non-LBBB

Currently, the lack of dyssynchrony in patients who meet criteria for CRT implantation by ECG criteria should not influence patient selection accordingly to published guidelines. In particular, it would be difficult to prove that echocardiographic dyssynchrony analysis would add significant information for routine clinical use in patients with LBBB and QRS >150 ms. On the other end of the QRS width spectrum, HF patients with narrow QRS width do not benefit and may be potentially harmed by CRT [10, 11]. Accordingly, perhaps the most potential influence echocardiographic dyssynchrony measures may have in patients with intermediate QRS duration between 120-149 ms and those with non-LBBB, namely intraventricular conduction delay and a subset of right

bundle branch block with some element of left sided conduction delay [38]. Hara et al. previously showed that these non-LBBB QRS morphologies can achieve a favorable response to CRT if dyssynchrony by IVMD or speckle tracking radial strain methods are present prior to implantation [39]. More work is needed to refine these patient selection approaches for the future.

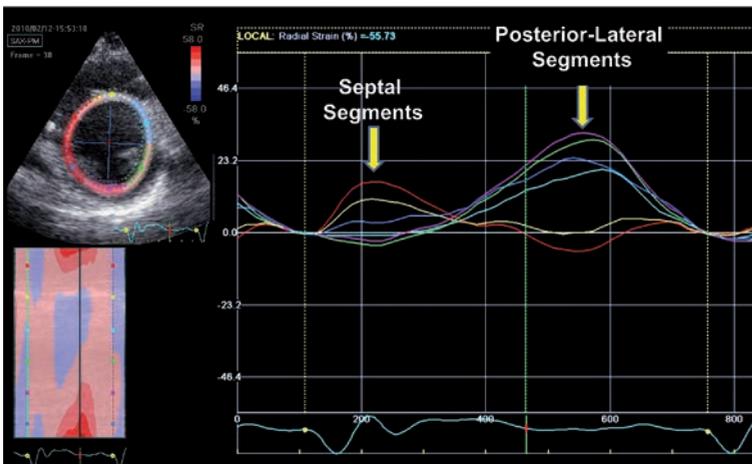


Figure 3. A representative example of speckle tracking radial strain at the mid-ventricular level from a heart failure patient with left bundle branch block. The peak strain in the septal segments occurs early (arrow) and the free wall segments, including posterior and lateral walls, occurs late (arrow). This delay in peak to peak strain of 290 ms represents severe mechanical dyssynchrony before cardiac resynchronization therapy (CRT), is typically associated with a favorable response.

Dyssynchrony after CRT and risk for ventricular arrhythmias

An important recent advance in the understanding of the meaning of dyssynchrony has been as a risk marker for ventricular arrhythmias after CRT. Whereas dyssynchrony at baseline before CRT is in general a marker for a good prognosis, the finding of dyssynchrony on follow-up echocardiography after CRT is associated with an increased risk for serious ventricular arrhythmias. Kutifa et al showed an increase of arrhythmic events in patients with mild HF and persistent dyssynchrony after implant, calculated by SD of time-to-peak transverse strain in 12 LV myocardial segments from a sub-group from MADIT-CRT trial [40]. Haugaa et al. more recently reported on 201 class III-IV HF patients with baseline and follow-up echocardiography 6 months after CRT-defibrillator therapy [41]. Dyssynchrony by speckle tracking radial strain antero-septal to posterior wall delay ≥ 130 ms after CRT was associated with appropriate anti-tachycardia pacing or shock after CRT. Specifically, the ventricular arrhythmic event rate: was 21 % for persistent dyssynchrony and 35 % for worsened dyssynchrony, versus 7 - 9 % for no dyssynchrony after CRT-D ($p < 0.001$, HR 3.76, 95 % confidence interval (CI) 1.71 - 8.27). It is not currently clear if worsening dyssynchrony after CRT is related to CRT pacing, perhaps suboptimal lead position within scar, or worsening of the myopathic disease

process itself, but remains a marker for arrhythmic risk.

Echocardiographic guided left ventricular lead placement

One of the most exciting advances is the use of echocardiography to guide the LV lead positioning. Two independent randomized clinical trials with very similar methods found clinical benefit of LV lead positioning guided by speckle tracking radial strain. The first published study, known as the TARGET trial, randomized 220 CRT patients to LV lead directed toward the site of latest peak strain and absence of scar (defined as < 10 % thickening) versus routine unguided placement toward anywhere in the posterior-lateral free wall [42]. TARGET showed that there was a greater proportion of responders at 6 months (70 % vs. 55 %, $p = 0.031$), giving an absolute difference in the primary endpoint of 15 % for end-systolic LV volume response. TARGET patients also had a higher clinical response rate at 83 % vs. 65

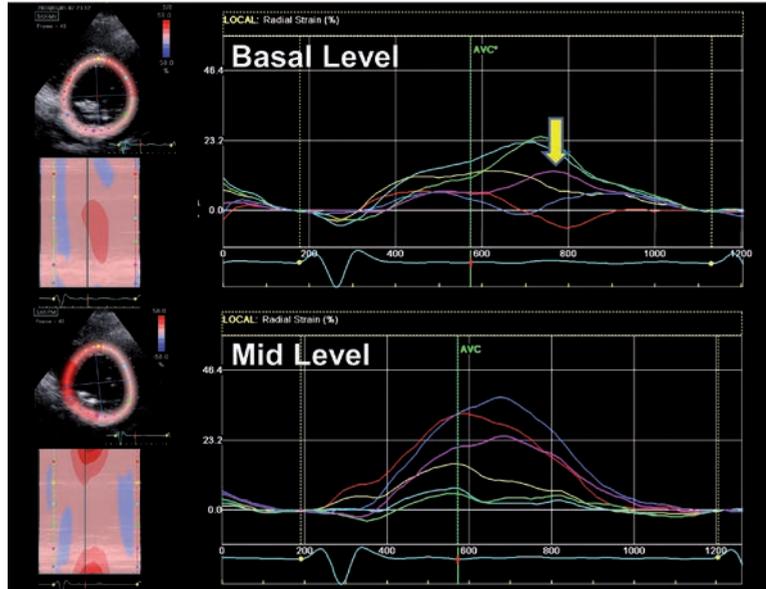


Figure 4. Speckle tracking radial strain curves from short axis echocardiographic views at basal ventricular level (top) and mid ventricular levels (bottom). Six segments per view are color-coded with the basal posterior segment (purple curve top arrow) representing the site of latest peak strain. Left ventricular leads located concordant with sites of latest peak strain are associated with more favorable response to cardiac resynchronization therapy.

% in the control group, ($p=0.003$). STARTER enrolled 187 HF patients with 110 randomized to echo guided and 77 to routine LV lead placement (figure 4). Using intention-to-treat, patients randomized to the echo-guided strategy had a more favorable 2-year event-free survival [77 % versus 57 % in the routine group; HR = 0.48, 95 % CI = 0.28 - 0.82, $p=0.006$] [43]. Exact or adjacent concordance of LV lead with latest site could be achieved in 85 % of the echo-guided group and occurred fortuitously in 66 % of controls ($p=0.010$). STARTER subgroup analysis estimated scar as <10 % segmental strain.

Event-free survival was most favorable in patients with nonischemic disease (79%), similarly favorable in patients with ischemic disease and LV lead remote from scar (74%), but significantly worse in ischemic disease patients with LV lead adjacent to (61 %) or within scar (41 %), $p=0.004$ [44]. When STARTER subgroups were examined by ECG criteria, patients with QRS width 120-149 ms or non-LBBB and LV lead concordant or adjacent to site of latest mechanical activation had similarly favorable outcomes after CRT as those with LBBB or QRS width ≥ 150 ms. In contrast, narrower QRS 120-149 ms or non-LBBB patients with remote LV leads had unfavorable outcomes: HR = 5.45, 95 % CI = 2.36 - 12.6, $p<0.001$ and HR=4.92, 95 % CI = 2.12 - 11.39 $p<0.001$, respectively [45]. These subgroup analysis results suggest

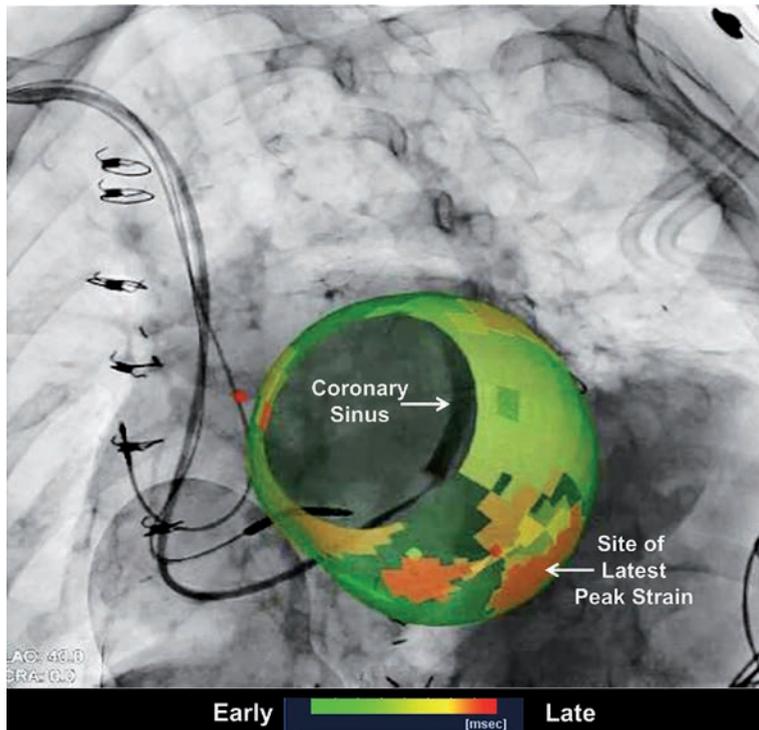


Figure 5. An example of a three-dimensional strain echocardiogram from a patient undergoing cardiac resynchronization therapy which is fused with the fluoroscopic image from the left anterior oblique view. Peak left ventricular occurring early is color coded early as green and peak strain occurring late as red. The coronary sinus is shown during a venogram to demonstrate the epicardial coronary veins that are accessed for lead positioning. The vein closest to the site of latest peak strain (arrow) is considered the more favorable site for left ventricular lead placement.

that echo-guided LV lead positioning may have the greatest clinical impact to avoid scar and in patients with intermediate ECG criteria. A further advance is 3-D echocardiographic techniques, which have also shown an acceptable ability to assess left ventricular dyssynchrony and describe the site of latest activation [46-48], which is potentially combinable with other images techniques in order to guide CRT implant inside the electrophysiology lab (figure 5). The fusion imaging techniques combine anatomical and functional data. In conclusion, the role of echocardiography in CRT continues to evolve. In particular, the meaning of echocardiographic dyssynchrony is more complicated than initially thought. It appears that at least a minimum component of electrical delay is needed for CRT response, and that the combination of electrical delay and mechanical dys-

synchrony results in the most favorable CRT response. At the very least, specific types of mechanical dyssynchrony can be identified before CRT as having prognostic value. Although mechanical dyssynchrony at baseline before CRT is a marker for a favorable outcome subsequent to implantation, persistent or worsening dyssynchrony has been identified as a marker for increased risk of arrhythmias. Finally, echocardiographic strain mapping has been shown to be perhaps most useful to map the site of latest mechanical activation to guide LV lead position and avoid regional scar, with future technological advances ongoing.

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