Electrophysiologic substrate and intraventricular left ventricular dyssynchrony in nonischemic heart failure patients undergoing cardiac resynchronization therapy

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BACKGROUND Electrocardiographic imaging (ECGI) is a method for noninvasive epicardial electrophysiologic mapping. ECGI previously has been used to characterize the electrophysiologic substrate and electrical synchrony in a very heterogeneous group of patients with varying degrees of coronary disease and ischemic cardiomyopathy.

OBJECTIVE The purpose of this study was to characterize the left ventricular electrophysiologic substrate and electrical dyssynchrony using ECGI in a homogeneous group of nonischemic cardiomyopathy patients who were previously implanted with a cardiac resynchronization therapy (CRT) device.

METHODS ECGI was performed during different rhythms in 25 patients by programming their devices to biventricular pacing, single-chamber (left ventricular or right ventricular) pacing, and native rhythm. The electrical dyssynchrony index (ED) was computed as the standard deviation of activation times at 500 sites on the LV epicardium.

RESULTS In all patients, native rhythm activation was characterized by lines of conduction block in a region with steep activation–recovery interval (ARI) gradients between the epicardial aspect of the septum and LV lateral wall. A native QRS duration (QRSd) >130 ms was associated with high ED (≥30 ms), whereas QRSd <130 ms was associated with minimal (25 ms) to large (40 ms) ED. CRT responders had very high dyssynchrony (ED = 35.5 ± 3.9 ms) in native rhythm, which was significantly lowered (ED = 23.2 ± 4.4 ms) during CRT. All four nonresponders in the study did not show significant difference in ED between native and CRT rhythms.

CONCLUSION The electrophysiologic substrate in nonischemic cardiomyopathy is consistent among all patients, with steep ARI gradients co-localizing with conduction block lines between the epicardial aspect of the septum and the LV lateral wall. QRSd wider than 130 ms is indicative of substantial LV electrical dyssynchrony; however, among patients with QRSd <130 ms, LV dyssynchrony may vary widely.

KEYWORDS Cardiac resynchronization therapy; Electrocardiography; Heart failure; Imaging

ABBREVIATIONS **ARI** = activation–recovery interval; **CRT** = cardiac resynchronization therapy; **ECGI** = electrocardiographic imaging; **ED** = electrical dyssynchrony index; **LV** = left ventricle; **LV-P** = left ventricular pacing; **NYHA** = New York Heart Association; **QRSd** = QRS duration; **RT** = total repolarization time

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Introduction

Cardiac resynchronization therapy (CRT) using biventricular pacing is a relatively new treatment modality designed to restore synchrony with the objective of improving cardiac mechanical performance in congestive heart failure.[1–4] CRT has been demonstrated to be clinically effective in 60% to 70% of patients, and its indication as therapy has increased exponentially over the last several years. A number of different echocardiographic measures have been used clinically to select potential CRT candidates. The recently concluded PROSPECT[2] trial has shown that none of the echocardiographic measures provides a consistent basis for clinical decisions regarding CRT implants. The ECG QRS duration (QRSd) is deemed to be the most clinically relevant measure for CRT. Although CRT has been shown to benefit the majority of symptomatic patients with wide

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QRSd >130 ms, reports on the usefulness of CRT in moderate ranges of QRSd (100–130 ms) are conflicting. The RethinQ trial[3] showed that CRT is not beneficial for patients with narrow QRSd. However, another recent study[4] demonstrated potential short-term improvement with CRT in patients with QRSd <120 ms. This indicates that there may be heart failure patients with QRSd in the range from 100 to 130 ms who may respond well to CRT, but the measures of dyssynchrony used in RethinQ could not identify this group. With the reliability of echocardiographic measures in question (PROSPECT), the quest for an alternative measure of dyssynchrony in the context of CRT continues.

Electrocardiographic imaging (ECGI)[5–8] is a novel imaging modality for cardiac electrophysiology, based on 250 body surface ECGs and an accurate, patient specific heart–torso anatomy derived from an ECG-gated computed tomographic scan. It noninvasively generates electroanatomic maps of epicardial potentials (voltage maps), electrograms, and activation and repolarization sequences. A previous study using ECGI in eight heart failure patients with ischemic cardiomyopathy undergoing CRT showed that the electrophysiologic substrate is extremely heterogeneous among these patients and that the efficacy of CRT depends strongly on the patient-specific substrate and pacing electrode placement relative to this substrate.[8] This was a study in a very heterogeneous group of patients with varying degrees of coronary disease and ischemic cardiomyopathy. The objective of the current study is to characterize the left ventricular (LV) electrophysiologic substrate and electrical dyssynchrony in a population of nonischemic cardiomyopathy patients previously implanted with a CRT device. A quantitative index for LV electrical dyssynchrony is defined and computed, and its relationship with QRSd is studied.

Methods

ECGI was performed in each patient in each of the following rhythms: (1) biventricular CRT pacing (CRT); (2) LV pacing (LV-P); (3) right ventricular (RV) pacing (RV-P); and (4) nonpaced native rhythm (NAT), if applicable. Two patients had optimized interventricular (V-V) delays different from the nominal value, and ECGI was performed with both optimal (CRT-OPT) and nominal (CRT-NOM) V-V delays. The nominal V-V delay is the standard "factory" setting (simultaneous biventricular pacing).

Custom algorithms[5,6] developed in our laboratory are used to combine the multielectrode body surface potential data with the heart–torso geometry obtained from computed tomography to generate electroanatomic maps of potentials, electrograms, and activation and repolarization sequences on the epicardial surface. The activation time was determined from each reconstructed epicardial electrogram by the time of steepest negative slope of the electrogram. The LV epicardium was delineated from computed tomography, including the epicardial aspect of the septum, and digitized using 500 points. An intra-LV electrical dyssynchrony index (ED) was computed in blinded fashion from the ECGI activation maps as the standard deviation of activation times (determined as explained earlier) at 500 sites on the LV epicardium, including the epicardial aspect of the septum.

Activation isochronal lines on the epicardial surface are depicted in black. Line/region of conduction block is determined if the activation times on its opposite sides differ by more than 40 ms. Regions of slow conduction are identified by crowding of isochrones. Regions of late LV activation are defined by sites where activation time is later than 80th percentile of QRS duration during native rhythm. Percentage of LV area activating late is computed by dividing the number of late LV sites (nodes) by the total number of nodes used to digitize the LV epicardium for ECGI images. Activation–recovery intervals (ARIs) over the epicardial surface are computed from the epicardial electrograms as the difference between recovery time (time corresponding to maximum dV/dt during T wave) and activation time (steepest downward slope during QRS) and displayed in color-coded maps. Epicardial dispersion of repolarization is computed as the difference between the largest and smallest ARI on the entire (RV and LV) epicardial surface.

Control value of ED in a population of 22 young healthy subjects without heart failure was determined at 20 ± 4 ms. A value above the control mean plus twice the standard deviation was deemed as abnormal (ED >28 ms). Hence, LV is defined to be electrically asynchronous when ED ≥28 ms. All study protocols were reviewed and fully approved by the Human Research Protection Office at Washington University, and written informed consent was obtained from all patients and/or their legal guardians prior to the study.

Statistical analysis

Continuous variables are represented as mean ± SD with these measures taken over the total patient population. Relationship between ED and QRSd, and activation time and repolarization ARI are evaluated using Pearson correlation coefficient (r). Student's t-test is used to assess the significance of correlation. $P < .05$ is considered significant.

Results

Study population

Between January 2007 and April 2010, 25 heart failure patients (age 51 ± 18 years, range 6–68 years) with a CRT implant and nonischemic dilated cardiomyopathy were recruited retrospectively for the study. Patients were selected from the database of patients who were implanted with a CRT/CRT-ICD device and were being seen at the heart failure clinic at Barnes Jewish Hospital and/or St. Louis Children's Hospital. The following inclusion criteria were used for patient selection: patients without any documented evidence of ischemia until study date, implanted with a CRT or CRT-ICD device at least 6 months prior to study date. CRT implant criteria were symptoms of New York Heart Association (NYHA) functional class III/IV heart failure with poor ejection fraction (<30%), accompanied by wide QRSd >120 ms and/or asynchronous wall motion seen on echocardiography. Post-CRT echocardiography and/or clinical response data were not used in selecting patients. Ischemia was ruled out by the latest coronary angiography performed for clinical reasons before the study and no documented hospitalizations or clinic visits for myocardial infarction until the date of study. No evidence of frank scar or aneurysm was found during echocardiographic evaluation (no areas of akinesis). Three patients (no. 1, 10, and 14) had no underlying rhythm (no atrioventricular [A-V] conduction and no ventricular escape beats at the time of the study). These patients were upgraded to biventricular pacing from RV pacing. Pre-CRT NYHA class was III to IV.