

Imaging the electromechanical activity of the heart in vivo

Jean Provost^a, Wei-Ning Lee^a, Kana Fujikura^b, and Elisa E. Konofagou^{a,b,1}

^aDepartment of Biomedical Engineering, Columbia University, New York, NY 10027; and ^bDepartment of Radiology, Columbia University, New York, NY 10032

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Cardiac conduction abnormalities remain a major cause of death and disability worldwide. However, as of today, there is no standard clinical imaging modality that can noninvasively provide maps of the electrical activation. In this paper, electromechanical wave imaging (EWI), a novel ultrasound-based imaging method, is shown to be capable of mapping the electromechanics of all four cardiac chambers at high temporal and spatial resolutions and a precision previously unobtainable in a full cardiac view in both animals and humans. The transient deformations resulting from the electrical activation of the myocardium were mapped in 2D and combined in 3D biplane ventricular views. EWI maps were acquired during five distinct conduction configurations and were found to be closely correlated to the electrical activation sequences. EWI in humans was shown to be feasible and capable of depicting the normal electromechanical activation sequence of both atria and ventricles. This validation of EWI as a direct, noninvasive, and highly translational approach underlines its potential to serve as a unique imaging tool for the early detection, diagnosis, and treatment monitoring of arrhythmias through ultrasound-based mapping of the transmural electromechanical activation sequence reliably at the point of care, and in real time.

strain | electromechanical coupling

The heart is an electromechanical pump that requires to first be electrically activated in order to contract. In the normal heart, action potentials are spontaneously generated by the sinus node in the right atrium and propagate through a specialized conduction system before reaching the cardiac muscle. The depolarization of a cardiac muscle cell, or myocyte, is followed by an uptake of calcium, which triggers contraction (1) after an electromechanical delay of a few milliseconds (2, 3). In the clinical setting, the electrical and mechanical functions of the heart are typically evaluated separately. The cardiac electrical function is usually assessed using an electrocardiogram (ECG) or catheter-based mapping systems. New noninvasive imaging technologies based on body surface potentials (4–6), cavity potentials (7), or magnetic fields (8) are also being developed. Methods used to measure the cardiac electrical activity typically ignore the cardiac motion. On the other hand, the cardiac mechanical function can be assessed using ultrasound or magnetic resonance (MR) techniques, but at such large time scales that the electrical activation occurs within one time frame and is hence ignored. In the laboratory, the cardiac electromechanical coupling has been and remains the topic of extensive research at the cellular level in vitro (3), in cardiac simulation models (9–12), and at the tissue level in animal models in vivo (2, 13–15). To perform such studies, it is necessary to map the electromechanics of the heart (i.e., the deformations occurring at the time scale of the electrical activation). For example, in refs. 13 and 14, a linear relationship between the electrical activation and contraction onset in healthy, paced, canine hearts was found in vivo, indicating the use of electromechanical mapping techniques to identify, for example, ectopic sites (14). To date, no imaging method can noninvasively provide sufficient temporal resolution, accuracy, or field of view to reliably map the electromechanics of the heart in vivo.

In this paper, an entirely ultrasound-based imaging technology, electromechanical wave imaging (EWI), is described and evaluated with respect to its capability of mapping the electromechanics of the heart in vivo. EWI can map the electromechanical activity in all four heart chambers at a very high temporal resolution (approximately 2 ms), noninvasively and with real-time feedback. At such a high temporal resolution, a number of phenomena occurring in the temporal vicinity of the electrical activation, including the onset of contraction resulting from the electrical activation, as well as the opening and closing of the valves and ventricular hemodynamics, can be separated in space and time, mapped and quantified (16). At the tissue level, the depolarization of myocardial regions triggers electromechanical activation (i.e., the first time at which the muscle transitions from a relaxation to a contraction state). Spatially, this electromechanical activation forms the electromechanical wave (EW) front that follows the propagation pattern of the electrical activation sequence.

As of today, no imaging method currently used in the clinic has been capable of mapping the EW. The EW lasts approximately 60 to 100 ms and requires a resolution of a few milliseconds (e.g., 2–5 ms) to generate precise activation maps. Moreover, the regional interframe deformation that has to be measured at these frame rates is very small (approximately 0.25% at a 2-ms temporal resolution) and requires a highly accurate strain estimator. Modalities such as standard echocardiography or MR tagging cannot detect the EW, because the time required to acquire a single image is similar to the duration of the entire ventricular depolarization. Effectively, because standard echocardiography was originally designed to assess the overall mechanics of specific cardiac segments over the entire heart cycle, images are typically acquired every 20–30 ms. Full-view speckle tracking techniques such as tissue Doppler or strain rate imaging have achieved motion estimation with high spatial resolution but require relatively low frame rates. Higher temporal resolution and motion estimation accuracy can be achieved using, e.g., motion mode, but at the expense of a very narrow field of view that does not allow spatial assessment of the propagation. Strain mapping methods based on MR imaging (MRI) in humans are not real time, and their frame rates are typically smaller than in echocardiography, although temporal resolution on the order of 15–20 ms has been achieved (17, 18).

EWI is currently implemented at frame rates up to 500 frames per second (fps) (corresponding to a 2-ms temporal resolution), which is five times higher than standard echocardiography while providing the same large field of view. At those frame rates, EWI uses radio frequency (RF)-based cross-correlation, a motion

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¹To whom correspondence should be addressed. E-mail: ek2191@columbia.edu.

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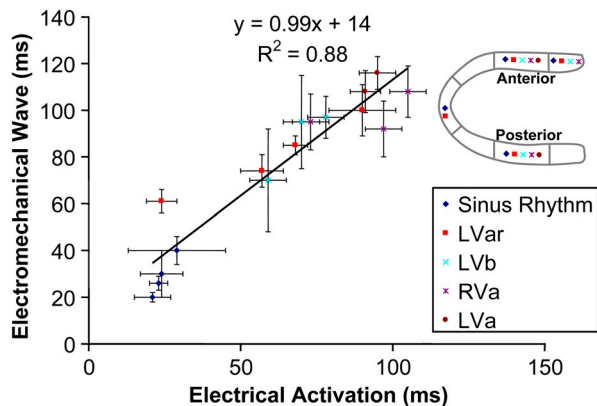


Fig. 4. Electrical and electromechanical activation times during the four pacing protocols and sinus rhythm in four different heart segments in the posterior and anterior walls, as indicated in the legend. A strong correlation was observed, with a slope of 0.99.

regions showing negative strains (compression) at the onset of the QRS complex.

Discussion

The objectives in this study were to determine the accuracy and reliability of EWI in depicting electromechanical events in the heart and to demonstrate feasibility in humans.

EWI was performed in canine hearts during four distinct pacing protocols and sinus rhythm. Isochronal maps of the EW onset were generated, and the earliest activation region was found to be highly correlated with the pacing site location. Electrodes were also implanted in the heart, allowing simultaneous measurements of the electrical activation times in selected echocardiographic segments of the heart. A linear relationship was found between the electrical activation times and the EW onset, thereby showing that at the scale of the cardiac segments, the EW follows the electrical activation sequence. The validation of the link between the EW and the electrical activation sequence in canines was twofold. First, the localization of the earliest activation time in the EWI isochrones was highly correlated with the pacing site, thus allowing the noninvasive identification of the pacing lead location. For instance, right-ventricular pacing (Fig. 3D) could easily be distinguished from left-ventricular free wall pacing, apical pacing, or sinus rhythm. Moreover, the EWI isochrones obtained during sinus rhythm (Fig. 3E) were in agreement with maps previously reported in the literature, which were obtained using electrography (25–27). Second, the electrical activation times and the EWI isochrones were highly correlated, with a slope of 0.99 (Fig. 4). Other groups have reported similar findings *in vivo*; i.e., a linear relationship between mechanical and electrical activations, with slopes of 1.1 (13), 1.06 (14), and 0.87–1.05 (28). This suggests that EWI could potentially become a noninvasive tool to map the electrical activation sequence. The minimum requirement for this to happen would be to obtain a monotonic relationship between the maps of electrical and electromechanical activation times. Comparing such maps, however, poses a significant challenge. The electrodes affect both the mechanical and electrical behavior of the heart muscle and can also generate artifacts on the ultrasound image. To circumvent this issue in this study, the imaging plane was selected in the vicinity of the plane defined by the electrode locations without being affected by the aforementioned artifacts. This approach showed that, at least on the scale of the heart segments in the regions studied, EWI reflects the electrical activity with accuracy. Further studies are needed, however, to establish at which resolution and under which physiological conditions this relationship is maintained. The observed propagation from the epicardium to the endocardium during pacing (e.g., Fig. 2 A–C) indicates that

EWI also provides information about the transmural electrical activity, which was also confirmed in simulations (29). However, in sinus rhythm, activation from endocardium to epicardium, which is expected, was not observed everywhere in the heart. This could be explained by the limited information obtained through 2D observation of an inherently 3D phenomenon such as the cardiac electrical activation in combination with the fact that strain measurements at the boundary of the heart wall are more susceptible to noise. Generalizing EWI to three dimensions could help in addressing those issues.

The EW was observed in the normal human atria (Fig. 5) and, although no validation with electrodes was provided in the atria in the current study, followed the expected electrical activation sequence in two human subjects. The earliest activation region was located in the right atrium, where the sinus node is located. Activation propagated in the atria during the P wave. Following the onset of the QRS complex, activation in the ventricles was observed in multiple regions near the midlevel, in agreement with previous *ex vivo* studies of the activation sequence in human hearts based on electrography (25). To our knowledge, the normal transmural electrical activation sequence in conscious subjects is not available in the literature. The electrical activation sequence in humans was initially obtained in isolated hearts (25) or during intraoperative mapping studies under nonphysiological conditions. More recently, the epicardial electrical activation sequence was obtained in the normal human heart under complete physiological conditions (30). However, such an approach is limited to the epicardium and thus cannot be used to map the endocardium or the septum, nor can it be used across the thickness of the heart walls. EWI might thus constitute an important complementary tool to the ECG to assess the normal electrical activation sequence in normal subjects.

Moreover, when the function of a region of the heart is compromised, both the normal electrical and mechanical behaviors of the heart can be altered. For example, scars following a myocardial infarction can lead to the formation of reentry circuits overriding the sinus node as the heart pacemaker and resulting

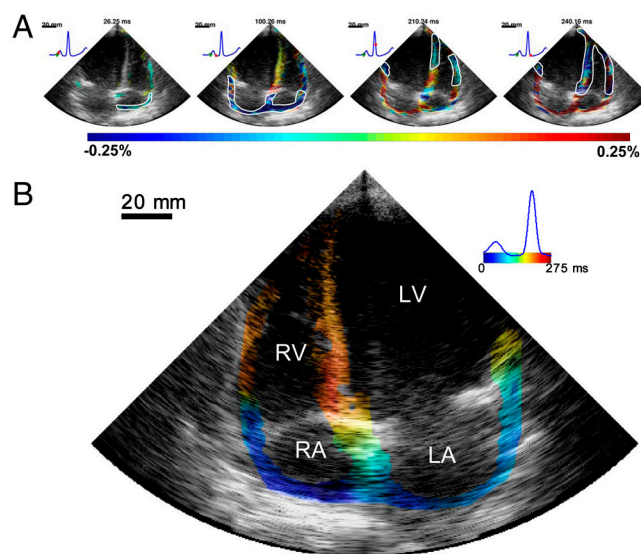


Fig. 5. Normal sinus rhythm in a healthy volunteer (23 y-old female). (A) The EW first occurred in the right atrium and propagated toward the left atrium (blue). This resulted in prestretching of the ventricles (red). The EW then appeared at the midlevel in the septum and close to the apex in the right-ventricular wall, and then propagated toward the apex and the base. (B) Corresponding isochrones. The earliest activation occurred in the right atrium. In the ventricles, it was possible to identify multiple regions of early activation, namely at the midlevel of the septum, near the apex of the right ventricle, and close to the base in the lateral wall. RA, right atrium; LA, left atrium.

the incremental displacements measured in the overlapping line of two sectors obtained at different heartbeats to synchronize the sectors. More specifically, the acquisition sequence is designed such that each sector contains at least one ultrasound beam that is also part of the following sector. Therefore, this overlapping beam is expected to result in identical (or highly similar) axial displacements whether they corresponds to heartbeat h that occurred when sector s was acquired or to heartbeat $h + 1$ that occurred when sector $s + 1$ was acquired. By comparing, over time, the displacements obtained in the overlapping beams, one can obtain the time delay corresponding to the maximum cross-correlation coefficient to synchronize each set of neighboring sectors. The procedure is repeated for each pair of sectors, allowing the reconstruction of the full-view of the heart, hence ensuring the continuity of the transition incremental displacements across sectors. This method does not rely on the ECG. Therefore, it is especially useful in cases where the ECG may be unavailable or too irregular to perform ECG gating (16). The axial incremental strains were then obtained by taking the spatial derivative of incremental strains in the axial direction using a least-squares estimator (35) with a kernel equal to 6.75 mm (Fig. 1D). The myocardium was segmented using an automated contour tracking technique (36), and displacement and strain maps were then overlaid onto the corresponding B-mode images (Fig. 1E). In this study, we considered incremental strains in the Eulerian description (37); i.e., the local change in length was measured with respect to the previous frame in a fixed coordinate system. Isochrones were generated by mapping the first time at which the incremental strains crossed zero following the Q wave. More specifically, the absolute value of the incremental strains was minimized in a temporal window following the Q wave in up to 100 manually selected regions. Noisy data were excluded. Subsample resolution was obtained through spline interpolation, and Delaunay interpo-

lation was used to construct continuous isochronal maps. Two echocardiographic planes, identical to the planes imaged in the standard apical four- and two-chamber views, were imaged across the long axis of the heart. These two views were temporally coregistered using the ECG signals, spatially coregistered by an echocardiography expert, and displayed in a three-dimensional biplane view in Amira 4.1 (Visage Imaging) (Figs. 1F and 2). In humans, the same acquisition sequence and algorithms were used, with the exception that acquisition was performed using an Ultrasonix MDP system. The least-square estimator kernel size was equal to 5.22 mm. To generate videos showing only electromechanical activation (Movies S8 and S9), the sign of the strains was inverted in the regions showing negative strains (compression) at the onset of the QRS complex. Following this operation, strains larger than -0.025% were not shown. Whenever necessary to reduce registration artifacts, subjects were asked to hold their breath for up to 18 s.

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- Bers DM (2002) Cardiac excitation-contraction coupling. *Nature* 415:198–205.
- Ashikaga H, et al. (2007) Transmural dispersion of myofiber mechanics: Implications for electrical heterogeneity in vivo. *J Am Coll Card* 49:909–916.
- Cordeiro JM, Greene L, Heilmann C, Antzelevitch D, Antzelevitch C (2004) Transmural heterogeneity of calcium activity and mechanical function in the canine left ventricle. *Am J Physiol Heart Circ Physiol* 286:H1471–H1479.
- Zhang X, et al. (2005) Noninvasive three-dimensional electrocardiographic imaging of ventricular activation sequence. *Am J Physiol Heart Circ Physiol* 289:H2724–H2732.
- Ramanathan C, Ghanem RN, Jia P, Ryu K, Rudy Y (2004) Noninvasive electrocardiographic imaging for cardiac electrophysiology and arrhythmia. *Nat Med* 10:422–428.
- Berger T, et al. (2006) Single-beat noninvasive imaging of cardiac electrophysiology of ventricular pre-excitation. *J Am Coll Card* 48:2045–2052.
- Schilling RJ, Peters NS, Davies DW (1998) Simultaneous endocardial mapping in the human left ventricle using a noncontact catheter: Comparison of contact and reconstructed electrograms during sinus rhythm. *Circulation* 98:887–898.
- Tavarozzi I, et al. (2002) Magnetocardiography: Current status and perspectives. Part II: Clinical applications. *Ital Heart J* 3:151–165.
- Greenstein JL, Hinch R, Winslow R (2006) Mechanisms of excitation-contraction coupling in an integrative model of the cardiac ventricular myocyte. *Biophys J* 90:77–91.
- Rice JJ, Wang F, Bers DM, de Tombe PP (2008) Approximate model of cooperative activation and crossbridge cycling in cardiac muscle using ordinary differential equations. *Biophys J* 95:2368–2390.
- Campbell SG, Flaim SN, Leem CH, McCulloch AD (2008) Mechanisms of transmurally varying myocyte electromechanics in an integrated computational model. *Philos Transact A Math Phys Eng Sci* 366:3361–3380.
- Gurev V, Constantino J, Rice JJ, Trayanova N (2010) Distribution of electromechanical delay in the heart: Insights from a three-dimensional electromechanical model. *Biophys J* 99:745–754.
- Badke FR, Boinay P, Covell JW (1980) Effects of ventricular pacing on regional left ventricular performance in the dog. *Am J Physiol Heart Circ Physiol* 238:H858–H867.
- Wyman BT, Hunter WC, Prinzen FW, McVeigh ER (1999) Mapping propagation of mechanical activation in the paced heart with MRI tagging. *Am J Physiol Heart Circ Physiol* 276:H881–H891.
- Prinzen FW, et al. (1992) The time sequence of electrical and mechanical activation during spontaneous beating and ectopic stimulation. *Eur Heart J* 13:535–543.
- Provost J, Lee W, Fujikura K, Konofagou E (2010) Electromechanical wave imaging of normal and ischemic hearts in vivo. *IEEE Trans Med Imaging* 29:625–635.
- Shehata M, Cheng S, Osman N, Bluemke D, Lima J (2009) Myocardial tissue tagging with cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 11:55.
- Zwanenburg JJM, et al. (2004) Timing of cardiac contraction in humans mapped by high-temporal-resolution MRI tagging: Early onset and late peak of shortening in lateral wall. *Am J Physiol Heart Circ Physiol* 286:H1872–H1880.
- Walker W, Trahey G (1994) A fundamental limit on the performance of correlation based phase correction and flow estimation techniques. *IEEE Trans Ultrason Ferroelectr Freq Control* 41:644–654.
- Wang S, Lee W, Provost J, Luo J, Konofagou EE (2008) A composite high-frame-rate system for clinical cardiovascular imaging. *IEEE Trans Ultrason Ferroelectr Freq Control* 55:2221–2233.
- Pernot M, Konofagou EE (2005) Electromechanical imaging of the myocardium at normal and pathological states. *Proceedings of the 2005 IEEE Ultrasonics Symposium* (Institute of Electrical and Electronic Engineers, New York) pp 1091–1094.
- Pernot M, Fujikura K, Fung-Kee-Fung SD, Konofagou EE (2007) ECG-gated, mechanical and electromechanical wave imaging of cardiovascular tissues in vivo. *Ultrasound Med Biol* 33:1075–1085.
- Konofagou EE, et al. (2007) Noninvasive electromechanical wave imaging and conduction velocity estimation in vivo. *Proceedings of the 2007 Ultrasonics Symposium* (Institute of Electrical and Electronic Engineers, New York) pp 969–972.
- Provost J, Gurev V, Trayanova N, Konofagou EE (2011) Mapping of cardiac electrical activation with electromechanical wave imaging: An in silico-in vivo reciprocity study. *Heart Rhythm* 8:752–759.
- Durrer D, et al. (1970) Total excitation of the isolated human heart. *Circulation* 41:899–912.
- Sengupta PP, Tondato F, Khandheria BK, Belohlavek M, Jahangir A (2008) Electromechanical activation sequence in normal heart. *Heart Fail Clin* 4:303–314.
- Scher AM, Young AC (1956) The pathway of ventricular depolarization in the dog. *Circ Res* 4:461–469.
- Faris OP, et al. (2003) Novel technique for cardiac electromechanical mapping with magnetic resonance imaging tagging and an epicardial electrode sock. *Ann Biomed Eng* 31:430–440.
- Gurev V, Provost J, Konofagou EE, Trayanova N (2009) In silico characterization of ventricular activation pattern by electromechanical wave imaging. *Heart Rhythm Suppl* 6:S357.
- Ramanathan C, Jia P, Ghanem R, Ryu K, Rudy Y (2006) Activation and repolarization of the normal human heart under complete physiological conditions. *Proc Natl Acad Sci USA* 103:6309–6314.
- Ghosh S, Rhee EK, Avari JN, Woodard PK, Rudy Y (2008) Cardiac memory in patients with Wolff-Parkinson-White syndrome: Noninvasive imaging of activation and repolarization before and after catheter ablation. *Circulation* 118:907–915.
- Lee W, et al. (2007) Theoretical quality assessment of myocardial elastography with in vivo validation. *IEEE Trans Ultrason Ferroelectr Freq Control* 54:2233–2245.
- Lee W, Provost J, Fujikura K, Wang J, Konofagou EE (2011) In vivo study of myocardial elastography under graded ischemia conditions. *Phys Med Biol* 56:1155–1172.
- Kimber S, et al. (1996) A comparison of unipolar and bipolar electrodes during cardiac mapping studies. *Pacing Clin Electrophysiol* 19:1196–1204.
- Kallel F, Ophir J (1997) A least-squares strain estimator for elastography. *Ultrasound Imaging* 19:195–208.
- Luo J, Konofagou EE (2008) High-frame rate, full-view myocardial elastography with automated contour tracking in murine left ventricles in vivo. *IEEE Trans Ultrason Ferroelectr Freq Control* 55:240–248.
- Lai WM, Rubin D, Krempl E (1993) *Introduction to Continuum Mechanics* (Pergamon, Oxford), 3rd Ed.