CHAPTER 2

Predicting response to CRT. The value of two- and three-dimensional echocardiography

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INTRODUCTION

In patients with severe, symptomatic drug-refractory heart failure and wide QRS complex, cardiac resynchronization therapy (CRT) has been demonstrated to have significant favorable effects on left ventricular (LV) remodeling and function and on clinical outcomes. However, a consistent percentage of patients fail to benefit from CRT when the established clinical and electrocardiographic selection criteria are applied. In particular, 20 to 30% of patients do not experience any clinical improvement after CRT and 40 to 50% of patients do not show any significant LV reverse remodeling or improvement in LV function. Therefore, at present attention has shifted towards a more accurate selection of CRT candidates, beyond the standard use of NYHA functional class, LV ejection fraction and QRS complex. Several contributory factors to CRT non-response have been reported, such as inappropriate LV lead positioning and, in patients with ischemic cardiomyopathy, the extent and location of scar tissue and viable myocardium. Furthermore, the presence of significant baseline LV mechanical dyssynchrony has been demonstrated to be predictive for a positive response to CRT. Echocardiography has been extensively used for a direct assessment of LV dyssynchrony with different approaches. In this review, the value of 2D and 3D echocardiographic modalities to predict response to CRT will be discussed, highlighting the advantages and drawbacks of each modality.

TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Two-dimensional (2D) echocardiography is widely applied in the selection and management of CRT patients, due to the low cost, broad availability, non-invasive approach and the extensive information that this technique can provide: 1) 2D echocardiography confirms the presence of an impaired LV systolic function at baseline and can evaluate CRT success at follow-up in terms of LV reverse remodeling and/or improvement of LV function; 2) 2D echocardiography evaluates the presence of other significant cardiac structural abnormalities that might affect therapy success, such as valvular pathologies and the extent of akinetic/thin (probably scar) myocardium; 3) 2D echocardiography can assess the presence of LV dyssynchrony with adequate temporal resolution. Visual assessment of wall motion synchrony by 2D echocardiography is probably the first and most straightforward step to approach a possible CRT candidate. However, the human eye with its limited temporal resolution is not able to precisely quantify the extent and location of myocardial dyssynchrony. Nevertheless, it is possible to identify typical phenomena that are associated with myocardial dyssynchrony. In the presence of delayed electrical conduction, the interventricular septum typically shows a characteristic multiphasic motion pattern (abnormal relaxation pattern) and the LV often demonstrates a rotating motion (typi-
cally oriented counter-clockwise in late systole, often also referred to as “rocking motion” or “apical shuffle”), as seen in the apical 4-chamber view. In a small study on 53 patients, Jansen et al. were able to demonstrate that the identification of these two phenomena predicted the presence of LV dyssynchrony (defined by tissue Doppler criteria) and LV reverse remodeling after CRT with a sensitivity of more than 90% and a positive predictive value above 85% 7. The septal multiphasic motion pattern can be also detected and quantified from the M-mode short axis view at the level of the papillary muscles. The ‘septal-to-posterior wall motion delay’ is calculated as the shortest interval between the maximal posterior displacement of the septum and the maximal inward displacement of the posterior wall 8. However, this parameter demonstrated a limited predictive value and, more importantly, a poor feasibility especially in ischemic patients 9.

Two-dimensional echocardiography also permits the quantification of myocardial dysynchrony based on the analysis of endocardial wall motion. Breithardt et al. evaluated a semi-automated contour detection algorithm, which had been originally developed for stress-echocardiography, in a small cohort of CRT patients 10. Semi-automatically contoured septal and lateral wall motion curves were constructed from digitized video recordings of the apical 4-chamber view and averaged over several cardiac cycles to calculate the phase angle difference between the opposing walls. Patients with significant dyssynchrony, defined by a phase angle difference below -25° or above +25°, were better hemodynamic CRT responders, defined by a >10% increase in LV peak positive dP/dt and/or pulse pressure. This quantitative approach is obviously limited by the restriction to two opposing walls, but similar algorithms have later been transferred to 3D technology.

Kawaguchi et al. quantified LV dyssynchrony before and during CRT with contrast enhanced 2D echocardiography 11. Temporal and spatial pixel intensity changes were analyzed in up to 50 sequential beats (contrast variability imaging) and demonstrated improved septal inward motion and reduced LV septal-lateral dyssynchrony by CRT. This novel approach is clearly limited by its time-consuming and costly image acquisition which necessitates the intravenous administration of contrast agents and the lack of a widely commercially available software tool.

Modern quantitative analyses, such as tissue Doppler imaging (TDI) and speckle tracking analysis, are also based on 2D echocardiography and are discussed in more detail elsewhere in this Supplement. Briefly, TDI is at present the most frequently used technique for LV dyssynchrony assessment 12. In particular, this technique allows the measurement of myocardial regional velocities with a very high temporal-resolution and, in relation to the electrical activity (QRS complex), enables the assessment of the electro-mechanical delay of 2 or more LV segments. Both two- and multiple-segmental approaches demonstrated their value for the prediction of clinical and echocardiographic response to CRT with high sensitivity and specificity 13,14. Recently, tissue synchronization imaging (TSI) has become available to simplify this approach, providing an intuitive color-coded image of the myocardium according to the
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automatically detected time-to-peak systolic velocity (Ts) of each LV segment, together with the possibility of an automated quantitative assessment \(^{15}\). Furthermore, when myocardial velocities are known, several other parameters can be derived off-line. Integrating velocities over time results in myocardial displacement, i.e. the total amount of tissue movement during systole. Alternatively, the spatial derivative of velocity and displacement leads to strain rate and strain calculation, respectively, as myocardial deformation measurements \(^{16}\) (Figure 1). However, these parameters have proven not to be as robust as myocardial velocity parameters for predicting response to CRT \(^{14,17}\), probably due to the relatively poor reproducibility, independent of the operator experience. Furthermore, for all myocardial motion and deformation measurements, angle-dependency of TDI analysis has to be considered a major drawback, limiting the application of this technique to few LV segments and to one component of contraction (longitudinal, radial and circumferential) at a time.

Speckle tracking analysis is a novel echocardiographic technique that allows myocardial deformation measurements (strain and strain rate) from standard 2D gray scale images, track-
ing frame-to-frame the movement of natural myocardial acoustic markers (‘speckles’). The advantage of this technique, compared to TDI, is the angle-independency, allowing for the assessment of the 3 components of myocardial contraction (longitudinal, radial and circumferential direction) in all LV segments. Initial studies have demonstrated the value of radial dysynchrony, assessed with this technique, to predict response to CRT. Furthermore, Gorcsan and colleagues suggested that combining radial dyssynchrony, measured by speckle tracking, with longitudinal dyssynchrony, measured by TDI, predicted echocardiographic response to CRT (88% sensitivity and 80% specificity) significantly better than either technique alone.

THREE-DIMENSIONAL ECHOCARDIOGRAPHY

Early approaches to 3D echocardiography were based on the principle that a 3D data set is reconstructed from a series of 2D images obtained using either freehand scanning or a mechanically driven rotating transducer that sequentially recorded images at predefined intervals. This approach was limited by several technical aspects during image acquisition and required significant time-consuming off-line data processing. Nowadays, 3D echocardiography is a real-time technique that permits a rapid (5–7 minutes) post-processing of the 3D dataset off-line or on the scanner itself. In addition, the post-processing of the 3D dataset provides, in one single analysis, highly accurate quantification of LV volumes and function as well as the assessment of LV dyssynchrony with different modalities. In particular, 3D echocardiography, applying a semi-automated contour-tracing algorithm in multiple planes, has been validated against MRI and found to be more accurate and reproducible than 2D echocardiography for the assessment of LV volumes and function. These are crucial measurements in the evaluation of CRT success and carry out important prognostic implications. Furthermore, a 3D assessment of LV dyssynchrony has the advantage of a simultaneous acquisition of all LV segments, allowing for more extensive intersegment comparison, as compared with other 2D techniques, and avoiding the problem of heart rate variability during image acquisition.

Tri-plane tissue Doppler imaging

Recently, color-coded TDI has been used in combination with tri-plane imaging, which allows for analysis of the 3D dataset along 3 major planes with a simultaneous visualization of the apical 4-, 2- and 3-chamber views (Figure 2). Sample volumes can be placed simultaneously in 12 LV segments and Ts of any LV segment can be compared during the same heartbeat. Van de Veire et al. applied this technique in 60 patients undergoing CRT and demonstrated that the standard deviation of Ts of 12 (6 basal and 6 mid segments) LV segments (Ts-SD-12), with a cut-off value of ≥33 ms, was able to predict echocardiographic response with a sensitivity...
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of 90% and a specificity of 83% \textsuperscript{25}. These findings further support the previous results of Yu et al. using single-plane TDI \textsuperscript{14}.

Similarly, it has become possible to apply TSI to the tri-plane view and this approach was found useful to identify the area of latest activation within the LV (Figure 3). Further studies are needed to confirm the feasibility of this technique in the clinical practice and to explore the value to predict response to CRT \textsuperscript{25}.

Analysis of volumetric changes by real-time three-dimensional echocardiography

Real-time three-dimensional echocardiography (RT3DE) has emerged as a novel echocardiographic technique for the assessment of LV dyssynchrony based on the analysis of regional volumetric changes. Briefly, LV 3D model is subdivided by the software in 17 wedge shaped (apart from the apex) sub-volumes according to standard segmentation (Figure 4). For the whole LV and for each volumetric segment, it is possible to derive time-volume data for the entire cardiac cycle and assess the time taken to reach the minimum systolic volume (Tmsv)
Segments should achieve the minimum volume at the same point in the cardiac cycle. However, when significant LV dyssynchrony is present, a wide dispersion of the Tmsv of the various segments occurs. The standard deviation of the Tmsv for 16 segments has been proposed as a measure of LV dyssynchrony and expressed as a percentage of the cardiac cycle (the systolic dyssynchrony index, SDI). Furthermore, parametric images, derived from over 800 virtual waveforms, are also provided by the software with a visual summary of LV regional contraction timings as a polar plot. The global Tmsv is used as timing reference and segments with a Tmsv that is approximately the same as global Tmsv are coded in green. Early segments are color-coded in blue, whereas late segments are coded in red/yellow, providing a rapid and intuitive assessment of the area of latest LV activation (Figure 5). This may be of particular importance to guide an optimal LV lead placement. Kapetanakis et al. demonstrated the feasibility of LV dyssynchrony assessment with RT3DE in a large group of patients and normal subjects using SDI. In 26 patients referred for CRT implantation, the authors observed that clinical responders (reduction in NYHA functional class) had significantly higher SDI at baseline as compared to non-responders (16.6±1.1% vs. 7.1±2.0%, p <0.001). In addition, after a mean follow-up of 10 months, a reduction in SDI was noted in responders,
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whereas an increase in SDI was observed in non-responders. In a more recent study, Marsan et al. addressed the predictive value of this parameter and found that a SDI ≥5.6% had a sensitivity of 88% and a specificity of 86% to predict acute volumetric response to CRT.

Currently, no data are available on the predictive value of long-term response to CRT and the technique needs further validation for this application. Furthermore, RT3DE has still some limitations. First, the temporal resolution is suboptimal, about 30 to 35 ms. Nonetheless, the feasibility of LV dyssynchrony assessment has been demonstrated in a large group of normal individuals and unselected patients with and without QRS prolongation. Furthermore, the image quality is somewhat lower than 2D echocardiography and the incomplete visualization of large ventricles may affect the quantitative analysis. However, several studies have reported a good feasibility in heart failure patients.

Figure 4. Example of 3D LV volumes generated by post-processing of a RT3DE dataset, acquired in a heart failure patient scheduled for CRT. The LV 3D model is subdivided by the software in 17 wedge shaped (apart from the apex) sub-volumes and for each volumetric segment, it is possible to derive time-volume data (lower panel) and assess the time taken to reach the minimum systolic volume (red dots).
Different echocardiographic approaches, with relative strengths and limitations, are available for the assessment of LV dyssynchrony and prediction of response to CRT. However, LV dyssynchrony assessment is a challenging goal, since it can not be considered an all-or-none phenomenon but a dynamic condition that may vary widely and can be dependent on loading conditions. Consequently, it is still not clear which parameters, among those of myocardial motion, myocardial deformation or volume changes, would best reflect the complex pathophysiologic substratum of LV dyssynchrony in heart failure and whether the two-segmental model should be preferred over the multiple-segmental model. Therefore, a consensus on the definition of LV dyssynchrony is still lacking. In addition, the predictive value of these echocardiographic indices have been generated from small, single-center, non-randomized studies that used non-uniform definitions of response to CRT and evaluated a relatively short-term follow-up. Consequently, the results need to be confirmed in larger prospective multi-center studies. Ideally, the optimal predictor of a favourable response to

**CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS**

**Limitations of current LV dyssynchrony evaluation**

Figure 5. Parametric image derived from 3D dataset of a patient scheduled for CRT. The LV is divided into the standard segments (from 1 to 17). Using color coding (blue indicating early activation and orange-red late activation) representing regional time-to-minimum systolic volumes, the posterior wall is identified as the latest activated before CRT (left panel). Six months after CRT (right panel) the overall green color indicates absence of regions with delayed activation.
CRT must have high sensitivity and specificity. In addition, it should also be simple to perform, widely available, easily reproducible and obtainable before and after CRT implantation.

**Future directions**

The PROSPECT trial is currently evaluating in 426 patients whether specific echocardiographic measurements of dyssynchrony, including M-mode, Doppler and TDI, could be used to better predict a favourable response to CRT. The first, preliminary results revealed that none of the echocardiographic parameters was associated with a relevant additional response rate. However, these findings may be explained by the fact that a marked inter-core lab variability was found for these parameters, highlighting the challenges that the interpretation of these exams offer even to experienced personnel. Importantly, it should be noted that the most recent, 3D and automated imaging techniques were not included in this trial. Furthermore, a combined approach using different and complementary parameters of LV dyssynchrony, rather than using single parameters, may provide better results. More large prospective studies are needed to fully appreciate the role of LV dyssynchrony assessed with echocardiography in the prediction of response to CRT. Consequently, at present LV dyssynchrony assessment is not yet recommended for patient selection for CRT. Furthermore, it should be kept in mind that other pathophysiological issues may also be important to consider before CRT, including extent and location of scar tissue, optimal LV lead position and availability of coronary veins.
REFERENCES


