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Myocardial motion and deformation patterns in an experimental swine model of acute LBBB/CRT and chronic infarct

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Abstract

Purpose: In cardiac resynchronization therapy (CRT), specific changes in motion/deformation happen with left-bundle-branch-block (LBBB) and following treatment. However, they remain sub-optimally studied. We propose a two-fold improvement of their characterization. This includes controlling them through an experimental model and using more suitable quantification techniques.

Methods: We used a swine model of acute LBBB and CRT with/without chronic infarct (pure-LBBB: N=11; LBBB + left-anterior-descending infarct: N=11). Myocardial displacement, velocity and strain were extracted from short-axis echocardiographic sequences using 2D speckle-tracking. The data was transformed to a single spatiotemporal system of coordinates to perform subject comparisons and quantify pattern changes at similar locations and instants.

Results: Pure-LBBB animals showed a specific intra-ventricular dyssynchrony pattern with LBBB (11/11 animals), and the recovery towards a normal pattern with CRT (10/11 animals). Pattern variability was low within the pure-LBBB population, as quantified by our method. This was not correctly assessed by more conventional measurements. Infarct presence affected the pattern distribution and CRT efficiency (improvements in 6/11 animals). Pattern changes correlated with global cardiac function (global circumferential strain) changes in all the animals (corrected: $p_{\text{LBBBvsBaseline}} < 0.001$, $p_{\text{CRTvsBaseline}} = \text{NS}$; non-corrected: $p_{\text{LBBBvsBaseline}} = \text{NS}$, $p_{\text{CRTvsBaseline}} = 0.028$).

Conclusion: Our LBBB/CRT experimental model allowed controlling specific factors responsible for changes in mechanical dyssynchrony and therapy. We illustrated the importance of our quantification method to study these changes and their variability. Our findings confirm the importance of myocardial viability and of specific LBBB-related mechanical dyssynchrony patterns.

Keywords

Speckle-tracking; Myocardial strain; Myocardial velocity; Cardiac Resynchronization Therapy; Dyssynchrony.

Introduction

Accurate characterization of myocardial motion and deformation patterns is essential for understanding changes in cardiac mechanics under the effect of disease and [therapy](#) [1]. Studies on Cardiac Resynchronization Therapy (CRT) mainly focused on the quantification of single value dyssynchrony indexes (e.g. time-to-event or peak measurements), and the qualitative description of the main pattern characteristics. In the first case, measurements are limited by the complexity of the mechanisms of cardiac dyssynchrony [2,3], [and the difficulty of defining CRT outcome and response as a dichotomic variable](#) [4,5]. In the second case, observations are qualitative and the pattern variability within groups of subjects is not directly measured [6-10].

In this study, we target the characterization of motion/deformation changes induced by pure left-bundle-branch-block (LBBB), and their evolution with CRT. Experimental models are relevant for such a purpose, as they allow controlling the factors responsible for such changes [11,12]. To our knowledge, only one of these models included chronic infarct [13], but tested it for lead positioning purposes. In contrast, our study partially aims at studying its influence on patterns of mechanical (dys)synchrony.

Our priority is to improve the characterization of these changes. This consists in quantifying the whole morphology and variability of motion/deformation curves (i.e., the patterns) within the studied animals. Naturally, data differs between animals in terms of the timing of physiological events, number of frames, and anatomy. For this reason, we rely on recent methods for the statistical comparison of individuals, which can be easily transposed to our data [14]. These methods derive from the fields of computational anatomy and statistical atlases, and mainly consist in aligning all the studied data to a common system of spatiotemporal coordinates.

The contribution of our study is two-fold: (i) we apply an appropriate comparison of motion and deformation patterns that overcomes the limits of previous studies on mechanical dyssynchrony; (ii) secondly, through an animal model of dyssynchrony with/without chronic infarct, we investigate the link between changes in mechanical dyssynchrony and induced electrical dyssynchrony (acute pure LBBB and following CRT). [Two factors](#)

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4 are tested and controlled by the experimental model: the relevance of correcting pure-LBBB dyssynchrony (non-
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6 infarcted animals), and the influence of an infarcted septum.
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9 10 **Methods**

11 12 13 14 15 16 **Animal model**

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20 Our study included 24 Landrace x Large White pigs (weight 37 [33-45] kg). Two subpopulations were
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22 created: 12 animals without structural disease, and 12 with localized chronic infarct. The infarct was induced one-
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24 month before the LBBB induction, as a result of 90min full occlusion of the left-anterior-descending coronary artery
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26 (LADi) [15]. Its position and extent were controlled 4 days before the LBBB induction using delayed-enhancement
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28 magnetic resonance (Magnetom-Symphony 1.5T, Siemens, Erlangen, Germany).
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33 Acute LBBB was induced in all animals using radiofrequency ablation, guided through an
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35 electroanatomical mapping device (CARTO-XP, Biosense Webster, Diamond Bar, CA), so that QRS width
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37 increased $\geq 50\%$ with respect to baseline. This resulted in 4(3-7) burnings, at 25mW during 30s. This procedure is
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39 reproducible in inducing LBBB, as previously validated in [16] against other pacing protocols.
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43 Two leads were implanted at baseline: right ventricle (RV, Beflex-RF45, Sorin Group, Milan, Italy) and
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45 left ventricle (LV, Situs-OTW, Sorin Group). The RV lead was located at the apex. The LV lead was implanted
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47 either by subxiphoid epicardial or via coronary sinus access, depending on the animal anatomy. The leads
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49 positioning was monitored by fluoroscopic guidance using a C-arm X-ray system (Arcadis Avantic, Siemens,
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51 Erlangen, Germany). Their position with respect to the infarct location was controlled a-posteriori using the
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53 electroanatomical mapping data (earliest activation locations vs. bipolar voltage maps between 0.5 and 1.5 mV).
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55 Pacing was performed with a pacing system analyzer (ERA-3000, Biotronik, Berlin, Germany), and optimized after
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57 the ablation.
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4 Further details about the leads positioning and the animal preparation protocol are given in [16]. Animal
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6 handling was approved by our Institutional Review Board and Ethics Committee, and conformed to current
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8 guidelines [17].
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10 11 12 **Echocardiography**

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16 An echocardiographic examination (Vivid-Q, GE Healthcare, Milwaukee, WI) was performed pre/post-
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18 ablation and during CRT using a transesophageal probe (6Tc-RS, GE Healthcare, 5MHz) via subxiphoid epicardial
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20 access. Short-axis 2D views of the LV were acquired at papillary muscles level, during breath-hold (controlled
21
22 through a respiratory device). Repeatability of the imaging plane between pre-ablation, post-ablation and CRT
23
24 acquisitions was checked offline using a multi-view representation. Machine settings (gain, time gain compensation,
25
26 and compression) were adjusted for optimal visualization, including harmonic imaging. Sequences with insufficient
27
28 image quality were discarded. Median frame rate and pixel size were of 67 [59-71] fps (heart rate: 80 [65-93] bpm)
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30 and $0.15 \times 0.15 \text{ mm}^2$, respectively.
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33 34 **Extraction of myocardial motion and deformation**

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38 *Speckle-tracking protocol.* Myocardial motion (displacement and velocities) and deformation (strain) were
39
40 estimated by 2D speckle-tracking (Echopac-v110.1.2, GE Healthcare). The temporal region of interest was manually
41
42 set to one cardiac cycle with approximately 100ms additional margin around it. The myocardial border was
43
44 manually segmented at end-systole, as required by the software interface (delineation of the endocardium and choice
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46 of a wall thickness).
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51 *Data export and post-processing.* Data was exported with the “store full trace” option, without any
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53 spatiotemporal smoothing. Motion (radial/circumferential displacement and velocity) and deformation
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55 (circumferential strain) were computed along the myocardial centerline. Drift removal was used to achieve cyclic
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4 motion. The position of the myocardial centerline was corrected with respect to its center-of-mass to compensate
5 probe motion¹. No additional spatial/temporal smoothing was added.
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10 *Intra- and inter-observer variability.* The repeatability of the speckle-tracking procedure was evaluated on
11 1 non-infarcted animal pre/post-ablation, and 1 LADi animal pre-ablation. Intra-observer variability was estimated
12 by repeating the measurements 10 times. Inter-observer variability was obtained from 3 different observers. Finally,
13 the inter-sequence variability was evaluated by repeating the measurements on another sequence.
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18 **Spatiotemporal alignment and data visualization**

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24 *Data alignment.* Speckle-tracking data is not immediately comparable between subjects. Indeed,
25 physiological events happen at different instants, and sequences also differ in number of frames and anatomy. We
26 used the method proposed in *Duchateau et al.* [14,18] to solve this (*Figure 1*). This mainly consists in aligning all
27 the studied data to a common system of spatiotemporal coordinates. *Temporal alignment* was based on the matching
28 of physiological events². *Spatial alignment* consisted in transporting the motion/deformation data of each subject to
29 a reference anatomy (the anatomy of a given animal). The importance of this spatiotemporal alignment was already
30 discussed [19,20] and is illustrated in *Figures 2a* and *2b*. Technical details about the whole procedure and its
31 validation can be found in *Duchateau et al.* [14,18]. The implementation of the method was realized using Matlab-
32 v.R2007a (MathWorks, Natick, MA), and is publically available³.
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45 *Data visualization.* Motion and deformation patterns are visualized by means of color-coded maps, in
46 which the horizontal axis stands for time (one cardiac cycle), and the vertical axis stands for the position along the
47 myocardium (*Figure 1c*). This visualization is similar to common commercial 2D speckle-tracking software.
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53 ¹ Strain is a spatially differential measure and is not affected by this correction.

54 ² The temporal alignment required the identification of 6 events per cycle. The onset of QRS (beginning and ending
55 of the cycle) was identified on the ECG. Valve events (aortic/mitral valve opening/closure
56 [AVO/AVC/MVO/MVC]) were identified using continuous-wave Doppler imaging on the corresponding valve,
57 when possible, or visually on short-axis 2D views.
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60 ³ <http://nicolasduchateau.wordpress.com/downloads/>
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4 However, such software only offers descriptive visualization of an individual and does not allow quantitative
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6 comparison between subjects, contrary to our implementation.
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10 11 12 13 **Pattern analysis of motion/deformation curves** 14 15 16

17 *Single indexes.* Differences in time-to-peak systolic strain between mid anteroseptal/inferolateral segments
18 [21] were used as “conventional” indexes of mechanical dyssynchrony. Two types of more advanced indexes were
19 also adapted from the ones recently proposed in *Kydd et al.* [22]: (i) the standard deviation of the time-to-peak
20 circumferential strain, over the myocardial centerline ($STD_{\text{time-to-peak}}$), and (ii) the “wasted energy”, which
21 corresponds to the average difference between peak circumferential strain and AVC circumferential strain, over the
22 myocardial centerline. The relevance of such measurements is commented on in the Discussion section.
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31 *Local changes in mechanical patterns.* Median and first/third quartiles radial displacement, radial velocity
32 and circumferential strain were computed at each spatiotemporal location of the color-coded maps. They were used
33 to quantify motion/deformation changes in the non-infarcted and LADi groups.
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40 *Global changes in cardiac function.* Global circumferential strain corresponded to the average of the
41 circumferential strain maps along their vertical dimension. We used the early-diastole shortening peak of global
42 circumferential strain (negative isovolumic relaxation peak) to estimate changes in cardiac function.
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48 **Statistical analysis** 49 50 51

52 Quantitative variables were expressed as median and first/third quartiles range. Non-parametric statistical
53 tests were used for inter-groups comparison (Mann-Whitney *U*-test) and paired data comparison (Wilcoxon signed-
54 rank test). *p*-values <0.05 were considered statistically significant. All data were analyzed using SPSS-v.15.0 (SPSS
55 Inc., Chicago, IL).
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Results

Animal model

The characteristics of the studied animals are detailed in *Table 1*. In 22/24 animals, the successful induction of LBBB was confirmed by significant changes in the QRS morphology, axis and width (53 [46-56] ms vs. 80 [76-86] ms, $p < 0.001$). This is illustrated in *Figure 3a* on a non-infarcted animal. The 2/24 remaining animals developed a complete atrio-ventricular block (1 non-infarcted and 1 LADi) and were discarded.

LAD infarcts (N=11) were located at the anteroseptal level. More frequently affected segments were: mid-anterseptal (8/11), apical-anterior (8/11), and apical-septal (10/11). Other affected segments were: mid-anterior (2/11), mid-inferoseptal (3/11), apical-inferior (2/11), apical-lateral (1/11), and apex (3/11).

Intra- and inter-observer variability

The quantitative results for the repeatability experiments are summarized in *Table 2* (standard deviation of the motion/deformation curves over the whole cycle and the whole myocardium) and *Figure 4* (repeated curves along the whole cycle at septal/lateral levels). Both indicate the low variability in the speckle-tracking measurements.

Pattern changes: conventional assessment

Figure 3b highlights the presence after the ablation of a specific abnormal motion pattern of the septum, referred to as septal flash (SF) [6]. It consists of early-systole fast inward/outward motion, as indicated by the yellow arrows. After the ablation, this pattern was observed in all the 11 non-infarcted animals, while it was harder to assess or absent in the 11 LADi ones. With CRT, mechanical dyssynchrony was partially or totally corrected in 10 of the 11 non-infarcted animals. Similarly, improvements in synchronicity were noted for 6 of the 11 LADi animals.

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6 *Table 1* includes measurements of mechanical dyssynchrony using time-to-peak systolic
7 radial/circumferential strain. Large intra-population variability and no significant changes were observed with
8 respect to pre-ablation data. This comes from the suboptimality of time-to-event indexes to characterize complex
9 abnormal patterns [2,3,23], as also illustrated in *Figure 5*. The wasted energy index led to similar observations. On
10 the non-infarcted animals, significant differences were observed for the $STD_{\text{time-to-peak}}$ index between pre- and post-
11 ablation data, while differences between pre-ablation and CRT data were not significant. No significant differences
12 were found for LADi animals. However, we doubt of the relevance of such a result, which is also based on time-to-
13 event measurements.
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27 **Pattern changes: group-wise spatiotemporal analysis**

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30 *Figure 6* represents the motion and deformation data for each subgroup of animals, pre/post-ablation and
31 with CRT. This consists of median and first/third quartiles curves at septal and lateral locations, and median
32 spatiotemporal maps.
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38 *Non-infarcted animals (Figure 6a)*. After the ablation, the SF is visible on the displacement and velocity
39 data (early-systole black arrows, septal level). It is accompanied by early-systole abnormal circumferential strain
40 (peak shortening of the septum and lateral wall stretching during the isovolumic contraction). Reduction of systolic
41 and diastolic velocities, loss of synchronicity (absence of vertical symmetry/uniformity of the maps), and post-
42 systolic abnormal motion (early-diastole black arrows) are also observed. With CRT, SF has disappeared,
43 synchronicity has been restored (improved vertical symmetry/uniformity of the maps), and the contraction/relaxation
44 patterns resemble to the pre-ablation ones.
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55 *LADi animals (Figure 6b)*. High variability of the circumferential strain curves is observed. This reflects
56 the heterogeneity of infarct extent in this subgroup: fully or partially infarcted septum at the papillary muscles level
57 vs. a more apical/anterior infarct. Motion is also slightly altered at the infarct location before the ablation. Velocities
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4 are lower before the ablation, in comparison with the non-infarcted animals. After the ablation, few changes are
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6 observed. No SF pattern is visible. Synchronicity is partially preserved (vertical symmetry of the maps), but motion
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8 is reduced. Post-systolic abnormal motion (early-diastole black arrows) is also observed. Few changes happen with
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10 CRT. Strain is partially improved in the lateral wall, which coincides with the non-infarcted zone.

11 12 13 14 **Changes in cardiac function**

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18 Global circumferential strain values are summarized in *Table 1*. Non-infarcted animals showed lower
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20 global deformation after the ablation, which was almost restored with CRT. The LADi subpopulation showed a
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22 larger dispersion of global strain values before the ablation, which confirms the observations of *Figure 6b*. Global
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24 strain values were lower before the ablation, worsened with LBBB and were not restored with CRT.

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28 These results are confirmed when animals are grouped according to CRT-induced improvements. Partial or
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30 total correction of LBBB-induced abnormal patterns (10 non-infarcted and 6 LADi animals) was accompanied by
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32 the restoration of cardiac function (11.0 [8.2-15.4] % [pre-ablation] vs. 7.1 [5.3-8.3] %, $p < 0.001$ [LBBB] and 9.5
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34 [6.3-12.5] %, $p = \text{NS}^4$ [CRT]). On the contrary, non-correction of dyssynchrony and undetermined changes (1 non-
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36 infarcted and 5 LADi animals) correlated with a lack of improvement of cardiac function (9.2 [6.8-14.5] % [pre-
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38 ablation] vs. 5.9 [4.9-9.1] %, $p = \text{NS}$ [LBBB] and 5.0 [3.7-6.3] %, $p = 0.028$ [CRT]).

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⁴ NS: Non-significant statistical difference (p-value > 0.05).
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4 **Discussion**
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10 In this study, we used local motion and deformation data to quantify mechanical (dys)synchrony patterns
11 induced by LBBB and following CRT in an animal model of dyssynchrony with/without chronic infarct. Our
12 objectives were (i) to apply an appropriate method to compare motion and deformation patterns at each stage of the
13 experiments; and (ii) to study the link between changes in mechanical dyssynchrony and induced electrical
14 dyssynchrony (acute pure LBBB and following CRT).
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22 **Conventional assessment of mechanical dyssynchrony**
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26 The limits of conventional methods for the assessment of mechanical dyssynchrony have been widely
27 debated [24,25]. The abundance of publications and extensively advertised multi-centric studies made the usefulness
28 of myocardial mechanics controversial [2,3]. Single indexes such as time-to-event or single location values discard
29 the complexity of the patterns observed (*Figure 5*) [23]. A similar remark can be made for more elaborated methods,
30 such as curve analysis (e.g. cross-correlation [26] or Fourier analysis [27]) and more advanced indexes (e.g. radial
31 discoordination [22,28] or the wasted energy [22]). Note that these limitations come from the analysis that is made
32 and not from the images. They are independent of the imaging technique, and therefore not specific to speckle-
33 tracking echocardiography.
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46 **Pattern analysis**
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50 Pattern-based observations were recently reported in the context of CRT to address the problem in a more
51 comprehensive way [6-10]. However, most works are still limited to qualitative pattern description, or single
52 pattern-specific measurements (e.g. peak magnitude of SF, systolic rebound shortening and pre-stretch [7,8], or
53 apical transverse motion for rocking [9]). In contrast, our method performs a more complete quantitative analysis,
54 and includes data of multiple types (displacement, velocities and strain). Moreover, this data is studied locally all
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4 along the myocardial centerline and not only in predefined regions such as myocardial segments. The usefulness of
5 the method has been demonstrated to characterize the variety of motion patterns that can be observed along the
6 myocardium [20,29].
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12 Our approach has a second advantage for this type of studies. It allows the computation of the pattern morphology
13 and variability within a given population. Looking at the average pattern confirms qualitative observations
14 previously made [6-10]. Looking at its variability is essential to understand the reproducibility of the clinical
15 observations. Both points are important for the clinical observer performing population studies. However, such a
16 pattern analysis is only possible if data are compared at the same locations along the myocardium and the same
17 temporal instants. With our method, data have been spatiotemporally aligned to a same reference system of
18 coordinates. Such computations are not possible with any other existing method, and in particular with the current
19 commercial speckle-tracking software. This relatively new pattern quantification was initially proposed in
20 *Duchateau et al.* [14] and applied to the comparison of velocity patterns to those of a normal population [14,18-
21 20,29]. In the present study, we extended this framework to other parameters than velocities (displacement and
22 strain), and illustrated it in our experimental model.
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36 **Animal model**

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41 Our method was applied to an experimental closed-chest model of pure LBBB undergoing CRT [16]. Such
42 a model (in comparison with clinical studies) allows controlling some of the factors responsible for changes in
43 mechanical dyssynchrony and following outcome. In particular, the non-infarcted animals before the ablation and
44 the infarcted ones before the infarct procedure have normal cardiac function, with no antecedent of cardiac disease.
45 This differs from patients that may show age-related physical and functional alterations. Thus, in non-infarcted
46 animals, only the relevance of correcting LBBB-induced dyssynchrony was tested, while a second factor (infarcted
47 septum) was tested on the LADi animals.
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57 Previous animal studies reported the changes in dyssynchrony induced by LBBB and following CRT
58 [11,12]. The closest models from our study were based on dogs. We preferred to perform on pigs for cost-
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4 effectiveness and experimental facilities reasons. Our observations on LBBB-related changes confirm the ones
5 described in the literature. Our contribution is on quantitative curve analysis, and in particular on the
6 characterization of the pattern morphology and its variability within a given population. Furthermore, to our
7 knowledge, only one of the models mentioned in the literature included chronic infarct [13] but for lead positioning
8 purposes, while our study examines its influence on patterns of mechanical dyssynchrony.
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18 **Changes in mechanical dyssynchrony patterns**

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22 The findings of our study confirm that a very specific pattern of mechanical dyssynchrony derives from
23 pure LBBB. This pattern is visible on both motion and deformation data (*Figures 3 and 6*). It consists of a fast
24 inward/outward motion of the septum during the isovolumic contraction, and early-systolic peak shortening of the
25 septum. Stretching of the lateral wall is observed during the same temporal period. We also noticed the presence of
26 LBBB-induced post-systolic abnormal motion, as discussed elsewhere [30]. Similar patterns were previously
27 described [31-34], and recently referred to as septal flash [6], septal rebound stretch [7,8], or apical rocking [9]. Our
28 experimental results confirm hypotheses about their link with electrical conduction delays and LBBB. This was
29 recently discussed using computer simulations [7,35], experimental [11-13,36] and clinical data [7,37,38]. Further
30 work is expected to fully understand how these specific electrical and mechanical alterations interact.
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42 The LBBB-induced dyssynchrony patterns are observed in all the non-infarcted animals (*Figure 6*).
43 However, patterns are less marked than in patients' sequences. In particular, the late systolic dyssynchrony and
44 lateral wall stretch are sometimes subtle to assess. This may come from the electrical dyssynchrony induced on the
45 animals. QRS width increased by more than 50%, but its post-ablation duration is of 83 ± 10 ms, which is within the
46 range of normal durations for human data. The use of dobutamine tests may probably increase the patterns
47 magnitude [39], but it is not clear if the QRS duration should change. The analysis of electroanatomical data may
48 complement this by looking for the presence of conduction block, as observed in humans [37]. One possible
49 difference with human data may be in how ablation actually damages the left-bundle-branch (punctual burnings in
50 pigs, against more diffuse natural damage in patients). The lack of delay between the induction of LBBB and
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4 imaging may be another reason for this. No time is left for remodeling processes, while remodeling may influence
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6 the mechanical dyssynchrony patterns of patients.
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9 10 **Changes in cardiac function**

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14 We reported that in the absence of structural disease, the correction of SF resulted in a significant
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16 improvement of cardiac function in all pigs, while the opposite was also true (the lack of SF correction in one non-
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18 infarcted animal resulted in no improvement of cardiac function). These results support previous observations on the
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20 relation between improvements of cardiac function, reverse remodeling and volume response to CRT [6,37].
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26 27 **Local viability of the myocardium**

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30 We also demonstrated that a localized infarct can strongly limit the presence of SF after the ablation. In
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32 case of LADi, the viability and contractility of the septum are strongly decreased at the scar location. The motion
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34 and deformation patterns of the septum are therefore altered, as previously described [6,7,20]. When CRT is applied,
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36 the presence of a LADi may be a possible cause of non-response, as electrical dyssynchrony is not anymore the only
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38 factor of changes in cardiac contraction.
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45 46 **Implications**

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49 From an *image analysis/quantification point-of-view*, our approach provides a complete characterization of
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51 motion and deformation patterns that is difficult to obtain with more conventional measurements. Our observations
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53 include spatiotemporal data alignment and efficient visualization tools for studying the patterns morphology and
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55 variability within a given population. [This may be challenging in clinical practice, in particular with the limited](#)
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57 [access to such post-processing tools. Our approach recommends at least including qualitative pattern observations in](#)
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59 [the analysis, as performed in \[6-10\]. Quantitative analysis should consider comparing data at the same locations](#)
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4 along the myocardium and the same physiological instants. The former may be achieved by segmental analysis, as
5 provided in a majority of commercial speckle-tracking software. The latter is more challenging. Temporal
6 measurements should at least be normalized by the length of the cardiac cycle, and if possible the length of the
7 systolic/diastolic phases. We also remind that our post-processing tools are publically available³.
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14 From a *clinical point-of-view*, our findings confirm the importance of the viability of the myocardium and
15 of specific mechanical dyssynchrony patterns related to LBBB. In case of pure-LBBB and the lack of other external
16 factors, CRT is likely to be effective, if normal motion and deformation are restored. *Infarcted patients may benefit*
17 *from CRT, but with a higher uncertainty due to the complexity of the infarct implications. For clinical practice, this*
18 *means being critical with respect to the classical inclusion criteria for CRT, and conventional methods for assessing*
19 *mechanical dyssynchrony. Pattern observations allow better understanding of the complex LBBB/CRT-induced*
20 *changes, as also considered qualitatively in [6-10].*
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32 **Additional comments and limitations**

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36 Our study used 2D views at the papillary muscles level. Additional 2D/3D views could improve our
37 understanding of the patterns observed [40]. However, these views were not available in our experimental protocol
38 with sufficient image quality and spatiotemporal resolution.
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45 The variability of the experimental protocol is a limitation. This includes the quality of the ablation
46 procedure (actual damage made to the left-bundle-branch), the infarct extent, and the leads location.
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51 Finally, it should be reminded that this study uses an experimental model built for understanding purposes.
52 No other forms of heart failure than dyssynchrony and infarction were considered (e.g. no rapid pacing was applied).
53 Similarly, no additional factors that may influence CRT response were studied (e.g. heart failure, the lack of
54 contractile reserve, the presence of atrial fibrillation, or a poor clinical condition at baseline). These aspects should
55 be taken into account when looking at clinical data [20,29].
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Conclusion

The use of a LBBB/CRT experimental model allowed controlling specific factors responsible for changes in mechanical dyssynchrony and therapy. We illustrated the importance of our quantification method, based on curve analysis rather than single measurements, to study these changes and their variability. Our study complements previous qualitative observations on specific LBBB/CRT-induced changes, aiming at a better understanding of motion and deformation in CRT candidates.

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Table 1. Animal characteristics and single motion/deformation measurements.

	Non-infarcted (N=11)			LAD infarcted (N=11)		
	Pre-ablation	LBBB	CRT	Pre-ablation	LBBB	CRT
Weight (kg)		35 [30/36]			45 [38/55]	
QRS width (ms)	55 [50/57]	84 [78/88] (p=0.005)*		52 [45/55]	78 [75/86] (p=0.005)*	
Radial strain delay (ms)	0 [0/0]	0 [-15/29] (p=NS)*	0 [-38/14] (p=NS) ⁺	0 [-25/0]	0 [-99/17] (p=NS)*	0 [-105/16] (p=NS) ⁺
Circumferential strain delay (ms)	22 [-42/51]	47 [-103/101] (p=NS)*	49 [-38/91] (p=NS) ⁺	-28 [-51/0]	-71 [-177/98] (p=NS)*	-43 [-102/63] (p=NS) ⁺
STD _{time-to-peak} (% of cycle)	15 [14/19]	22 [20/26] (p=0.006)*	20 [10/22] (p=NS) ⁺	17 [14/23]	19 [13/23] (p=NS)*	20 [14/25] (p=NS) ⁺
Wasted energy (%)	6.3 [5.3/7.6]	7.6 [7.1/8.3] (p=NS)*	5.9 [3.4/9.2] (p=NS) ⁺	5.6 [3.4/11.3]	6.1 [4.3/10.0] (p=NS)*	8.9 [5.0/12.0] (p=NS) ⁺
Global strain (%)	11.3 [9.6/14.6]	6.7 [6.0/8.1] (p=0.003)*	8.9 [6.9/12.8] (p=NS) ⁺	8.2 [6.4/15.6]	5.9 [4.7/11.7] (p=0.01)*	5.9 [3.9/11.0] (p=0.01) ⁺

LAD: left-anterior-descending. LBBB: left-bundle-branch-block. CRT: cardiac resynchronization therapy.

NS: Non-significant statistical difference (p-value > 0.05).

*: Wilcoxon signed-rank test (LBBB vs. Pre-ablation)

⁺: Wilcoxon signed-rank test (CRT vs. Pre-ablation)

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Table 2. Variability of the speckle-tracking procedure. Intra-observer, inter-observer, and inter-sequence variability (standard deviation of the motion/deformation curves over the whole cycle and the myocardial centerline).

		Non-infarcted		LAD infarct	
		Pre-ablation	LBBB	Pre-ablation	
Radial displacement (mm)	Intra-obs.	0.2±0.1	0.2±0.1	0.1±0.1	
	Inter-seq.	0.5±0.4	0.3±0.3	0.4±0.4	
	Inter-obs.	0.4±0.2	0.4±0.3	1.0±0.7	
Radial velocity (mm/s)	Intra-obs.	1.9±1.5	3.3±2.7	1.5±1.5	
	Inter-seq.	7.0±6.5	7.1±7.3	4.5±4.2	
	Inter-obs.	4.6±4.1	4.4±3.6	8.0±6.3	
Circumferential strain (%)	Intra-obs.	2.2±1.1	2.2±1.3	0.8±0.6	
	Inter-seq.	3.7±3.7	2.9±2.2	0.3±0.2	
	Inter-obs.	3.8±2.9	3.3±2.3	5.0±3.9	

LAD: left-anterior-descending; LBBB: left-bundle-branch-block.

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Figure legends

Figure 1: Pipeline for the comparison of motion and deformation patterns.

Figure 2: Effect of temporal alignment. Prevention of artifacts (black arrows) in pre/post-ablation radial velocity (median, non-infarcted animals).

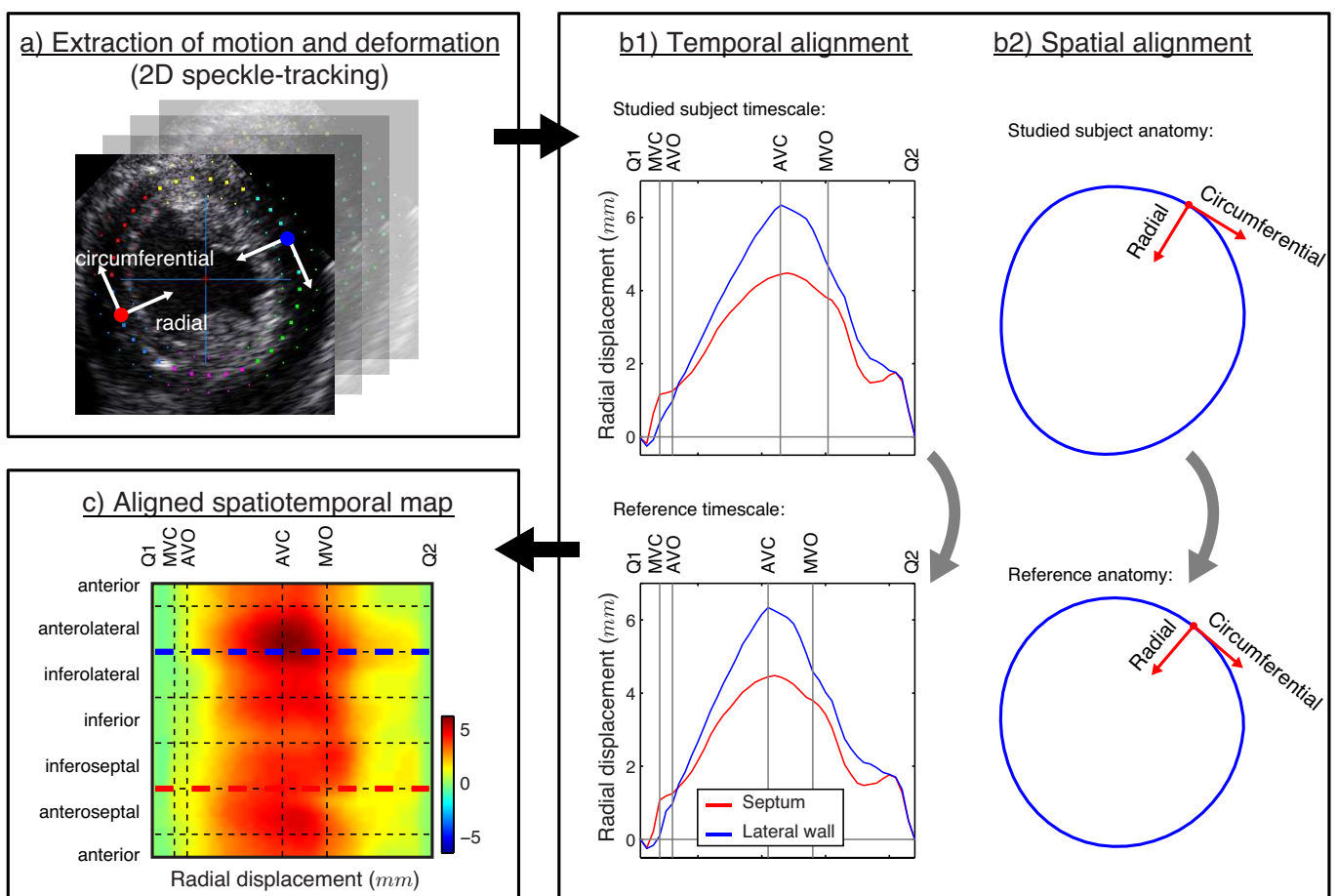
Figure 3: Post-ablation changes on one non-infarcted animal. (a) ECG signals. (b) M-mode traces highlighting the presence of SF (yellow arrows).

Figure 4: Repeatability of the computations illustrated for one non-infarcted animal.

Figure 5: Difficulty of characterizing dyssynchrony by single measurements (peak identification), on one non-infarcted animal.

Figure 6: Radial displacement, velocity and circumferential strain for each subgroup. Septal/lateral curves (median and first/third quartiles) and full spatiotemporal (median) maps. Black arrows highlight the presence of SF, double-peaked systolic septal shortening, early-systole lateral wall stretch and post-systolic abnormal motion.

Figure1
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Q1, Q2: onset of QRS; AVO/AVC/MVO/MVC: aortic/mitral valve opening/closure.

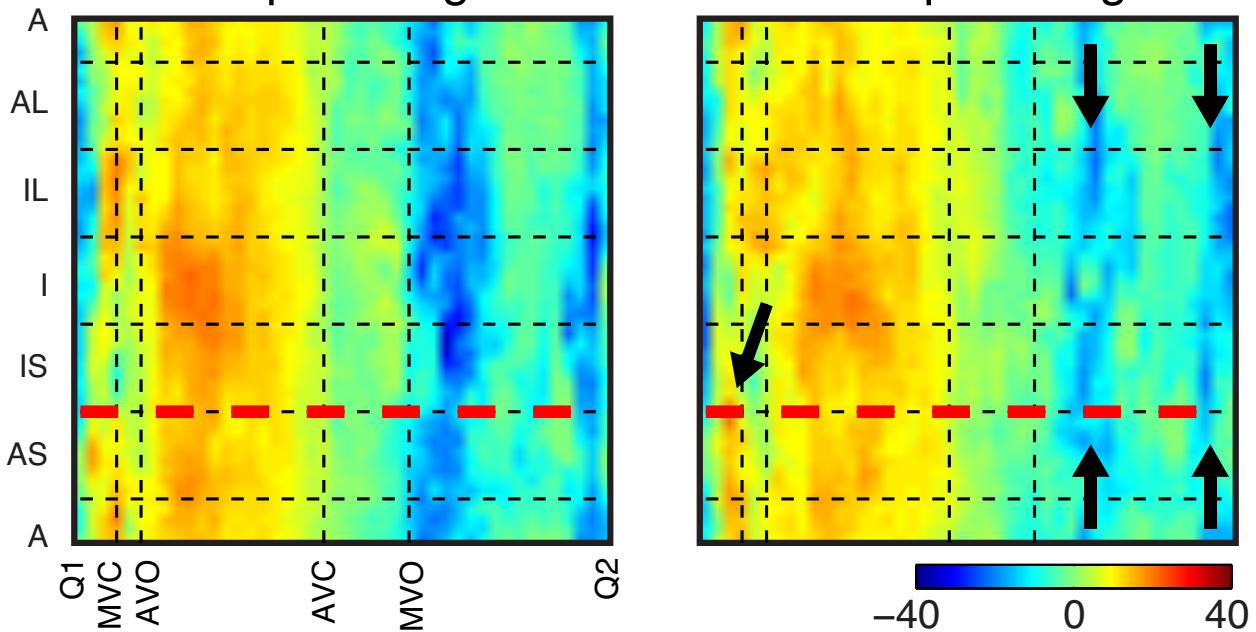
Figure2

[Click here to download Figure: Figure2.png](#)

a) Pre-ablation, Radial velocity (mm/s)

With temporal alignment

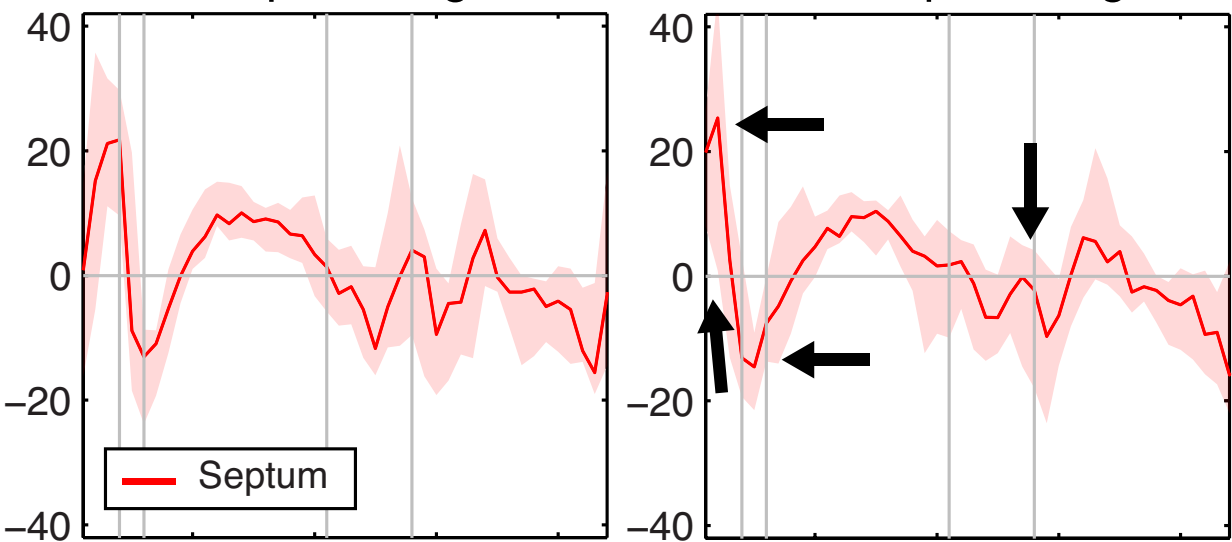
Without temporal alignment



b) LBBB, Radial velocity (mm/s)

With temporal alignment

Without temporal alignment



Q1, Q2: onset of QRS; AVO/AVC/MVO/MVC: aortic/mitral valve opening/closure.

A: anterior; AL: anterolateral; IL: inferolateral; I: inferior; IS: inferoseptal; AS: anteroseptal.

LBBB: left-bundle-branch-block.

Figure3

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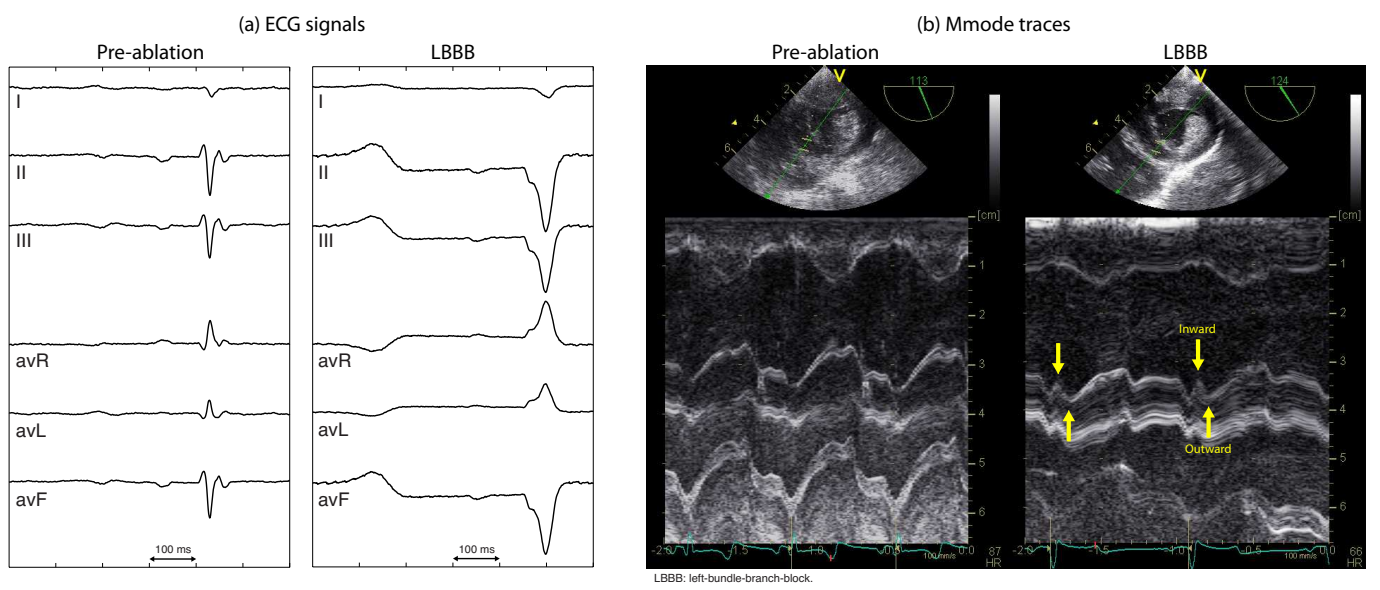


Figure4

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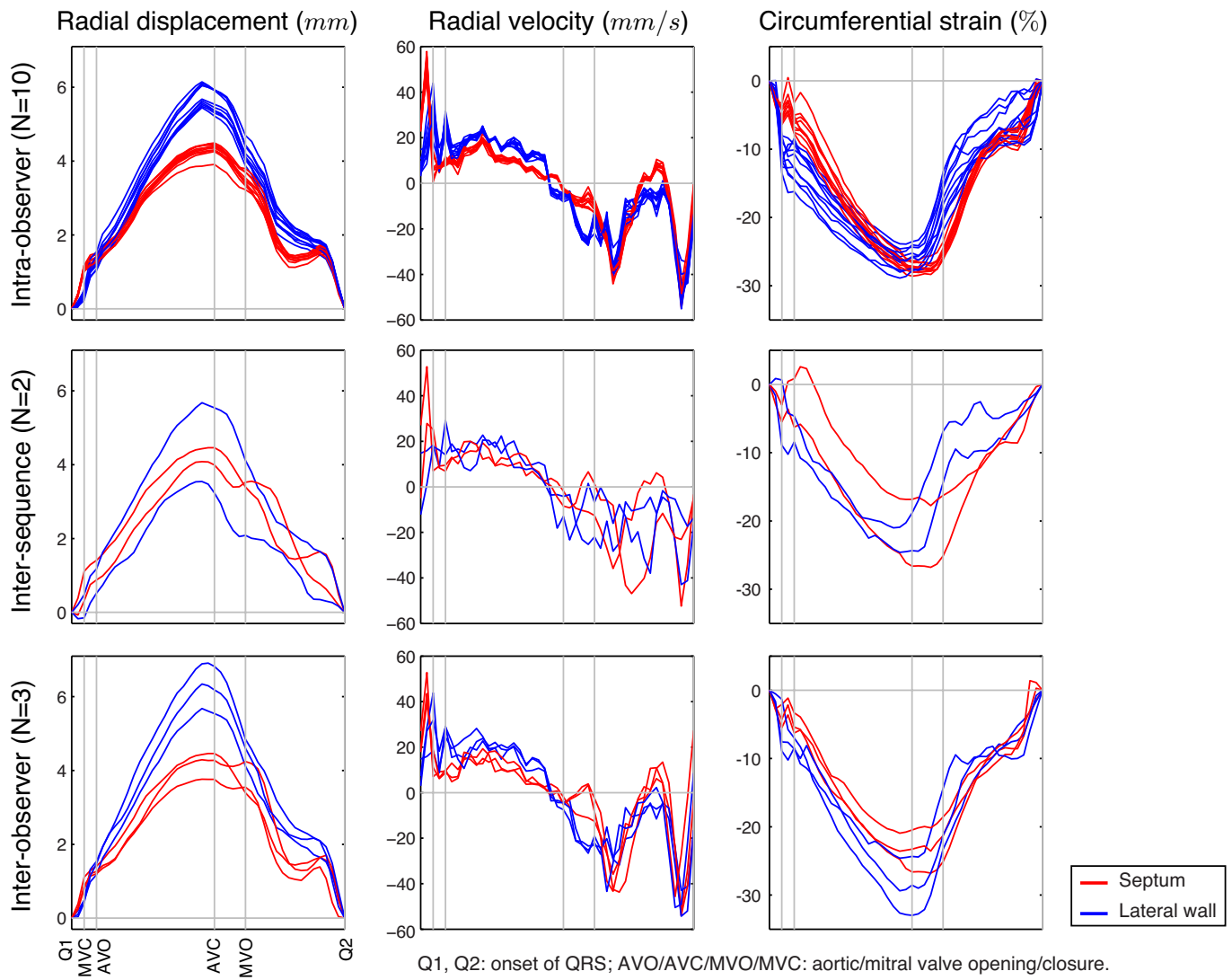
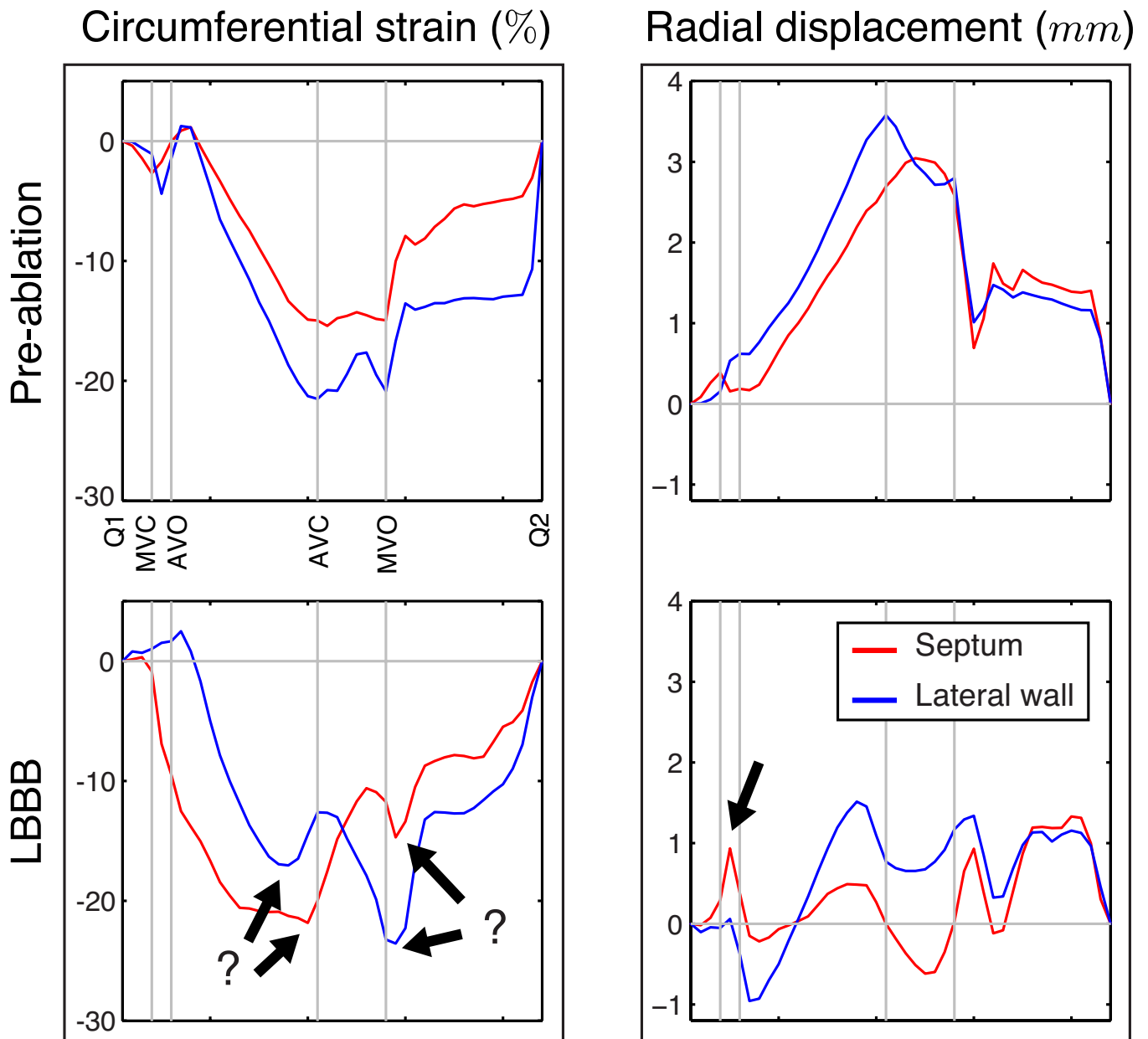
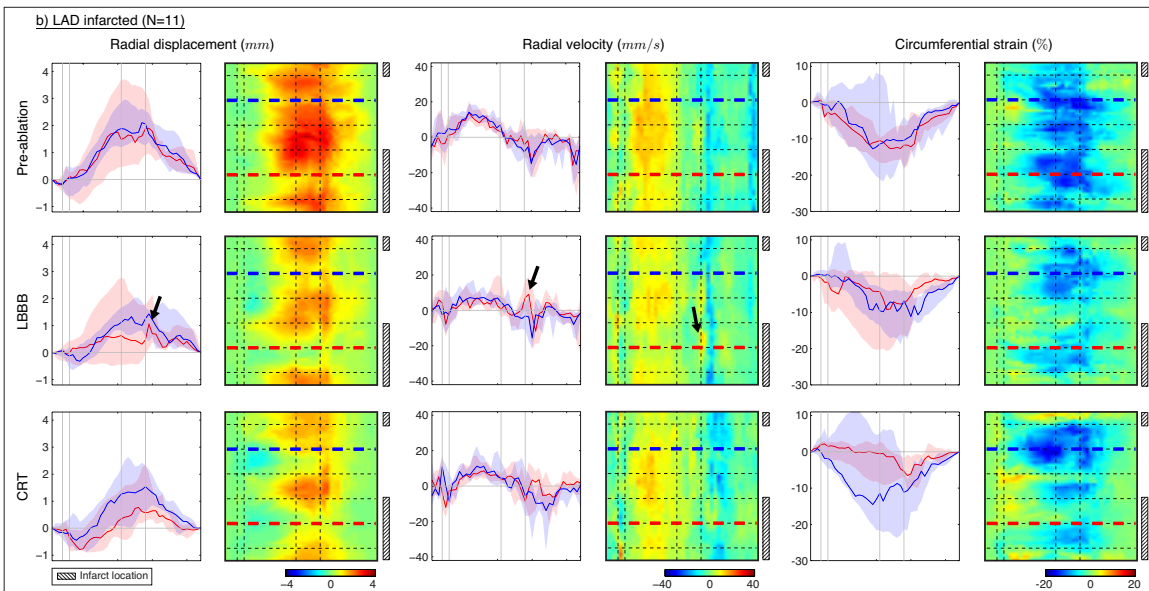
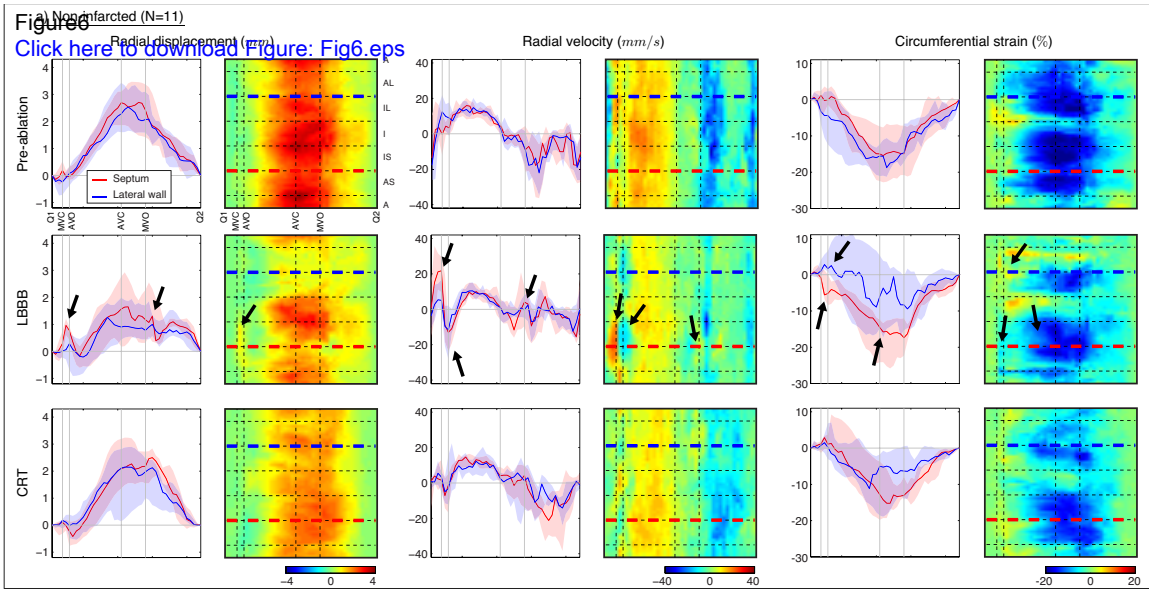


Figure5
[Click here to download Figure: Fig5.eps](#)



Q1, Q2: onset of QRS; AVO/AVC/MVO/MVC: aortic/mitral valve opening/closure.
LBBB: left-bundle-branch-block.



Q1, Q2: onset of QRS; AVO/AVC/MVO/MVC: aortic/mitral valve opening/closure.
 A: anterior; AL: anterolateral; IL: inferolateral; I: inferior; IS: inferoseptal; AS: antero-septal.
 LBBB: left-bundle-branch-block; CRT: cardiac resynchronization therapy; LAD: left-anterior-descending.