Mechanical Dyssynchrony by Tissue Doppler Cross-Correlation is Associated with Risk for Complex Ventricular Arrhythmias after Cardiac Resynchronization Therapy

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Background: Tissue Doppler cross-correlation analysis has been shown to be associated with long-term survival after cardiac resynchronization defibrillator therapy (CRT-D). Its association with ventricular arrhythmia (VA) is unknown.

Methods: From two centers 151 CRT-D patients (New York Heart Association functional classes II–IV, ejection fraction $\leq$ 35%, and QRS duration $\geq$ 120 msec) were prospectively included. Tissue Doppler cross-correlation analysis of myocardial acceleration curves from the basal segments in the apical views both at baseline and 6 months after CRT-D implantation was performed. Patients were divided into four subgroups on the basis of dyssynchrony at baseline and follow-up after CRT-D. Outcome events were predefined as appropriate antitachycardia pacing, shock, or death over 2 years.

Results: Mechanical dyssynchrony was present in 97 patients (64%) at baseline. At follow-up, 42 of these 97 patients (43%) had persistent dyssynchrony. Furthermore, among 54 patients with no dyssynchrony at baseline, 15 (28%) had onset of new dyssynchrony after CRT-D. In comparison with the group with reduced dyssynchrony, patients with persistent dyssynchrony after CRT-D were associated with a substantially increased risk for VA (hazard ratio [HR], 4.4; 95% CI, 1.2–16.3; P = .03) and VA or death (HR, 4.0; 95% CI, 1.7–9.6; P = .002) after adjusting for other covariates. Similarly, patients with new dyssynchrony had increased risk for VA (HR, 10.6; 95% CI, 2.8–40.4; P = .001) and VA or death (HR, 5.0; 95% CI, 1.8–13.5; P = .002).

Conclusions: Persistent and new mechanical dyssynchrony after CRT-D was associated with subsequent complex VA. Dyssynchrony after CRT-D is a marker of poor prognosis. (J Am Soc Echocardiogr 2015;28:1474-81.)

Keywords: Cardiac resynchronization defibrillator therapy, Echocardiography, Dyssynchrony, Ventricular arrhythmia, Heart failure

Ventricular arrhythmias (VAs) are of increased prevalence in patients with symptomatic heart failure (HF) with depressed left ventricular (LV) ejection fractions and are a significant cause of sudden cardiac death.[1,2] Cardiac resynchronization defibrillator therapy (CRT-D) has been shown to reduce morbidity and mortality, but reported effects on VAs are conflicting. Different single-center and multicenter trials have suggested CRT-D as antiarrhythmic,[3-6] proarrhythmic,[7-9] or not associated[10] with the occurrence of VAs.

A few studies have shown that mechanical heterogeneity of LV segmental contraction is associated with VA in patients with HF of various etiologies.[11,12] CRT-D reduces LV mechanical dyssynchrony, which in theory would reduce the occurrence of VA. However, a subset of patients have been reported to deteriorate after CRT-D, which may increase the risk for VA and death.[5,13] These patients are important to recognize and may even benefit from discontinuation of CRT-D.

LV dyssynchrony by cross-correlation analysis (CCA) of tissue Doppler myocardial systolic acceleration has been associated with favorable reverse remodeling and long-term survival after CRT-D.[14,15] The association of dyssynchrony by CCA with risk for VA is unknown. Accordingly, the aim of this study was to

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Abbreviations

AD = Activation delay

AD-max = Maximal absolute activation delay

CCA = Cross-correlation analysis

CRT-D = Cardiac resynchronization defibrillator therapy

HF = Heart failure

HR = Hazard ratio

LBBB = Left bundle branch block

LV = Left ventricular

VA = Ventricular arrhythmia

VT = Ventricular tachycardia

investigate the association between changes in LV dyssynchrony with VAs after CRT-D implantation.

METHODS

Study Population

We included a series of patients with HF who underwent CRT-D implantation for routine clinical indications and underwent Doppler tissue imaging echocardiography before and a median of 6 months after CRT-D implantation. This cohort comprised patients with symptomatic HF in New York Heart Association functional classes II to IV, with LV ejection fractions ≤ 35% and QRS durations ≥ 120 msec, who were receiving optimal medical therapy and had undergone successful CRT-D device implantation. Patients with atrial fibrillation and right ventricular pacing were excluded. Overall, 151 patients were included from two different centers (131 patients from the University of Pittsburgh Medical Center from 2002 to 2011 and 20 patients from Aalborg University Hospital from 2011 to 2013). A total of 235 patients were initially enrolled from the two centers. Of these, 18 patients (8%) died or underwent heart transplantation or LV assist device implantation before 6-month follow-up echocardiography, and 63 (27%) were excluded because of a lack of follow-up echocardiography. Three (1%) were excluded as a result of loss to follow-up. The respective institutional review boards approved the study protocol, and patients gave informed consent before the study. The study design was prospective, with CCA applied to the selected study cohort from a consecutive patient series meeting the inclusion criteria with prespecified end points. A single observer performed the CCA analysis on the total study population blinded to the outcomes. Ischemic cardiomyopathy was defined as a previously documented history of myocardial infarction, prior revascularization, or presence of significant coronary artery disease (≥70% stenosis in at least one major coronary artery). All patients underwent CRT-D device implantation with a right atrial lead, right ventricular apical lead, and LV lead through the coronary sinus implanted in the posterolateral or lateral LV free wall.

Echocardiography

All echocardiographic studies (GE Vivid 7 and E9; GE Vingmed Ultrasound AS, Horten, Norway) were performed to obtain color tissue Doppler cine loops of three cardiac cycles in each of the three standard apical views. Image sector width and depth were adjusted to optimize frame rates at 112 ± 10 frames/sec. Offline analysis was performed using EchoPAC PC version BT11 (GE Vingmed Ultrasound AS). LV volumes and LV ejection fraction were assessed using the biplane Simpson rule. The inter- and intraobserver variability of end-systolic volume from our echocardiography laboratory has been reported previously.[16]

CCA of Myocardial Systolic Acceleration

The CCA method has previously been discussed in detail.[14,15] Briefly, regions of interest measuring 7 × 15 mm were placed on the basal segments of the opposing walls in each of the standard apical views, and the resulting velocity text files were saved. These text files were then imported into a customized Excel spreadsheet (Microsoft Corporation, Redmond, WA), which has a prewritten algorithm to perform CCA analysis. This customized Excel spreadsheet with a macro written for CCA was provided as supplemental material to previously published work.[15] The Excel spreadsheet first converts the velocity data into myocardial acceleration curves by time differentiation. A three-point filter for noise was used to filter the resulting acceleration curves. CCA of the acceleration traces was performed according to the following equation:

$$Xcc_d = \frac{\sum_i[(x_i - \bar{x})(y_{i-d} - \bar{y})]}{\sqrt{\sum_i(x_i - \bar{x})^2}\sqrt{\sum_i(y_{i-d} - \bar{y})^2}},$$

where XCC_d is the cross-correlation coefficient at a time shift d, x_i and y_i are the acceleration traces from the LV basal segments, and $\bar{x}$ and $\bar{y}$ represent the mean acceleration values of the two traces. Only data from the systolic phase of the cardiac cycle were used and were defined by the onset of the QRS complex to the closure of the aortic valve. Aortic valve closure was defined using pulsed-wave Doppler in the LV outflow tract with a 2-mm sample volume. The cross-correlation coefficient measures the degree of association between the direction and magnitude of the acceleration traces of opposing walls. The two myocardial systolic acceleration curves are correlated against each other without any time shift and again correlated by time shifting against each other until 15 frames in both direction. The time point that results in the highest positive correlation is the activation delay (AD). The maximal absolute AD among the three views is the AD-max. As reported previously, a cut off of AD-max > 35 msec is used to define the presence of dyssynchrony, and AD-max ≤ 35 msec is used to define patients with no dyssynchrony.[14] The acceleration curves were noisier than the velocity curves and required additional filtering. However, velocity curves were affected by the rotational motion of the heart, which made the calculation of AD-max weaker, as discussed previously by Risum *et al.*[15] This was not the case with acceleration curves, and AD by acceleration yielded stronger results.[15]

The patients were divided into the following four groups on the basis of the presence or absence of dyssynchrony at baseline and follow-up after CRT-D: (1) no dyssynchrony: no dyssynchrony at both baseline and follow-up; (2) reduced dyssynchrony: dyssynchrony at baseline, but no dyssynchrony at follow-up (Figure 1); (3) persistent dyssynchrony: dyssynchrony at both baseline and follow-up; and (4) new dyssynchrony: no dyssynchrony at baseline, but dyssynchrony at follow-up (Figure 2).

Study End Points

The primary end point was predefined as any incidence of appropriate antitachycardia pacing or appropriate shock for ventricular tachycardia (VT) or ventricular fibrillation over a period of 2 years after CRT-D device implantation. The secondary end point was any incidence of appropriate defibrillator therapy or death over the same follow-up period. All device electrocardiograms were examined by an experienced electrophysiologist to confirm appropriate defibrillator therapy for VA. In case of the combined event of VA or death, patients were screened at the first event of VA.

INTRA- AND INTEROBSERVER VARIABILITY

The presence of dyssynchrony (≥35 msec) by CCA was evaluated in 30 randomly selected patients by two observers blinded to each other. It was reevaluated by the original observer after a few days.