Predicting the Development of Reduced Left Ventricular Ejection Fraction in Patients With Left Bundle Branch Block

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Left bundle branch block (LBBB) increases the likelihood of developing reduced left ventricular (LV) ejection fraction (EF) but predicting which patients with LBBB and normal LVEF will develop decreased LVEF remains challenging. Fifty patients with LBBB and normal LVEF were retrospectively identified. Clinical, electrocardiographic, and echocardiographic variables were compared between patients who developed a decreased LVEF and those who did not. A total of 16 of 50 patients developed reduced LVEF after 4.3 (SD = 2.8) years of follow-up. Baseline patient and electrocardiographic variables were similar between patients who did and did not develop decreased LVEF. Baseline LVEF was lower in patients who developed decreased LVEF than in those who did not (51.9% [SD = 2.2%] vs 54.9% [SD = 4.4%], p <0.01). Diastolic filling time (DFT) accounted for a significantly smaller percentage of the cardiac cycle in patients who developed decreased LVEF than in those who did not (35.9%, [SD = 6.9%] vs 44.4% [SD = 4.5%] p <0.01). In univariable logistic regression, DFT had a C-statistic of 0.86 (p <0.0001) for prediction of development of decreased LVEF. In conclusion, patients in whom DFT accounted for <38% of the cardiac cycle had a relative risk of developing decreased LVEF of 7.0 (95% confidence interval 3.0 to 16.0) compared to patients with DFT accounting for ≥38% of the cardiac cycle. **(Am J Cardiol 2020;137:39−44)**

Up to 1/3 of otherwise healthy patients with left bundle branch block (LBBB) go on to develop decreased left ventricular (LV) ejection fraction (EF) a unique clinical entity defined by LV dilation occurring in the setting of a LBBB with evident dyssynchrony.[1] Three retrospective studies show that decreased LVEF is less responsive to ACC/AHA HF guideline directed medical therapies compared with decreased LVEF occurring in the setting of normal conduction.[2−4] Cardiac resynchronization therapy (CRT) improves heart failure (HF) symptoms and survival in patients with LBBB, symptomatic HF, and LVEF ≤35%.[5,6] Early reports suggest that both systolic and diastolic function are impaired in patients with LBBB and symptomatic HF with preserved LVEF and both systolic and diastolic function can be improved with CRT.[7] CRT implantation ≤9 months after the diagnosis of decreased LVEF in patients with LBBB is associated with a higher likelihood of LV reverse remodeling compared with implantation >9 months after diagnosis[4] but it is unclear if prophylactic CRT implantation could prevent decreased LVEF in patients with LBBB. The purpose of this study is to determine if electrocardiographic and echocardiographic assessments of systolic and diastolic LV performance in patients with LBBB can predict the likelihood of developing decreased LVEF.

Methods

This study complied with the Declaration of Helsinki and was approved by the Duke Institutional Review Board. The study cohort was identified in the Duke Echocardiographic Laboratory Database[8,9] after linking to the electrocardiogram database. The study population consisted of patients aged ≥18 years with a standard 12 lead electrocardiogram obtained within 30 days of a clinically obtained echocardiogram and a follow-up echocardiogram performed >6 months later. Baseline echocardiograms were obtained between January 1, 1998 and December 31, 2013. The baseline echocardiogram was the earliest qualifying echocardiogram after the first electrocardiogram diagnosis of LBBB which was defined using ACC/AHA criteria.[10]

To reduce the frequency of competing sources of decreased LVEF, patients were excluded if they had a history of previous valve intervention, end-stage renal disease, previous left ventricular assist device, heart transplantation,

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metastatic cancer, moderate or severe valve disease, atrial fibrillation, previous myocardial infarction, previous implantable cardiac device, or conduction abnormality other than LBBB. Patients were also excluded if echocardiogram images were inadequate to measure diastolic function using tissue Doppler imaging (due to sinus tachycardia, a rhythm other than sinus or inadequate spectral tissue Doppler images with sampling at the septal mitral annulus), or if they had an LVEF <50% at the time of the baseline echocardiogram. In cases where multiple echocardiograms were obtained after baseline, end point ascertainment was performed using the study with the lowest LVEF measurement. If the LVEF remained unchanged, the latest echocardiogram was used.

Decreased LVEF was defined as a new reduction in LVEF to ≤45% at least 6 months after the baseline echocardiogram without having had an intercurrent myocardial infarction. All echocardiogram data were abstracted from the Duke Echocardiogram Laboratory Database which contains clinical interpretations by cardiologists with level III training in echocardiography. All baseline echocardiograms were reanalyzed by a single investigator (KE) for this study and verified by other investigators (JK, LL).

Echocardiographic analysis

All measurements were performed in Xcelera R3.2LA SP2 (Phillips Medical Systems Nederland B.V., Best, the Netherlands). The presence and severity of valvular disease were evaluated as described in the echocardiographic guidelines.[11–13] Diastolic dysfunction grading was based on the latest recommendations from the American Society of Echocardiography.[14] Transmitral flow was recorded from the apical 4-chamber view at end expiration at the mitral leaflet tips. Pulse wave (PW) Doppler recordings were made at a sweep speed of 100 mm/s with an electrocardiogram superimposed. The E wave amplitude and duration, E wave deceleration time (DT) and A wave amplitude and duration were measured manually and the E/A ratio was calculated. Isovolumic contraction time (ICT), ejection time (ET), isovolumic relaxation time (IRT) and diastolic filling time (DFT) were measured on spectral tissue Doppler images with sampling at the septal mitral annulus in the apical 4-chamber view.[15] The ICT was defined as the interval from the end of the a'-wave to the beginning of the s'-wave, ET was defined as the interval from the onset to end of the s'-wave, and IRT was defined as the interval from the end of the s'-wave to the beginning of the e'-wave. The DFT was defined as the interval from the beginning of the e'-wave to the end of the a'-wave. The duration of each phase was then expressed as a percentage of the RR interval measured from the peak of the QRS complex on the measured electrocardiogram recording. All measurements were repeated on up to 3 consecutive cardiac cycles and averaged.

Continuous variables with a normal distribution were presented as mean with standard deviation (SD) whereas variables with a non-Gaussian distribution were presented as median with interquartile range. Categorical variables were presented as n (%). Groups were compared using Student's *t* test for continuous variables and Fisher's exact test for categorical variables. Logistic regression modeling was performed to identify variables that predicted the development of decreased LVEF and receiver operator characteristic curve analysis was performed to identify the variable threshold value that optimized prediction of decreased LVEF. Variables were included in the multivariable model if they differed between groups. The number of variables entered into the model was limited based on the number of observed end points (in a 1:10 ratio) to avoid overfitting. The outcome of interest was a reduction in LVEF to ≤45% on follow-up echocardiography at least 6 months after the baseline echocardiogram. A 2-sided p-value of <0.05 was considered statistically significant.

Results

A total of 50 patients fulfilled eligibility criteria and were included in the analysis (Figure 1), 16 patients developed decreased LVEF and 34 patients did not. The mean time to follow-up echocardiogram was 4.3 years (SD = 2.8

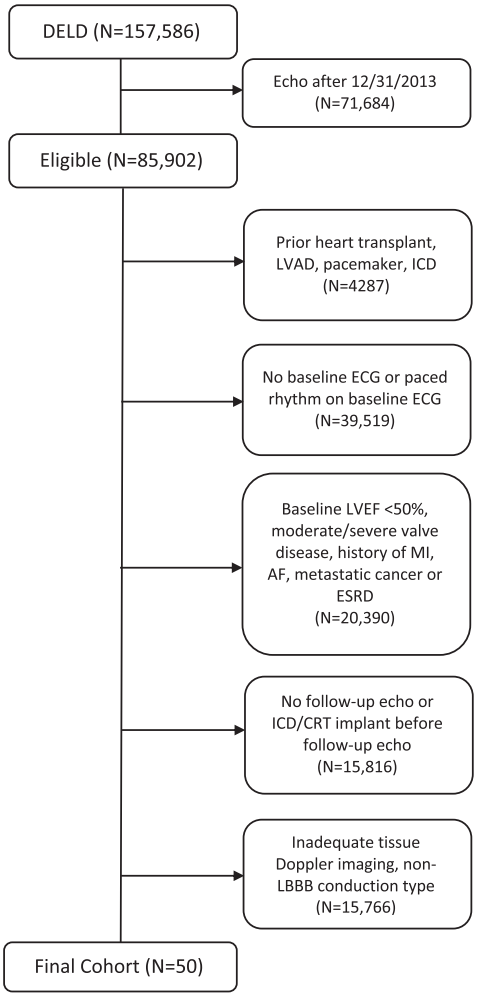

Figure 1. Cohort derivation. AF = atrial fibrillation; CRT = cardiac resynchronization therapy; DELD = Duke Echocardiographic Laboratory Database; ESRD = end stage renal disease; Echo = echocardiogram; ECG = electrocardiogram; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

Table 1
Baseline characteristics

Variable	Decreased f/u left ventricular ejection fraction (N = 16)	Normal f/u left ventricular ejection fraction (N = 34)	p-Value
Age (years) mean	65 ± 12	68 ± 15	0.43
Men	7 (44%)	13 (38%)	0.76
Height (inches) mean	66 ± 4	66 ± 5	0.89
Weight (pounds) mean	178 ± 46	198 ± 47	0.17
Hypertension	13 (81%)	25 (74%)	0.73
Diabetes mellitus	5 (31%)	9 (26%)	0.75
Coronary artery disease	3 (19%)	13 (38%)	0.21
Heart failure	7 (44%)	15 (44%)	1.0
Medications			
Beta-Blockers	6 (38%)	11 (32%)	0.76
Angiotensin converting enzyme inhibitor/Angiotensin receptor blocker	8 (50%)	11 (32%)	0.35
Aldosterone Antagonist	2 (13%)	3 (9%)	0.65
ECG Findings			
Heart Rate (beats per minute) mean	70 ± 16	76 ± 15	0.28
PR	193 ± 22	179 ± 34	0.08
QRS	146 ± 14	141 ± 14	0.19
QT	448 ± 39	438 ± 39	0.47

years) in both patients with decreased LVEF and those without unchanged follow-up LVEF, p = 0.95 for difference between groups. Patients who developed decreased LVEF had a mean follow-up LVEF of 37.0% (SD = 8.1%) with a mean LVEF change of −14.9% (SD = 8.3%) whereas patients who had normal follow-up LVEF had a mean follow-up LVEF of 54.5% (SD = 2.5%) with a mean change in LVEF of −0.4% (SD = 4.5%).

Baseline patient characteristics stratified by outcome are summarized in Table 1. Patients who developed decreased LVEF were similar to those who did not in all respects. Nearly half the population had a diagnosis of HF with preserved EF at the time of the baseline echocardiogram. Baseline echocardiogram findings stratified by outcome are summarized in Table 2. Patients who developed decreased LVEF had a lower baseline LVEF than patients who did

Table 2
Baseline echocardiogram characteristics

Variable	Decreased f/u left ventricular ejection fraction (N = 16)	Normal f/u left ventricular ejection fraction (N = 34)	p-Value
Left ventricular ejection fraction (%) mean	51.9 ± 2.2	54.9 ± 4.4	0.003
Global longitudinal strain (%) mean	−16.7 ± 3.0	−16.7 ± 3.1	0.99
Dyssynchrony pattern			0.19
Classical	8 (50%)	14 (41%)	
Transitional	2 (13%)	12 (35%)	
Other	6 (37%)	8 (24%)	
Septal thickness (mm) mean	11.9 ± 3.0	12.5 ± 3.4	0.57
Lateral thickness (mm) mean	11.4 ± 1.6	10.9 ± 3.0	0.41
Left ventricular hypertrophy	6 (32%)	10 (32%)	1.0
E wave amplitude (m/s) mean	78.3 ± 27	80.9 ± 30	0.76
A wave amplitude (m/s) mean	94.3 ± 30	93.8 ± 31	0.96
E/A ratio mean	0.88 ± 0.4	0.90 ± 0.3	0.85
E/e' ratio mean	13.6 ± 4.6	15.4 ± 6.9	0.28
Diastolic dysfunction grade			0.25
0	1	7	
I	10	18	
II	4	9	
III	1	0	
Heart rate (beats per minute) mean	72 ± 11	67 ± 8	0.34
Isovolumic contraction time (% RR) mean	13.8 ± 3.9	11.5 ± 2.5	0.04
Ejection time (% RR) mean	33.4 ± 3.4	31.3 ± 4.2	0.07
Isovolumic relaxation time (% RR) mean	16.7 ± 3.6	13.2 ± 2.3	0.002
Diastolic filling time (% RR) mean	35.9 ± 6.8	44.4 ± 4.5	0.0002
Myocardial performance index mean	0.92 ± 0.23	0.80 ± 0.2	0.05

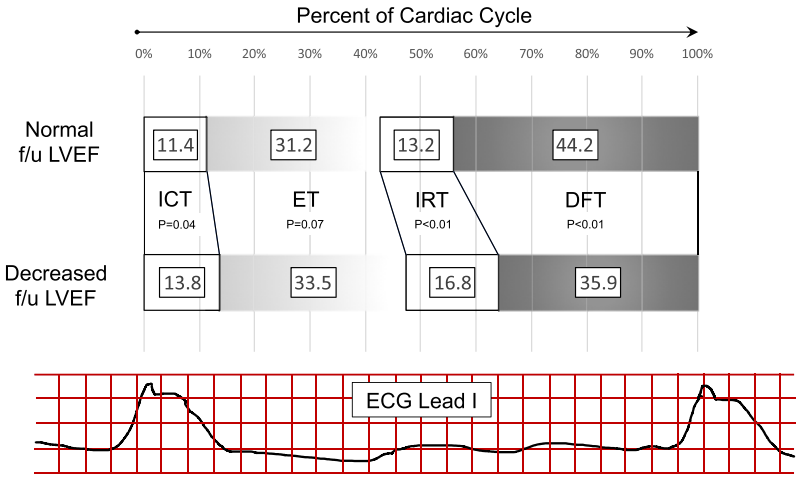

Figure 2. Box plots comparing the mean percentage of the cardiac cycle occupied by each of the 4 cardiac phases by study group. Patients who did not develop left bundle branch block associated decreased left ventricular ejection fraction *(top)* are compared to patients who did develop left bundle branch block associated decreased ejection fraction *(bottom)*. Differences in the mean isovolumic contraction time, isovolumic relaxation time, and diastolic filling time were statistically significant ($p < 0.05$ for all). ECG lead I demonstrates left bundle branch block. DFT = diastolic filling time; ECG = electrocardiogram; ET = ejection time; f/u = follow-up; IRT = isovolumic relaxation time; ICT = isovolumic contraction time; LVEF = left ventricular ejection fraction.

not (51.9%, SD = 2.2% vs 54.9%, SD = 4.4%, $p < 0.01$ for difference). Isovolumic contraction made up a larger percentage of the cardiac cycle in patients who later developed decreased LVEF (13.8%, SD 3 .9%) than in those who did not (11.5%, SD = 2.5%, $p = 0.04$ for difference). Isovolumic relaxation also made up a larger percentage of the cardiac cycle in patients who later developed decreased LVEF than in those who did not (16.7% SD = 3.6% vs 13.2% SD = 2.2%, $p < 0.01$ for difference). As a consequence, DFT accounted for a smaller percentage of the cardiac cycle in patients who developed decreased LVEF (35.9%, SD = 6.9%) compared with those who did not (44.4%, SD = 4.5%) $p < 0.01$ for difference (Figure 2). ET was prolonged in patients who later developed decreased LVEF compared with those who did not, but this difference was not significant ($p = 0.07$). The distributions of DFT in patients with and without development of decreased LVEF are shown in Figure 3.

Logistic regression modeling including DFT as a percentage of the cardiac cycle as the sole variable had a Wald Chi-square of 22.7 and a C-statistic of 0.86 ($p < 0.0001$) for prediction of decreased LVEF. A DFT interval <38% of the cardiac cycle had a sensitivity of 68.8%, a specificity of 97.3%, a positive predictive value of 91.7% and a negative predictive value of 86.8% for the development of decreased LVEF. Patients with a DFT interval accounting for <38% of the cardiac cycle had a relative risk of developing decreased LVEF of 6.97 (95% CI 3.0 to 16.0) compared with patients with a DFT interval accounting for ≥38% of the cardiac cycle.

Logistic regression modeling including DFT as a % of the cardiac cycle and baseline LVEF as the only included variables had a Wald Chi-square of 27.0 and a C-statistic of 0.90, ($p < 0.0001$) for prediction of decreased LVEF. The multivariable model had a sensitivity of 93.8%, specificity of 82.3%, positive predictive value of 71.4% and negative predictive value of 96.6% for the development of decreased LVEF.

Discussion

In our cohort of 50 patients with LBBB and normal LVEF, 16 (32%) developed decreased LVEF. Baseline patient characteristics were not associated with the risk of developing decreased LVEF, however, baseline echocardiographic variables including lower LVEF, longer ICT and IRT, and shorter DFT were associated with the risk of developing decreased LVEF.

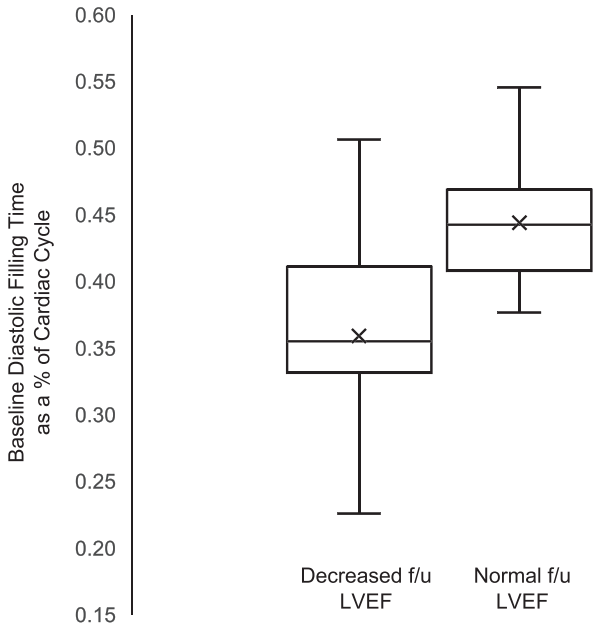

Figure 3. Box and whisker plot of diastolic filling time as % of the cardiac cycle among patients who developed left bundle branch block-associated decreased left ventricular ejection fraction and those who did not. Median is solid line, box demarcates the 25th and 75th percentiles, and whiskers mark the minimum and maximum values, the X marks the mean. LVEF = left ventricular ejection fraction.

The current ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR appropriate use criteria statement supports the use of CRT as a class I indication for treatment of HF in patients with LBBB, QRS duration ≥150 ms, NYHA class II−IV HF, and LVEF ≤35%.[16] Few data exist supporting the use of CRT in patients with an LVEF >35%,[17] despite this, CRT implantation receives a class IIb indication in patients with LBBB, LVEF 36% to 50%, and QRSd >150 ms.[18] LBBB associated decreased LVEF rarely improves with the use of guideline directed medical therapies but has a high likelihood of improving with CRT, particularly if it is implemented early after diagnosis.[2,4,19] Our data suggest that echocardiographic assessment of DFT using tissue Doppler imaging may facilitate the identification of patients with LBBB at high risk for developing decreased LVEF. Based on these findings, patients with LBBB and LVEF ≥50% who have a DFT that accounts for <38% of the cardiac cycle may benefit from close clinical and echocardiographic follow-up to facilitate early CRT implantation. Additionally, future studies evaluating whether prophylactic CRT implantation may prevent decreased LVEF in this high-risk group may be warranted.

Recently a variety of clinical[20] and echocardiographic[21] characteristics have been evaluated to determine if it is possible to predict the development of LBBB associated reduced LVEF. LV hypertrophy, defined as LV mass >300 g predicted a higher likelihood of developing decreased LVEF in one series.[21] Dyssynchronous LV contraction results in early septal contraction against a passive lateral wall resulting in stretching of the contractile apparatus of the lateral wall. This additional stretch leads to abnormally vigorous late contraction of the lateral wall by the Starling mechanism.[22] Over time this vigorous contraction can lead to lateral wall hypertrophy.[23] We did not find any association of LV hypertrophy or HF with preserved EF with the likelihood of development of decreased LVEF. Specifically, we found no association between the lateral wall thickness and risk of development of decreased LVEF. This may be due to the strict entry criteria employed in our study, designed to reduce the likelihood of including patients at high risk for developing decreased LVEF from causes other than LBBB.

Isovolumic contraction, ejection, isovolumic relaxation and diastolic filling must all occur within the fixed period of the cardiac cycle as determined by the heart rate. Assuming the heart rate remains fixed, prolongation of one cardiac phase necessitates shortening of others (Figure 2). When LBBB initially develops, the newly dyssynchronous LV contraction results in immediate attenuation of $dP/dT_{maximum}$[24] and prolongation of isovolumic contraction. Similarly, dyssynchronous LV relaxation results in immediate attenuation of $dP/dT_{minimum}$[23] and prolongation of isovolumic relaxation. Prolongation of the isovolumic phases with an unchanged heart rate may then result in compression of the DFT as observed in our patients. It is conceivable that chronically compressed DFT may cause chronic LV underfilling and symptomatic HF with preserved EF in patients with LBBB, particularly at faster heart rates. Chronic LV underfilling due to compressed DFT may also contribute to the protein dysregulation and Ca^{++} handling abnormalities observed in patients who go on to develop LV dilation and reduced LVEF.[25] Conversely, compressed DFT may simply be an effective marker of the severity of LV dysfunction occurring as a result of LBBB-induced dyssynchrony. Further, experimental work evaluating the effect of DFT compression on the fundamental mechanisms of LV remodeling is warranted.

This is a single center retrospective series designed to explore whether baseline echocardiographic data could predict subsequent development of decreased LVEF. As such, it is limited by the referral and ascertainment biases of this study design. The patients were carefully selected and had few cardiovascular co-morbidities to try to ensure we captured LBBB-associated decreased LVEF and minimized the frequency of other causes of decreased LVEF. The findings should be verified in larger datasets from other locations. The small sample size is a result of the strict entry criteria applied to increase the specificity of the findings for prediction of LBBB-associated decreased LVEF over other causes of decreased LVEF. This small sample size limited our ability to perform extensive multivariable analyses and may have prevented us from identifying other weaker associations between echocardiographic, electrocardiographic, and clinical variables and the development of LBBB associated decreased LVEF. The derived predictive model should be validated in an independent validation cohort.

In conclusion, echocardiographic tissue Doppler imaging assessment of DFT predicted the risk of developing decreased LVEF among patients with LBBB and normal baseline LVEF.

Disclosures

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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