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ORIGINAL RESEARCH

Long-Term Outcome After CRT in the Presence of Mechanical Dyssynchrony Seen With Chronic RV Pacing or Intrinsic LBBB

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ABSTRACT

OBJECTIVES The aim of this study was to compare the volumetric response and the long-term survival after cardiac resynchronization therapy (CRT) in patients with intrinsic left bundle branch block (LBBB) versus chronic right ventricular pacing (RVP) with respect to the presence of mechanical dyssynchrony (MD).

BACKGROUND Chronic RVP induces an iatrogenic LBBB and asynchronous left ventricular contraction that is potentially reversible by upgrading to CRT.

METHODS A total of 914 patients eligible for CRT (117 with conventional pacemakers and 797 with intrinsic LBBB) were included in the study. MD was visually assessed before CRT and was defined as the presence of either apical rocking and/or septal flash on baseline echocardiograms. Patients with a left ventricular end-systolic volume decrease of ≥15% during the follow-up were considered responders. Patients were followed for all-cause mortality during the median follow-up of 48 months (interquartile range: 29 to 66 months).

RESULTS MD was observed in 51% of patients with RVP versus 77% in patients with intrinsic LBBB ($p < 0.001$). Patients with RVP and MD had a similar likelihood of volumetric response as did patients with intrinsic LBBB and MD (adjusted odds ratio: 0.71; 95% confidence interval: 0.33 to 1.53; $p = 0.385$). There was no significant difference in long-term survival between patients with RVP and intrinsic LBBB (adjusted hazard ratio: 1.101; 95% confidence interval: 0.658 to 1.842; $p = 0.714$). Patients with visual MD and either intrinsic LBBB or RVP had a more favorable survival than those without MD ($p < 0.001$).

CONCLUSIONS The likelihood of volumetric response and a favorable long-term survival of patients with RVP was similar to those of patients with intrinsic LBBB and were mainly determined by the presence of MD and not by the nature of LBBB. (J Am Coll Cardiol Img 2017;10:1091–9) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ApRock = apical rocking

ATM = apical transverse motion

CI = confidence interval

CRT = cardiac resynchronization therapy

LBBB = left bundle branch block

LV = left ventricle

LVEF = left ventricular ejection fraction

NYHA = New York Heart Association

RVP = right ventricular pacing

SF = septal flash

Cardiac resynchronization therapy (CRT) has become a standard therapeutic option for patients with chronic heart failure and wide QRS complex who remain symptomatic despite optimal medical therapy (1). However, a high rate of nonresponders to this expensive treatment remains unaffected despite years of accumulated experience and technological advances. However, patients with wide QRS width and left bundle branch block (LBBB) morphology have the highest likelihood of improvement after CRT (1). It leads to an early activation of the ventricular septum and a delayed activation of posterolateral wall and may result in dyssynchronous left ventricle (LV) contraction and deleterious remodeling (2,3). This typical contraction pattern induced by an intrinsic LBBB can be described by septal flash (SF) and apical rocking (ApRock) and is potentially correctable by CRT (4–7). Successful correction of SF and ApRock has been associated with volumetric response and an improved long-term survival following CRT but neither all patients with intrinsic LBBB exhibit SF and ApRock nor all benefit from CRT (8–11).

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Chronic right ventricular pacing (RVP) in patients with bradyarrhythmias prolongs the QRS duration and induces an asynchronous electrical activation pattern of the LV similar to that of an intrinsic LBBB (2,12). Similar to patients with intrinsic LBBB, patients with chronic RVP may also benefit from upgrading to biventricular pacing (13,14) but the prevalence and prognostic implications of SF and ApRock in this subgroup of patients are unknown. Furthermore, the studies comparing long-term outcomes between the CRT candidates with RVP and an intrinsic LBBB are scarce.

In this retrospective analysis of the PREDICT-CRT (Relationship of Visually Assessed Apical Rocking and Septal Flash to Response and Long-Term Survival Following Cardiac Resynchronization Therapy) study, we assessed the prevalence of visual SF/ApRock in patients with heart failure with conventional pacemakers who underwent upgrading to CRT and also compared the long-term survival after CRT in patients with intrinsic LBBB versus RVP with respect to the presence of visual mechanical dyssynchrony.

METHODS

The primary results of the PREDICT-CRT study have been published (9). After excluding all patients with non-LBBB QRS morphology from the PREDICT-CRT study population, a total of 914 patients (117 with conventional pacemakers and 797 with intrinsic LBBB) who underwent CRT according to guideline criteria (LV ejection fraction [LVEF] ≤35%, QRS duration ≥120 ms, New York Heart Association [NYHA] functional class II to IV, and on optimized pharmacological therapy at least 3 months before implantation) were included into this retrospective analysis. The availability of standard echocardiographic examination before CRT was also a prerequisite for inclusion. LBBB was defined according to conventional criteria: a wide QRS, QS, or rS in lead V_1, and monophasic R-wave with no Q waves in leads V_6 and I. Patients with ischemic origin of heart failure, proven by coronary angiography or by a documented history of myocardial infarction, were eligible for the study provided they were optimally revascularized. Data on all-cause mortality were acquired from medical records, by interview with the patients' general practitioner or relatives, and/or from national death registries. The study was approved by the ethical committee of the University Leuven.

ECHOCARDIOGRAPHIC DATA. Echocardiographic data were acquired using commercially available scanners (Vivid 7 and E9, GE Vingmed Ultrasound, Horten, Norway) and digitally stored for off-line analysis using EchoPac (GE Vingmed Ultrasound). To assess the volumetric response to CRT, the LV volumes and LVEF were calculated using the modified biplane Simpson method. Patients with an LV end-systolic volume decrease of ≥15% during follow-up were regarded as responders (15).

VISUAL ASSESSMENT OF MECHANICAL DYSSYNCHRONY. Mechanical dyssynchrony was visually assessed by evaluating ApRock and SF and was defined as a presence of either ApRock or SF. This method for assessing dyssynchrony has been described and evaluated in previous studies (6,9). Briefly, in the apical 4-chamber

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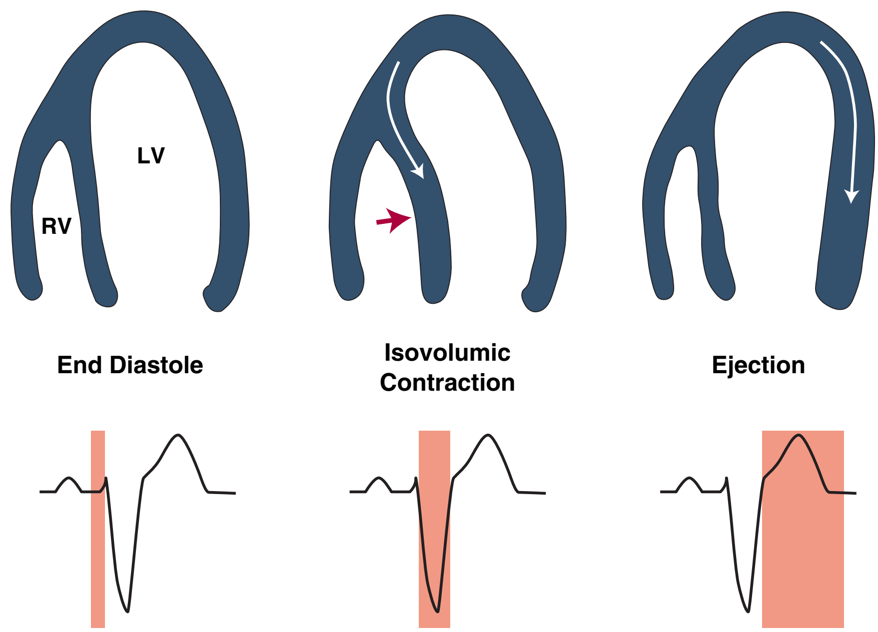
FIGURE 1 **Typical Left Ventricular Motion Pattern in a Patient With Left Bundle Branch Block and Mechanical Dyssynchrony**



Septal regions of the left ventricle (LV) shorten very early during isovolumic contraction (within QRS width) and cause the apex to move septally **(white arrow, middle panel)** while the septum moves leftward (septal flash, **red arrow, middle panel**). A delayed onset of systolic shortening in the lateral and posterior LV region pulls the apex laterally during the ejection phase **(white arrow, right panel)** while stretching the septum. This typical sequence of the septal-to-lateral apex motion is described as apical rocking. RV = right ventricle.

view, ApRock is characterized by a short septal motion of the apex caused by early septal contraction in systole and a subsequent long motion to the lateral wall during ejection phase (**Figure 1**, Online Videos 1 and 2). The presence of SF was identified visually in apical 4-chamber view as a short inward motion of the septum in early systole (within the QRS width) (Online Video 1). All readings were initially performed by 2 readers blinded to clinical data, using the same criteria for patients with RVP and intrinsic LBBB. In case of disagreement, the readings of a blinded third reader were used to reach a majority decision.

QUANTIFICATION OF MECHANICAL DYSSYNCHRONY. Quantification of SF and ApRock was performed in a subset of patients and the results compared with those obtained by visual approach. ApRock was quantified by measuring apical transverse motion (ATM), the motion of the LV apex perpendicular to the LV long axis, using high frame rate tissue Doppler data that were available in 110 patients with intrinsic LBBB. Details may be found in Online Figure 1. Based on previous experience, ATM in the apical 4-chamber view during ejection time was used as the quantitative measure of ApRock, with a cutoff value of 1.5 mm (4,8). SF was semiquantified by detecting a fast inward/outward motion of the septum occurring during the isovolumetric contraction period (within the QRS width) (5). Using M-mode in apical 4-chamber view, all 3 septal segments (basal, mid, and apical) were interrogated for the presence of SF in 40 patients with intrinsic LBBB and RVP (20 random patients in both groups).

CARDIAC RESYNCHRONIZATION THERAPY. All patients underwent biventricular pacemaker implantation following standard protocols. The LV pacing lead was inserted by a transvenous approach via the coronary sinus and preferably implanted in the lateral or posterolateral vein. Properly functioning right ventricular and atrial leads of previously implanted conventional pacemakers were used in patients who were upgraded to CRT.

STATISTICAL ANALYSIS. Continuous data were expressed as mean ± SD and compared between groups using unpaired Student *t* test. In case of significant deviation from the normal distribution, median and interquartile range and a Wilcoxon rank sum test were used. Categorical data were summarized by their observed frequencies and percentages, and compared using a Fisher exact test. Using Kappa statistics, intraobserver variability was tested in 100 randomly selected patients with intrinsic LBBB and

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TABLE 1 Baseline Characteristics of Study Population

		Intrinsic LBBB		Paced LBBB		
	All Patients	With Dyssynchrony	Without Dyssynchrony	With Dyssynchrony	Without Dyssynchrony	p Value
Age, yrs (n = 914)	64 ± 11	64 ± 11	65 ± 10	67 ± 11	68 ± 11	0.012
Female (n = 824)	205 (25)	175 (32)	16 (10)	9 (17)	5 (10)	<0.001
NYHA functional class (n = 892)	2.9 ± 0.5	2.9 ± 0.5	3.0 ± 0.5	2.9 ± 0.7	3.0 ± 0.6	0.417
Ischemic etiology (n = 824)	345 (42)	192 (35)	106 (64)	26 (49)	21 (40)	<0.001
QRS width, ms (n = 887)	175 ± 26	175 ± 24	165 ± 26	183 ± 24	196 ± 31	<0.001
Atrial fibrillation (n = 814)	202 (25)	111 (20)	50 (31)	16 (30)	25 (49)	<0.001
LVEDD, mm (n = 811)	69 ± 10	70 ± 10	49 ± 9	65 ± 9	68 ± 9	0.004
LVEF, % (n = 767)	26 ± 7	25 ± 7	27 ± 7	26 ± 6	29 ± 7	<0.001
LVEDV, ml (n = 767)	226 ± 85	234 ± 88	216 ± 73	199 ± 69	211 ± 91	0.027
LVESV, ml (n = 767)	167 ± 72	176 ± 76	156 ± 62	149 ± 57	143 ± 65	<0.001
ACEi/ARB (n = 775)	751 (97)	500 (97)	154 (99)	51 (96)	46 (89)	0.002
Beta-blockers (n = 783)	730 (93)	491 (94)	145 (92)	46 (87)	48 (92)	0.205
Aldosterone antagonists (n = 777)	585 (75)	383 (74)	122 (78)	42 (79)	38 (73)	0.727
ICD (n = 792)	288 (36)	182 (35)	74 (46)	16 (30)	16 (31)	0.029

Values are mean ± SD or n (%).

ACEi/ARB = angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; ICD = implantable cardioverter defibrillator; LBBB = left bundle branch block; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association.

100 patients with RVP; interobserver variability was tested in the whole study population. Survival rates were assessed with Kaplan-Meier analysis, whereas differences in survival were compared between groups by a log-rank test. Univariable and multivariable regression analyses were performed to determine the parameters associated with volumetric response and long-term survival. The multivariable regression model included variables with univariate $p < 0.05$. Baseline clinical characteristics that were significantly different between patients with paced and intrinsic LBBB were forced into multivariable models regardless of univariate p value. All statistical tests were 2-tailed, and a value of $p < 0.05$ was considered significant. Statistical analysis was performed using commercially available software (PASW Statistics 18, version 18, SPSS, Inc., Chicago, Illinois).

RESULTS

Baseline patients' characteristics are shown in Table 1. Patients with RVP were older, more often male, had wider QRS width, and more atrial fibrillation than those with intrinsic LBBB ($p < 0.05$, for all). Patients with RVP also had smaller LV dimensions and volumes and were less often treated with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers ($p < 0.05$, for all). In patients with intrinsic LBBB, intraobserver agreement for visual assessment of ApRock and SF was 93% (k = 0.86; 95% confidence interval [CI]: 0.76 to 0.96) and 94% (k = 0.88; 95% CI: 0.79 to 0.97), respectively, whereas interobserver agreement was 88% (k = 0.72; 95% CI: 0.67 to 0.78) for ApRock and 86% (k = 0.68; 95% CI: 0.62 to 0.74) for SF. In patients with RVP, intraobserver agreement for visual assessment of ApRock and SF was 86% (k = 0.72; 95% CI: 0.58 to 0.86) and 89% (k = 0.78; 95% CI: 0.66 to 0.90), respectively, whereas interobserver agreement was 73% (k = 0.32; 95% CI: 0.13 to 0.51) for ApRock and 84% (k = 0.57: 95% CI: 0.41 to 0.72) for SF.

MECHANICAL DYSSYNCHRONY AND VOLUMETRIC RESPONSE TO CRT. One patient with a conventional pacemaker presented with intrinsic rhythm at baseline examination and was excluded from all analyses. Visual assessment of mechanical dyssynchrony was possible in 824 patients (105 patients with RVP and 719 patients with intrinsic LBBB), resulting in 90% feasibility in both groups (p = 0.868). Mechanical dyssynchrony was identified in 53 patients (51%) with RVP versus 554 patients (77%) with intrinsic LBBB ($p < 0.001$). The prevalence of visual SF, ApRock, their combination or absence is summarized in Table 2. Both SF and ApRock were found in 66% of

TABLE 2 Prevalence of Visual Septal Flash and Apical Rocking in Patients With Intrinsic Left Bundle Branch Block and Chronic Right Ventricular Pacing

	Intrinsic LBBB	RVP
No dyssynchrony	165 (23)	52 (49)
Septal flash only	43 (6)	28 (27)
Apical rocking only	36 (5)	1 (1)
Septal flash and apical rocking	475 (66)	24 (23)

Values are n (%).

RVP = right ventricular pacing; other abbreviation as in Table 1.

patients with intrinsic LBBB versus 23% of patients with RVP ($p < 0.001$). Video examples of SF and ApRock in patients with RVP and intrinsic LBBB are available in Online Videos 2, 3, 4, 5, 6, 7, 8, and 9.

Disagreement between measured and visually assessed ApRock was observed in 13% of patients (k = 0.75; 95% CI: 0.63 to 0.87) who had the amplitude of ATM below the cutoff for dyssynchrony but appeared visually dyssynchronous in all cases. In addition, in case of no discordance in visual assessment of ApRock between 2 observers, patients with visual ApRock had the mean ATM of 2.9 ± 1.3 mm versus 0.5 ± 0.4 mm in those without visual ApRock. In patients with discordance in ApRock assessment between 2 observers, the mean value of ATM was 0.9 ± 0.4 mm. In patients with intrinsic LBBB, there was a complete agreement between visual and M-mode assessment of SF. In patients with RVP, SF was present on M-mode but missed on visual assessment by both readers in 3 patients (15%). Examples of M-mode recordings of SF in patients with intrinsic LBBB and RVP and are shown in Online Figures 2 and 3, respectively.

The baseline echocardiographic study was available in all patients, but a reliable assessment of volumetric data was possible in 767 patients. The follow-up echo study was available in 707 patients, whereas a valid assessment of volumetric response was possible in 590 patients from which 361 (61%) responded to CRT. The median time from baseline to follow-up echo examination was 12 months (interquartile range: 9 to 18 months). From 454 patients with visual mechanical dyssynchrony, 338 (74%) responded to CRT: 23 patients (66%) with RVP and 315 patients (75%) with intrinsic LBBB. From 136 patients without mechanical dyssynchrony, 23 patients (17%) responded to CRT: 4 patients (17%) with RVP and 19 patients (17%) with intrinsic LBBB.

Although there were no significant differences in most baseline clinical characteristics between patients included and excluded from analysis of volumetric response, excluded patients more often had atrial fibrillation and were less frequently treated with beta-blockers and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers than those included ($p < 0.05$) (Online Table 1). However, there was no significant difference in long-term survival between excluded and included patients (log-rank $p = 0.169$) (Online Figure 4).

A significantly lower rate of responders was observed among patients with RVP versus intrinsic LBBB (47% vs. 63%, respectively; $p = 0.023$). The extent of LV reverse remodeling was also significantly lower in patients with RVP compared with intrinsic LBBB (27 ± 33% vs. 14 ± 28%, respectively; $p = 0.002$).

TABLE 3 Univariate and Multivariate Regression Analyses to Identify Parameters Associated With Volumetric Response to Cardiac Resynchronization Therapy

	Univariate		Multivariate	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Mechanical dyssynchrony	14.316 (8.722–23.496)	<0.001	11.204 (6.347–19.778)	<0.001
Right ventricular pacing	0.527 (0.306–0.907)	0.021	0.712 (0.330–1.533)	0.385
Female	2.326 (1.564–3.460)	<0.001	1.518 (0.897–2.569)	0.120
Age, yrs	1.005 (0.989–1.021)	0.561	1.014 (0.992–1.036)	0.230
NYHA functional class	0.689 (0.491–0.967)	0.031	0.720 (0.436–1.188)	0.198
QRS width, ms	1.002 (0.995–1.008)	0.634	0.998 (0.989–1.007)	0.723
Ischemic etiology	0.472 (0.338–0.659)	<0.001	0.650 (0.405–1.043)	0.074
Atrial fibrillation	0.774 (0.523–1.147)	0.202	0.992 (0.577–1.705)	0.976
ACEi/ARB	1.542 (0.275–1.247)	0.542	1.365 (0.190–9.804)	0.757
LVEF at baseline, %	0.973 (0.949–0.998)	0.034	0.965 (0.932–1.000)	0.049
LVEDD at baseline, mm	0.977 (0.961–0.993)	0.005	0.968 (0.945–0.991)	0.007

CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

In univariate logistic regression analysis, both visual dyssynchrony and the presence of RVP were associated with volumetric response. However, in the multivariate analysis, visual dyssynchrony remained independently associated with volumetric response, whereas the presence of RVP did not (Table 3).

COMPARISON OF LONG-TERM SURVIVAL. During a median follow-up of 48 months (interquartile range: 29 to 66 months), 232 (25%) of 914 patients died. There were 37 deaths (32%) in the RVP group and 195 deaths (25%) in the intrinsic LBBB group. In the univariate regression analysis, mechanical dyssynchrony, RVP, gender, age, NYHA functional class, etiology of heart failure, heart rhythm, and the use of beta-blockers were all associated with long-term survival after CRT (Table 4). However, multivariate Cox proportional hazards analysis identified

TABLE 4 Univariate and Multivariate Regression Analyses to Identify Parameters Associated With All-Cause Mortality After Cardiac Resynchronization Therapy

	Univariate		Multivariable	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Mechanical dyssynchrony	0.303 (0.230–0.398)	<0.001	0.274 (0.192–0.391)	<0.001
Right ventricular pacing	1.550 (1.090–2.207)	0.015	1.101 (0.658–1.842)	0.714
Female	0.470 (0.331–0.665)	<0.001	0.704 (0.441–1.126)	0.143
Age, yrs	1.039 (1.025–1.054)	<0.001	1.030 (1.012–1.049)	0.001
NYHA functional class	1.720 (1.323–2.235)	<0.001	1.563 (1.112–2.196)	0.010
QRS width, ms	1.000 (0.995–1.005)	0.958	0.999 (0.993–1.006)	0.887
Ischemic etiology	1.994 (1.539–2.584)	<0.001	1.423 (0.996–2.035)	0.053
Atrial fibrillation	1.433 (1.076–1.909)	0.014	1.303 (0.897–1.892)	0.165
Beta-blockers	0.570 (0.367–0.886)	0.013	0.640 (0.345–1.187)	0.156
ACEi/ARB	0.586 (0.275–1.247)	0.165	0.646 (0.232–1.799)	0.403
LVEF at baseline, %	0.990 (0.983–1.005)	0.136	0.963 (0.934–0.992)	0.013
LVEDD at baseline, mm	1.001 (0.988–1.015)	0.862	1.008 (0.989–1.023)	0.402

HR = hazard ratio; other abbreviations as in Tables 1 and 3.

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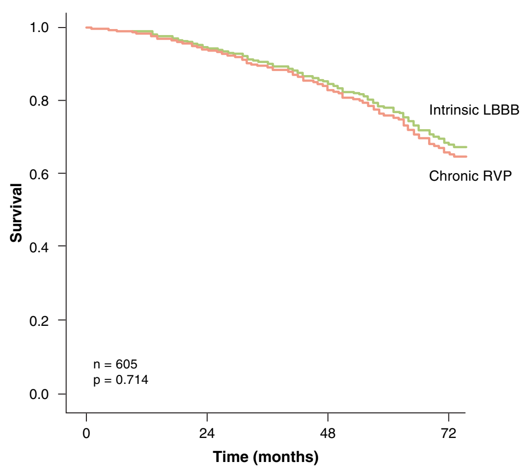
FIGURE 2 Long-Term Survival After Cardiac Resynchronization Therapy



Fully adjusted survival curves of patients with intrinsic left bundle branch block (LBBB) and chronic right ventricular pacing (RVP), based on the Cox model shown in Table 4. Patients with RVP had a similar long-term survival as patients with intrinsic LBBB.

visual dyssynchrony, age, NYHA functional class, and baseline LVEF as parameters independently associated with all-cause mortality. There was no significant association between RVP and long-term survival (Figure 2).

Kaplan-Meier analysis revealed that patients with mechanical dyssynchrony and either intrinsic LBBB or RVP had a more favorable overall survival than those without dyssynchrony (Figure 3). No significant differences in long-term survival were observed in patients with mechanical dyssynchrony with respect to the nature of LBBB (log rank $p = 0.992$). Also, there was no such difference in patients without mechanical dyssynchrony (log rank $p = 0.279$).

DISCUSSION

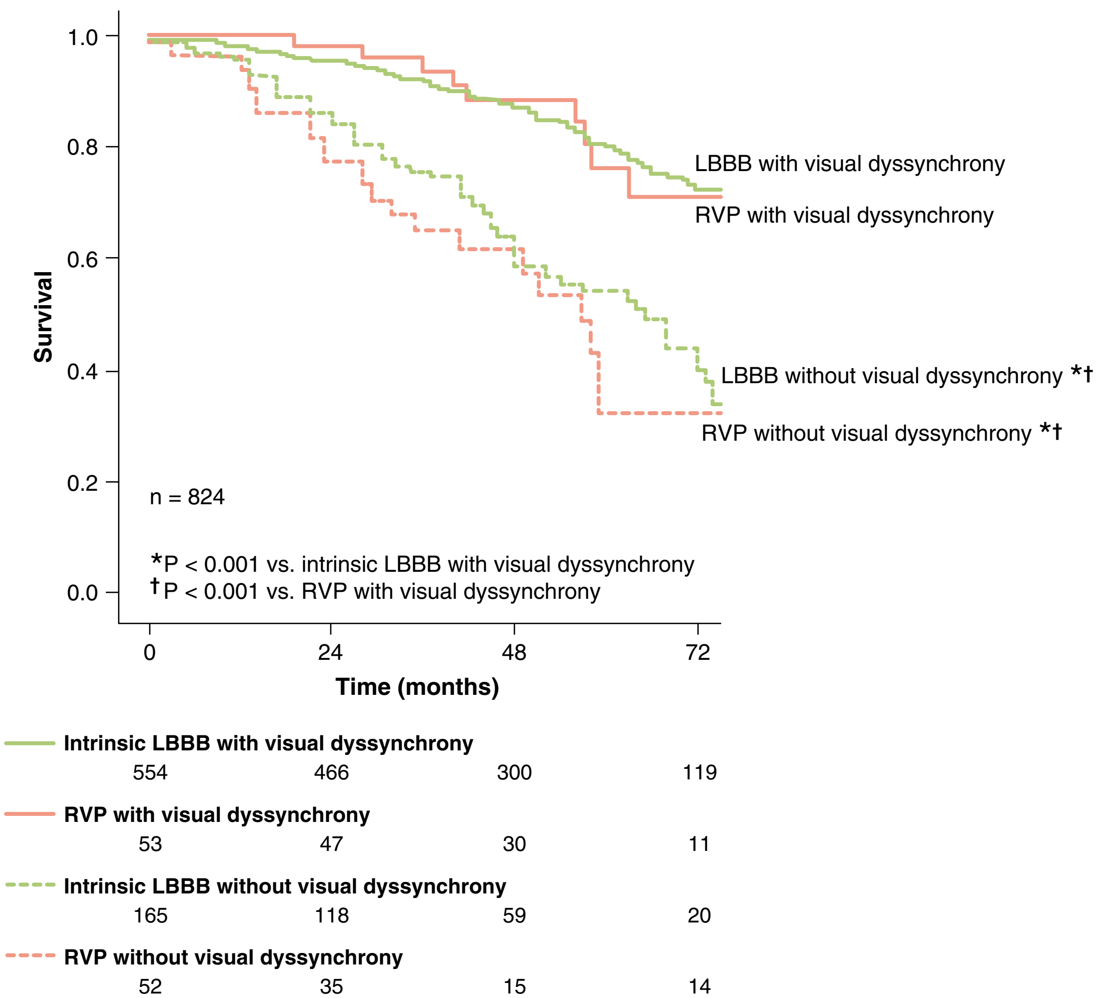
In this study, we demonstrate that patients with RVP derived similar benefits from upgrading to CRT as patients with intrinsic LBBB who underwent de novo implantation. Similar to patients with intrinsic LBBB, the likelihood of volumetric response and improved long-term survival in patients with RVP was mainly determined by the presence of mechanical dyssynchrony.

The prevalence of visual mechanical dyssynchrony in patients with intrinsic LBBB was comparable with previous studies using similar approaches, whereas in the chronically RVP group, it was lower than previously reported (12,16,17). One reason could be that Tayal et al. (12) excluded patients with QRS width <150 ms, whereas patients with conventional LBBB morphology were included in the current study regardless of QRS duration. Furthermore, contraction patterns in intrinsic and paced LBBB are not completely similar. In a recent study by Tayal et al. (12), based on the same pathophysiological approach (18) as the current study but using the longitudinal strain for assessing mechanical dyssynchrony, it has been shown that contraction patterns in patients with RVP and intrinsic LBBB are very similar but not identical. In some patients with RVP, the apical septal segment contracts earlier than mid and basal septal segments, whereas the opposite septal segmental activation sequence was predominantly observed in patients with intrinsic LBBB. Possibly because of these differences in contraction patterns between RVP and intrinsic LBBB, there was a significant difference in the occurrence of visual SF and ApRock between patient groups; both SF and ApRock were observed in 66% of patients with intrinsic LBBB versus 23% of patients with RVP. Also, there was significantly higher intraobserver and interobserver variability of visually assessed SF and ApRock in patients with RVP compared with intrinsic LBBB. Therefore, the temporal resolution of the human eye may not be sufficient to detect these subtle changes and our visual approach of mechanical dyssynchrony assessment may therefore be complemented by a strain pattern analysis in patients with RVP. However, this hypothesis warrants further research, whereas our preliminary comparison of visual and quantitative assessment of SF and ApRock performed in a subset of patients suggests that quantitative methods may both increase (SF) and decrease (ApRock) the prevalence of dyssynchrony.

The extent of LV reverse remodeling and the volumetric response rate were both significantly lower in patients with RVP than in patients with intrinsic LBBB. However, it should be noted that several factors known to negatively impact the likelihood of response to CRT (higher age at implantation, male gender, atrial fibrillation, less treatment with heart failure medication) were more prevalent in patients with RVP. When adjusted for these and other confounding variables, the presence of mechanical dyssynchrony, but not chronic RVP, was independently associated with volumetric response to CRT. After similar adjustment, mechanical dyssynchrony, advanced age, higher NYHA functional class and baseline LVEF were identified as the only remaining parameters associated with long-term survival.

Previous trials also reported that patients with RVP upgraded to CRT derived similar, if not higher, benefits

FIGURE 3 **Survival in Cardiac Resynchronization Therapy Patients With and Without Previous Right Ventricular Pacing**



Kaplan-Meier curves depicting long-term survival after cardiac resynchronization therapy in patients with intrinsic LBBB and chronic RVP with respect to the presence of visual mechanical dyssynchrony before cardiac resynchronization therapy implantation/upgrade. Patients with visual mechanical dyssynchrony had a more favorable overall survival than patients without visual dyssynchrony, regardless of the nature of LBBB. Abbreviations as in **Figure 2**.

as other wide QRS heart failure patients (12,14,19). Our data support these observations, additionally underlining the effect of mechanical dyssynchrony on the outcome in these 2 subgroups of patients.

Similar to the present study, a large European survey found no significant difference in the outcome of RVP patients upgraded to CRT and de novo implantations (19). Further, 2 recent trials reported a more favorable outcome of RVP patients compared with those with intrinsic LBBB (12,14). In both trials, as in the present study, RVP patients had smaller end-systolic volumes, were older, and had more atrial fibrillation before CRT. However, in the current study, the primary outcome measure was all-cause mortality, whereas the primary endpoint in the other 2 studies also included heart failure hospitalizations (19), or LV assist device implantation and heart transplantation (12), which possibly contributed to the observed differences in long-term outcome.

However, our findings concur with those of Tayal et al. (12) that correction of mechanical consequences of RVP (i.e., mechanical dyssynchrony) is a rationale for beneficial effects of CRT in the RVP patients (12). Therefore, it seems that a visual recognition of a typical LBBB contraction pattern by ApRock, SF, or longitudinal strain analysis may be useful for identifying potential responders among patients with conventional pacemakers and heart failure.

CLINICAL IMPLICATIONS. Even though the upgrades from conventional pacemakers to biventricular pacing systems constitute more than one-quarter of all CRT implantations (14), randomized clinical trials investigating this particular subgroup of patients are lacking. The current guidelines, therefore, do not specify when RVP patients should be upgraded to CRT from antibradycardia pacing or implantable defibrillator. The substudies of 2 previous randomized trials suggested a causal relationship between high RVP (either from conventional pacemaker or implantable cardioverter defibrillator) and a significant increase in the risk of long-term mortality and attenuated device efficacy in case of implantable cardioverter defibrillator (20,21). It has been further shown that the deleterious effects of RVP on LV function may be mediated by the induction of mechanical dyssynchrony, which acutely occurs in approximately one-third of patients and increases over time, eventually leading to a significant decline in LVEF even among patients with normal pre-pacing LVEF (3,22,23). Showing that long-term outcomes were determined by the presence of mechanical dyssynchrony and not by the nature of LBBB, the present study corroborates the unfavorable impact of mechanical dyssynchrony in patients with chronic RVP and further emphasizes the role of dyssynchrony assessment in this patient population. However, disappointing results of the PROSPECT study (24) raised serious doubts regarding the reproducibility and accuracy of echocardiographic dyssynchrony assessment based on time-to-peak velocity parameters. As a result, the assessment of mechanical dyssynchrony is not a guideline-proposed criterion for CRT patient selection. Although our visual approach for assessing mechanical dyssynchrony and several other quantitative approaches based on the same pathophysiological rationale go beyond the limitations of the PROSPECT study (24), the revision of current CRT patient selection criteria should only be recommended when superior performance of novel dyssynchrony parameters has been confirmed in by a well-designed, randomized trial.

STUDY LIMITATIONS. Because of a retrospective, observational nature of the current study, there was no control group, and the outcomes of patients with either RVP or intrinsic LBBB without CRT upgrade or implantation remain unknown. Furthermore, mostly because of suboptimal image quality, volumetric response to CRT was assessed only in a part of the study population with a few significant differences in baseline clinical characteristic between patient included in and excluded from volumetric analysis. Therefore, our inferences on volumetric response to CRT should be interpreted with caution and ideally confirmed in a large-scale prospective study. Importantly, in contrast to perhaps all other dyssynchrony parameters, visual assessment of SF and ApRock is not directly dependent on image quality and is feasible in otherwise unanalyzable cases (Online Video 10). Finally, other common outcome measures, such as heart failure hospitalization, LV assist device implantation, and heart transplantation, were not included in the present study also because of its retrospective, multicenter design. Different thresholds for heart failure hospitalization, along with nonuniform availability and patient selection criteria for rescue therapies among the participating centers were the main reasons for not including these clinical events as primary outcomes in the current study.

CONCLUSIONS

Mechanical dyssynchrony, characterized by visual ApRock and SF, was associated with volumetric response and a more favorable overall survival following CRT in both patients with RVP and intrinsic LBBB. Patients with chronic RVP upgraded to CRT have similar long-term survival as do patients with intrinsic LBBB.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Chronic RVP induces asynchronous LV contraction that is potentially reversible by upgrading to CRT but the current guidelines do not specify when RVP patients should be upgraded to CRT. This study shows that the likelihood of volumetric response and improved long-term survival in patients with RVP is mainly determined by the presence of mechanical dyssynchrony.

TRANSLATIONAL OUTLOOK: This study demonstrates that patients with RVP derive similar benefits from upgrading to CRT as patients with intrinsic LBBB who undergo de novo implantation.

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KEY WORDS apical rocking, cardiac resynchronization therapy, mechanical dyssynchrony, right ventricular pacing, septal flash

APPENDIX For a supplemental table, figures, and videos and their legends, please see the online version of this article.