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RESEARCH ARTICLE

How can Anatomical and Biomarkers help in the Management of CRT patients

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Introduction

Since its approval by the Food and Drug Administration in 2001 for the treatment of chronic heart failure (HF), cardiac resynchronization therapy (CRT) has been consolidated as an alternative therapy for patients with HF, advanced left ventricular systolic dysfunction, and dyssynchrony identified by electrocardiogram (ECG). Improvement in HF functional class, exercise capacity, quality of life, reduction in the number of hospitalizations, and prolonged survival have been demonstrated in several randomized clinical trials.1–4 The current indications for CRT are directed towards patients in functional classes III/IV of the New York Heart Association (NYHA), with optimal pharmacological therapy, left ventricular ejection fraction (LVEF) ≤35%, and QRS ≥120 ms with left bundle branch block pattern (LBBB).5

However, around 30% of patients do not get a satisfactory clinical response to CRT, and approximately 40% do not show reverse remodeling of the left ventricle (LV) (15% reduction in end-systolic volume), a predictor of long-term clinical outcomes.6

Widening of the QRS on the ECG is not the ideal method to identify dyssynchrony. An absence of dyssynchrony may be found in patients with LBBB, and, in contrast, dyssynchrony may occur in patients with narrow QRS.7 This fact could justify the percentage of non-responders presenting in clinical trials.

In this way, several echocardiographic indices have been developed for the evaluation of dyssynchrony and response to CRT. However, when evaluated in the PROSPECT trial (Predictors of Response to Cardiac Resynchronization Therapy), these indices showed no clinically relevant impact on improving response to CRT, with a high rate of inter- and intraobserver variability.8

Other factors have been identified as markers of poor response to CRT, such as ischemic HF, extensive myocardial scars, and suboptimal lead placement. Therefore the role of echocardiography, as well as other cardiovascular imaging techniques, has become increasingly significant in the evaluation of dyssynchrony and response to CRT.9–11

In healthy hearts with adequate generation, conduction, and muscular responses to electrical stimulation, there is a modulation of contractility maintaining synchrony between the chambers, leading to optimal cardiac performance.

The loss of synchrony is related to the worsening of the myocardial dynamic and may occur at atrioventricular, inter- and/or intraventricular levels.

Atrioventricular dyssynchrony

Frequently, patients with advanced HF have delay in atrioventricular conduction. Such a change in atrioventricular synchrony leads to the shortening of left ventricular filling and may cause the appearance of diastolic mitral regurgitation. In the analysis of mitral inflow with pulsed Doppler, the fusion of E and A waves may appear, as well as an increase in total isovolumic times, showing a reduction in left ventricular filling time (LVFT).12 LVFT in relation to cardiac cycle length (RR) as measured by transmural Doppler echo expressed as a

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Interventricular dyssynchrony

Interventricular dyssynchrony can be assessed by determining the interventricular mechanical delay (IVMD), which is the difference between the aortic and pulmonary pre-ejection periods. This index can be obtained by measuring the interval time between the onset of the R wave of the electrocardiogram and the onset of ventricular ejection, through the analysis of flow velocities by pulsed Doppler in the outflow tract of both ventricles. The critique against this method is that measurements are not taken simultaneously.13 Values ≥49 ms were associated with improvements in clinical outcomes after CRT in a large clinical trial.14 However, a low predictive value of the index for response to CRT was later shown.15 Therefore, the IVMD has a higher value in predicting response to CRT when combined with intraventricular dyssynchrony.

Intraventricular dyssynchrony

Defined as an uncoordinated regional myocardial contraction–relaxation pattern, its genesis usually takes place in delays conducting the electrical stimulus, which results in heterogeneity in the LV contraction patterns, as well as damaging the normal functioning of the mitral valve. Intraventricular dyssynchrony in theory is what best correlates with response to CRT, which is why it has been studied exhaustively in various clinical trials, and now has an immense repertoire of echocardiographic methods and other modalities of cardiovascular imaging for its evaluation.15

Echocardiographic methods to detect asynchrony

M mode

Owing to easy execution and high availability in echocardiography laboratories, this imaging modality is often used in the evaluation of left ventricular dyssynchrony. It consists of measuring the delay between septal and posterior wall contractions. This measurement is performed in the parasternal long axis view or short axis view of the LV, with the M-mode cursor at the medioventricular level, measuring the time delay from the septal excursion peak to the posterior excursion peak.15 Values ≥130 ms define the presence of left ventricular dyssynchrony and showed positive results in response to CRT in studies conducted by Pitzalis et al.16,17 Because of the questionable reproducibility and high variability of this method,9 its isolated use on echocardiographic assessment of dyssynchrony is not advised.

Color tissue Doppler (color TD) can aid the M mode in a better characterization of the excursions of the walls. Associated with M mode, it uses colors to codify the changes in myocardial directions, thus facilitating the precise identification of the electromechanical delay. In typical LBBBs there can exist a premature “in and out” septal movement pattern (Septal Flash) visualized in the M mode, also seen with the addition of color TD, and described as a marker of left ventricular dyssynchrony.18

Tissue Doppler imaging

Until the present time, tissue Doppler imaging (TDI) has been the most studied method in the assessment of mechanical dyssynchrony and response to CRT, especially through the analysis of longitudinal velocities. The electromechanical delay (EMD) can be assessed by determining the period between the beginning of the QRS complex and peak systolic velocity in the ejection phase (Ts).15 The existence and value of this delay between opposite segments of the LV defines the presence and severity of intraventricular dyssynchrony. TDI provides analysis of various segments of the left ventricular wall. Data acquisition with color TD is simpler than pulsed TD, and allows the off-line analysis of the images. For this reason, this type of acquisition is being increasingly used in both research and everyday practice in the laboratory.

Data acquisition requires a high frame rate. Owing to interference of breathing, acquisition is advocated during the end of expiration. Three imaging planes (apical four-chamber view, apical two-chamber view, and apical long axis view) should be recorded, delimiting the four opposite segments (basal and mid-segments) of each view. The LV ejection interval using pulsed Doppler at the outflow tract should be determined, which is then superimposed on the TDI tracing during time–velocity curve analysis.

In the detection of the systolic peak, measurement on the isovolumic phases or during post-systolic shortening should be avoided. When there are multiple peaks in the ejection phase, the highest peak will be selected. If there are two or more peaks with the same amplitude in velocity, the earliest peak will be selected.

So the mechanical dyssynchrony index (Ts-SD) or Yu index is determined by calculating the standard deviation of Ts of the 12 segments. A value ≥33 ms defines the presence of dyssynchrony.20

The analysis of the maximum difference of Ts among all segments can be performed. A value ≥100 ms predicts the response to CRT.15

In the same way, the analysis of Ts can be performed in a smaller number of segments, and an opposing wall delay ≥65 ms is consistent with dyssynchrony.15

Yu et al21,22 have demonstrated the value of Ts-SD as a predictor of outcomes from CRT in their studies, and afterwards showed the superiority of the index in relation to QRS in predicting outcomes from CRT.

Measurement of post-systolic shortening velocities showed low specificity in predicting LV reverse remodeling.25
Even within the spectrum of TDI, there was an attempt to use derivatives of the velocities, such as strain and strain rate in the study of dyssynchrony and response to CRT. however, the analysis of these derivatives showed questionable values constrained by the limitations of the method, which is highly angle dependent and affected by problems with signal noise, and, like other indices obtained by DTI, coursing with high variability and low reproducibility.

**Speckle tracking**

Speckle tracking is based on the principle that the interference of the reflected ultrasound with myocardial fibers leads to a random distribution of acoustic markers (speckles), and, therefore, each myocardial region has a pattern of displacement.

Thus speckle tracking allows the differentiation between active and passive movement of the wall without the disadvantage of the angle of incidence of a Doppler technique. Furthermore, the technique allows the realization of the radial, longitudinal, circumferential, and transverse strain, and enables the study of ventricular torsion. In this way, this new echocardiography tool is being increasingly studied, and its positive impact on better assessment of dyssynchrony and response to CRT has been shown. Delgado et al using speckle-tracking strain, demonstrated the superiority of radial dyssynchrony compared with longitudinal and circumferential dyssynchrony in predicting response to CRT. Recently, the results of STAR (Speckle Tracking and Resynchronization), the first prospective multicenter study to evaluate the role of speckle tracking as a new echocardiography tool, is being increasingly studied, and its positive impact on better assessment of dyssynchrony and response to CRT has been shown. Delgado et al using speckle-tracking strain, demonstrated the superiority of radial dyssynchrony compared with longitudinal and circumferential dyssynchrony in predicting response to CRT. Recently, the results of STAR (Speckle Tracking and Resynchronization), the first prospective multicenter study to evaluate the role of speckle tracking as a new echocardiography tool, is being increasingly studied, and its positive impact on better assessment of dyssynchrony and response to CRT has been shown. DELGADO ET AL.

A technical limitation is that speckle-tracking echocardiography is dependent on frame rates, as well as image resolution.

**3D echocardiography**

Real-time three-dimensional (3D) echocardiography is a promising method for the study of intraventricular dyssynchrony and response to CRT. It allows one to capture the dynamics of the entire LV in the same cardiac cycle, providing a better understanding of dyssynchrony using a 3D approach. The technique allows functional evaluation of all segments of the LV, and, through the integration of these segments’ function, Kapetanakis et al developed the systolic dyssynchrony index (SDI), which is the standard deviation of times to the minimum volumes normalized for cardiac cycle length. Other models such as analysis of 800 segments and 3D contraction front mapping can add information about regional contraction. Kapetanakis et al further demonstrated the predictive value of SDI in response to CRT, and recently confirmed the existence of intercenter reproducibility of the results obtained by this index, including raising the possibility of identifying candidates for CRT independently of QRS morphology and duration. However, the technique currently has the drawback of low temporal and spatial resolution because of low frame rates.

**Other imaging modalities that may help in CRT patients**

**Cardiovascular magnetic resonance**

Cardiovascular magnetic resonance (CMR) is currently considered to be the gold standard in the study of myocardial viability, allowing excellent structural and functional assessment of the heart.

Recent studies have demonstrated that scar burden and scar transmurality are related to poor response to CRT, whereas stimulation of scarified areas leads to prolongation and fragmentation of ventricular activation. Thus, currently the main role of CMR in CRT is in the detection and quantification of scars, assessing myocardial viability, and aiding in optimal LV lead placement. The use of CMR has been studied in the assessment of dyssynchrony, demonstrating good reproducibility and high spatial resolution. However, the technique currently has limitations related to security, due to incompatibility with implanted devices, the cost, and problems with slowness and complexity of data analysis.

**Nuclear imaging**

Nuclear imaging with phase analysis of ECG-gated single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) has proven to be a useful tool in CRT.

Currently, its role in CRT is well defined, with good results in the assessment of left ventricular dyssynchrony, identification of the site of latest mechanical activation, and detection and quantification of scars.

Its advantages include high reproducibility and ability to provide all information obtained with the method through a single scan.

In the assessment of left ventricular dyssynchrony, phase analysis of gated SPECT MPI compared with TDI 2D and 3D echocardiography showed good correlation with both methods. In a study conducted by Henneman et al data obtained by phase analysis were effective in predicting the response to CRT.

One of its disadvantages is the inability to identify the coronary venous anatomy and the rate of radiation offered in serial studies.
Cardiac computed tomography

The role of cardiac computed tomography (CT) in response to CRT is focused on detailed assessment of cardiac anatomy and location of the phrenic nerve.

As LV lead placement away from the region of greatest delay is related to worse outcomes from CRT, cardiac CT may contribute significantly by providing a complete assessment of the cardiac venous system, locating possible tortuosities and anatomical variations. The identification of the cardiophrenic bundle and its correlation with the cardiac veins is useful to avoid diaphragmatic irritation, and the high doses of radiation provided during application of the technique in sequential scanning to optimize LV lead placement.

As described previously, approximately one-third of patients submitted to resynchronization therapy had no satisfactory response. The rate of non-responders is higher (54%) in those with QRS between 120 and 150 ms and lower in those with QRS >150 ms. However, the questionable value of QRS as a marker of dyssynchrony led to the development of methods to identify mechanical dyssynchrony, although it is not always determined by the presence of electrical dyssynchrony. Studies using different imaging methods revealed the presence of mechanical dyssynchrony in patients with narrow QRS. Other factors, such as advanced-stage HF, dependent predictor of mortality in HF patients, are a member of the transforming growth factor (TGF)-β cytokine superfamily, with affects cardiomyocyte biology.

In a study evaluating the role of GDF-15 in 158 patients who had undergone CRT, it was concluded that the pre-implant GDF-15 levels are strong predictors of poor long-term outcome after CRT, independent of NT pro-BNP, QRS duration, and LVEF.

Other neurohormonal biomarkers and cytokines involved in HF have been assessed in small studies. Recently, Dong et al, evaluating the effect of CRT on neurohormonal biomarkers in HF, found that the less elevated level of amino-terminal propeptide of type III procollagen (PIIINP) is a predictor of response to CRT. Therefore, there is a need for larger prospective studies to understand better the role of these cytokines and other hormonal biomarkers in the CRT.

In conclusion, imaging provides information related to the presence of asynchrony and the different tools that may help in identifying responders to CRT therapy. However, larger trials are required to show which method is the most sensitive for detecting responders. Both anatomic and biological markers should be considered when selecting candidates for this type of treatment.

Brain natriuretic peptide and N-terminal pro-brain natriuretic peptide

Brain natriuretic peptide (BNP) is produced by and then secreted from cardiomyocyte in its active form (BNP) and an N-terminal fragment (NT pro-BNP). Both act as markers of high pressure and end diastolic volume. Elevated plasma levels of natriuretic peptides correlate with the severity of HF, and have prognostic value in the course of the disease. Likewise, changes in the values of natriuretic peptides have been shown to predict the response to CRT. Data from the Cardiac Resynchronisation Heart Failure (CARE-HF) study demonstrated early and sustained reduction in NT pro-BNP levels after CRT apparently corresponding to rapid functional improvement of the LV. Lelouche et al. found that the value of pre-implantation BNP is an independent predictor of response to CRT.

Growth differentiation factor 15

The growth differentiation factor (GDF)-15, an independent predictor of mortality in HF patients, is a member of the transforming growth factor (TGF)-β cytokine superfamily, with affects cardiomyocyte biology.

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