JACC: CARDIOVASCULAR IMAGING VOL. 14, NO. 11, 2021

ORIGINAL RESEARCH

Lateral Wall Dysfunction Signals Onset of Progressive Heart Failure in Left Bundle Branch Block

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ABSTRACT

OBJECTIVES This study sought to investigate if contractile asymmetry between septum and left ventricular (LV) lateral wall drives heart failure development in patients with left bundle branch block (LBBB) and whether the presence of lateral wall dysfunction affects potential for recovery of LV function with cardiac resynchronization therapy (CRT).

BACKGROUND LBBB may induce or aggravate heart failure. Understanding the underlying mechanisms is important to optimize timing of CRT.

METHODS In 76 nonischemic patients with LBBB and 11 controls, we measured strain using speckle-tracking echocardiography and regional work using pressure-strain analysis. Patients with LBBB were stratified according to LV ejection fraction (EF) ≥50% ($EF_{preserved}$), 36% to 49% (EF_{mid}), and ≤35% (EF_{low}). Sixty-four patients underwent CRT and were re-examined after 6 months.

RESULTS Septal work was successively reduced from controls, through $EF_{preserved}$, EF_{mid}, and EF_{low} (all $p < 0.005$), and showed a strong correlation to left ventricular ejection fraction (LVEF; $r = 0.84$; $p < 0.005$). In contrast, LV lateral wall work was numerically increased in $EF_{preserved}$ and EF_{mid} versus controls, and did not significantly correlate with LVEF in these groups. In EF_{low}, however, LV lateral wall work was substantially reduced ($p < 0.005$). There was a moderate overall correlation between LV lateral wall work and LVEF ($r = 0.58$; $p < 0.005$). In CRT recipients, LVEF was normalized (≥50%) in 54% of patients with preserved LV lateral wall work, but only in 13% of patients with reduced LV lateral wall work ($p < 0.005$).

CONCLUSIONS In early stages, LBBB-induced heart failure is associated with impaired septal function but preserved lateral wall function. The advent of LV lateral wall dysfunction may be an optimal time-point for CRT.
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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received January 21, 2021; revised manuscript received April 13, 2021, accepted April 19, 2021.

ISSN 1936-878X https://doi.org/10.1016/j.jcmg.2021.04.017

JACC: CARDIOVASCULAR IMAGING, VOL. 14, NO. 11, 2021
NOVEMBER 2021:2059–2069

ABBREVIATIONS AND ACRONYMS

CRT = cardiac resynchronization therapy

ECG = electrocardiogram

EF = ejection fraction

$EF_{preserved}$ = left bundle branch block patients with ejection fraction ≥50%

EF_{mid} = left bundle branch block patients with ejection fraction 36%-49%

EF_{low} = left bundle branch block patients with ejection fraction ≤35%

LBBB = left bundle branch block

LV = left ventricular

LVEF = left ventricular ejection fraction

LVP = left ventricular pressure

Left bundle branch block (LBBB) occurs in about 25% of patients with congestive heart failure and worsens the prognosis (1). In patients with pre-existing heart failure, LBBB may develop and lead to more rapid progression of the disease. Growing evidence suggest that LBBB itself may cause heart failure in otherwise healthy hearts (2–5), and that such patients respond well to cardiac resynchronization therapy (CRT) (6). However, less is known about determinants of left ventricular (LV) function in the individual patient with LBBB.

The contractile disturbance in LBBB includes impairment of septal function and compensatory hyperfunction of the late-activated LV lateral wall. The resulting marked asymmetry in workload between the 2 opposing walls acts as a stimulus for adverse remodeling (7,8). Such contractile disturbance is seen both in healthy animal hearts immediately after induction of LBBB and in CRT candidates with advanced heart failure (9–14). We have previously shown that septal-to-lateral work asymmetry identifies CRT responders (15) and that homogenization of workload is an important mechanism for CRT response (16). Therefore, asymmetry in regional function is crucial for LV function in LBBB.

In the present study, we hypothesized that LV function in patients with LBBB is determined by the degree of septal dysfunction and the ability of the LV lateral wall to compensate. Therefore, in patients where reduction in septal function is compensated by LV lateral wall hyperfunction, we expect preserved global LV function, whereas in patients with more severe septal dysfunction and inadequate LV lateral wall compensation, we expect reduced global LV function. By studying patients with LBBB with different levels of global LV function, we sought to outline a potential pathophysiological mechanism of heart failure in patients with LBBB. Furthermore, we studied a number of patients after CRT to determine whether LV lateral wall dysfunction affects the potential for recovery of LV function with CRT.

We included nonischemic patients without any other known driver for cardiac disease than LBBB, including patients with preserved and various degrees of reduced LV ejection fraction (EF). To incorporate the effects of afterload and differences in timing of segmental contraction, we used myocardial work by echocardiography to quantify regional LV function. A healthy control group without LBBB was included for comparison.

METHODS

STUDY POPULATION. We included all patients from 2 previous studies (15,17) fulfilling the following criteria: 1) sinus rhythm; 2) LBBB according to the Strauss electrocardiogram (ECG) criteria (18); and 3) no ischemic heart disease. In total, we included 76 patients, with average age 66 ± 10 years, from the cardiology departments at 3 university hospitals (Oslo University Hospital, Oslo, Norway; University Hospitals Leuven, Leuven, Belgium; and Rennes University Hospital, Rennes, France), and an outpatient cardiology practice (Ostlandske Hjertesenter, Moss, Norway). Furthermore, for comparison, we included 11 healthy controls without LBBB and of similar age (60 ± 10 years) from a previous study (17). They were recruited by voluntary enrollment in the community (Oslo, Norway). In 62 of the patients, myocardial scar was excluded using late gadolinium enhancement cardiac magnetic resonance. In the remaining 14 patients, ischemic cause of cardiac disease was excluded based on medical history and coronary angiogram. The inclusion criteria were set to minimize presence of other common causes of heart failure such as coronary artery disease, severe valve disease, and myocardial scar. Patients with heart failure were medically treated according to guidelines (**Table 1**).

Patients were stratified into 3 groups based on LV EF: EF ≥50% ($EF_{preserved}$) (n = 11), EF 36% to 49% (EF_{mid}) (n = 21), and EF ≤35% (EF_{low}) (n = 44). Medical history, clinical examination, ECG, and echocardiography were obtained in all participants.

Sixty-four patients received CRT based on decision by the responsible electrophysiologist, and were re-examined using echocardiography at 6 months follow-up to investigate the response of resynchronization on global and regional myocardial function.

Approval was obtained from the Regional Ethics Committees and written, informed consent was obtained from all participants.

ECHOCARDIOGRAPHY AND STRAIN ANALYSIS. Vivid E9 or E95 cardiac ultrasound scanners (GE Ultrasound) were used. Two-dimensional grey-scale echocardiographic images from parasternal (short- and long-axis) and apical (2-, 3-, and 4-chamber) views were acquired. Average frame rate was 65 ± 11 frames/s. M-mode was obtained from parasternal views to measure wall thickness and LV-diameter at end-diastole. Continuous wave and color Doppler recordings were carried out for quantification of valvular regurgitations. All LV volumes were calculated using the biplane Simpson's method by

TABLE 1 Baseline Characteristics of Study Population

		LBBB			ANOVA
	Controls (n = 11)	$EF_{preserved}$ (n = 11)	EF_{mid} (n = 21)	EF_{low} (n = 44)	*P* Value
Age, yrs	60 ± 10	63 ± 9	66 ± 9	67 ± 10	NS
Heart rate, beats/min	68 ± 10	66 ± 11	62 ± 8	68 ± 11	NS
Systolic blood pressure, mm Hg	137 ± 23	129 ± 20	141 ± 20	123 ± 21[c]	<0.05
Diastolic blood pressure, mm Hg	79 ± 7	73 ± 10	72 ± 12	71 ± 14	NS
QRS duration, ms	98 ± 20	149 ± 14[a]	163 ± 15[a,b]	165 ± 16[a,b]	<0.05
MR grade, n (0-1/2/3/4)	8/3/0/0	5/6/0/0	13/6/2/0	11/18/15/0[d]	
Medication, n (%)					
ACEi/ARB	2 (18)	4 (36)	19 (90)[a,b]	42 (95)[a,b]	
Beta-blocker	0 (0)	5 (45)[a]	18 (86)[a,b]	38 (86)[a,b]	
Loop diuretic agents	0 (0)	0 (0)	10 (48)[a,b]	31 (70)[a,b]	
Aldosterone antagonists	0 (0)	1 (9)	9 (43)[a]	19 (43)[a,b]	
Echocardiographic data					
Septal thickness, mm	9 ± 1	10 ± 1	10 ± 2	9 ± 2	NS
LV internal diameter, mm	50 ± 6	53 ± 4	56 ± 6[a]	65 ± 8[a,b,c]	<0.05
LV posterior wall thickness, mm	8 ± 1	9 ± 2	9 ± 1	9 ± 2	NS
LV end-diastolic volume, ml/m^2	52 ± 7	59 ± 13	81 ± 16[a,b]	121 ± 38[a,b,c]	<0.05
LV end-systolic volume, ml/m^2	21 ± 3	26 ± 8a	48 ± 10[a,b]	88 ± 30[a,b,c]	<0.05
LV stroke volume, ml	61 ± 10	65 ± 16	58 ± 12	62 ± 22	NS
LV ejection fraction, %	60 ± 4	57 ± 5	40 ± 4[a,b]	28 ± 5[a,b,c]	<0.05

Values are as mean ± SD or n (%). [a]$P < 0.05$ vs controls. [b]$P < 0.05$ vs $EF_{preserved}$. [c]$P < 0.05$ vs EF_{mid}. [d]$P < 0.05$ vs controls, $EF_{preserved}$ and EF_{mid}.

ACEi = angiotensin-converting enzyme inhibitor; ANOVA = analysis of variance; ARB = angiotensin II receptor blocker; $EF_{preserved}$ = patients with ejection fraction ≥50%; EF_{mid} = patients with ejection fraction 36%-49%; EF_{low} = patients with ejection fraction ≤35%; LBBB = left bundle branch block; LV = left ventricular; MR = mitral regurgitation; NS = nonsignificant.

experienced readers in all participating centers, and the average of these measurements was used to calculate left ventricular ejection fraction (LVEF).

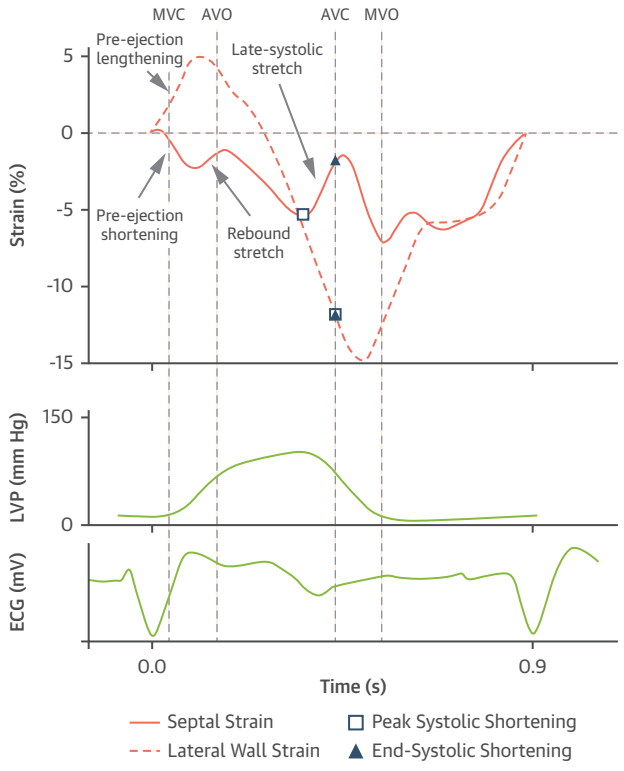
Global and segmental strain analyses were performed off-line using speckle-tracking echocardiography (Echopac, version 202, GE Ultrasound). Septal and LV lateral wall strain were obtained from single wall analyses in the apical 4-chamber view. From the curves representing each wall, shortening was measured at peak and end-systole. LV lateral wall pre-ejection lengthening, and septal pre-ejection shortening, septal rebound stretch, and late-systolic stretch were measured as shown in **Figure 1**.

ESTIMATION OF REGIONAL WORK. Segmental myocardial work was estimated using noninvasive LV pressure-strain analysis (19) using a semi-automated analysis tool (Echopac, version 202, GE Ultrasound, Horten, Norway) as described in detail by Russell et al (19,20). In brief, this method uses a normalized LV pressure trace (waveform) that is made patient specific by scaling its amplitude to the patient's brachial systolic pressure, and measure timing of valve events to scale the duration of the cardiac phases. The work index (mm Hg·%) is calculated by multiplying rate of segmental shortening (strain rate) with instantaneous LV pressure (LVP) as estimated. This results in a measure of instantaneous power, which is integrated over time to give work as a function of time in systole, defined as the time interval from mitral valve closure to mitral valve opening (20). In addition to the time used to measure blood pressure and strain, the analysis typically takes <1 min to perform.

Work performed during shortening was defined as positive, whereas work performed during lengthening was defined as negative. Net work for a myocardial segment was calculated as the sum of positive and negative work. Septal and LV lateral wall work was calculated as the average of the respective basal and mid segments in the apical 4-chamber view. In this study, global myocardial work was calculated as the average value from all 18 LV segments from the 3 apical views. We used the average of female and male lower limit of normal global myocardial work, as reference for regional myocardial work (21).

ESTIMATION OF REGIONAL WALL STRESS. To evaluate the effect of differences in regional load due to curvature and wall thickness in LBBB, we calculated wall stress. Wall stress analysis was performed in 32 randomly selected individuals (8 from each group), after exclusion of patients without sufficient image quality for short-axis measurements of curvature.

FIGURE 1 Regional Strain Patterns in LBBB



Strain traces **(red)** with corresponding pressure and ECG curves **(green)** from a representative patient with LBBB. **Dotted red line** is LV lateral wall strain trace and **solid red line** is septal strain trace. The LVP curve was non-invasively estimated by adjusting a normalized LVP trace to systolic brachial artery pressure and LV valve event timings (see Methods for details). ECG is included for timing-reference. AVC= aortic valve closure; AVO = aortic valve opening; ECG = electrocardiogram; LBBB = left bundle branch block; LV = left ventricular; LVP = left ventricular pressure; MVC = mitral valve closure; MVO = mitral valve opening.

Circumferential wall stress was measured, because we expected less pronounced changes in longitudinal wall stress. Wall stress was calculated in the septum and LV lateral wall according to the law of Laplace:

$$\sigma(t) = \frac{P(t) \times r(t)}{h(t) \times 7.5}$$

where σ(t) = wall stress, P(t) = LV pressure, r(t) = radius, h(t) = wall thickness, and 7.5 is the conversion factor to kiloPascals. Regional radius was measured from parasternal short axis images in the mid-papillary level, whereas M-mode for the same region was used to measure wall thickness. Non-invasively estimated LVP, as described previously, was used for the pressure component (19,20). Measurements were performed at peak LVP.

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD if not otherwise stated, or as confidence intervals. Comparisons between groups were performed using paired- or independent samples Student's *t*-test, chi-square test, Fisher exact test, Mann-Whitney *U* test, and 1-way analysis of variance as appropriate. Univariate and multivariate linear regression were used to identify predictors of LV systolic function and remodeling. A value of $P < 0.05$ was considered significant. SPSS 25.0 (SPSS, IBM) was used for the analyses.

RESULTS

Age and heart rate were similar in all 4 groups (Table 1). QRS duration was somewhat shorter in patients with $EF_{preserved}$ as compared with EF_{mid} and EF_{low}, whereas degree of mitral regurgitation was significantly larger in EF_{low} compared with all other groups.

REGIONAL LV WORK AND ITS RELATION TO LVEF. Septal work was substantially lower in $EF_{preserved}$ compared with controls, although both groups had similar LVEF (Table 2). Furthermore, LV lateral wall work was numerically higher than in the controls, and there was a large difference in work between septum and LV lateral wall (Table 2). As shown in the Central Illustration, such asymmetrical distribution of LV work was consistently present among all groups of patients with LBBB. When considering all participants, there was a strong correlation between septal work and LVEF. The correlation between LV lateral wall work and LVEF, on the other hand, was only moderate, and LV lateral wall work was numerically increased in $EF_{preserved}$ and EF_{mid} compared with controls. When excluding patients with severe LV dysfunction (LVEF <35%), septal work still showed a strong correlation with LVEF ($r = 0.71$; $P < 0.005$), whereas LV lateral wall work and LVEF were not significantly correlated ($r = 0.31$; $P = 0.087$).

Including all participants, indexed end-diastolic volume correlated with both septal- ($r = -0.60$; $P < 0.005$) and LV lateral wall work ($r = -0.62$; $P < 0.005$) (Figure 2). Furthermore, in multivariate analysis including septal work, LV lateral wall work and QRS duration, septal work was the strongest determinant of LVEF (Table 3).

REGIONAL LV CONTRACTION PATTERN. In all patients with LBBB, end-systolic septal shortening was reduced compared with controls (Table 2). In the $EF_{preserved}$ group, however, peak septal systolic shortening values were similar as the controls. This difference between end-systolic and peak systolic shortening values was reflected in premature

TABLE 2 Shortening and Myocardial Work

		LBBB			
	Controls (n = 11)	$EF_{preserved}$ (n = 11)	EF_{mid} (n = 21)	EF_{low} (n = 44)	ANOVA *P* Value
Strain data, %					
Global longitudinal shortening	21 ± 2	18 ± 1[a]	14 ± 2[a,b]	9 ± 2[a,b,c]	<0.05
Peak systolic septal shortening	19 ± 3	17 ± 3	10 ± 4[a,b]	7 ± 3[a,b,c]	<0.05
Peak systolic LV lateral wall shortening	19 ± 4	18 ± 3	16 ± 4	11 ± 4[a,b,c]	<0.05
End-systolic septal shortening	18 ± 3	14 ± 2[a]	7 ± 4[a,b]	2 ± 4[a,b,c]	<0.05
End-systolic LV lateral wall shortening	18 ± 4	18 ± 3	16 ± 4	11 ± 4[a,b,c]	<0.05
Septal ejection shortening		12 ± 3	7 ± 3[b]	3 ± 3[b,c]	<0.05
LV lateral wall ejection shortening		21 ± 2	19 ± 4	14 ± 4[b,c]	<0.05
Septal rebound stretch		0 ± 0	1 ± 1[b]	3 ± 3[b,c]	<0.05
Late systolic septal stretch		4 ± 2	4 ± 2	4 ± 3	NS
Pre-ejection shortening septum		6 ± 1	4 ± 2	5 ± 2	NS
Pre-ejection lengthening LV lateral wall		3 ± 1	3 ± 2	3 ± 2	NS
Myocardial work, mm Hg·%					
Global myocardial work	2,281 ± 536	1,723 ± 352[a]	1,437 ± 286[a,b]	781 ± 323[a,b,c]	<0.05
Septum	1,977 ± 506	1,025 ± 342[a]	601 ± 494[a,b]	-41 ± 303[a,b,c]	<0.05
LV lateral wall	2,062 ± 459	2,367 ± 459	2,252 ± 449	1,473 ± 568[a,b,c]	<0.05
LV lateral wall-to-septal work difference	127 ± 595	1,342 ± 318[a]	1,664 ± 647[a]	1,539 ± 649[a]	<0.05

Values are mean ± SD. [a]$P < 0.05$ vs controls. [b]$P < 0.05$ vs $EF_{preserved}$. [c]$P < 0.05$ vs EF_{mid}.
Abbreviations as in Table 1.

termination of septal shortening in patients with LBBB as illustrated in the septal shortening trace in Figure 1 and the Central Illustration. Furthermore, all patients with LBBB showed marked pre-ejection septal shortening with concomitant pre-ejection lengthening in the late-activated LV lateral wall. In the $EF_{preserved}$ group, septal pre-ejection shortening was immediately followed by a new shortening phase as the aortic valve opened (ejection shortening). In EF_{mid} and most EF_{low} patients, there was instead septal elongation (septal rebound stretch) (Figure 1, Central Illustration, Table 1), which was followed by severely reduced septal shortening in the remaining ejection phase. A late-systolic septal stretch was present in all LBBB patient groups with no significant differences among EF groups.

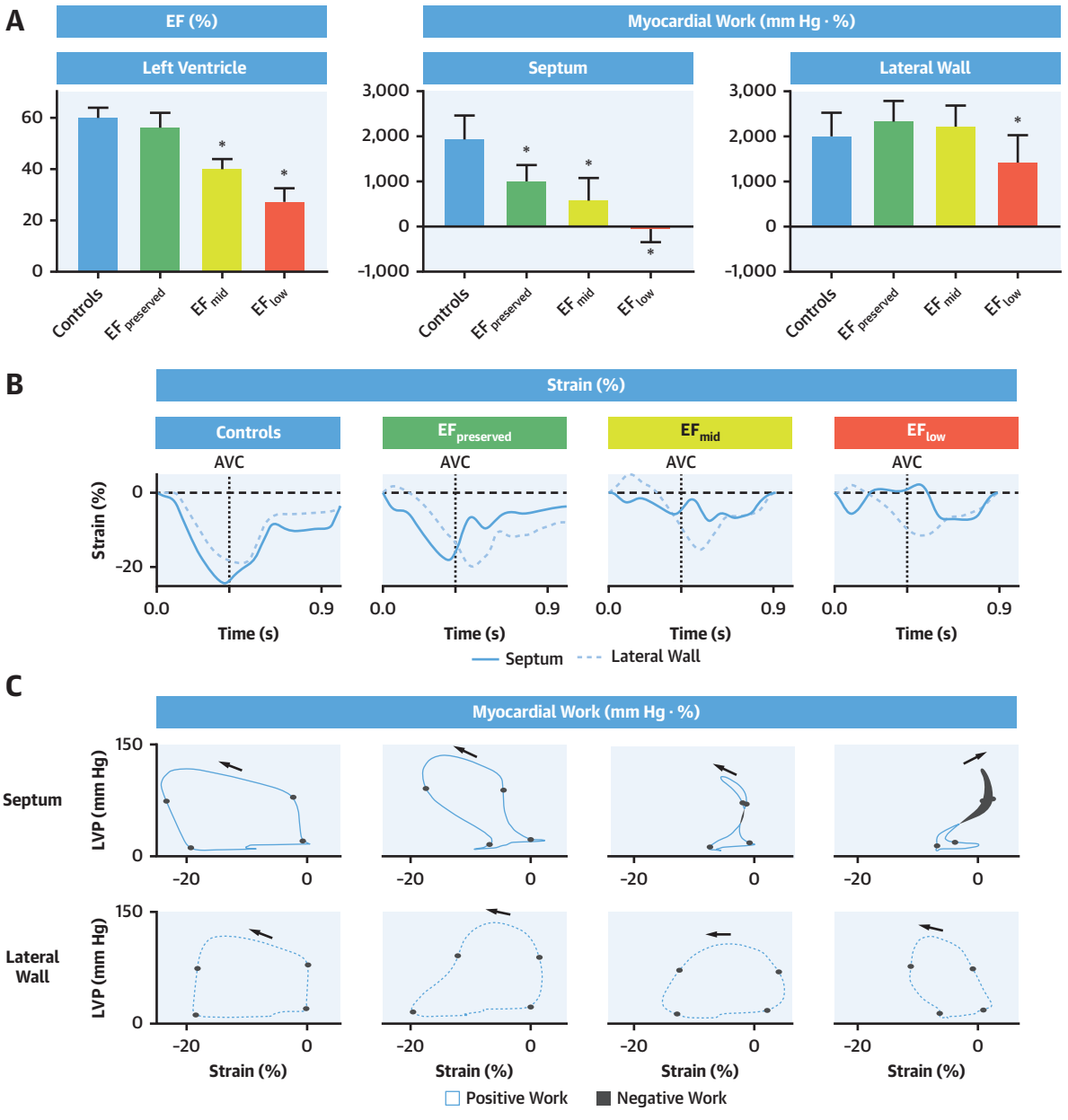
WALL STRESS. During peak LVP, septal radius was larger (ie, flatter curvature) and the wall thinner than the LV lateral wall, leading to excessive septal wall stress in patients with LBBB (Table 4). Peak septal wall stress was higher in patients with LBBB compared with controls, including patients with preserved EF (Figure 3). In contrast, peak LV lateral wall stress was not significantly increased compared with controls, except in EF_{low}. Importantly, LV internal diameter was markedly increased in this group (Table 1). Septal wall stress increased with decreasing LVEF ($r = -0.63$; $P < 0.005$), whereas there was no significant correlation between LV lateral wall stress and LVEF ($r = -0.34$; $P = 0.11$).

EFFECT OF CRT. Sixty-four patients underwent CRT. At 6 months of follow-up LVEF increased from 32 ± 8 to 47 ± 10% ($P < 0.005$). As illustrated in Figure 4, septal work increased substantially with CRT from 165 ± 485 to 1,288 ± 523 mm Hg·% ($P < 0.005$), and was followed by improved global myocardial work (1,011 ± 439 to 1,396 ± 435 mm Hg·%; $P < 0.005$). LV lateral wall work, on the other hand, decreased with CRT (1,730 ± 620 to 1,264 ± 490 mm Hg·%; $P < 0.005$). Among the 48 patients with normal LV lateral wall work values prior to CRT, LVEF increased to normal levels in 54% of patients. In the 16 patients with reduced LV lateral wall work, LVEF increased to normal levels in 13% of patients ($P < 0.005$).

DISCUSSION

The novel finding in this study is that LV lateral wall function was preserved in patients with LBBB with normal or moderately reduced LVEF, whereas in patients with severely reduced LVEF, LV lateral wall function was also reduced. These findings, together with stress and work analysis, indicate that progressive septal dysfunction eventually leads to LV lateral wall decompensation and reduced global LV function. Furthermore, these observations suggest that assessment of LV lateral wall function may provide information regarding optimal timing of CRT in patients with mild to moderate reduction in global LV function.

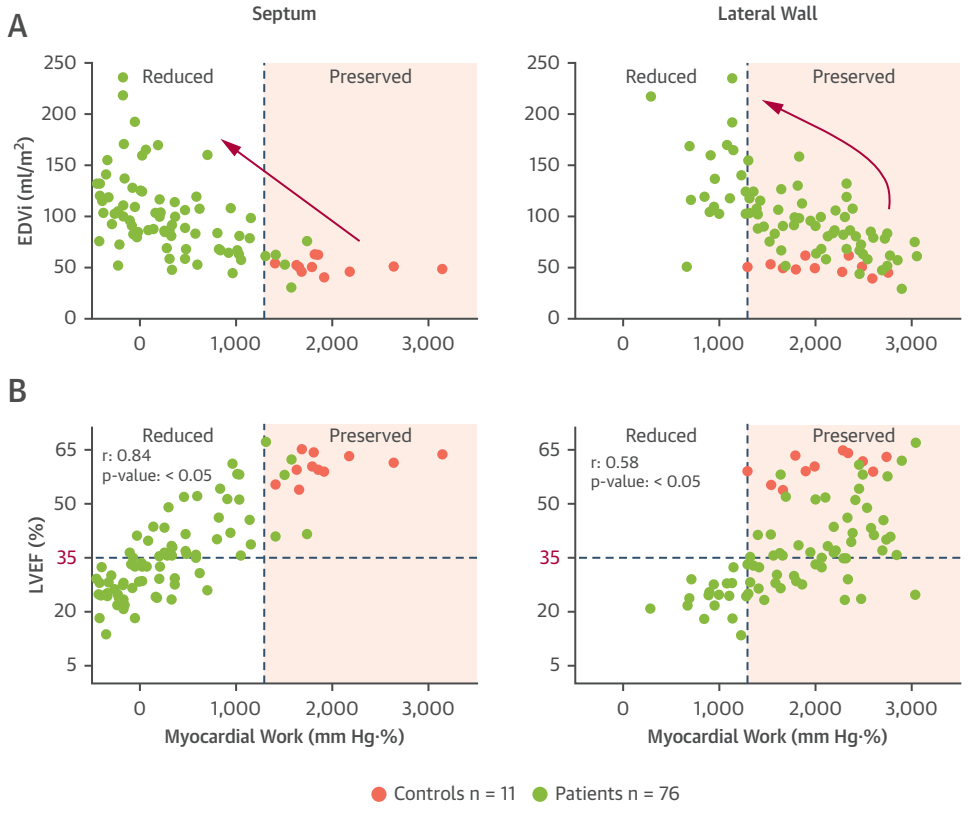
CENTRAL ILLUSTRATION **LV Lateral Wall Dysfunction Signals Onset of Progressive Heart Failure in LBBB**



Sletten, O.J. et al. J Am Coll Cardiol Img. 2021;14(11):2055-2069.

(A) Mean and standard deviation of EF, septal work, and LV lateral wall work in the different groups. Note the substantial reduction in septal work in all patients with LBBB as opposed to the preserved LV lateral wall work in patients with LBBB with normal or mildly reduced LV function. **(B)** Segmental strain traces from the septum and LV lateral wall of representative individuals in each group. **(C)** Segmental pressure-strain loops from the septum and LV lateral wall of representative individuals in each group. Note the negative septal work marked as a black loop area in EF_{mid} and EF_{low}. Groups of patients with LBBB: $EF_{preserved}$ = EF ≥50%; EF_{mid} = EF 36%-50%; EF_{low} = EF ≤35%. *P < 0.05 vs controls. AVC = aortic valve closure; EF = ejection fraction; LBBB = left bundle branch block; LV = left ventricular; LVP = left ventriculalr pressure.

FIGURE 2 **Regional Myocardial Work in Relation to LV Size and Function**



Data from all participants. **(A)** Scatter plots displaying septal **(left)** and LV lateral wall **(right)** work versus indexed end-diastolic volume. The lower limit of normal myocardial work is marked by the **dotted line** (1,290 mm Hg·%) (21). Note the difference in volumetric effect on regional function, where the LV lateral wall initially remains well-functioning despite LV dilatation, as opposed to the rapid decrease seen in the septum. **(B)** Scatter plots of septal **(left)** and LV lateral wall **(right)** work versus LVEF. Note the strong correlation of septal work with LVEF, and the absence of patients with LVEF >35% and reduced LV lateral wall work. EDVi = indexed end-diastolic volume; LVEF = left ventricular ejection fraction; other abbreviations as in Figure 1.

MECHANISMS OF LV DYSFUNCTION IN LBBB. It has been shown that approximately one third of patients with LBBB with normal LVEF underwent LV remodeling with subsequent reduction in LVEF over a 4-year period (22), but the authors were not able to identify risk factors. In the present study, we have shown that septal dysfunction is closely linked to LV dysfunction in patients with LBBB. Even in patients with preserved LVEF, there was substantially reduced septal function and subclinical LV dysfunction as indicated by reduced global longitudinal strain. Therefore, septal function is an important determinant of LV systolic function and, possibly, degree of septal dysfunction can identify patients with high risk of progressive LV dysfunction. In contrast to septal dysfunction, LV lateral wall function was preserved or compensatorily increased in patients with LBBB with subclinical or mild-to-moderate LV dysfunction. Hence, our results suggest that septal dysfunction is the initial driver for deterioration of global LV function in LBBB and, possibly, LV lateral wall dysfunction arises at a time when dilatation of the LV leads to unbearable LV lateral wall workload. Such mechanism can be appreciated by the scatterplots in Figure 2, illustrating how septal work is rapidly decreasing with LV dilatation, whereas LV lateral wall work is maintained despite mild-to-moderate LV dilatation, and is supported by the finding of up-regulation of proteins involved in hypertrophy in the lateral wall of dyssynchronous ventricles (8). LV lateral wall decompensation was, therefore, a sign of advanced heart failure and, hence,

TABLE 3 Multivariate Linear Regression Analysis in All Patients With Left Ventricular Ejection Fraction as Dependent Variable (n = 76; R2 = 0.69)

Regression Variable	B	VIF	95% CI	*P* Value	Pearson Correlation
Constant term	31.356				
Septal work	0.012	1.360	0.008 to 0.016	<0.001	0.759
LV lateral wall work	0.006	1.379	0.004 to 0.008	<0.001	0.642
QRS duration	−0.114	1.101	-0.212 to -0.026	<0.05	−0.386

B = unstandardized coefficients; CI = confidence interval; VIF = variance inflation factor; other abbreviations as in Table 1.

potentially less beneficial effect of CRT (23). This was supported by the present finding that only a small fraction of patients with reduced LV lateral wall work showed complete recovery of LVEF with CRT, whereas the majority of patients with preserved LV lateral wall work achieved normalization of LVEF. It is also in line with several previous studies showing reduced response to CRT in patients with severe LV systolic dysfunction (24,25). Furthermore, it is in accordance with a previous study from our group (26) showing that LV lateral wall function is an important determinant of LBBB-induced septal dysfunction and, hence, the potential for recovery of LV function with CRT (15). The cause of incomplete recovery of LV function in more advanced heart failure is not entirely clear, but fibrosis likely plays a role. In the present study, however, we excluded patients with macroscopic fibrosis as determined using late gadolinium enhancement cardiac magnetic resonance, but microscopic fibrosis may play an important role and there is need for further studies on this topic.

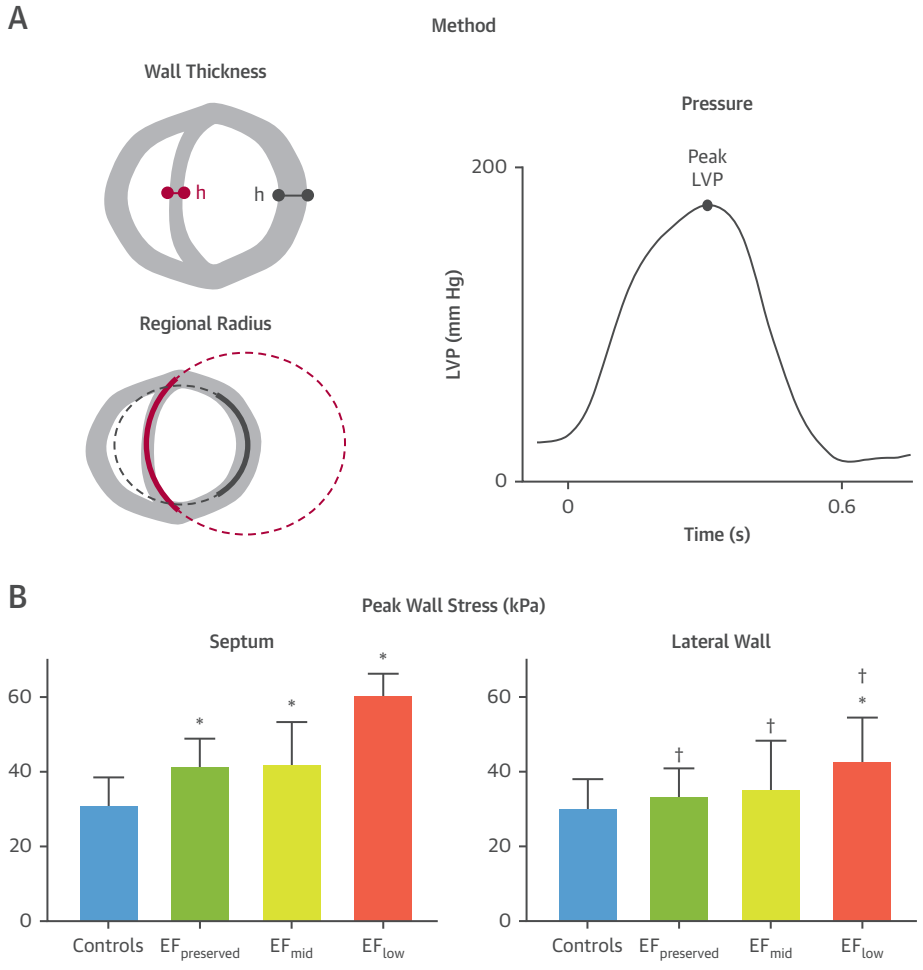
POTENTIAL EXPLANATIONS FOR PROGRESSIVE SEPTAL DYSFUNCTION IN PATIENTS WITH LBBB. Wall stress analysis in patients with LBBB revealed elevated septal wall stress at peak LVP (**Figure 3**), suggesting amplified wall stress as a mechanism for increasing septal dysfunction. In the current study we found flattening of the septum as a determinant of increased wall stress. This is in accordance with our previous findings of afterload hypersensitivity in patients with LBBB (17), where we demonstrated a similar appearance of increasingly dysfunctional septal contractile pattern with elevated afterload. On the other hand, the late activated LV lateral wall is stretched in early systole prior to ejection, experiencing an increase in regional preload. Hence, asymmetrical load leads to septal dysfunction when the wall stress is highest (i.e., during systole), and it leads to LV lateral wall hyperfunction according to the Frank-Starling principle (27). Dyssynchrony has previously been shown to cause asymmetrical wall hypertrophy in a chronic animal model where the earliest activated regions became thinner (7). It has also been demonstrated that this was reversed by CRT in patients with LBBB (9). Considering these findings, it is likely that septal wall stress becomes potentiated and LV lateral wall stress remains relatively unaltered in the initial phases of remodeling in patients with LBBB. This is supported by our finding of rapidly decreasing septal work with increasing end-diastolic volume, as opposed to the initially preserved LV lateral wall work (**Figure 2**) and, furthermore, by the finding of increased septal work and reduced LV lateral wall work after 6 months of CRT, where regional myocardial work balance was restored and LVEF substantially increased (**Figure 4**). Moreover, it is in accordance with a previous study (9), where LBBB-like conduction was shown to cause asymmetrical perfusion and remodeling of the myocardium, and that CRT reversed this relative perfusion mismatch, causing reverse remodeling.

TABLE 4 Wall Stress Analysis During Peak LV Pressure

	Controls (n = 8)		LBBB (n = 24)	
LV pressure (mm Hg)	132 ± 20		135 ± 25	
	Septum	**LV Lateral Wall**	**Septum**	**LV Lateral Wall**
Radius, mm/m^2	10.6 ± 2.6	10.1 ± 2.2	15.9 ± 2.7[a]	14.0 ± 3.3[a,b]
Wall thickness, mm/m^2	6.0 ± 0.2	5.9 ± 0.8	6.1 ± 1.4	6.8 ± 1.0[a,b]
Wall stress, kPa	31 ± 7	30 ± 7	48 ± 12[a]	37 ± 11[a]

Values are mean ± SD. [a]$P < 0.05$ vs controls. [b]$P < 0.05$ compared with septum for specific group.
kPa = kilopascal; other abbreviations as in Table 1.

FIGURE 3 **Peak Wall Stress is Increased in Septum of Patients With LBBB Compared With Controls**

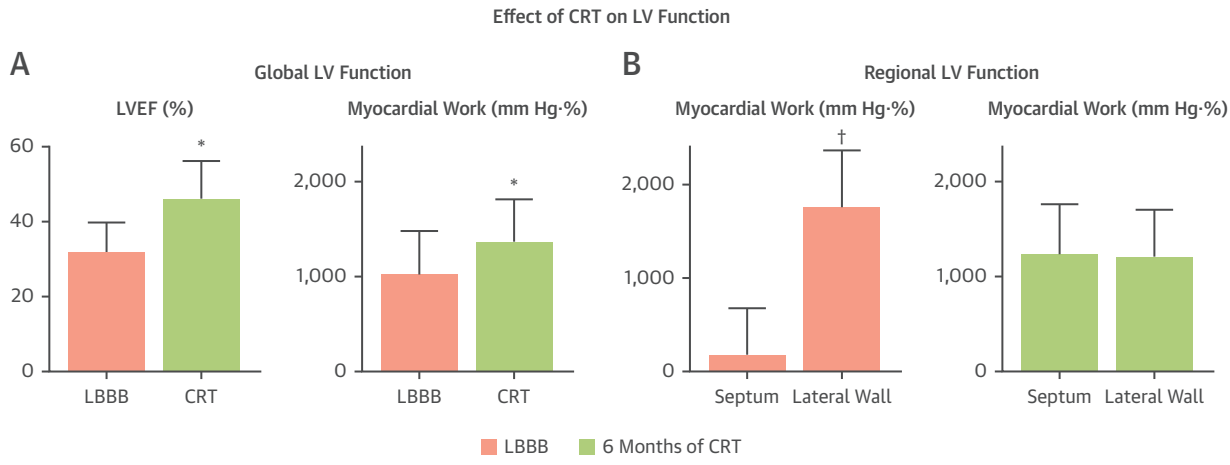


(A) The method of wall stress measurements. Wall thickness was measured at papillary muscle level in septum and LV lateral wall. Regional radius was measured in the same region. All shown measurements are at peak LVP. **(B)** Data from 8 randomly selected individuals in each group, controls **(blue)**, $EF_{preserved}$ **(green)**, EF_{mid} **(yellow)**, and EF_{low} **(red)** given as mean ± SD. The **left panel** shows septal wall stress and **right panel** shows LV lateral wall stress. Note how septal wall stress is higher in patients than controls, and compared with the LV lateral wall. *$P < 0.05$ compared with same region in controls. †$P < 0.05$ compared with septum for specific group. h = wall thickness; kPa = kilopascal; LV = left ventricular; LVP = LV pressure; other abbreviations as in Figures 1 and 2.

CLINICAL IMPLICATIONS. We have proposed a mechanistic pathway for development of heart failure due to LBBB, but prospective data are needed to assure causality between LBBB, uneven wall stress distribution, and heart failure. Our findings suggest that it may be advantageous to implant CRT at a relatively early stage of LBBB-induced heart failure where LV lateral wall systolic function is preserved or compensatory increased, to achieve optimal recovery of LV function. Because reduced LVEF can be due to other causes than LBBB-induced dyssynchrony, assessment of LV lateral wall function may be superior to LVEF to determine the optimal timepoint for CRT implantation. Early CRT implantation in LBBB-induced heart failure is supported by the reduced effect of medical heart failure treatment in patients with LBBB compared with patients with narrow QRS duration (28) and the observation that CRT also reduces mortality in patients with mild LV dysfunction (29).

STUDY LIMITATIONS. The present study is mainly cross-sectional with a limited number of patients and, therefore, prospective data are needed to further explore the suggested pathophysiological model of LBBB-induced heart failure. In particular, extrapolation of time course of LV remodeling based on

FIGURE 4 CRT Effectively Reduces Contractile Inefficiency



Data from 64 patients undergoing CRT at baseline **(red)** and 6 months follow-up **(green)**; data given as mean ± SD. **(A)** LVEF **(left)** and global myocardial work **(right)** prior to and 6 months after cardiac resynchronization device implantation. Note the improvement in LVEF and global myocardial work. **(B)** Regional myocardial work prior to and 6 months after cardiac resynchronization device implantation. Note the large net difference in work between septum and LV lateral wall for all patients prior to device implantation, and the recovery of septal work at 6 months of follow-up, restoring contractile efficiency. *$P < 0.05$ versus pre-CRT. †$p < 0.05$ versus septum. CRT = cardiac resynchronization therapy; other abbreviations as in Figures 1 and 2.

patients with a wide range of LVEF warrants caution when interpreting results. However, the finding that CRT substantially improved LV function by increased septal work and reduced LV lateral wall workload support the suggested model.

We did not include the transseptal pressure gradient when calculating wall stress, which may introduce an error, especially considering patients with elevated right ventricular pressures.

Strain is inherently dependent on the size of its measured region, ie, a larger ventricle will have reduced strain compared with a smaller ventricle, despite having the same absolute shortening. Accordingly, due to increased regional preload, we may have under-reported the hyperfunction of the LV lateral wall.

The decision to implant CRT was made by the responsible electrophysiologist, whereas LV volumes were measured by experienced readers in all participating centers. This led to some patients being implanted with CRT despite having a LVEF >35%. This should not limit the conclusions of the study, but rather strengthen the conclusions. By following patients with LVEF >35%, we gained additional insight into the same mechanism.

CONCLUSIONS

Heart failure development and adverse remodeling in patients with LBBB is associated with progressively reduced septal function. LV lateral wall function, however, is preserved in patients with mild LV dysfunction and it seems LV lateral wall decompensation is a sign of substantial adverse remodeling leading to markedly reduced global LV function, possibly due to unbearable loading conditions. The time-point when LV lateral wall function becomes reduced may be an optimal time for CRT.

ACKNOWLEDGMENTS The authors thank study nurse Kari Melberg for her valuable contributions to the study.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Drs Sletten and Aalen were supported by grants from the Norwegian Health Association. Dr Larsen was a recipient of a clinical research fellowships form the South-Eastern Norway Regional Health Authority. Prof Voigt holds a personal research mandate of the Flemish Research Council. Prof Voigt and Dr Duchenne were further supported by a grant of the University of Leuven. Dr Smiseth is co-inventor, but since May 24, 2017 has had no financial relations to the patent "Method for myocardial segment work analysis," which was used to calculate the myocardial work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The typical patient with LBBB has septal dysfunction, but no LV lateral wall dysfunction without concomitant heart failure.

COMPETENCY IN PATIENT CARE: LV lateral wall dysfunction is a sign of severe heart failure in patients with LBBB.

TRANSLATIONAL OUTLOOK: Future studies should determine if onset of LV lateral wall dysfunction in patients with LBBB can be used to optimize timing of CRT. Prospective studies should determine if assessment of LV lateral wall work can improve selection of CRT candidates, including patients who are currently not included in the guidelines for CRT.

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KEY WORDS cardiac resynchronization therapy, heart failure, left bundle branch block, myocardial work, septal rebound stretch, strain