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Non-invasive characterization of focal arrhythmia with Electromechanical Wave Imaging *in vivo*

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Abstract

There is currently no established method for the non-invasive characterization of arrhythmia and differentiation between endocardial or epicardial triggers at the point of care. Electromechanical Wave Imaging (EWI) is a novel ultrasound-based imaging technique based on time-domain transient strain estimation that can map and characterize electromechanical activation in the heart *in vivo*. The objectives of this initial feasibility study were to demonstrate that EWI is capable of differentiating between endocardial and epicardial sources of focal rhythm, and, as a proof-of-concept, that EWI could characterize focal arrhythmia in one patient with premature ventricular contractions (PVC), prior to radiofrequency (RF) ablation treatment. First, validation of EWI for differentiation of surface of origin was performed in seven (n=7) adult dogs using four epicardial and four endocardial pacing protocols. Second, one (n=1) adult patient diagnosed with PVC was imaged with EWI prior to their scheduled RF ablation procedure and EWI results were compared to mapping procedure results. In dogs, EWI was capable of detecting whether pacing was from an endocardial or epicardial origin in 6 out of 8 cases (75% success rate). In the PVC patient, EWI correctly identified both regions and surface of origin, as confirmed by results from the electrical mapping obtained from the RF ablation procedure. These results show that EWI can map the electromechanical activation across the myocardium, and indicate that EWI could serve as a valuable pre-treatment planning tool in the clinic.

Keywords

Arrhythmias; Electromechanical activation; Electromechanical wave imaging; Noninvasive imaging; Premature ventricular contraction; Strain; Ultrasound

Introduction

Sources of focal ventricular arrhythmia may be located in the left or right ventricle, on the endocardium, in mid-myocardium, or on the epicardium (Kaltenbrunner et al. 1991). For

example, the prevalence of epicardial focal ventricular tachycardia (VT) is around 7–13% of all focal VTs (Sacher et al. 2008; Tada et al. 2001). Radio-frequency (RF) catheter ablation for the treatment of VT, introduced in the early 1980s, has become one of the main options available to treat VT and successful ablation will hinge on correctly determining the site of origin of the arrhythmia (Njeim and Bogun 2015). The 12-lead electrocardiogram (ECG) is used for initial diagnostic and may show characteristics to enable physicians to infer the location of the origin, although the criteria seem to be limited (Bazan et al. 2007; Berruezo et al. 2004). The most commonly used methods to determine the origin of an arrhythmia are invasive catheterization techniques such as activation sequence mapping and pace-mapping (Nademanee and Kosar 1998; Moreno et al. 2005). Endocardial and epicardial mapping approaches differ and since there is currently no non-invasive imaging technique capable of differentiating between endocardial and epicardial origin, an ablation procedure often consists of an electrophysiology study during which endocardial catheter mapping is performed and which may be followed by epicardial catheter mapping when endocardial mapping fails to identify an origin, (Sosa et al. 1998).

Electromechanical wave imaging (EWI) is a non-invasive, non-ionizing, ultrasound-based imaging modality that can map the electromechanical activity of the heart in all four chambers at high spatial and temporal resolution, with real-time feedback capabilities (Provost et al. 2010; Konofagou et al. 2010; Provost et al. 2011b; Provost et al. 2011a; Provost et al. 2013; Costet et al. 2014). At the tissue level, the depolarization of the myocardium triggers the electromechanical activation, i.e. the first time at which the muscle transitions from a relaxation to a contraction state, and the spatial propagation of the electromechanical activation forms the electromechanical wave (EW) that follows the pattern of propagation of the electrical activation sequence. Unlike Tissue Doppler methods which rely on the use of frequency domain technique to estimate velocity and strain (Uematsu et al. 1995; Koyama et al. 2003), EWI relies on speckle-tracking techniques in order to estimate minute displacements and incremental (or inter-frame) strains in the time-domain at a sufficiently high framerate to enable tracking the EW through systole.

Electromechanical activation times rely on the onset of the mechanical activation and are essentially a surrogate for the electrical activation. Indeed, previous studies have shown that the EW propagation is highly correlated with the underlying electrical activation in all four chambers of the heart in normal canine hearts during sinus rhythm and various pacing protocols *in vivo* and *in silico* (Provost et al. 2011b; Provost et al. 2011a; Costet et al. 2016). Additionally, EWI has been shown capable of mapping the electromechanical activation sequence in both human (Provost et al. 2013; Provost et al. 2015) and canine (Costet et al. 2014; Costet et al. 2015; Provost et al. 2010; Provost et al. 2011a; Provost et al. 2011b) models, during sinus rhythm, pacing, and both focal and reentrant arrhythmias. EWI is not limited to the endocardial or epicardial surface and is capable of mapping the EW transmurally, but it has not yet been shown that EWI was capable of differentiating between endocardial and epicardial origins. If EWI had the potential to not only identify the region of the heart responsible for a focal ventricular arrhythmia, but also distinguish between endocardial and epicardial origins, it would be a particularly useful clinical tool for planning treatment with radio-frequency (RF) catheter ablation as it could eliminate unnecessary endocardial mapping when the origin of the arrhythmia is located at the epicardial level.

In this study, we hypothesize that EWI is capable of differentiating between endocardial and epicardial source of focal arrhythmia, and that it could be used to plan intracardiac mapping and RF ablation procedures. In order to test this hypothesis, we first aim to demonstrate that EWI is capable of differentiating between endocardial and epicardial source of focal rhythm, and, second, we present a proof-of-concept that EWI is capable of characterizing focal arrhythmia and predicting its origin non-invasively prior to mapping and ablation. In order to reach that goal, we first performed a feasibility study in a paced animal model in which we attempt to simulate focal ventricular arrhythmia by pacing the hearts of adult mongrel dogs from the epicardium and the endocardium. Then, we acquired EWI in one patient diagnosed with premature ventricular contraction (PVC) prior to their scheduled mapping and RF ablation procedures. PVCs are additional, abnormal heart beats that originate in either one of the ventricle which can be treated by ablating the region from which they originate. Pseudo-3D maps of the PVC patient's electromechanical activation as well as videos of the activation were generated. These were used to demonstrate that EWI is capable of identifying the earliest region of activation and of correctly differentiating between endocardial and epicardial foci, and, as a proof-of-concept in one patient, EWI results were compared to the findings of the electrophysiology mapping procedures in order to confirm the accuracy of the prediction.

Materials and Methods

Experimental animal protocol

This study complied with the Public Health Service Policy on Humane Care and Use of Laboratory Animals and was approved by the Institution Animal Care and Use Committee of Columbia University. Seven adult mongrel dogs ($N = 7$) were used in this study. Following lateral thoracotomy, the pericardium was removed and a pericardial cradle was formed to exclude the lungs and support the heart in order to expose the apex. Epicardial pacing was performed in four animals ($n=4$). A bipolar electrode of an ablation catheter (TactiCath, St. Jude Medical, Secaucus, NJ) was used in two dogs ($n=2$) for epicardial pacing by manually placing the electrode at the mid-level, slightly towards the apex. In two other dogs, epicardial pacing was performed through pacing electrodes sutured to the lateral wall, near the base ($n=1$) or to the posterior-lateral wall at the mid-level ($n=1$). Endocardial pacing was performed on four animals ($n=4$) by placing a 64-electrode basket catheter (Constellation, Boston Scientific, Natick, MA) in the left ventricle (LV) and pacing using two of its adjacent electrodes. For endocardial pacing with the basket catheter, we chose electrodes located at the mid-level providing good contact with the endocardium. Please note that out of the 7 animals, 1 was used for both epicardial and endocardial pacing. The pacing rate was chosen just high enough to overdrive the intrinsic sinus rhythm and the voltage output was set at 10V. For this validation study, EWI acquisition was performed open chest by placing the probe coated with ultrasound gel directly at the apex. Pacing locations are summarized in Table 1. EWI was acquired while pacing open-chest canines in the standard apical echocardiographic views (4-chamber, 2-chamber, and 3-chamber), with the addition of a view taken in between the 2- and 4-chamber views that we call "3.5-chamber" view.

Clinical study protocol and patient selection

The clinical study protocol was approved by the Institutional Review Board (IRB, protocol AAAA9333) of Columbia University, and written informed consent was obtained from the human subject prior to scanning. One 70 years old patient diagnosed with PVC underwent EWI scanning by a trained cardiologist a few minutes prior to an electroanatomical mapping and ablation procedure. The ablation procedure was successful and mapping results were obtained in order to compare them to EWI findings for validation. Non-invasive EWI acquisition was performed transthoracically in the standard apical echocardiographic views (4-chamber, 2-chamber, and 3-chamber) with the addition of the 3.5-chamber view as previously described. EWI was acquired during pre-excitation as seen on the electrocardiogram (ECG).

Electromechanical Wave Imaging

Acquired data was processed as previously described elsewhere (Costet et al. 2014; Grondin et al. 2016; Provost et al. 2011b; Provost et al. 2013). Briefly, an unfocused transmit sequence was implemented on a Verasonics system (Verasonics, Redmond, WA) in order to acquire frames at 2000 fps using a 2.5-MHz ATL P4–2 phased array (Figure 1–1) (Provost et al. 2011b). Beamforming on the signals obtained from each of the elements was performed during post-processing, resulting in the reconstruction of one radio-frequency (RF) frame per transmit. RF frames denote the beamformed, unprocessed, and unfiltered ultrasound images and contain phase information that is lost when generating B-mode images. The reconstructed images had an angular sampling of 0.7° or 0.025 rad (128 lines spanning 90°) and an axial sampling frequency of 20 MHz (axial sampling of 0.0385 mm) (Figure 1–2). Segmentation of the LV myocardium was manually performed on the first frame of the anatomical B-mode sequence and the myocardial contour was subsequently automatically tracked throughout the cardiac cycle using the estimated displacements (Luo and Konofagou 2008). Displacement estimation was performed in Matlab (Mathworks, Natick, MA) using a fast, 1D RF-based cross-correlation algorithm because it has been shown that RF-based speckle tracking offers far greater accuracy than B-mode speckle tracking (Luo and Konofagou 2010; Walker and Trahey 1994). Axial incremental strains (i.e. the inter-frame strain in the axial direction) were estimated using a least-square estimator with a 5-mm, 1D-kernel (Figure 1–4) (Kallel and Ophir 1997). Electromechanical activation was defined as the time at which the incremental strain value changes from positive (lengthening in the axial direction) to negative (shortening or contraction in the axial direction), i.e., the first time point at which the incremental strain curve crosses zero after the Q-wave as seen on the ECG (Figure 1–4). Isochrones were generated by manual selection of the first occurrence of the incremental strain zero crossing (transition from positive (relaxation) to negative (contraction) strain, i.e., onset of contraction) in the LV after the onset of the QRS for up to 100 automatically selected points within the segmented wall. Sub-sample resolution of the zero-crossings was obtained through cubic spline interpolation. Smooth continuous isochronal maps were then generated through Delaunay triangulation-based cubic interpolation (Provost et al. 2010). All views were co-registered in Amira 5.3.3 (Visage Imaging, Chelmsford, MA, USA), both temporally (using ECG) and spatially (using B-mode anatomical landmarks such as the position of the valves and apex), to construct a pseudo-3D isochrone (Figure 1–5). The color bar ranges from red for earliest activation

timings, to black for the latest activation timings. Finally, videos of the electromechanical activation propagation were generated from the electromechanical activation times.

Results

Animal study - Endocardial vs Epicardial pacing origin

Figures 2 and 3 depict the results of EWI during endocardial and epicardial pacing, respectively. The pseudo-3D isochrones of the electromechanical activation are presented for each pacing location and a magnified region of interest (ROI) selected manually showing details of the earliest region of activation is depicted as well.

Figure 2 and supplementary video 1 depict the results obtained during epicardial pacing. Locations of pacing included the LV anterior-lateral wall (Figure 2-A, B), the LV basal lateral wall (Figure 2-C), and the LV posterior-lateral wall (Figure 2-D). In all four animals, the origin of the electromechanical activation was correctly detected at the location of pacing. During epicardial pacing in dog #1 (Figure 2-A), the earliest region of electromechanical activation was detected on the anterior-lateral wall at the mid-level. The magnified ROI clearly shows that the activation started in the epicardium and propagated to the endocardium. During epicardial pacing in dog #2 (Figure 2-B), the earliest region of electromechanical activation was also detected epicardially on the anterior-lateral wall, near the apex. Early activation observed epicardially on the lateral wall suggests that the electromechanical activation propagated along the epicardial wall toward the lateral wall. The magnified ROI shows early epicardial activation followed by propagation toward the base (to the right of the magnified ROI). During epicardial pacing in dog #3 (Figure 2-C), the earliest activated region was detected on the lateral wall on the epicardium, near the base. The electromechanical activation propagated from the epicardium down toward the apex and the endocardium as can also be seen in magnified ROI. In dog #6, EWI was not capable of showing the early activation originating from the epicardium and propagating to the endocardium, although it correctly detected the earliest region of activation on the posterior-lateral wall (Figure 2-D). Videos of the activation for dogs #1, 2 and 3 (supplementary video 1) clearly depict the electromechanical activation originating epicardially and propagating toward the endocardium.

Figure 3 presents the results obtained during endocardial pacing. Locations of pacing included the LV posterior-lateral wall (Figure 3-A), the LV anterior-lateral wall (Figure 3—B), the LV anterior wall (Figure 3-C), and the LV posterior wall (Figure 3-D). In all four animals, the origin of the electromechanical activation was correctly detected at the location of pacing. During endocardial pacing in dog #1 (Figure 3-A), the earliest electromechanical activation was detected in the posterior-lateral wall at the mid-level. The magnified ROI shows the activation originating at the endocardium and propagating toward the epicardium. During endocardial pacing in dog #5 (Figure 3-B), regions activated the earliest were detected on the lateral and anterior-lateral walls. The magnified ROI at the region of earliest activation on the lateral wall shows the activation starting sub-endocardially and subsequently propagating toward the epicardium. During endocardial pacing in dog #6 (Figure 3-C), the electromechanical activation originated on the anterior wall at the midway between base and apex. The magnified ROI shows details of the activation on the anterior

wall endocardium propagating toward the epicardium. Finally, during posterior pacing in dog #7 (Figure 3-D), EWI was not capable of detecting the earliest activation starting from the endocardium although it correctly identified the earliest region of activation as being located posteriorly. Videos of the activation for dogs #1, 5 and 6 (supplementary video 2) depict the electromechanical activation originating endocardially and propagating toward the epicardium.

Clinical proof-of-concept - PVC patient

Figure 4 depicts the results obtained from EWI acquisition in one PVC patient scheduled for ablation. Pseudo 3D EWI isochrones are presented on the left while the electrophysiology results obtained after the mapping and ablation procedure are presented on the right. EWI isochrones for this patient depict the earliest activated region posteriorly in the right ventricle (RV). Early activation can also be posteriorly seen in the LV, which leads us to postulate that the PVC originates from the RV outflow tract (RVOT). Electrophysiology mapping results show that the PVC origin was located in the low posterior RVOT as can be seen on the activation map in Figure 4. Ablation at this location terminated PVC activity in the patient.

Discussion

The goal of this study was to verify our hypothesis that EWI is capable of differentiating between endocardial and epicardial source of focal arrhythmia and that it could be used to plan RF ablation procedures. The hypothesis was tested using an animal model in which we could induce a focal arrhythmia and control its location and surface of origin. We also assessed whether EWI could be used to plan RF ablation by acquiring data in a patient diagnosed with PVC and scheduled for an RF ablation, comparing EWI results with the findings of the electromechanical mapping performed during the procedure. More precisely, we assessed the potential role of EWI in characterizing focal arrhythmia by demonstrating that EWI is capable of not only detecting the origin of the arrhythmia, but also to discriminate between surfaces of origin; using ventricular pacing as a surrogate rhythm for focal ventricular arrhythmia. The isochrones and videos of the electromechanical activation during pacing from endocardial and epicardial sites demonstrated that EWI correctly detected the origin of the electromechanical activation, i.e. the onset of deformation following electrical activation, at the location of pacing. Furthermore, in six out of eight cases EWI was capable of discriminating between epicardial and endocardial pacing by depicting the earliest region of electromechanical activation as being located on either the epicardial (Figure 2) or the endocardial surface (Figure 3), in accordance with the site of pacing. These results confirm previous findings by our group where we showed that EWI was capable of correctly detecting the pacing origin from multiple locations in both the LV and RV (Costet et al. 2014; Provost et al. 2011a; Provost et al. 2011b; Provost et al. 2013) and extend previous results by defining a novel role of EWI in determining the transmural origin of rhythm initiation. Second, a clinical proof-of-concept in one patient diagnosed with PVC and scheduled for RF ablation was presented. The goal was to determine whether EWI was capable of identifying the site of origin of PVC and to confirm that location with electrophysiological mapping. We showed that EWI correctly detected the region of origin

as confirmed during the mapping procedure, and that ablation of the target resulted in acute termination of the arrhythmia.

During electrophysiological procedures for the treatment of ventricular such as PVC-induced VT, mapping of the arrhythmia is essential in order to target the adequate region to ablate. One of the shortcomings of intracardiac mapping is that it prolongs the procedure time, sometimes by a couple of hours, which may increase risks to the patient. Pre-procedure non-invasive mapping to determine the origin of the arrhythmia is thus of great interest to physicians. Previous efforts include solving an inverse problem using body surface potential in order to reconstruct the epicardial activation sequence (Ramanathan et al. 2004; Jamil-Copley et al. 2014; Erkapic et al. 2015). Although the newest techniques show a lot of promise, they still require CT or MRI acquisition, as well as for the patient to wear a 256-electrode vest, which can be contraindicated for some. Several algorithms using 12-lead ECG acquisitions to guide ablation have also been developed (Bazan et al. 2007; Betensky et al. 2011; Ouyang et al. 2002; Valles et al. 2010). Although non-invasive, these algorithms are region-dependent and often involve numerous steps and measurements to reach a diagnosis, which increases the probability of error and variability in the results. As a non-invasive, ultrasound-based imaging modality, we presented a proof-of-concept in which EWI was capable of providing relevant insights into the origins of an arrhythmia. This and previous results (Provost et al. 2011b; Provost et al. 2015) suggest that EWI could have the potential to position itself in the clinic as a uniquely valuable pre-procedure planning tool for the non-invasive characterization of focal arrhythmias.

Limitations include the small number of animals and patients involved in this study. In order to further confirm EWI capability in discriminating between epicardial and endocardial source and to confirm EWI value as a pre-treatment planning tool, an increase in the number of subjects is required. Technical limitations of EWI include 2D acquisition of apical views of the heart. Indeed, the focal arrhythmia origin might not be exactly situated in the same views as the ones used during EWI acquisition. This limitation is mitigated by acquiring numerous views that are then co-registered in space and time. Thus, when the focal source is located in between acquisition planes, the immediately neighboring walls may both show early activated region which may as a result facilitate localization of the source (see Figures 2-B and 3-B for example). However, this fails in some cases and although EWI can provide insight into the region of origin, it is not capable of determining the surface of origin during pacing (Figure 2-D and 3-D). Additionally, mis-registration of 2D views may lead to incorrect localization of the origin: for example, EWI may locate an origin on the anterior wall when it is in fact on the anterior-lateral wall. Even without the exact location, EWI may still be of value to clinicians and help them plan for the mapping and ablation procedure. For example, determining if an arrhythmia originates from the left or right atrium may help clinicians plan for the potential need of a transeptal puncture. Of course, true 3D EWI may help mitigate this issue. EWI currently relies on 1D displacement and strain estimation which may result in false positives that may show as early activated regions far from the pacing location or focal arrhythmia foci. This may be due to errors in the displacement and strain estimations caused by a poor acoustic window or the misalignment between the myocardium fibers and the direction of estimation. True 3D EWI may help limiting false positive by offering a more accurate displacement and strain estimation and is currently

being investigated in our lab. Another limitation of this study could arise from the fact that the pseudo-3D electromechanical activation isochrones are generated from four subsequent but separate acquisitions. This was not deemed as a concern in this study, however, because EWI was acquired in the case of highly organized, stable rhythms and because we have previously shown EWI to be reproducible and repeatable between heart cycles both within the same acquisition and between separate acquisitions and views (Costet et al. 2014; Provost et al. 2013). Finally, in its current implementation the total EWI acquisition time for all four views ranged from 2 to 10 minutes per subject, and data processing was performed offline. Although the processing time to generate pseudo-3D maps and activation videos was no more than an hour per subject, EWI will require on-line implementation to truly be clinic-ready. This is something that is currently being investigated in our lab.

Conclusion

In this study, we showed that EWI was capable of accurately localizing the source of focal pacing in an animal model. EWI was also shown capable of discriminating between epicardial and endocardial origin. We also presented a proof-of-concept in which EWI was capable of non-invasively identifying the location and surface of origin of PVC in one patient as confirmed by electrophysiology mapping. EWI is a non-invasive, non-ionizing ultrasound-based imaging modality, which has real-time capabilities and is easily translatable to existing clinical ultrasound systems. As a result, EWI has the potential to position itself in the clinic as a valuable pre-procedure planning tool for the non-invasive characterization of focal arrhythmias

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1: EWI acquisition and motion and strain estimation flowchart.

(1) 2s high frame-rate acquisition (2000 Hz) in standard apical views with an unfocused transmit sequence. (2) RF image formation using channel data. (3) Segmentation and 1D axial displacement estimation using 1D cross-correlation. (4) Axial incremental strain estimated using a least-square estimator. (5) EWI isochrones for each apical view are obtained by selecting the zero-crossings within the mask and pseudo-3D isochrones are generated. RF = radio-frequency.

Figure 2: EWI results from epicardial pacing.

Pseudo-3D isochrones show the location of the earliest region of activation. Magnified ROIs show the earliest region of activation. (A-C) Activation originated from the epicardium and propagated toward the endocardium. (D) Earliest region of activation corresponded to the location of pacing, but surface of origin was not distinguishable.

Figure 3: EWI results from focal endocardial pacing.

Pseudo-3D isochrones show the location of the earliest region of activation. Magnified ROIs show the earliest region of activation. (A-C) Activation originated from the endocardium and propagated toward the epicardium. (D) Earliest region of activation corresponded to the location of pacing, but surface of origin was not distinguishable.

Figure 4. EWI results in one patient scheduled for PVC ablation.

The location of the earliest region of activation on the EWI isochrone (on the left) corresponded to the origin found during electrophysiology studies (on the right). Red arrows indicate region of early activation. EP = electrophysiology.

Table 1:

Summary of pacing locations for the paced animal model

Animal	Pacing site	Location	Pacing Rate	Pacing Voltage
Dog #1	Epicardial	Anterior-lateral	400 ms	10 V
Dog #2	Epicardial	Anterior-lateral	550 ms	10 V
Dog #3	Epicardial	Lateral	400 ms	10 V
Dog #4	Epicardial	Posterior-lateral	500 ms	10 V
Dog #1	Endocardial	Posterior-lateral	400 ms	10 V
Dog #5	Endocardial	Anterior-lateral	600 ms	10 V
Dog #6	Endocardial	Anterior	500 ms	10 V
Dog #7	Endocardial	Posterior	500 ms	10 V