Echocardiographic Prediction of Cardiac Resynchronization Therapy Response Requires Analysis of Both Mechanical Dyssynchrony and Right Ventricular Function: A Combined Analysis of Patient Data and Computer Simulations

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Background: Pronounced echocardiographically measured mechanical dyssynchrony is a positive predictor of response to cardiac resynchronization therapy (CRT), whereas right ventricular (RV) dysfunction is a negative predictor. The aim of this study was to investigate how RV dysfunction influences the association between mechanical dyssynchrony and left ventricular (LV) volumetric remodeling following CRT.

Methods: One hundred twenty-two CRT candidates (mean LV ejection fraction, 19 ± 6%; mean QRS width, 168 ± 21 msec) were prospectively enrolled and underwent echocardiography before and 6 months after CRT. Volumetric remodeling was defined as percentage reduction in LV end-systolic volume. RV dysfunction was defined as RV fractional area change < 35%. Mechanical dyssynchrony was assessed as time to peak strain between the septum and LV lateral wall, interventricular mechanical delay, and septal systolic rebound stretch. Simulations of heart failure with an LV conduction delay in the CircAdapt computer model were used to investigate how LV and RV myocardial contractility influence LV dyssynchrony and acute CRT response.

Results: In the entire patient cohort, higher baseline septal systolic rebound stretch, time to peak strain between the septum and LV lateral wall, and interventricular mechanical delay were all associated with LV volumetric remodeling in univariate analysis ($R = 0.599$, $R = 0.421$, and $R = 0.410$, respectively, $P < .01$ for all). The association between septal systolic rebound stretch and LV volumetric remodeling was even stronger in patients without RV dysfunction ($R = 0.648$, $P < .01$). However, none of the mechanical dyssynchrony parameters were associated with LV remodeling in the RV dysfunction subgroup. The computer simulations showed that low RV contractility reduced CRT response but hardly affected mechanical dyssynchrony. In contrast, LV contractility changes had congruent effects on mechanical dyssynchrony and CRT response.

Conclusions: Mechanical dyssynchrony parameters do not reflect the negative impact of reduced RV contractility on CRT response. Echocardiographic prediction of CRT response should therefore include parameters of mechanical dyssynchrony and RV function. (J Am Soc Echocardiogr 2017;■:■-■.)

Keywords: Cardiac resynchronization therapy, Dyssynchrony, Echocardiography, RV function, Interventricular interaction, Computer simulations

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Abbreviations

2DS-RV = Right ventricular free wall peak strain

CRT = Cardiac resynchronization therapy

LBBB = Left bundle branch block

LV = Left ventricular

LVEDV = Left ventricular end-diastolic volume

LVEF = Left ventricular ejection fraction

LVESV = Left ventricular end-systolic volume

NYHA = New York Heart Association

RV = Right ventricular

RVFAC = Right ventricular fractional area change

SRSsept = Septal systolic rebound stretch

Strain-SL = Time to peak strain delay between the septum and the lateral wall

TRPG = Tricuspid regurgitation peak gradient

Cardiac resynchronization therapy (CRT) is an established treatment for patients with heart failure and evidence of electrical conduction delay.[1,2] Despite the success of CRT in large clinical trials, predicting CRT response in individual patients remains challenging. Response prediction is difficult because the mechanisms through which CRT response occurs are still not completely understood. An important mode of action of CRT is the correction of mechanical dyssynchrony caused by an electrical conduction delay, resulting in improvement in myocardial efficiency.[3] Attempts to predict outcome after CRT by identifying such electrical or mechanical substrates have yielded variable results, however.[4]

Right ventricular (RV) function is an important predictor of echocardiographic and clinical outcomes following CRT.[5] The impact of RV function on prognosis has been demonstrated in both observational studies and in landmark CRT trials.[5-7] RV dysfunction is strongly associated with more advanced heart failure.[8,9] Moreover, changes in RV function and loading can lead to mechanical dyssynchrony through ventricular interaction, even without underlying electrical dyssynchrony.[10] Whether RV function directly affects mechanical dyssynchrony and CRT response, and how this relates to the association with more advanced heart failure, remains unclear.[5-7,10,11] We therefore used echocardiographic deformation imaging to investigate whether RV dysfunction affects baseline mechanical dyssynchrony indices in a CRT population. We also investigated how these indices related to CRT response (i.e., volumetric remodeling). CRT response was defined as the reduction in left ventricular (LV) end-systolic volume 6 months after CRT. We further hypothesized that RV dysfunction could directly influence both mechanical dyssynchrony and CRT response, independent of LV condition. Because determining causation in the interaction between RV and LV myocardial dysfunction and mechanical dyssynchrony using patient data is challenging, we also performed computer simulations. Simulations were performed with the multiscale CircAdapt model of the human heart and circulation to isolate and explain the effects of RV and LV myocardial dysfunction on both mechanical dyssynchrony and CRT response.[12]

METHODS

Study Population and Protocol

The study population consisted of a cohort of prospectively enrolled patients undergoing CRT because of medication-refractory heart failure (New York Heart Association [NYHA] classes II–IV, LV ejection fraction [LVEF] < 35%) and evidence of conduction disturbances (QRS width ≥ 120 msec) with a left bundle branch block (LBBB)–like morphology on surface electrocardiography. Patients were excluded from the analysis if they had poor echocardiographic image quality ($n = 20$). Echocardiographic and clinical characteristics were prospectively assessed in all patients before and 6 months after CRT. Care was taken to optimize heart failure medication before the implantation of a CRT device. The execution of the study complied with the principles outlined in the Declaration of Helsinki on research in human subjects and with the procedures of the local medical ethics committee. In compliance with Dutch law, the requirement to obtain written informed consent was waived by the local medical ethics committee, as all echocardiograms and CRT implantations were part of standard clinical care.

Echocardiographic Protocol

All echocardiographic data were obtained using a Vivid 7 ultrasound machine (GE, Chicago, IL). A minimum of three loops were acquired at breath hold and analyzed offline (EchoPAC version 6.0.1; GE). In patients with atrial fibrillation, all parameters are averages over five representative beats.

Two-Dimensional Echocardiography and Doppler Imaging. LVEF, LV end-systolic volume (LVESV), and LV end-diastolic volume (LVEDV) were measured using the biplane Simpson method.[13] Reverse remodeling after CRT was defined as the percentage of reduction in LVESV between echocardiographic examination before and 6 months after CRT implantation. Response was defined as a reduction in LVESV of ≥15%.

Mitral regurgitation effective regurgitant orifice was quantified by the proximal isovelocity surface area method. RV measurements were performed in the apical four-chamber view. RV end-diastolic and end-systolic areas were traced and were used to calculate RV fractional area change (RVFAC). RV dysfunction was defined as RVFAC < 35%.[13] Tricuspid annular plane systolic excursion and transtricuspid pressure gradient were also measured. RVFAC was chosen to define RV dysfunction, as we expected that RVFAC would provide the most adequate estimation of RV function in the presence of mechanical dyssynchrony.[14]

For offline deformation imaging, additional narrow-sector single-wall images of the septum, lateral wall of the left ventricle, and free wall of the right ventricle were prospectively acquired from the standard apical views at 51 to 109 Hz. The onset of the QRS complex was taken as the zero reference for timing and strain measurements. Systole was defined using mitral valve closure and aortic valve closure, derived from Doppler flow patterns. Interventricular mechanical delay was assessed as the delay between pulmonary and aortic valve opening.

Deformation Analysis. Dedicated speckle-tracking software (EchoPAC 2DS version 6.1; GE) was used to derive longitudinal strain curves. The region of interest was placed from base to apex and adapted to match wall thickness. Tracking was visually checked and the region of interest adjusted if necessary. Global longitudinal deformation was calculated over the entire length of the wall. To assess LV dyssynchrony, time to peak strain delay between the septum and the lateral wall (Strain-SL) was calculated. Septal systolic rebound stretch (SRSsept) was determined by summing all systolic stretch following prematurely terminated shortening in the septum, as previously described (Figure 1).[15,16] Septal strain patterns were also categorized as type I (double-peaked), type II (predominant stretch during ejection), and type III (pseudonormal), as previously described (Figure 1).[17]