Assessment of Left Ventricular Mechanical Dyssynchrony in Left Bundle Branch Block Canine Model: Comparison Between Cine and Tagged MRI

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Purpose: To compare cine and tagged magnetic resonance imaging (MRI) for left ventricular dyssynchrony assessment in left bundle branch block (LBBB), using the time-to-peak contraction timing, and a novel approach based on cross-correlation.

Materials and Methods: We evaluated a canine model dataset (n = 10) before (pre-LBBB) and after induction of isolated LBBB (post-LBBB). Multislice short-axis tagged and cine MRI images were acquired using a 1.5 T scanner. We computed contraction time maps by cross-correlation, based on the timing of radial wall motion and of circumferential strain. Finally, we estimated dyssynchrony as the standard deviation of the contraction time over the different regions of the myocardium.

Results: Induction of LBBB resulted in a significant increase in dyssynchrony (cine: 13.0 ± 3.9 msec for pre-LBBB, and 26.4 ± 5.0 msec for post-LBBB, P = 0.005; tagged: 17.1 ± 5.0 msec at for pre-LBBB, and 27.9 ± 9.8 msec for post-LBBB, P = 0.007). Dyssynchrony assessed by cine and tagged MRI were in agreement (r = 0.73, P = 0.0003); differences were in the order of time difference between successive frames of 20 msec (bias: –2.9 msec; limit of agreement: 10.1 msec). Contraction time maps were derived; agreement was found in the contraction patterns derived from cine and tagged MRI (mean difference in contraction time per segment: 3.6 ± 13.7 msec).

Conclusion: This study shows that the proposed method is able to quantify dyssynchrony after induced LBBB in an animal model. Cine-assessed dyssynchrony agreed with tagged-derived dyssynchrony, in terms of magnitude and spatial direction.

Cardiac resynchronization therapy (CRT) is an effective treatment for selected heart failure (HF) patients,1 resulting in reduced mortality,2 and reversed ventricular remodeling.3 However, 30–40% of the patients selected according to the current guidelines4 do not respond to therapy5; therefore, criteria to predict CRT response continue to constitute an active research area.6

Among cardiac conduction delays, left bundle branch block (LBBB) has been extensively characterized. When a block occurs along the left bundle branch, it results in a slower and more regionally heterogeneous contraction of the left ventricle (LV), with septal regions presenting early activation through the preserved right ventricular conduction system. This condition is often referred to as mechanical dyssynchrony, and it has emerged recently as a prognostic marker for HF patients,7,8 relevant for patient stratification. LBBB has been shown to be more amenable with CRT9,10 than other conduction delays.11,12 Many studies have shown dyssynchrony assessment in HF13,14 but only a few considered isolated,15 or induced LBBB.16

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Although the relationship between mechanical dyssynchrony and CRT response remains controversial, there is increasing evidence that the assessment of the mechanical dyssynchrony could provide a major contribution to optimize CRT delivery.

Magnetic resonance imaging (MRI) presents several advantages for this task. Cine MRI allows accurate tracking of the wall motion from the endocardial and epicardial borders, with good temporal resolution and higher spatial accuracy than echocardiography. Myocardial strain can be derived using tagged MRI; strain patterns have been shown to identify changes in myocardial deformation due to resynchronization therapy and LBBB induction. Tagged MRI can be considered the reference standard for myocardial deformation analysis, although it has not yet reached common clinical practice due to the complexity of image postprocessing. The assessment of mechanical dyssynchrony by cine and tagged MRI has been extensively described in the literature; however, only few studies compared results from both techniques. Dyssynchrony assessment methods based on cine MRI are often based on feature-tracking, which allows deriving transmural regional strain patterns. The proposed method is contour-based and derived from endocardial wall motion only, yielding a more intuitive representation of the contraction; however, twist dynamics cannot be accurately determined.

Different dyssynchrony measures have been proposed, mainly measuring the spread in time of peak strain or peak contraction. The shortcomings of these measures are the ambiguity in the presence of multiple contraction peaks such as in dysynchronous hearts, and their requirement of accurate tracking during postsystolic shortening. Moreover, additional investigation of the aortic valve closure and opening time is required. Finally, not only the contraction but also the relaxation phase of the cardiac cycle, neglected by time-to-peak analysis, contributes to the normal pump function. Measures taking into account the multiple phases during the cardiac cycle have shown higher diagnostic power and higher predictive value for CRT response.

In this work we sought to compare cine and tagged MRI for left ventricular dyssynchrony assessment in LBBB, using a novel approach based on cross-correlation in comparison with commonly used time-to-peak contraction timing.

Materials and Methods

Data Acquisition

ANIMAL PREPARATION AND LBBB INDUCTION. We utilized a dataset of previously acquired MRI images in adult mongrel dogs (n = 10) before (pre-LBBB) and after inducing LBBB (post-LBBB). After the induction by pentothal, anesthesia was maintained by the intravenous infusion of midazolam (0.25 mg/kg-h) and sufentanil (3 µg/kg-h). Radiofrequency ablation of the proximal LBB was performed with combined fluoroscopy and contact electrogram guidance, as described in detail previously. Animal handling was performed according to the National Law on Animal Experimentation and the European Directive for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes (86/609/EU). The protocol was approved by the Institutional Animal Experimental Committee.

MRI. A 1.5 T Philips Intera MRI scanner (Philips Healthcare, Best, the Netherlands) was used in combination with a SENSE cardiac coil for the acquisition of dynamic image sequences. An electrocardiogram (ECG)-triggered, balanced fast field echo (B-FFE) protocol was used to derive cine MR images throughout the cardiac cycle. A combination of repetition time (TR)/echo time (TE)/flip angle of respectively 3.5 msec/1.6 msec/50° was used. The temporal resolution of the acquisition was on the order of 22 msec, with a spatial resolution of 1.56 × 1.56 mm and a slice thickness of 8 mm. Typically, seven short-axis view slices were acquired with a reconstructed image size of 256 × 256 pixels. A prospectively triggered gradient echo planar imaging sequence was used to acquire the tagged MRI series. A typical number of seven slices were acquired in short-axis view; a flip angle of 18° was used with a TR/TE of 15/5.8 msec, resulting in a temporal resolution of 15 msec and spatial resolution of 0.78 × 0.78 × 8 mm; acquisition was repeated for vertical and horizontal tag line patterns. Acquisition was terminated after 540 msec, thus excluding late diastolic phases where tag line decay was severe.

Tagged MRI and cine MRI image were acquired during the same imaging session, with the same orientation and location for the short-axis views; manually operated breath-holds were obtained by temporarily halting the ventilator.

Data Processing

IMAGE ANALYSIS. Cine MRI. For offline analysis of the cine MR images, the LV endocardial borders were segmented semiautomatically for all slices and for all the time frames using CAAS MRV 3.4 (Pie Medical Imaging, Maastricht, the Netherlands). A segmentation method was used to include papillary muscles in the LV blood pool, resulting in convex contours composed of 360 points equally spaced. We computed the distance between the centroid of the LV blood pool and each of the points on the endocardial border during the cardiac cycle, deriving a time-displacement curve (TDC) for each point on the endocardial border. The computed TDCs were used to characterize the radial motion pattern of the endocardium. An example of TDCs is presented in Fig. 1. We used a fixed centroid position during the whole cardiac cycle, as the use of a moving center combined with the motion of dysynchronous regions would introduce false apparent motion relative to the dynamic LV center for the whole endocardium. In order to assess the reproducibility of the proposed method, semiautomated segmentation was performed a second time by a different observer, and subsequent analysis was repeated.

Tagged MRI. The tagged MRI images were analyzed using the SinMod method in order to calculate circumferential strain. Circular regions of interest were drawn manually around the
myocardium. Anterior and posterior left–right ventricular junction points were used as a reference to define segment positioning. Strain vs. time curves (STCs) were derived in 32 segments per slice by averaging over a finite region by using a decreasing weighting function, with its peak in the mid-wall and decreasing toward the endocardial and epicardial borders. An example of an STC is shown in Fig. 1.

**Contraction Time Estimates**

In order to derive contraction time estimates, generalized cross-correlation was used. To take into account the variability in the contraction pattern in different subjects, each TDC was cross-correlated with a subject-specific and slice-specific reference TDC, as described previously. The same approach was separately applied for the STCs derived from tagged MRI. Contraction time for a segment was defined as the location of the peak of the cross-correlation between TDC (or STC) and the reference TDC (or STC). The contraction time estimates were visualized using bull’s-eye plots composed of several rings, each representing an imaging slice, containing 32 equally sized segments. The contraction times were relative to the first contracting segment in the specific subject. The method was implemented in custom-made software in MATLAB 2014a (MathWorks, Natick, MA).

**Measures of Dyssynchrony**

Global measures of dyssynchrony were defined to classify the presence of LBBB in the considered subjects. CINE or tagged tissue synchronization index (CINE-TSI or TAG-TSI) was defined as the standard deviation of the contraction time derived from the TDCs (or STCs). The standard deviation was computed in both cases over all slices, with each slice divided into 32 segments. Higher values of TAG-TSI and CINE-TSI indicated a higher degree of dysynchrony. In order to complement the TSI with information on the spatial orientation, the activation delay vector (ADV) was computed. This vectorial indicator was computed as:

\[
ADV = \frac{1}{N_{Sl} N_{Segm}} \sum_{iSl} \sum_{iSegm} CT(iSl, iSegm) \cos \theta_{Segm} \sin \theta_{Segm}
\]

where \(N_{Sl}\) and \(N_{Segm}\) were the number of slices and the number of segments, respectively, \(CT(iSl, iSegm)\) was the contraction time estimated in the segment \(iSegm\) and slice \(iSl\), and \(\theta_{Segm}\) was the considered angle defined from the septal to free wall.

We compared the proposed measures to the frequently used systolic dyssynchrony index given by the standard deviation of the time-to-peak radial motion (CINE-SDI), or by the standard deviation of the time-to-peak circumferential strain (TAG-SDI).
Statistical Methods

Continuous variables are presented with their mean and standard deviation. Bland–Altman analysis was used to compare dysynchrony measured by tagged and cine MRI. To compare the global measures of dysynchrony between pre-LBBB and post-LBBB, a two-sided Mann–Whitney U-test was used. To evaluate the changes in the global measures after the LBBB induction, a two-sided Wilcoxon signed-rank test was applied. In both cases, a significance level of 0.05 was used; P-values smaller than 0.05 were considered significant. Receiver operating characteristic (ROC) curve analysis was performed to assess the classification performances of the proposed indicators. The point along the ROC curve that was closest to the top-left corner (100% sensitivity and specificity) determined the optimal threshold for classification. Classification was performed using 3-fold cross-validation repeated 10 times. Agreement between the observers for the classification between pre-LBBB and post-LBBB was evaluated by Cohen’s kappa.

Results

Example bull’s-eye plots of contraction time before and after LBBB induction on the same animal are shown in Fig. 2.

CINE-TSI and TAG-TSI were linearly correlated ($r = 0.73$, $P = 0.0003$). The differences between CINE and TAG dyssynchrony estimates for all the animals are shown in Fig. 3. Bland–Altman analysis revealed a bias of $-2.9$ msec ($P = 0.08$) with 95% limits of agreement of $-15.8$ to $10.1$ msec. The average difference between CINE-TSI and TAG-TSI was $-4.1$ msec ($P = 0.08$) for the pre-LBBB group, and $-1.5$ msec ($P = 0.51$) for the post-LBBB group; the average of absolute differences for the whole population was $5.8$ msec. The mean difference between CINE and TAG derived contraction time estimates per bull’s-eye segment was $3.6 \pm 13.7$ msec.

FIGURE 2: Bull’s-eye plot showing the contraction time estimate for one subject using cine MRI and tagged MRI. Contraction time estimates before (A: by cine, C: by tagged) and after (B: by cine, D: by tagged) left bundle branch block induction. Color coding was used to display the contraction times with shades of blue representing early activation and shades of red representing late activation. Capital letters indicate the corresponding myocardial regions (A = Anterior, AL = Antero-Lateral, IL = Infero-Lateral, I = Inferior, IS = Infero-Septal, AS = Antero-Septal). The black arrow in the center of the bull’s-eye represents amplitude and direction of the activation delay vector.

FIGURE 3: Bland–Altman comparison between tissue synchronization index (TSI) estimated from cine MRI and tagged MRI. Black circles represent pre-LBBB animals, while white-filled squares represent the same animals after induction of left bundle branch block (LBBB).
Values of the proposed global measures of dyssynchrony are presented in Table 1. We observed significant differences between pre-LBBB and post-LBBB subjects in CINE-TSI and TAG-TSI ($P = 0.0003$ and $P = 0.004$, respectively). A significant increase was observed in TAG-TSI ($P = 0.007$) and CINE-TSI ($P = 0.005$) on the same animals after LBBB induction ($n = 10$). The increase in the global dyssynchrony measures after the induction of LBBB is shown in Fig. 4. The CINE-ADV and TAG-ADV for all the animals are shown in Fig. 5. The average difference between CINE-ADV and TAG-ADV in post-LBBB animals was $21.8 \pm 25.0$ degrees in direction ($P = 0.04$), and $5.0 \pm 5.9$ msec in magnitude ($P = 0.02$), while the average absolute difference was 6.4 msec.

The average difference between CINE-SDI measured by the first and second observer was $4.9 \pm 16.0$ msec ($P = 0.54$), and it was $-0.7 \pm 6.4$ msec ($P = 0.28$) and $-2.5 \pm 2.2$ msec ($P = 0.03$ for pre-LBBB $P = 0.20$ for post-LBBB) for CINE-TSI and $||$CINE-ADV$||$, respectively. The agreement between the observers for the classification between pre-LBBB and post-LBBB was good for CINE-TSI and $||$CINE-ADV$||$ (Cohen’s kappa = 0.89 and 0.80, respectively), while it was only fair for CINE-SDI (kappa = 0.57).

### Discussion

In this study we evaluated a novel method for quantification of dyssynchrony in LBBB using short-axis view cine MRI. We evaluated the method using specific animal models of isolated LBBB, thus excluding other conduction defects and other comorbidities, frequent in HF patients. In a canine model of LBBB, the proposed method shows good correlation with tagged MRI, which can be considered the reference standard for myocardial motion analysis. The use of MRI in the context of CRT delivery presents advantages over echocardiography, especially for ischemic heart disease, as late gadolinium enhancement imaging allows avoiding LV lead deployment in the scarred myocardium.

| TABLE 1. Changes in global measures of dyssynchrony derived from cine and tagged MRI |
|----------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                  | Pre-LBBB (n=10) | Post-LBBB (n=10) | Increase$^a$ | AUC             |
|----------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| CINE-SDI [ms]                    | 48.2 ± 14.8     | 53.9 ± 14.8     | p=0.02          | 0.71 ± 0.03     |
| TAG-SDI [ms]                     | 44.5 ± 5.0      | 55.5 ± 12.0     | p=0.012         | 0.83 ± 0.01     |
| CINE-TSI [ms]                    | 13.0 ± 3.9      | 26.4 ± 5.0      | p=0.005         | 0.92 ± 0.02     |
| TAG-TSI [ms]                     | 17.1 ± 5.0      | 27.9 ± 9.8      | p=0.007         | 0.88 ± 0.02     |
| $||$CINE-ADV$||$ [ms]            | 4.5 ± 2.0       | 15.4 ± 4.5      | p=0.005         | 0.96 ± 0.01     |
| $||$TAG-ADV$||$ [ms]             | 3.2 ± 1.6       | 10.5 ± 5.1      | p=0.005         | 0.95 ± 0.01     |

$^a$Wilcoxon signed-rank test

$\text{TSI} = \text{tissue synchronization index estimated by cross-correlation}$

$\text{SDI} = \text{systolic dyssynchrony index derived from time-to-peak measures}$

$||\text{ADV}|| = \text{magnitude of activation delay vector}$

AUC = Area under the receiver operating characteristic curve for the classification between Pre-LBBB and Post-LBBB

FIGURE 4: Increase in global measures of dyssynchrony after the induction of left bundle branch block. Systolic dyssynchrony index (SDI) (A: cine MRI, B: tagged MRI), tissue synchronization index (TSI) (C: cine MRI, D: tagged MRI) and magnitude of the activation delay vector (ADV) (E: cine MRI, F: tagged MRI) (*Wilcoxon signed-rank test).
Regional contraction time estimates can be used to characterize global contraction patterns, recently proposed as a marker for CRT response, in addition to recognized LBBB. The measured contraction time maps in LBBB appeared to be similar with the activation pattern from other modalities shown in the literature, for instance, by invasive electrophysiological measures. Agreement between results derived from cine and tagged MRI was found with respect to the contraction maps. Agreement was also observed on the spatial direction of the contraction for LBBB subjects, shown by differences in the orientation of CINE-ADV and TAG-ADV, which were on the order of the segment size. Both CINE-TSI and TAG-TSI measures are able to accurately detect the presence of isolated LBBB, as both methods found significant differences between the pre-LBBB and post-LBBB groups. The cross-correlation-derived TSI indices discriminated better between pre-LBBB and post-LBBB animals than SDI indices. This indicates that indices like TSI that take into account the full contraction cycle using cross-correlation, perform better than time-to-peak-derived measures such as SDI. Also, time-to-peak analysis requires marking valve opening and closure time to discriminate between pre- and post-systolic shortening in order to provide meaningful estimates. ADV indices taking into account the spatial direction of the contraction had discriminatory power similar to TSI. An additional advantage of the proposed method is that no assumptions are made about the shape of the TDC (or of the STC); a sinusoidal model to describe the wall motion over time, as proposed previously, has a limited physiological basis.

We compared quantitative dyssynchrony estimates based on the analysis of circumferential strain and radial wall motion timing and showed substantial agreement between the results of the two quantifications. The differences may be explained by the fact that the strain was obtained by averaging the deformation detected from the tags in segments over the whole myocardium. Instead, the radial motion was derived from the displacement of the endocardial border only; therefore, the STCs were influenced also by the transmural heterogeneity of the strain pattern. This may motivate the significant differences observed comparing CINE-ADV and TAG-ADV; however, the differences were on the order of the temporal resolution for the magnitude of the ADV, and on the order of segment size for the orientation of the ADV. Moreover, the temporal resolutions of the two acquisitions were different (22 msec vs. 15 msec), potentially introducing errors in the comparison; however, our method is less influenced by the temporal resolution of the acquisition, as the contraction time estimates are not limited to the sampling period of the signals, which corresponds to the MRI acquisition frame rate, contrary to methods that use frame counting to determine, e.g. time-to-peak measurements. Based on the agreement observed between CINE-TSI and TAG-TSI, cine MRI may be preferred over tagged MRI because it does not require additional image acquisition and it requires simpler postprocessing. With respect to cine MRI, tagging MRI inherently reduces the resolution of the image signal used for tracking, depending on the tag period. Moreover, the proposed method requires a simpler image postprocessing compared to tissue-tracking or image registration methods also based on cine MRI images, and it does not require additional image acquisition such as velocity-encoded imaging, which yields similar results to cine-based methods.

The agreement in segmental contraction time by cine and by tagged MRI is generally limited by the accuracy of the left–right ventricle junction localization and
consequently by the correspondence in the myocardial segment definition in the different acquisitions. A common drawback of cine MRI and tagged MRI analysis is that only contraction and deformation can be imaged; active force development, giving better insight on the cardiac pump function, would require invasive pressure measurements. However, the current guidelines for patient selection include the assessment of ejection fraction, which is derived by measures taking into account the spatial direction of the contraction, such as ADV with respect to TSI. Despite the cross-correlation method being automatic and user-independent, the proposed method may be affected by the variability of the cine MRI LV segmentation, which has been reported in the literature. A preliminary assessment of the reproducibility of the method was presented in this study; good agreement was found between CINE-TSI and CINE-ADV estimated from the LV segmentation performed by two independent observers, whereas the agreement was fair for CINE-SDI. In this article we presented results on animal models only; future validation with a larger dataset in humans would be necessary to evaluate the clinical value of the proposed method.

In conclusion, we proposed a method to quantify intraventricular mechanical dyssynchrony. The method can be used to analyze circumferential strain development and radial wall motion patterns from MR images. We evaluated the method on an animal model dataset, where isolated LBBB was induced. Regional contraction time can be visualized; the derived maps from tagged and cine MRI are in agreement with the LBBB contraction patterns reported in the literature. Global measures of dyssynchrony derived from tagged and cine MRI are in agreement in the validation data. The method allows accurate classification of isolated LBBB presence in a canine model.

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References


11. Rickard MDJ, Wilkoff B, Tang WH. Echocardiographic response to cardiac resynchronization therapy is less pronounced in non-left bundle branch block morphologies even when QRS width is more than 150 milliseconds. J Am Coll Cardiol 2012;59:971.


