Diagnostic performance of left ventricular mechanical dyssynchrony indices using CMR feature tracking

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# Abstract

Background: Cardiac imaging-based indices of left ventricular (LV) mechanical dyssynchrony have failed at accurately predicting response to cardiac resynchronization therapy (CRT). The aim of the study was to evaluate the diagnostic performance of mechanical dyssynchrony indices in a study population of patients with severely reduced ejection fraction and no LV myocardial scar assessed by cardiovascular magnetic resonance (CMR), and either left bundle branch block (LBBB) or normal QRS duration. Methods: We retrospectively identified 80 patients from three centers, with LV ejection fraction %, no scar by CMR late gadolinium enhancement, and either normal electrocardiographic QRS duration (ms) and normal frontal plane electrical axis (-30 to +90 degrees) (control, n=36) or LBBB by Strauss’ criteria (LBBB, n=44). CMR feature tracking was used to derive circumferential strain in a midventricular short-axis cine image. Using circumferential strain, mechanical dyssynchrony was quantified as the circumferential uniformity ratio estimate (CURE) and the systolic stretch index (SSI), respectively. Results: Both CURE and SSI resulted in measures of mechanical dyssynchrony that were more severe (lower CURE, higher SSI) in LBBB compared to controls (CURE 0.63 [0.54, 0.75] vs 0.79 [0.69, 0.86], p<0.001; SSI 9.4 [7.4, 12.7] vs 2.2 [1.2, 3.6], p<0.001). SSI outperformed CURE in the ability to discriminate between LBBB and controls (area under receiver operating characteristics curve [95% confidence interval] 0.98 [95% CI: 0.95, 1.00] vs 0.77 [95% CI: 0.65, 0.87]; p<0.001; sensitivity 93 [95% CI: 84, 100] vs 75 [95% CI: 61, 86] %, p=0.02; specificity 97 [95% CI: 92, 100] vs 67 [95% CI: 50, 81] %, p=0.003. Conclusions: The ability to discriminate between LBBB and normal QRS duration among patients with severely reduced ejection fraction and no scar was fair for CURE and excellent for SSI. When developing and evaluating indices aimed at accurately identifying mechanical dyssynchrony amenable to CRT, it is important to also evaluate the performance of a proposed index in control subjects with normal QRS duration, severely reduced ejection fraction, and the absence of myocardial scar.

# Background

Cardiac resynchronization therapy (CRT), also referred to as biventricular pacing has proven to be a treatment capable of inducing reverse remodeling, improving symptoms, and reducing mortality in well-selected heart failure (HF) patients (1). However, a nonresponse rate of 30-40% is still observed (2), indicating a need for further refinement of current criteria for selecting patients to undergo CRT. Left ventricular (LV) dyssynchrony is a discoordination of intraventriular regional mechanical LV activation. Mechanical dyssynchrony has been proposed as one of the principal therapeutic targets of CRT (3). As such, mechanical dyssynchrony makes for a potential predictor of CRT response.

Cardiovascular magnetic resonance (CMR) feature tracking has been used to characterize mechanical features in patients with left bundle branch block (LBBB) compared to healthy controls (4). Both the COMPANION, REVERSE, and MADIT-CRT trials demonstrated that patients with LBBB derived greater benefit from CRT compared to those without (5–7). Furthermore, positive response and “super-response” to CRT have to an even greater extent been found to be associated with a strict LBBB, as defined by Strauss et al. (8), when compared to LBBB defined by conventional criteria (9,10)

Abnormalities of regional myocardial mechanics are often caused by focal myocardial fibrosis, also referred to as scar (11). Myocardial scarring has been found to be negatively associated with CRT response (12–15). Indices of mechanical dyssynchrony are often derived from measurements of cardiac deformation, e.g strain. Strain measurements have been found to be greatly affected by the presence of myocardial scar (16–18) or myocardial oedema (17,18). Importantly, the failure of most indices of mechanical dyssynchrony can be attributed to a lack of specificity (19). Consequently, the goal of dyssynchrony analysis should be detection of a mechanical dyssynchrony pattern amenable to CRT, and not the detection of mechanical dyssynchrony per se (19). Information about mechanical dyssynchrony characteristics in patients with a high likelihood of CRT response, while at the same time controlling for concomitant pathology, e.g myocardial scar, is of great interest in identifying predictors of CRT response. However, information about this is scarce.

Therefore, the aim of this study was to investigate mechanical dyssynchrony characteristics of patients with strict LBBB and controls that both had a left ventricular ejection fraction and were completely free from myocardial scar assessed by CMR late gadolinium enhancement (LGE).

# Methods

This is an observational case-control study where patients were retrospectively identified by cross-referencing the CMR and electrocardiography (ECG) databases from three centers (Duke University Medical Center, NC, USA; Pittsburgh University Medical Center, PA, USA; and Karolinska University Hospital, Stockholm, Sweden). The study was approved by the respective local human subject research ethics committees, and all subjects either provided written informed consent or there was a retrospective waiver of informed consent provided by the local ethics committee.

## Patient selection

Patients considered for inclusion in the present study had to have a LV ejection fraction , no scar by CMR late gadolinium enhancement (LGE), CMR cine images in a LV short-axis stack, and either normal ECG QRS duration ( ms) and frontal plane electrical axis (-30 to +90 degrees, controls, n=36), or LBBB (n=44) defined by Strauss’ strict ECG criteria, defined as a terminal negative deflection in lead and (QS or rS configuration), a QRS duration for men and for women, and the presence of mid-QRS notching or slurring of leads (8). Reasons for exclusion were a history of congenital heart disease, CMR evidence of myocardial storage disease, atrial fibrillation, prior open heart surgery, or LV septal wall flattening, indicative of clinically significant pulmonary hypertension. The following baseline characteristics were collected: age, sex, height, weight, body surface area (BSA), body mass index (BMI), and CMR measures of LV volumes, function and mass. Among the patients who met the inclusion criteria (n=88), patients were excluded due to having takotsubo cardiomyopathy (n=1), atrial fibrillation discovered at time of feature tracking analysis (n=1), CMR cine images of only systolic part of cardiac cycle (n=1), missing or insufficient number of diagnostic quality CMR cine images (n=4), or missing informed consent (n=1). As a result, the final study group included 80 patients.

## CMR image acquisition

All imaging was performed with clinically available scanners at the respective centers. Scanners included 3T (Siemens Verio, Erlangen, Germany) and 1.5T systems (Siemens Avanto, Espree or Aera, Erlangen, Germany, or Philips Intera , Best, the Netherlands), all using ECG gating and phased-array receiver coils. Typical acquisition parameters for cine images were: repetition time 43.54ms, echo time 1.22ms, flip angle 60 degrees, matrix 190 x 190, slice thickness 6 mm, and temporal resolution 24 frames per cardiac cycle. Clinical reports of cardiac viability assessment were reviewed for mention of any myocardial scar by LGE.

## Image and strain analysis

Cine CMR images exported in the digital imaging and communications in medicine (DICOM) format were used for offline myocardial strain analysis performed by a single observer (DEL) using commercially available software for CMR feature tracking (Segment version 2.2 R6960) Medviso, Lund, Sweden) (20). All analysis was performed blinded to ECG classification. Endocardial and epicardial borders, excluding papillary muscles and trabeculations, were manually delineated in the end-diastolic reference timeframe. The end-diastolic reference timeframe was set to the timeframe immediately following halting of the counterclockwise (as viewed from the apex) movement and lengthening performed by the LV during diastole. This was due to observation of an often delayed closure of the mitral valve, otherwise commonly used as end-diastolic reference. The delineation was performed in a single midventricular short-axis slice. A non-rigid elastic registration strategy is used by the software to measure myocardial strain over time. In short, inter-frame deformation fields are found by warping one image to the next in the cine sequence. The deformations field is found through an iterative process, during which, regularization is performed by the addition of a smoothness penalty. This process uses the entire image, as compared to only tracking the endo- and epicardial borders. The resulting maps describe the difference between consecutive images. The software then automatically propagates the delineated endo- and epicardial borders throughout the cardiac cycle. For regional strain assessment, the area encompassed by the endo- and epicardial borders is segmented in to regions of interest according to the American Heart Association 17-segment model. In short-axis images, the location of regional segments is determined using an angle relative to the right anterior insertion point. Circumferential strain is evaluated from the Lagrangian strain tensor between adjacent points. Mechanical dyssynchrony was quantified using the circumferential uniformity ratio estimate (CURE) (22) and the systolic stretch index (SSI) (25,26). In short, CURE is derived from Fourier transformation of the spatial distribution of strain from myocardial segments averaged over the number of short axis slices. CURE is then calculated as

where is the zero order, and is the first order term in the fourier transformation, and is the number of timeframes covering the cardiac cycle. CURE ranges between 0 (perfect dyssynchrony) and 1 (perfect synchrony). SSI was originally developed through computer simulations (26), and later presented in slightly simplified version (25), and is calculated as the sum of LV lateral wall systolic pre-stretch (SPS) and septal rebound stretch (SRS).

Systolic pre-stretch is defined as the sum of LV lateral wall stretch before aortic valve opening, averaged over the anterolateral and inferolateral segment. Septal rebound stretch is defined as the sum of septal stretch following early systolic shortening and before aortic valve closure, averaged over the anteroseptal and inferoseptal segment.

## Statistical analysis

Categorical data are reported as number (percentages). Continuous variables are reported as median [first quartile, third quartile]. Stratified bootstrapping with 4000 replicates was used to calculate the nonparametric 95% confidence interval (CI) for the difference in median dyssynchrony. Univariable logistic regression models with LBBB status as dependent variable were fitted separately for the two dyssynchrony indices. Restricted cubic splines with knots placed at the 0.05, 0.5, and 0.95 quantiles were used to test for any apparent violations of log-linearity. The le Cessie-van Houwelingen normal test statistic for the unweighted sum of squared errors was used for test of goodness-of-fit. Specificity, sensitivity, discriminatory performance, and cut-off values were derived from receiver-operating characteristics (ROC) analysis using the Youden’s index. Multivariable linear regression models fit separately for each dyssynchrony index in LBBB, and controls respectively, were used to test for associations with covariates age, end-diastolic volume index (EDVI), LV mass index (LVMI), and sex, indicating any need for covariate-adjusted, or covariate-specific ROC curves. Nonlinearities were entertained by use of restricted cubic splines, as were interactions between EDVI, and LVMI with sex, respectively. Areas under the paired ROC curves were compared using nonparametric stratified bootstrapping using 4000 replicates. Bootstrapped CIs were calculated using the percentile method. A two-sided was considered statistically significant. Secondary analysis of the linear correlation between dyssynchrony indices and QRS duration was exploratory and assed by Pearson’s correlation coefficient. Data processing and statistical analysis were performed in the R statistical programming environment 3.6.1 (27), using package dplyr 0.8.3 (28) for data transformation, ggplot2 3.2.1 (29) for graphical visualizations, pROC 1.15.3 (30) for ROC analysis, rms 5.1.3.1 for regression modeling, and knitr 1.25 (31) for reproducible documentation.

# Results

## Patient characteristics

Patients (n=80, 56% female) were included in the study. Patient characteristics are presented in Table 1. Characteristics were similar in the two sample groups except for older age and lower LVMI in LBBB.

## Dyssynchrony measurements

As shown in Figure 2, both CURE and SSI showed group differences between LBBB and controls. Consistent with a greater amount of mechanical dyssynchrony in LBBB, CURE was lower in LBBB (median () = 0.63, interquartile range () = [0.54, 0.75]) compared to controls ( = 0.79, = [0.69, 0.86]), difference in medians -0.16 [95% CI: -0.23, -0.07], and SSI was higher in LBBB ( = 9.4, = [7.4, 12.7]) compared to controls ( = 2.2, = [1.2, 3.6]), difference in medians 7.2 [95% CI: 5.7, 9.6]. The CURE model had an area under ROC curve of 0.77 [95% CI: 0.65-0.87] (Fig 1) and a Nagelkerke of 0.28. This yielded an odds ratio (OR) of 2.16 [95% CI: 0.31, 0.69] per 0.10 decrease in CURE value. The Wald for CURE was 14.75 (p<0.001). The goodness-of-fit test of le Cessie-van Houwelingen yielded a value of 15.61 (p=0.861) indicating an adequate model fit. The SSI model had an area under ROC curve of 0.98 [95% CI: 0.95-1.00] (Fig 1) and a Nagelkerke of 0.86. This yielded an OR of 3.4 [95% CI: 1.84, 6.28] per 1 percentage unit increase in SSI value. The Wald for SSI was 13.92 (p<0.001). The goodness-of-fit test of le Cessie-van Houwelingen yielded a value of 4.07 (p=0.635) indicating an adequate model fit. In evaluating the need for covariate-adjusted and/or covariate-specific ROC curves, we used linear regression models to test the association between dyssynchrony indices and covariates: age, EDVI, LVMI, and sex, allowing for interactions between LVMI and EDVI, with sex, respectively. Nonlinear effects were entertained by means of restricted cubic splines. We found no evidence in support of an association between dyssynchrony indices and covariates in controls, or between CURE and covariates in LBBB. We found evidence in support of an association between SSI and age, keeping other covariates fixed, in LBBB. This suggests that the discriminatory ability of SSI might vary with respect to age. Due to limited sample size we choose to present the pooled ROC curve.

In secondary analysis we investigated the linear correlation between dyssynchrony indices and QRS duration in LBBB, and control respectively. We found no evidence in support of a correlation between QRS duration and CURE (LBBB = -0.09 [95% CI: -0.38, 0.21], p=0.552; control = 0.04 [95% CI: -0.29, 0.36], p=0.814), or between QRS duration and SSI (LBBB = 0.17 [95% CI: -0.13, 0.45], p=0.264; control = -0.16 [95% CI: -0.46, 0.18], p=0.353).

# Discussion

The main finding of the study is that the ability to discriminate between LBBB and normal QRS duration among patients with severely reduced ejection fraction and no scar was fair for CURE and excellent for SSI. This highlights that when developing and evaluating indices aimed at accurately identifying mechanical dyssynchrony amenable to CRT, it is important to also evaluate the performance of a proposed index in control subjects with normal QRS duration, severely reduced ejection fraction, and the absence of myocardial scar.

A few studies have found an increased rate of CRT response by using a more strict definition of LBBB (9,10,32), as proposed by Strauss et al. (8). The novelty of the current study is the evaluation of two dyssynchrony indices for an electromechanical dyssynchrony pattern associated with strict LBBB. By controlling for focal LV myocardial scarring, which is known to affect both the timing and magnitude of strain measurements, differentiation is made against the mechanical dyssynchrony inherent to patients with severely reduced ejection fraction and a normal QRS duration.

While both CURE and SSI capture differences in the pattern of discoordination on a group level, we found SSI superior to CURE with regards to the ability to differentiate between LBBB and controls. Our results suggest that the incremental mechanical dyssynchrony component associated with LBBB is better characterized by quantification of the absolute extent of stretch during the opposing directions of movement in the septum and lateral wall.

SSI was developed in an attempt to characterize the electromechancial substrate predictive of outcomes following CRT (26). In a study of patients enrolled in the Adaptive CRT trial, it was found that SSI was independently associated with CRT outcome, adjusting for QRS morphology, QRS duration, sex, HF etiology and treatment with angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (25). However, whether SSI has added prognostic value over strict LBBB morphology is still unknown. SSI can potentially be used to identify non-LBBB patients that are suitable for CRT, while strict LBBB morphology only requires ECG analysis.

The association between mechanical dyssynchrony, quantified as the systolic dyssynchrony index, and myocardial scar has been studied in patients with systolic heart failure (33). That study found that 25% of patients with narrow QRS () presented with mechanical dyssynchrony, despite no difference in scar burden compared to narrow QRS patients without mechanical dyssynchrony. Those findings suggest that mechanical dyssynchrony in such patients might be secondary to myocardial scar rather than electrical dyssynchrony. There is no generally agreed upon definition of mechanical dyssynchrony, and software vendor dependence of strain measurements limit straightforward comparisons between studies. However, the results of the current study illustrate that patients with severely reduced LVEF and normal QRS duration present with mechancical dyssynchrony to some degree, even in the absence of scar. This would suggest that other factors beyond scar and LBBB contribute to mechanical dyssynchrony. Such factors may include variations in pre-load and/or afterload, and regional wall motion abnormalities due to chronic ischemia or other non-ischemic cardiomyopathies that impair contractile function without causing myocardial scar.

While CURE and SSI both displayed group differences between LBBB and controls, the current study found no evidence in support of a linear correlation between either CURE or SSI, and QRS duration within LBBB and control groups, respectively. These hypothesis generating results suggest a need for a multifactorial approach when evaluating, and adds to the notion of the complex relationship between electrical- and mechanical dyssynchrony.

The results of the current study further highlight the heterogeneity of mechanical dyssynchrony, and emphasizes that when developing novel mechanical dyssynchrony indices aimed at predicting CRT response, adequate controls should be used as to improve specificity for the electromechanical substrate amenable to CRT.

# Limitations

Identification of time point for aortic valve opening, and aortic valve closure was performed by visual assessment of CMR cine images, the accuracy of which is limited by the temporal resolution of CMR images. However, any variations in accuracy would be equally likely in both patient groups and hence should not have a major effect on the overall results. The software used for strain analysis reports segmental strain measurements according to the AHA-17 model. Hence, CURE calculation was limited to Fourier transformation applied to six individual myocardial segments in the short-axis slice. The impact of the spatial resolution of measurement in CURE quantification has not previously been reported. However, it can not be excluded that quantification of CURE using higher spatial resolution could potentially influence the results.

# Conclusion

SSI was superior to CURE with regards to the ability to discriminate between strict LBBB and normal QRS duration among patients with severely reduced ejection fraction and no scar. The amount of dyssynchrony in patients with no scar, severely reduced ejection fraction, yet no expectation of having dyssynchrony needs to be taken into account when developing and evaluating indices aimed at accurately identifying mechanical dyssynchrony amenable to CRT. We suggest that control subjects with normal QRS duration, severely reduced ejection fraction, and the absence of myocardial scar, be included when developing and evaluating mechanical dyssynchrony indices aimed at predicting CRT response.

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# Appendix

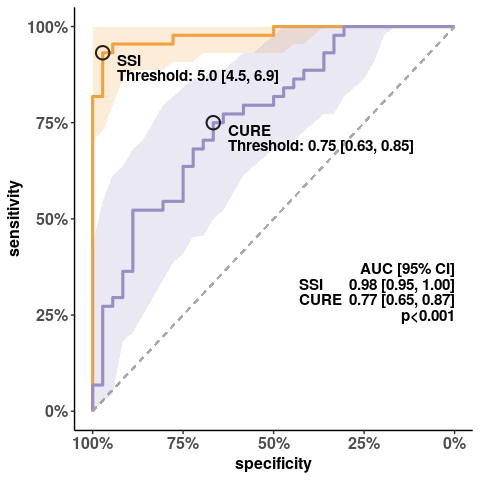


Figure 1: Receiver operating characteristics (ROC) for univariable logistic regression models to differentiate between left bundle branch block (LBBB) and controls using the circumferential uniformity ratio estimate (CURE) and the systolic stretch index (SSI), respectively. Better discriminatory ability for LBBB is seen for SSI compared to CURE. AUC = area under the ROC curve, CI = confidence interval.

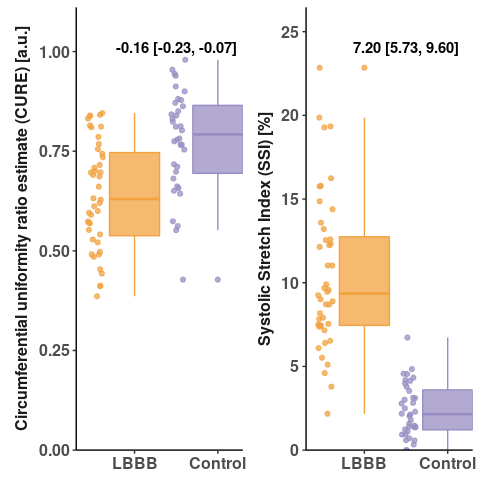


Figure 2: Values for the circumferential uniformity ratio estimate (CURE) and the systolic stretch index (SSI) for left bundle branch block (LBBB) and controls. The box and whisker plots show the median (horizontal line), interquartile range (box), and data points within interquartiles ranges of the first and third quartile, respectively (whiskers). Note, there is more pronounced mechanical dyssynchrony (lower CURE, higher SSI) in LBBB compared to control. CURE is more homogenously distributed between groups compared to SSI. Numbers presented represent difference in medians [95% confidence interval].

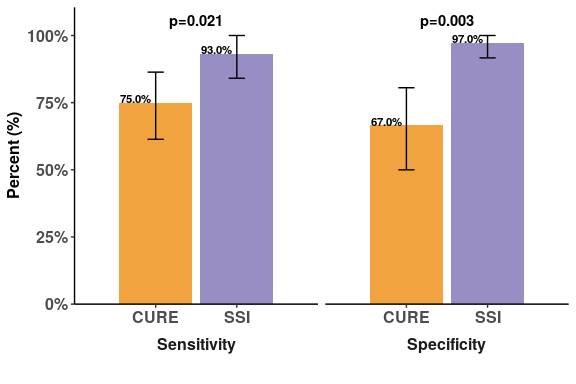


Figure 3: Bar plot showing sensitivity and specificity for detecting left bundle branch block using the systolic stretch index (SSI) and the circumferential uniformity ratio estimate (CURE), respectively. Error bars denote 95% confidence intervals.

Table 1:

| Descriptive Statistics *(N=80)*. | | |  |  |
| --- | --- | --- | --- | --- |
|  | **Control *N=36*** | | **LBBB *N=44*** | |
| Age yrs | 47.9 | [36.0, 59.8] | 64.0 | [58.8, 69.0] |
| EDV mL | 253.5 | [163.6, 307.0] | 255.0 | [209.8, 291.2] |
| EDVI mL/m2 | 122.5 | [100.6, 150.2] | 127.0 | [114.0, 153.5] |
| LVM mg | 182.7 | [156.0, 223.2] | 159.0 | [131.0, 184.0] |
| LVMI mg/m2 | 99.8 | [81.7, 117.1] | 85.0 | [67.0, 96.2] |
| Sex : M | 0.44 | 16⁄36 | 0.43 | 19⁄44 |
| BMI kg/m2 | 27.3 | [25.4, 34.2] | 26.7 | [24.1, 29.4] |
| LVEF % | 25.0 | [21.0, 30.2] | 27.0 | [23.8, 32.0] |
| QRS ms | 90 | [84, 101] | 158 | [150, 170] |
| *a [b, c]* represent the median *a*, the lower quartile *b*, and the upper quartile *c* for continuous variables. EDV = End-diastolic volume, EDVI = End-diastolic volume index, LVM = Left ventricular mass, LVMI = Left ventricular mass index, LVEF = Left ventricular ejection fraction, BMI = Body mass index. | | | | |