Clinical Investigation

Prediction of Acute Response to Cardiac Resynchronization Therapy by Means of the Misbalance in Regional Left Ventricular Myocardial Work

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ABSTRACT

Background: Patients with left ventricular (LV) dyssynchrony have a marked misbalance in LV myocardial work distribution, with wasted work in the septum and increased work in the lateral wall. We hypothesized that a low septum-to-lateral wall (SL) myocardial work ratio at baseline predicts acute LV pump function improvement during cardiac resynchronization therapy (CRT).

Methods and Results: Twenty patients (age 65 ± 10 y, 15 men) underwent cardiac magnetic resonance (CMR) tagging for regional LV circumferential strain assessment and invasive pressure-volume loop assessment at baseline and during biventricular pacing. Segmental work at baseline was calculated from regional strain rate and LV pressure. Subsequently, the SL work ratio was calculated and related to acute pump function (stroke work [SW]) improvement during CRT. During biventricular pacing, SW increased by 33% ($P < .001$). SL work ratio at baseline was found to be significantly related to SW improvement by means of CRT ($R = –0.54$; $P = .015$). Moreover, it proved to be the only marker that was significantly related to acute response to CRT, whereas QRS duration and other measures of dyssynchrony or dyscoordination were not.

Conclusions: The contribution of the septum to LV work varies widely in CRT candidates with left bundle branch block. The lower the septal contribution to myocardial work at baseline, the higher the acute pump function improvement that can be achieved during CRT. (*J Cardiac Fail 2016;22:133–142*)

Key Words: Cardiac resynchronization therapy, pressure-volume loops, CMR tagging, myocardial work.

Cardiac resynchronization therapy (CRT) is an established therapy for patients with drug-refractory heart failure (HF) and left bundle branch block (LBBB). CRT, however, does not always lead to improvement in ventricular function and clinical symptoms. Rates of nonresponse to CRT are still reported to be 20%–50%, despite substantial efforts to derive predictive parameters from both electrical and mechanical dyssynchrony assessment.[1–4] Several studies found mechanical dyscoordination (opposing shortening and stretch within the left ventricle [LV]) to be a more powerful tool to predict CRT response than timing indices.[5–9] In 1974, Dillon et al were the first to describe a unique abnormal septal motion in LBBB patients with the use of echocardiographic techniques.[10] In these patients, the septum typically demonstrates a substantial preejection inward motion causing stretch of the LV lateral wall. Subsequently a paradoxic outward motion of the septum is observed during contraction of the late-activated LV lateral wall.[11] Indices that reflect this dyscoordination, such as systolic rebound stretch (SRS) and internal stretch factor (ISF) are based on regional fiber strain and were found to be significantly related to CRT response in single-center studies.[6–8,12] Nonetheless, these indices of regional fiber strain are load dependent and therefore may not reflect actual regional myocardial work.[13,14] Regional myocardial work can be determined by combining regional fiber strain with instantaneous LV pressure, as shown by Urheim et al[14] and Delhaas et al.[15] Recently, Russell et al validated this approach by demonstrating that the area of regional LV pressure-strain loops reflects regional myocardial metabolism.[16]

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Previous studies have shown that CRT candidates have a marked misbalance in regional myocardial work resulting in an inefficient LV pump function and a significant waste of work in the septum.[17] Moreover, CRT was shown to increase the contribution of septal work, thus restoring a more homogeneous septal to lateral myocardial work distribution.[16] Based on the finding that CRT can recruit myocardial work that is wasted by LBBB, we hypothesized that the amount of misbalance in regional myocardial work determines response to CRT. For that purpose, we investigated the relationship between the misbalance in regional myocardial work and acute LV pump function improvement during CRT.

Methods

Subjects

Twenty patients (age 65 ± 10 y, 15 male [75%]) referred for CRT system implantation were selected from the Temporary Biventricular Stimulation (TBS) database containing data on the acute hemodynamic effects of temporary multisite pacing in patients with advanced heart failure, as previously described.[18,19] Inclusion criteria for the original TBS study were sinus rhythm, moderate to severe heart failure (New York Heart Association functional class II or III), severely depressed LV function (LV ejection fraction ≤35%) and ≥3 months of stable optimal tolerated medical therapy. QRS duration was not an inclusion criterion. Patients with myocardial infarction or acute coronary syndrome within 3 months before study inclusion, previous pacemaker implantation, aortic valve stenosis, or mechanical aortic valve replacement, or presence of LV thrombus were excluded. For the present analysis, patients were selected from this database with (i) typical LBBB (according to AHA/ACC/HRS recommendations[20]), (ii) pressure-volume (PV) loop measurements, and (iii) cardiac magnetic resonance (CMR)–derived myocardial strain data of sufficient quality (see below). This study complied with the Declaration of Helsinki, and the local Research Ethics Committee approved it. Informed consent was obtained from each of the patients before the study procedures.

Cardiac Magnetic Resonance Imaging

CMR imaging was performed on a 1.5-T whole body system (Magnetom Sonata; Siemens, Erlangen, Germany) with the use of a phased-array cardiac receiver coil. Functional imaging was performed with the use of retrospectively electrocardiography (ECG)–gated steady-state free-precession cine imaging with breath-holding (temporal resolution <50 ms, repetition time 3.2 ms, echo time 1.6 ms). Per patient, 8–12 short-axis slices were obtained every 10 mm, covering the entire left ventricle. From these images, LV volumes were measured and ejection fraction (EF) was calculated. Myocardial scar territory was assessed by means of late gadolinium enhancement (LGE) imaging. Complementary tagged myocardial images were acquired with the use of steady-state free-precession imaging and a multiple brief expiration scheme (temporal resolution 15 ms, repetition time 3.6 ms, echo time 1.8 ms).[21] Images for 2-dimensional strain analysis were acquired in 3 short-axis planes evenly distributed over the LV. Furthermore, high-temporal-resolution (temporal resolution ~15 ms, repetition time 3.4 ms, echo time 1.7 ms) cine imaging of the LV in the 3-chamber view was performed to assess the opening and closure times of the mitral and aortic valves. From the tagged images, circumferential strain (CS) curves were obtained from the 50% mid-myocardial wall by in-house software using the harmonic phase method, as previously reported.[22] Segmental strain curves were calculated for every slice (base, middle, and apex).[23] The CS reflects the percentage change in length of a small line segment in the circumferential direction, with respect to the end-diastolic length. Septal strain was calculated as the averaged strain from the anteroseptal and inferoseptal segments from the 3 slices. Lateral wall strain was calculated as the averaged strain from the anterolateral and inferolateral segments from the 3 slices. The strain curves were discarded in case of low signal-to-noise ratio as judged by 2 independent investigators. The strain rate was calculated as the change in strain per time frame.

Temporary Biventricular Pacing

Within the same week of the CMR, all patients underwent temporary biventricular stimulation as described previously.[19] In brief, after infusion of 5000 IE of heparin, 2 temporary bipolar pacing leads were placed, one in the right atrium and the other in the right ventricular apex. A unipolar pacing lead (Visionwire; Biotronik, Berlin, Germany) was targeted at the mid-posterolateral (PL) position. A conductance catheter (CD Leycom, Zoetermeer, the Netherlands) was placed in a stable position in the LV apex to obtain PV loops. Baseline PV loops were recorded during intrinsic rhythm before and after each biventricular run. Approximately 30 representative cardiac cycles were averaged, disregarding all inappropriate beats (ie, extrasystoles) with the use of Conduct NT software (version 3.18.1). Biventricular pacing was performed in VDD mode with the use of a fixed atrioventricular delay set to <100 ms, ensuring full ventricular capture, and a VV interval of 0 ms. CMR-derived LV volumes were used for the calibration. LV function was quantified by end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), and EF. Also, end-systolic pressure (ESP), end-diastolic pressure (EDP), and maximum rate of systolic and diastolic pressure change (dP/dt_{max}, dP/dt_{min}) were determined. Stroke work (SW) was directly calculated as the area of the pressure-volume loop. The effect of biventricular pacing was calculated as the relative SW change compared with the mean of the 2 flanking baseline measurements. Patients with an SW increase of >20% compared with baseline were classified as CRT responders, because that cutoff value accurately predicted long-term response to CRT in an earlier study.[24]

Data Analysis

Mechanical dyssynchrony was defined as the delay in onset of contraction between the septum and the lateral wall (SL