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REPRODUCIBILITY AND ANGLE INDEPENDENCE OF ELECTROMECHANICAL WAVE IMAGING FOR THE MEASUREMENT OF ELECTROMECHANICAL ACTIVATION DURING SINUS RHYTHM IN HEALTHY HUMANS

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Abstract

Electromechanical Wave Imaging (EWI) is an ultrasound-based technique that can non-invasively map the transmural electromechanical activation in all four cardiac chambers in vivo. The objective of this study was to demonstrate the reproducibility and angle independence of EWI for the assessment of electromechanical activation during normal sinus rhythm (NSR) in healthy humans. Acquisitions were performed transthoracically at 2000 frames/s on seven healthy human hearts in parasternal long-axis, apical four- and two-chamber views. EWI data was collected twice successively in each view in all subjects, while four successive acquisitions were obtained in one case. Activation maps were generated and compared 1) within same acquisitions across consecutive cardiac cycles; 2) within same views across successive acquisitions; and 3) within equivalent left ventricular regions across different views. EWI was capable of characterizing the electromechanical activation during NSR and of reliably obtaining similar patterns of activation. For consecutive heart cycles, the average 2D correlation coefficient between the two isochrones across the 7 subjects was 0.9893 with a mean average activation time fluctuation in LV wall segments across acquisitions of 6.19%. A mean activation time variability of 12% was obtained across different views with a measurement bias of only 3.2 ms. These findings indicate that EWI can map the electromechanical activation during normal sinus rhythm in human hearts in transthoracic echocardiography in vivo, and leads to reproducible and angle-independent activation maps.

Keywords

Electromechanical wave imaging; Reproducibility; Angle independence; Electromechanical activation sequence; Echocardiography

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INTRODUCTION

Cardiac conduction abnormalities and arrhythmias can often lead to stroke, heart failure, and sudden cardiac death (Mehra 2007; Mozaffarian et al. 2016; Zipes and Wellens 1998). These diseases remain a major cause of death worldwide. In fact, although the rate of deaths attributable to cardiovascular diseases has decreased by 28.8% in the last decade, cardiovascular diseases still accounted for 30.8% of all death in the US in 2013: approximately 1 of every 3 deaths (Mozaffarian et al. 2016; Zoni-Berisso et al. 2014). Yet, despite this health impact and the urgent need for prevention, the imaging techniques currently available clinically for heart activation sequence mapping are invasive, ionizing, time-consuming and costly (Knackstedt et al. 2008; Packer 2004).

Mapping the electrical activation of the heart is necessary for the diagnosis and treatment of arrhythmias. Providing physicians with simpler tools that allow early detection of arrhythmias and more prompt and precise treatment would undoubtedly improve treatment outcomes. Our group has developed a direct and non-invasive ultrasound-based technique to study the electromechanical behavior of the heart: Electromechanical Wave Imaging (EWI) (Konofagou et al. 2010). This ultrasound-based modality, capable of mapping the electromechanical activation in all four cardiac chambers in vivo (Provost et al. 2011a), is transmural, has a high temporal resolution (0.5–3 ms), a high spatial resolution and real-time feedback capabilities (Provost et al. 2010; Provost et al. 2011b; Wang et al. 2008).

The heart needs to be electrically activated before it can mechanically contract (Glass et al. 1991). The Electromechanical Wave (EW) refers to the propagation of the onset of the cardiac contraction in response to the electrical activation of the heart. The EW has been shown to be highly correlated with the electrical activation sequence in the left ventricle (LV), both in normal and paced canines in vivo (Provost et al. 2011a, 2011b). Furthermore, the electromechanical delay is defined as the lag between the depolarization of the cardiomyocytes, i.e. the electrical activation, and the onset of their contraction, i.e. the electromechanical activation. Typically, this delay is on the order of tens of ms (Bers 2002; Cordeiro et al. 2004; Provost et al. 2011a).

EWI has been previously reported in a variety of applications, such as ischemia and infarct assessment in canines, as well as Cardiac Resynchronization Therapy (CRT) in heart failure patients. EWI was shown capable of detecting infarcted regions in the canine hearts and monitoring the formation of myocardial infarction over several days (Costet et al. 2017). In addition, not only was EWI successful in distinguishing between healthy and heart failure patients, but also capable of mapping the electromechanical activation pattern of the ventricles under CRT and differentiating responders from non-responders (Bunting et al. 2017).

In previous studies, EWI was shown reproducible in simulations and canine experiments (Provost et al. 2011c), as well as repeatable within the same acquisition across consecutive cardiac cycles in open-chest dogs (Costet et al. 2014). However, reproducibility in closed-chest humans has yet to be investigated. Furthermore, it is critical for clinical applications to reliably measure the activation sequence independently of the imaging view. Our group

recently established that EWI is not only capable of properly identifying the origin of activation of focal rhythms, but also of distinguishing between epicardial and endocardial origins in a focal paced canine heart in vivo (Costet et al. 2016b). These findings result from an open-chest animal model and still require further investigation in closed-chest.

Initial results on premature ventricular contractions (PVCs) and Wolff Parkinson White (WPW) syndrome patients have been reported (Costet 2016a) for potential applications in radiofrequency (RF) ablation treatment planning (Papadacci et al. 2017b, Bunting et al. 2016). Accordingly, it is essential that the arrhythmic focus or re-entry pathway locations identified with EWI remain consistent, no matter the position and orientation of the ultrasound probe. Current techniques for localizing the accessory pathways in patients with WPW in the clinic mostly rely on 12-lead electrocardiogram (ECG) interpretation, intracardiac electrophysiology and fluoroscopy. Recently, noninvasive approaches without radiation exposure have emerged, such as Tissue Doppler Imaging (Esmaeilzadeh et al. 2013) or 3D Speckle Tracking Echocardiography (STE) (Ishizu et al. 2016). However, strain imaging with STE on B-mode images typically operate at lower frame rates and is less accurate than RF-based cross-correlation (Walker and Trahey 1995), while Pulsed Wave (PW) Doppler estimation is known to be angle dependent. Therefore, assessing the angle independence of our technique is not only crucial for accurate diagnosis and treatment planning of arrhythmias such as PVCs, persistent atrial fibrillation or focal tachycardia, but would also prove the advantage of EWI over tissue Doppler-based techniques.

In this study, our aim was to demonstrate the reproducibility and angle independence of EWI for the assessment of electromechanical activation during normal sinus rhythm (NSR) in healthy humans in vivo. To achieve this goal, activation maps of five healthy male volunteers were generated and compared 1) within the same acquisition across consecutive cardiac cycles; 2) within the same standard echocardiographic view across successive acquisitions; and finally 3) within equivalent LV regions across different imaging views.

METHODS

A. Experimental protocol

The human subject study protocol was approved by the Institutional Review Board of Columbia University, and informed consent was obtained before all procedures described herein. Seven healthy male volunteers (aged 23 to 33 years old) were imaged lying down on their left side in the lateral decubitus position by a trained cardiologist with a Vantage 256 system (Verasonics, Redmond, WA, USA).

Ultrasound acquisition for EWI was performed in three standard echocardiographic views: parasternal long-axis, and apical 4- and 2-chamber. A 2.5 MHz phased array probe (P4-2 ATL/Philips, Andover, MA, USA) was used to emit unfocused circular waves (Provost et al. 2011a), and in order to achieve high enough frame rates for displacement estimation applications, RF channel data were acquired at 2000 fps at 20 cm depth. The latter were followed by a standard 64-line B-mode anatomical acquisition of 1.5s at 30fps and 20 cm depth, which was later used for precise manual myocardium segmentation. We acquired RF frames up to four successive times for each view during sinus rhythm. The consecutive scans

were recorded less than a minute apart and the probe was repositioned on the patient in between acquisitions. The processing was later performed on a separate computer in Matlab (The Mathworks, Natick, MA, USA) using a GPU (Tesla NVIDIA, Santa Clara, CA, USA) and Parallel Processing.

Simultaneous recording of the electrical activity was performed with three electrodes placed on the subject's chest and connected to an ECG unit (77804A, HP, Palo Alto, CA, USA). During processing, the ECG data was retroactively used to temporally align the anatomical B-mode acquisition with the high frame rate RF sequence.

B. Electromechanical Wave Imaging

Electromechanical Wave Imaging (EWI) was performed at a high frame rate of 2000 fps at 20 cm depth in the standard transthoracic echocardiographic views by emitting circular waves with a virtual source located 10.2 mm behind the 2.5 MHz phased array probe (Fig. 1.1). This flash EWI sequence, relying on unfocused diverging waves, was acquired within a single heartbeat and the entire field of view was covered at each transmit (Provost et al. 2011b). RF data was acquired for 2 seconds on six of the seven healthy volunteers twice successively, while longer 6-second acquisitions were performed on the remaining volunteer four successive times. EWI uses dynamic focusing in receive: the RF signal at each pixel is reconstructed by performing a standard sum and delay algorithm in post-processing. The latter consists of using the delayed channel data from each element of the probe and summing all the resulting RF signals (Grondin et al. 2015). The reconstructed RF frames had an angular sampling of 0.7° (ie. 128 lines over a 90° field of view) and an axial sampling frequency of 20 MHz. After beamforming of the radiofrequency signals on a Tesla GPU (NVIDIA, Santa Clara, CA, USA) for faster computation speed, motion estimation (Fig. 1.2 (b)) was performed using a 1D axial RF cross correlation algorithm (Luo and Konofagou 2010) with a window size of 10 wavelengths (6.2 mm) and 90% overlap (window shift of 0.62 mm). Then, the axial incremental strains were estimated using a least squares estimator (Kallel and Ophir 1997) with a kernel of 5 mm. The unfocused EWI transmit sequence was followed by a standard 64-line anatomical B-mode acquisition of 1.5s at 30 fps and 20 cm depth. The myocardium was manually segmented on the 1st systolic frame of this anatomical B-mode, selected based on the ECG, and automatically tracked in all subsequent frames through one entire heart cycle using the previously estimated displacements (Luo and Konofagou 2008). The incremental axial displacement maps (Fig. 1.2 (a)) and corresponding incremental axial strain maps (Fig. 1.3 (a)), were thus easily generated by overlaying the estimated motion and strains in the segmented myocardium contour on the anatomical B-mode image respectively.

The wavefront of the electromechanical activation was defined as the time-point at which the incremental strain value changes from relaxation to contraction after the onset of the QRS complex (Provost et al. 2010). In fact, during active contraction, a change from lengthening to shortening in the axial direction was detected. Therefore, to generate the EWI isochrones or activation time maps (Fig. 1.4), the local zero-crossing time-points of the incremental strain curves need to be mapped. In the apical views, this corresponds to a positive-to-negative zero-crossing, while this corresponds to a negative-to-positive zero-crossing for the

parasternal long-axis view as the myocardium walls are not axially aligned with the ultrasound beam in that case (Fig. 1.3 (b)). The onset of the QRS complex was chosen manually on the ECG and defined by selecting the first downward inflection occurring on the ECG trace after the P-wave. This time point was considered as our activation time origin for the isochrones: $t = 0$ ms (black dotted line on Figure 1.3 (b) corresponding to the dark blue color on the activation maps).

For computational efficiency of the isochrones generation, only a subset of points was randomly and automatically selected in Matlab by down sampling the total number of pixels contained in the myocardium mask. The corresponding zero-crossings (ZCs) were manually selected on the incremental strain curves. Regions with noisy strain curves where the locations of the zero-crossing (ZC) could not be determined without ambiguity were discarded and other points were selected. This happened for about 10% of the total number of points in the subset. This included: no apparent ZC, multiple successive ZCs of low amplitude and “flat” ZC, where the slope of the strain curve was equal to zero for more than 10 ms. Finally, in order to obtain smooth and complete EWI isochrones over the entire myocardium mask grid, we applied a Delaunay triangulation-based cubic interpolation to the 2D scattered ZC timing values. This was performed with the “griddata” function in Matlab. Cubic interpolation method was applied, as it has been shown to yield uniform activation maps (Costet et al. 2014; Provost et al. 2010). The complete EWI pipeline with its consecutive processing steps can be found on the flowchart in Figure 1. All the processing was performed on MATLAB and using the parallel processing toolbox (The Mathworks, Natick, MA, USA).

C. Reproducibility

Activation maps of the seven male human subjects in normal sinus rhythm were generated for the three different echocardiographic views. Two successive acquisitions were processed for each of the three views and two consecutive cardiac cycles were considered per acquisition for all the seven healthy volunteers ($84 \text{ maps} = 7 \text{ subjects} \times 2 \text{ cycles} \times 3 \text{ views} \times 2 \text{ acquisitions}$). Eight out of the 84 activation maps could not be generated due to lack of data for the consecutive cardiac cycles, leading to a total of 76 maps (Table 1). This happens when the 2-second ECG does not contain two full heart cycles, but rather the end of one cycle, a full second one and the beginning of a third one. Subsequently, to address these shortcomings, at least five full consecutive heart cycles per acquisition, we acquired longer sequences (6 seconds) on one of the seven volunteers four successive times in each view. This allowed us to evaluate the reproducibility of our activation maps on a larger amount of measurements with two additional acquisitions per view and three additional consecutive heartbeats per acquisition ($48 \text{ maps} = [2 \text{ extra cycles} \times 3 \text{ views} \times 2 \text{ acquisitions}] + [5 \text{ cycles} \times 3 \text{ views} \times 2 \text{ extra acquisitions}]$). The diagram of the protocol for the different datasets acquired is detailed in Figure 2. The cells in bold font correspond to the standard protocol for all subjects, while the dotted lines and cells in regular font represent the extra data obtained for the seventh volunteer.

To quantify the repeatability and angle independence of EWI activation maps in human hearts, three different approaches were used in order to compare the isochrones generated.

1) Comparison within the same acquisition across consecutive cardiac cycles

—Because the mask resulting from the myocardium segmentation was the same for the two consecutive heart cycle maps in a given acquisition, we were able to compute the absolute activation time difference between the isochrones by comparing both maps pixel by pixel. Difference maps were generated and the resulting activation time difference histograms were plotted (Fig. 3). Our group has already developed and applied this approach to illustrate EWI repeatability across consecutive cardiac cycles during both sinus rhythm and paced open-chest dogs (Costet et al. 2014). 2-D correlation coefficients were also computed between the consecutive heart cycle isochrones to quantify their similarity.

2) Comparison within the same view across successive acquisitions—

When comparing isochrones between consecutive acquisitions, a pixel wise comparison is not possible due to similar yet different segmentation. In fact, the isochrone masks varied slightly between acquisitions as the consecutive acquisitions were not entirely identical. Therefore, to assess the reproducibility, isochrone activation time values were averaged in the septal, posterior, lateral and anterior walls of the LV for each view and subsequently compared across the two consecutive acquisitions. We manually segmented the regions of interest on the B-mode (Fig. 4): septal and posterior walls were selected for the parasternal long-axis, septal and lateral walls were considered for the 4-chamber and finally, posterior and anterior walls were examined for the 2-chamber view. We then subdivided each LV wall into up to three segments: apical, mid and basal (Fig. 4 bottom row).

3) Comparison within equivalent LV wall segments across different imaging views—

When comparing different views, a similar approach to comparison between consecutive acquisitions was used. Indeed, in order to quantify the angle independence of EWI, we compared the LV activation time averages in the mid and basal posterior wall segments between the parasternal and apical 2-chamber views and in the basal septal wall segment between the parasternal and apical 4-chamber views (Fig. 4).

RESULTS

A. Reproducibility within same acquisition

Figure 3 illustrates the EWI isochrones maps during normal sinus rhythm for one of the seven healthy subjects (Subject 1) within the same acquisition across consecutive heart cycles. The origin of the isochrones corresponds to the onset of the QRS complex of each cardiac cycle and we always consider an activation period of 200 ms after that. The regions of earliest activation are represented in blue, while the latest are displayed in red. The top row corresponds to the parasternal long-axis view, and the bottom two rows show the apical 4-chamber view and the 2-chamber view, respectively.

Qualitatively, the activation patterns on the isochrones were deemed very similar for the three standard views (Fig. 3-a, -d, -g). In fact, the difference maps appearing mainly in dark blue show very little disparities (less than 10 ms) between the isochrones (Fig. 3-b, -e, -h), except in some localized regions displayed in orange/red, which present more important differences in activation time (over 40 ms). These regions are located at the mid-level on the anterior wall of the 2-chamber view and near the base and apex on the lateral wall of the 4-

chamber view. More quantitatively, in the parasternal long-axis view, 80% of the myocardium exhibits activation time differences between two consecutive isochrones of less than 5 ms, which corresponds to 3% of the maximum activation time (Fig. 3-c), compared to 90% in the 2-chamber view (Fig. 3-i). In the apical 4-chamber view, 50% of the activation time differences fall under 5 ms and 80% are under 10 ms (Fig. 3-f).

Table 1 summarizes the repeatability results across cardiac cycles obtained in all seven subjects. The values listed correspond to the 2D correlation coefficients between the two consecutive activation maps. The less satisfying repeatability performance was observed for Subject 6 in parasternal long-axis view with the lowest correlation coefficient at 0.9681. On the other hand, our best reproducibility case corresponds to the apical 2-chamber view for Subject 1 with a high correlation value of 0.999. Finally, the average 2D correlation coefficient between the two consecutive cycle isochrones across all subjects was 0.9893.

More specifically, Figure 5 depicts a heat map of the 2D correlation coefficients for the 4 successive acquisitions in each view for Subject 7. Since the acquisitions were 6-seconds long in that case, we were able to generate the activation maps of 5 consecutive heart cycles, resulting in a total of 10 comparisons per acquisition (cycle i vs cycle j where $i \neq j$ and $i, j \in [1:5]$). Each square corresponds to a color coded correlation coefficient from 1 in dark green for perfect similarity to 0.95 in dark red. Overall the large majority of squares displayed on the figure are green: only 13 comparisons out of the 120 lay below 0.975 (yellow to red on colorbar). The lowest correlation coefficient was 0.9548 in acquisition 1 of the parasternal long-axis view when comparing cycle 1 to cycle 4, while the highest was 0.9977 in the third acquisition of the apical 4-chamber view when comparing cycles 2 and 3.

B. Reproducibility within same view

The EWI reproducibility during sinus rhythm within the same view across successive acquisitions is depicted in Figure 6 for the same healthy subject as in Figure 3. The isochrones for the 1st acquisition of each view (a parasternal long-axis, c 4-chamber and e 2-chamber) and 2nd acquisition for these same views (b, d and f) are shown. The origin of the isochrones corresponds to the onset of the QRS complex and the color bar spans from 0 to 200 ms. Comparison across acquisitions in the same view yielded very similar results in terms of the EW propagation pattern (Fig. 6-a vs -b, Fig. 6-d vs -e, Fig. 6-g vs -h). Regardless of the view, the earliest and latest activated regions remain at the same regions from one acquisition to the other.

In addition, the boxplots on the right column of Figure 6 show the activation time distribution in the left ventricle walls through two successive acquisitions for each standard view: c) posterior and septal walls in parasternal long-axis, f) lateral and septal walls in apical 4-chamber and i) posterior and anterior walls in apical 2-chamber. The colors are consistent with the ROIs selected on Figure 4: the cyan boxes correspond to the posterior wall, the red boxes to the septal wall, the green to the lateral wall and the orange to the anterior wall. Lastly, the black dots represent the means of the distributions and the horizontal colored lines in the boxes are the medians. The two vertical dotted segments extending from the top and bottom of the boxes are called “whiskers”. The latter are displayed to indicate the variability outside the upper and lower quartiles of the datasets. It

should be noted that for all boxplots displayed in this paper, the whisker extremities were defined as the highest/lowest values included within 3 times the interquartile range (IQR) of the box edges, contrary to the usual standard $1.5 \times \text{IQR}$ value.

Qualitatively, the spread of activation times in each wall was found to be comparable between acquisitions for all the cases; the interquartile ranges represented by the box spans are overall identical. More specifically, we focused on the means of the distribution in each LV wall segment as our final comparison metric (Table 2 Subject 1). Nevertheless, for the sake of visibility on the boxplot, entire walls were considered before subdivision into segments (Fig. 4 top row). Average activation times in parasternal long-axis (Fig. 6-c) varied by 0.44% in the septal wall (93.6 to 94.3 ms), respectively 0.14% in the posterior wall (108 to 108.2 ms). In the apical 2-chamber view (Fig. 6-i), the anterior wall average activation times differed from each other by 2.02% (100.2 to 103.7 ms) and the posterior wall average activation times varied by 1.5% (99.7 to 102.3 ms). Finally, in the 4-chamber view (Fig. 6-f), the highest average activation time fluctuation of 4.27% is noted in the lateral wall (79.2 to 86.6 ms), with the smallest variation of 0.02% for the septal wall (89.43 to 89.47 ms).

A summary of the reproducibility results obtained for all seven subjects across 2 successive acquisitions in the same imaging views can be found in Table 2. We always performed the comparison between the first cardiac cycles processed for each acquisition. The variation in average activation times within the smaller LV wall segments (Fig. 4 bottom row) across the 2 consecutive acquisitions are listed in percentage. The latter are calculated as the percent deviation with respect to the latest activation time displayed in the 2 successive acquisitions in ms. Variation percentages range from 0.02% in the basal anterior wall segment in the apical 2-chamber view for Subject 5 to 25.31% in the basal posterior wall segment in the apical 2-chamber view for Subject 2. Although 8 values out of 105 exceed 15%, the average variation value satisfyingly lies at 6.19%.

C. Angle independence

Figure 7 depicts a Bland-Altman plot of the LV wall activation time averages for the seven healthy subjects. The plot illustrates the EWI reproducibility during sinus rhythm for all the volunteers within equivalent LV wall segments across different imaging views. The 7 different colors correspond to the 7 different subjects. The 2 consecutive acquisitions were averaged for each of the 3 standard echocardiographic views, and each subject is represented by 3 points. The first point is the comparison of activation time measurements in the basal septal wall between the parasternal long-axis and apical 4-chamber views, while the second and third represent the comparison of the basal, respectively mid posterior wall between the parasternal long-axis and apical 2-chamber views. The x-axis displays the mean of the LV wall segments activation time averages for both methods, while the y-axis is the difference between the two values in milliseconds.

All the measurements were within the limit of agreement or 95% confidence interval defined by the mean plus or minus 1.96 times the standard deviation, and the bias found was 3.2 ms. The latter was computed from the Bland-Altman plot as the mean activation time average difference between the two views among the seven healthy volunteers. The standard deviation of the mean values, also called coefficient of variation was 12%. These results

indicate that EWI and its subsequent generation of LV wall activation time averages can be used reliably to characterize the activation sequence of healthy subjects in normal sinus rhythm independently of the imaging view.

DISCUSSION

EWI is an ultrasound-based imaging technique that can non-invasively map the electromechanical activity in all four heart chambers in vivo at very high spatial and temporal resolution. At the tissue level, the depolarization of the cardiomyocytes triggers the electromechanical activation, corresponding to the first time at which the cardiac muscle transitions from a relaxation to a contraction state. Spatially, this electromechanical activation forms the EW front that follows the propagation pattern of the electrical activation sequence. In this paper, we used EWI to transthoracically image healthy human hearts in normal sinus rhythm. The objectives of this study were to demonstrate the reproducibility and angle independence of our method for the assessment of electromechanical activation in normal human subjects in vivo.

In Figure 3, we established the EWI repeatability within a single heart for a given acquisition across consecutive cardiac cycles during NSR in humans for the three different echocardiographic standard views by performing a point by point comparison of the isochrone maps. These results confirm previous findings by our group where we showed that EWI was repeatable within same acquisitions across consecutive cardiac cycles in open-chest dogs (Costet et al. 2014). Those results also demonstrate that despite the loss in resolution in transthoracic human echocardiography due to the additional layers the ultrasound waves have to go through, the reproducibility of our technique is confirmed. According to the difference maps and the histograms of the difference in activation time, more than 80% of the pixels have a difference in activation time below 5 ms, both for the apical 2-chamber and the parasternal long-axis views (Fig. 3-c and -i). In the apical 4-chamber view, 50% of the myocardium has lower than 5 ms difference and 80% under 10 ms (Fig. 3-f). However, the discrepancies displayed in orange/red on the 4-chamber difference map are very sparse (Fig. 3-e). These regions are restricted to “high activation time gradient” locations on the lateral wall in the consecutive isochrones. In fact, the few difference areas appear close to discontinuities and not in the center of a homogeneous pattern such as the lateral mid-wall (Fig. 3-d). The high gradient term refers to the sudden jumps in activation times on the isochrones; near the apex mid-basally and close to the left atria junction for instance. Since the electromechanical activation is a wave, it is assumed to propagate continuously. Thus, we would expect smooth transitions in the activation time gradient on the maps.

Discontinuities in the pattern of activation may be explained by the fact that, albeit standard, only 2D slices were acquired while the EW is a 3D propagation phenomenon. Thus, disruption in the gradient might result from out of plane motion. In addition, this could also be due to the fact that when generating the isochrones, the points considered in the myocardium are randomly chosen and not all taken into account before interpolation, as indicated previously. Thus, a higher-point density in the late activated region compared to fewer points in the surrounding early activated one could impact the interpolation step and

result in disparities in the isochrone patterns. This issue could be overcome by automating the processing pipeline and examining every single pixel contained in the mask, without requiring manual zero-crossing selection. Our group is currently investigating the implementation of a new processing algorithm for automated isochrone generation. This algorithm considers all points in the mask, automatically selects the zero-crossings according to a list of conditions that ZCs should satisfy, and gets rid of the uncertain points. “Clear” ZCs would be defined based on the amplitude of the crossing peak, the steepness of the strain curve slope at the crossing and the number of multiple successive ZCs (Bunting et al. 2017).

In Table 1, we further investigated the EWI reproducibility across consecutive cardiac cycles for the seven healthy volunteers using 2D correlation coefficient as our similarity metric. More than three quarters of the correlation coefficients listed in the table were satisfyingly above 0.985. Furthermore, the heat map of the 2D correlation coefficients for Subject 7 (Fig. 5) demonstrated that even when increasing the number of comparisons to 5 consecutive heart beats and 4 successive acquisitions, we were still able to obtain reproducible results with an average correlation of 0.9844. Besides, we notice that all the coefficients below 0.970 appear only in the comparisons resulting from the parasternal long-axis view acquisitions. This may be due to the higher uncertainty in the zero-crossing selection, since the orientation of the LV walls with respect to the ultrasound beam direction isn’t always the same in this view. This alignment variation is further explained below in the study limitations paragraph.

In Figure 6, we also assessed the EWI activation timing reproducibility between separate acquisitions of the same view during NSR for Subject 1. The general EW propagation pattern displayed on the activation maps was unchanged from one acquisition to the successive one. In the apical 4-chamber view, the highest activation time average fluctuation was obtained in the lateral wall reaching 4.27%, with a small variation of 0.02% for the septal wall. Global average activation times in parasternal long-axis and 2-chamber view walls varied only by 0.29%, respectively 1.76%. As for the activation time average variation in the smaller LV wall segments (Table 2), the mean across all seven subjects was at 6.19% with more than three quarters of the average values lying below a 10% disparity between successive acquisitions.

Finally, we demonstrated that we were able to achieve similar activation times across different views in the same cardiac regions of the isochrones. As seen on the Bland-Altman plot in Figure 7, LV wall segment activation time averages were fairly consistent within the same subject across the different standard echocardiographic imaging views. Indeed, all the measurement points were within the limits of agreement. The largest activation time average difference across views was observed for Subject 3 with a value of 26.8 ms. This is still low compared to known characteristic variations within a single conduction disorder patient. In fact, typical values for transseptal conduction times are in general larger than 40 ms in patients with Left Bundle Branch Block (Prinzen and Auricchio 2008). These findings confirm the angle independence of EWI for the assessment of electromechanical activation in vivo as previously established in silico (Provost et al. 2011c).

There are several limitations to this study. A limitation arises from the orientation of the LV walls with respect to the ultrasound beam direction. In fact, EWI relies on a 1D RF cross correlation and the strains are estimated axially. For the apical 4- and 2-chamber views, selection of the correct zero-crossings is quite straight forward. Since the walls are axially aligned with the ultrasound beam on the B-mode (Fig. 4-b and -c), the first positive to negative zero-crossing after the onset of the QRS complex was selected. However for the parasternal long-axis view, these may not constitute the optimal criteria. The LV walls are not always parallel to the bottom and top borders of the B-mode image (Fig. 4-a), they are slightly angled; neither completely perpendicular to the ultrasound beam nor axially aligned. Thus, negative and positive slopes were considered. Identifying the most suitable orientation transition is challenging. This limitation could be mitigated by implementing an automated technique of discriminating between the two types of zero-crossings. Systematically computing the angle between the orientation of the wall and the direction of the ultrasound beam could be a good alternative in order to determine whether we should expect thickening or thinning of the wall for a given point. Such computer vision techniques already exist for automated and robust Doppler angle estimation between the insonifying ultrasound beam and the vessel walls (Pan et al. 2000; Saad et al. 2009). The latter rely on least-squares line fitting algorithms of the segmented vessel and could be adapted to the assessment of the myocardium wall orientation by fitting a higher-order polynomial or spline. This additional feature will be implemented into the automated isochrone processing pipeline.

Another main limitation lies in the fact that it is challenging to quantitatively compare the electromechanical activation patterns across different acquisitions and imaging views without averaging the activation times, as the segmentation wasn't precisely the same and the walls cannot be registered perfectly. For a more accurate comparison and better quantification of the reproducibility, we should consider acquiring data with a 2D matrix array. Three-dimensional echocardiography in a single cardiac cycle would require additional hardware and processing methods, but has been shown to be feasible using plane waves (Papadacci et al. 2017a) or diverging waves for a wider field of view. Our group recently showed initial feasibility of 3D strain imaging in the heart at very high volume rates (Papadacci et al. 2017b). Further optimization will be conducted to perform 3D Electromechanical Wave Imaging.

Finally, EWI was recently validated in canine hearts against two clinically available mapping techniques. Electromechanical activation patterns were compared to electrical results obtained from a 64-electrode basket catheter inserted into the LV, during sinus rhythm, as well as under epicardial and endocardial pacing (Grondin et al. 2016). EWI was also validated both epicardially and endocardially in all four chambers of the heart under normal sinus rhythm and epicardial LV pacing with conventional 3D electroanatomic mapping using a St Jude's EnSite system (Costet et al. 2016). Electromechanical activation times were shown to be highly correlated with the electrical activation times obtained from both electroanatomic mapping techniques in canines.

EWI is currently being studied as a potential tool to assist clinicians in identifying arrhythmogenic zones and guide ablation procedures. An ongoing clinical study deals with arrhythmia patients undergoing electrophysiological EP studies and RF-ablation.

Combination of EWI with Myocardial Elastography (Bunting et al. 2016; Grondin et al. 2015; Papadacci et al. 2017) and their complementarities is also a topic of ongoing studies. In conjunction with the catheter-based electroanatomic mapping frequently used in the clinic, EWI could non-invasively help physicians for the early detection, diagnosis, treatment planning, monitoring and follow-up of patients with arrhythmia through ultrasound-based mapping of their electromechanical activation sequence. In addition, EWI could easily be integrated into existing echocardiography systems and, therefore, diagnostic protocol and assessment clinical routine, at no or minimal additional cost.

CONCLUSION

EWI was hereby shown capable of transthoracically characterizing the sinus rhythm electromechanical activation and of reliably obtaining similar activation time averages in the LV wall segments between different echocardiographic acquisitions and views. These findings indicate that EWI can non-invasively map the electromechanical activation in sinus rhythm in human hearts in vivo and leads to reproducible and angle-independent activation maps 1) across consecutive heart cycles; 2) across separate acquisitions; and 3) across different views.

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Fig. 1.

Complete Electromechanical Wave Imaging (EWI) processing flowchart. 1- Radiofrequency (RF) unfocused circular transmit sequence at a high frame-rate (2000fps) of a standard apical 4-chamber view. 2- Displacement map (a) obtained by applying a 1D axial RF cross-correlation algorithm (b) with a window size of 10 wavelengths and a 90% overlap. 3- Axial incremental strains estimated with a least-squares estimator (kernel size: 5mm) are overlaid on the anatomical B-mode (a) to create the axial incremental strain map. The incremental strain curves (b) for 100 points in the myocardium mask are used to select the first local zero-crossing (intersection with the red horizontal line) after the onset of the P-wave for the atria, respectively the onset of the QRS complex for the ventricles. 4- Resulting 2D 4-chamber view activation map from a healthy subject in normal sinus rhythm (NSR). The earliest activation time (0 ms) is represented in blue, while the latest (270 ms) in red. RV = right ventricle, LV = left ventricle, RA = right atrium and LA = left atrium.

Fig. 2.

Acquisition protocol diagram for the three standard echocardiographic views (parasternal long-axis, apical 4-and 2-chamber). The bold cells correspond to the common protocol for all the seven healthy subjects (2 successive acquisitions with 2 consecutive heart cycles each), while the dotted lines and normal font cells represent the additional datasets obtained for the seventh volunteer (2 additional acquisitions with 5 consecutive heart cycles, as well as 3 supplementary beats for the first 2 acquisitions).

Fig. 3.

EWI reproducibility during sinus rhythm for a healthy subject within the same acquisition across consecutive heart cycles. The origins of the isochrones correspond to the onset of the QRS complex. (a) Parasternal long-axis view isochrones for two consecutive cardiac cycles. (b) Difference map and (c) histogram of the absolute activation time difference between the two parasternal-long axis isochrones. (d) Apical 4-chamber view isochrones for two consecutive cardiac cycles. (e) Difference map and (f) histogram of the absolute activation time difference between the two apical 4-chamber isochrones. (g) Apical 2-chamber view isochrones for two consecutive cardiac cycles. (h) Difference map and (i) histogram of the absolute activation time difference between the two apical 2-chamber isochrones. LV = left ventricle, RV = right ventricle.

Fig. 4. Standard EWI echocardiographic imaging views. (a) Parasternal long-axis view. (b) Apical 4-chamber view. (c) Apical 2-chamber view. The left ventricle walls (excluding the apex) were segmented manually and the colored ROIs are overlaid on the grayscale B-mode. The septal wall is visible in red, the posterior wall in cyan, the lateral wall in green and the anterior wall in orange. The bottom row shows a schematic of each view with the subdivision of the LV walls into segments. RV = right ventricle, LV = left ventricle, RA = right atrium and LA = left atrium.

Fig. 5.

Heat map of the 2D correlation coefficients between consecutive cardiac cycle activation maps for Subject 7 in three different views (parasternal long-axis, apical 4- and 2-chamber) with four successive acquisitions each. Five consecutive heart beats were studied, leading to a total of 10 comparisons per acquisition (cycle i vs cycle j where $i \neq j$ and both $\in [1:5]$). The 12 squares each represent one acquisition. Each small cell within the 5 by 5 squares corresponds to a color coded correlation coefficient; the highest similarity values are represented in green, while the lowest are displayed in red.

Fig. 6. EWI reproducibility during sinus rhythm for a healthy subject within the same view across 2 successive acquisitions. The origin of the isochrones correspond to the onset of the QRS complex. (a) Parasternal long-axis view isochrone for the 1st acquisition. (b) Parasternal long-axis view isochrone for the 2nd acquisition. (c) Apical 4-chamber view isochrone for the 1st acquisition. (d) Apical 4-chamber view isochrone for the 2nd acquisition. (e) Apical 2-chamber view isochrone for the 1st acquisition. (f) Apical 2-chamber view isochrone for the 2nd acquisition. The boxplots display the activation time distribution in the left ventricle

walls through two successive acquisitions for each standard view: (c) Parasternal long-axis view, (f) Apical 4-chamber view and (i) Apical 2-chamber view. The colors on the plots are consistent with the ROIs selected on Fig. 2: the cyan boxes represent the posterior wall (POST), the red boxes correspond to the septal wall (SEPT), the green to the lateral wall (LAT) and the orange to the anterior wall (ANT). The top of the boxes mark the 75th percentile of the datasets, while the bottom corresponds to the 25th percentile. LV = left ventricle, RV = right ventricle.

Fig. 7.

Bland-Altman plot of the LV wall activation time averages for the 7 healthy subjects. The plot illustrates the EWI reproducibility during SR for 7 healthy subjects within equivalent LV wall segments across different imaging views. The 7 different colors correspond to the 7 different subjects. The 2 consecutive acquisitions were averaged for each of the 3 views, and each subject is represented by 3 points. The first point corresponds to the comparison of the basal septal wall between the parasternal long-axis and apical 4-chamber views, while the second and third represent the comparison of the basal, resp. mid posterior wall between the parasternal long-axis and apical 2-chamber views. CV = Coefficient of Variation (standard deviation of the mean values in %), PLAX = parasternal long-axis view.

Table 1

2D correlation coefficients between the isochrone activation maps of the two consecutive heart cycles (N=7). N/A refers to the 8 cases where the data from the second cardiac cycle was not available for the point by point absolute time difference comparison. This happens when the ECG recorded simultaneously with the 2-second EW1 acquisition doesn't contain 2 full heart cycles; but rather the end of one cycle, a full one and the beginning of a third one.

Subject	PLAX #1	PLAX #2	4-chamber #1	4-chamber #2	2-chamber #1	2-chamber #2
1	0.9982	N/A	0.9945	N/A	0.9990	N/A
2	N/A	0.9932	0.9916	0.9923	0.9878	0.9886
3	0.9933	0.9918	0.9813	0.9896	0.9871	0.9971
4	0.9952	0.9985	0.9811	0.9989	0.9922	0.9753
5	N/A	N/A	N/A	0.9906	0.9974	N/A
6	0.9851	0.9681	0.9861	0.9840	0.9742	0.9795
7	0.9876	0.9854	0.9908	0.9960	0.9963	0.9877

Table 2

Variation in average activation times within LV wall segments across 2 consecutive acquisitions in the three imaging views (N=7). We always performed the comparison between the 1st cardiac cycles processed for each acquisition.

Parasternal long-axis view					
Subject	Basal posterior	Mid posterior	Basal septum		
1	2.20%	3.30%	0.44%		
2	2.91%	1.69%	1.15%		
3	2.12%	7.23%	2.53%		
4	12.07%	7.39%	4.22%		
5	11.53%	1.57%	5.01%		
6	1.48%	0.99%	1.37%		
7	6.07%	6.56%	9.28%		

4-chamber apical view					
Subject	Basal lateral	Mid lateral	Apical lateral	Basal septum	Mid septum
1	4.58%	10.49%	3.95%	1.06%	2.19%
2	4.47%	18.74%	2.76%	17.97%	14.67%
3	19.68%	6.35%	5.85%	9.42%	3.34%
4	1.98%	3.77%	0.05%	7.94%	2.66%
5	4.34%	3.12%	3.88%	1.04%	4.87%
6	2.84%	5.71%	2.41%	2.42%	1.02%
7	12.89%	10.40%	7.67%	23.24%	1.94%

2-chamber apical view					
Subject	Basal posterior	Mid posterior	Apical posterior	Basal anterior	Mid anterior
1	3.11%	1.92%	0.10%	2.81%	2.09%
2	25.31%	10.10%	5.87%	1.78%	14.20%
3	15.16%	19.72%	6.14%	7.01%	2.84%
4	7.62%	8.66%	0.44%	12.34%	6.51%
5	1.04%	1.18%	1.75%	0.02%	0.36%

Subject	Basal posterior	Mid posterior	Apical posterior	Basal anterior	Mid anterior	Apical anterior
1	3.11%	1.92%	0.10%	2.81%	2.09%	5.92%
2	25.31%	10.10%	5.87%	1.78%	14.20%	0.51%
3	15.16%	19.72%	6.14%	7.01%	2.84%	1.17%
4	7.62%	8.66%	0.44%	12.34%	6.51%	8.35%
5	1.04%	1.18%	1.75%	0.02%	0.36%	0.77%

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Parasternal long-axis view					
Subject	Basal posterior	Mid posterior	Basal septum		
6	8.99%	10.46%	8.57%	2.96%	10.83%
7	13.47%	6.54%	4.29%	6.15%	13.54%
					21.52%
					3.95%