Title: Left Ventricular Regional Contraction Abnormalities by Echocardiographic Speckle Tracking in Combined Right Bundle Branch with Left Anterior Fascicular Block Compared to Left Bundle Branch Block

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Abstract

Background: In contrast to LBBB patients less is known about patients with RBBB+LAFB regarding LV contractile abnormalities and the potential role of CRT. This study investigated whether patients with RBBB+LAFB morphology have echocardiographic mechanical strain abnormalities between the inferior and anterior LV walls, similar to abnormalities between septal and lateral walls in LBBB.

Methods and Results: Ten healthy volunteers with no-BBB, 28 LBBB and 28 RBBB+LAFB patients were included in this retrospective study. Two-dimensional regional-strains were obtained by speckle-tracking. Scar was assessed by CMR. Response on echo was defined as a Classical, Borderline or Other pattern. The number of Classical patterns in LBBB was significantly higher than in RBBB+LAFB and no-BBB groups ($p<0.001$ for both). Contrary, the RBBB+LAFB group showed a significantly higher number of Borderline patterns compared to other groups (LBBB: $p=0.042$, no-block: $p=0.012$). In addition, RBBB+LAFB patients had more scar than LBBB patients (9.9% vs 3.4%, $p=0.041$), and the average amount of scar in each wall was also higher in RBBB+LAFB (<5% in LBBB and <16% in RBBB+LAFB).

Conclusions: Patients with RBBB+LAFB on ECG and clinical HF demonstrate echocardiographic wall motion abnormalities between inferior and anterior LV walls, similar to abnormalities found between septal and lateral LV walls in patients with LBBB and HF. Fewer patients with RBBB+LAFB showed a Classical pattern of opposing wall motion compared to LBBB. Factors that might alter strain patterns in RBBB+LAFB, including the detailed presence or absence of LV scar and coexisting block of the central fascicle, should be assessed in future studies.

Keywords: right bundle branch block, left anterior fascicular block, speckle tracking echocardiography, regional strain, strain patterns, dyssynchrony

Introduction

Cardiac resynchronization therapy (CRT) has been shown to improve left ventricular (LV) function, decrease clinical symptoms of heart failure, improve quality of life, and decrease mortality in selected patients with LV systolic dysfunction and prolonged QRS duration.¹⁻³ However, only when this is caused by complete left bundle branch block (LBBB).^{4,5}

In the presence of LBBB, the time between electrical activation of the interventricular septum and the LV lateral wall is prolonged. However, it has been demonstrated that approximately one-third of patients with heart failure and low ejection fraction, diagnosed with LBBB by “conventional LBBB criteria”, fail to respond to CRT.⁶⁻⁸ These patients may have a widening of the QRS caused by slow conduction through the LV myocardium due to ischemia, scar or other reasons, rather than by a true block of the left bundle.⁹ To differentiate these causes from a true LBBB, Strauss et al. recently proposed strict electrocardiographic (ECG) criteria for LBBB,⁸ while Risum et al. showed a relationship between these criteria and mechanical LV contraction, determined by echocardiographic speckle tracked strain analysis.¹⁰ In addition, recent studies demonstrated that patients who met the strict LBBB criteria on ECG¹¹⁻¹³ and those with the physiologically based echo strain abnormality of LBBB⁹ more frequently benefited from CRT. However, also the amount and location of scar influences response.

Compared to LBBB, patients with right bundle branch block (RBBB) are less likely to respond to CRT,^{14,15} since there is no target myocardium to be resynchronized using conventional CRT lead placements, in the absence of LV conduction delay.¹⁶ However, patients with both RBBB and left anterior fascicular block (RBBB+LAFB) may provide a potential target for CRT due to an activation delay between their inferior and anterior LV walls.¹⁷ This may be clinically relevant, as it has been demonstrated that patients with heart failure in combination with conduction disorders have an increased mortality rate compared to patients with a narrow QRS,¹⁸ even though a recent analysis found no significant difference between LBBB and other types of bifascicular blocks (RBBB+LAFB or RBBB+LPFB).¹⁹ To our knowledge, no studies have been conducted investigating the contraction pattern in patients with RBBB and LAFB. Accordingly, this study was performed to test the hypothesis that patients with combined RBBB and LAFB morphology on ECG showed echocardiographic contractile abnormalities indicating a significant activation delay between the inferior and anterior LV walls, similar to the abnormalities between septal and lateral LV walls in patients with LBBB. To answer this question we performed two separate analyses, one small feasibility study comparing different strain vendor methods and one analysis in the overall study population using only one strain vendor method.

Material and methods

Study population

Sixty-six subjects from Duke University Medical Center were included in this retrospective study between 2011 and 2013. There were ten normal volunteers (without bundle branch block) and 56 patients with prior diagnosis of heart failure (28 with LBBB and 28 with RBBB+LAFB). Heart failure diagnosis was identified by International Classification of Disease 9th revision (ICD-9) billing codes.

The 10 normal volunteers had no cardiac history and had a normal ECG, chest X-ray and echocardiogram. Cardiac magnetic resonance (CMR) studies were not performed in this group. Subjects in the LBBB and RBBB+LAFB groups were randomly selected from those with a clinical diagnosis of heart failure, and underwent a transthoracic echocardiogram and cardiovascular magnetic resonance studies as part of routine clinical care. Among these patients, many had multiple echocardiographic and ECG studies performed and therefore those studies closest in time to CMR were selected. The study protocol was approved by the Duke University Institutional Review Board.

Electrocardiography

A standard 12-lead ECG was recorded at a paper speed of 25 mm/s. Subjects were allocated to 3 groups: no bundle branch block (no-BBB) (Group I), strict LBBB (Group II), or RBBB+LAFB (Group III). All ECGs were interpreted independently by three observers blinded to all patient data, except for gender. Differences in interpretation were resolved by consensus.

Strict LBBB was defined as: (1) QRS duration ≥ 140 ms in men or ≥ 130 ms in women, (2) QS or rS in lead V1, and (3) mid-QRS slurring or notching in ≥ 2 contiguous leads of V1, V2, V5, V6, I, and aVL.⁸

RBBB+LAFB was defined as: (1) QRS duration ≥ 120 ms, (2) left axis deviation of -45° to -90° , and (3) end of QRS positive in lead V1.

Cardiac magnetic resonance imaging

All CMR studies were performed using clinical 1.5-T scanners (Siemens Sonata or Avanto; Siemens, Malvern, Pennsylvania) using a previously described full CMR protocol.^{20,21} Studies were read by consensus of two experienced readers, blinded to clinical data. Delayed-enhancement MRI was used to detect myocardial scar. Hyperenhancement was visually scored by using the 17-segment model with a five-point scale for every segment, in which 0 = no hyperenhancement, 1 = 1-25%, 2 = 26-50%, 3 = 51-75%, and 4 = 76-100%. Total size of left ventricular scarring as a percentage of LV myocardium was calculated by summing the regional scores

(using the midpoint of the range of hyperenhancement for every segment) and dividing by the total number of regions (n=17). Ejection fraction (EF) was also measured. The presence of any amount of scar (>0%) and the total amount of scar in any wall (% LV) in both the LBBB and RBBB+LAFB groups were measured.

Echocardiography

All echocardiograms were performed using either GE Vivid E9 (GE Healthcare, Horten, Norway) or Philips iE33 (Philips Medical Systems, Andover, MA, USA) ultrasound systems with mid frequency (~3.5 MHz) broadband probes according to standard clinical protocols, that included apical two, three, and four chamber views. Equipment used for the echocardiographic examination was random in the sense that it was based solely on equipment availability at the time and place of fulfilment of the clinical requested echo. All echocardiograms were reviewed by two investigators, where LV internal dimensions in diastole (LVID_d) and systole (LVID_s) were measured according to American Society of Echocardiography standards²², and the quality of the echocardiograms for subsequent strain analysis was recorded.

Strain analysis

All qualifying echo studies underwent longitudinal regional and global strain analysis in all available apical views. For consistency of method, all echocardiographic strain analyses were performed by one unblinded investigator, experienced in obtaining and analyzing regional and global speckle tracked strain using multiple software programs. The strain reference point was placed at the beginning of the QRS complex in all studies, while time to aortic valve closure (AVC) was measured by pulsed-wave Doppler in the left ventricular outflow tract and appropriately noted.

The studies performed on a GE machine, with frame rates of approximately 60 frames/second available in native data, underwent strain analysis from vendor specific software (VSS) (GE EchoPACS BT 11, General Electric Ultrasound, Horten, Norway). Such VSS studies fulfilled generally accepted standards of frame rate and native data requirements for strain analysis. All studies, whether performed on GE or Philips machines, were available in DICOM format, capitated at 30 frames/second and were analyzed in this format using vendor-independent software (VIS) (TomTec Cardiac Performance Analysis, version 4.5, Munich, Germany). Thus, TomTec VIS strain information was available in all subjects while GE VSS was available for comparison to VIS in only a few subjects. The investigator performing the VSS and VIS was obviously unblinded to the results of the different methodologies in the cases where correlative strain information was available.

Global and regional strain curves, whether by VSS or VIS, were then recorded in .jpg format for all apical views. Each .jpg image was de-identified, randomly and uniquely numbered and then made available for later review by three other investigators, who were completely blinded to clinical and patient personal data. While the .jpg images were identified as derived from two, three, or four chamber views, the various views could not be related to one another in the same subject. Available strain patterns in each of the three apical views in each subject, whether by VSS or VIS, were classified as Normal, Classical, Borderline or Other. No time-to-peak or other timing analysis was performed. For the purpose of this study, a Normal regional strain pattern was determined when all segments peaked at, or peaked near AVC. A Classical pattern was identified according to the criteria previously described by Risum et al.^{9,10} The definition of a Classical pattern (Figure 1) for LBBB consisted of: (1) early contraction of at least one basal or midventricular segment in the septal or anteroseptal wall and early stretching in at least one basal or midventricular segment in the opposing lateral wall, (2) early peak contraction does not exceed 70% of ejection phase (in case of double peaks, only the first peak is considered), and (3) the early stretching wall shows peak contraction after AVC. This definition, for the purpose of this study, was extended to include all strains that fulfilled the timing requirements of Risum et al.,⁹ no matter the opposing wall pairs, to include patients with RBBB+LAFB.

The Borderline pattern was introduced for the purpose of this study and identified as a Classical pattern, except for termination of contraction of the opposite early wall, which was not within the 70% criteria of the estimated ejection phase noted in the Classical pattern group. Thus, a Borderline pattern “almost” fulfilled Classical criteria. The Other pattern comprised those who did not fulfil Normal, Classical or Borderline criteria. This group included any other minor or major heterogeneous or other timing abnormalities. Examples of strain patterns found in each Group are shown in Figure 2. Differences in interpretations were resolved by consensus between all observers.

Feasibility subpopulation evaluating TomTec reproducibility

While TomTec was available in all of our subjects to answer our main hypothesis, to our knowledge there have not been any studies that compare regional strain patterns between TomTec and GE. However, TomTec has been shown to have good reproducibility as well as quantitative pattern correlation to those determined by GE EchoPAC 18 (BT11) for Global Longitudinal Strains (GLS).²³ To be able to use TomTec methods for regional strains in our overall population a small feasibility comparison between the two methods first had to be performed. Next, the analysis for our main hypothesis in the overall study population (‘Overall

Population') was performed. GE VSS uses native ultrasound data, while TomTec uses DICOM data, and GE and TomTec methods vary in the algorithms used for strain determination. Accordingly, a "feasibility echo subpopulation" was created from amongst the 12 subjects, who had available GE VSS analyses at native data (60 frames/second) and TomTec VIS analyses (30 frames/second) DICOM data. The purpose of the subpopulation was to determine whether GE and TomTec regional patterns were at all comparable before the main body of the study, using only TomTec VIS, could continue. Of the 12 subjects included in this feasibility subpopulation, two had no-BBB, nine had LBBB and one had RBBB+LAFB.

This small feasibility subpopulation was not meant to be a complete comparative analysis between GE VSS and TomTec VIS. As explained in the Discussion, there are many reasons to assume these should not compare precisely in amplitude or timing of individual regional segments. The intent was only to establish some preliminary context, as to whether regional VSS and VIS strain results used in this study could produce somewhat similar patterns, to allow derivation of patterns from the large retrospective populations.

Overall population

Next, as part of our main hypothesis, strain patterns between all subjects with LBBB and those with RBBB+LAFB were evaluated. Only TomTec was used in this experimental population (Figure 3). All investigators and procedures were identical as in the first part of this study unless mentioned otherwise. The moving two-dimensional echocardiograms were then reviewed in conference of two investigators where internal LV diameter in diastole (LVID_d) and systole (LVID_s) from the parasternal long axes were determined for each subject.

Statistical analysis

Continuous variables (mean $\pm$ SD and median with interquartile ranges) were compared using a two-sided *t* test. Categorical variables (percentages) were compared using χ^2 statistics, including the number of subjects showing a Normal, Classical, Borderline, or Other strain pattern. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics (Version 22.0, SPSS Inc, Chicago, IL, USA).

Results

Study population

Baseline characteristics of the subjects are listed in Table 1. No differences between the LBBB and RBBB+LAFB groups were observed regarding age, gender, QRS duration, LVEF, LVID_d, LVID_s and global strain. The no-BBB (compared to the LBBB and RBBB+LAFB groups) were significantly younger, had shorter QRS duration, smaller LVID_s and larger LVEF and global strain. None of the subjects had documented any significant mitral regurgitation.

ECGs were obtained at a median of seven and four days after the echocardiogram (interquartile range 1-109 vs 1-86 days, $p=0.777$) for the LBBB and RBBB+LAFB groups, respectively, while cardiac MRIs were obtained at a median of 19 and seven days after the echocardiogram (interquartile range 2-75 vs 2-109 days, $p=0.592$). In the subjects without bundle branch block, LVEF was reviewed by multiple observers in a different study to document normal ($\geq 50\%$). Also, ten LBBB and 15 RBBB+LAFB subjects showed a normal LVEF ($\geq 50\%$).

Feasibility subpopulation

The TomTec and GE regional strains were compared ($n=12$). As can be seen from Table 2, ten subjects showed the same pattern in both software modalities in any view and two subjects showed disagreements. Thus, there was an overall agreement between GE and TomTec software in 83% (10/12) of the subjects. This number allowed us to use TomTec regional strains to answer the main hypothesis, since the little discrepancies would not affect our overall conclusion. The inter-observer agreement was 92% (33/36 strain images).

Overall population

The distributions of strain pattern by conduction abnormality are shown in Figure 4 for all subjects in the study ($n=66$). 9/10 subjects with no-BBB showed a Normal strain pattern. One subject with no-BBB showed an Other pattern in the three chamber view. Twenty LBBB subjects showed the Classical pattern, five the Borderline, and three the Other pattern. No patients with LBBB had the Normal pattern. In the RBBB+LAFB group, six Classical patterns were observed, 12 Borderline, nine Other and one Normal pattern. Patients with LBBB were more likely to show the Classical dyssynchrony pattern than patients in the RBBB+LAFB and no-BBB groups ($p<0.001$). Patients with RBBB+LAFB were more likely to demonstrate the Borderline strain pattern compared to the other groups (LBBB $p=0.042$, no block $p=0.012$). Patients with RBBB+LAFB were more likely to demonstrate LV scar compared to patients with LBBB (67.9% vs 46.4% of patients), but this

difference was not statistically significant ($p=0.105$). However, the overall amount of scar was higher in RBBB+LAFB patients compared to LBBB patients (9.9% vs 3.4%, $p=0.041$), more specifically in the anterior (15.2% vs 2.1%, $p=0.016$) and septal walls (14.1% vs 4.7%, $p=0.022$).

Discussion

This study showed that some subjects with combined RBBB and LAFB morphology on ECG have a Classical strain pattern between the inferior and anterior LV walls, indicating the presence of a significant activation delay in the anterior LV. This is similar to previous observation in patients with ECG LBBB morphology showing abnormalities between septal and lateral LV walls. In those subjects with RBBB+LAFB who do not manifest the Classical pattern, a high rate of evident Borderline patterns is seen in comparison to LBBB and Normal subjects. Taken together, 18/28 patients with RBBB+LAFB (64%) showed evidence of LV mechanical delay between the inferior and anterior LV walls. To our knowledge, this is the first series to detect this pattern of opposing wall motion in multiple patients and compare it to patients with LBBB.

Opposing wall motion in bundle branch block by strain

There is accumulating evidence that the Classical pattern of opposing wall motion detected by echo gray scale speckle tracked strain reflects the abnormal physiology of LBBB, postulated over the years by Gwartz and Franklin in dogs²⁴, Breithardt²⁵, and others. Risum first reported the opposing wall motion using speckle tracked strain in patients undergoing CRT, to predict successful reduction in LV end systolic volume and increase in EF in nearly 92% of subjects with a Classic pattern from a single center study.⁹ Near simultaneously, Leenders and Prinzen²⁶ used computer modelling of strain to validate the principle. Forsha et al. reported the Classical pattern in a large series of children with dilated cardiomyopathy and ECG evidence of strict LBBB while Risum et al. also correlated the Classical pattern to strict ECG LBBB criteria.¹⁰ More recently, Risum et al also reported a large number of patients from multiple centers that further established the utility of the Classical strain pattern, that suggested the pattern was useful in predicting long term survival in patients undergoing CRT, even in patients with minimal widening of the QRS complex.²⁷ The current analysis is building upon the principle of the Classical pattern, but except for patients with LBBB, who mostly show this pattern, also includes a new group of patients with RBBB+LAFB.

Reproducibility of interpretations

Interpretations of both ECG and strain data had a high rate of inter-observer reproducibility (93% for ECG and 92% for echo) in this study, with interpreters blinded to patient identifiers. Echo strain studies were identified only by unique random numbers and view. Each echo interpreter was blinded to the results of the others and the few discrepancies noted were adjudicated by group agreement.

The feasibility comparisons

An initial inquiry into the ability of TomTec software to detect opposing wall motions, as compared to GE software in the same images, was necessary before applying the TomTec methodology to the larger group of subjects in this study. To date, only GE systems have been used in reported series. Unfortunately, GE software cannot be used to analyze images from other manufacturers of ultrasound imaging equipment and this limitation restricts the use of GE software in retrospective series where non-GE equipment was used. Thus, the feasibility comparisons were performed. While data does exist in global strains between systems, there is no data concerning the correlations between software analytic systems.

The comparison of GE VSS and TomTec VIS for regional strains, while limited in numbers, was surprisingly encouraging and indicated that proceeding to apply TomTec to the retrospective DICOM images from other manufacturers was appropriate, when strain images were subjected to blinded interpretation by multiple interpreters. These feasibility observations, while adequate for this limited investigation, should not be construed as a complete validation of methodologies for regional strains. While patterns could be adequately discerned and differentiated, there were differences in precise measures of timing and amplitude that require more detailed study, if quantitative measures are ever applied. Clinical experience with TomTec indicates that it takes two or more analyses in each view before confirming that a tracing is acceptable for review. Furthermore, it should be noted that the investigator who prepared the strain curves was unblinded to the results of the comparative software, likely biasing the comparisons as favorable. For the purposes of this study, such bias can be argued as acceptable, since it was applied equally to strain analysis from all subjects in this study.

Patient selection

Note that the subjects in this study with LBBB or RBBB+LAFB all had symptomatic heart failure, but were qualified for inclusion only because they had ECG evidence of either LBBB or RBBB+LAFB, MRI and echocardiography, without excluding myocardial infarction. As such, the subjects in this study were from populations of convenience to initially explore the possibility that such opposing wall delays could be seen in

subjects with RBBB+LAFB. There were no qualifications for abnormal ventricular size or reduced ejection fraction, resulting in a large variance in LVEF (between 15-60% for RBBB+LAFB and 10-60% for LBBB patients). However, previous studies assessing the Classical strain pattern have only included patients with ejection fraction <35%.

MRI and echo studies were indicated for a variety of symptoms related to heart failure, but there was no attempt to clinically include or exclude patients for other reasons. The original purpose was to include 30 patients in each of the BBB groups. The patients included in each group were otherwise unselected in any way. It is likely that there are other patients with ECG evidence of BBB without both imaging studies, who possessed a variety of other clinical factors that may have influenced the results. Likewise, there were other patients with the qualifications that were not included once the patient groups reached 30 subjects each. All previous studies of the Classical pattern were performed in patients qualifying for CRT (ejection fraction $\leq$ 35%, Class II-IV NYHA heart failure, and widened QRS), which is not the case in the current study.

No implications of the presence or absence of any abnormal strain pattern in relationship to history of myocardial infarction, ventricular size and ejection fraction should be made from the present data. Menet et al. showed that the frequency of mechanical dyssynchrony in patients with HFpEF was similar to patients with HFrEF without LBBB.²⁸ There were subjects in this study with altered strain patterns (Classical, Borderline or Other), who had normal LV size and normal EF, but no implications regarding heart failure with preserved EF (HFpEF) can be made.

Classical, Borderline and Other patterns

While there is substantive evidence that the Classical pattern on speckle tracking echocardiography can be related to unopposed contraction of the early wall, with late contraction of the wall affected by delayed activation, it should be noted that all evidence to date requires that the early wall terminates contraction within 70% of the ejection phase.⁹ The current study introduces a Borderline pattern only because there were multiple subjects in this study with late contraction of one wall, but the early termination of the opposing wall was not within 70% of the ejection phase. There has only been one other retrospective study concerning the onset of abnormal strain patterns in relationship to the onset of LBBB.²⁹ Clinical experience in this echocardiographic laboratory indicates that the Borderline pattern may appear soon after LBBB onset and before the LV dilates. Whether the Borderline pattern progresses to the Classical pattern is not proven and the concept of progression awaits further examination and review. Obviously, not all patients with LBBB progress to LV dilatation and

reduced EF. Such is also likely true of RBBB+LAFB subjects. It is, nevertheless, curious that the Classical strain pattern was manifest less commonly among subjects with RBBB+LAFB than among subjects with LBBB (21.4 vs. 71.4%). The Other pattern used in this study has no special identity, except that it does not include those with a clear Classic or Borderline pattern. This is more a category of exclusion for the purposes of this investigation and the possibility that it contains subpatterns or other characteristics of potential importance is not excluded.

Relationship to scar burden

The present study suggests that patients with RBBB+LAFB have higher overall amount of scar than those with LBBB alone. Many of the present findings (such as the Borderline pattern) may be explained by variable conduction through the interventricular septum, or differences in LV scar amount. Leenders and Prinzen²⁶ have suggested that progression of strain patterns is possible from their computer modelling when the presence, location and extent of myocardial scar are taken into consideration. If the mechanical delay resulting from an electrical activation delay involves muscle capable of contracting, it is likely correctable. When muscle is extensively scarred, the involved wall cannot contract normally and frequently results in a stretch of the involved segments by strain analysis. We did not encounter any subject with holosystolic stretch of an LV wall. Becker³⁰ has suggested that the amount and location of scar by MRI has importance regarding the ability of a given segment to mechanically respond. In this study, many of the subjects in the two bundle branch block populations had scar, although the average scar in each wall (anterior, inferior, lateral, septal) was relatively low (<5% for LBBB and <16% for RBBB+LAFB). However, there were individual patients that had higher amounts of scar in any single wall, potentially explaining why the Classical pattern was less prevalent among RBBB+LAFB patients. The relationship between amounts of scar in specific walls with regard to dyssynchrony patterns will be assessed in detail in a future study.

Location of strain abnormalities

The current study hypothesized that the mechanical delay in a subject with RBBB+LAFB would be between the inferior or inferolateral and anterior or anteroseptal LV walls. Indeed, when shown as a Classical or Borderline pattern, this was true. It needs to be remembered that echo examinations were conducted in the standard apical 2, 3 and 4 chamber views and it is possible the opposing walls of late contraction and early termination were between these standard interrogating planes.³¹ It is also possible that LV strain determined from conventional ultrasound frame rates between 30-100 frames/second are inadequate to detect the rapid activation changes noted by ECG. Standard echocardiographic frame rates sample between 10-30 msec. Inferior echo

image quality due to poor sound transmission characteristics might also confound proper tracking of the longitudinal wall movement.

Central fascicle

When considering RBBB+LAFB, another factor that could confound precise correlation of ECG and strain findings and have implications for CRT, could be the presence or absence of central fascicular block. The central fascicle, when present, lies between the left anterior and left posterior fascicle and depolarizes the interventricular septum from left to right. The septum is also normally activated from right to left by the right bundle branch. When RBBB+LAFB is present with an intact central fascicle, the septum may be activated normally and there may be no, or less, mechanical delay between the anterior and inferior LV walls. But, when RBBB+LAFB occurs and includes a block of the central fascicle, the septum will be activated late starting from the left posterior fascicle. Thus, in cases of RBBB+LAFB + central fascicular block, a patient may be more likely to have appropriate mechanical delays amenable to benefit from CRT. Identifying ECG patterns associated with central fascicular block in the setting of RBBB+LAFB may be beneficial if this phenomenon is associated with the presence of anterior wall delay. In our patient population, we did not have the information needed to test this hypothesis and further study of this phenomenon is necessary.

Future considerations

It remains to be determined whether these findings have therapeutic implications for CRT in patients with RBBB+LAFB. The current study has no information as to the use of CRT in any of our patient groups. A future study should include a CRT population to determine the value of speckle tracking in the selection of RBBB+LAFB patients for therapy.

Limitations

In addition to the factors previously discussed, further limitations should be noted. Clinical diagnostic ECG and imaging assessments were performed for a variety of clinical purposes, and time between performance of ECG, MRI and echocardiogram was sometimes more than three months. The populations examined were small and used only to initially explore the possibility of the original hypothesis. This population was chosen from amongst those patients with clinical evidence of heart failure selected from ICD-9 billing codes, which had ECG evidence of LBBB or RBBB+LAFB and had both MRI and

echocardiography. It is likely that there are other patients with ECG evidence of BBB who did not have both imaging studies, but possessed a variety of other clinical factors that may have influenced the results.

Conclusions

Patients with RBBB+LAFB and clinical HF frequently demonstrate echocardiographic speckle tracked wall motion abnormalities between the inferior and anterior LV walls similar to the abnormalities found between the septal and lateral LV walls in patients with LBBB and HF. Such a possibility has been conjectured, but heretofore, never shown. Fewer patients with RBBB+LAFB show a Classical pattern of opposing wall motion by echo compared to LBBB subjects. Factors that might alter echocardiographic strain patterns in patients with RBBB+LAFB, including details about the presence or absence of LV scar and coexisting block of the central fascicle, will be assessed in a future study.

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References

1. Moss A, Hall W, Cannom D, Klein H, Brown M, Daubert J, Estes N, 3rd, Foster E, Greenberg H, Higgins S, Pfeffer M, Solomon S, Wilber D, Zareba W, Investigators MADIT-CRT. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med*. 2009;361:1329-38.
2. Tang A, Wells G, Talajic M, Arnold M, Sheldon R, Connolly S, Hohnloser S, Nichol G, Birnie D, Sapp J, Yee R, Healey J, Rouleau J, Resynchronization-Defibrillation for Ambulatory Heart Failure Trial I. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med*. 2010;363:2385-95.
3. Linde C, Abraham W, Gold M, St John Sutton M, Ghio S, Daubert C, Group R. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol*. 2008;52:1834-43.
4. Zusterzeel R, Selzman K, Sanders W, Canos D, O'Callaghan K, Carpenter J, Pina I, Strauss D. Cardiac resynchronization therapy in women: US food and drug administration meta-analysis of patient level data. *JAMA Intern Med*. 2014;174:1340-8.
5. Zusterzeel R, Curtis J, Canos D, Sanders W, Selzman K, Pina I, Spatz E, Bao H, Ponirakis A, Varosy P, Masoudi F, Strauss D. Sex-specific mortality risk by QRS morphology and duration in patients receiving CRT: Results from the NCDR. *J Am Coll Cardiol*. 2014;64:887-94.
6. Auricchio A, Fantoni C, Regoli F, Carbucicchio C, Goette A, Geller C, Kloss M, Klein H. Characterization of left ventricular activation in patients with heart failure and left bundle-branch block. *Circulation*. 2004;109:1133-9.
7. Vassallo J, Cassidy D, Marchlinski F, Buxton A, Waxman H, Doherty J, Josephson M. Endocardial activation of left bundle branch block. *Circulation*. 1984;69:914-23.
8. Strauss D, Selvester R, Wagner G. Defining left bundle branch block in the era of cardiac resynchronization therapy. *Am J Cardiol*. 2011;107:927-34.

9. Risum N, Tayal B, Hansen TF, et al. Identification of Typical Left Bundle Branch Block Contraction by Strain Echocardiography Is Additive to Electrocardiography in Prediction of Long-Term Outcome After Cardiac Resynchronization Therapy. *J Am Coll Cardiol*. 2015;66:631-41.
10. Risum N, Strauss D, Sogaard P, Loring Z, Hansen T, Bruun W, Wagner G, Kisslo J. Left bundle-branch block: The relationship between electrocardiogram electrical activation and echocardiography mechanical contraction. *Am Heart J*. 2013;166:340-8.
11. Tian Y, Zhang P, Li X, Gao Y, Zhu T, Wang L, Li D, Wang J, Yuan C, Guo J. True complete left bundle branch block morphology strongly predicts good response to cardiac resynchronization therapy. *Europace*. 2013;15:1499-06.
12. Galeotti L, van Dam P, Loring Z, Chan D, Strauss D. Evaluating strict and conventional left bundle branch block criteria using electrocardiographic simulations. *Europace*. 2013;15:1816-21.
13. Mascioli G, Padeletti L, Sassone B, Zecchin M, Lucca E, Sacchi S, Boggian G, Tondo A, Belvito C, Bakhtadze N, Borrelli A, Sinagra G. Electrocardiographic criteria of true left bundle branch block: A simple sign to predict a better clinical and instrumental response to CRT. *Pacing Clin Electrophysiol*. 2012;35:927-34.
14. Zareba W, Klein H, Cygankiewicz I, Hall W, McNitt S, Brown M, Cannom D, Daubert J, Eldar M, Gold M, Goldberger J, Goldenberg I, Lichstein E, Pitschner H, Rashtian M, Solomon S, Viskin S, Wang P, Moss A. Effectiveness of cardiac resynchronization therapy by qrs morphology in the multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (madit-crt). *Circulation*. 2011;123:1061-72.
15. Rickard J, Bassiouny M, Cronin E, Martin D, Varma N, Niebauer M, Tchou P, Tang W, Wilkoff B. Predictors of response to cardiac resynchronization therapy in patients with a non-left bundle branch block morphology. *Am J Cardiol*. 2011;108:1576-80.
16. Risum N. Cardiac pacing in patients with heart failure and right bundle branch block. *J Electrocardiol*. 2015;48:74-8.

17. Hara H, Oyenuga O, Tanaka H, Adelstein E, Onishi T, McNamara D, Schwartzman D, Saba S, Gorcsan J 3rd. The relationship of QRS morphology and mechanical dyssynchrony to long-term outcome following cardiac resynchronization therapy. *Eur Heart J*. 2012;33:2680-91.
18. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML, Investigators MADIT II. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346:877-83.
19. Marti-Almor J, Cladellas M, Bazan V, Altaba C, Guijo M, Delclos J, Bruguera-Cortada J.. Long-term mortality predictors in patients with chronic bifascicular block. *Europace*. 2009;11:1201-7.
20. Kim R, Albert T, Wible J, Elliott M, Allen J, Lee J, Parker M, Napoli A, Judd R. Performance of delayed-enhancement magnetic resonance imaging with gadoversetamide contrast for the detection and assessment of myocardial infarction: An international, multicenter, double-blinded, randomized trial. *Circulation*. 2008;117:629-37.
21. Sievers B, Elliott M, Hurwitz L, Timothy A, Klem I, Rehwald W, Parker M, Judd R, Kim R. Rapid detection of myocardial infarction by subsecond, free-breathing delayed contrast-enhancement cardiovascular magnetic resonance. *Circulation*. 2007;115:236-44.
22. Lang R, Badano L, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf F, Foster E, Goldstein S, Kuznetsova T, Lancellotti P, Muraru D, Picard M, Rietzschel E, Rudski L, Spencer K, Tsang W, Voigt J. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the american society of echocardiography and the european association of cardiovascular imaging. *J Am Soc Echocardiogr*. 2015;28:1-39.
23. Risum N, Ali S, Olsen N, Jons C, Khouri M, Lauridsen T, Samad Z, Velazquez E, Sogaard P, Kisslo J. Variability of global left ventricular deformation analysis using vendor dependent and independent two-dimensional speckle-tracking software in adults. *J Am Soc Echocardiogr*. 2012;25:1195-03.

24. Gwirtz PA, Franklin D, Mass HJ. Modulation of synchrony of left ventricular contraction by regional adrenergic stimulation in conscious dogs. *Am J Physiol.* 1986;251:490-5.
25. Breithardt OA, Stellbrink C, Herbots L, Claus P, Sinha A, Bijnens B, Hanrath P, Sutherland G. Cardiac resynchronization therapy can reverse abnormal myocardial strain distribution in patients with heart failure and left bundle branch block. *J Am Coll Cardiol.* 2003;42:486-94.
26. Leenders G, Lumens J, Cramer M, DeBoeck B, Doevendans P, Delhaas T, Prinzen F. Septal deformation patterns delineate mechanical dyssynchrony and regional differences in contractility: Analysis of patient data using a computer model. *Circ Heart Fail.* 2012;5:87-96.
27. Kirn B, Jansen A, Bracke F, van Gelder B, Arts T, Prinzen FW. Mechanical discoordination rather than dyssynchrony predicts reverse remodeling upon cardiac resynchronization. *Am J Physiol Heart Circ Physiol.* 2008;295:640-6.
28. Menet A, Greffe L, Ennezat PV, Delelis F, Guyomar Y, Castel AL, Guiot A, Graux P, Tribouilloy C, Marechaux S. Is mechanical dyssynchrony a therapeutic target in heart failure with preserved ejection fraction? *Am Heart J.* 2014;168:909-16.
29. Klein M, Sundh F, Simlund J, Harrison J, Jackson J, Hughes G, Wagner G, Risum N, Sogaard P, Strauss D, Kisslo J. Immediate mechanical effects of acute left bundle branch block by speckle tracked strain. *J Electrocardiol.* 2015;48:643-51.
30. Becker M, Hoffmann R, Kühl H, Grawe H, Katoh M, Kramann R, Bucker A, Hanrath P, Heussen N. Analysis of myocardial deformation based on ultrasonic pixel tracking to determine transmuralit y in chronic myocardial infarction. *Eur Heart J.* 2006;27:2560-6.
31. Negishi K, Lucas S, Negishi T, Hamilton J, Marwick T. What is the primary source of discordance in strain measurement between vendors: Imaging or analysis? *Ultrasound Med Biol.* 2013;39:714-20.

Table 1. Baseline characteristics

Baseline variable	Overall population		
	NO-BBB N = 10	LBBB N = 28	RBBB+LAFB N = 28
Age (years $\pm$ SD) at echo	34 $\pm$ 10	64 $\pm$ 11	68 $\pm$ 13
Female (%)	6 (60.0)	13 (46.4)	8 (28.6)
QRS duration (ms)	93 $\pm$ 14	157 $\pm$ 16	149 $\pm$ 14
LVEF (%)	≥ 50	39 $\pm$ 15	43 $\pm$ 19
LVID _d (cm)*	4.6 $\pm$ 0.6	5.1 $\pm$ 1.0	5.1 $\pm$ 1.0
LVID _s (cm)*	3.2 $\pm$ 0.6	4.3 $\pm$ 1.1	4.1 $\pm$ 1.1
Global strain (%)	-19.1 $\pm$ 3.0	-9.7 $\pm$ 3.9	-11.0 $\pm$ 5.4
Classical pattern in any view	0 (0)	20 (71.4)	6 (21.4)
Borderline pattern in any view	0 (0)	5 (17.9)	12 (42.9)
Other pattern in any view	1 (10.0)	3 (10.7)	9 (32.1)
Normal pattern in any view	9 (90.0)	0 (0.0)	1 (3.6)

Abbreviations: LVEF = left ventricular ejection fraction, LVID_d = left ventricular internal diameter in diastole,

LVID_s = left ventricular internal diameter in systole.

* In one subject without block, LVID_d and LVID_s could not be measured

Table 2. Comparison of blinded GE and TomTec strain interpretations

TomTec	GE				
		Normal	Classical	Borderline	Other
	Normal	4	1		
	Classical	1	4		
	Borderline			1	
	Other				1

Figure Titles and Legends

Figure 1. Definition of Classical patterns

All 3 criteria must be fulfilled: (1) Early contraction of at least one basal or midventricular segment in the septal/anteroseptal wall in LBBB or inferior wall in RBBB+LAFB (green curve) and early stretching in at least one basal or midventricular segment in the opposing lateral wall in LBBB or anterior/anteroseptal wall in RBBB+LAFB (dark blue curve), (2) Early peak contraction does not exceed 70% of the ejection phase (red vertical line) (in case of double peaks, the first peak is considered), and (3) The early stretching wall shows peak contraction after AVC. AVO, aortic valve opening - MVO, mitral valve opening. Re-used with permission of Risum et al. Am Heart J.⁹

Figure 2. Example of complete agreement between TomTec and GE in a patient with LBBB

A four chamber view from the same patient is created with both TomTec and GE modalities, which both show an early contracting septal wall and late contracting lateral wall, thus a Classical pattern in LBBB. Of note, TomTec and GE modalities use different colors for each wall.

Figure 3. TomTec strain pattern examples from the study population

Strain patterns indicate a Classical (top left) (four chamber), Borderline (top right) (four chamber), Other (bottom left) (two chamber) and a Normal pattern (bottom right) (two chamber). Of note, colors do not indicate similar walls in different chamber views. The Classical pattern was taken from a patient with LBBB. The arrows in the Classical pattern show an early contracting septal wall (green) and a stretching and late contracting lateral wall (purple). In the Borderline pattern, also taken from a patient with LBBB, only the stretching and late contracting lateral wall (purple) could be seen, the septal wall (green) is not contracting early.

Figure 4. Distribution of regional strain patterns by bundle branch block

Figure 1.

Figure 2.

Figure 3.

Figure 4.