

## CLINICAL RESEARCH

## Resolution of Left Bundle Branch Block–Induced Cardiomyopathy by Cardiac Resynchronization Therapy

Caroline Vaillant, MD,\* Raphaël P. Martins, MD,\*† Erwan Donal, MD, PhD,\*†  
 Christophe Leclercq, MD, PhD,\*† Christophe Thébault, MD,\* Nathalie Behar, MD,\*  
 Philippe Mabo, MD,\*† Claude Daubert, MD, FACC\*†

Rennes, France

- Objectives** The study sought to describe a specific syndrome characterized by isolated left bundle branch block (LBBB) and a history of progressive left ventricular (LV) dysfunction, successfully treated by cardiac resynchronization therapy (CRT).
- Background** Isolated LBBB in animals causes cardiac remodeling due to mechanical dyssynchrony, reversible by biventricular stimulation. However, the existence of LBBB-induced cardiomyopathy in humans remains uncertain.
- Methods** Between 2007 and 2010, 375 candidates for CRT were screened and retrospectively included in this study if they met all criteria of a pre-defined syndrome, including: 1) history of typical LBBB for >5 years; 2) LV ejection fraction (EF) >50%; 3) decrease in LVEF to <40% and development of heart failure (HF) to NYHA functional class II to IV over several years; 4) major mechanical dyssynchrony; 5) no known etiology of cardiomyopathy; and 6) super-response to CRT with LVEF >45% and decrease in NYHA functional class at 1 year.
- Results** The syndrome was identified in 6 patients (1.6%), 50.5 years of age on average at the time of LBBB diagnosis. HF developed over a mean of 11.6 years. At the time of referral, Doppler echocardiograms showed major mechanical dyssynchrony at left atrioventricular, interventricular, and left intraventricular levels. During CRT, NYHA functional class decreased, LV dimensions normalized and mechanical dyssynchrony was nearly resolved in all patients, and mean LVEF increased from  $31 \pm 12\%$  to  $56 \pm 8\%$  ( $p = 0.027$ ).
- Conclusion** These observations support the existence of a specific LBBB-induced cardiomyopathy resolved by CRT. Its prevalence, time course, and risk factors need to be prospectively studied. (J Am Coll Cardiol 2013;xx:xxx) © 2013 by the American College of Cardiology Foundation

The prevalence of left bundle branch block (LBBB) in the general population is approximately 1% (1). Occasionally isolated (2), LBBB is more often associated with structural heart disease. It is an independent predictor of cardiovascular mortality and heart failure (HF) events, suggesting that HF might develop as a result of LBBB (3,4). There is firm evidence from clinical and experimental studies (5,6) that LBBB induces abnormal left ventricular (LV) contraction and impairs global LV function, which might cause progressive LV remodeling and HF. In addition, cardiac resynchronization therapy (CRT) is a major means of reverse remodeling and protection against HF events in patients presenting with typical LBBB (7,8), one of the

most powerful predictors of a super-response to CRT (9). Though the clinical evidence remains weak, these observations support the existence of a LBBB-induced cardiomyopathy (10). In absence of a prospective registry to assess the natural history of isolated LBBB, we hypothesized that the most persuasive evidence would be provided by well-documented clinical cases, illustrative of an original syndrome including a history of LBBB and LV dysfunction, reversed by CRT.

### Methods

**Patient population.** Patients scheduled to undergo CRT between 2007 and 2010 were included in this single-center observational study if they presented with all characteristics of a syndrome, including: 1) normal sinus rhythm and >5-year history of typical LBBB (11); 2) LV ejection fraction (EF) >50% at the time of diagnosis of LBBB; 3) progressive decrease in LVEF to  $\leq 40\%$ ; LV end-diastolic diameter  $\geq 55$  mm and development of New York Heart Association (NYHA) functional class II to IV; 4) presence

From the \*Department of Cardiology and Vascular Diseases, University Hospital, Rennes, France; and †INSERM, CIC-IT 804, Rennes, France. All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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**Abbreviations  
and Acronyms****CRT** = cardiac  
resynchronization therapy**EF** = ejection fraction**HF** = heart failure**LBBB** = left bundle branch  
block**LV** = left ventricular**NYHA** = New York Heart  
Association

of major left heart mechanical dyssynchrony; 5) no other identifiable cause of cardiomyopathy (12); and 6) indication for (13), and super-response to, CRT, defined as a LVEF  $\geq 45\%$  and decrease in NYHA functional class within  $\geq 12$  months.

**Data collection.** The onset of LBBB and history of LV function were retrospectively ascertained by review of medical records.

**ELECTROCARDIOGRAM.** The 12-lead surface electrocardiograms were recorded at 25 mm/s during spontaneous rhythm, before implantation and after 12 months of biventricular pacing, and analyzed by 2 independent observers. The QRS duration was measured as previously reported (8).

**ECHOCARDIOGRAPHY AND CARDIAC DYSSYNCHRONY.** Transthoracic echocardiograms were recorded before (baseline) and after  $\geq 12$  months of CRT, using a ViVid Seven system (GE Healthcare, Milwaukee, Wisconsin). The LV dimensions were recorded using 2-dimensional echocardiogram-directed M-mode, and analyzed by 2 independent observers. LVEF was estimated by LV biplane Simpson's method. LV contractile function was analyzed by speckle tracking, using global longitudinal strain (14).

Left atrioventricular dyssynchrony was defined as a LV filling time/R-R interval ratio  $< 40\%$ , and interventricular dyssynchrony as a  $> 45$  ms interval between pre-aortic and pre-pulmonary ejection times (15). Intra-LV dyssynchrony was first ascertained by M-mode echocardiography, in search of "septal flash," defined as a systolic stretch occurring after initial shortening of the early activated septum (16). Using the B-mode speckle tracking software (17), dyssynchrony was ascertained as the delay between the earliest and latest peaks of longitudinal strain recorded in the mid-segment of the lateral and septal walls in the apical 4-chamber view, and radial strain recorded in the antero-septal and posterior walls in the parasternal short axis view. Intra-LV dyssynchrony was defined as a  $\geq 130$  ms delay, a peak strain occurring after the aortic valve closure, or both.

**Implantation and programming of the CRT systems.** The CRT devices were implanted transvenously. The right ventricular lead was placed preferentially in the mid-septum. The LV lead was placed in a lateral or posterolateral tributary of the coronary sinus. Systematic efforts were made to obtain the narrowest biventricular paced QRS during the implant procedure and initial programming.

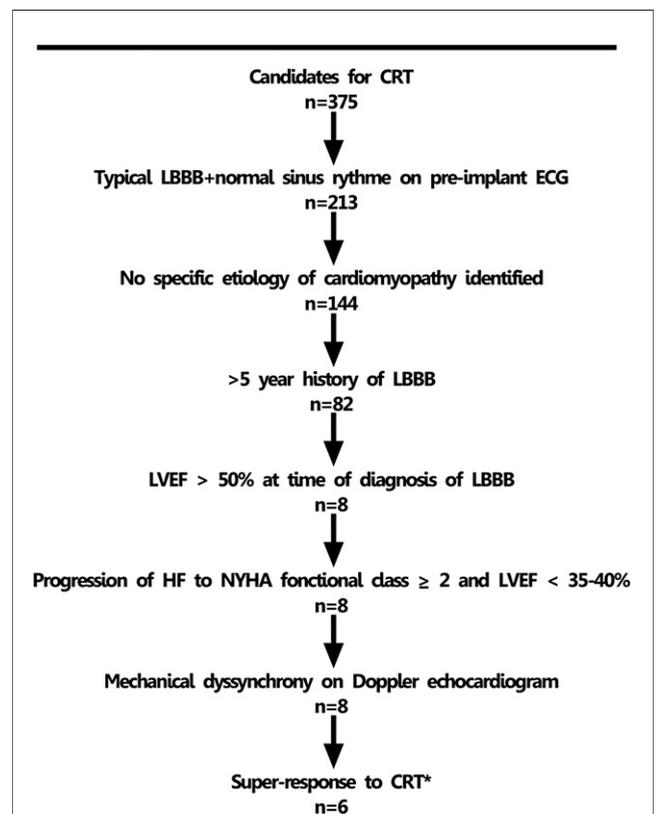
**Statistical analyses.** Individual data are reported because of the small sample size. Paired measurements before and after 12 months of CRT were compared, using nonparametric Wilcoxon test for quantitative variables and McNemar test

for qualitative variables. A p value  $< 0.05$  was considered significant.

**Results**

**Initial observations.** Among 375 recipients of CRT systems during the study period, 6 patients (1.6 %) ranging in age between 36 and 60 years had the pre-defined components of the syndrome including super-responses to CRT (Fig. 1). The main characteristics of the 3 women and 3 men at the time of LBBB diagnosis are shown in Table 1. The indication for the qualifying electrocardiogram was chest pain in 2, and undetermined in 4 asymptomatic patients. LBBB was intermittent and rate-dependent in 2 patients, before becoming permanent within 1 and 3 years, respectively. The mean intrinsic QRS duration was  $137 \pm 21$  ms. The baseline LVEF was  $\geq 50\%$  in all patients.

Symptoms consistent with HF developed within a mean of 11.6 years (range 5 to 21 years) after LBBB diagnosis. All patients reported chest pain on exertion. Combined treatment with an angiotensin-converting enzyme inhibitor and beta-adrenergic blocker was initiated in 5 patients, and a beta-adrenergic blocker alone in 1 patient.



\* LVEF  $\geq 45\%$  and  $\geq 1$  point decrease in NYHA class

**Figure 1** Patient Screening Process

Flow of patients from the screening to the selection of the final patient. CRT = cardiac resynchronization therapy; HF = heart failure; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

**Table 1** Main Characteristics of Individual Patients

Patient No.	Sex/Age	At Time of LBBB Diagnosis				Follow-Up			
		Chest Pain as First Symptom	Rate-Related LBBB	Intrinsic QRS Duration (ms)	QRS Axis	Time Between Diagnosis of LBBB and Onset of Heart Failure Symptoms (yrs)	Time Between Diagnosis of LBBB and CRT System Implant (yrs)	Intrinsic QRS Duration (ms)*	Implanted System
1	M/36	–	+	160	–65	7	19	175	CRT-D
2	M/41	+	+	150	61	21	22	150	CRT-D
3	F/51	–	–	120†	15	17	18	155	CRT-P
4	F/51	–	–	140	–30	9	9	160	CRT-P
5	M/56	–	–	100†	15	11	11	160	CRT-D
6	F/60	+	–	155	–14	5	5	155	CRT-P

\*Before cardiac resynchronization therapy (CRT) implantation. †Patients with intermittent left bundle branch block (LBBB).  
D = defibrillator; P = pacemaker.

**Time to referral for CRT.** The persistence, despite optimal medical therapy, of symptoms consistent with NYHA functional class II in 2, and class III in 4 patients, prompted the decision to proceed with CRT. The mean delay between the first manifestations of HF and the CRT implant ranged between 6 months and 12 years. At the time of referral, the intrinsic QRS duration was >150 ms in all patients (Fig. 2). Coronary angiography was normal in 5 patients, while the distal right coronary artery was occluded with collateral circulation from the left anterior descending artery in 1 patient. Detailed, pre-implant echocardiographic studies showed evidence of mechanical dyssynchrony at the left atrioventricular (LV filling time/R-R ratio: 20% to 36%), interventricular (mechanical delay: 57 to 111 ms), and intra-LV (longitudinal and radial strain) levels (Table 2). The characteristics of dyssynchrony were similar among patients.

**Post-CRT evolution.** An improvement in functional status was observed within <3 months in 5, and within 6 months in 1 patient. At 1 year, 4 patients were in NYHA functional class I, while in 2 patients it had decreased from III to II. Individual QRS and echocardiographic measurements are shown before and after 12 months of CRT in

Table 2 and Figure 3. Mean QRS duration decreased by 29 ms with CRT ( $p = 0.027$ ). Mean LVEF increased from  $31 \pm 12\%$  before CRT to  $56 \pm 8\%$  after 12 months of CRT ( $p = 0.027$ ), while the mean time to reach  $\geq 45\%$  was 7 months (range 3 to 12 months). Mean LV end-diastolic diameter decreased from  $64 \pm 14$  mm to  $52 \pm 5$  mm ( $p = 0.027$ ) (Fig. 3). At 12 months, the echocardiographic signs of atrioventricular mechanical dyssynchrony had disappeared in all patients, while minor signs of interventricular dyssynchrony persisted in 1 patient. The septal flash, present before CRT in 4 patients, resolved in all 4. Consistent with the similar dyssynchrony pattern observed before CRT, the response to CRT was similar among patients (Fig. 4), with a more homogeneous deformation of the LV segments, reaching its peak at the time of aortic valve closure, except in 1 patient, in whom the peak of deformation occurred 10 ms later.

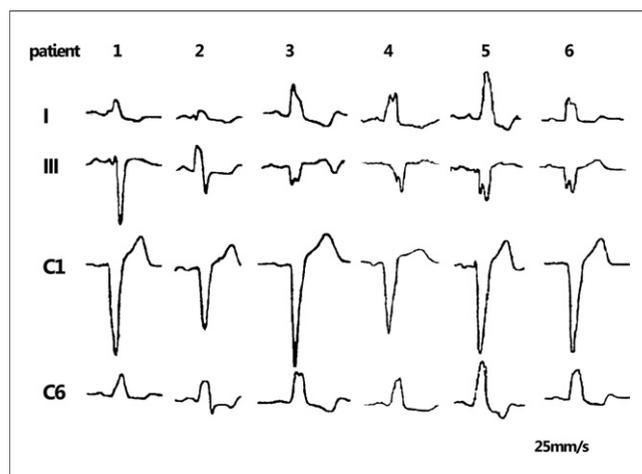
Over a mean follow-up of 36 months (range 16 to 56 months), no patient died or suffered a major adverse clinical event, including hospitalization for management of HF.

## Discussion

The patients included in this study, who presented with a long history of apparently isolated LBBB and progressive LV dysfunction, possessed the characteristics of an original syndrome suspected from previous animal experiments, epidemiological studies, and clinical observations, though never demonstrated in individual patients. These original observations strongly support the concept of LBBB-induced cardiomyopathy treatable with CRT.

Isolated LBBB causes abnormalities of LV dysfunction, manifest by a shortening of the filling time, a decreased septal contribution to LV ejection, and a globally depressed EF, compared with normal matched controls (5). High-amplitude oscillations of the interventricular septum were also described, similar to the “septal flash,” a sign of mechanical dyssynchrony (present in 4 of our 6 patients) and a putative predictor of echocardiographic response to CRT (16).

The clinical value of several techniques and measures proposed to detect and quantify LBBB-induced mechanical

**Figure 2** QRS Morphology on Surface Electrocardiography

Surface electrocardiography in leads I, III, V1, and V6 during intrinsic conduction showing typical pattern of left bundle branch block.

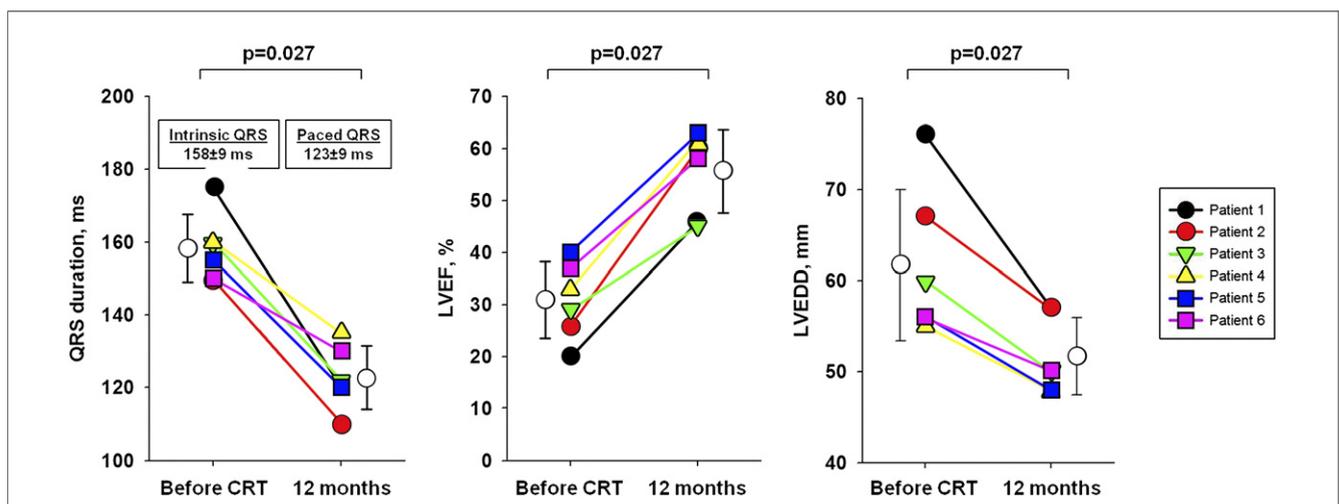
**Table 2** Individual Electrocardiographic and Echocardiographic Measurements Before and After 12 Months of Cardiac Resynchronization

	Patient Number						Mean ± SD	p Value
	1	2	3	4	5	6		
<b>QRS duration, ms</b>								
Before	175	150	155	160	160	155	159 ± 9	0.027
After	120	120	110	120	135	130	123 ± 9	
<b>Left ventricular</b>								
<b>Ejection fraction, %</b>								
Before	20	26	29	33	40	37	31 ± 7	0.027
After	46	60	45	62	63	58	56 ± 8	
<b>End-diastolic diameter, mm</b>								
Before	76	67	60	55	56	56	62 ± 14	0.027
After	57	57	50	48	48	50	52 ± 12	
<b>End-diastolic volume, ml</b>								
Before	313	231	211	100	NA	100	191 ± 91	ns
After	152	164	154	102	78	107	126 ± 35	
<b>Filling time/R-R interval, %</b>								
Before	25	53	20	25	NA	36	32 ± 13	0.043
After	47	57	55	65	47	43	52 ± 8	
<b>Pre-ejection interval, ms</b>								
Before	69	111	57	91	NA	110	88 ± 24	0.043
After	39	30	47	7	18	46	31 ± 16	
<b>Anteroseptal-post time to peak strain delay, ms</b>								
Before	363	150	218	311	NA	177	243 ± 90	0.043
After	17	43	22	26	25	29	27 ± 9	
<b>Septolateral time to peak strain delay, ms</b>								
Before	394	228	347	301	NA	246	303 ± 69	0.043
After	22	22	16	26	45	15	24 ± 11	
<b>Longitudinal global strain, %</b>								
Before	-7	-6	-6	-8	NA	-12	-8 ± 2	0.043
After	-11	-12	-12	-18	-13	-15	-14 ± 3	

NA = not available.

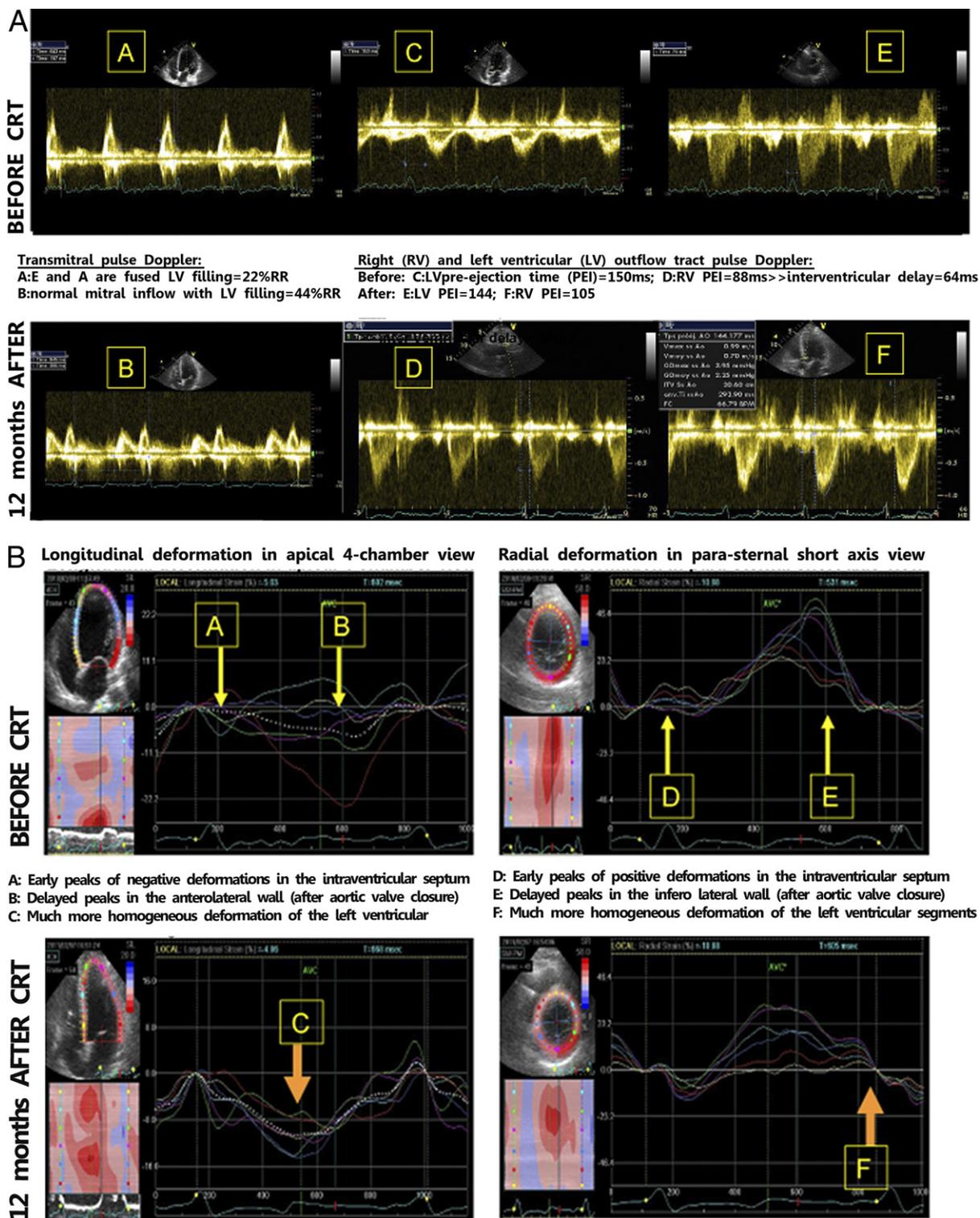
dyssynchrony remains controversial, as they have failed to predict the response to, and improve the patient selection for CRT (18). Our assessment of mechanical dyssynchrony

was for a different objective. Mechanical dyssynchrony, the critical link between conduction abnormalities and LV dysfunction, is at the root of LBBB-induced cardiomyopa-



**Figure 3** Individual Changes After 12 Months of CRT

Changes in QRS duration, LVEF, and LV end-diastolic diameter between before and after 12 months of CRT. Abbreviations as in Figure 1.



**Figure 4** Mechanical Dyssynchrony Before and After 12 Months of CRT

(A) Patient no. 1: dyssynchrony assessed by Doppler echocardiography. Atrioventricular and interventricular dyssynchrony alleviated by CRT. (B) Patient no. 1: dyssynchrony assessed by 2-dimensional strain speckle tracking (radial and longitudinal deformation). Intra-LV dyssynchrony alleviated by CRT. Abbreviations as in Figure 1.

thy. We used several techniques to assess dyssynchrony at multiple levels, combining simple and reproducible Doppler-echocardiographic measurements of LV filling time and intraventricular mechanical delay (15), and 2-dimensional strain for the intra-LV analysis (17). This revealed that mechanical dyssynchrony was present at all levels in all patients, and the pattern of dyssynchrony and its alleviation by CRT was similar among patients.

In animal experiments, a link was found between LBBB, mechanical dyssynchrony and LV dysfunction, whereby isolated LBBB induces functional septal hypoperfusion and progressive ventricular remodeling (6). A mean 23% decrease in LVEF and 25% increase in LV end-diastolic volume, associated with a regional redistribution of circumferential shortening and myocardial blood flow was observed at 8 weeks, in a canine model of isolated LBBB. In absence of long-term, serial echocardiographic studies in patients with isolated LBBB, whether similar changes occur in humans remains unclear. In case control studies, LV dilatation and decrease in LVEF were greater in patients presenting with chronic LBBB than in controls (19). However, whether this prominent remodeling is the consequence of LBBB, or whether LBBB is a marker of a more progressive disease, remains unclear.

In the animal model of isolated LBBB, 8 weeks of biventricular stimulation largely reversed the functional and structural LV abnormalities (20), an observation concordant with observations made in controlled trials, where the decreases in echocardiographic LV volumes and increase in LVEF were significantly greater in CRT recipients with than without LBBB (8,9). While it strengthens the hypothesis that LBBB might be a “reversible cause of nonischemic cardiomyopathy with severe HF” (10), it does not prove it.

Our patients’ histories of LBBB and LV dysfunction strongly support the concept of LBBB-induced cardiomyopathy. As observed in animals (6), persistent mechanical ventricular dyssynchrony caused by isolated LBBB might induce progressive LV dysfunction and chronic HF in humans. Complete or nearly complete recovery of cardiac mechanical function by CRT is further support of the concept, as the treatment of dyssynchrony alone cured the cardiomyopathy. This might explain the various responses to CRT among the different types of dilated cardiomyopathy as well as the profile of certain “super-responders.”

**Study limitations.** The aim of this retrospective analysis was to describe a putative LBBB-induced cardiomyopathy, perhaps curable by CRT. While our methodology did not allow a precise measurement of the prevalence of the syndrome, we believe that the 1.6% observed in our study is an underestimation due to the retrospective data collection and missing data. Indeed, in an undetermined proportion of initially asymptomatic patients, LBBB may be a silent cause of “primary” dilated cardiomyopathy and HF particularly responsive to CRT. The time needed for the syndrome to develop and the factors promoting its development need to be examined prospectively in patients presenting with iso-

lated LBBB, though the feasibility of such study is uncertain. One might also hypothesize that, in an undetermined proportion of patients, LBBB was the first manifestation of a cardiomyopathy of unknown etiology, which slowly evolved toward HF. This hypothesis finds support in the failure of 2 of the 8 patients to “super-respond” to CRT. Furthermore, because of the retrospective design of our study, detailed evaluations of the patients with LBBB and a “preserved” LV function were not available. Finally, the proportion of patients with isolated LBBB who do not develop HF and, therefore, do not become candidates for CRT is unknown.

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**Reprint requests and correspondence:** Dr. Jean-Claude Daubert, Department of Cardiology and Vascular Diseases, Cardio-thoracic Center/CHU, 2, rue Henri Le Guilloux, CEDEX 35003, Rennes, France. E-mail: jean-claude.daubert@chu-rennes.fr.

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**Key Words:** cardiac dyssynchrony ■ cardiac resynchronization ■ cardiomyopathy ■ left bundle branch block ■ systolic dysfunction.