Journal of the American College of Cardiology
© 2014 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 63, No. 16, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.02.533

Cardiac Resynchronization Therapy

Impact of Mechanical Activation, Scar, and Electrical Timing on Cardiac Resynchronization Therapy Response and Clinical Outcomes

Kenneth C. Bilchick, MD, MS,* Sujith Kuruvilla, MD,* Yasmin S. Hamirani, MD,* Raghav Ramachandran, MS,† Samantha A. Clarke, BS,† Katherine M. Parker, PHD,† George J. Stukenborg, PHD, MA,‡ Pamela Mason, MD,* John D. Ferguson, MBCHB, MD,* J. Randall Moorman, MD,* Rohit Malhotra, MD,* J. Michael Mangrum, MD,* Andrew E. Darby, MD,* John DiMarco, MD, PHD,* Jeffrey W. Holmes, MD, PHD,*† Michael Salerno, MD, PHD,*†§ Christopher M. Kramer, MD,*§ Frederick H. Epstein, PHD†§

Charlottesville, Virginia

Objectives Using cardiac magnetic resonance (CMR), we sought to evaluate the relative influences of mechanical, electrical, and scar properties at the left ventricular lead position (LVLP) on cardiac resynchronization therapy (CRT) response and clinical events.

Background CMR cine displacement encoding with stimulated echoes (DENSE) provides high-quality strain for overall dyssynchrony (circumferential uniformity ratio estimate [CURE] 0 to 1) and timing of onset of circumferential contraction at the LVLP. CMR DENSE, late gadolinium enhancement, and electrical timing together could improve upon other imaging modalities for evaluating the optimal LVLP.

Methods Patients had complete CMR studies and echocardiography before CRT. CRT response was defined as a 15% reduction in left ventricular end-systolic volume. Electrical activation was assessed as the time from QRS onset to LVLP electrogram (QLV). Patients were then followed for clinical events.

Results In 75 patients, multivariable logistic modeling accurately identified the 40 patients (53%) with CRT response (area under the curve: 0.95 [$p < 0.0001$]) based on CURE (odds ratio [OR]: 2.59/0.1 decrease), delayed circumferential contraction onset at LVLP (OR: 6.55), absent LVLP scar (OR: 14.9), and QLV (OR: 1.31/10 ms increase). The 33% of patients with CURE $<$0.70, absence of LVLP scar, and delayed LVLP contraction onset had a 100% response rate, whereas those with CURE $\geq$0.70 had a 0% CRT response rate and a 12-fold increased risk of death; the remaining patients had a mixed response profile.

Conclusions Mechanical, electrical, and scar properties at the LVLP together with CMR mechanical dyssynchrony are strongly associated with echocardiographic CRT response and clinical events after CRT. Modeling these findings holds promise for improving CRT outcomes. (J Am Coll Cardiol 2014;63:1657–66) © 2014 by the American College of Cardiology Foundation

From the *Department of Medicine, Cardiovascular Division, University of Virginia Health System, Charlottesville, Virginia; †Department of Biomedical Engineering, University of Virginia Health System, Charlottesville, Virginia; ‡Department of Public Health Sciences, University of Virginia Health System, Charlottesville, Virginia; and the §Department of Radiology and Medical Imaging, University of Virginia Health System, Charlottesville, Virginia. Dr. Bilchick has received support from the National Institutes of Health (NIH) (K23 grant HL094761); and has served as a consultant to Biosense Webster. Dr. Parker is an employee of Sorin Group USA, Inc. Dr. Mason has received grant support from Medtronic and Boston Scientific; and has received support from St. Jude Medical and Johnson & Johnson. Dr. Ferguson has received consulting support from Biosense Webster and St. Jude Medical; and has received honoraria from Medtronic. Dr. Malhotra has received grant support from Medtronic and Boston Scientific. Dr. Mangrum has received grant and consulting support from St. Jude Medical; and has received research funding from St. Jude Medical, Hansen Medical, EndoSense, CardioFocus, and Boston Scientific. Dr. Darby has served as a consultant for Biosense Webster; has received speaking honoraria from Medtronic; and has received research support from Boston Scientific. Dr. DiMarco has received consulting support from Medtronic, St. Jude Medical, and Boston Scientific. Dr. Holmes has received support from the NIH (R01 grant HL085160). Dr. Kramer has received grant support from Siemens Healthcare; and has served as a consultant to Synarc and St. Jude Medical. Dr. Epstein has received support from the NIH (R01 grant EB001763); and has received grant support from Siemens Healthcare. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received October 31, 2013; revised manuscript received January 2, 2014, accepted February 4, 2014.

Abbreviations and Acronyms

CMR = cardiac magnetic resonance

CRT = cardiac resynchronization therapy

CURE = circumferential uniformity ratio estimate

DENSE = displacement encoding with stimulated echoes

E_{CC} = circumferential strain

LGE = late gadolinium enhancement

LV = left ventricle/ventricular

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

LVESV = left ventricular end-systolic volume

LVLP = left ventricular lead position

QLV = QRS to left ventricular electrogram interval

Outcomes after cardiac resynchronization therapy (CRT) are influenced by a complex interaction between the myocardial substrate and the left ventricular lead position (LVLP). The myocardial substrate may be characterized both by the pattern of mechanical activation (1) and the distribution of scar (2). Recent echocardiographic methods such as 3-dimensional echocardiography and speckle tracking (3,4) offer the potential for better performance than previous methods, as do dyssynchrony assessments based on cardiac magnetic resonance (CMR) (5) and the circumferential uniformity ratio estimate (CURE) (6–8). Scar in the posterolateral left ventricle (LV), a common location for the LV lead, has been associated with CRT nonresponse (9), whereas late-activated sites based on electrical parameters (LV lead electrical delay and QRS to left ventricular intrinsic activation interval [QLV]) (10,11) or mechanical criteria (12,13) appear to be better locations for LV leads.

CMR is the gold standard for assessment of myocardial scar. We have recently shown that CMR displacement encoding with stimulated echoes (DENSE) generates high-quality circumferential strain data (5,8,14–16) that can precisely describe the state of mechanical dyssynchrony using the CURE parameter (6), which does not require manual detection of regional time to peak strain (8). We now report the results of a cohort study of patients referred for CRT based on the hypothesis that favorable CMR findings (lower CURE from CMR DENSE, no scar at the LVLP, and delayed onset of circumferential contraction at the LVLP) and late electrical activation at the LVLP are strongly associated with CRT response and clinical events during follow-up. The clinical significance is that CMR applied this way could improve upon current criteria for patient selection (17,18) and facilitate more effective implementation of CRT.

Methods

Cohort selection. The study was approved by the Institutional Review Board for Human Subjects Research at the University of Virginia. Patients were required to have a clinical indication for CRT based on established guidelines (18) and a glomerular filtration rate of at least 45 ml/min/1.73 m^2 in order to receive gadolinium.

CMR protocol. Prior to the CRT procedure, patients underwent a research CMR protocol including steady-state free precession imaging, cine DENSE imaging, and late gadolinium enhancement (LGE) on a 1.5-T Avanto scanner (Siemens Healthcare, Erlangen, Germany) with a 4-channel phased-array chest radiofrequency coil. Cine DENSE imaging (previously validated by comparison with myocardial tagging in heart failure) (8) was performed in 4 short-axis and 3 long-axis planes with displacement encoding applied in 2 orthogonal in-plane directions for each plane with the following parameters (14,15): interleaved spiral readout with 6 interleaves per image; repetition time/echo time 17 ms/1.9 ms; slice thickness 8 mm; field of view 350 × 350 mm; flip angle 15°; pixel size 2.8 × 2.8 mm; fat suppression; and displacement-encoding frequency 0.1 cycles/mm.

Determination of echocardiographic volumes before and after CRT. Standard 2D echocardiographic images with Doppler were obtained for all patients at baseline and 3 months and 6 months after CRT with standard short- and long-axis views. The left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV), and left ventricular ejection fraction (LVEF) before and after CRT were determined using Simpson's rule for 2- and 4-chamber long-axis views using EchoPAC software (GE, Fairfield, Connecticut).

Clinical CRT procedure. Patients then underwent the clinical CRT procedure. During the procedure, venograms of the coronary sinus were recorded in 2 projections. Final cine images of the leads were recorded in the usual left anterior oblique, anterior-posterior, and right anterior oblique projections.

Clinical follow-up and determination of CRT response. The echocardiographic evaluation at 3 months included standard A-V and V-V optimization. CRT response was defined as a 15% reduction in LVESV at 6 months (or the last follow-up echocardiogram prior to death if the patient died prior to 6 months after implantation). After the procedure, subsequent clinic notes, device interrogations, and discharge summaries for inpatient hospitalizations were reviewed for all study patients. Sustained ventricular tachyarrhythmia events were defined as episodes of ventricular tachycardia or ventricular fibrillation requiring implantable cardioverter-defibrillator therapies or untreated ventricular tachyarrhythmia episodes >30 s detected by the implantable cardioverter-defibrillator, and these events were also recorded in the database.

CMR DENSE image processing and strain analysis. Following image acquisition, segmentation of the LV myocardium was performed semiautomatically for cine DENSE images (19), a phase-unwrapping algorithm was applied to LV myocardium pixels, and displacements were calculated (5). Lagrangian strain was computed from displacements in 24 short-axis segments in multiple slices and was then projected in both the radial and circumferential (circumferential strain [E_{CC}]) directions relative to the LV center of mass. LV volumes, mass, and ejection fraction were calculated from cine steady-state free precession images using Argus software (Siemens, Erlangen, Germany).