Noninvasive reconstruction of the three-dimensional ventricular activation sequence during pacing and ventricular tachycardia in the canine heart

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Han C, Pogwizd SM, Killingsworth CR, He B. Noninvasive reconstruction of the three-dimensional ventricular activation sequence during pacing and ventricular tachycardia in the canine heart. Am J Physiol Heart Circ Physiol 302: H244–H252, 2012. First published October 7, 2011; doi:10.1152/ajpheart.00618.2011.—Single-beat imaging of myocardial activation promises to aid in both cardiovascular research and clinical medicine. In the present study we validate a three-dimensional (3D) cardiac electrical imaging (3DCEI) technique with the aid of simultaneous 3D intracardiac mapping to assess its capability to localize endocardial and epicardial activation sites and image global activation sequences during pacing and ventricular tachycardia (VT) in the canine heart. Body surface potentials were measured simultaneously with bipolar electrical recordings in a closed-chest condition in healthy canines. Computed tomography images were obtained after the mapping study to construct realistic geometry models. Data analysis was performed on paced rhythms and VTs induced by norepinephrine (NE). The noninvasively reconstructed activation sequence was in good agreement with the simultaneous measurements from 3D cardiac mapping with a correlation coefficient of 0.74 ± 0.06, a relative error of 0.29 ± 0.05, and a root mean square error of 9 ± 3 ms averaged over 460 paced beats and 96 ectopic beats including premature ventricular complexes, couplets, and nonsustained monomorphic VTs and polymorphic VTs. Endocardial and epicardial origins of paced beats were successfully predicted in 72% and 86% of cases, respectively, during left ventricular pacing. The NE-induced ectopic beats initiated in the subendocardium by a focal mechanism. Sites of initial activation were estimated to be ~7 mm from the measured initiation sites for both the paced beats and ectopic beats. For the polymorphic VTs, beat-to-beat dynamic shifts of initiation site and activation pattern were characterized by the reconstruction. The present results suggest that 3DCEI can noninvasively image the 3D activation sequence and localize the origin of activation of paced beats and NE-induced VTs in the canine heart with good accuracy. This 3DCEI technique offers the potential to aid interventional therapeutic procedures for treating ventricular arrhythmias arising from epicardial or endocardial sites and to noninvasively assess the mechanisms of these arrhythmias.

Ventricular arrhythmias continue to be a leading cause of death and disability, with more than 400,000 cases of sudden death annually in the United States alone. Cardiac electrophysiological mapping emerges as an important tool to aid in diagnosis [e.g., characterizing the electrophysiological substrates and mechanisms of ventricular tachycardia (VT)] and clinical management [e.g., guiding catheter ablation] or implantation of cardiac resynchronization therapy] of ventricular arrhythmias. Cardiac electrical imaging techniques provide a novel means that aims to estimate the cardiac electrical activity over the epicardial surface, the activation sequence over the epicardial and endocardial surfaces, and the activation sequence throughout the three-dimensional (3D) myocardium. Investigations have been made in modeling and imaging the 3D cardiac electrical activity with the aid of a heart cellular automaton model. Recently, a physical-model-based 3D cardiac electrical imaging (3DCEI) approach has been proposed to image the ventricular activation sequence from the inversely reconstructed equivalent current densities (ECDs) and has been rigorously validated using 3D intracardiac mapping in the rabbit heart. The present study extends the validation of this novel 3DCEI approach using a well-established 3D intracardiac mapping procedure in the canine heart, which is closer to the human heart in cardiac size and electrophysiological characteristics. Plunge-needle electrodes were placed in the left ventricle (LV) and right ventricle (RV), and the body surface potentials and intramural bipolar recordings were measured simultaneously in a closed-chest condition. Pacing was performed at the subendocardium and subepicardium of the canine ventricles. Furthermore, norepinephrine (NE) was infused to induce ventricular ectopic activities including multiform premature ventricular complexes (PVCs), couplets, and runs of nonsustained monomorphic VTs (MVTs) and polymorphic VTs (PVTs). The 3DCEI imaging results were quantitatively compared with the intracardiac mapping results to assess the imaging performance.

Materials and Methods

Canine model and experimental procedures. Healthy control canines (of either sex) were studied under a protocol of simultaneous body surface potential mapping and 3D intracardiac mapping of ventricular electrical activity. The protocol was approved by the Institutional Animal Care and Use Committees of the University of Minnesota and the University of Alabama at Birmingham. Figure 1 shows the schematic paradigm of the experiment. Each canine was anesthetized using 0.04 mg/kg intramuscular atropine and ~20 mg/kg intravenous pentothal. The animal was then intubated and placed on a ventilator. Anesthesia was maintained with 2% to 3% isoflurane delivered in 100% oxygen. Up to 124 repositionable BSPM electrodes (3M, St. Paul, MN) were uniformly placed to cover both the anterior and posterior chest, and up to 42 transmural plunge-needle electrodes were inserted in the LV and RV (up to 21 intramural sites). Each LV plunge-needle electrode contains four bipolar electrode-pairs (inter-electrode distance of 500 μm) each separated by 2.5 mm (29, 30, and

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from UFCT images for each animal, using a commercial software.

In brief, the realistic geometry heart-torso model was constructed to facilitate precise 3D localization of the transmural electrodes. The forward modeling and inverse computation of the 3DCEI approach were described previously (10, 11, 22).

Noninvasive reconstruction of the activation sequence throughout the 3D ventricular myocardium. The forward modeling and inverse computation of a detailed heart model and 3D localization of plunge-needle electrodes located at subendocardium and subepicardium of the ventricles using a specially designed junction box. Furthermore, a chest and skin were then carefully closed with a silk suture, and the mapping electrode wires were externalized above and below the sternotomy incision. Bipolar electrograms were continuously recorded from all electrode-pairs together with body surface potentials from surface electrodes. Bipolar electrograms were acquired at 1 kHz, using a 256 channels cardiac mapping system (Crescent Electronics, Salt Lake City, UT). Body surface potentials were simultaneously recorded using a 128 channels mapping system (Compumedics, Charlotte, NC) at a sampling rate of 1 kHz.

During the pacing study, rapid pacing was performed (10–20 s) in canines C1-C5 via bipolar electrode-pairs on selected plunge-needle electrodes located at subendocardium and subepicardium of the ventricles using a specially designed junction box. Furthermore, NE was infused to induce ventricular arrhythmias including PVCs, couplets, nonsustained MVTs, and PVTs in canines C3-C5 after the pacing study.

At the completion of simultaneous mapping study, two sets of ultra fast computed tomography (UFCT) (Philips, Amsterdam, NH, Netherlands) images were obtained on the living animal to obtain the anatomical information. One without intravenous contrast (a continuous volume scan with slice thickness of 3 mm from the level of the midneck down to the lower abdomen) was used to construct the torso model and extract the location of BSPM electrodes. Another one with intravenous contrast (from the great vessel level down to the diaphragm with slice thickness of 0.33 mm) was obtained for construction of a detailed heart model and 3D localization of plunge-needle electrodes. The in-plane resolution of UFCT images was 512 x 512 pixels. Contrast (30 cc iv) was administered at 3.0 cc/s to visualize the heart chambers during the cardiac UFCT scan. The plunge-needle electrodes were then carefully localized as described previously (11) by replacing each with a labeled pin. A postoperative UFCT scan of the formalin-fixed canine heart was subsequently performed to further facilitate precise 3D localization of the transmural electrodes.

3DCEI. The physical-model-based 3DCEI approach was used to noninvasively reconstruct the activation sequence throughout the 3D ventricular myocardium. The forward modeling and inverse computation of the 3DCEI approach were described previously (10, 11, 22).

In brief, the realistic geometry heart-torso model was constructed from UFCT images for each animal, using a commercial software package CURRY 6.0 (Compumedics, Charlotte, NC). This heart-torso model was exported for further forward and inverse computation in a software package developed in MATLAB2008a (MathWorks, Natick, MA). The 3D ventricular myocardium was discretized into thousands of grid points. A distributed ECD model was used to represent the cardiac electrical sources within the ventricular myocardium. Derived from the bidomain theory (24), potentials measurable over the body surface are linearly related to the 3D ECD distribution given a tessellated geometrical heart-torso model which includes myocardial tissue, blood masses, lungs, and torso. The electrical conductivities were set to 0.2, 0.67, 0.05, and 0.21 S/m, respectively, according to Refs. 22 and 37. A spatiotemporal regularization technique and lead-field normalized weighted minimum norm (LFN-WMN) estimation (42) were used to solve the inverse problem to reconstruct the time course of local ECD at each myocardial site. In brief, the singular value decomposition was employed to decompose the spatiotemporal ECG data matrix into orthogonal spatial and temporal components. The spatial components that did not satisfy the discrete Picard condition (12) were assumed to be dominated by noise perturbation, and thereby were truncated. The LFN-WMN estimation was applied to each remaining spatial component. The LFN-WMN solutions multiplied with the corresponding singular values, and temporal components were summed to obtain the spatiotemporal ECD estimates. The activation time at each myocardial site was determined as the instant when the time course of the estimated local ECD reached its maximum magnitude (22).

Evaluation and statistical analysis. The performance of 3DCEI was evaluated by comparing the noninvasively imaged activation sequence with the simultaneously direct measurements obtained from 3D intracardiac mapping. The measured activation sequence within the 3D ventricular myocardium was constructed to allow for a quantitative comparison. The orientation and location of each needle within the 3D ventricular myocardium was determined directly from the same UFCT images used for constructing the detailed heart model after the mapping study (11). To facilitate the identification and localization of the needles, an alternative heart surface model was built from the postoperative UFCT images of the isolated heart with labeled pins (representing the sites of transmural needles). The corresponding activation time of each recording electrode was assigned on the basis of peak criteria (30, 31) and then interpolated to obtain the

Fig. 1. Schematic diagram of the experimental protocol for validating the 3-dimensional (3D) cardiac electrical imaging (3DCEI) technique with simultaneous measurements from 3D intracardiac mapping in the canine heart. A: experimental recordings including cross-sectional computed tomography (CT) images, ECGs recorded from multiple surface electrodes, and multiple-channel intramural recordings of bipolar electrograms during 3D intracardiac mapping procedure. B: realistic geometry heart-torso model. C: body surface potential maps (BSPMs). D: reconstruction from CT images of an isolated canine heart with labeled pins. E: activation sequence noninvasively imaged from 3DCEI. F: measured activation sequence from invasive 3D intracardiac mapping.
numerical data are presented as mean ± SD. The correlation coefficient (CC) and relative error (RE) were computed, respectively, to quantify the agreement of overall activation pattern and the consistency of the activation time between the invasively measured activation sequence and the noninvasively imaged activation sequence. The root mean square error (RMSE) was computed to quantify the timing difference between measured and imaged activation sequences. The CC, RE, and RMSE are defined as:

\[
CC = \frac{\sum_{i=1}^{n} (AT^E_i - AT^M_i)(AT^M_i - AT^M)}{\sqrt{\sum_{i=1}^{n} (AT^E_i - AT^E)^2} \sqrt{\sum_{i=1}^{n} (AT^M_i - AT^M)^2}}
\]

\[
RE = \sqrt{\frac{\sum_{i=1}^{n} (AT^E_i - AT^M_i)^2}{\sum_{i=1}^{n} (AT^M_i)^2}}
\]

\[
RMSE = \sqrt{\frac{\sum_{i=1}^{n} (AT^E_i - AT^M_i)^2}{n}}
\]

where \(n\) is the number of grid points of the heart model, \(AT^E_i\) and \(AT^M_i\) are the noninvasively estimated activation time and measurement constructed activation time at the \(i\)-th myocardial grid point, \(\bar{AT}^E\) and \(\bar{AT}^M\) are their respective mean values. The localization error (LE), which is defined as the distance between the site of earliest activation from 3D intracardiac measurements and the center of mass of the myocardial region with the earliest imaged activation time was computed to evaluate the performance of 3DCEI in localizing the origin of activation. Statistical significance of differences was evaluated by Student’s t-test (paired or unpaired) and ANOVA test, and a \(P\) value < 0.05 was considered statistically significant.

**RESULTS**

**Experimentation and modeling.** Five canines were studied during the in vivo experiments. After insertion of plunge-needle electrodes, closure of the chest did not alter heart rate or mean arterial blood pressure (115 ± 15 vs. 120 ± 20 beats/min, \(P > 0.05\), paired t-test; and 60 ± 3 vs. 57 ± 6 mmHg, \(P > 0.05\), paired t-test) or total activation times of sinus beats (43 ± 2 ms vs. 44 ± 2 ms, \(P > 0.05\), paired t-test) for each canine. The realistic geometry heart-torso model was constructed for each animal from two sets of UFCT images obtained after the mapping study. The ventricular myocardium was tessellated into 21,332 ± 7,036 evenly spaced grid points. The spatial resolution of the ventricle models was 1.5 mm. There were 200 ± 10 intramural bipolar electrodes during 3D intracardiac mapping and 114 ± 7 BSPM electrodes on the canine body surface.

**Pacing in the canine heart.** Simultaneous body surface potential mapping and 3D intra-cardiac mapping were performed under single-site pacing in canine C1-C5. The pacing sites were chosen to include multiple regions of the LV and RV. Figure 2 shows a representative example of the comparison between the measured and imaged activation sequences when canine C2 was paced, respectively, at subepicardium and subendocardium via a plunge-needle electrode located in the left lateral free wall midway between the base and the apex. The spatial distribution of the activation time within the ventricles were compared to the activation time sequence measured from 3D intracardiac measurements. The activation sequence is color-coded from white to blue, corresponding to earliest and latest activation. In the left column, the activation sequence is displayed on epicardial and endocardial surfaces, respectively, in the anterior view. At right, a series of four representative axial slices in a row, starting from the ventricular base, are displayed from left to right. The pacing site and the estimated initial site of activation are marked by a black asterisk in the left column and a black spot and a purple arrow in the right column. The scale bar is given for the axial slices. Correlation coefficient (CC) is 0.72, relative error (RE) is 0.25, root mean square error (RMSE) is 8 ms, and localization error (LE) is 6.6 mm for the beat in A, and CC is 0.71, RE is 0.26, RMSE is 9 ms, and LE is 6.2 mm for the beat in B.
RMSE over both LV and RV pacing were 0.74 observed averaging all animals. The averaged CC, RE, and LV pacing in the canine heart (0.76 the global activation pattern during apical pacing in term of CC tions. In general, slightly decreased performance when imaging performance varied among difference anatomical pacing loca-
subepicardial pacing sites). For each animal, the imaging 3DCEI in imaging ventricular activation during RV pacing (18 cardial pacing sites and subepicardial origins for 12 subepi-
died for these two cases, respectively, from the imaged origin of activation was localized to be 6.6 mm and 6.2 mm for 
these two cases, respectively.

tricular myocardium is color-coded. The white corresponds to early activation, whereas blue corresponds to late activation. The left column shows the comparison of the activation sequence on the epicardial and endocardial surfaces. The right column shows four axial slices starting from ventricular base. The subendocardial and the subepicardial sites of origin were identified for these two cases, respectively.

A total of 280 beats of single-site LV pacing from 14 subendocardial sites and 14 subepicardial sites (10 beats for each single site) were analyzed. The performance of 3DCEI in imaging ventricular activation during LV pacing is summarized in Table 1. A slightly better performance of imaging epicardial pacing was observed in terms of CC (0.75 ± 0.06 vs. 0.72 ± 0.06, P < 0.05, paired t-test) and LE (6.9 ± 1.5 mm vs. 7.3 ± 1.4 mm, P < 0.05, paired t-test). The 3DCEI approach was able to identify the subendocardial origins for 10 subendocardial pacing sites and subepicardial origins for 12 subepicardial pacing sites. Table 2 summarizes the performance of 3DCEI in imaging ventricular activation during RV pacing (18 subepicardial pacing sites). For each animal, the imaging performance varied among difference anatomical pacing locations. In general, slightly decreased performance when imaging the global activation pattern during apical pacing in term of CC (0.76 ± 0.05 vs. 0.71 ± 0.06, P < 0.05, unpaired t-test) was observed averaging all animals. The averaged CC, RE, and RMSE over both LV and RV pacing were 0.74 ± 0.06, 0.29 ± 0.05, and 9 ± 3 ms, respectively, suggesting good agreement between measured and estimated activation sequences. The averaged LE was 7.2 ± 1.4 mm, suggesting reasonable localization accuracy when imaging subjects with larger cardiac size.

PVCs and VTs in the canine heart. Frequent multiform PVCs and runs of nonsustained MVTs and PVTs were dem-

Table 1. Quantitative comparison between measured activation sequence and imaged activation sequence during single-site LV pacing in the canine heart

<table>
<thead>
<tr>
<th>Canine and Pacing Needle Location</th>
<th>CC</th>
<th>RE</th>
<th>LE, mm</th>
<th>RMSE, ms</th>
<th>Canine and Pacing Needle Location</th>
<th>CC</th>
<th>RE</th>
<th>LE, mm</th>
<th>RMSE, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1 BLW</td>
<td>0.75</td>
<td>0.36</td>
<td>7.9</td>
<td>13</td>
<td>C1 Anterior BRW</td>
<td>0.77</td>
<td>0.28</td>
<td>7.4</td>
<td>11</td>
</tr>
<tr>
<td>Posterior MLW</td>
<td>0.79</td>
<td>0.28</td>
<td>5.3</td>
<td>7</td>
<td>MRW</td>
<td>0.78</td>
<td>0.31</td>
<td>7.7</td>
<td>12</td>
</tr>
<tr>
<td>LVA</td>
<td>0.80</td>
<td>0.37</td>
<td>7.6</td>
<td>9</td>
<td>RVA</td>
<td>0.68</td>
<td>0.33</td>
<td>7.5</td>
<td>8</td>
</tr>
<tr>
<td>C2 Posterior MLW</td>
<td>0.70</td>
<td>0.29</td>
<td>8.2</td>
<td>11</td>
<td>C2 RVA</td>
<td>0.66</td>
<td>0.33</td>
<td>7.4</td>
<td>9</td>
</tr>
<tr>
<td>MLW</td>
<td>0.73</td>
<td>0.26</td>
<td>6.9</td>
<td>10</td>
<td>MRW</td>
<td>0.79</td>
<td>0.24</td>
<td>6.3</td>
<td>7</td>
</tr>
<tr>
<td>LVA</td>
<td>0.69</td>
<td>0.21</td>
<td>5.1</td>
<td>9</td>
<td>Anterior MRW</td>
<td>0.80</td>
<td>0.29</td>
<td>10.3</td>
<td>4</td>
</tr>
<tr>
<td>C3 MLW</td>
<td>0.65</td>
<td>0.31</td>
<td>7.4</td>
<td>11</td>
<td>Posterior MRW</td>
<td>0.76</td>
<td>0.28</td>
<td>7.9</td>
<td>11</td>
</tr>
<tr>
<td>LVA</td>
<td>0.62</td>
<td>0.25</td>
<td>9.1</td>
<td>8</td>
<td>Anterior BRW</td>
<td>0.79</td>
<td>0.33</td>
<td>5.7</td>
<td>12</td>
</tr>
<tr>
<td>C4 BLW</td>
<td>0.70</td>
<td>0.24</td>
<td>10.2</td>
<td>8</td>
<td>C3 Posterior RVA</td>
<td>0.74</td>
<td>0.24</td>
<td>8.6</td>
<td>10</td>
</tr>
<tr>
<td>MLW</td>
<td>0.78</td>
<td>0.23</td>
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<td>0.73</td>
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<td>10</td>
</tr>
<tr>
<td>Mean 0.72 ± 0.06</td>
<td>0.28 ± 0.05</td>
<td>7.3 ± 1.4</td>
<td>9 ± 2</td>
<td>0.75 ± 0.06</td>
<td>0.29 ± 0.07</td>
<td>6.9 ± 1.5</td>
<td>8 ± 3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For mean, values are means ± SD. LV, left ventricle; CC, correlation coefficient; RE, relative error; LE, localization error; RMSE, root mean square error; BLW, basal left wall; MLW, middle left wall; LVA, left ventricle apex.

Table 2. Quantitative comparison between measured activation sequence and imaged activation sequence during single-site RV pacing in the canine heart

<table>
<thead>
<tr>
<th>Canine and Pacing Site</th>
<th>CC</th>
<th>RE</th>
<th>LE, mm</th>
<th>RMSE, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1 Anterior BRW</td>
<td>0.77</td>
<td>0.28</td>
<td>7.4</td>
<td>11</td>
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<tr>
<td>MRW</td>
<td>0.78</td>
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<td>7.7</td>
<td>12</td>
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<tr>
<td>RVA</td>
<td>0.68</td>
<td>0.33</td>
<td>7.5</td>
<td>8</td>
</tr>
<tr>
<td>C2 RVA</td>
<td>0.66</td>
<td>0.33</td>
<td>7.4</td>
<td>9</td>
</tr>
<tr>
<td>MRW</td>
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<td>5.7</td>
<td>12</td>
</tr>
<tr>
<td>C3 Posterior RVA</td>
<td>0.74</td>
<td>0.24</td>
<td>8.6</td>
<td>10</td>
</tr>
<tr>
<td>RVA</td>
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<td>6.3</td>
<td>9</td>
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<tr>
<td>BRW</td>
<td>0.73</td>
<td>0.39</td>
<td>7.4</td>
<td>10</td>
</tr>
<tr>
<td>MRW</td>
<td>0.84</td>
<td>0.34</td>
<td>8.2</td>
<td>9</td>
</tr>
<tr>
<td>C4 MRW</td>
<td>0.84</td>
<td>0.33</td>
<td>10.7</td>
<td>11</td>
</tr>
<tr>
<td>Posterior MRW</td>
<td>0.77</td>
<td>0.33</td>
<td>6.2</td>
<td>12</td>
</tr>
<tr>
<td>RVA</td>
<td>0.68</td>
<td>0.38</td>
<td>6.3</td>
<td>5</td>
</tr>
<tr>
<td>C5 Posterior MRW</td>
<td>0.68</td>
<td>0.23</td>
<td>7.3</td>
<td>12</td>
</tr>
<tr>
<td>BRW</td>
<td>0.77</td>
<td>0.28</td>
<td>6.7</td>
<td>11</td>
</tr>
<tr>
<td>MRW</td>
<td>0.79</td>
<td>0.31</td>
<td>6.1</td>
<td>14</td>
</tr>
<tr>
<td>Mean 0.76 ± 0.05</td>
<td>0.30 ± 0.05</td>
<td>7.4 ± 1.4</td>
<td>10 ± 2</td>
<td></td>
</tr>
</tbody>
</table>

For mean, values are means ± SD. BRW, basal right wall; MRW, middle right wall; RVA, right ventricle apex.

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onstrated during the infusion of NE. A total of 96 ventricular ectopic beats including 26 PVCs, 5 couplets, 4 runs of MVTs and 6 runs of PVTs were analyzed. PVCs in each canine demonstrated different initial sites of activation. Twelve PVCs initiated in the LV and 14 in the RV. The PVCs and VT beats were observed to initiate by a focal mechanism from a single site or sequentially from multiple sites in the subendocardium of ventricles, including lateral walls and apex. Quantitative comparisons were made between noninvasively imaged activation sequence and invasively measured activation sequence for these PVCs and VT beats in the canine heart. The comparison results are summarized in Table 3. The methods to image PVCs and VT beats are similar to those to image beats paced from the LV or RV (P > 0.05 for CC, RE, LE, and RMSE, respectively, ANOVA test).

Figure 3 shows examples of two nonsustained MVT beats in canine C3. As shown in Fig. 3A for a representative MVT beat, this VT beat initiated at a subendocardial site at the anterior LV apex by a focal mechanism and propagated to the RV basal wall. The subsequent eight VT beats demonstrated focal initiation at the same LV site and similar global activation pattern. The averaged coupling interval of these maintained VT beats was 329 ± 9 ms. The imaged activation sequence matched measured activation sequence in its overall activation pattern, image PVCs and VT beats paced from the LV or RV (P > 0.05 for CC, RE, LE, and RMSE, respectively, ANOVA test).

Table 3. Quantitative comparison between measured activation sequence and imaged activation sequence in norepinephrine-induced ventricular tachycardia in the canine heart

<table>
<thead>
<tr>
<th>Canine and Origin Site</th>
<th>Arrhythmia Type</th>
<th>Number of Ectopic Beats</th>
<th>CC</th>
<th>RE</th>
<th>LE, mm</th>
<th>RMSE, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3</td>
<td>BRW PVC</td>
<td>1</td>
<td>0.67</td>
<td>0.30</td>
<td>8.7</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>MLW PVC, Couplet, MVT, PVT</td>
<td>18</td>
<td>0.71</td>
<td>0.26</td>
<td>5.8</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Posterior MRW PVC, Couplet, PVT</td>
<td>11</td>
<td>0.78</td>
<td>0.23</td>
<td>7.5</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>LVA MVT, PVT</td>
<td>17</td>
<td>0.73</td>
<td>0.28</td>
<td>7.1</td>
<td>5</td>
</tr>
<tr>
<td>C4</td>
<td>LVA MVT</td>
<td>16</td>
<td>0.72</td>
<td>0.33</td>
<td>10.6</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>MRW PVC</td>
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<td>0.29</td>
<td>6.8</td>
<td>13</td>
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<tr>
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<tr>
<td>C5</td>
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<tr>
<td></td>
<td>BRW PVC, Couplet, PVT</td>
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<tr>
<td>Mean</td>
<td></td>
<td>0.72 ± 0.03</td>
<td>0.28 ± 0.04</td>
<td>7.9 ± 1.8</td>
<td>10 ± 3</td>
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For mean, values are means ± SD. PVC, premature ventricular complex; PVT, polymorphic ventricular tachycardia; MVT, monomorphic ventricular tachycardia.

Fig. 3. Comparison between measured activation sequence and imaged activation sequence for 2 nonsustained monomorphic ventricular tachycardia beats in canine C3. The epicardial and endocardial surfaces are displayed, respectively, in a left anterior view. The pacing site and the estimated initial site of activation are marked by a black asterisk in the left column and a black spot and a purple arrow in the right column. CC is 0.72, RE is 0.28, RMSE is 8 ms, and LE is 7.2 mm for the beat in A, and CC is 0.78, RE is 0.24, RMSE is 9 ms, and LE is 6.8 mm for the beat in B.
with a CC of 0.72, an RE of 0.28, and an RMSE of 8 ms for this beat. The initiation of the activation was well localized with an LE of 7.2 mm. The VT then accelerated into a fast four-beat episode, as shown in Fig. 3B. The activation pattern of these four beats looked similar, and the initiation site of the activation moved to the LV lateral wall. The averaged coupling interval for these four VT beats was 140 ± 10 ms. The imaged activation sequence was consistent with the direct measurement, with a CC of 0.78, an RE of 0.24, and an RMSE of 9 ms. The initiation of the activation was well localized with an LE of 6.8 mm for the fast VT beat shown in the red box of ECG in Fig. 3B.

Another example is shown in Fig. 4 for a four-beat PVT in canine C3. As shown in measured activation sequence in Fig. 4A, the first VT beat initiated at a RV site close to apex by a focal mechanism and propagated to the LV basal wall. The second beat initiated at anterior LV apex and activation pattern was similar to the beat shown in Fig. 3A. Beat 3 and beat 4 demonstrated the focal initiation at the same RV site close to posterior middle wall and similar global activation pattern, as shown in Fig. 4B. The coupling interval for this VT was 271 ± 33 ms. The imaged activation sequence matched the measured activation sequence in its overall activation pattern, with a CC of 0.73, an RE of 0.26, and an RMSE of 5 ms for the beat in Fig. 4A, and a CC of 0.79, an RE of 0.25, and an RMSE of 10 ms for the beat in Fig. 4B. The initiation of the activation was well localized with an LE of 7.4 mm and 7.8 mm, respectively.

DISCUSSION

The present study extends our validation of a physical-model-based 3DCEI technique in noninvasively reconstructing the 3D ventricular activation sequence and localizing the origin of activation in the canine heart with the aid of simultaneous 3D intracardiac mapping from up to 216 intramural sites. The quantitative comparison showed a good agreement between the noninvasively imaged activation sequence and its directly measured counterparts, as quantified by a CC of 0.74, an RE of 0.29, and an RMSE of 9 ms averaged over all paced and ectopic beats. The origins of the activation were reasonably estimated to be ~7 mm from the initiation sites determined from intracardiac mapping. These findings imply that 3DCEI is feasible in reconstructing spatial pattern of 3D ventricular activation sequences and localizing the arrhythmogenic foci on a beat-to-beat basis.

Considerable efforts have been undertaken to localize and image cardiac electrical activity by solving the ECG inverse problem from BSPMs (1–5, 8–11, 13–17, 19, 21–23, 25–28, 32, 33, 36, 37, 39–41, 48). The current imaging technique has a notable feature of imaging the cardiac activation sequence throughout the 3D ventricular myocardium, which represents an important alternative to other heart surface based imaging techniques. It is also noted that this physical-model-based 3DCEI approach only uses the general biophysical relationships governing the cardiac electrical activity and does not need to build a sophisticated cardiac electrophysiological model. By solving the spatial-temporal linear inverse problem, the 3DCEI approach estimated the instantaneous current density at each grid point and then estimate the local activation time as the time instant at peak of current density magnitude (22) throughout the ventricular myocardium. It is challenging to estimate the spatial distribution of ECD distribution from BSPM at a given time point, but the activation time as determined from the peak of the ECD time course is not distorted substantially by such spatial relationship between ECD distribution and BSPM, as we have demonstrated.

**Fig. 4.** Comparison between measured activation sequence and imaged activation sequence of the first beat (A) and fourth beat (B) from a 4-beat nonsustained polymorphic ventricular tachycardia for canine C3. The epicardial and endocardial surfaces are displayed, respectively, in a right posterior view. The pacing site and the estimated initial site of activation are marked by a black asterisk in the left column and a black spot and a purple arrow in the right column. CC is 0.73, RE is 0.26, RMSE is 5 ms, and LE is 7.4 mm for the beat in A, and CC is 0.79, RE is 0.25, RMSE is 9 ms, and LE is 7.8 mm for the beat in B.
in previous computer simulation (22) and in animal experiments in rabbits (11) and dogs. Therefore, this physical-model-based 3DCEI approach is minimally dependent on the physiological knowledge of cardiac electrical properties and has the potential to image various cardiac arrhythmias. Note that our imaging approach involves solving a linear inverse problem and no initialization is needed (22).

Rigorous validation studies in biological systems are critical for any imaging approaches. The present study has used a novel in vivo experimental design in which BSPMs were obtained simultaneously with intramural electrical recordings from plunge-needle electrodes in a closed-chest condition and thus provided quantitative assessments of the 3DCEI approach. The present work extended our validation study to the canine heart. When compared with previous validation study in the rabbit heart (11), the canine model provides larger heart-torso geometry and closer approximation to humans in cardiac size and electrophysiological characteristics. As we experienced in the rabbit heart, we also observed that there was a slight discrepancy in timing between the measured and computed activation times. This was due to the intrinsic smoothing effects when we solved the inverse problem, especially at the earliest and latest activation times, when body surface potentials are of relatively small magnitudes compared with noise. As such, the resultant solution may lead to spatially smoothed images and thus caused the slightly delayed initiation and premature termination. Nevertheless, the imaging activation sequence still provided a close match to the direct measurements, suggesting that important information regarding ventricular excitation (e.g., global activation pattern, regions of early and late activation) has been preserved in imaged results. Furthermore, the initiation sites were estimated to be ~7 mm from the measured sites, suggesting that resolution in the canine heart (12 times greater mass than rabbit heart) is associated with only a small (40%) change in resolution (vs. ~5 mm in rabbit heart). The present study suggests that the imaging accuracy does not necessarily scale linearly to the geometric size of the subject, but rather is mainly determined by experimental procedures. It could be expected that in a clinical setting when human subjects are studied and different procedures are involved (e.g., more BSPM electrodes would be used, and there would be no sternotomy), the imaging and localization errors would not increase further.

It is noted that two sets of UFCT images with and without intravenous contrast were obtained on the anesthetized animals immediately after the mapping studies to accurately model the heart-torso geometry and localize the plunge-needle electrodes within the heart. However, it was difficult to determine the exact name and label for each needle directly from the intravenously contrasted UFCT images for constructing the detailed heart model. Therefore, these needles were carefully replaced with labeled pins after the mapping study, and the isolated heart was fixed in formalin. A third UFCT scan was performed on the formalin-fixed isolated heart to build the isolated heart model with 3D localization of plunge-needle electrodes, and the label for each needle in this isolated heart model was determined by photographs taken on the formalin-fixed isolated heart. This isolated heart model was carefully compared with the previously constructed detailed heart model from the heart-torso model so that the label of each needle within that detailed heart model could be identified.

It has been shown from direct intracardiac mapping techniques (29–31, 47) that ventricular arrhythmias could arise from either subendocardium or subepicardium. Computational modeling of cardiac excitation plays an important role in dissecting the arrhythmia mechanisms throughout the 3D myocardium (6, 18, 20, 38, 43, 44). The 3DCEI approach represents an important and novel means, which offers the potentials to provide the additional noninvasive assessments of the underlying arrhythmia mechanisms throughout the ventricular myocardium and may facilitate interventional therapeutic procedures (e.g., catheter by using a more targeted approach and shortening the procedure time.

Single-beat noninvasive imaging of myocardial activation is important for the clinical diagnosis and management of hemodynamically unstable arrhythmias. Considering that not all arrhythmogenic substrates are accessible from endocardium, the necessity of applying epicardial ablation needs to be determined in some cases (34). Being able to noninvasively assess the transmurual location of the arrhythmogenic site before the procedure is likely to translate into a shortened time for the ablation procedure and potentially a reduction in risk to the patient by using a more targeted approach. In the present study, we have infused NE in the canine heart to simulate the activation of the sympathetic nervous system, and highly arrhythmic activities were induced including multiform PVCs and runs of nonsustained MVTs and PVTs. The measured activation sequence also showed that these arrhythmias usually originated within the subendocardium and may arise continuously from a single site or consecutively from multiple sites located at Purkinje cells or subendocardial myocardium. The focal activation with NE-induced VT resembles idiopathic VT in the human heart (7, 45). The origins have been well localized by the noninvasive 3DCEI approach with reasonably good accuracy. The performance is also consistent with those when imaging LV and RV pacing both in term of global pattern and timing difference. Furthermore, the beat-to-beat difference in activation pattern for the PVTs has been well characterized from the imaged activation maps. These results imply that this approach may be valuable for single-beat imaging of focal ventricular arrhythmias arising in the deeper myocardium and facilitating the selection of clinical treatment options for these arrhythmias.

Limitation. It is noted that the current experimental protocol (e.g., median sternotomy) may affect the imaging accuracy due to the change of the torso volume conductor property. However, with careful surgery procedure (e.g., multilayer-suture chest closing) and sectional computed tomography images after the mapping study to accurately model the heart-torso geometry, we minimized such changes on the volume conductor. Besides, to perform a quantitative comparison for the global pattern between the imaged and measured activation sequences, an interpolation algorithm was used in the intracardiac mapping procedure to obtain the measured activation sequence throughout the 3D ventricular myocardium. However, we found that this yielded only a very slight decrease in performance by comparing the CC and RE in one dog with and without interpolation.

Future directions. In this study, we have focused the validation work on the normal canine heart without considering the heart with structure diseases such as infarction and ischemia. Such experimental setting provided a well-controlled paradigm...
to rigorously validate the 3DCEI technique by using pacing and drug-induced ventricular arrhythmias. Future studies will be needed to further define the imaging performance using animal models with structural cardiac diseases and to establish its clinical role through clinical study.

Conclusion

The present study suggests that the 3DCEI approach can reconstruct 3D ventricular activation sequence and localize the origin of activation during pacing and focal ventricular arrhythmias, as validated by 3D intracardiac mapping procedure in the canine heart. It also implies the potential application of 3DCEI as a clinically complimentary tool to aid in localizing the origins of ventricular arrhythmias and understanding the mechanism of these arrhythmias.

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GRANTS

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DISCLOSURES

B. He is an inventor of a United States patent related to the imaging technique used in this experimental study.

AUTHOR CONTRIBUTIONS


REFERENCES


