Patient assessment for cardiac resynchronization therapy: Past, present and future of imaging techniques

Dominique Auger MD, Anique Ducharme MD MSc, François Harel MD, François Marcotte MD, Bernard Thibault MD, Eileen O'Meara MD

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It has been proposed that dyssynchrony assessment before cardiac resynchronization therapy (CRT) implantation could help predict response to CRT. It is known that up to 40% of patients who receive a CRT device for established indications do not respond to CRT. Great expectations came from the Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT) study, which would finally identify the ultimate echocardiographic dyssynchrony criteria to help select responders. The recently published PROSPECT trial failed to identify an ideal parameter of dyssynchrony. Patient selection for CRT should involve a multimodal approach, and new promising tools are being investigated in that view. The present review integrated new data coming from the exciting field of imaging with currently available evidence to generate a stepwise approach to patient selection.

Key Words: Cardiac magnetic resonance; Cardiac resynchronization therapy; Echocardiography; Nuclear medicine; Strain rate

Cardiac resynchronization therapy (CRT) is currently indicated on top of optimal medical therapy for patients with moderate to severe left ventricular (LV) systolic dysfunction (ejection fraction [EF] of 35% or less), a QRS width of more than 120 ms, and New York Heart Association (NYHA) class III or IV heart failure (HF) symptoms. Unfortunately, up to 40% of patients do not respond to CRT, depending on which definition of response is used. The latter has varied widely. Previous data have suggested that the identification of echocardiographic (echo) markers of dyssynchrony before device implantation could predict response to CRT in single-centre studies. The recently published Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT) trial (1), a multicentre study, failed to identify an ideal echo measure of dyssynchrony that could easily and reproducibly predict response to CRT in patients selected based on current recommendations. Dyssynchrony assessment before device implantation should theoretically improve patient selection and thus, the response rate to CRT. However, the correlation between clinical and echo responses is low (2). Another important question raised in recent literature is whether patients with less advanced HF could benefit from CRT. A recently published trial (3) suggested that patients with a narrow QRS and echo markers of dyssynchrony had no significant improvement in maximal oxygen consumption (VO_2 max) when randomly assigned to CRT, based on echo criteria. Is echo the ideal method for the evaluation of dyssynchrony? Different modalities, such as three-dimensional (3D) echo, strain rate, tissue synchronization imaging (TSI), nuclear medicine and cardiac magnetic resonance imaging (CMR), are currently being used in the search for a reproducible tool to help predict response to CRT. The detection of scarring, and the evaluation of its extent and location appear to be essential components of patient assessment before CRT. Perhaps the future will involve a multimodal approach in patient selection.

L'évaluation des patients en vue d'une thérapie de resynchronisation cardiaque : Le passé, le présent et l'avenir des techniques d'imagerie

Il est postulé que l'évaluation de la désynchronisation avant une thérapie de resynchronisation cardiaque (TRC) peut contribuer à prévoir la réponse à l'intervention. On sait que jusqu'à 40 % des patients qui reçoivent un dispositif de TRC en raison d'indications établies n'y réagissent pas. On avait de grandes attentes à l'égard de l'étude PROSPECT sur les prédicteurs des réponses à la TRC, qui devait enfin déterminer les critères ultimes de désynchronisation échocardiographique afin de sélectionner les personnes y réagissant. Cette étude, qui a récemment été publiée, n'a pu déterminer de paramètre idéal de désynchronisation. La sélection des patients admissibles à une TRC devrait faire l'objet d'une démarche multimodale, et de nouveaux outils prometteurs sont en cours d'exploration à cet effet. La présente analyse intègre de nouvelles données tirées du domaine passionnant de l'imagerie et propose des données probantes à jour pour produire une démarche progressive de sélection des patients.

The aim of the present review was to propose a stepwise approach to patient evaluation before and after CRT, based on the extensive literature published on this topic over the past decade. We first reviewed the outcomes expected from CRT, or the 'response', then the value of the QRS width in patient selection, and finally, the role of echo as well as other modalities in assessing patients before and after device implantation.

STEP 1: DEFINING RESPONSE TO CRT

Before considering CRT, optimal medical therapy and a stable medical condition should be obtained. The next question is: What do we want to accomplish with CRT for HF patients? Ideally, CRT, as with any other treatment, should provide clinical benefits in nearly all patients who receive such therapy, with minimal complication rates. These predefined clinical outcomes would be correlated with surrogate markers of survival, such as reverse LV remodelling, improvements in biomarkers (eg, brain natriuretic peptide, procollagen type III N-terminal peptide) or both. Finally, because CRT is an expensive therapy, it should be considered in patients with a reasonable life expectancy.

A reduction of the mortality rate with CRT was clearly demonstrated in the Cardiac Resynchronization-Heart Failure (CARE-HF) (4) and Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) (5) trials. An improvement by at least one NYHA functional class is a well-accepted marker of clinical benefit in HF patients and was used as an end point in all CRT trials. NYHA class is the most widely used scale to assess functional status, although it has several limitations such as considerable interobserver variability, and perhaps a lack of sensitivity in detecting significant changes in exercise capacity (6). Other prospectively assessed clinical outcomes used in CRT trials include a 10% to 25% increase (7,8) in the 6 min walk test

Montreal Heart Institute, Montreal, Quebec

Correspondence: Dr Eileen O'Meara, Montreal Heart Research Centre, 5000 Bélanger Street, Montreal, Quebec H1T 1C8. Telephone 514-376-3330, fax 514-523-1754, e-mail eileenomeara@bellnet.ca

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(6WMT) distance and an improvement in quality-of-life scores (9,10). The patient global assessment score uses a seven-point rating scale, allowing for the evaluation of the patient's own perspective of his or her overall health compared with a previous point in time. Because of its somewhat retrospective nature, it is exposed to a recall bias. The 6WMT could be more sensitive to clinical improvement, namely in advanced HF (11). Improvement in VO_2 max was also assessed as a primary end point in the Pacing Therapies in Congestive Heart Failure (PATH-CHF) (9) and PATH-CHF II (12) trials. VO_2 max is subject to many confounders and is an imperfect tool for assessing exercise capacity, but has been widely used for HF patients, especially for heart transplant evaluation. However, what change in VO_2 max corresponds with improvement in daily activities perceived by the patient? The correlation between VO_2 max and self-administered activity questionnaires seems poor (13). Hence, many are now relying on the submaximal VO_2 , which is believed to be more representative of the patients' daily limitations.

The impact of CRT on cardiac structure and function has also been used to define response. These remodelling parameters (mainly echo) have included reduction of the LV end-systolic volume (LVESV) by at least 15%. An elevated LVESV has been associated with a linear increase in mortality and is a powerful predictor of clinical outcomes (14-16). Its reduction after CRT was a strong predictor of lower long-term mortality and HF hospitalizations in 141 patients, followed for a mean ($\pm$ SD) of 695 ± 491 days after device implantation (17). LVEF is strongly related to prognosis, and its absolute increase of 5% or greater has been considered to be a positive response to CRT (18). This same 5% increase in LVEF has been observed with other effective HF treatments, such as beta-blocker therapy (19).

Defining response to CRT is a difficult task, and defining an individual's response might be even more challenging. A practical definition should probably involve functional capacity, quality-of-life assessment, or patient-perceived improvement and surrogate markers of mortality. We believe it should include improvement by at least one NYHA class and improvement in patient global assessment score, coupled with a 15% increase in LVESV and probably a 10% to 25% increase in 6WMT distance (20,21).

STEP 2: QRS DURATION

A wide QRS is associated with poor outcomes in HF with systolic dysfunction; patients with the widest QRS (220 ms or greater) have a fivefold increased mortality rate compared with those with a narrow QRS (less than 90 ms) (22). A wide QRS has been associated with asynchronous contraction of the right and left ventricles (interventricular dyssynchrony) (23), but not with left intraventricular dyssynchrony (24). Interventricular dyssynchrony has not consistently been shown to predict response to CRT (25,26), but the echo marker of interventricular mechanical dyssynchrony was predictive of significant reductions in the clinical composite score and in LVESV in the PROSPECT trial (1). As a corollary, CRT reduced the interventricular mechanical delay (IVMD) in CARE-HF (4).

Data from the PATH-CHF II (12) and CARE-HF (4) trials suggested a greater benefit from CRT among patients with a wider QRS (greater than 150 ms and 160 ms, respectively). QRS duration reduction has also been used to predict response to CRT – a reduction of more than 10 ms had a sensitivity of 73% but a specificity of only 44% in predicting response to CRT in a study of 61 patients (27). A later published work involving 139 HF patients confirmed these results (28).

QRS duration, a marker of electrical dyssynchrony, cannot be used alone to reflect mechanical dyssynchrony or predict response to CRT, but is easy to assess, and remains an important element for patient selection in current practice.

STEP 3: THE ECHO

Will echo still be playing a central role in patient selection for CRT after PROSPECT? Echo allows readily accessible measurements of LV dimensions, volumes, EF and mitral regurgitation severity, which are essential data for all HF patients, whether they are CRT candidates or not.

Multiple single-centre studies evaluating the role of echo in assessing dyssynchrony and predicting response to CRT have been published. Echo is a noninvasive, rapid and widely available technique, but adequate measurements of multiple dyssynchrony parameters and sometimes complex patterns can be time consuming. The overall low reproducibility of such measurements was recently demonstrated for the first time in the multicentre PROSPECT trial (1). The latter was an observational nonrandomized trial assessing the value of several echo indexes of interventricular and intraventricular dyssynchrony in predicting clinical (a composite score of NYHA class, hospitalization, patient global assessment and death) or echo (15% or greater reduction in LVESV) response to CRT. Three central laboratories were involved and a vast array of echo equipment was used in this multicentre trial, which has undoubtedly increased the variability of measurements. We briefly reviewed the various echo dyssynchrony parameters that have been studied over the past 10 years, using increasingly complex technologies.

M-mode echo

One of the first indexes of intraventricular dyssynchrony, the septal to posterior wall motion delay (SPWMD), was described by Pitzalis et al (29,30). Using a cut-off of 130 ms, the SPWMD had a sensitivity of 100% and a specificity of 63% to predict the response to CRT in two small ($n=20$) groups of patients. However, when applied retrospectively to a larger group of patients from the CONTAK-CD trial (31), the SPWMD could not be assessed in 50% of patients because of septal or posterior wall akinesis, or poor acoustic windows. In the PROSPECT study, SPWMD could not predict clinical response to CRT (54% sensitivity and 50% specificity), and a 72% interobserver variability was shown for this parameter (1).

Doppler imaging

The LV filling time to RR interval ratio (LVFT/RR) (31) is an index of atrioventricular (dys)synchrony. Cazeau et al (32) noted that in their prospective study of 31 patients, LVFT/RR was significantly increased immediately after CRT implantation because the clinical condition of the patients improved. Using a 40% or greater LVFT/RR cut-off, the PROSPECT investigators found a low sensitivity but good specificity for clinical and remodelling responses (36% and 76% for clinical response, and 41% and 74% for LVESV, respectively) to predict response to CRT (area under the curve [AUC] of approximately 0.60).

The IVMD, an index of interventricular dyssynchrony, is measured by the difference between pre-ejection times at the right and left outflow tracts, using pulsed-wave Doppler imaging (cut-off at 40 ms or more between pre-ejection times) (32). It showed modest sensitivity and specificity (AUC of approximately 0.60) in the PROSPECT trial (1).

The LV pre-ejection interval (LPEI), an index of intraventricular dyssynchrony, or time from onset of QRS to onset of aortic ejection by pulsed-wave Doppler imaging, was also used in the PROSPECT trial (cut-off at 140 ms or more). This parameter had low intra- and interobserver variability (3.7% and 6.5%, respectively), could be performed in 95% of echos, and predicted both clinical improvement and reverse remodelling after CRT, although with rather low sensitivity and specificity (AUC 0.60) (1) (Figure 1).

Tissue Doppler imaging

Tissue Doppler imaging (TDI) (Figure 1) can be used to measure myocardial longitudinal (or radial) velocities, and allow analysis of the timing of motion of a certain segment (or many) in relation to electrical activation (ie, electromechanical delays). With pulsed-wave TDI, only one segment at a time can be analyzed. Simultaneous measurements can be obtained using colour-coded TDI and quantitative Q analysis (TDI velocity curves; Figure 1). This offers the advantage of measurements made on a single heart beat, perhaps leading to reduced variability.

In a four-segment model (apical four-chamber view), Bax et al (33) demonstrated that the 'time to peak' septal to lateral delay (time difference from onset of QRS to peak systolic velocity between segments [Ts])

in the ejection phase predicted reverse LV remodelling (Ts cut-off at 65 ms or more). The clinical response to CRT could also be predicted using Ts, with 80% sensitivity and specificity. The same group published a simpler two-segment model in a small study ($n=25$), where a delay of 60 ms or more was related to an LVEF increase of 5% or more after CRT (34). The latter criterion was used in the PROSPECT trial (1) and could predict LV remodelling rather well, but could not predict clinical response to CRT (35). Consistent with many parameters studied in PROSPECT, the reproducibility was poor (33.7% interobserver variability).

Yu et al (36) created a more complex 12-segment-based dyssynchrony index (Ts-SD), using the SD of the time to peak systolic velocity in the ejection phase. With a population-derived cut-off value of 32.6 ms, the Ts-SD could predict reverse remodelling after CRT (sensitivity 96% and specificity 78%) (36). The same group reproduced these results in a three-centre study (256 patients) (37), in which reverse remodelling was observed in 55% of patients (93% sensitivity and 78% specificity). This may be due to the complexity of such a model in a multicentre trial context and the caveats of PROSPECT, but Ts-SD could not predict reverse remodelling after CRT in this study (1).

In single- (or few-) centre studies, selected echo-derived parameters of dyssynchrony seemed to represent promising predictors of response. However, when applied by less experienced readers in a larger population, none of these parameters seemed to adequately predict clinical or echo response to CRT.

STEP 4: A 'NEWER' ECHO TECHNOLOGY?

TSI

TSI (Figure 2) is a TDI-derived technique that allows for automatic calculations of time from the onset of QRS to peak systolic velocities, illustrated through a colour-coded map: the earliest segments are shown in green, and the most delayed in red. It includes postsystolic contraction. It is then possible to identify regions of interest from apical views, and generate time-velocity tracings (quantitative analyses). In a pilot study conducted by Gorcsan et al (38), a cut-off value of 65 ms or more between opposite LV walls predicted acute LVESV diminution of 15% or more, with a sensitivity of 87% and a specificity of 100%. In a single-centre study, Yu et al (39) used TSI to predict the response to CRT. The intra- and interobserver variability was 4.2% and 5.9%, respectively. The SD of Ts in the ejection phase (12-segment model consisting of six basal and six mid segments) was the best predictor of reverse remodelling ($r=-0.61$), and had a sensitivity of 87% and a specificity of 81% when a cut-off of 34.4 ms was used. The authors concluded that the presence of a qualitative delay in the lateral wall is a 'quick and specific guide' to predict reverse remodelling. In a recent trial (40), 60 HF patients received CRT according to current guidelines, but included patients with an EF of up to 40%. Dyssynchrony assessment was determined by the septal to lateral delay in colour-coded TDI, as well as by TSI. Response was predefined as combined clinical and echo end points, including improvement by one or more NYHA class, a 25% increase in 6WMT distance and a 15% or greater decrease in LVESV. The correlation between TDI and TSI was very good ($r=0.99$). Using a cut-off of 65 ms, TSI could predict reverse remodelling with 81% sensitivity and 89% specificity, and clinical response with 80% sensitivity and 92% specificity. TSI could provide a less time-consuming way of assessing dyssynchrony on a single heart beat than with standard TDI and appears to be a promising tool to predict response to CRT. It also has the advantage of being less operator-dependent.

Strain, strain rate and speckle tracking

Velocities measured with TDI tend to underestimate the individual movement of each myocardial segment because of translational motion or tethering. To overcome this limitation, a new method has been developed. Strain is a measure of deformation – with each contraction, the ventricle shortens in its longitudinal and circumferential dimensions (negative strain), and thickens in the radial dimension (positive strain). Strain rate is the rate of shortening (change in length) or the difference between two velocities for a given distance (Figure 3). Tissue tracking is

Figure 1 Examples of simple dyssynchrony assessment using pulsed Doppler (left ejection pre-interval) and tissue Doppler imaging Q analysis septolateral delay. In this example, according to cited criteria, no dyssynchrony is identified

a measure of strain over a given time. For strain evaluation, the direction of the tissue's movement must be less than 30 degrees from the point of interrogation. Therefore, technical precision is very important for such measurements because it has a major impact on the quality and reproducibility of data (41).

The initial results of dyssynchrony assessment using strain imaging have been conflicting, mainly regarding correlation with reverse remodelling (42,43). In a recent study, TDI Ts-SD in a 12-segment model predicted reverse remodelling with a sensitivity of 93% and a specificity of 73%, but correlation with strain was poor (44). Moreover, Knebel et al (45) recently demonstrated that strain analysis did not predict clinical response to CRT (AUC 0.432 and 0.368 for radial and longitudinal strain, respectively, versus 0.651 for TDI), although there was a significant decrease in radial and longitudinal strain following CRT. The place of strain and strain rate imaging in dyssynchrony assessment remains to be determined, and is not ready for clinical application on a routine basis.

The physiology of ventricular contraction is complex. The fibers are oriented in a longitudinal direction in the subendocardium, in a radial direction in the mid myocardium, and are obliquely oriented in the subepicardium (46,47). Tissue deformation imaging (strain) has been performed using speckle-tracking software, which maps natural acoustic markers (speckles) on grey-scale short-axis two-dimensional images. Their movements can be followed through the cardiac cycle, and changes in length or position can be computed to strain curves (Figure 4). Endocardial definition is very important to determine the region of interest, and is dependent on the quality of the acoustic window. The predictive value of radial speckle was recently assessed, with or without longitudinal dyssynchrony assessment (known TDI criteria), to

Figure 2 A patient with ischemic cardiomyopathy who underwent cardiac resynchronization therapy. The upper left panel shows the pre-implantation colour-coded velocity curves derived from the basal septal (yellow) and lateral (green) segments. There is a delay of 90 ms between the septal and lateral peak systolic velocities, indicating left ventricular dyssynchrony. The upper right panel shows the corresponding tissue synchronization imaging (TSI) pre-implantation analysis. The red colour at the basal lateral wall indicates delay in mechanical activation. The automatically calculated difference in peak systolic velocities between the septal and lateral wall is 85 ms. The lower left panel shows the postimplantation velocity curves of the basal septal and lateral wall. No delay remains between the peak systolic velocities. The lower right panel shows the corresponding TSI analysis after implantation. The absence of late activation is evident. Pos vel Positive velocity. Reproduced with permission from reference 40

predict response to CRT in a two-centre prospective study of 176 HF patients (48). Significant dyssynchrony was defined by a strain of 130 ms or greater (49). A change in EF of 15% or more occurred in 116 patients, and could be predicted by speckle-derived methods with good sensitivity and specificity (84% and 73%, respectively). Further multicentre trials are needed to establish the clinical applicability of speckle tracking in dyssynchrony assessment and patient selection for CRT.

3D echo

Real-time 3D (RT3D) echo provides regional volume-time curves that can be derived from each segment (Figure 5). It requires off-line analyses. Timing differences between segments can be measured. Remodelling of each segment could be assessed, including the radial, circumferential and longitudinal evaluation of the different segments (50), providing new insights into the response to CRT. In a recent paper by Burgess et al (51), RT3D echo was compared with TDI Ts-SD in 100 unselected patients with ischemic cardiomyopathy. Satisfactory myocardial velocity curves for all 12 segments could not be derived in 39 cases; artefacts were reported in five patients and 3D images were suboptimal in 18, leaving 77 patients for analysis (77%). A cut-off value of 32 ms was used for Ts-SD, and a cut-off of 8.35% was used for the time from QRS onset to minimal systolic volume between 12 segments. TDI identified a greater proportion of patients as having significant dyssynchrony compared with RT3D (64% versus 42%) in that population, with a majority of patients having a QRS of greater than 100 ms, and a mean NYHA class of 1.8 (51). In a recently published study of 49 HF patients undergoing CRT, acute (within 48 h) responders were defined by a change of 15% or more in LVESV. A colour-coded 3D TDI acquired the SD of all 12 segments, and an SD of 35.8 ms or greater had a sensitivity of 91% and a specificity of 85% to predict acute response to CRT. Septal to lateral delay had a sensitivity and specificity of 87% and 81%, respectively (cut-off 65 ms) (52). A more homogeneous methodology probably needs to be applied for 3D assessment, and the predictive value of RT3D has to be demonstrated in a larger number of patients.

$$\epsilon = \frac{\Delta L}{L_0} \quad (1) \quad \text{SR} = \frac{\Delta L/L_0}{\Delta t} = \frac{v(I_0) - v(\Delta L + L_0)}{L_0} \quad (2)$$

Figure 3 Equations to calculate strain (1) and strain rate (2), where ΔL is an absolute change in length and L_0 is the baseline length

Figure 4 Dyssynchrony using speckle-tracking strain. The left panel demonstrates time-strain curves of a patient without dyssynchrony at baseline. This patient did not show left ventricular (LV) remodelling during follow-up (LV end-systolic volume [LVESV] was 84 mL at baseline versus 73 mL at six-month follow-up). The right panel demonstrates time-strain curves of a patient with LV dyssynchrony at baseline (earliest activated segments: purple, green and dark blue; latest activated segments: light blue, yellow and red). This patient showed LV remodelling during follow-up (LVESV was 122 mL at baseline versus 77 mL at the six-month follow-up). Reproduced with permission from reference 74

STEP 5: OTHER IMAGING TECHNIQUES

Nuclear imaging

Two different modalities have been developed with nuclear medicine. The first is derived from myocardial perfusion imaging (MPI) and the second from radionuclide ventriculography (gated blood pool analysis). Both approaches are derived from the first Fourier harmonic fit on the activity variations located either in the myocardial wall or in the LV blood pool. Phase analysis refers to the timing of these variations within the cardiac cycle from zero to 360 degrees (53). Applied to the left ventricle, it measures the homogeneity of the LV contraction (synchrony). For the MPI approach, the normal phase histogram is narrow and highly peaked (Figure 6). A 'bull's-eye' image is generated by the 3D analysis of the LV segments. Henneman et al (54) compared this modality with TDI dyssynchrony assessment by the delay in peak velocity between the latest and the earliest of the four basal segments. In 75 HF patients potentially eligible for CRT, the correlations with TDI were good. A further study was performed to attempt to predict a response to CRT in 42 patients (67% with an ischemic cardiomyopathy) referred for biventricular devices. Responders were defined by an improvement by one or more NYHA functional class. A total of 71% of patients were responders at six months and the histogram bandwidth was significantly higher in these patients, as was phase SD. A cut-off value of 135 degrees in bandwidth could predict response with a sensitivity and specificity of 70% (AUC 0.78). For phase SD, a cut-off of 43 degrees could predict response with good sensitivity and specificity (74% for both) (55).

MPI methodology has the advantage of evaluating scar tissue and myocardial viability. Ypenburg et al (56) reported that patients with scar tissue and LV dysfunction showed no improvement after CRT at six months, and that the extent of viable myocardium is directly related to a decrease in LV volume and improvement in LVEF. This has also been observed by two other groups of investigators (57,58).

Our group (59) worked on a new tool to assess dyssynchrony through equilibrium radionuclide ventriculography, using gated blood pool single photon emission computed tomography (3D). A contraction homogeneity index (CHI) was established based on an algorithm relating the ratio of wall movement contributing to stroke volume to total wall movement (Figure 7). CHI was scaled from 0 to 100 (100 was equivalent to total synchrony). This method was tested in 97 patients referred for LVEF evaluation who underwent radionuclide ventriculography. A lower CHI

Figure 5 Three-dimensional echocardiography and left ventricular dyssynchrony. **A** Full volume acquisition. **B** Left ventricular cast produced by quantitative analysis. **C** Regional volume curves in normal systolic function. **D** Regional volume curves in severe intraventricular dyssynchrony. Reproduced with permission from reference 50

was correlated with higher NYHA class, lower EF and wider QRS. In a recently published study, by the same group (60), on 235 patients referred for LVEF assessment, the gated blood pool single photon emission computed tomography-acquired CHI value decreased significantly ($P < 0.05$) with each gain in NYHA class. Prospective validation of this promising index against other markers of dyssynchrony is currently under investigation and the predictive value of the measured indexes should be tested. Such a technique has the clear advantage of precise evaluation of LVEF, while providing a global index of dyssynchrony. However, it is less clear whether a segmental analysis could help in guiding the optimal location of LV lead placement.

CMR

CMR has the potential advantage, like perfusion nuclear imaging, of providing information about LV function, characterization of scar tissue and viability. Kim et al (61) reported that the extent of scarring in a given myocardial segment was a strong predictor of functional recovery in 50 patients referred for revascularization. Segments with transmural or nearly transmural (more than 75%) scarring (also called grade 3 to 4) did not regain contractility after revascularization. The impact of scar tissue on the response to CRT was examined in 57 consecutive HF patients eligible for CRT. Dyssynchrony was assessed through TDI, measuring the time to onset of systolic velocity from the QRS onset. In 41% of all the segments analyzed, grade 1 to 2 scarring (compromising less than 50% of segment thickness) was found. The localization of scar tissue and its link with the response to CRT has also been assessed. Reverse remodelling was observed in only four patients with posterolateral (PL) scarring, nine patients without PL scarring and 25 patients with no scarring. However, in a multivariate analysis, only the presence of dyssynchrony could predict an acute response to CRT (62). In a head-to-head comparison of TDI with magnetic resonance imaging (MRI) assessing septal to lateral delays, a good correlation was observed between the two modalities (63). Recently, assessment of dyssynchrony with MRI through TSI was developed using short-axis views of the LV. Construction of a polar map (Figure 8) and derivation of a tissue synchronization index (64) were obtained from the analysis of segmental radial wall motion data. Intra- and interobserver correlations were 0.99 and 0.98, respectively.

Figure 6 Phase analysis with gated myocardial perfusion single-photon emission computed tomography (GMPS). **A** Example of a patient without left ventricular (LV) dyssynchrony on GMPS. The non-normalized (upper panel) and normalized (lower panel) phase distribution bull's eyes are nearly uniform, and the corresponding phase histograms are highly peaked, narrow distributions (with a small SD). **B** Example of a patient with LV dyssynchrony derived from GMPS. The non-normalized (upper panel) and normalized (lower panel) phase distribution bull's eyes show significant nonuniformity and the corresponding phase histograms are widely spread distributions (greater SD and bandwidth). Reproduced with permission from reference 54

A cut-off of 40 ms gave a sensitivity of 94% and a specificity of 100% to discriminate between normal patients, and HF patients with QRS durations of less than 120 ms, 120 ms to 149 ms, and 150 ms or greater. Over a mean follow-up period of 764 days, patients with a CMR index of 110 ms or greater were five times more likely to die from any cause or be hospitalized for major cardiac events, 11 times more likely to die from any cause or to be hospitalized for HF, and 19 times more likely to die from cardiovascular cause than those with a CMR TSI of less than 110 ms.

Clearly, the quantity and location of scar tissue influenced the ability of CRT to lead to reverse remodelling. Studies of small numbers of patients have produced interesting findings. Bleeker et al (65) suggested the importance of PL wall scar in predicting lack of response to CRT in 40 patients. However, White et al (66) suggested that the total scar burden (less than 15%, including less than 40% of septal scar) was predictive of CRT response in 23 patients. Early reports have shown the potential of contrast-enhanced navigator-gated 3D CMR in providing coronary sinus and great cardiac vein anatomy (67) compared with cardiac computed tomography, the present gold standard (68). Although work is ongoing in determining the role of cardiac computed tomography in viability and scar assessment (69), contrast-enhanced CMR is currently the gold standard in providing scar evaluation. While CMR

Figure 7 A gated blood pool single photon emission computed tomography reconstruction (A) is used to detect endocardial walls with 400 vertexes per ventricle (B). Normal vectors to the surface are used to analyze radial motion (C) of each vertex. A Fourier analysis is used to extract phase and amplitude of each motion curve, and create the phase diagram (D). Simple vectorial algebra is used to determine the contraction homogeneity index

holds promise in patient selection for CRT, warranting larger-scale studies, patients with permanent pacemakers or defibrillators are currently ineligible to undergo repeated CMR.

STEP 6: POSTIMPLANTATION ASSESSMENT

As with any other therapy, once a CRT device has been implanted, it should be ensured that it is functional and efficient, and that it causes no harm to the patient. Certain objective measurements of synchronization and cardiac function improvement should be performed before the patient leaves the hospital. Programmed proprietary synchronization optimization (built-in) is often offered by the devices' manufacturers. Echo assessment of cardiac output (whether it has improved or is not reduced) and evaluation of diastolic filling can also easily be performed in the acute postimplantation phase. Programming of the auriculo-ventricular and ventricular-ventricular delays can be optimized according to cardiac output and diastolic filling (70-72). Improvement of a given patient's LV electromechanical delays should also be observed at the same time, using TDI or TSI. Other parameters beyond echo should be considered, such as lead position and fixation, which are also determinants of response. Many questions about CRT optimization following implantation remain unanswered at the present time.

A MULTIMODAL APPROACH

The benefits of CRT have largely been demonstrated for patients with advanced HF, but the rate of nonresponders remains a problem. Before considering CRT, we propose to evaluate potential candidates in a step-wise approach (Figure 9), and (consistent with many other invasive procedures) the patient should be aware of the risks and benefits of this therapy. A 6MWT should probably be included in the initial evaluation. At the present time, QRS width is still an important tool in patient selection. Studies addressing the value of CRT in patients with a narrow QRS are still ongoing and will help determine the place of this parameter in patient selection. Third, an echo evaluation has the advantage of accessibility, and it rapidly provides essential information such as EF and wall motion abnormalities (with some degree of scar evaluation [ie, fibrotic, thin hyperechogenic segments]). Dyssynchrony parameters assessed through TSI seem promising. Most TDI measurements cannot be recommended as part of a routine clinical pre-CRT assessment at this time,

Figure 8 Dyssynchrony assessments through cardiac magnetic resonance imaging. A Division of the left ventricular (LV) myocardium into slices and segments. B The junction between the interventricular septum and the right ventricular (RV) free wall delimits the beginning of segment 1 and the end of segment 6, counting clockwise. C and D Representative graphs of radial wall motion of LV segments throughout the cardiac cycle in an LV basal slice in a control subject (C), and in a patient with heart failure (HF) and left bundle branch block (LBBB) (D). Polar maps are shown. Note the late contraction of the inferoposterior wall in the patient with HF and LBBB. Reproduced with permission from reference 64

namely because of the technical complexity of currently proposed measurements, leading to a demonstrated low reproducibility. Some of these parameters (eg, LPEI) may, however, prove to be useful and are easy to perform. We must keep in mind that the presence of LV dyssynchrony per se has prognostic implications (64). Speckle tracking is among the newer promising tools, using a simple, more global approach to dyssynchrony evaluation. Nuclear medicine techniques could also provide global indexes of dyssynchrony while performing other tests for viability or LVEF assessment. Dyssynchrony is certainly not the only aspect to consider before CRT implantation. Finally, evaluation of scar tissue and viability seems to bring new angles to this dynamic area of research. Many ongoing trials will also provide new insights. Finally, device optimization and lead positioning are important aspects to be developed in the near future. As emphasized by other authors, the facility of measurement, and the reproducibility of few and robust indexes are key, whichever modality

Figure 9 A multimodal approach (see text). 6MWT 6 min walk test distance in metres; CMR Cardiac magnetic resonance imaging; CRT Cardiac resynchronization therapy; EF Ejection fraction; IVMD Interventricular mechanical delay; LPEI Left ejection pre-interval; NYHA New York Heart Association; TSI Tissue synchronization imaging

is used (73). We propose adding to optimal medical therapy and QRS-guided selection some echo-derived dyssynchrony assessment (LPEI, IVMD, TSI) and a viability study (nuclear or CMR).

CONCLUSION

The present review highlighted the current state of knowledge in patient assessment for CRT. It revisited the current criteria for patient selection, and the contributions of echo and other imaging techniques in dyssynchrony assessment. We believe a multimodal stepwise approach to patient selection for CRT could improve the current response rates. Many trials are still ongoing to evaluate the undoubtedly important contributions of scar tissue characterization, lead positioning and postimplantation optimization.

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