Right Ventricular Function Is a Determinant of Long-Term Survival after Cardiac Resynchronization Therapy

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Background: Right ventricular (RV) dysfunction is a marker of poor prognosis in patients with heart failure. The aim of this study was to investigate the impact of RV function on the long-term outcomes of patients undergoing cardiac resynchronization therapy (CRT).

Methods: A total of 120 consecutive patients treated with CRT according to guideline criteria were followed over 5 years. Comprehensive echocardiographic analyses of RV function and radial and longitudinal mechanical left ventricular dyssynchrony were performed at baseline and 6 months after implantation. RV function was evaluated by two-dimensional longitudinal strain of the free wall, fractional area change, tricuspid annular plane systolic excursion, and tricuspid annular systolic velocity. Long-term follow-up events were defined as all-cause mortality, heart transplantation, or assist device implantation.

Results: Long-term events occurred in 38 patients. Among the studied variables for RV function, RV strain < 18% had the highest sensitivity (79%) and specificity (84%) to predict a poor outcome after CRT (area under curve, 0.821; $P < .0001$). When adjusted for confounding baseline variables of ischemic etiology, mechanical dyssynchrony, left ventricular end-systolic volume, mitral regurgitation, and medical therapy, RV dysfunction remained independently associated with outcomes, indicating a 5.7-fold increased risk for hard events ($P < .0001$).

Conclusions: Preserved RV function as assessed by speckle-tracking strain imaging appears to be an independent predictor of long-term event-free survival after CRT. (J Am Soc Echocardiogr 2013;26:706-13.)

Keywords: Echocardiography, Right ventricle, Resynchronization therapy, Survival

Cardiac resynchronization therapy (CRT) is an established treatment for drug-refractory heart failure. Despite favorable results, significant subgroup of patients derive less benefit than expected from CRT, such as patients with ischemic cardiomyopathy,[1] severely dilated ventricles,[2] or suboptimal lead localization.[3] Right ventricular (RV) dysfunction is a major determinant of clinical outcomes in patients with heart failure.[4,5] Therefore, it may be another parameter that plays a role in the clinical response to CRT, but few studies have characterized RV function among patients treated with CRT.[6-8] Recently, subgroup data analyses from the Cardiac Resynchronization–Heart Failure (CARE-HF) trial showed that RV dysfunction may have unfavorable effects on reverse remodeling in patients undergoing CRT.[9] However, prospective studies investigating the impact of RV dysfunction on outcomes of CRT are needed.[6] Several methods have been recommended for the echocardiographic quantification of RV function that can be readily used in daily practice.[10]

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Our objectives were to test the hypothesis that RV dysfunction is a predictor of poor outcomes in patients undergoing CRT and to determine the best quantification tool for RV function to predict survival free of death, heart transplantation, and assist device implantation after CRT.

METHODS

A series of 120 consecutive patients with heart failure were prospectively enrolled in the present study. Our study complies with the Declaration of Helsinki, the protocol was approved by the ethics committee of the University of Başkent, and all patients gave informed consent consistent with this protocol. Patients undergoing CRT with ejection fractions (EFs) ≤35% and QRS durations ≥120 msec were consecutively enrolled. All patients had New York Heart Association functional class III or IV heart failure symptoms on optimal pharmacologic therapy, as tolerated, consistent with the guidelines. Devices were implanted with a standard RV apical lead and left ventricular (LV) lead positioned through the coronary sinus targeting the posterolateral or lateral branches. Atrioventricular and ventriculoventricular delay adjustments were performed before discharge under echocardiographic guidance and repeated whenever necessary during follow-up.

Echocardiography

Echocardiographic images were obtained using a cardiac ultrasound machine (Vivid i; GE, Haifa, Israel) equipped with a 3S probe. LV

Abbreviations

CARE-HF = Cardiac Resynchronization–Heart Failure

EF = Ejection fraction

ESV = End-systolic volume

CMR = Cardiac magnetic resonance

CRT = Cardiac resynchronization therapy

IVMD = Interventricular mechanical delay

LV = Left ventricular

PROSPECT = Predictors of Response to Cardiac Resynchronization Therapy

RV = Right ventricular

TAPSE = Tricuspid annular plane systolic excursion

2D = Two-dimensional

volumes and EF were assessed using the modified Simpson's rule from the apical four-chamber and two-chamber views. Mitral regurgitant volume (calculated using the proximal isovelocity surface area method), RV transverse diameter, and systolic and diastolic areas were measured in the apical four-chamber view. In the same view, tricuspid annular plane systolic excursion (TAPSE) was measured using the M-mode recordings through the lateral plane of the tricuspid annulus as the systolic base-to-apex displacement, and tricuspid annular S-wave velocity was measured using pulsed-wave tissue Doppler (Figure 1).[10] The RV myocardial performance index was calculated as the sum of isovolumetric contraction time and isovolumetric relaxation time divided by S duration.

Grayscale digital cine loops triggered to the QRS complex were acquired from the LV short axis at the basal and mid levels for radial dyssynchrony analysis and from the apical four-chamber view for speckle-tracking two-dimensional (2D) strain analysis of the right ventricle at a frame rate of 60 to 100 frames/sec. Cine loops for tissue Doppler data were acquired from the apical four-chamber, two-chamber, and long-axis views to assess longitudinal dyssynchrony at a frame rate of ≥100 frames/sec. Data were analyzed offline using commercial software (EchoPAC BT 9.0; GE Vingmed Ultrasound AS, Horten, Norway).

For 2D strain analyses, a curved region of interest was traced on the LV endocardial cavity interface in the short-axis views and on the RV free wall in the apical four-chamber view. From the traced endocardium, a region of interest was automatically constructed approximating the myocardium between the endocardium and epicardium. The region of interest width was adjusted as needed to fit the wall thickness. Average longitudinal RV free wall strain curve was then derived (Figure 2). For ease of communication, RV longitudinal strain values (all negative) are presented as positive numbers throughout the text. Regional time-strain curves were also extracted from the LV short-axis images. Radial dyssynchrony was determined as the time difference between the anteroseptal and posterior wall, with ≥130 msec predefined as significant.[11,12] Intraventricular longitudinal dyssynchrony was determined using Doppler tissue imaging. Doppler tissue imaging regions of interest (6 × 13 mm) were placed in the basal and mid LV segments on the three apical views for 12 sites. A semiautomatic tracking algorithm was applied to maintain the region of interest within the wall throughout the cardiac cycle. Time from QRS onset to peak systolic velocity was measured in each site. Maximal opposing wall delay at the basal or mid level ≥ 80 msec was predefined as significant longitudinal dyssynchrony.[12,13] Interventricular mechanical delay (IVMD) was calculated as the difference between aortic and pulmonary preejection delays, which were measured from the onset of the QRS complex to the onset of aortic and pulmonary ejection flows, respectively, using pulsed-wave Doppler in the apical four-chamber and parasternal short-axis views. IVMD ≥40 msec was predefined as significant dyssynchrony.[14] All measurements were derived from the average of three consecutive cardiac cycles acquired during a breath-hold period.

Follow-Up

Long-term unfavorable outcome events, prespecified as death, heart transplantation, and assist device implantation, were considered the primary end point. Long-term follow-up after CRT was tracked up to 5 years. Volume responders were defined by a decrease in end-systolic volume (ESV) of >15% at 6 months.

Statistical Analysis

Data are presented as mean ± SD for continuous variables and as percentages for categorical variables. Continuous and categorical variables were compared using Student's t tests and χ^2 tests, respectively. The sensitivity and specificity of the best performing cutoff value for RV parameters was determined using receiver operating characteristic curve analysis. Receiver operating characteristic curves were compared using the areas under the curves with the method of DeLong *et al.*[15] Event-free survival curves were determined according to the Kaplan-Meier method, with comparison of cumulative event rates by the log-rank test between patients with and without RV dysfunction. A Cox proportional-hazards model was used to assess the influence of potential confounding variables. For comparison of continuous variables before and after CRT, paired-samples t tests and Wilcoxon's test were used for subgroups as appropriate. Interobserver and intraobserver variability analysis for speckle-tracking was performed in 15 randomly selected patients using the identical cine loop for each view, and variability was expressed as the absolute difference divided by the mean value of the measurements. Two-sided P values $< .05$ were considered significant for all tests. SPSS version 15.0 for Windows (SPSS, Inc., Chicago, IL) and MedCalc version 10.4.0.0 (MedCalc Software Inc., Mariakerke, Belgium) were used for statistical analyses.

RESULTS

Of 120 consecutive patients, seven (5.8%) were excluded (three because of loss to follow-up and four because of technically inadequate images for quantitative analysis of RV free wall strain and RV area). Intraobserver and interobserver variability were 4.5 ± 3.2% and 7.5 ± 5.7%, respectively, for 2D RV strain. In the remaining 113 patients, 87 (77%) had biventricular pacemakers with cardioverter-defibrillators and 26 had only biventricular pacemakers. The mean age was 62 ± 11 years, and 21 patients (19%) were women. Six patients (5.3%) had atrial fibrillation, three of whom underwent atrioventricular node ablation. Atrioventricular node ablation was performed for seven additional patients who developed permanent atrial fibrillation during follow-up to ensure an adequate biventricular pacing rate. In the overall study group, the mean ventricular pacing rate was 96.8 ± 3.7%. Sixty-seven patients (59%) had ischemic cardiomyopathy, 34 of whom had undergone previous coronary artery bypass surgery. Five patients had mitral valve replacement, three had tricuspid annuloplasty, and four had aortic valve replacement. Six patients were upgraded from conventional RV apical pacing to