Full Title: Imaging the propagation of the electromechanical wave in heart failure patients with cardiac resynchronization therapy

Short Title: Electromechanical Wave Imaging for CRT

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Imaging the propagation of the electromechanical wave in heart failure patients with cardiac resynchronization therapy

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Abstract

Background: Current electrocardiographic and echocardiographic measurements in heart failure (HF) do not take into account the complex interplay between electrical activation and local wall motion. The utilization of novel technologies to better characterize cardiac electromechanical behavior may lead to improved response rates with cardiac resynchronization therapy (CRT). Electromechanical Wave Imaging (EWI) is a non-invasive ultrasound-based technique that uses the transient deformations of the myocardium to track the intrinsic electromechanical wave that precedes myocardial contraction. In this paper, we investigate the performance and reproducibility of EWI in the assessment of HF patients and CRT.

Methods: EWI acquisitions were obtained in 5 healthy controls and 16 HF patients with and without CRT pacing. Responders (n=8) and non-responders (n=8) to CRT were identified retrospectively on the basis of left ventricular (LV) reverse remodeling. Electromechanical activation maps were obtained in all patients and used to compute a quantitative parameter describing the mean activation time of the LV lateral wall (LWAT).

Results: Mean LWAT was increased by 52.1 ms in HF patients in native rhythm compared to controls (p<0.01). For all HF patients, CRT pacing initiated a different electromechanical activation sequence. Responders exhibited a 56.4±28.9 ms reduction in LWAT with CRT pacing (p<0.01), while non-responders showed no significant change.

Conclusion: In this initial feasibility study, EWI was capable of characterizing local cardiac electromechanical behavior as it pertains to HF and CRT response. Activation sequences obtained
with EWI allow for quantification of LV lateral wall electromechanical activation, thus providing a novel method for CRT assessment.

**Keywords:** cardiac resynchronization therapy, electromechanical, ultrasound, strain, heart failure

**Introduction**

Heart failure (HF) affects more than 5 million Americans each year and is projected to cost the U.S. healthcare system over $40 billion annually by 2020[1]. Cardiac resynchronization therapy (CRT) is an established treatment for HF patients with left ventricular (LV) systolic dysfunction and QRS prolongation in patients with left bundle branch block (LBBB). Large, randomized clinical trials of HF patients have demonstrated that CRT decreases HF hospitalizations and mortality, reverses LV remodeling and improves patient quality of life[2,3]. However, there remains a large subset of patients (30-40%) that are considered non-responders and do not derive significant benefits from CRT[4,5]. Currently, clinical assessment of cardiac dyssynchrony and CRT candidacy in systolic HF is mainly performed on the basis of electrical parameters assessed using the electrocardiogram (ECG).

QRS duration (QRSd) reflects total ventricular activation and provides a general prediction of CRT response, although clinical trials have shown poor correlation between QRSd and outcome[6,7].

LBBB morphology has been recognized as a potentially better indicator of delayed LV activation and dyssynchrony; however some patients with non-LBBB pattern can also demonstrate a favorable response to CRT[8].

Mechanical parameters to predict CRT response have also been investigated over recent years with limited success. Assessment of mechanical dyssynchrony using echocardiography initially showed promise in determining response in small observational studies, but large, multi-center trials failed to validate the predictive power of these approaches. The largest prospective trial (PROSPECT) showed poor predictive value of several echocardiographic parameters derived using tissue Doppler[5]. Speckle-tracking echocardiography has also been used to quantify dyssynchrony.
associated with response to CRT[9], but recent studies using speckle tracking dyssynchrony measures to predict response to CRT have shown mixed results[10,11].

Although conventional imaging techniques are mainly targeted at either the electrical or mechanical aspects of excitation-contraction coupling, recent studies have suggested that the complexities of the electromechanical relationship may be important in understanding patient response to CRT[12,13]. This relationship has been previously identified as the electromechanical wave (EW), i.e. the depolarization wave that initiates cardiac contraction[14–16]. Since the EW lasts only 60 to 100 ms, a resolution of a few milliseconds (e.g., 2–5 ms) is required to generate precise maps of electromechanical activation. Thus, the EW reflects the behavior of the heart at the onset of systole, where the electrical and mechanical systems of the heart are highly coupled. Conventional echocardiography operating at low frame-rates (<100 Hz) does not provide the required temporal sampling to precisely capture the strain changes corresponding to the EW (Figure 1). Spatial mapping of the cardiac electromechanics warrants further investigation since it may offer additional insights into CRT compared to electrical or mechanical parameters taken alone.

Electromechanical wave imaging (EWI) is a non-invasive, ultrasound-based technique that uses the transient initiation of myocardial strain to depict the electromechanical activation of the heart[17,18]. Using high temporal and spatial resolutions, the onset of contraction resulting from electrical activation can be separated in space and time, mapped and quantified. EWI differs from conventional strain imaging in two major ways. First, EWI uses a transmission sequence that allows for extremely high frame rates (up to 2000 Hz) to capture the electromechanical activation at very small time increments (0.5-ms temporal resolution). High frame-rate ultrasound has consistently been shown to be of particular use in cardiac applications to capture the rapid deformations experienced by the heart[19,20]. Secondly, EWI uses a strain estimation technique based on cross-correlation of radiofrequency (RF) signals instead of conventional B-mode block matching, allowing for the calculation of sub-pixel displacements (on the order of 10 microns) that occur when imaging.
at such a high frame-rate. Several ultrasound-based research groups have reported the superiority of cross-correlation techniques compared to B-mode block matching, especially for small deformations[21,22]. The strain estimation technique employed by EWI has been previously validated using a simulation model[23] and sonomicrometry[24]. Accurate detection of such small motion at high frame-rates allows EWI to map the rapid onset of strain that occurs in response to electrical activation, i.e. the electromechanical wave (Figure 1).

The EW as measured by EWI has been shown to be correlated with electrical activation in pacing and sinus rhythm using a canine model with simultaneous electrical mapping[18,25]. Previous studies have demonstrated the feasibility of EWI in mapping the site of earliest activation in atrial tachyarrhythmia and ventricular pacing[17,26]. In this retrospective study, we use EWI as a novel technique to characterize the myocardial electromechanical activation in five healthy volunteers and 16 HF patients that have been clinically identified as either responders or non-responders. Differences between the two response groups in native rhythm and with CRT pacing are quantified on the basis of a parameter derived from ventricular EWI maps. The reproducibility of EWI is also investigated in six patients using consecutive acquisitions of the same pacing protocol.

Methods

Study Recruitment

Using a protocol approved by the Columbia University Institutional Review Board, HF patients with CRT devices were recruited for the study from November 2012 to November 2013 at Columbia University Medical Center. Implantation of CRT devices was performed prior to the time of the study according to ACC/AHA standard guidelines[27]. All patients were programmed for biventricular pacing. Inclusion criteria for recruitment consisted of a diagnosis of LBBB or IVCD by 12-lead electrocardiogram (ECG) with minimum QRSd of 130 ms, a sustainable underlying rhythm (non-pacemaker dependent), and the absence of atrial fibrillation.
Among 25 recruited subjects, nine patients were excluded from the final analysis on the basis of poor echocardiogram window (n=3) and lack of sufficient clinical data to determine response (n=6), resulting in a study sample of 16 HF patients (10 non-ischemic, 6 ischemic). Separately from EWI imaging, patients also underwent routine echocardiographic evaluation before implantation and again at least 3 months after implant. All standard echocardiograms were performed at the Columbia University echocardiography lab and LV ejection fraction (LVEF) was determined by a blinded observer. Response to CRT was defined as an absolute ≥5% increase in LVEF relative to the pre-implant echocardiogram. Using this definition, eight patients (n=8) were identified as responders. The mean time from CRT implant to EWI data acquisition was 1216±977 days in responders compared to 1062±924 days in non-responders. Finally, a second control group of five healthy volunteers without CRT was also recruited. Baseline statistics of all subjects included in the final analysis are listed in Table 1.

**EWI Acquisition**

After obtaining informed consent, EWI acquisitions were obtained in all patients by a trained echocardiographer in the standard apical 4-chamber view. CRT pacing settings were adjusted using telemetry, allowing for imaging of several different pacing protocols for each patient. For all patients, acquisitions were obtained during pre-programmed biventricular (BiV) pacing and during native rhythm with the CRT device set to a sensing only mode.

Ultrasound acquisitions were performed at a depth of 20cm using a Verasonics V-1 system (Verasonics Inc., Kirkland, WA) with a P4-2 phased array probe ($f_0 = 2.5$ MHz). A diverging beam transmission was used to simultaneously interrogate a full 90° field of view with a single transmit, allowing for extremely high frame-rates up to 2000 Hz (Figure 2-1)[17]. Acquisitions lasted a full two seconds to ensure the uninterrupted capture of a full cardiac cycle. Radiofrequency (RF) signals were acquired throughout the entire diverging beam sequence for each of the 64 individual transducer elements. Following the diverging beam acquisition, a conventional, focused acquisition was
performed for two seconds at a framerate of 30 Hz, bringing the total acquisition length to four seconds. On-line beamforming was used to reconstruct RF signals from the conventional sequence into high quality B-mode images, which were solely used for visualization and segmentation purposes and not used for any strain calculations. Recordings of Lead II in the standard 12-lead electrocardiogram (ECG) were also obtained by the system in parallel with the ultrasound acquisitions.

**Incremental Strain Estimation**

EWI processing of the ultrasound data was performed blinded to the CRT response status of each patient. First, a delay-and-sum algorithm was used offline to reconstruct the signals obtained with the diverging beam sequence into 64 RF lines per frame at an axial sampling frequency of 20 MHz[26]. Using the ECG recordings, RF frame sequences were truncated to a time window of 700 ms around the peak of the R wave for motion estimation. A normalized cross-correlation algorithm (window size = 5.85 mm) was used to estimate inter-frame axial displacements throughout the entire image (Figure 2-2) [28]. Axial displacement estimates were obtained at an axial spacing of 0.36 mm and a lateral spacing of approximately 0.19 mm. Inter-frame axial strains were then estimated from the displacements using a least square strain estimator with a window size of 7.83 mm (Figure 2-3) [29]. Axial displacements were smoothed in time (Gaussian low-pass filter, cutoff frequency = 125 Hz) and in space (6.0 x 12.3mm averaging filter). Due to the high frame-rate used in EWI and the fact that strains were not accumulated over systole, the estimated inter-frame strains during systole were on the order of 0.01% (Figure 1). In the apical 4-chamber window, axial strains correspond to longitudinal strains for the vast majority of the ventricle; however, the cardiac strain vector measured in the most apical regions is not well-defined. The ventricular tissue structure was segmented using manually drawn contours in the first frame of the conventional acquisition. These contours were then synchronized to the ECG and tracked through time using the estimated displacements[30].

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Activation Map Generation and Lateral Wall Activation Time

Previous EWI studies have used manual selection of the “zero-crossings” of inter-frame strain signals to generate an electromechanical activation map[17,26]. The existence of a zero-crossing, defined as a sharp transition from positive to negative strain, reflects myocardial shortening that occurs in the walls of the heart in the apical 4-chamber view in response to electrical activation (Figure 2-4). In this study, a robust algorithm was used to automatically identify and select the zero-crossings corresponding to electromechanical activation for each point in the tissue.

Zero-crossings were initially selected by identifying the clear negative peaks of the inter-frame strains over time and searching backwards in time to find the corresponding zero crossing. “Clear” negative peaks were constrained to only include peaks associated with:

1. a negative magnitude ≥20% of the global minimum of the strain and
2. a negative first derivative ≥20% of the global maximum.

These criteria allowed for filtering of zero-crossings associated with progressive shortening that are not indicative of electromechanical activation. For many strain signals, a single negative peak existed and thus computation of the zero-crossing was relatively simple. However, some strain signals exhibited more than one negative peak following the onset of the QRS complex. In these instances, the algorithm searched the surrounding region for a strain signal containing a single, clear peak and chose the zero-crossing closest in time. Once all zero-crossings had been identified, the activation time of each zero-crossing was computed with respect to a reference point, selected to be the onset of the QRS complex. Activation times were only computed within the ventricular tissue as determined from segmentation. A spatial rendering of these activation times is referred to as the EWI activation map. It should be noted that for all activation maps, activation occurring in the extreme apex (where the tissue is oriented perpendicular to the axial direction of the ultrasound beam) is computed differently compared to other parts of the tissue. Since the contractile dynamics

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and fiber orientation are less well-defined in this location, both positive-to-negative and negative-to-positive zero-crossings were considered.

A quantitative parameter, the LV lateral wall activation time (LWAT) was also calculated from the activation maps by computing the mean activation time occurring in the LV lateral wall (Figure 2-5). Selection of the LV lateral wall was manually performed on the basis of anatomical structures observed on the B-mode images. The selected region included only the portion of the LV lateral wall which was oriented parallel to the axial direction of the ultrasound beam (Figure 2-5). The most apical region of the LV lateral wall that is oriented perpendicular to the ultrasound beam was thus excluded from the LWAT calculation. The basal boundary of the LV lateral wall was defined below the mitral valve as observed from the B-mode. Statistical comparison between LWAT values was performed using either paired or unpaired Student’s t-test.

**Results**

**Healthy subjects**

EWI ventricular activation maps for two healthy subjects in sinus rhythm are displayed in Figure 3. Early myocardial activation is designated in blue, while late activation is marked in red. The exact time of activation with respect to the onset of the QRS complex is indicated by the color scale superimposed over each patient’s ECG tracing below the image. Ventricular electromechanical activation is initiated at the mid-level of the interventricular septum before propagation to RV free wall and LV lateral wall. Although slightly varying patterns of activation are observed between subjects, activation of the LV lateral wall, septum, and RV free wall occurs nearly simultaneously during the early portion of the QRS complex. Activation of the entire lateral wall progresses quickly, and mean LWAT for healthy subjects was 61.1±24.0 ms.

**Heart Failure Patients**
Mean baseline LVEF in 8 responders was 18.9±7.3%, which increased significantly to 42.8±9.5% following CRT (p<0.01). In non-responders, mean LVEF decreased slightly from 25.7±7.2% to 20.0±6.7% after CRT, although this change was not significant (p>0.05). Responders also exhibited a statistically significant reduction in QRSd as a result of CRT, while non-responders showed no significant change (Table 1).

Activation maps for representative HF patents in native rhythm are shown in Figure 4 (Ia-IIIa) for CRT responders and Figure 5 (Ia-IIIa) for CRT non-responders. Early electromechanical activation is again frequently observed in the mid-septal region. Early activation near the RV apex also occurs in most patients. However, in all patients, electromechanical activation in the LV lateral wall is delayed with varying levels of severity. The delay in LV lateral wall activation in HF patients in native rhythm can be qualitatively observed in Figures 4 and 5 and is also reflected by the increased mean patient LWAT (113.2±25.2 ms) compared to healthy subjects as shown in Figure 6. The difference in mean LWAT between all HF patients in native rhythm and healthy controls was 52.1 ms, which was found to be statistically significant (p<0.01).

Corresponding EWI isochrones for the same HF patients during biventricular pacing are also shown in Figures 4 and 5. For all patients, the spatiotemporal sequence of LV activation is markedly different compared to native rhythm. Differences are especially noted in the LV lateral wall, where several patients exhibit significantly earlier activation sequences. Mean LWAT was decreased by 29.5±40.9 ms in all HF patients during CRT (Figure 6), although separation by treatment response yielded more significant differences. Patients in Figure 4, which have been retrospectively identified as responders to CRT, qualitatively showed more homogenous activation sequences and reduced delay in lateral wall activation in response to CRT. Responders experienced a corresponding mean reduction in LWAT of 56.4±28.9 ms (Figure 6), which was found to be statistically significant using a paired comparison (p<0.01). Although non-responders also experienced changes in electromechanical activation in response to CRT, the resulting activation was highly variable,
especially in lateral wall region. Non-responders still experienced largely delayed electromechanical activation even with CRT pacing and as a whole exhibited very little change in LWAT (0.7±24.9 ms) compared to native rhythm (Figure 6).

**EWI Reproducibility**

The reproducibility of the EWI method and the computed LWAT parameter was investigated in six patients in biventricular pacing. Consecutive EWI acquisitions were obtained of each patient in the same pacing protocol, allowing for two similar activation maps to be generated. Consecutive acquisitions were recorded less than a minute apart and the probe was removed from the patient between acquisitions and replaced at approximately the same location. Figure 7 depicts a Bland-Altman of the test-retest variability of LWAT for all six patients where consecutive acquisitions were obtained. All repeated measurements fell within the 95% confidence level of agreement (1.96σ).

**Discussion**

In this study, we demonstrate the feasibility of a novel imaging technique, Electromechanical Wave Imaging, in mapping the electromechanical activation in HF patients and demonstrating the differences according to response to CRT. A parameter derived from EWI activation maps, LWAT, was used to quantify the local electromechanical behavior of the LV lateral wall and differentiate HF patients from healthy controls and responders from non-responders to CRT.

In healthy subjects, EWI depicts relatively uniform activation of the ventricular tissue, including both interventricular and intraventricular synchrony. In contrast, HF patients in native rhythm all experienced significantly delayed activation in the left ventricular lateral wall. Electromechanical activation sequences for HF patients were also more variable compared to healthy subjects, especially in the region of the LV lateral wall. In some cases, areas of early activation were located in close proximity to areas of late activation. This phenomenon has been observed in several previous studies using contact and non-contact mapping techniques and is referred to in these studies as...
“conduction block” [31,32]. Furthermore, the existence of ischemic or infarcted regions of tissue is known to cause fractionated electrical signals and mechanical decoupling [33], which may also contribute to the discontinuous activation patterns observed in HF patients.

CRT pacing was shown to initiate a different electromechanical activation pattern within the ventricular tissue of HF patients compared to their underlying rhythm. Indeed, it is clear from Figures 4 and 5 that both the origins of activation and propagation pathways are altered with CRT pacing in the same patient. In native rhythm, several HF patients exhibited activation origins in the mid-septal region of the LV. However, with CRT pacing, activation origins consistently appeared in the RV apex and in the LV lateral wall. Notably, the locations of these early activated regions correlate well with the standard biventricular lead locations used for CRT.

CRT pacing also induced different behavior in the left ventricular lateral wall in responders compared to non-responders. In responders, early activation of the lateral wall was widespread, while non-responders showed only a small, contained area of early activation. The differences observed in LV lateral wall electromechanical activation between responders and non-responders highlights the importance of the local electromechanical relationship in CRT. Indeed, several recent investigations into local cardiac electromechanics have indicated that this relationship can vary drastically between HF patients, which may be related to the variability in CRT response [12,13,34]. Furthermore, several publications have discussed the importance of local electrical activation in the context of CRT and have developed their own techniques to evaluate this behavior [35,36]. The importance of the local behavior of the cardiac tissue lends support to recent studies that have advocated for “patient-specific” optimization of various aspects of CRT to increase the likelihood of response [32,34,37,38].

Clinical trials have failed to demonstrate a strong correlation between initial QRS duration and CRT response, especially for QRSd < 150 ms [6,7]. Although ECG parameters including QRSd remain important in the evaluation of HF and CRT, it may be of significant clinical benefit to identify other methods for evaluation of cardiac electromechanics. Ultimately, QRS duration reflects the electrical...
behavior of both ventricles at a macroscopic level, which may not sufficiently capture the cardiac excitation-contraction coupling as it pertains to CRT. The parameter investigated in this study (LWAT) is an electromechanical measurement localized to the LV, which may be affected differently by tissue geometry, myocardial scar, and patterns of electrical conduction compared to QRSd. In this study, QRSd was slightly increased in responders compared to non-responders, as was LWAT. This observation is not surprising, since it is generally accepted that patients with prolonged ventricular activation will benefit most from CRT. Following CRT, responders exhibited significant reductions in both QRSd and LWAT; however, the differences observed in LWAT were of greater magnitude compared to QRSd (Figure 8). It is also of note that the standard deviations of the LWAT measurements are increased compared to the QRSd measurements. As such, clinical use of an electromechanical parameter such as LWAT and its correlation to QRSd requires further validation in a large patient trial.

Cardiac strain has previously been used to assess dyssynchrony in HF patients with mixed success[9–11]. However, these studies mainly used B-mode-based speckle tracking techniques to map the heart on the basis of peak strain rather than the onset of strain. While peak strain may be closely correlated to the mechanical behavior of the heart, tracking the rapid onset of contraction may better reflect the underlying electromechanical characteristics of the tissue[38,39]. As can be seen in Figure 1, the zero-crossing occurs very rapidly (<50 ms) and would be extremely difficult to detect using low frame-rate imaging, especially after accumulation of the strains over systole. Inter-frame strains measured using tissue Doppler could conceivably be extended to electromechanical mapping; however, Doppler-based techniques traditionally suffer from a strong angle dependency and have been shown previously to be poorly correlated with CRT response[5,40]. By precisely identifying electromechanical activation on the basis of the inter-frame zero-crossing, EWI is capable of capturing and mapping the interaction between the electrical and mechanical aspects of the
heart. This approach may be especially useful in applications involving CRT, which by nature affects both the electrical and the mechanical behavior of the heart.

The reproducibility of results obtained using novel imaging techniques is always important, especially for those involving clinical applications. Although EWI has previously been validated using simulations and electrical mapping [17,23], a small investigation into the reproducibility of the LWAT measurement obtained from EWI in HF patients was performed in this study. As seen in Figure 7, LWAT values are fairly consistent within the same patient. These results indicate that EWI and its subsequent generation of LWAT can be used reliably to characterize the activation sequence of HF patients with biventricular pacing.

Study Limitations

This was a single-center, non-randomized retrospective study. The small number of patients is the largest limitation in this study. However, the aim of this study was to demonstrate the feasibility of EWI as a novel technique to characterize dyssynchrony in HF patients and their subsequent response to CRT as measured by improvement in LV systolic function. In the future, our results should be further investigated in a prospective study using a large cohort of HF patients, including comparison to conventional strain imaging and/or electroanatomical mapping. Clinical parameters such as the 6-minute walk were not used to further characterize response to CRT and responders were identified on the basis of one echocardiographic parameter, LVEF. Absence of data regarding change in LV end-systolic volume constitutes another limitation. Finally, activation maps were generated only in the apical four chamber view which may limit assessment of propagation patterns of the electromechanical wave.

Conclusion

The primary goal of this paper was to demonstrate the initial feasibility of EWI in studying the electromechanical activation of HF patients and the changes that accompany CRT. We have shown
that EWI can be used to map the ventricular electromechanics of both healthy and HF patients and is capable of distinguishing between these two groups both quantitatively and qualitatively. We have also reported the differences in electromechanical activation that occur in response to CRT for responders versus non-responders and that this information can be localized to the LV and quantified. Finally, our parameter derived to quantify LV electromechanical behavior (LWAT) was shown to be reproducible within the same patient, reinforcing the findings and trends reported in this paper.

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Disclosures

None.

References


Figure Legends

Figure 1: Comparison of the strain computed using EWI and traditional strain imaging methods. EWI (blue) captures small inter-frame strains and to identify the strain zero-crossing in response to electromechanical activation (orange circle), while traditional strain imaging (green) computes the global total strain and often relies on time to peak strain (red circle).

Figure 2: Brief overview of the EWI workflow.

Figure 3: Ventricular activation isochrones from two healthy volunteers. Activation times are mapped to the ECG displayed below the images (total time = 200 ms).
Figure 4: Ventricular activation isochrones from three HF patients identified as responders to CRT. Isochrones are shown for (a) native rhythm and (b) biventricular pacing. Activation times are mapped to the ECG displayed below the images (total time = 200 ms). Patient I has been diagnosed with ischemic cardiomyopathy while Patients II and III have been diagnosed with non-ischemic cardiomyopathy.

Figure 5: Ventricular activation isochrones from HF patients identified as non-responders to CRT. Isochrones are shown for (a) native rhythm and (b) biventricular pacing. Activation times are mapped to the ECG displayed below the images (total time = 200 ms). Patients I and II have been diagnosed with ischemic cardiomyopathy while Patient III has been diagnosed with non-ischemic cardiomyopathy.
Figure 6: Cumulative statistics of LWAT for all normal subjects (n=5) and HF patients (n=15). HF patients have also been separated into responders (n=7) and non-responders (n=8). * indicates p<0.01 by unpaired or paired Student’s t test where appropriate.

Figure 7: Bland-Altman plot of LWAT reproducibility for consecutive EWI acquisitions of the same patient (n=6) in the same protocol.
Figure 8: Mean change in QRSd and LWAT within each patient as a result of CRT.

Table 1: Clinical characteristics of healthy subjects and HF patients involved in the study. * indicates a significant change (p<0.01) in either QRSd or LVEF as a result of CRT by paired Student’s t-test.

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