

Validation of electromechanical wave imaging in a canine model during pacing and sinus rhythm



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BACKGROUND Accurate determination of regional areas of arrhythmic triggers is of key interest to diagnose arrhythmias and optimize their treatment. Electromechanical wave imaging (EWI) is an ultrasound technique that can image the transient deformation in the myocardium after electrical activation and therefore has the potential to detect and characterize location of triggers of arrhythmias.

OBJECTIVES The objectives of this study were to investigate the relationship between the electromechanical and the electrical activation of the left ventricular (LV) endocardial surface during epicardial and endocardial pacing and during sinus rhythm as well as to map the distribution of electromechanical delays.

METHODS In this study, 6 canines were investigated. Two external electrodes were sutured onto the epicardial surface of the LV. A 64-electrode basket catheter was inserted through the apex of the LV. Ultrasound channel data were acquired at 2000 frames/s during epicardial and endocardial pacing and during sinus rhythm. Electromechanical and electrical activation maps were

synchronously obtained from the ultrasound data and the basket catheter, respectively.

RESULTS The mean correlation coefficient between electromechanical and electrical activation was 0.81 for epicardial anterior pacing, 0.79 for epicardial lateral pacing, 0.69 for endocardial pacing, and 0.56 for sinus rhythm.

CONCLUSION The electromechanical activation sequence determined by EWI follows the electrical activation sequence and more specifically in the case of pacing. This finding is of key interest in the role that EWI can play in the detection of the anatomical source of arrhythmias and the planning of pacing therapies such as cardiovascular resynchronization therapy.

KEYWORDS Arrhythmias; Electromechanical activation; Electrical mapping; Ultrasound; Noninvasive imaging; Pacing; Canine model
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Introduction

Cardiac arrhythmia is experienced by approximately 5.8 million people per year in the United States.¹ Electrocardiography (ECG) is widely used to noninvasively detect and diagnose cardiac arrhythmia. However, ECG has a low spatial resolution and cannot always accurately determine the location of the regions triggering arrhythmia. Surgical ablation of arrhythmias involves catheterization of the heart and detailed endocardial mapping to determine the source of the arrhythmia, which may be time-consuming, operator-dependent, and limited by accessibility of the tissue. Once the source of the arrhythmia is found, radiofrequency (RF) ablation can be used to terminate the arrhythmia. However, the procedure is highly dependent on the ability of the clinician to accurately determine the location of the

arrhythmogenic source. A time-effective and noninvasive method to identify the candidate regions for ablation could significantly decrease the duration of the procedure. ECG has been developed to map the electrical activity of the heart at high spatial resolution noninvasively.² However, this technique requires special hardware as well as computed tomography and/or magnetic resonance imaging scans.

Electromechanical wave imaging (EWI) is an ultrasound-based technique that can noninvasively map the minute deformation of the myocardium resulting from local electrical activation at high temporal resolution. The terminology *EWI* is preferred to *mechanical wave imaging* to avoid possible confusion with other mechanical waves propagating in the myocardium resulting from mitral or aortic valve closure³ or from blood-wall interaction and to be distinguished from time to peak strain.⁴ Previous feasibility studies have shown that EWI is capable of transmurally mapping the electromechanical activation sequence during sinus rhythm and pacing, localizing pacing sites,^{5,6} characterizing arrhythmias in cardiac resynchronization therapy (CRT) and in patients with atrial flutter,⁷ and mapping the electromechanical activation during reentrant and focal arrhythmias.⁸ It has been reported

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that 20%–40% of patients do not respond to CRT.⁹ Several studies reported a strong influence of the pacing lead placement on CRT response.¹⁰ Therefore, EWI could prove to be of key interest in providing assistance in optimizing lead placement by mapping the electromechanical activity of the heart during the procedure.

In the myocardium, local electrical activation is followed by a localized minute muscle contraction after a delay in the order of tens of milliseconds.¹¹ It is hypothesized that EWI can detect the onset of contraction because of its high axial and temporal resolution. This technique is different from the onset of shortening obtained from the strain curves with speckle tracking echocardiography (STE) or tissue Doppler imaging.^{12,13} For STE, envelope-detected signals are used typically with a frame rate of 50–70 Hz,¹⁴ although for both STE and tissue Doppler imaging higher frame rates can be obtained at the cost of a reduced field of view. In this study, EWI is performed with interframe strain obtained from RF signals that preserve the phase information and at a frame rate of 2000 Hz with a full field of view, which allows for capturing the onset of contraction in response to electrical activation. Previous studies from our group reported a good correlation between electromechanical activation determined by EWI and electrical activation measured by epicardial or endocardial electrodes sutured on the heart.^{5,6} These previous initial feasibility studies, however, were limited to a low number of subjects and limited recording sites and imaging planes. A dedicated validation study with different pacing configurations and a higher number of subjects, recording sites, and imaging planes has yet to be carried out. Multiple ultrasound imaging planes and higher-density electrical mapping of the endocardial surface allow for better rendering of the electromechanical and electrical activation of the endocardial surface, respectively. This would also allow for mapping of the distribution of electromechanical delays. The objectives of this study were to investigate the relationship between the electromechanical and the electrical activation of the endocardial surface of the canine left ventricle (LV) during epicardial and endocardial pacing and during sinus rhythm as well as to map the distribution of electromechanical delays.

Methods

Animal preparation

The study was approved by the Institutional Animal Care and Use Committee of Columbia University and conforms to the *Guide for the Care and Use of Laboratory Animals*. Six canines (weighing 24.1 ± 0.4 kg) were premedicated with diazepam (0.5–1 mg/kg) injected intravenously and subsequently anesthetized with an intravenous injection of propofol (2–5 mg/kg). The canines were mechanically ventilated with a rate- and volume-regulated ventilator on a mixture of oxygen and titrated 0.5%–5% isoflurane. Lidocaine (50 μ g/(kg·min)) was injected intravenously throughout the procedure and until the end of the experiment to minimize the occurrence of ventricular arrhythmia. A left lateral thoracotomy was performed with electrocautery, and 1 rib was removed to expose the heart. Two external bipolar electrodes were sutured onto the epicardial

surface of the LV in the vicinity of the anterior and lateral regions (Figure 1). A 38-mm diameter 64-electrode basket catheter (Constellation, Boston Scientific, Marlborough, MA) with 8 flexible splines and 8 equally spaced (3-mm) electrodes per spline was introduced into the LV through the apex. The basket catheter was carefully positioned inside the LV to optimize electrode contact with the myocardium. A suture was attached beforehand to 1 spline of the basket catheter to serve as a landmark in order to determine the location of the splines using B-mode imaging. The thoracic cavity was filled with saline for acoustic impedance matching during ultrasound data acquisition.

Pacing protocol

The epicardial electrodes were connected to a data acquisition system (DAQ 1) (NI USB-6259, National Instruments, Austin, TX), which could send a 10-V amplitude, 2-ms pulse width, and 500-ms cycle length pacing signal. The pacing signal was also acquired by the data acquisition system.

Endocardial pacing was also achieved by pacing from any electrode on the basket catheter using an Arduino board equipped with a microcontroller (Mega 2560, Arduino, Somerville, MA). An electrode with good contact with the endocardial wall was used for pacing. Only 1 electrode at a time was used for pacing. Epicardial or endocardial pacing was sustained until all echocardiographic views were acquired.

Ultrasound data acquisition

Ultrasound data were acquired either during sinus rhythm or during epicardial or endocardial pacing. Four apical views were acquired: the standard 4-, 2-, and 3-chamber views as well as the 3.5-chamber view, which is located between the 4- and the 2-chamber views. A 2.5-MHz center frequency phased array (P4-2, ATL/Philips, Andover, MA) operated by a Verasonics ultrasound system (V-1, Verasonics, Kirkland, WA) was used to acquire RF channel data at 2000 frames/s using diverging wave imaging. The ECG signal was acquired synchronously with ultrasound data using an ECG unit (77804A, HP, Palo Alto, CA) connected to another data acquisition system (DAQ 2) (NI USB-6210, National Instruments) and triggered by the Verasonics ultrasound system. A standard delay-and-sum method was used to reconstruct the entire image for each single diverging beam transmitted. Conventional B-mode images were also acquired at 30 frames/s to assist myocardial segmentation. Axial displacements in the myocardium were estimated between consecutive RF frames using normalized 1-dimensional (1D) cross-correlation¹⁵ with a window length of 6.2 mm and an overlap of 90%. Interframe axial strains were estimated from the interframe axial displacements using a least-squares estimator implemented with a Savitzky-Golay filter with a 5-mm kernel. Positive strains in the longitudinal direction indicate longitudinal lengthening, whereas negative strains indicate longitudinal shortening. During ventricular contraction, there is longitudinal shortening. Therefore, the electromechanical activation time point at a given location was defined when the temporal curve of interframe axial strain changed sign, that is, as the first zero crossing,⁵ after the onset

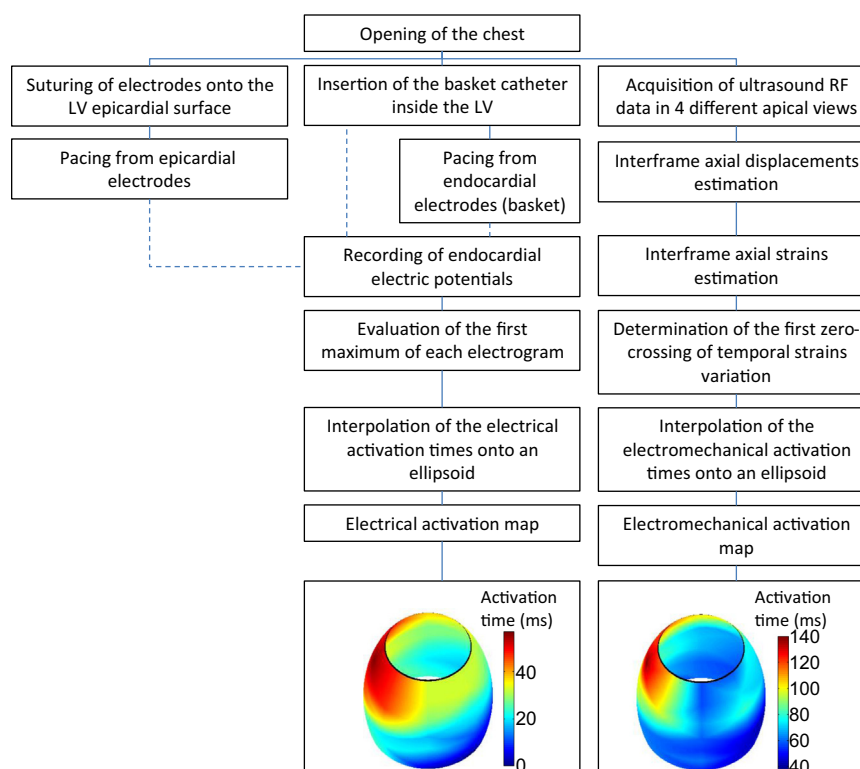


Figure 1 Flowchart of the methodology of synchronous acquisition of the electrical and electromechanical activation maps during epicardial and endocardial pacing and during sinus rhythm in the left ventricle of a canine. Regions in blue indicate early activation, and regions in red indicate late activation. LV = left ventricle/ventricular; RF = radiofrequency.

of electrical activation defined below. Isochrones of electromechanical activation were obtained for each echocardiographic view. Electromechanical activation times were obtained on the endocardial surface in the vicinity of each electrode of the basket catheter. Conventional B-mode images were used to assist for the location of the electrodes that could be seen because of their high echogenicity (Figure 2). For each ultrasound view, we tried to angle the ultrasound transducer so that the electrodes on the splines were visible on the ultrasound image. Manual selection was performed on the endocardial surface of the LV at mid-distance between each pair of electrodes to determine electromechanical activation times to be correlated with electrical activation times. Regions for which no clear zero crossing was observed or for which the catheter was pushing on the myocardium during contraction and therefore giving nonphysiological deformation were excluded.

Electrical data acquisition

The basket catheter was connected to 4 custom-built acquisition boards (2 splines per acquisition board). Bipolar electrograms were obtained from adjacent electrodes on the same spline. Bipolar signals were preferred to unipolar signals since they reduce far-field effects.¹⁶ Fifty-six bipolar electrograms (7 bipolar electrograms per spline) were multiplexed and output to DAQ 1, which was controlled using MATLAB (MathWorks, Natick, MA). Each bipolar electrogram was sampled at 1 kHz. The trigger of the Verasonics ultrasound system was also connected to DAQ

1 in order to acquire electrograms synchronously with the ultrasound data. Electrograms were high-pass filtered with a cutoff frequency of 0.5 Hz and then low-pass filtered with a cutoff frequency of 100 Hz. The maximum peak of each of the 56 electrograms regardless of polarity was determined using parabolic interpolation and defined the electrical activation times that were associated with the depolarization of the myocardium. Some electrograms were excluded because of poor electrode contact with the endocardium or

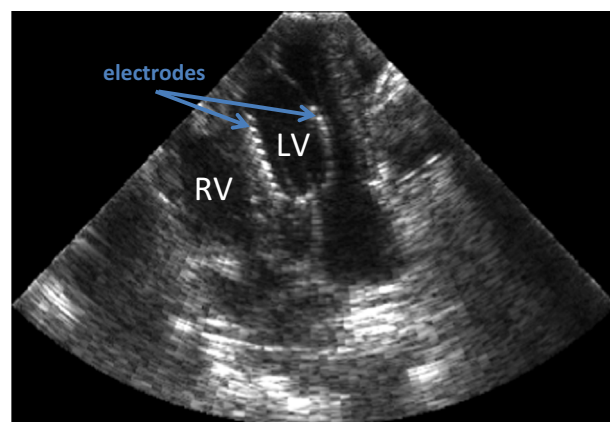


Figure 2 B-mode image of the apical 4-chamber view with the basket catheter inserted in the left ventricle. The electrodes of the basket catheter can be distinguished as bright spots because of their high echogenicity and are indicated by blue arrows at the septal and lateral walls. LV = left ventricle; RV = right ventricle.

because of damaged electrodes and were thus discarded. Peaks within the range of ± 0.5 mV were discarded.

Statistical analysis

Regions where the electromechanical or the electrical activation time could not be determined were linearly interpolated. Linear regression was performed between electromechanical and electrical activation times; the correlation coefficient, the associated *P* value, the slope, and the intercept were obtained.

Ellipsoidal rendering of activation time

Electromechanical and electrical activation times on the endocardial surface of the LV were obtained for 4 echocardiographic views. Electromechanical and electrical activation times were then linearly interpolated onto an ellipsoid of the same geometry as the basket catheter to represent the isochrones on the endocardial surface. It was assumed that the spacing between neighboring splines remained identical and constant after insertion in the LV. The propagation of the electromechanical and of the electrical activation was illustrated by depicting activated regions as a function of time on the ellipsoid.

Results

Electromechanical and electrical activation maps were obtained in the LV of 6 canines during epicardial and endocardial pacing and during sinus rhythm.

Epicardial pacing

Electrical and electromechanical activation times as well as the corresponding linear regression during epicardial pacing around the anterior region of the LV are shown in [Figure 3A](#) for 1 canine. Early activated regions are displayed in blue, whereas late activated regions are displayed in red. Both the electrical and electromechanical activation maps show that the first activated regions are located in the anterior region and the last activated regions are located approximately in the posterior region.

Electrical and electromechanical activation times as well as the corresponding linear regressions were also performed during epicardial pacing around the lateral region of the LV and are shown in [Figure 3B](#) for 1 canine. The electrical and electromechanical activation maps show that the first activated regions are located approximately in the lateral region whereas the septal region is activated last. Good agreement was observed between electrical and electromechanical activation times for both anterior and lateral epicardial pacing. The correlation coefficient, slope, and intercept for all 6 canines are listed in [Table 1](#). The mean correlation coefficient across all canines during epicardial lateral pacing was 0.79, the mean slope was 2.2, and the mean intercept was 29 ms. During epicardial anterior pacing, the mean correlation coefficient was 0.81, the mean slope was 1.8, and the mean intercept was 32 ms.

Endocardial pacing

Electrical and electromechanical activation times as well as the corresponding linear regressions were also performed during endocardial pacing from 1 electrode on the basket catheter and are shown in [Figure 3C](#) for 1 canine. Electrical activation maps indicate that activation starts in the paced region, subsequently propagating in the opposite direction. The location of the paced region differed across canines because of different choices of electrodes used to pace the ventricle. The electrical and electromechanical activation maps show a similar activation pattern. The mean correlation coefficient across all canines was 0.69, the mean slope was 1.4, and the mean intercept was 41 ms.

Sinus rhythm

Electrical and electromechanical activation times as well as the corresponding linear regressions during baseline acquisition (sinus rhythm) are shown in [Figure 3D](#) for 1 canine. The first activated regions are located approximately in the septal region, whereas the last activated regions are located approximately in the posterior-lateral region. Also, the apical region is activated before the basal region. The electrical and electromechanical activation maps show a similar activation pattern. The mean correlation coefficient across all canines was 0.56, the mean slope was 2.2, and the mean intercept was 39 ms.

Electromechanical delay

The distribution of electromechanical delays in the LV was performed during epicardial and endocardial pacing and during baseline acquisitions. [Figure 4](#) shows the distribution of electromechanical delays during epicardial anterior, epicardial lateral, and endocardial pacing as well as during sinus rhythm for the same canine described in [Figure 3](#). During epicardial and endocardial pacing, the electromechanical delay is shorter near the pacing origin while it increases with distance. During sinus rhythm, the apical region presents shorter electromechanical delays whereas the basal region presents longer electromechanical delays. The regions of shortest and longest electromechanical delays for all 6 canines are indicated in [Table 2](#).

Discussion

Noninvasive and efficient mapping of the electrical activity of the heart can improve the identification of the regions responsible for arrhythmia, which is of paramount interest to optimize their associated therapies. EWI is a high temporal resolution, ultrasound-based technique that can map the electromechanical activity of the heart. The aims of this study were to show how the electromechanical activation maps obtained with EWI can be associated with the electrical activation and to show that EWI can map the electromechanical activation during sinus rhythm and during epicardial and endocardial pacing.

During epicardial and endocardial pacing, the electromechanical and electrical activations in the LV followed a similar pattern. It was also shown that the paced region (eg, anterior) had early activation times, whereas regions farther away from the pacing site (eg, posterior) were electrically and electromechanically activated later, which

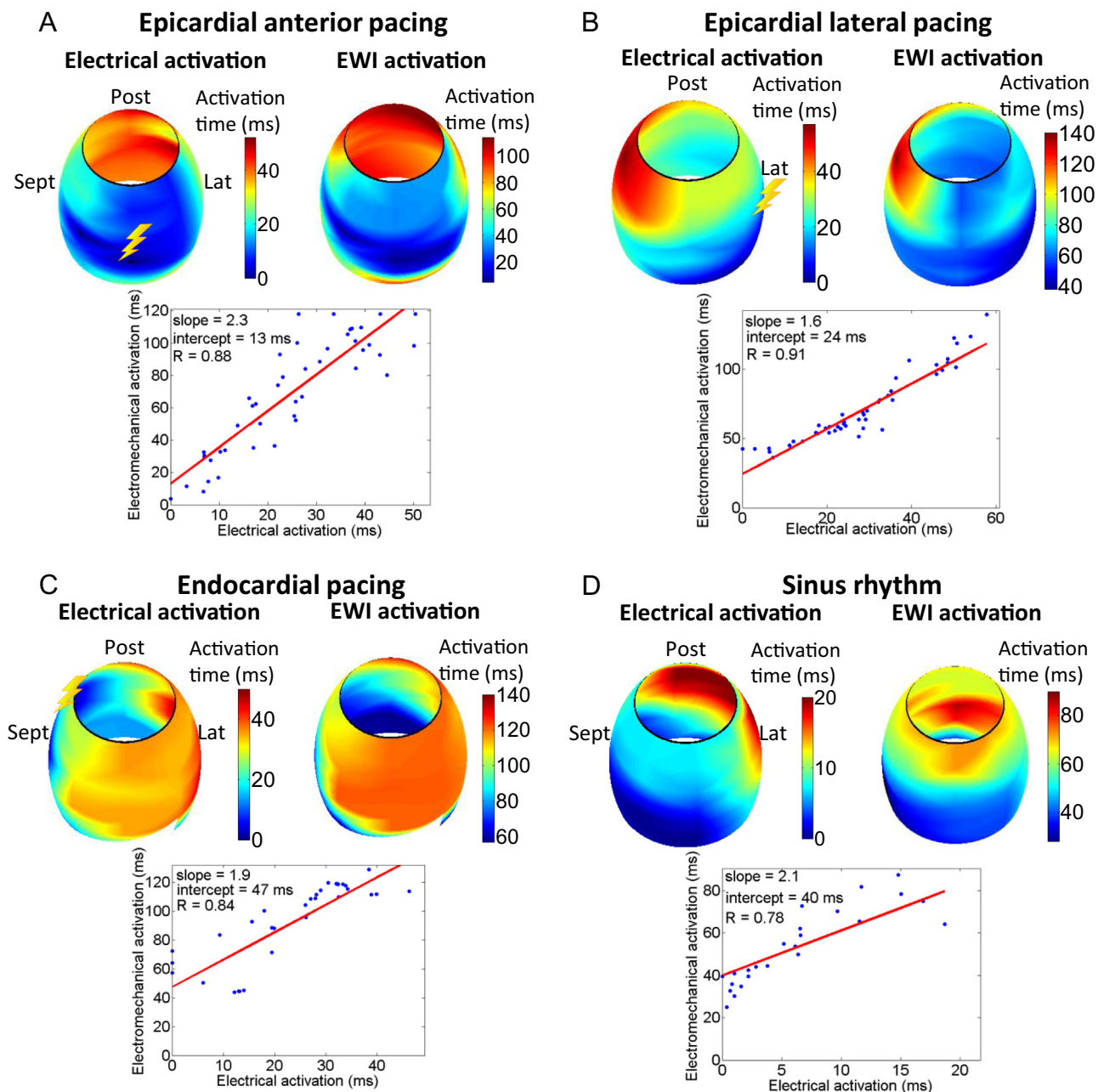


Figure 3 Electrical and electromechanical activation times in a canine left ventricle during epicardial anterior (A), epicardial lateral (B), and endocardial (C) pacing and during sinus rhythm (D). The electrical and electromechanical maps show a similar pattern in each case. Linear regression between electromechanical and electrical activation times is performed. The lightning cartoon indicates the paced region. EWI = electromechanical imaging; Lat = lateral; Post = posterior; R = correlation coefficient; Sept = septum.

is consistent with previous studies.^{17–19} The correlation coefficient across all canines for epicardial pacing ranged from 0.47 to 0.94 and had a mean value of 0.79, the mean slope was 2.0, and the mean intercept was 30 ms. EWI is thus shown to be a good surrogate for electrical mapping, confirming reports of other studies^{17,19–21} although using different definitions of electrical and mechanical activation. For endocardial pacing, the correlation coefficient ranged from 0.61 to 0.84 and had a mean value of 0.69, a mean slope of 1.4, and a mean intercept of 41 ms. Electrograms during endocardial pacing were not as sharp as those during epicardial pacing. Therefore, the activation time derived

from electrograms may be less accurate, which can partly explain the lower correlation coefficient obtained during endocardial pacing compared with the one obtained during epicardial pacing. The electromechanical delay distribution during epicardial and endocardial pacing was not homogeneous. As mentioned in a previous study, the distribution of electromechanical delays depends on the sequence of activation. The early activated regions have a shorter electromechanical delay than do the late activated regions.^{17,18,22}

For baseline acquisitions, electromechanical and electrical activation maps also showed a similar pattern. During sinus rhythm, the activation sequence was different from that during

Table 1 Linear regression results of electromechanical and electrical activation times in 6 canines during epicardial and endocardial pacing and during sinus rhythm

Variable	Dog 1	Dog 2	Dog 3	Dog 4	Dog 5	Dog 6	Mean value
Epicardial lateral pacing	$R = 0.87^{***}$ $s = 3.6$ $i = 19$ ms	$R = 0.80^{***}$ $s = 2.5$ $i = 12$ ms	$R = 0.91^{***}$ $s = 1.6$ $i = 24$ ms	$R = 0.94^{***}$ $s = 1.9$ $i = 47$ ms	$R = 0.47^{***}$ $s = 1.9$ $i = 39$ ms	$R = 0.89^{***}$ $s = 1.5$ $i = 34$ ms	$R = 0.79$ $s = 2.2$ $i = 29$ ms
Epicardial anterior pacing	NA	$R = 0.76^{**}$ $s = 1.5$ $i = 54$ ms	$R = 0.63^{**}$ $s = 1.7$ $i = 31$ ms	$R = 0.89^{***}$ $s = 2.3$ $i = 16$ ms	$R = 0.88^{***}$ $s = 2.3$ $i = 13$ ms	$R = 0.80^{***}$ $s = 1.4$ $i = 44$ ms	$R = 0.81$ $s = 1.8$ $i = 32$ ms
Endocardial pacing	$R = 0.84^{***}$ $s = 1.9$ $i = 47$ ms	$R = 0.74^{***}$ $s = 1.8$ $i = 22$ ms	$R = 0.63^{**}$ $s = 1.6$ $i = 33$ ms	NA	$R = 0.61^{**}$ $s = 0.9$ $i = 52$ ms	$R = 0.61^{**}$ $s = 0.9$ $i = 50$ ms	$R = 0.69$ $s = 1.4$ $i = 41$ ms
Sinus rhythm	$R = 0.61^{***}$ $s = 2.7$ $i = 34$ ms	$R = 0.43^{**}$ $s = 1.2$ $i = 23$ ms	$R = 0.76^{***}$ $s = 2.4$ $i = 60$ ms	$R = 0.78^{***}$ $s = 2.1$ $i = 40$ ms	$R = 0.39^{**}$ $s = 2.7$ $i = 33$ ms	$R = 0.41^{**}$ $s = 1.9$ $i = 46$ ms	$R = 0.56$ $s = 2.2$ $i = 39$ ms

Values indicate the correlation coefficient (R), the slope (s), and the intercept (i) of the regression. In 2 cases, data were not available (NA).
** $P < .01$
*** $P < 0.001$.

pacing. The first activated regions were posterior-septal, septal, and anterior-septal, and the last activated regions were anterior-lateral, lateral, and posterior-lateral. Early activation in the septal region of the LV has been previously reported.^{18,23} In addition, the apical region was activated before the basal region. This apex to base propagation is also consistent with previous studies.^{18,23,24} The correlation coefficient across all canines ranged from 0.39 to 0.78 and had a mean value of 0.56. This indicates that the electromechanical activity depicted by EWI is associated with the electrical activity obtained by endocardial electrical mapping. The mean slope of the linear regression of electromechanical activation times vs electrical activation times was 2.2, which is > 1 and indicates that electrical activation was followed by electromechanical activation. More specifically, depolarization was followed by the contraction with an increasing delay.

The mean intercept was 39 ms, indicating that the electromechanical delay in the first activated region in the ventricle was 39 ms on average. The map of electromechanical delays was obtained by representing the difference between electromechanical and electrical activation times. The distribution of electromechanical delays in the LV during sinus rhythm was different from the paced distribution. The apical region had shorter electromechanical delays than did the basal region. This observation is consistent with a previous study by Gurev et al,¹⁸ which is a simulation study using an electromechanical model.

Although similar electromechanical and electrical activation maps were found, this study presents several limitations that may affect the quantitative aspects reported herein. The orientation of the splines of the basket catheter inside the LV was determined by the specular reflection from a suture attached to one of the splines using conventional B-mode imaging. Although the reflection from the suture was not always easily identifiable, the activation maps obtained from the basket catheter by pacing from epicardial electrodes sutured at a known location were in good agreement with the expected earliest activated spline. In addition, although significant efforts to align

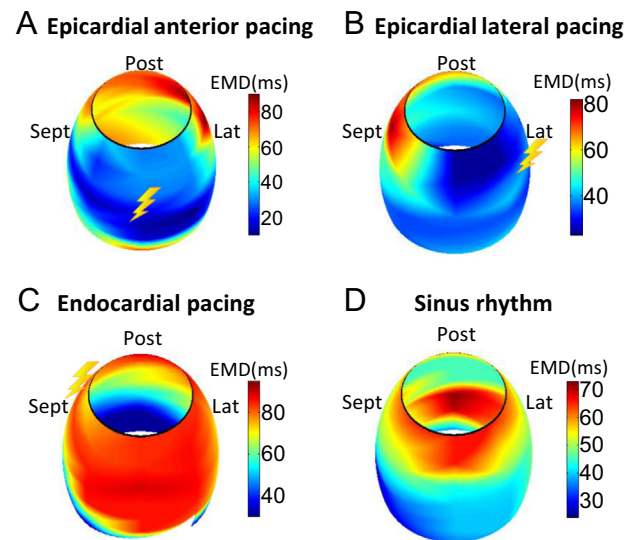


Figure 4 Electromechanical delays in a canine during epicardial anterior (A), epicardial lateral (B), and endocardial (C) pacing and during sinus rhythm (D). The electromechanical delays are shorter near the first activated regions and longer for the last activated regions. The lightning cartoon indicates the paced region. EMD = electromechanical delay; Lat = lateral; Post = posterior; Sept = septum.

Table 2 Regions of shortest and longest electromechanical delays in 6 canines during epicardial and endocardial pacing and during sinus rhythm

Variable	Dog 1	Dog 2	Dog 3	Dog 4	Dog 5	Dog 6
Epicardial lateral pacing						
Shortest	A-L	P-L	A-L	P-L	L	L
Longest	P-S	P-S	P-S	A-S	S	P-S
Epicardial anterior pacing						
Shortest	NA	A-L	A	A-L	A	A
Longest		P-S	P-L	P-S	P-L	P-S
Endocardial pacing						
Shortest	P-S	L	P-L	NA	A-L	P
Longest	A	A	A-L		S	S
Sinus rhythm						
Shortest	A-S	S	P-S	S	P-S	S
Longest	P-L	A	A-L	P	L	L

In 2 cases, data were not available (NA).
A = anterior; L = lateral; P = posterior; S = septal.

the splines of the basket catheter with the echocardiographic views were made, the alignment was imperfect. Therefore, the anatomical locations corresponding to electrical and electromechanical activation times used for correlation analysis may not optimally match. The activation propagates throughout the entire volume of the myocardium. However, the electromechanical maps were obtained from 2D echocardiographic views and the electrical measurements are obtained from 56 bipolar endocardial electrograms.

As shown in Table 1, linear regression could not be performed in 2 cases: for one canine, during epicardial pacing, ultrasound data were not saved properly and could not be processed; and for another canine, endocardial pacing was not performed.

For this basket catheter, the electrode spacing was 3 mm. Considering a conduction velocity of 0.4–0.7 m/s at the endocardium,²⁵ the time delay between 2 neighboring electrodes would be 4.3–7.5 ms for a propagation along the axis defined by the 2 electrodes. In that case, 2 temporally separated depolarization peaks can be detected on bipolar electrograms and this can yield an uncertainty in the order of the time delay between those 2 peaks for the determination of electrical activation times.

Electromechanical activation times were defined at the zero crossings on the strain curves. The zero crossings indicate the time when the myocardium locally transitions from relaxation to contraction. However, some regions may start to contract later than other regions because of distinct loading conditions or prestretched regions.²² Therefore, although a contraction force may start to develop locally after electrical excitation, the shortening of muscles may take additional time in prestretched myocardial regions. This may partly be explained by the distribution of electromechanical delays and results in a slope of > 1 for the regression analysis between electromechanical and electrical activation times.

Conclusion

This study shows that the electromechanical activation sequence determined by EWI follows the electrical activation sequence during epicardial and endocardial pacing and during sinus rhythm. A higher correlation between electrical and electromechanical activation times was obtained during pacing than during sinus rhythm. These findings indicate that EWI has great potential to noninvasively characterize and identify regions responsible for arrhythmias as well as to provide assistance during cardiac ablation and pacing therapy. Future studies will include 3D mapping of the electromechanical activation sequence.

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