Published in final edited form as:

Ultrasonics. 2010 February ; 50(2): 208–215. doi:10.1016/j.ultras.2009.09.026.

Noninvasive electromechanical wave imaging and conduction-relevant velocity estimation *in vivo* (ICU 2009/Laugier)

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Abstract

Electromechanical Wave Imaging is a novel technique for the noninvasive mapping of conduction waves in the left ventricle through the combination of ECG gating, high frame rate ultrasound imaging and radio-frequency (RF)-based displacement estimation techniques. In this paper, we describe this new technique and characterize the origin and velocity of the wave under distinct pacing schemes. First, *in vivo* imaging (30 MHz) was performed on anesthetized wildtype mice (n=12) at high frame rates in order to take advantage of the transient electromechanical coupling occurring in the myocardium. The RF signal acquisition in a long-axis echocardiographic view was triggered on the R-wave peak of the mouse electrocardiogram (ECG) and yielded an ultra-high RF frame rate of 8000 fps. The ultrasound RF signals in each frame were digitized at 160 MHz. Axial, frame-to-frame displacements were estimated using 1D cross-correlation (window size of 240 microns, overlap of 90%). Three pacing protocols were sequentially applied in each mouse: 1) sinus rhythm (SR), 2) right-atrial (RA) pacing and 3) right-ventricular (RV) pacing. Pacing was performed using an eight-electrode catheter placed into the right side of the heart with the capability of pacing from any adjacent bipole. During a cardiac cycle, several waves were depicted on the electromechanical wave images that propagated transmurally and/or from base to apex, or apex to base, depending on the type of pacing and the cardiac phase. Through comparison between the ciné-loops and their corresponding ECG obtained at different pacing protocols, we were able to identify and separate the electrically induced, or contraction, waves from the hemodynamic (or, blood-wall coupling) waves. In all cases, the contraction wave was best observed along the posterior wall starting at the S-wave of the ECG, which occurs after Purkinje fiber, and during myocardial, activation. The contraction wave was identified based on the fact that it changed direction only when the pacing origin changed, i.e., it propagated from the apex to the base at SR and RA pacing and from base to apex at RV pacing. This reversal in the wave propagation direction was found to be consistent in all mice scanned and the wave velocity values fell within the previously reported conduction wave range with statistically significant differences

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between SR/RA pacing (0.85 ± 0.22 m/s and 0.84 ± 0.20 m/s, respectively) and RV pacing (-0.52 ± 0.31 m/s; $p < .0001$). This study thus shows that imaging the electromechanical function of the heart noninvasively is feasible. It may therefore constitute a unique noninvasive method for conduction wave mapping of the entire left ventricle. Such a technology can be extended to 3D mapping and/or used for early detection of dyssynchrony, arrhythmias, left bundle branch block, or other conduction abnormalities as well as diagnosis and treatment thereof.

Keywords

Cross-correlation; displacement; electromechanical; left ventricle; myocardial; pacing

A. Introduction

The emergence of cardiac resynchronization therapy (CRT) as a commonly used treatment modality has focused attention on the development of noninvasive techniques that can precisely map electrical propagation and the resulting contractile patterns of the left ventricle in order to better assess a patient's candidacy for such a device. While direct imaging of electrical propagation would be ideal, currently available methods are unsuitably invasive [1–3, 5,6]. Attention has therefore turned to contractile imaging techniques such as M-mode and tissue Doppler echocardiography⁷. However, these modalities have the disadvantage of having limited spatial and temporal resolution.

Sudden cardiac death results from an abrupt loss of heart function (cardiac arrest). The victim may or may not have previously diagnosed heart disease. About 310,000 people a year die of coronary heart disease (CHD) without being hospitalized or admitted to an emergency room. This is about half of the total deaths occurring as a result of CHD — about 850 Americans each day, i.e., about 1 American every 2 minutes (<http://www.americanheart.org>). All known heart diseases can lead to cardiac arrest and sudden cardiac death. Despite this high mortality, there is currently no imaging modality that can directly and noninvasively map the conduction wave in the entire heart or its disruption in the presence of an abnormality or disease. Standard techniques such as electrocardiography (ECG) can be inconclusive and/or insensitive. The situation is particularly grave for patients with heart failure (HF), where morbidity and mortality rates remain exceptionally high [1]. Fifty percent of patients die within 5 years of being diagnosed. Among the HF population, the most common electromechanical disorder is the bundle branch block (BBB). The ability to non-invasively image conduction in the failing heart would thus significantly improve the diagnosis, treatment and management of this condition. In a normal heart, the contraction wave follows a specific pattern of activation sequentially so that systole can start. In a pathological heart, this contraction wave pattern will be disrupted at the site of the abnormality, e.g., due to BBB, arrhythmia or ischemia, and, if mapped correctly, the pathological region can be identified and localized. If this region is detected early, it can be treated in a timely manner and cardiac arrest could be avoided.

However, currently, there are no noninvasive electrical conduction mapping techniques of the heart that can be applied diagnostically in a clinical setting. The only methods currently

available for conduction mapping *in vivo* involve the use of contact electrode arrays, either by mounting an electrode sock around the heart through open-heart surgery [2,3] or reconstruction from body surface potentials [4] to map the epicardial activation or, using a balloon electrode catheter through catheterization for endocardial mapping [5,6]. However, none of the medical imaging techniques clinically available provide conduction mapping, since, as indicated above, this would require invasive procedures, which are not typically used diagnostically. Conventional echocardiography using M-mode, Tissue Doppler and other methods offer the capability of assessing electromechanical dyssynchrony as an indication of arrhythmia and is used to monitor the performance of such treatments such as Cardiac Resynchronization Therapy (CRT) [7]. M-mode echocardiography is often effective in examining intraventricular dyssynchrony [7]. For example, it is possible to compare the activation times of the posterior and septal walls by noting the times of peak contraction in the case of a left bundle branch block (LBBB). Due to electromechanical coupling, a mechanical delay is a direct consequence of a delayed electrical activation – a chief symptom of LBBB. Although no single standard exists, a septal-to-posterior wall motion delay of 130ms has been suggested as a marker of intraventricular dyssynchrony [7]. Tissue Doppler is another ultrasound-based technique used to indirectly detect conduction abnormalities by successfully identifying time delays at which peak displacement or strain rate occurs in distinct segments of the heart [7]. After treatment, these delays are used as indices to verify whether they were reduced to minimal or normal range values. However, none of the aforementioned technique images the conduction wave or directly characterizes the electrical function.

The only non-contact imaging technique that can directly map the conduction wave is optical imaging. Optical imaging techniques use voltage-sensitive dyes, which bind to cardiac cell membranes and following illumination, fluoresce if the cell undergoes electrical activation, thus allowing the assessment of the cardiac electrical function. Optical imaging techniques are capable of reliably mapping the conduction wave as well as re-entrant activity in the epicardial and subepicardial cell layers [8,9]. These techniques can be applied at the organ, cellular, and subcellular levels. However, due to the fact that optical imaging techniques are affected by mechanical artifacts, they require the use of an electromechanical decoupler that inhibits cardiac contraction during imaging. As a result, conduction mapping using optical imaging can only be applied in excised hearts. Typically, an isolated, Langendorff-perfused animal (e.g., mouse, rabbit, pig) heart is stimulated by an electrode at the right atrium or epicardium in order to simulate the sinus rhythm or pacing. The action potentials on the epicardial surface are recorded in a specific imaging field-of-view (e.g., from $2 \times 2 \text{ mm}^2$ to $3 \times 3 \text{ cm}^2$, although panoramic imaging systems recording from the entire anterior or posterior surface of the heart have recently been implemented), after perfusion with voltage-sensitive dyes. The isochronal, or isophase, maps of activation, or depolarization, sequence, conduction direction and velocity are obtained through spatiotemporal analysis [10, 11]. Due to depth penetration and mechanical artifact limitations, optical imaging is typically performed on the epicardial surface of *ex vivo* perfusion models and cannot map the cardiac electrical activity *in vivo* [8, 9]. Therefore, optical imaging cannot be used as a diagnostic technique in humans.

In summary, 2D conduction mapping has been restricted to *in vivo* invasive techniques that entail the use of epicardial electrode measurements or to perfused heart models using optical imaging. The main reason for the lack of noninvasive techniques for accurate electrical mapping lies in the fact that standard imaging modalities are either limited by the penetration depth (i.e., optical techniques) or by the frame rate required (conventional ultrasound or MRI). In other words, the currently available noninvasive techniques cannot map the electrical conduction or depict the propagation of the conduction during systole or diastole due to slow frame rates and inadequate precision of the motion estimation techniques.

Electromechanical wave imaging has been shown capable of noninvasively mapping contractile wavefronts in the left ventricles of mice with a temporal and spatial resolution that exceeds currently available echocardiographic techniques [12–15]. Preliminary feasibility of applying this technique to human subjects has also been shown [15]. In this paper, we aim at accurately identifying and confirming the nature and origin of the imaged contractile wavefronts in the mouse heart.

B. Methods

B.1. Animal Preparation

In this study, approved by the Institutional Animal Care and Use Committee of Columbia University, twelve wild-type C57BL/6 mice were anesthetized with 50 mg/kg intraperitoneal injection of sodium pentobarbitol. Each mouse was placed supine on an ECG platform and the ECG was simultaneously and continuously acquired during the entire imaging process (Fig. 2(a)). Under a microscope, the skin of the mouse was incised and using a combination of blunt and sharp dissection, the internal jugular vein was exposed. It was then tied off distally, and a purse string suture was placed proximally. Pacing was achieved after catheterization through the right side of the heart (Fig. 2(c)). Using microscissors, a veinotomy was performed and an octapolar catheter was introduced into the internal jugular vein and then into the heart. The catheter carried eight electrodes (Fig. 2(b)) that could be separately activated for varying the pacing location (Fig. 2(c)). Once the position of the catheter was confirmed using a combination of the morphology of the intracardiac electrograms and surface ECG morphology during ventricular pacing, the catheter was secured by tying down the proximal suture. In some of the ultrasound scans, the catheter could be detected within the imaging field-of-view, allowing thus imaging of the pacing location and the resulting wave.

B.2. Ultrasound RF Data Acquisition and Pacing Protocols

A previously developed high frame-rate data acquisition system was used in this study [16–17]. After hair removal, a 30-MHz ultrasound sector probe (Vevo 770, VisualSonics Inc., Toronto, ON, Canada) was placed on the mouse chest in the parasternal position to obtain a longitudinal (long-axis) view of the murine left ventricle (Fig. 2(a)). Degassed ultrasound gel (Aquasonic 100, Parker Laboratories, Inc., Orange, Fairfield, NJ) was used as a coupling medium. The field of view was equal to $12 \times 12 \text{ mm}^2$, the axial resolution was equal to $50 \text{ }\mu\text{m}$ and the lateral resolution was equal to $115 \text{ }\mu\text{m}$. In order to align the image acquisition

orientation with the path of electrical activation (Fig. 1), long-axis views of the left ventricle were used as shown in Fig. 1.

In the EKV™ (ECG-based kilohertz visualization) mode provided by the Vevo system, the transducer worked on a line-by-line basis, i.e., the ultrasound RF signals were acquired at a pulse-repetition frequency (PRF) of 8 kHz at each position of the transducer (Fig. 3). After acquisition over one cardiac cycle, the transducer element changed position and the same acquisition was triggered on the R-wave of the ECG at the new position. This was repeated sequentially until the entire field of view, i.e., long-axis view of the left ventricle, was completed. Synchronization of the individual RF signals was achieved through ECG gating (Fig. 3A). Using this technique, a total of 190 RF signals were acquired at the pulse-repetition frequency (PRF) of 8 kHz over the course of approximately 7 min, yielding an RF frame rate of 8000 frames/s (or, temporal resolution of 0.125 ms). A two-channel, 14-bit waveform digitizer (CompuScope 14200, Gage Applied Technologies, Inc., Lachine, QC, Canada) was used to simultaneously acquire the RF signals and the corresponding ECG at 160 MSamples/s at each transducer location. The average heart rate of the mice was on the order of 350 beats/minute (bpm). After data acquisition, all acquired RF signals were gated between two consecutive R-waves in the ECG to reconstruct the entire RF image sequence corresponding to a complete cardiac cycle at the extremely high frame rate of 8000 fps [16–17]. This allowed for calculation of wave speeds up to 96 m/s in a 12×12 mm² field of view [18], which was well above the speeds of the physiological waves to be imaged in the heart (0.5–1 m/s) [19]. Each one of the twelve mice underwent all three protocols sequentially, i.e., it was initially imaged during sinus rhythm (SR) (i.e., at the natural pacing of the heart at a period of 170 ms), then right-atrial (RA) pacing (at 120 ms) and, finally, right-ventricular (RV) pacing (at 120 ms) (Fig. 1). When pacing, shorter periods are typically used in order to override the sinus rhythm period so that the natural and induced pacing of the heart do not counteract one another. An intermittent period of 1–2 min was used between consecutive pacing schemes to allow for normal myocardial function to be reinstated.

B.3. Ultrasound RF data processing

The axial displacement between consecutive RF frames (Fig. 3) was estimated off-line using a 1D normalized cross-correlation function [20]. In the ultrasonic view selected (i.e., long-axis), except at the apex, the axial direction corresponded to the radial orientation, i.e., in the direction towards the centroid of the left-ventricular cavity in the image plane used. The RF window size was equal to 240 μm, while the window overlap was equal to 90%, deemed high enough to retain high axial resolution [21]. Axial resolution of the resulting displacement image has been shown to be highly dependent on the window overlap used. The aforementioned displacements were the instantaneous, or incremental, displacements (Fig. 3) occurring between two consecutive frames, i.e., at time intervals of 0.125 ms apart. The frame rate was kept at 8000 fps as every RF frame was used for motion estimation. In addition, using a previously developed technique by our group, manually-initialized endocardial borders in the left ventricle could be automatically tracked throughout the entire cardiac cycle to better delineate the myocardial wall region [22]. In this method, the pre-defined borders are automatically tracked based on the displacements estimated using the same cross-correlation technique. Ciné-loops of the incremental displacements were

generated to map the wave propagation and overlaid onto the corresponding B-mode images for visualization. The propagating wavefront was identified as the change from positive (i.e., upwards denoting diastole) to negative (i.e., downwards denoting systole) motion, or vice versa. In other words, unless the electromechanical wavefront propagates through a specific region, the motion of that region will continue in the same direction, i.e., the myocardium will continue within the same phase (systole or diastole). All aforementioned methods were implemented in MATLAB 7.1 (MathWorks, Inc., Natick, MA, USA).

C. Results

Throughout the entire cardiac cycle, several different waves were visualized that could be categorized as electrically or hemodynamically induced. The most pronounced wave propagating during sinus rhythm (Fig. 4) and right-atrial pacing (Fig. 5) was the contraction wave, or wave originating at the isovolumic contraction phase, that propagated along the longitudinal direction of the heart initiating inward radial motion, or thickening (i.e., contraction), in its path. Positive displacements (in red) denote motion towards the transducer whereas negative displacements (in blue) denote motion away from the transducer. The ECG is provided in each case in order to determine the cardiac phase, at which the wave is visualized. The contraction wave started at the apex right at the beginning of the QRS complex, propagated along the septum and then the left-ventricular posterior wall. Therefore, in a long-axis view, the wave propagation along the posterior wall was shown to occur from apex to base (Figs. 4 and 5). Right-ventricular (RV) pacing (Fig. 6) induced a reverse wave direction with two waves propagating from base to apex during the same cardiac phase: one along the septum and one along the posterior wall (Fig. 6). This reversal in the wave propagation direction was found to be consistent in all mice scanned and paced. The wave velocity was then calculated in each one of the cases shown in Figs. 4–6 by tracking the wavefront (identified by the white arrow in each case), estimating its displacement between the consecutive frames shown and dividing it by the frame period. The wave velocities were found to be within the reported conduction wave range [19] with statistically significant differences between SR/RA pacing (0.85 ± 0.22 m/s and 0.84 ± 0.20 m/s), respectively and RV pacing (-0.52 ± 0.31 m/s; $p < 0.0001$) (Fig. 7). This was also verified by other animal studies, where RV pacing has been shown to both slow down the wave and reduce the efficiency of cardiac contraction [25]. Depolarization induces thickening, repolarization induces thinning, which can also be mapped (Fig. 8) and measured in a similar way as what was shown during depolarization, both from base to apex (Fig. 8(i)) and from endocardium to epicardium (Fig. 8(ii)).

D. Discussion and Conclusion

Arrhythmias and bundle branch blocks affect more than 5 million Americans, and 550,000 new cases are diagnosed each year. Despite this widespread nature of these diseases, there is no reliable imaging technique that can image the normal or abnormal conduction. Contraction and relaxation activation are transient phenomena that occur prior to systole and diastole, respectively. The action potential initiated by the sinoatrial node travels along the bundle of His to the right and left bundles and finally to the Purkinje fibers at an

approximate speed of ~0.5 m/s, inducing depolarization, and hence contraction, in its path. In systole, this occurs during isovolumic contraction (IVC), which lasts approximately 10 ms and 80 ms in mice and humans, respectively. In diastole, it occurs during isovolumic relaxation (IVR), which typically has similar durations as IVC. In order to map the resulting wave, and thereby its potential blocks or re-entries, ultra-fast imaging needs to be performed in order to ‘capture’ the wave during propagation. Optical imaging can achieve such frame rates. However, for clinical, diagnostic imaging, in addition to high temporal resolution, noninvasive and deep-penetrating imaging is required. Despite the urgent need for properly diagnosing aforementioned pathologies and subsequent efficacy of their treatment, currently available imaging techniques do not directly map the conduction waves and instead are limited to depicting an indirect, overall functional abnormality or are restricted by depth penetration constraints.

In this paper, an ultra-high frame rate imaging study was carried out and the localized motion of the myocardium resulting from electromechanical coupling during both depolarization (end-diastole) and repolarization (end-systole) was imaged in mice. The transient nature of the wave captured on the electromechanical wave images is in sharp contrast to strain imaging techniques that typically accumulate the overall peak strain, or strain rate, in the myocardium and ignore the transient effects or electrical activation altogether. In mice, strong contraction waves were imaged at 8000 fps in the septum and the posterior wall and were depicted to maintain or change direction depending on the pacing scheme induced. The contraction wave changed direction only when the pacing origin changed, i.e., it propagated from apex to base at SR and RA pacing and from base to apex at RV pacing. This reversal in the wave propagation direction was reproducible in all 12 mice used in the study. More importantly, the wave velocities, which were measured to average around 0.84 m/s (± 0.21 m/s) in the sinus rhythm and RA pacing cases, were found to be well within the reported conduction wave velocity range in murine myocytes *in vitro* (0.84 m/s) [19]. These preliminary results indicate that through the electromechanical coupling, high precision motion estimation at high frame rates may yield a novel, non-invasive method for conduction mapping of the live myocardium, diagnosis of related diseases and quantitative analysis of the electrophysiological function.

This study demonstrates thus that the new technique of Electromechanical Wave Imaging may constitute a unique noninvasive method for clinical conduction wave mapping of the entire left ventricle and has potential in identifying as well as reliably mapping and quantifying normal and abnormal conduction patterns. Such a technology can easily be implemented for noninvasive 2D mapping of the same wave under dyssynchrony, arrhythmia or other conduction abnormalities, such as right- and left-bundle branch blocks, as well as treatment such as cardiac resynchronization therapy, radiofrequency ablation or pharmacological treatment. It is important to note that the Electromechanical Wave Imaging technique measures mechanical contraction, not electrical action potentials. There is naturally a delay between the electrical and the mechanical response, which is defined as the electromechanical delay [20]. The electromechanical delay is equal to 28 ms when measured using myocytes *in vitro* and we have recently demonstrated that the electromechanical delay

measured with Electromechanical Wave Imaging *in vivo* is very similar to what is measured using electrosonomicrometry [26].

Compared to existing techniques used to detect conduction abnormalities, the Electromechanical Wave Imaging method could serve as complementary tool. For example, bundle branch blocks can be reliably detected using a 12-lead ECG but cannot be currently quantified or precisely localized. Electromechanical Wave Imaging could be used to confirm both the occurrence of the abnormality, its size and its location. Another method, Tissue Doppler, can currently determine whether two regions of the ventricle are synchronous but cannot map the propagation of the underlying conduction waves in those regions and localize a conduction abnormality. Electromechanical Wave Imaging could help further confirm and assess dyssynchrony and validate efficacy of treatment techniques such as cardiac resynchronization therapy. Finally, Electromechanical Wave Imaging will be tested as to its potential of detection of arrhythmia origins and thereby guidance of RF ablation wire placement. The proposed imaging technique could thus serve as a unique tool for clinicians for diagnosis and treatment monitoring and assessment as well as understanding and linking electrical to mechanical abnormalities and vice versa. An important drawback lies with the ECG gating technique used, whereby signals and sectors from different cardiac cycles are used, the method assumes that the electromechanical wave pattern is repeatable over multiple cardiac cycles. In such cases as ventricular fibrillation and occurrence of meandering single spiral waves, the patterns will not necessarily be periodic across multiple cardiac cycles and the method may not be as applicable. In order to overcome such limitations, the novel technique of motion-matching was recently developed by our group [26] that relies on RF frame reconstruction based on the displacements estimated, not the corresponding ECG signals, and has been successfully shown to generate composite frames independent of the repeatability of the ECG. Together with the fact that the Electromechanical Wave Imaging technique has been successfully implemented in a clinical scanner and been shown to identify similar waves in humans [15], we believe that this technique holds great promise and offers a unique opportunity for noninvasively mapping the conduction patterns in the heart across different species, both at its normal and pathological state and during treatment.

Acknowledgments

This study was supported in part by the American Heart Association (SDG 0435444T), the Wallace H. Coulter Foundation (WHCF CU02650301) and the National Institutes of Health (R01-EB006042). We wish to express our sincere appreciation to Shunichi Homma, M.D., Department of Medicine at Columbia University for kindly allowing us access to the Vevo 770 scanner and Viktor Gamarnik, B.S., Department of Biomedical Engineering at Columbia University for help with the literature search.

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Figure 1.

The cardiac conduction system (Purkinje network is shown in yellow) of the heart indicating the three pacing origins (small blue rectangles) and the left-ventricular ultrasound imaging plane (green rectangle) used in the study.

Figure 2.

a) Picture of the setup used in the mouse experiments; b) Illustration of the 8-electrode catheter used with magnification in the white rectangle shown on the image on the right showing all eight electrodes c) Localization of the 8-electrode catheter in the right ventricle of the mouse heart during the experiments. In blue is denoted the Purkinje network.

Figure 3.

A) RF line acquisition at multiple transducer locations (three examples are shown here): each line is synchronized relative to the R-wave (T_0); B) Multiple frame reconstruction from ECG-gated RF data. Reconstructed RF frames were acquired at a composite frame rate of 8000 frames/s (fps) and analyzed with cross-correlation techniques to produce wall displacement images (overlaid color images).

Figure 4.

Sinus rhythm (170 ms): Red denotes motion upwards while blue denotes motion downwards, indicating sequence of contraction of the myocardium from a) to d). Note that the contraction starts at the apex (left-most tip of the left-ventricle) in (a) and propagates along the posterior wall (not the septum), finally covering the entire posterior wall in (d). [Top: septum, Bottom: posterior wall]. The red dot on the ECG denotes the time occurrence of the corresponding image.

Figure 5.

Right-atrial pacing at 120 ms: Note the slight difference in the propagation due to the change of origin (pacing now is from a region closer to the middle of the right atrium, i.e., below the sinoatrial node) and the field of view. A similar wave to that seen propagating along the posterior wall in Fig. 4 can also be seen from (a) to (d), indicating that the origin is similar to the case in Fig. 4. The red dot on the ECG denotes the time occurrence of the image above it.

Figure 6.

Right-ventricular pacing at 120 ms: Note the reversal in the direction of propagation in the posterior wall due to the change of origin (pacing now is performed from the right ventricle). The wave propagates from base to apex along the posterior wall, indicating that the wave mapped was electrically induced (i.e., opposite from the natural pattern of the heart, Fig. 4). The red dot on the ECG denotes the time occurrence of the image above it.

Figure 7.

Conduction velocity measurements at sinus rhythm (n=12), RA (n=12) pacing and RV (n=12) pacing.

Figure 8.

Repolarization waves during right-ventricular pacing (120 ms): Red denotes motion upwards while blue denotes motion downwards, indicating relaxation of the myocardium from a) to d). Note that the relaxation in (i) starts at mid-level in (a) and propagates along the posterior wall finally covering the entire wall in (d) while in (ii) it propagates from the endo- to the epicardial level. The same mouse was used in both (i) and (ii). The wave from base to apex along the posterior wall occurs first (i) followed by the transmural propagation in the septum (ii).