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A Clinical Feasibility Study of Atrial and Ventricular Electromechanical Wave Imaging

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Abstract

Background—Cardiac Resynchronization Therapy (CRT) and atrial ablation currently lack a noninvasive imaging modality for reliable treatment planning and monitoring. Electromechanical Wave Imaging (EWI) is an ultrasound-based method that has previously been shown to be capable of noninvasively and transmurally mapping the activation sequence of the heart in animal studies by estimating and imaging the electromechanical wave, i.e., the transient strains occurring in response to the electrical activation, at both very high temporal and spatial resolution.

Objective—Demonstrate the feasibility of noninvasive transthoracic EWI for mapping the activation sequence during different cardiac rhythms in humans.

Methods—EWI was performed in CRT patients with a left bundle-branch block (LBBB), during sinus rhythm, left-ventricular pacing, and right-ventricular pacing and in atrial flutter (AFL) patients before intervention and correlated with results from invasive intracardiac electrical mapping studies during intervention. Additionally, the feasibility of single-heartbeat EWI at 2000 frames/s, is demonstrated in humans for the first time in a subject with both AFL and right bundle-branch-block.

Results—The electromechanical activation maps demonstrated the capability of EWI to localize the pacing sites and characterize the LBBB activation sequence transmurally in CRT patients. In AFL patients, the propagation patterns obtained with EWI were in agreement with results obtained from invasive intracardiac mapping studies.

Conclusion—Our findings demonstrate the potential capability of EWI to aid in monitoring and follow-up of patients undergoing CRT pacing therapy and atrial ablation with preliminary validation in vivo.

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Keywords

Ablation; Arrhythmias; Noninvasive Imaging; Pacing

Introduction

Left bundle branch block (LBBB) and atrial tachyarrhythmias are associated with heart failure, morbidity, and mortality and can be treated with biventricular pacing therapy and radiofrequency ablation respectively. One of the major limitations in the utility of these treatment strategies is the current lack of access to a noninvasive imaging modality capable of accurate mapping of electrical activation in the heart. The only noninvasive tool widely available to the physician is the 12-lead electrocardiogram (ECG). The 12-lead ECG does, however, have limitations in reliably determining the site of origin or specific underlying mechanism of atrial tachyarrhythmias, such as macro-reentrant atrial flutter (AFL) vs. focal atrial tachycardia. Detailed mapping of cardiac electrical activity during arrhythmias can be achieved with intracardiac electroanatomical mapping. This approach is, however, costly and time-consuming, and, as with any invasive procedure, carries some degree of risk. Both 12-lead ECG and invasive methods are also limited in their utility for monitoring response to CRT therapy over an extended period of time. The mechanisms by which CRT can reverse heart failure are not fully understood and the lack of tools to longitudinally study the electromechanical effects of CRT has limited the development of effective techniques for optimization of pacing parameters (1, 2).

Electromechanical Wave Imaging(3–6) (EWI) is an ultrasound-based imaging method that can noninvasively map the cardiac electromechanical activity in all four heart chambers (5) by tracking, at very high temporal and spatial resolutions, the electromechanical wave (EW), i.e., the transient deformations occurring in response to the local electrical activation. Previous *in vivo* and *in silico* animal studies indicated that EWI can map the activation sequence in normal and abnormal hearts in which the electrical and electromechanical activations remain correlated, such as sinus rhythm, electrical pacing, LBBB, atrio-ventricular block, and even fibrillation *in vivo* (7–9). When this correlation disappears in conditions such as ischemia, the ischemic region could be mapped with high accuracy (4). Other studies have also reported a correlation between the onset of mechanical activity and the electrical activation sequence (10–12). Additionally, the EWI isochrones obtained in normal human subjects reflected accurately the expected activation sequence of normal sinus rhythm (5). In this study, we investigate the clinical feasibility of EWI for the treatment monitoring of cardiac resynchronization therapy in patients with left bundle branch block and treatment planning of atrial flutter ablation.

Methods

Patient Selection

The study protocol was approved by the Institutional Review Board (IRB) of Columbia University, and informed consent was obtained from all human subjects prior to scanning. Normal subjects (21–23 years old, n=3) were imaged by a trained cardiologist. Three

subjects with CRT ($n = 3$) were scanned during scheduled routine device checks. The device was first configured to pace only from the LV, after which EWI was performed in the four-chamber view. EWI was then performed when the device was set to pace only from the RV and when the device was not pacing. The pacing rate was adjusted to sufficiently high values to minimize beats triggered by sinus rhythm. In patients with AFL ($n = 3$), EWI was performed a few minutes to a few hours prior to the scheduled mapping and ablation procedure.

EWI

EWI is performed by mapping the transient deformations (strains) occurring during the electrical activation of the heart using RF speckle cross-correlation. Achieving sufficient imaging frame rate is the main challenge in mapping the EW for two reasons. First, the EW must be tracked without aliasing, a condition that we estimated to be above approximately 120 fps. Second, the mapped displacements and strains have to be estimated with high accuracy. This accuracy is mostly dependent on the frame rate: it is acceptable above 300 fps, but optimal when reaching approximately 1000 fps. Such frame rates are not typically achieved with commercial imaging sequences in a full field of view for cardiac applications.

Two imaging methods were used to perform EWI in this study. The automated composite technique (13) (Fig 1–4) is based on conventional image formation: images are formed using focused ultrasound emissions, i.e., one per line. To achieve sufficient frame rates (320 to 400 fps in this study), the full view of the heart was divided in overlapping sectors and reconstructed using motion-matching (4), a method similar to ECG-gating. Images in single-heartbeat EWI (Fig 5) are formed using diverging emissions that probe the entire field of view in a single emission (7). This technique allows frame rates that are typically 100 times larger (up to 2000 fps in this study) than with conventional image formation. While the automated composite technique is easier to implement on existing ultrasound scanners, it requires long acquisition times (~20 s) and is limited to repeatable rhythms. Single-heartbeat EWI requires a modern ultrasound scanner that allows the sampling of individual piezoelectric elements, but can be performed in real-time. A detailed description of the EWI methods is provided in Supplementary Material 1.

Results

Bi-plane EWI ciné-loops and isochrones were obtained in apical views (Fig. 1), in which the electromechanical activation corresponds to a transition from lengthening (positive strains) to shortening (negative strains). Our previously described methodology (5) was used for all the patients in this study, with the exception of the patient with AFL and RBBB presented in Fig. 5, for which single-heartbeat EWI was used (7).

Normal Subjects

In all 3 normal subjects scanned for this study (Fig. 2a-c, Supplemental Material 2), the EW was found to originate in the RA, propagating towards the LA. During the QRS complex, the EW propagated in the ventricles from multiple origins and propagated transmurally from the endocardium to the epicardium. Figure 2d-e depicts the atrial (Fig. 2d) and ventricular

(Fig. 2e) activation of the first normal subject (Fig. 2a) in greater detail. The EW originated in the superior wall of the RA, near the lateral wall, and propagated towards the LA (Fig. 2d). The site of earliest activation is compatible with the expected location of the sinus node. In the two-chamber view (Fig. 2d), which depicts the LA and the LV, the EW originated in the superior wall of the LA and propagated toward the posterior and anterior walls. The last region to undergo electromechanical activation was located in the LA anterior wall, near the mitral valve (Fig. 2d). Following a delay similar to the PR segment, the ventricles were activated from three main origins, i.e., near the apex in the posterior wall, at the mid-level of the septum, and near the base in the anterior wall, as depicted in the electromechanical activation isochrones (Fig. 2e). From these three origins, the EW propagation occurred transmurally from the endocardium towards the epicardium (Fig. 2e, Supplemental Material 2).

Cardiac Resynchronization Therapy

EWI was performed in CRT subjects with an underlying LBBB during either sinus rhythm, LV epicardial pacing only, or RV pacing only, in three (n=3) subjects with NYHA class I non-ischemic cardiomyopathy (Subject 1), NYHA class IV non-ischemic cardiomyopathy (subject 2), and NYHA class III ischemic cardiomyopathy (subject 3) (Fig. 3, Supplemental Material 3). Only the four-chamber view was acquired. In all three subjects, the EW originated on the epicardium of the LV lateral wall during LV epicardial pacing (Fig. 3a,d,g) and at the apex of the RV during RV pacing (Fig. 3b,e,h). During sinus rhythm, the septum and the RV wall were activated prior to the LV lateral wall (Fig. 3c,f,i). The time required for both ventricles to be electromechanically activated varied significantly, from under 100 ms (e.g., Subject 1 during RV pacing and sinus rhythm, Fig. 3b,c), to over 200 ms (e.g., Subject 1 during LV epicardial pacing, Fig. 3A, and Subject 3 in all pacing schemes, Fig. 3g,h,i). More specifically, during LV epicardial pacing, the transmural EW propagation originated from the epicardium of the lateral wall in all three subjects. In subjects 1 and 3 (Fig. 3a,g), the earliest activation was located on the epicardium of the lateral wall near the base. In Subject 2 (Fig. 3d), the earliest electromechanical activation was detected on the epicardium at the mid-myocardium. During RV pacing, the earliest electromechanical activation was located near the apex in all three subjects, either at the apex (Fig. 3b), in the septum (Fig. 3e), or on the RV wall (Fig. 3h). Finally, during sinus rhythm, the EW originated from multiple locations in the septum and the RV wall (as opposed to the sole site when pacing), with the RV and septal walls being electromechanically activated prior to the lateral wall in all cases. In Subject 1, one early activation site was mapped in the basal region of the septum (Fig. 3c); in Subjects 2 and 3, two sites were identified at the basal and apical regions of the septum (Fig. 3f,i). In subjects 2 and 3, the strains measured in the lateral wall remained minute (Fig. 3, black region) and did not display a clear transition from relaxation to contraction. Remarkably, these regions underwent large strains (Supplemental Material 3) when the heart was paced.

Atrial flutter

EWI was performed in three subjects with AFL, immediately prior to a scheduled mapping and ablation procedure (Fig 4, Supplemental material 4). The intracardiac electrical mapping procedure indicated that the patients (Fig. 4) had right (Fig. 4a) and left AFL (Fig. 4b),

respectively. In the subject with right AFL, the results of the activation sequence mapping (Supplemental Material 4) demonstrate the close correlation between EWI and the electrical activation sequence. Indeed, in both EWI and electrical mapping, propagation from the tricuspid valve toward the superior wall in the lateral wall of the RA is observed, with the activation of the septum occurring from the superior wall towards the tricuspid valve. In the subject with left AFL (Fig. 4b), the EW propagated from the LA to the RA. More specifically, the EW originated in the left side of the septum, propagated towards the superior wall of the LA and finally reached the RA. The ablation site that led to successful termination was located at the right-inferior pulmonary vein. Again, this specific site was not imaged for EWI mapping. In both cases, the propagation was repeated at each P-wave, suggesting that the electromechanical activation has a similar cycle length as the electrical activation and confirming the reproducibility of EWI (see Supplemental Material 4).

Atrial flutter and right bundle branch block

Finally, we performed EWI in a single-heartbeat (7) by insonifying the entire field of view with a circular ultrasound wave and therefore reaching a frame rate of 2000 frames/s. We applied this methodology on a subject with typical right AFL and RBBB (Fig. 5, Supplemental Material 5). The EWI isochrones (Fig. 5b) displayed periodic conduction in the atria with an electromechanical cycle length (214 ms) similar to the one found with electrocardiography (206 ms). In the ventricles, regions of early activation were observed at the mid-level of the septum and near the base in the left lateral wall (Fig. 5a). Unlike in the normal case (Fig. 2e), the EWI isochrones (Fig. 5b) show that activation of the RV wall occurs near the base, and later than in the LV lateral wall, in accordance with the expected propagation pattern during RBBB (14).

Discussion

The objectives of this study were (1) to determine the potential for clinical role of EWI, by predicting activation patterns in normal subjects, (2) to identify the myocardial activation sequence in patients undergoing CRT, and (3) to determine the feasibility of EWI to identify the site of origin in subjects with tachyarrhythmia. In normal subjects (Fig. 2), the EW propagated, in both the atria and the ventricles, in accordance with the expected electrical activation sequences based on reports in the literature. In subjects with CRT (Fig. 3), EWI successfully characterized two different pacing schemes, i.e., LV epicardial pacing and RV endocardial pacing versus sinus rhythm with conducted complexes. Moreover, during pacing from different sites the location of the earliest electromechanical activation was correlated with the location of the appropriate pacing electrodes, as was previously observed and confirmed in canines *in vivo*(5). In two subjects with AFL (Fig. 4), the propagation patterns obtained with EWI were in agreement with results obtained from invasive intracardiac mapping studies, indicating that EWI may be capable of distinguishing LA from RA flutters transthoracically. Finally, we have shown the feasibility of EWI to describe the activation sequence during a single heartbeat in a patient with AFL and RBBB (Fig. 5).

One third of subjects with heart failure also have dyssynchrony due to LBBB. CRT is an evolving therapy that has led to lower mortality and improved clinical status(15). However,

approximately 30% of subjects show no functional benefit after implantation (16). This limited success likely reflects both an incomplete understanding of basic mechanisms as well as inadequate tools for optimizing the use and programming of existing pacing therapies. As we show in this study, EWI characterized each pacing scheme in accordance with the expected electrical activation sequence, i.e., in a unique and predicted fashion. Although validation against mapping in the human ventricle is beyond the scope of this feasibility study, previous reports have established a strong linear correlation between the electrical and electromechanical activations in canines in vivo during pacing using implanted beads (10), magnetic resonance tagging (11, 12) and, more recently, EWI (5, 7, 17, 18). The availability of this information has the potential to guide optimization of CRT and device programming. Optimization of device programming is frequently not pursued by practitioners, in large part due to lack of effective tools and methodologies (19). EWI could be uniquely positioned to provide critical information for these purposes, given that it is noninvasive, non-ionizing, low-cost, and can be readily implemented in most ultrasound scanners already available at the point of care.

ECG recordings have limitations in the determination of specific atrial tachyarrhythmia mechanisms. In patients who have undergone a previous catheter procedure, the surface ECG may not be helpful in distinguishing LA from RA flutters (20, 21). Intracardiac mapping and ablation procedures for LA and RA flutters can differ significantly with regard to complexity, procedural risk, anticipated success rates, appropriate patient selection and requirements for preprocedural planning (22, 23). The results of our study indicate that EWI may play a role in clinical decision-making by identifying the chamber of origin of AFL prior to any invasive procedure. Future applications of EWI could theoretically be expanded to include insights with regard to specific arrhythmia mechanism (i.e., macro reentry vs. focal atrial tachycardia) and transmural localization of likely sites for successful ablation (e.g., epicardial vs. endocardial site of ongoing ventricular tachycardia).

EWI relies on strain mapping, a robust technique that does not require any assumptions involving the geometry or physiology of the heart. This is a key difference with body surface potential methods (24–26) that are based on, and highly sensitive to, extensive patient-specific models (27). For example, in a wide array of cardiac conditions or unusual anatomy, the strains remain reliable (8) and can be interpreted by the physician within the context of the patient's condition. Although multiple myocardial deformation imaging techniques are currently used in the clinic (28), standard strain mapping methods are limited by the difficulty of simultaneously achieving high imaging frame rates and high accuracy in a large field of view, noninvasively. By using novel imaging sequences, EWI can noninvasively map the electromechanical activation at high frame rates and with high accuracy, in a full view of the heart, in real time using equipment readily available in cardiology suites. Limitations of the implementation of EWI used for figures 1–4 included the reliance on multiple heartbeats to map the EW in humans and onedimensional strain mapping. Recent work by our group (7, 8) showed that it is possible to achieve very high EWI frame rates (~2000 fps) in a single heartbeat by using temporally-unequispaced (8) or unfocused imaging methods (7) (or a combination of both (7)) while providing higher signal-to-noise ratio than with the multiple heartbeat method (8), and we have hereby shown its initial feasibility in humans. In addition, as observed in the AFL cases of this study, the

ventricular contraction can, by pre-stretching the atria, modify activation times. This limitation can be circumvented simply by mapping the atrial contraction during ventricular diastole.

Limitations to this feasibility study include the small number of subjects for each condition. In this initial feasibility study, the objective is to assess the versatility of the methodology, i.e., the capability of EWI to map different types of abnormal rhythms in all four chambers. Studies involving larger sample sizes and better characterization of the patients' conditions using clinical gold standards will be required before the utility of EWI can be fully assessed. Additionally, while the capability of EWI to map ventricular activation times during pacing has been shown in animal models (5, 7, 8, 17, 18), further studies involving complete electrical mapping and larger groups of subjects will be necessary to validate the proposed clinical applications in the atria. The characterization of a subset of rhythms with EWI may also require the use of three-dimensional maps; while this can be compensated with the use of multiple planes (Fig. 1), using 3-D ultrasound in a single heartbeat would be advantageous and theoretically possible but would require additional technical developments to achieve sufficient frame rates. Finally, this technique relies on transthoracic ultrasound imaging for which the image quality can be limited in patients with poor acoustic windows or who are overweight, although the EWI methodology could be implemented with transesophageal or intra-cardiac probes.

Conclusion

We demonstrated the feasibility of EWI to noninvasively and accurately map the transmural electromechanical activation sequence in all four chambers of the heart in humans during sinus rhythm, cardiac resynchronization therapy, and atrial tachyarrhythmia for the first time. In CRT patients EWI provides a new relevant quantitative measurement that reflects by its very nature the complex coupling existing between the electrical and mechanical activities of the heart that can be used to localize pacing sites and quantify total electromechanical activation times. In patients with atrial tachyarrhythmia such as atrial flutter, EWI could be of assistance in the planning of ablation procedures and potentially reduce their duration and avoid unnecessary ones.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Disclosures

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Glossary

AFL	Atrial Flutter
CRT	Cardiac Resynchronization Therapy
ECG	Electrocardiogram
EW	Electromechanical Wave
EWI	Electromechanical Wave Imaging
IRB	Institutional Review Board
LA	Left Atrium
LBBB	Left Bundle Branch Block
LV	Left Ventricle
NYHA	New York Heart Association
RA	Right Atrium
RBBB	Right Bundle Branch Block
RV	Right Ventricle

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Fig. 1.

EWI flowchart. a High frame-rate acquisition of standard four and two-chamber RF images is performed by dividing the full-view of the heart in 5 to 7 sectors recorded during separate heartbeats and reconstructed using motion-gating; or using a circular ultrasound wave to insonify the entire field of view in one ultrasound transmission (Fig. 6). b Motion maps are generated with RF cross-correlation and used to track the segmented heart throughout the cardiac cycle in both views (the first frame of each view is segmented manually). Axial incremental strains are then estimated and overlaid onto the B-mode images to produce the EWI ciné-loop. c EWI isochrones are obtained by mapping the local zero-crossing time of the strains. d Bi-plane representations of the EWI ciné-loop can then be generated by synchronizing (using the ECG) and combining both views. The example shown

here is from a 23-year old male healthy volunteer. e EWI isochrones are finally obtained by mapping the first zero-crossing time of incremental strains following the onset of the P-wave (in the atria) or the onset of the QRS (ventricles).

Fig. 2.

EWI isochrones of three normal subjects a-c The atrial activation sequence originates from the RA and propagates in the LA. In the two chamber view, propagation from the top of the LA is observed. In the ventricles, arrows indicate the sites of early activation, located in the septum at the mid-level, in the anterior wall near the base and in the posterior wall near the apex. d EWI isochrones of a normal subject (a) in the two and four-chamber views with different color bars to highlight the atrial and ventricular activation sequences. The atrial activation sequence originates from the RA and propagates in the LA. In the two chamber view, propagation from the superior wall of the LA is observed. In the ventricles, arrows indicate the sites of early

activation, located in the septum at the mid-level, in the anterior wall near the base and in the posterior wall near the apex, in the left ventricle, and near the apex of the right ventricle, in accordance with existing literature.

Fig. 3.

Ventricular EWI isochrones of three CRT patients with LBBB during RV pacing, LV pacing and sinus rhythm. Electromechanical activation times could not be obtained in blackened regions. All three patients presented similar activation patterns: from the right ventricular apex during RV pacing, from the epicardium of the LV lateral wall during LV pacing. During sinus rhythm, the right ventricle was electromechanically activated rapidly, followed by the LV lateral wall. Large portions of the LV lateral wall were not electromechanically activated in two cases (patients 2 & 3).

Fig. 4.

a EWI ciné-loop and isochrones of a patient undergoing typical right-atrial flutter. The EW originated in the lateral wall of the RA (20 ms) and propagated towards the septum and the LA (80 ms). EWI isochrones also depict this propagation pattern in greater details. b EWI cinéloop and isochrones of a patient undergoing atypical left-atrial flutter. In this case, the EW originated in the left endocardium of the septum, and propagated in the LA (70 ms), before reaching the RA (120 ms). EWI isochrones also depict this propagation pattern in greater details.

Fig. 5.

Single-heartbeat EWI a ciné-loop and b isochrones of a patient during atrial flutter and RBBB. In the atria, activation originated from the atrial septum and right atrial lateral wall and propagated in the superior wall of the RA and in the LA. A region of slow conduction could be identified (red arrow). The ventricular EW was initiated at the mid-level of the septum, and propagated in the LV lateral wall. The RV wall was activated last. Arrows indicates regions undergoing activation.