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Intraventricular Dyssynchrony Predicts Mortality and Morbidity After Cardiac Resynchronization Therapy

A Study Using Cardiovascular Magnetic Resonance Tissue Synchronization Imaging

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Objectives We aimed to assess a novel measure of left ventricular (LV) dyssynchrony, a cardiovascular magnetic resonance-tissue synchronization index (CMR-TSI), in patients with heart failure (HF). A further aim was to determine whether CMR-TSI predicts mortality and major cardiovascular events (MCE) after cardiac resynchronization therapy (CRT).

Background Cardiac dyssynchrony is a predictor of mortality in patients with HF. The unparalleled spatial resolution of CMR may render CMR-TSI a predictor of clinical benefit after CRT.

Methods In substudy A, CMR-TSI was assessed in 66 patients with HF (age 60.8 ± 10.8 years, LV ejection fraction 23.9 ± 12.1% [mean ± SD]) and 20 age-matched control subjects. In substudy B, CMR-TSI was assessed in relation to clinical events in 77 patients with HF and with a QRS ≥120 ms undergoing CRT.

Results In analysis A, CMR-TSI was higher in patients with HF and a QRS <120 ms (79.5 ± 31.2 ms, $p = 0.0003$) and in those with a QRS ≥120 ms (105.9 ± 55.8 ms, $p < 0.0001$) than in control subjects (21.2 ± 8.1 ms). In analysis B, a CMR-TSI ≥110 ms emerged as an independent predictor of the composite end points of death or unplanned hospitalization for MCE (hazard ratio [HR] 2.45; 95% confidence interval [CI] 1.51 to 4.34, $p = 0.0002$) or death from any cause or unplanned hospitalization for HF (HR 2.15; 95% CI 1.23 to 4.14, $p = 0.0060$) as well as death from any cause (HR: 2.6; 95% CI 1.29 to 6.73, $p = 0.0061$) and cardiovascular death (HR 3.82; 95% CI 1.63 to 16.5, $p = 0.0007$) over a mean follow-up of 764 days.

Conclusions Myocardial dyssynchrony assessed by CMR-TSI is a powerful independent predictor of mortality and morbidity after CRT. (J Am Coll Cardiol 2007;50:243–52) © 2007 by the American College of Cardiology Foundation

The benefits of cardiac resynchronization therapy (CRT) are well established. In the CARE-HF (Cardiac Resynchronization Heart Failure) study, CRT was associated with 36% reduction in all-cause mortality (1). It is well accepted, however, that the prognostic benefit of CRT in individual patients is difficult to predict from pre-implant assessments, such as echocardiography.

Studies using tissue Doppler imaging have shown that, in patients with heart failure (HF), intraventricular dyssynchrony is associated with a higher rate of cardiac decompensation (2). In patients with hypertrophic cardiomyopathy, intraventricular dyssynchrony is an independent predictor of sudden cardiac death (3). With regard to patients undergoing CRT, numerous studies have focused on echocardiographic predictors of reverse left ventricular (LV) remodeling and/or symptoms (4,5), but few have explored cardiac dyssynchrony in relation to mortality.

In the assessment of cardiac dyssynchrony, echocardiography is limited to imaging only a portion of the LV. In contrast, cardiovascular magnetic resonance (CMR) allows imaging of the entire heart. In this study, a novel technique for assessing cardiac dyssynchrony, CMR-tissue resynchronization imaging, was developed using short-axis views of the LV. Segmental radial wall motion data were used to construct tissue synchronization polar maps of the LV and to derive a global dyssynchrony measure, the tissue synchronization index (CMR-TSI). This study comprised 2 analyses: in the first, the CMR-TSI was assessed in healthy

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Abbreviations and Acronyms

CMR-TSI = cardiovascular magnetic resonance-tissue synchronization index
CRT = cardiac resynchronization therapy
HF = heart failure
LV = left ventricle/ventricular
LVEDV = left ventricular end-diastolic volume
LVEF = left ventricular ejection fraction
LVESV = left ventricular end-systolic volume
MCE = major cardiovascular events
NYHA = New York Heart Association
ROC = receiver-operating characteristic

subjects and in patients with HF; in the second, the CMR-TSI was assessed in relation to mortality as well as hospitalizations, LV remodeling, functional capacity, and quality of life in patients with HF undergoing CRT.

Methods

This study consisted of 2 substudies, both of which entailed quantification of LV volumes, LV ejection fraction (LVEF), and CMR-TSI.

Substudy 1. In this substudy, the measurements as described in the preceding text were studied in relation to QRS duration in 66 consecutive patients with HF in New York Heart Association (NYHA) functional class III or IV and with an LVEF <35%. The etiology was coronary heart disease in 53 patients and dilated cardiomyopathy in 13. These were compared with 20 age-matched, healthy control subjects with a QRS duration <120 ms.

Substudy 2. The aim of this substudy was to determine the ability of the CMR-TSI to predict cardiovascular death, death from any cause, major cardiovascular events (MCE), and HF admissions in 77 patients with HF and a QRS ≥120 ms undergoing CRT. This group included 42 patients from substudy 1.

Patients in substudy 2 also underwent a 6-min hall walk test (6), a quality-of-life assessment using Minnesota Living with Heart Failure questionnaire (7), and transthoracic echocardiography on the day before implantation, at 1, 3, and 6 months thereafter. Follow-up data on patients who died relates to the last available review before death.

Device therapy. All patients in substudy 2 underwent transvenous biventricular pacemaker implantation using standard techniques under local anesthesia. Patients were entered into the study only after a successful implantation and were followed-up in a dedicated CRT clinic. None of the patients in atrial fibrillation underwent atrioventricular node ablation. Patients in sinus rhythm (n = 68) underwent transmitral Doppler-directed optimization of atrioventricular delay (8) before discharge and at every scheduled visit thereafter. Backup atrial pacing was set at 60 beats/min, and the pacing mode was set to DDDR with an interventricular delay of 4 ms. For patients in chronic atrial fibrillation (n = 9), right ventricular and LV leads were implanted, and a Medtronic InSync III generator (model 8042, Medtronic, Minneapolis, Minnesota) was used, plugging the atrial port and programming the generator to a ventricular triggered mode. Generators used included the Medtronic InSync III model 8040 8042 (n = 61), St. Jude Frontier (St. Jude Medical, St. Paul, Minnesota) (n = 2), Vitatron CRT 8000 (Vitatron B.V., Arnhem, the Netherlands) (n = 2), Biotronik Stratos (Biotronik GmbH, Berlin, Germany) (n = 8), and Guidant Contak Renewal TR2 (Guidant Corp., St. Paul, Minnesota) (n = 4).

CMR. Images were acquired on a 1.5-T (General Electric Signa, GE Healthcare Worldwide, Slough, United Kingdom) scanner using a phased-array cardiac coil during repeated 8-s breathholds. A short-axis stack of LV images was acquired using a steady-state in free precession sequence (repetition time 3.0 to 3.8 ms; excitation time 1.0 ms; image matrix 224 × 224; field of view 36 to 42 cm; flip angle 45°) in sequential 8-mm slices (2-mm interslice gap) from the atrioventricular ring to apex. Left ventricular volumes, ejection fraction, and mass (myocardial density = 1.05 g/cm^3) were quantified using manual planimetry of all short-axis steady state free precession cine images with MASS analysis software (Medis, Leiden, the Netherlands). Each slice in the short-axis stack (Fig. 1A) was divided into 100 cords, running clockwise from a first cord located at the junction between the inferior right ventricular free wall and the interventricular septum. Radial wall motion was quantified semiautomatically for all cords at up to 20 phases (time points) in each R-R interval. This yielded up to 16,000 raw data points per patient (100 cords for each of 8 slices imaged over 20 phases. Radial wall motion data were obtained for each of 6 segments (Fig. 1B) in each of, typically, 8 slices, for 20 phases (time points). The observer was blinded to all other clinical details of the patients, including the outcome measures.

TSI. The maximum radial wall motion value of a segmental radial wall motion time series was chosen to parameterize the peak radial wall motion for each segment for this analysis. The time-dependent segmental radial wall motion data (y) were fitted to an empirical sine wave function $y = a + b * \sin(t/RR + c)$. The sine wave function was chosen to account for the cyclic nature of myocardial motion and to specifically obtain the main cyclic radial wall motion component from the radial wall motion data. The mean segmental radial wall motion (a), the cyclic segmental radial wall motion amplitude (b), and the segmental phase shift of the maximum radial wall motion (c) were extracted from the fit. The CMR-TSI was finally calculated as the standard deviation (SD) of all segmental phase shift of the radial wall motion extracted from the fit.

Echocardiography. Standard 2-dimensional echocardiography was performed using System 5 (GE Healthcare Worldwide). Standard left parasternal long-axis and short-axis, and apical, 4-, 5-, and 2-chamber views were obtained. Digital images were transferred to a computer (EchoPAC, GE Healthcare Worldwide) for off-line analysis. Left ventricular volumes were assessed using planimetry of apical 4-chamber views and Simpson's equation. The LVEF was calculated as follows: (left ventricular end-diastolic volume