Imaging cardiac activation sequence during ventricular tachycardia in a canine model of nonischemic heart failure

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Submitted 24 March 2014; accepted in final form 13 November 2014

Recentiy, cardiac resynchronization therapy (CRT) has evolved as an important treatment option to improve the cardiac mechanical performance by restoring the cardiac electrical synchrony in congestive HF patients (35). Invasive catheter-based mapping of endocardial activation also emerges as an important tool to study the electrophysiological mechanism of CRT in congestive HF patients.

Noninvasive cardiac electrical imaging techniques provide a novel and much needed means (3, 9, 38), which offers the potential to help with delineation of the underlying arrhythmia mechanisms related to HF and to facilitate corresponding selections of patient-specific treatment options for HF and its related arrhythmias. Previously we have rigorously evaluated a three-dimensional (3D) cardiac electrical imaging (3DCEI) technique in imaging VTs in rabbit (9, 11) and in dog (10) without structure diseases. This study aims to (1) investigate the arrhythmia mechanisms of spontaneously occurring or norepinephrine (NE)-induced VTs in a canine model of nonischemic HF by means of 3DCEI and (2) assess the performance of 3DCEI in imaging the activation patterns of VTs associated with nonischemic HF with the aid of invasive 3D intracardiac mapping (28–30). We performed simultaneous body surface potential mapping and 3D intracardiac mapping in a closed-chest condition in HF dogs. The 3DCEI technique was applied to characterize the dynamic activation patterns of both spontaneously occurring VTs and NE-induced VTs. The imaged activation sequence was also compared with the simultaneously measured activation sequence from 3D intracardiac mapping.

MATERIALS AND METHODS

HF canine model and experimental procedures. The experimental protocol, approved by the Institutional Animal Care and Use Committees of the University of Minnesota and the University of Alabama at Birmingham, was performed on three canines. HF in each dog was produced by induction of aortic insufficiency, which was later followed by constriction of the abdominal aorta. Aortic insufficiency was created via the carotid artery, in which a Fogarty balloon catheter was used to perforate 1 to 2 valve leaflets under fluoroscopic guidance. Aortic constriction was created through an abdominal incision in which a suture was placed around the abdominal aorta so that the systolic blood pressure gradient increased by 50–60 mmHg compared with baseline measurement. The dogs survived for 22 ± 5 mo, after which a terminal mapping study was performed. Progression of HF was assessed by left ventricle (LV) end-diastolic dimension, LV end-systolic dimension, and LV fractional shortening using Doppler echocardiography.

Simultaneous body surface potential mapping and 3D intracardiac mapping was performed on the dogs when HF developed. The anesthesia regimen and the surgical procedure for the mapping study were similar to the previous normal canine experiment (10).
Up to 128 repositionable body surface potential map (BSPM) electrodes were uniformly placed to cover both the anterior-lateral chest up to the mid-axillary line and the posterior chest. The heart was exposed via median sternotomy, and up to 47 transmural plunge-needle electrodes were inserted in the LV and right ventricle (RV). Each LV plunge-needle electrode contains four bipolar electrode-pairs (inter-electrode distance of 500 µm), each separated by 2.5 mm (28, 29), and each RV electrode contains eight bipolar electrode-pairs with an inter-electrode distance of 500 µm (30). There were no significant changes in heart rate or mean arterial blood pressure after electrode insertion (heart rate, 99 ± 8 to 101 ± 2 beats/min; mean arterial blood pressure, 82 ± 17 to 76 ± 5 mmHg; both P = not significant). The chest and skin were then carefully closed with 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. Spontaneously occurring ventricular arrhythmias including premature ventricular complex (PVC), couplet, and VT were recorded during the mapping study. NE was later infused at 1.6–6.25 µg·kg⁻¹·min⁻¹ to induce VTs in all three animals. At the completion of simultaneous mapping study, two sets of ultra-fast computed tomography (UFCT) images were obtained on the living animal to obtain the anatomical information. One without IV contrast (with slice thickness of 3 mm) was used to construct the torso model and extract the location of BSPM electrodes. Another one with IV contrast (with slice thickness of 0.33 mm) was obtained for construction of a detailed heart model and 3D localization of plunge-needle electrodes. The plunge-needle electrodes were then carefully localized as previously described (9, 10) 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 and data analysis. 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 previously described (8–10, 21). Briefly, the realistic geometry heart-torso model was constructed from UFCT images for each animal. The 3D ventricular myocardium was discretized into thousands of grid points. A distributed equivalent current density model was used to represent the cardiac electrical sources within the ventricular myocardium. Derived from the bidomain theory (23, 35a), potentials measurable over the body surface are linearly related to the myocardium equivalent current density distribution given a tessellated geometrical heart-torso model that includes myocardial tissue, blood masses, lungs, and torso. The QRS segment for each beat was extracted to construct the BSPM matrix. The start of Q wave and end of S wave were annotated from both the root mean square ECG and butterfly plot of all ECGs. A spatiotemporal regularization technique and lead-field normalized weighted minimum norm estimation (37) were used to solve the inverse problem to reconstruct the time course of local ECD at each myocardial site. 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 (21).

Numerical data are presented as means ± SD. The performance of 3DCEI was evaluated by comparing the noninvasively imaged activation sequence with the measured activation sequence obtained from 3D intra-cardiac mapping. The measured activation sequence was constructed in the same way as we did in normal dogs (10). The Pearson’s product moment correlation coefficient (CC) was computed to quantify the agreement of overall activation pattern between the measured activation sequence and the noninvasively imaged activation sequence. The CC is defined as

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CC = \frac{\sum_{i=1}^{n} (\hat{A}_i^E - \hat{A}_i^M)(\hat{A}_i^E - \hat{A}_i^M)}{\sqrt{\sum_{i=1}^{n} (\hat{A}_i^E - \hat{A}_i^E)^2 \times \sum_{i=1}^{n} (\hat{A}_i^M - \hat{A}_i^M)^2}},
\]

where \( n \) is the number of grid points of the heart model and \( \hat{A}_i^E \) and \( \hat{A}_i^M \) are the noninvasively estimated activation time and measurement constructed activation time at the \( i \)-th myocardial grid point. \( \hat{A}_i^E \) and \( \hat{A}_i^M \) are their respective mean values. Common biostatistics rules were used to interpret the value of CC (4). The CC values from 0 to 0.25 or from 0 to −0.25 were considered the absence of correlation, CC values from 0.25 to 0.50 or from −0.25 to −0.50 were considered to be poor correlation, CC values from 0.50 to 0.75 or from −0.50 to −0.75 were considered to be moderate to good correlation, and CC values from 0.75 to 1 or from −0.75 to −1 were considered to be very good to excellent correlation (4). The localization error (LE), which is defined as the distance between the site of earliest activation from 3D intra-cardiac 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 a \( P \) value <0.05 was considered statistically significant.

RESULTS

Experimentation and modeling. With HF, LV end-diastolic dimension increased by 47% (from 3.70 ± 0.08 cm to 5.43 ± 0.26 cm), LV end-systolic dimension increased by 63% (from 2.20 ± 0.16 to 3.59 ± 0.35 cm), and LV fraction shortening decreased by 16% (from 41 ± 3% to 34 ± 3%) (all \( P < 0.05 \)). During the simultaneous body surface potential mapping and 3D intra-cardiac mapping, spontaneously occurring PVCs and couplets were recorded in all three dogs, whereas spontaneous VTs were recorded in two dogs. VTs were also induced using NE in all three dogs. For all three animals, the realistic geometry canine heart-torso model was constructed from UFCT images obtained after the mapping study. The canine ventricular myocardium was tessellated into 28,871 ± 4,309 evenly spaced grid points. The spatial resolution of the ventricular models was 2 mm.

Spontaneously occurring VTs and NE-induced nonsustained VTs. Data analysis was performed on four episodes of spontaneously occurring VTs (total of 24 VT beats) and eight episodes of NE-induced nonsustained VTs (total of 111 VT beats) recorded during the mapping study. Table 1 shows the comparison between spontaneously occurring VTs and NE-induced VTs in HF dogs. The NE-induced VTs were longer (14 ± 2 vs. 6 ± 3 beats long, \( P < 0.05 \)) and were also more rapid than the

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Spontaneous VT</th>
<th>NE-induced VT</th>
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<tr>
<td></td>
<td>No. of Beats</td>
<td>Cycle Length, ms</td>
</tr>
<tr>
<td>1</td>
<td>4 ± 1</td>
<td>395 ± 49</td>
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<tr>
<td>2</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>5 ± 7</td>
<td>380 ± 95</td>
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<tr>
<td>Mean</td>
<td>6 ± 3</td>
<td>388 ± 11</td>
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Values are means ± SD. VT, ventricular tachycardia; NE, norepinephrine.

Table 1. Summary of ectopic activity during mapping study in heart failure dogs
spontaneously occurring VTs (cycle length of 232 ± 25 vs. 388 ± 11 ms, P < 0.05). Both the 3D intra-cardiac mapping and 3DCEI show these VT beats initiated by a focal activation, mostly arising from different subendocardial sites of the ventricles.

Figure 1 shows an example of a spontaneously occurring five-beat VT preceded by PVCs and sinus rhythm in a pattern of bigeminy. As shown in Fig. 1A, a PVC beat initiated at subendocardium of LV apex and the wavefront then terminated at the basal posterior ventricles. Figure 1B shows the first VT beat, which had the same activation pattern and same initiation site as the preceding isolated PVC in Fig. 1A. Figure 1C shows the second VT beat, where the initiation site has shifted to the middle lateral wall of LV. This VT was maintained by shifting the initiation site within the two sites (VT beat X1 and VT beat X2 in Fig. 1, B and C) for the following three beats. The noninvasively imaged activation sequence showed good agreement with the measured activation sequence, and the shift of initiation site was well captured from the imaged maps.

Another example of a 31-beat VT induced by NE (in which all VT beats were mapped and imaged) is shown in Fig. 2 for dog 1. All the ectopic beats in this VT had focal activation pattern. As shown in Fig. 2, A and B, the beginning of this VT has been continuously firing in a monomorphic pattern at the LV apex site slightly closer to anterior wall, which is similar to the sites in the spontaneous VT in Fig. 1. However, starting from middle stage of this VT, other initiation sites were also observed among different ectopic beats, which were not seen in the mapped spontaneously occurring VTs. Figure 2C shows that VT beat X17 (indicated in the red box of ECG lead II in the figure) had a slightly different activation pattern where the initiation site has shifted to the low LV apex. Figure 2D shows another activation pattern for the VT beat X26 (also indicated in the red box of ECG lead II in the figure), where the initiation site moved to posterior base of LV. Figure 2E shows VT beat X30 had a focal initiation site at the subepicardium of inferior lateral wall of LV. Such dynamic shift of initiation site has been well captured in the noninvasively imaged activation sequence.

Figure 3 shows a 14-beat polymorphic VT induced by NE for dog 3. Five initiation sites were identified for this VT. As shown in Fig. 3A, the first VT beat initiated at posterior basal lateral wall of RV, and the initiation site has shifted to middle lateral of LV for the following six VT beats (Fig. 3B for a representative beat). The initiation site for eighth VT beat has further moved to middle anterior LV wall, as shown in Fig. 3C. The initiation sites were also identified at LV apex (Fig. 3D) for beat 9 and beat 10 and at anterior LV apex (Fig. 3E) for beats 11–14. The initiation sites were well identified in the noninvasively imaged activation sequence.

Table 2 summarizes the spatial dispersion of focal initiation sites and the quantitative comparison between imaged and measured activation sequences for the mapped VT beats. The NE-induced nonsustained VTs that were mapped had more initiation sites, as compared with the spontaneously occurring VTs (13 focal sites vs. 8 focal sites). Furthermore, out of the 16 focal sites, most initiation sites were located at apex (7 sites), right ventricular outflow tract (2 sites), and left lateral wall (6 sites). The 3DCEI technique successfully detected and located the dispersed focal initiation sites for these VT beats. Good
correlation was obtained between the imaged activation sequence and the simultaneous measurement (averaged CC of \(0.70\) over 135 ectopic VT beats from 16 focal sites). Furthermore, the initiation sites were reconstructed to be \(10\) mm from measured sites, suggesting good localization in a large animal model with cardiac size similar to a human.

**DISCUSSION**

In this study, we report a novel investigation of 3DCEI for characterizing the global activation pattern and localizing origin of activation during both the spontaneously occurring VTs and NE-induced nonsustained VTs in a novel irreversible model of nonischemic HF. We showed that both spontaneously occurring VTs and NE-induced nonsustained VTs in this HF model were initiated by a focal mechanism from multiple endocardial, and at times, epicardial sites, which are similar to VTs in human HF heart. Good agreement was obtained between the noninvasively imaged activation sequence and its directly measured counterpart, as quantified by a CC of \(0.70\) and an LE of \(10\) mm averaged over 135 ectopic VT beats. These findings imply that 3DCEI is feasible in noninvasively characterizing the spatial patterns of ventricular activation sequences, localizing the arrhythmogenic foci on a beat-to-beat basis, and helping define the arrhythmia mechanism in the setting of nonischemic HF.

Much effort has been devoted to the development of noninvasive cardiac electrical imaging techniques to estimate the equivalent cardiac sources from BSPM, by solving the ECG

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**Fig. 2.** A–E: comparison between measured activation sequence and imaged activation sequence for a 31-beat VT induced by norepinephrine (NE) in dog 1. The red box in ECG indicated the mapped beats. The initial site of activation is marked by a black asterisk and a purple arrow.
inverse problem (1-3, 6-15, 17-19, 21, 22, 25, 26, 32, 34, 36, 38, 40). To translate the cardiac electrical imaging techniques into a clinically powerful tool, it is important to show their clinical relevance and validate such techniques under the various conditions of clinically relevant cardiac diseases. Our previous study (10) provided validation for the 3DCEI approach to assess NE-induced VT in control dogs, but it provided no information on the performance of this approach in a failing heart. The present work extended the validation of 3DCEI into a novel irreversible large animal model of non-ischemic HF induced by combined pressure and volume overload (unlike the most commonly used model of nonischemic HF, the rapid pacing model, which is reversible following cessation of pacing). Although the mapping approach is similar to the previous study, the development of a new arrhythmogenic HF model that is irreversible and the simultaneous closed-chest mapping studies with concurrent 3DCEI imaging followed by postmapping UFCT scan are extremely challenging series of studies to perform in a failing heart. Meanwhile, the VTs induced by NE in control hearts activated more rapidly

Fig. 3. A–E: comparison between measured activation sequence and imaged activation sequence of a 14-beat nonsustained polymorphic VT induced by NE for dog 3. The red box in ECG indicated the mapped beats. The initial site of activation is marked by a black asterisk and a purple arrow.
than those in failing hearts and VTs initiated from relatively fewer sites in control hearts. Furthermore, the altered substrate of the failing heart (e.g., cardiac enlargement, hypertrophy, altered shape, remodeling) may also make noninvasive imaging of cardiac activation more challenging. Nevertheless, we showed that the imaging performance was consistent with our previous findings in the control dogs both in term of the correlation of global activation pattern and localization of focal initiation sites in such a large animal model with cardiac size similar to human. Meanwhile, the more dispersed VT focal sites in the failing heart were also successfully detected and localized. In addition, our validation results indicate that the novel imaging principle, which is based upon basic biophysics, is applicable to imaging cardiac activation in failing hearts. This represents an important finding in our effort in establishing noninvasive 3D cardiac activation imaging capability for imaging cardiac diseases.

This study also shows the potential role of 3DCEI in complementing invasive cardiac mapping techniques to define the arrhythmia mechanism. Previous invasive 3D intra-cardiac mapping showed that spontaneously occurring PVCs and VTs in a nonschematic HF rabbit model were initiated in the subendocardium by a nonreentrant mechanism (30). Focal mechanism was also observed in patients with idiopathic dilated cardiomyopathy (28). In the present study, the findings for the mechanism of spontaneously occurring arrhythmias were consistent with the previous invasive mapping results (20). Both the spontaneously occurring VTs and the NE-induced nonsustained VTs initiated by a focal mechanism primarily from the subendocardium. Most focal initiation sites were located at apex, right ventricular outflow tract, and left lateral wall. These findings indicate 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 spontaneously occurring VTs could be attributed to the elevated activation of sympathetic nervous system in HF dogs. When compared with the spontaneously occurring VTs, the NE-induced VTs were faster, longer, and had more focal initiation sites. We also identified a few VT beats induced by NE (3 out of 135 VT beats) that initiated from the subepicardium. Furthermore, this novel canine HF model exhibits no significant differences in LV fibrosis compared with controls (S. M. Pogwizd, personal communication). These mechanistic findings and their noninvasive assessment and characterization by 3DCEI will provide the foundation for a wide range of studies in which this noninvasive approach can be applied to other scenarios (such as later studies in patients) where concurrent 3D intra-cardiac mapping is not possible. The good correlation between the measured and imaged activation sequences and the good localization accuracy of initiation sites imply that 3DCEI may become an important clinical tool to benefit the clinical decision of the choice of the optimal interventional procedures (e.g., during catheter ablation to help shorten the ablation time and help with a critical question of whether an endocardial or epicardial approach is needed, or during implantation of CRT device to investigate the electrical synchronization for the optimal placement of pacemaker leads) when treating HF patients.

It is also noted that CC was used to quantify the overall agreement between measured activation sequence and imaged activation sequence, and we used common biostatistics rules to interpret the value of CC. We realized that the interpretation of the CC value could vary depending on the problem, and therefore we compared the interpretation of the CC value with other similar studies by other groups on other approaches of cardiac inverse solutions (3, 16, 38). We believe that our interpretation of CC value as good correlation is reasonable.

**Conclusion**

Both the spontaneously occurring and the NE-induced nonsustained VTs associated with nonschematic HF could have focal activation pattern. The 3DCEI approach is feasible to image the activation pattern and localize the initiation site of sustained VTs associated with nonischemic HF could have a critical question of whether an endocardial or epicardial approach is needed, or during implantation of CRT device to investigate the electrical synchronization for the optimal placement of pacemaker leads) when treating HF patients.

**GRANTS**

This work was supported in part by National Heart, Lung, and Blood Institute Grants HL-080093 (to B. He) and HL-073966 (to S. M. Pogwizd) and National Science Foundation Grant CBET-0756331 (to B. He). C. Han was supported in part by a Predoctoral Fellowship from the American Heart Association, Midwest Affiliate.
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