A clinical feasibility study of atrial and ventricular electromechnical wave imaging

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BACKGROUND Cardiac resynchronization therapy (CRT) and atrial ablation procedures 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, that is, the transient strains occurring in response to the electrical activation, at both high temporal and spatial resolutions.

OBJECTIVE To demonstrate the feasibility of transthoracic EWI for mapping the activation sequence during different cardiac rhythms in humans.

METHODS EWI was performed in patients undergoing CRT and a left bundle branch block (LBBB) during sinus rhythm, left ventricular pacing, and right ventricular pacing, as well as in patients with atrial flutter (AFL) before intervention, EWI findings from patients with AFL were subsequently correlated with results from invasive intracardiac electrical mapping studies during intervention. In addition, the feasibility of single-heartbeat EWI at 2000 frames/s is demonstrated in humans for the first time in a patient with both AFL and right bundle branch block (RBBB).

RESULTS The electromechanical activation maps demonstrated the capability of EWI to localize the pacing sites and characterize the bundle branch block activation sequence transmurally in patients with CRT. In patients with AFL, the EWI propagation patterns obtained with EWI were in excellent agreement with those obtained from invasive intracardiac mapping studies.

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

KEYWORDS Ablation; Arrhythmias; Noninvasive imaging; Pacing

ABBREVIATIONS AFL = atrial flutter; CRT = cardiac resynchronization therapy; ECG = electrocardiogram; EW = electromechanical wave; EWI = electromechanical wave imaging; LA = left atrium/atrial; LBBB = left bundle branch block; LV = left ventricle/ventricular; NYHA = New York Heart Association; RA = right atrium/atrial; RBBB = right bundle branch block; RF = radiofrequency; RV = right ventricle/ventricular

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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 (RF) ablation, respectively. These treatment strategies would benefit significantly from the availability of a noninvasive imaging modality capable of accurately mapping of the 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 macroreentrant atrial flutter (AFL) vs focal atrial tachycardia. A detailed mapping of cardiac electrical activity during arrhythmias can be achieved with intracardiac electroanatomical mapping. This approach is, however, costly, 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 cardiac resynchronization therapy (CRT) 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 electromagnetic effects of CRT has limited the development of effective techniques for the optimization of pacing parameters.

Electromechanical wave imaging (EWI) is an ultrasound-based imaging method that can noninvasively map the cardiac electromechanical activity in all 4 heart chambers by tracking, at high temporal and spatial
resolutions, the electromechanical wave (EW), that is, 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 electrical and electromechanical activations remain correlated, such as sinus rhythm, electrical pacing, LBBB, atrioventricular block, and even fibrillation in vivo.\(^{5,7–9,18}\) When this correlation disappears in conditions such as ischemia, the ischemic region could be mapped with high accuracy.\(^{5}\) Other studies have also reported a correlation between the onset of mechanical activity and the electrical activation sequence.\(^{10–12}\) In addition, 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 treatment monitoring of CRT in patients with LBBB and treatment planning of AFL ablation.

**Methods**

**Patient selection**

The study protocol was approved by the Institutional Review Board of Columbia University, and informed consent was obtained from all human subjects prior to scanning. Normal subjects (aged 21–23 years; \(n = 3\)) were imaged by a trained cardiologist. Three subjects treated with CRT (\(n = 3\)) were scanned during scheduled routine device checks. The device was first configured to pace only from the left ventricle (LV), after which EWI was performed in the 4-chamber view. EWI was then performed when the device was set to pace only from the right ventricle (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 procedures.

**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 2 reasons: First, the EW must be tracked without aliasing, which we estimated could be avoided above approximately 120 fps.\(^{8}\) 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\(^{15}\) (Figures 1–4) is based on conventional image formation using standard ultrasound systems: images are formed by using focused ultrasound emissions, that is, 1 per line. To achieve sufficiently high frame rates (320–400 fps in this study), the full view of the heart was divided into overlapping sectors and reconstructed by using motion matching,\(^{4}\) a method similar to ECG gating. Images in single-heartbeat EWI (Figure 5) are formed by 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 seconds) 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**

Biplane EWI ciné loops and isochrones were obtained in apical views (Figure 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 right bundle branch block (RBBB) presented in Figure 5, for which single-heartbeat EWI was used.\(^{7}\)

**Normal subjects**

In all 3 normal subjects scanned for this study (Figures 2A–C; Supplementary Material 2), the EW was found to originate in the right atrium (RA), propagating toward the left atrium (LA). During the QRS complex, the EW propagated in the ventricles from multiple origins and propagated transmurally from the endocardium to the epicardium. Figures 2D and 2E depict, respectively, the atrial and ventricular activation of the first normal subject (Figure 2A) in greater detail. The EW originated in the superior wall of the RA, near the lateral wall, and propagated toward the LA (Figure 2D). The site of the earliest activation is compatible with the expected location of the sinus node. In the 2-chamber view (Figure 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 (Figure 2D). After a delay similar to the PR segment, the ventricles were activated from three main origins, that is, 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 (Figure 2E). From these three origins, the EW propagation occurred transmurally from the endocardium toward the epicardium (Figure 2E; Supplementary Material 2).

**Cardiac resynchronization therapy**

EWI was performed in subjects with CRT with an underlying LBBB during either sinus rhythm, LV epicardial pacing only, or RV pacing only in three subjects (\(n = 3\)) with New
York Heart Association (NYHA) class I nonischemic cardiomyopathy (subject 1), NYHA class IV nonischemic cardiomyopathy (subject 2), and NYHA class III ischemic cardiomyopathy (subject 3) (Figure 3; Supplemental Material 3). Only the 4-chamber view was acquired. In all three subjects, the EW originated on the epicardium of the LV lateral wall during LV epicardial pacing (Figures 3A, 3D, and 3G) and at the apex of the RV during RV pacing (Figures 3B, 3E, and 3H). During sinus rhythm, the septum and the RV wall were activated prior to the LV lateral wall (Figures 3C, 3F, and 3I). The time required for both ventricles to be electromechanically activated varied significantly from < 100 ms (eg, subject 1 during RV pacing and sinus rhythm [Figures 3B and 3C]) to > 200 ms (eg, subject 1 during LV epicardial pacing [Figure 3A] and subject 3 in all pacing schemes [Figures 3G–3I]). 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 (Figures 3A and 3G), the earliest activation originated from the epicardium of the lateral wall near the base. In subject 2 (Figure 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 (Figure 3B), in the septum (Figure 3E), or on the RV wall (Figure 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, an
early activation site was mapped in the basal region of the septum (Figure 3C); in subjects 2 and 3, two sites were identified at the basal and apical regions of the septum (Figures 3F and 3I). In subjects 2 and 3, the strains measured in the lateral wall remained minute (Figure 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 procedures (Figure 4; Supplemental material 4). The intracardiac electrical mapping procedure indicated that the patients (Figure 4) had right (Figure 4A) and left (Figure 4B) AFL, respectively. In the subject with right AFL, the results of the activation sequence mapping (Supplemental Material 4) demonstrate good 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 toward the tricuspid valve. In the subject with left AFL (Figure 4B), the EW propagated from the LA to the RA. More specifically, the EW originated in the left side of the septum, propagated toward the superior wall of the LA, and finally reached the RA. The ablation site that led to the successful termination was located at the right inferior pulmonary vein. 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 (Supplemental Material 4).

**AFL and RBBB**

Finally, we performed EWI using a single cardiac cycle 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 in a subject with typical right AFL and RBBB (Figure 5; Supplemental Material 5). The EWI isochrones (Figure 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 (Figure 5A). Unlike in the normal case (Figure 2E), the EWI isochrones (Figure 5B) show that the 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.

**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 in identifying the site of origin in subjects with tachyarrhythmia. In normal subjects (Figure 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 undergoing CRT (Figure 3), EWI successfully characterized two pacing schemes, that is, LV epicardial pacing and RV endocardial pacing vs 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. In two subjects with AFL (Figure 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 (Figure 5).

One-third of the 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. However, approximately 30% of the subjects show no functional benefit after implantation. This limited success likely reflects 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, that is, in a unique but 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.
magnetic resonance tagging,\textsuperscript{11,12} and, more recently, EWI.\textsuperscript{5,7,17,18} The availability of this information has the potential to guide the optimization of CRT and device programming. The optimization of device programming is frequently not pursued by practitioners, in large part due to a lack of effective tools and methodologies.\textsuperscript{19} EWI could be uniquely positioned to provide critical information for these purposes, given that it is noninvasive, nonionizing, less costly, 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.\textsuperscript{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.\textsuperscript{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 into specific arrhythmia mechanisms (ie, macroreentry vs focal atrial tachycardia) and transmural localization of likely sites for successful ablation (eg, epicardial vs endocardial site of ongoing ventricular tachycardia).

EWI relies on high precision 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\textsuperscript{24–26} that are based on, and highly sensitive to, extensive patient-specific models.\textsuperscript{27} For example, in a wide array of cardiac conditions or unusual anatomy, the strains remain reliable\textsuperscript{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,\textsuperscript{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 one-dimensional strain mapping. Recent work by our group\textsuperscript{7,8} showed that it is possible to achieve high EWI frame rates (~2000 fps) in a single heartbeat by using temporally unequispaced\textsuperscript{8} or unfocused imaging methods\textsuperscript{7} (or a combination of both\textsuperscript{7}) while providing higher signal-to-noise ratio than with the multiple heartbeat method,\textsuperscript{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 prestretching 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, that is, the capability of EWI to map different types of abnormal rhythms in all 4 chambers. Studies involving larger sample sizes and better characterization of the patients’ conditions by using clinical gold standards will be required before the utility of EWI can be fully assessed. In addition, while the capability of EWI to map ventricular activation times during pacing has been shown in animal models, further studies involving complete electrical mapping and larger groups of human 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 (Figure 1), using three-dimensional 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, although the EWI methodology could be implemented with transesophageal or intracardiac probes.

Conclusions

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, CRT, and atrial tachyarrhythmia for the first time. In patients undergoing CRT, EWI provided a new relevant quantitative measurement that reflects by its 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 AFL, EWI was shown possible in a single heartbeat could guide diagnosis and/or the preprocedural planning of ablation procedures.

Appendix

Supplementary data

Supplementary material cited in this article is available online http://dx.doi.org/10.1016/j.hrthm.2013.02.028.

References