Comparative Mechanical Activation Mapping of RV Pacing to LBBB by 2D and 3D Speckle Tracking and Association With Response to Resynchronization Therapy

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OBJECTIVES The goals of this study were to compare patterns of mechanical activation in patients with chronic right ventricular (RV) pacing with those with left bundle branch block (LBBB) using 2-dimensional and novel 3-dimensional speckle tracking, and to compare ejection fraction (EF) response and long-term survival after cardiac resynchronization therapy (CRT).

BACKGROUND Several randomized CRT trials have excluded patients with chronic RV pacing, and current guidelines for CRT include patients with intrinsically widened QRS, typically LBBB.

METHODS We studied 308 patients who were referred for CRT: 227 had LBBB, 81 were RV paced. Dyssynchrony was assessed by tissue Doppler, routine pulsed Doppler, and 2-dimensional speckle-tracking radial strain. 3D strain was assessed using speckle tracking from a pyramidal dataset in a subset of 57 patients for mechanical activation mapping. Survival after CRT was compared with survival in a group of 46 patients with attempted, but failed, CRT.

RESULTS Patients with chronic RV pacing and LBBB had similar intraventricular dyssynchrony, with opposing wall delays by tissue Doppler of 82 ± 45 ms versus 87 ± 63 ms and anteroseptum-to-posterior delays by speckle tracking of 225 ± 142 ms, versus 211 ± 107 ms, respectively. RV-paced patients, however, had greater interventricular dyssynchrony: 44 ± 24 ms versus 35 ± 21 ms (p < 0.01), which correlated with their greater QRS duration (p < 0.001). Sites of latest mechanical activation were most often posterior or lateral in both groups, but RV-paced patients had sites of earliest activation more often from the inferior-septum and apex (p < 0.05). EF response was similar in RV-paced and LBBB groups, and survival free from transplantation or mechanical support after CRT was similarly favorable as compared with failed CRT patients over 5 years (p < 0.01).

CONCLUSIONS RV-paced patients, when compared with LBBB patients, had similar dyssynchronous patterns of mechanical activation and greater interventricular dyssynchrony. Importantly, RV-paced patients had similar EF response and long-term outcome as those with LBBB, which supports their candidacy for CRT. (J Am Coll Cardiol Img 2010;3:461–71) © 2010 by the American College of Cardiology Foundation

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Right ventricular (RV) pacing is the only effective treatment for patients with symptomatic atrioventricular block. Several trials have shown that conventional RV pacing is associated with left ventricular (LV) dysfunction and an increased risk for heart failure (HF) and death (1–4). Although the exact cause of the deleterious effects of RV pacing, specifically from the apical site, is not known, the prevailing hypothesis is that RV pacing may create mechanical dysynchrony, which may induce LV dysfunction and clinical HF (5,6). It remains unclear whether patients with QRS widening induced by chronic RV pacing would have a similar pattern of mechanical activation, thus a substrate for dysynchronous HF. Cardiac resynchronization therapy (CRT) has greatly improved symptoms and survival in HF patients with intrinsic QRS widening (7–9). A current criterion for consideration of CRT is a QRS duration ≥120 ms, typically with left bundle branch block (LBBB). Although RV-paced HF patients have been excluded from randomized CRT trials and are not part of current guidelines, upgrading of RV pacing systems to CRT devices is often performed (10). Accordingly, the objectives of this study were to compare mechanical activation patterns in patients with RV pacing–induced QRS widening to those with intrinsic LBBB using 2-dimensional (2D) and novel 3-dimensional (3D) speckle-tracking strain imaging, and to compare their ejection fraction (EF) response and long-term outcome after CRT.

**Methods**

The study group consisted of 333 consecutive HF patients with QRS duration ≥120 ms (either LBBB or chronic RV pacing) referred for CRT with EF ≤35% and New York Heart Association (NYHA) functional class III or IV HF despite optimal pharmacological therapy. This protocol was approved by the Institutional Review Board on Biomedical Research, and all patients gave informed consent consistent with this protocol. Twenty-five patients (8%) with suboptimal echocardiographic images were excluded from all subsequent analysis. Accordingly, the patient study group consisted of 308 patients (Table 1). Eighty-eight (28%) were female. The group mean age was 66 ± 12 years, EF was 25 ± 6% (all ≤35%), and QRS duration was 159 ± 27 ms (all ≥120 ms). One hundred seventy-six patients (57%) had ischemic cardiomyopathy. No patients had atrial fibrillation. The intrinsic LBBB group consisted of 227 patients, defined as QRS ≥120 ms with an RS or QS morphologic type in lead V1 and a broad R-wave without a Q-wave in either lead I or V6. Mean age was 65 ± 12 years, 68 (30%) were female, mean EF was 24 ± 6%, and mean QRS duration was 152 ± 24 ms. The remaining 81 patients had previously undergone implantation of a permanent dual-chamber pacemaker at least 1 year before enrollment. Patients with chronic RV pacing ≥90% on device interrogation at the time of enrollment were considered as having a paced QRS complex. All RV pacing devices were specifically programmed to minimize RV pacing (3). Mean age in the RV-paced groups was 69 ± 12 years, 20 (25%) were female, mean EF was 25 ± 7%, and mean QRS duration was 181 ± 25 ms. Mean duration of RV pacing was 4 ± 2 years and the indications shown in Table 2. A biventricular pacing system was routinely implanted with an RV apical lead and an LV lead positioned in a posterior or lateral epicardial vein through the coronary sinus.

An additional group of 46 patients who met standard CRT implant criteria, but in whom transvenous LV lead implantation failed and no epicardial LV lead was implanted, comprised a control

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**AV = atrioventricular; other abbreviations as in Table 1.**
group. The decision to forgo surgical epicardial lead placement was usually based on patient refusal. The failed CRT patients reflected the overall CRT population at our institution (Table 1). All CRT patients received a CRT-defibrillator device, and all failed CRT patients received a standard implantable cardioverter-defibrillator.

**Echocardiography.** All echocardiographic studies were performed with commercially available echocardiography systems (Vivid 7, GE-Vingmed, Horten, Norway, and/or Aplio Artida, Toshiba Medical Systems Corporation, Tokyo, Japan). Routine digital grayscale 2D and tissue Doppler cine loops were obtained at end-expiratory apnea from standard apical and parasternal views. Specific views for the study included mid-LV short-axis views at the level of the papillary muscle, routine apical views and pulsed Doppler of the RV and LV outflow tract in all patients, and a full pyramidal 3D dataset from an apical transducer site in a subset of patients. Sector width was optimized to allow for complete myocardial visualization while maximizing frame rate. EF was assessed by biplane Simpson rule using manual tracing of digital images (11). Follow-up echocardiograms were available on 176 patients (mean 7 ± 6 months) to assess EF response. Response to CRT was defined as reverse remodeling detected by a relative increase in EF ≥15% from baseline (12–14).

**Interventricular dyssynchrony analysis.** Routine pulsed Doppler was used to determine interventricular dyssynchrony as previously described (15,16). Interventricular mechanical delay (IVMD) was determined as the time difference in onset of RV ejection velocity to LV ejection velocity (Fig. 1A). An IVMD of ≥40 ms was considered significant dyssynchrony (12,15).

**Longitudinal tissue Doppler dyssynchrony analysis.** Longitudinal dyssynchrony was determined using tissue Doppler cine loops from 3 consecutive beats obtained in 3 standard apical views as previously described in detail (16–18). Regions of interest (7 × 15 mm) were placed in the basal and mid-LV segments for 12-site time-to-peak velocity analysis. Manual adjustments were made so that the regions of interest produced the most reproducible peak velocity. Segmental time-to-peak systolic wave velocity was calculated from the onset of the QRS complex. Longitudinal tissue Doppler dyssynchrony was determined as the maximal time difference in peak systolic velocities from opposing walls in each view (Fig. 1B), with ≥65 ms considered significant (15,17,18).

**2D speckle-tracking dyssynchrony analysis.** Radial dyssynchrony was determined using speckle-tracking strain from routine grayscale mid-LV short-axis images as previously described in detail (12–15). Briefly, an end-diastolic circular region of interest was traced slightly within the endocardial cavity using a point-and-click approach, with special care taken to adjust tracking of all endocardial segments. A second larger concentric circle was then automatically generated and manually adjusted near the epicardium. Speckle tracking automatically analyzed frame-by-frame movement of the stable patterns of natural acoustic markers, or speckles, over the cardiac cycle. Segmental time to peak strain was measured. Radial dyssynchrony was then determined by measuring the time difference between the anteroseptal and posterior wall (Fig. 1C). A radial speckle-tracking dyssynchrony of ≥130 ms was considered significant dyssynchrony (12–15).

**3D speckle-tracking dyssynchrony analysis.** A subset of 57 patients was also studied by a 3D speckle-tracking strain system as previously described in detail (19). Briefly, 3D speckle tracking used a pyramidal volume from the matrix array transducer. Acquisition of a full-volume dataset required 4 smaller wedge-shaped subvolumes from 4 consecutive cardiac cycles during a breath hold, which were combined to provide the larger pyramidal volume. The 3D datasets were displayed in 5 different cross sections including standard 3 short-axis views and apical 4- and 2-chamber views that could be modified interactively. Regions of interest were placed on the endocardium and epicardium from apical views. The software automatically divided the LV into 16 standard segments (11) and generated corresponding time-strain curves from each segment. The 3D speckle-tracking radial dyssynchrony was quantified from mechanical activation opposing wall delay in time-to-peak strain and standard deviation of time-to-peak strain. The 3D cine loops of regional strain were generated and displayed with color coding of strain.

**Long-term outcome analysis.** Long-term outcome was assessed as survival free from transplant or mechanical circulatory support. This end point was pre-determined because only patients with end-stage HF would undergo transplant or ventricular assist device implantation in our institution. Long-term follow-up data after CRT were available in 234 patients (174 intrinsic LBBB and 60 RV-paced patients). For further comparison, a control group of 46 patients with similar baseline characteristics (Table 1) who met standard implant criteria but had...
failed attempted CRT and who did not undergo epicardial LV lead implantation over a 5-year period were followed.

Statistical analysis. All group data were presented as mean ± SD and were compared with the 2-tailed Student t test for paired and unpaired data, respectively. Comparisons between the LBBB and RV-paced patients were made technically to demonstrate noninferiority, and no corrections for type I error were applied. Linear regression analysis was expressed as a Pearson correlation coefficient. Event-free survival curves were determined accord-

Figure 1. Assessment of Dyssynchrony

(A) Pulsed Doppler of right and left ventricular outflow tracks with time from onset of QRS to onset of flow (red arrows) to measure interventricular mechanical delay as the time difference in onset of ejection. (B) Time-velocity plots from septum (yellow line) and lateral wall (blue line) using the apical 4-chamber view to measure the opposing wall delay (red arrow) during the ejection interval. (C) Time-strain plots from the mid-ventricular short-axis view to measure anteroseptal (yellow line) to posterior wall (purple line) delay in peak 2-dimensional speckle-tracking radial strain (red arrow). AVC = aortic valve closure; AVO = aortic valve opening.
ing to the Kaplan-Meier method, with comparisons of cumulative event rates by the log-rank test. Statistical significance was p < 0.05.

**RESULTS**

The study group consisted of 308 HF patients (227 intrinsic LBBB patients and 81 RV-paced patients), with follow-up survival data available on 234 patients and EF data available on 163 patients. Baseline clinical characteristics were similar between patient groups, except that RV-paced patients had greater QRS duration than LBBB patients (181 ± 25 ms vs. 152 ± 24 ms, respectively; p < 0.001) (Table 1).

**Variability of dyssynchrony measures.** Intraobserver variability for determining routine pulsed Doppler dyssynchrony measures was 3 ± 4%, and interobserver variability was 4 ± 5%. Intraobserver variability for determining tissue Doppler longitudinal dyssynchrony was 8 ± 7%, and interobserver variability was 8 ± 7%. Intraobserver variability for determining 2D speckle-tracking strain data from the identical digital cine loops used for dyssynchrony was 9 ± 7%. The interobserver and intraobserver variabilities of 3D speckle-tracking dyssynchrony were 9 ± 8% and 9 ± 7%, respectively.

**Prevalence and degree of dyssynchrony.** The prevalence and degree of intraventricular dyssynchrony was similar in intrinsic LBBB and RV-paced patients (longitudinal tissue Doppler dyssynchrony: 73% vs. 70% and 87 ± 63 ms vs. 82 ± 45 ms; radial speckle-tracking dyssynchrony: 77% vs. 70% and 211 ± 107 ms vs. 225 ± 142 ms) (Fig. 2A). The 3D speckle-tracking strain-derived dyssynchrony indexes were also similar in both groups (SD: 120 ± 46 ms vs. 124 ± 54 ms, and opposing wall delay: 308 ± 99 ms vs. 318 ± 124 ms) (Fig. 2A). The only observed difference was that RV-paced patients had a higher degree and incidence of significant IVMD than those with intrinsic LBBB patients: 44 ± 24 ms versus 35 ± 21 ms and 58% versus 40% (p < 0.01 vs. LBBB) (Fig. 2A). The greater degree of IVMD in RV-paced patients correlated with their greater QRS duration, (r = 0.53, p < 0.001).

**Mechanical activation by 2D speckle tracking.** Using time-to-peak maximal 2D speckle-tracking radial strain, we determined the prevalence of the site of earliest and latest mechanical activation from 6 mid-LV short-axis views in LBBB and RV-paced patients. Overall, 75% of LBBB patients and 79% of RV-paced patients had the site of earliest mechanical activation in the anterior septum or inferior septum. However, the site of earliest mechanical

![Figure 2. Degree and Prevalence of Dyssynchrony](http://imaging.onlinejacc.org/)
activation in RV-paced patients was more often located in the inferior septum compared with LBBB patients (47% vs. 30%, p < 0.05) (Fig. 3). Despite these differences in earliest activation, the site of latest mechanical activation was similarly located in the posterior or lateral wall in 80% of intrinsic LBBB patients and 81% of RV-paced patients (Fig. 3). The EF response rate in patients with the site of earliest activation from the anterior septum or inferior septum was significantly higher at 66% compared with those in whom the site of earliest activation was posterior or lateral, which was 33% (p < 0.05).

**Site of mechanical activation by 3D speckle tracking.** We also determined the site of earliest and latest mechanical activation from all 16 LV sites using a 3D dataset in a subset of 57 patients (35 LBBB and 22 RV-paced patients) with time-to-peak maximal 3D speckle-tracking radial strain. Slight differences in the site of earliest mechanical activation were observed in RV-paced patients, occurring more often from the apex (28% vs. 6% of intrinsic LBBB patients, p < 0.05) and inferior septum (55% vs. 34% of intrinsic LBBB patients) (Fig. 4). Similar to the 2D strain data, the site of latest mechanical activation in intrinsic LBBB patients was similarly distributed to that in RV-paced patients (Fig. 4). Overall, the site of latest mechanical activation was located in posterior or lateral regions in 83% of intrinsic LBBB patients and in 86% of RV-paced patients at the mid- or basal levels (Fig. 5).

**Ventricular functional response to CRT.** There were 176 patients with follow-up EF data available. Both intrinsic LBBB and RV-paced patients had similar EF improvement (24 ± 6 to 32 ± 11 and 25 ± 8 to 33 ± 12, p < 0.001 vs. baseline) (Fig. 6). An EF response was observed in 119 patients, using an LV functional response defined as a relative change in EF ≥15% as we have used in our previous investigations (12–14). This represented an overall 68% EF response rate, which was similar in both RV-paced and LBBB patients (71% vs. 67%, respectively). An absolute 5% increase in EF response rate in LBBB patients was 62%, which was similar to RV-paced patients at 61%. Furthermore, the relative decrease in end-systolic volume ≥10% in LBBB and RV-paced patients was similar at 62% and 60%, respectively. 2D speckle-tracking radial dyssynchrony ≥130 ms predicted a 15% relative EF response in the LBBB group with a sensitivity of 77% and specificity of 72%, which was similar to the RV-paced group, with a sensitivity of 80%, and a specificity of 66%.

**Event-free survival after CRT.** There were 280 patients with follow-up outcome analysis available after CRT,
including 174 intrinsic LBBB, 60 RV-paced, and 46 failed CRT patients. The follow-up duration was 24 ± 18 months. Survival free from transplant or ventricular assist device was similar in patients with intrinsic LBBB and RV pacing (Fig. 7). Both had a significantly more favorable prognosis than the patients with attempted, but failed, CRT (p < 0.01). Furthermore, speckle-tracking radial dyssynchrony ≥130 ms also predicted event-free survival after CRT in both the LBBB patients with a sensitivity of 55% and specificity of 69%, and in the RV-paced patients with a sensitivity of 55% and specificity of 73%.

**DISCUSSION**

This study of a large series of consecutive HF patients referred for CRT demonstrates that chronically RV-paced patients have similar dyssynchronous patterns of mechanical activation as those with intrinsically widened LBBB. The 2D and novel 3D speckle-tracking strain analyses demonstrated slight differences in sites of earliest mechanical activation as expected by lead positioning, but confirmed striking similarities in sites of latest mechanical activation in RV-paced and LBBB patients. The only significant difference observed between groups was a greater IVMD in RV-paced patients, which was associated with their comparatively greater QRS width. Importantly, long-term event-free survival and EF response were similarly favorable in RV-paced patients compared with LBBB patients following CRT. These results strongly support the candidacy of chronically RV-paced HF patients for upgrade to CRT.

**Pathophysiology of RV pacing–induced dyssynchrony.** RV pacing is performed commonly for patients with symptomatic or high-risk bradycardia atrioventricular block. Although RV pacing may be lifesaving, it may induce mechanical dyssynchrony, which may have detrimental long-term consequences (5,6). Dohi et al. (5) used an animal model to demonstrate that the pattern of dyssynchrony induced by RV pacing simulated LBBB, which was characterized by early mechanical activation of septal segments and delayed activation of free-wall segments, and was corrected by CRT. Furthermore, changes in stroke work by pressure-volume loops were correlated with changes in degrees of RV pacing–induced dyssynchrony. The deleterious effects of dyssynchrony on LV function were accentuated with decreased LV contractility in an HF...
model of high-dose esmolol, supporting the observation that dyssynchronous RV pacing may have more of an unfavorable effect on patients with depressed cardiac function (20). Tanabe et al. (6) more recently demonstrated a similar pattern dysynchrony induced by RV pacing using speckle-tracking radial strain, which mimicked the pattern of LBBB seen in humans. Several trials have shown that conventional RV pacing is associated with an increased risk for development of HF and death (1,3). The DAVID (Dual Chamber and VVI Implantable Defibrillator) trial randomized 506 patients with implantable cardiovertor defibrillators and EF ≤40% to rate-responsive pacing at 70/min or RV backup pacing at 40/min and observed a lower HF hospitalization rate and mortality in those with back-up pacing (3). It is believed that RV pacing–induced dyssynchrony contributed to the less favorable outcomes in the patients with depressed EF who were RV paced more often.

Comparison to other studies of RV pacing and CRT. This study confirms previous reports describing the beneficial effect of an upgrade from RV pacing to biventricular pacing in HF patients with depressed LV function. Leon et al. (21) observed favorable effects of upgrade of RV pacing to CRT in 20 HF

Figure 5. Color-Coded 3D Strain of the Left Ventricle, Bull’s Eye Plots, and Corresponding Time-Strain Curves

(A) An example of a patient with left bundle branch block (LBBB) (top), where the site of earliest mechanical activation is the basal-anterior septum segment (red arrow), and the site of latest mechanical activation is the mid-posterior segment (green arrow). (B) An example of a patient with chronic right ventricular (RV) pacing (bottom), where the site of earliest mechanical activation is the apical-septum segment (red arrow), and the site of latest mechanical activation is the mid-lateral segment (green arrow). ant = anterior; ant-sept = anterior-septum; inf = inferior; lat = lateral; post = posterior; sept = septum.
patients with previous atrioventricular node ablation for refractory atrial fibrillation where EF improved from 22 ± 7% to 31 ± 12%, and NYHA functional class improved from 3.4 ± 0.5 to 2.4 ± 0.6. Vatankulu et al. (22) reported similar results with CRT. Our findings also confirm the outcome benefits of RV pacing to CRT reported by Foley et al. (23) and Delnoy et al. (24). Tops et al. (20) previously studied 58 patients with His ablation and RV pacemaker dependence, and observed that 57% had dyssynchrony associated with a deterioration of LV systolic function and HF functional class over approximately 4 years. Their mean baseline HF functional class was 1.7 and mean EF was 48%, which was in contrast to our patients in the present report; all with NYHA functional class III or IV, with a group mean EF of 25%. The observed prevalence of dyssynchrony at 70% in our present study may likely be related to greater degrees of LV dysfunction and HF (5). In addition, the PAVE (Post AV Nodal Ablation Evaluation) trial prospectively compared CRT with RV pacing in patients undergoing atroventricular node ablation for refractory atrial fibrillation (25). A significantly greater follow-up EF was observed in the CRT group compared with the RV-pacing group, and greater improvements in 6-min walk distance occurred in patients with EF >45% or NYHA functional class II/III symptoms receiving CRT compared with patients with normal EF or NYHA functional class I symptoms.

Others have previously reported a similar degree of dyssynchrony in RV-paced patients and intrinsic LBBB (26,27). Witte et al. (27) demonstrated that septal-to-posterior wall motion delay by M-mode, time difference in peak systolic velocities from mitral and lateral mitral annulus, and IVMD were similar in intrinsic LBBB and RV-paced patients. Marai et al. (26) also demonstrated that longitudinal tissue Doppler dyssynchrony and IVMD were
similar in both groups. Our present study extended these previous observations using the newly developed 3D speckle-tracking system that provided a more comprehensive LV dyssynchrony evaluation than previously possible (19). Although both 2D and 3D speckle tracking demonstrated differences in sites of earliest activation in LBBB and RV-paced patients, the sites of latest activation were similarly distributed in predominantly posterior and lateral sites. Since pacing the site of latest activation is thought to be the principal therapeutic effect of CRT, these results support the similar results of CRT in these 2 patient groups. Interestingly, we observed significantly greater interventricular dyssynchrony in the RV-paced patients and that IVMD was correlated with QRS duration, which was also greater in the RV-paced group. This finding suggests that the overall IVMD dyssynchrony induced by RV pacing may be even more severe than LBBB (28).

**Study limitations.** There are several possible technical limitations in tissue Doppler and speckle-tracking analysis, and both require a training period and experience to achieve reproducible results (16,29). A specific limitation of 2D and 3D speckle tracking is the need for careful image tracing to manually fine tune the region of interest and capture the appropriate regional strain for dyssynchrony analysis. Another limitation was that a substantial number of patients were referred to our institution for CRT implantation and received follow-up medical care elsewhere. Accordingly, we did not have access to their follow-up echocardiograms to perform quantitative EF analysis. However, patients with and without follow-up EF data had similar baseline characteristics, including similar age, gender distribution, QRS duration, prevalence of ischemic heart disease, and EF. Overall, 8% were completely lost to follow-up. Potential sites of RV pacing other than the RV apex include the RV outflow tract and the interventricular septum, or direct pacing of the His bundle. The RV outflow tract is the most extensively studied alternate site for RV pacing, and offers a good alternative for RV apical pacing due to the stability of the current active fixation leads and the good long-term pace/sense thresholds. In this study, the site of the RV pacing lead was routinely implanted in the RV apex. It is likely that the site of the RV pacing lead is associated with the site of earliest mechanical activation; however, precise localization of the lead position was not part of this study. It is an acknowledged limitation that the control group of patients with standard CRT indications failing LV lead placement may have had greater degrees of cardiac disease associated with more complex or distorted coronary venous anatomy, resulting in technical difficulties with LV lead positioning. Accordingly, a randomized trial design would be important for future confirmation.

**Conclusions**

The sites of latest mechanical activation in chronically RV-paced patients were similar to intrinsic LBBB patients by 2D and 3D speckle-tracking radial strain. However, differences in sites of earliest mechanical activation in RV-paced patients were more often from the apex and inferior septum, likely due to lead positioning. RV-paced patients had a similar prevalence and degree of intraventricular dyssynchrony as those with LBBB. The only difference between these groups was a greater IVMD in RV-paced patients. Importantly, RV-paced patients had a similar EF response and long-term outcome, and therefore appear to be suitable candidates for CRT.

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Key Words: echocardiography • pacing therapy • heart failure.