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Noninvasive Cardiac Activation Imaging of Ventricular Arrhythmias during Drug-induced QT Prolongation in the Rabbit Heart

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Abstract

Background—Imaging myocardial activation from noninvasive body surface potentials promises to aid in both cardiovascular research and clinical medicine.

Objective—This study investigates the ability of a noninvasive 3-dimensional cardiac electrical imaging (3DCEI) technique for characterizing the activation patterns of dynamically changing ventricular arrhythmias during drug-induced QT prolongation in rabbit.

Methods—Simultaneous body surface potential mapping and 3-dimensional intra-cardiac mapping were performed in a closed-chest condition in eight rabbits. Data analysis was performed on premature ventricular complexes, couplets, and torsades de pointes (TdP) induced during i.v. administration of clofilium and phenylephrine with combinations of various infusion rates.

Results—The drug infusion led to significant increase of QT interval (175 ± 7 ms to 274 ± 31 ms) and rate-corrected QT interval (183 ± 5 ms to 262 ± 21 ms) during the first dose cycle. All the ectopic beats initiated by a focal activation pattern. The initial beat of TdPs arose at focal site, whereas the subsequent beats were due to focal activity from different sites or two competing focal sites. The imaged results captured the dynamic shift of activation patterns and were in good correlation with the simultaneous measurements with a correlation coefficient of 0.65 ± 0.02 averaged over 111 ectopic beats. Sites of initial activation were localized to be ~ 5 mm.

Conclusion—The 3DCEI technique could localize the origin of activation and image activation sequence of TdP during QT prolongation induced by clofilium and phenylephrine in rabbit. It offers the potential to non-invasively investigate the proarrhythmic effects of drug infusion and assess the mechanisms of arrhythmias on a beat-to-beat basis.

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Conflict of Interest Disclosures: Bin He is an inventor of a US Patent for the imaging technique used in this study.

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Keywords

cardiac imaging; electrocardiography; cardiac mapping; torsades de pointes; QT prolongation; rabbit model

Introduction

Torsades de pointes (TdP)¹ is a life-threatening arrhythmia that might degenerate into ventricular fibrillation and cause sudden cardiac death. TdP can occur during QT prolongation, as a consequence of genetic alteration or drug administration. Various investigations have been made to examine the potential of drugs to prolong QT interval and cause TdP, which usually exhibits a characteristic twisting of QRS complexes around the isoelectric axis.¹ TdP has a continuously changing QRS morphology and thus requires single-beat mapping techniques to characterize the dynamic activation patterns within the heart. Three-dimensional (3D) intra-cardiac mapping technique emerges as an important tool to investigate the electrophysiological mechanism underlying the ventricular arrhythmias associated with QT prolongation in *in vivo* animal models.^{2–5}

Noninvasive cardiac electrical imaging techniques represent a novel means which offer the potential to help define the underlying arrhythmia mechanisms and facilitate therapeutic treatments in clinical medicine.^{6–8} By estimating the equivalent cardiac sources from body surface potential maps (BSPMs), such techniques could provide noninvasive information with regard to the global cardiac activation pattern in a single beat and thus may be used to study the proarrhythmic effects of drug infusion. In this study, we apply a novel 3D cardiac electrical imaging (3DCEI) technique^{8–10} to study the activation patterns of TdP during drug-induced QT prolongation in rabbit. We performed simultaneous body surface potential mapping and 3D intra-cardiac mapping^{11–13} in a closed-chest condition^{8,14} in rabbits. The class III antiarrhythmic drug clofilium¹⁵ and phenylephrine were infused in the *in vivo* rabbit model to prolong QT interval and induce ventricular arrhythmias¹⁶ including premature ventricular complex (PVC), couplet, and TdP. The imaged activation sequence was also compared with the simultaneously measured activation sequence from 3D intra-cardiac mapping.

Methods

Experimental Procedures

Eight healthy New Zealand white rabbits of either sex (3.6 to 4.3 kg) were studied under a protocol approved by the Institutional Animal Care and Use Committees of the University of Minnesota and the University of Alabama at Birmingham. The animal preparation and surgical procedure were as described in reference.⁸ Up to 64 repositionable BSPM electrodes were uniformly placed to cover the anterior-lateral chest up to the mid-axillary line, and up to 27 transmural plunge-needle electrodes were inserted in the left ventricle (LV) and right ventricle (RV) of the rabbits. Each LV plunge-needle electrode contains 8 bipolar electrode-pairs with an inter-electrode distance of 500 μm , while each RV electrode contains 2 bipolar electrode-pairs with an inter-electrode distance of 500 μm . The chest and skin were then carefully closed with silk suture. Bipolar electrograms were continuously recorded from all electrode-pairs together with body surface potentials from surface electrodes. At the completion of the mapping study, post-operative ultra fast computed tomography (UFCT) scans were performed on the living rabbit to build realistic geometry model and localize the plunge-needle electrodes within the myocardium.⁸ We performed pre-operative UFCT scans on all animals. However, the pre-operative UFCT images were only used when the post-operative UFCT images were unavailable. For all rabbits, the

plunge-needle electrodes were carefully localized by replacing each with a labeled pin. The heart was then fixed in formalin and underwent an *ex vivo* UFCT scan to further facilitate precise 3D localization of the transmural electrodes.

Drug Infusion Protocol

Ventricular arrhythmias including PVCs, couplets, and TdPs were induced by i.v. administration of clofilium and phenylephrine in combinations of various infusion rates in the *in vivo* normal rabbit heart using an established protocol.¹⁶ Figure 1.A shows the protocol for drug infusion. For the first dose cycle, the phenylephrine infusion rate was begun at $75 \text{ nmol kg}^{-1} \text{ min}^{-1}$, and gradually increased to 150, 225 and $300 \text{ nmol kg}^{-1} \text{ min}^{-1}$ for every 3 min, while clofilium was infused at $20 \text{ nmol kg}^{-1} \text{ min}^{-1}$ 5 min after the infusion of phenylephrine. This protocol was repeated at higher doses of clofilium at 60 and $200 \text{ nmol kg}^{-1} \text{ min}^{-1}$ with the same infusion rate for phenylephrine for the second and third dose cycles. There were 10 min intervals between different dose cycles.¹⁶

Principles of 3DCEI

The cardiac electrical activity throughout the ventricular myocardium was represented by a distributed equivalent current density model. Derived from bidomain theory,^{17,18} potentials measurable over the body surface were linearly related to the equivalent current density distribution. A spatiotemporal regularization technique and lead-field normalized weighted minimum norm estimation^{10,19} were used to reconstruct the time course of local equivalent current density at each myocardial site. The activation time at each myocardial site was determined as the instant when the time course of the estimated local equivalent current density reached its maximum magnitude.¹⁰

Data Analysis

Post-experiment data analysis was performed for the recorded ECG data. The QT interval was manually annotated from the beginning of Q wave to the end of the T wave using ECG lead I and lead II, as well as body surface ECGs. The rate-corrected QT (QT_c) interval was calculated according to Carlsson's formula: $QT_c = QT - 0.175(RR - 300)$.²⁰

The measured activation sequence was constructed in the method previously described in^{8,9} when the post-operative UFCT scans were available. When post-operative UFCT scans were unavailable (rabbits 3, 4, and 8), the pre-operative UFCT images were used to build the *in vivo* heart-torso model. An alternative *ex vivo* heart model was built based on the *ex vivo* UFCT images of the isolated heart. The plunged-needle electrodes were localized and each needle was represented by a line in this *ex vivo* heart model. A registration process was used by shifting and rotating the *ex vivo* heart model to minimize the distance error of the anatomical landmarks (e.g., apex, outflow tract, and atria appendages) between the *in vivo* heart model and *ex vivo* heart model. After registration, each line representing the needle was extended and the intersection point between the line and the surface of the *in vivo* heart model was identified. Based on this intersection point, the direction of the line, and the structure information of each needle, the locations of the plunge-needle electrodes in the *in vivo* heart model were estimated. The corresponding activation time of each recording electrode was assigned on the basis of peak criteria,^{13,14,15,21} and then an interpolation algorithm as described in⁸ was applied to obtain the complete 3D measured activation sequence throughout the ventricular myocardium.

Numerical data are presented as mean $\pm$ SEM. The correlation coefficient (CC) was computed to quantify the overall agreement between the measured and imaged activation sequences. The localization error (LE), which is defined as the distance between 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, and a P value < 0.05 was considered statistically significant.

Results

Experimentation and Modeling

After insertion of plunge electrodes, closure of the chest did not alter heart rate or mean arterial blood pressure (232 ± 6 vs 238 ± 6 bpm and 62 ± 4 vs 62 ± 3 mm Hg, respectively, $P = \text{NS}$ vs pre-closure) or total activation times (TATs) of sinus beats (31 ± 1 ms vs 29 ± 1 ms, $P = \text{NS}$ vs pre-closure), which were consistent with previously published data in control rabbits.⁸ The infusion of clofilium and phenylephrine led to significant increase of the RR interval (255 ± 14 ms to 376 ± 34 ms, $P < 0.05$), the QT interval (175 ± 7 ms to 274 ± 31 ms, $P < 0.05$), and the QT_c interval (183 ± 5 ms to 262 ± 21 ms, $P < 0.05$) during the first dose cycle, as shown in Figure 1.C. The change of QT interval and QT_c interval was greater in the first dose cycle, as compared to the other two cycles. Table 1 summarizes the ventricular arrhythmias induced during the infusion of clofilium and phenylephrine. Ectopic activities in terms of multiform PVCs were observed in all animals. TdPs were induced in four rabbits (See Figure 1.B for an example of TdP on ECG). Rabbit 3 degenerated into ventricular fibrillation. Rabbits 4 and 8 degenerated into ventricular asystole during the last dose cycle.

The realistic geometry rabbit heart-torso model was constructed for each animal from the UFCT images. The rabbit ventricular myocardium was tessellated into 6987 ± 330 evenly-spaced grid points. The spatial resolution of the ventricle models was 1 mm. There were 151 ± 7 intramural bipolar electrodes during 3D intra-cardiac mapping and 59 ± 1 BSPM electrodes on the body surface.

PVCs and Couplets

Data analysis using 3DCEI and 3D intra-cardiac mapping performed on a total of 31 isolated PVCs and 7 couplets from all rabbits suggests that these ectopic beats initiated in the subendocardium by focal activation. For each rabbit, the PVCs were observed to continuously initiate at several myocardial sites. The initiation sites covered both LV and RV outflow tract (RVOT). PVCs initiated with a cycle length (CL) of 407 ± 18 ms and conducted with a TAT of 53 ± 2 ms, while the CL and TAT for couplets were 387 ± 32 ms and 56 ± 2 ms respectively, as shown by 3D intra-cardiac mapping.

Figure 2.A and Figure 2.B show the comparison between the measured and imaged activation sequences for two PVC beats in rabbit 1. The first PVC initiated at basal anterior RVOT, and the wavefront then propagated over the septum and terminated at middle lateral LV. The second PVC initiated at the basal anterior LV and terminated at posterior RV. The imaged results resembled the measured counterparts with respect to the overall activation patterns. Furthermore, the initiation sites were reconstructed at basal anterior RVOT and basal anterior LV respectively. Multiple PVCs and beats from TdPs in rabbit 1 were observed to be continuously firing at these two sites. Figure 3 shows a couplet in rabbit 7. The first beat in Figure 3.A initiated at basal lateral wall of RVOT and terminated at middle left wall. The second beat of this couplet initiated at the basal anterior septum of LV and terminated at RV lateral wall. The imaged results captured the overall activation patterns for this couplet and the initial sites were identified respectively.

Figure 4 shows PVC beat in rabbit 8 that degenerated into the ventricular asystole. The ECG suggested there was no ventricular electrical activity after two ventricular ectopic beats. These two ventricular ectopic beats had the same activation pattern, with a focal initiation at

basal lateral of RVOT. The imaged activation sequence captured the overall activation pattern and identified the initiation site at basal lateral wall of RVOT for the beat indicated in the red box of ECG.

TdPs

TdPs were induced in four rabbits. The QT interval and QT_c interval of sinus beats right before the onset of first TdPs were increased as compared with those of sinus beats before drug infusion ($285\pm 29\text{ms}$ vs $180\pm 14\text{ms}$, $P<0.05$ for QT interval and $258\pm 22\text{ms}$ vs $188\pm 9\text{ms}$, $P<0.05$ for QT_c interval). Data analysis was performed on a total of 73 beats from 10 episodes of TdPs (three to twenty-two beats for each episode). The averaged CL was $263\pm 10\text{ms}$ and TAT was $52\pm 1\text{ms}$. All these ectopic beats had focal initiation.

Figure 5.A and Figure 5.B show the simultaneous recordings of ECG tracings (CH1-CH9) in 3DCEI and bipolar electrograms of a ten-beat TdP in rabbit 2. The ECG morphology exhibited twisted QRS complexes around the isoelectric axis in lead I. More negative QRS-complexes turned into more positive complexes with an intervening transition zone. The averaged CL was $195\pm 8\text{ms}$ and TAT was $52\pm 5\text{ms}$ for this TdP. Figure 5.B suggests the focal activation pattern for the first two beats of this TdP, based on the selected bipolar electrograms throughout the ventricles. Figure 5.C, Figure 5.D, and Figure 5.E show the activation sequences for beat 2, beat 7, and beat 9 respectively. At the beginning of this TdP, activation initiated from a subendocardial site of the basal LV (site “L”). From there, it spread to the basal lateral wall of RVOT. This activation pattern did not change significantly for the first 6 ectopic beats and the site of latest activation during an ectopic beat was far from the site of earliest activation of the following beat. Beat 9 and beat 10 demonstrated another typical activation pattern, with initiation located at the RV base (site “R”), as shown in Figure 5.E. The mapping results further suggested that in the middle of this TdP, there was simultaneous early activation at two sites, with one site located at basal lateral RVOT and another site located at basal LV, indicating the fusion beats with two completing foci (sites “L+R”), as shown in Figure 5.D for beat 7 and beat 8. The imaged activation sequences clearly captured such dynamic transition of activation patterns and identified two initiation sites for this TdP. Besides, the two initiation sites of this TdP were well localized from the imaged activation maps.

Figure 6 shows another example of a 6-beat TdP in rabbit 3. In Figure 6.A, the first ectopic beat had an initiation site at anterior RVOT, and then the initiation site shifted to anterior middle wall of LV for the second ectopic beat (Figure 6.B). The last four ectopic beats had continuously been firing at the same site at post-lateral wall of middle RV (Figure 6.C). The averaged CL was $220\pm 8\text{ms}$ and TAT was $48\pm 2\text{ms}$ for this TdP. The imaged activation sequence clearly captured such shift of initial activation sites and the overall activation patterns were in good agreement with the measurements.

The quantitative comparison was also performed between imaged and measured activation sequences. Averaging 111 ectopic beats from PVCs, couplets, and TdPs with single focal initiation site, the CC was 0.65 ± 0.02 , suggesting good agreement between the imaged results and the simultaneous measurements. Furthermore, the origin of arrhythmias was estimated to be $5.9\pm 0.3\text{mm}$ from the measured site, implying the reasonably good localization accuracy.

Discussion

The present study reports the use of a novel 3DCEI technique to non-invasively investigate the global activation pattern of cardiac arrhythmias during drug-induced QT-prolongation in the *in vivo* rabbit heart. We showed that the infusion of clofilium and phenylephrine led to

QT prolongation and induced different forms of ventricular arrhythmias during simultaneous body surface potential mapping and 3D intra-cardiac mapping. The data analysis suggested that the ectopic beats including PVCs, couplets, and TdPs were all initiated by a focal mechanism and the TdPs were then maintained with the dynamical shift of initiation sites or two completing foci. The imaged activation sequences were in good correlation with the simultaneous intra-cardiac measurements with an averaged CC of 0.65 ± 0.02 and LE of $\sim 5\text{mm}$ over 111 ectopic beats with single initiation site. These findings imply that 3DCEI is feasible in reconstructing global activation pattern and imaging dynamically changing arrhythmias on a beat-to-beat basis.

Much effort has been devoted to the development of noninvasive cardiac electrical imaging techniques to estimate the equivalent cardiac sources from BSPMs.^{6–10,14,22–33} The current imaging method has a notable feature of imaging cardiac activation sequence throughout the ventricular myocardium, which represents an important alternative over other heart surface-based imaging techniques. 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 protocol, and thus enabled quantitative assessments of the 3DCEI approach in animal models with clinically relevant cardiac diseases. This work extended our previous study in the control rabbits⁸ into investigating the 3DCEI technique for imaging activation sequence in the setting of drug-induced prolongation of action potential and QT interval in rabbits. This also represented an important effort to define the potential role of this method in facilitating clinical diagnosis and management of cardiac arrhythmias. The imaging performance was consistent with our previous findings in the control rabbits⁸ in terms of CC and LE. The close match between the imaged activation sequence and the direct measurement suggests that significant information regarding ventricular excitation (e.g., global activation pattern and regions with earliest and latest activation) has been preserved in the imaged activation maps in this animal model of human disease.

In this study, post-operative UFCT scans were unavailable in three rabbits. Therefore the pre-operative UFCT images were used to build the *in vivo* heart model and the registration process was used to estimate the locations of the plunge-needle electrodes in this pre-operative *in vivo* heart model. In our previous study, we have shown that similar activation pattern was obtained between the registration-based procedure and the 3D activation mapping procedure using hand drawing on templates of axial slices of the rabbit heart.¹⁴ In this study, we further evaluated the accuracy of the registration process in two rabbits in which the post-operative *in vivo* CT images were available to directly localize the plunge-needle electrodes in the *in vivo* heart model. The averaged CC between the activation sequence from directly localized plunged-needle electrodes and the activation sequence from registration-based plunged-needle electrodes was 0.91 ± 0.04 (ranged from 0.86 to 0.97) from ectopic beats with six different initiation sites. We believed that the registration error was modest and registration process would not affect significantly the characterization of activation pattern in arrhythmias, which is the key focus of this study.

The results suggest the potential clinical role of 3DCEI in diagnosing arrhythmia mechanisms and complementing cardiac mapping techniques. Different ventricular arrhythmias including PVCs, couplets, and TdPs were induced during the infusion of clofilium and phenylephrine in the *in vivo* rabbit heart. The mechanism of TdP perpetuation is still not clear. Two possible mechanisms have been suggested: focal activity due to triggered activity and reentry. Both arrhythmogenic mechanisms have been documented during cardiac mapping studies.^{2–5,34,35} In the present study, both the 3D intra-cardiac mapping results and the noninvasive imaging results suggested a focal mechanism for the initiation of TdPs that were recorded. The results also found two competing foci, which

provided the underlying electrophysiological mechanism for the twisted QRS morphology in ECG in the episodes of TdP. It is noted that the focal mechanism is found particularly in this animal model and the current study cannot provide a clear cut answer to explain the discrepancies between focal and reentry mechanisms for the termination of TdP especially for human or other animal models. Nevertheless, the findings imply the potential role of 3DCEI for characterizing the activation patterns of dynamically-changing ventricular arrhythmias and studying the proarrhythmic effects during drug infusion.

In this study, we defined nonreentrant activation as has been done in a number of previous studies.^{11,12,13} We have found that mapping from ~200 sites in the rabbit heart (which is equivalent to mapping from over 2600 sites in the canine heart) provides adequate resolution to assess arrhythmia mechanism. We realize that we cannot completely rule out microreentry, but for a small reentrant circuit to occur between electrodes would require a conduction velocity that is at least an order of magnitude slower than the slowest conduction velocity we observed, making reentry extremely unlikely. It is also likely that multi-cellular early afterdepolarizations (EADs) might lead to the fluctuations in body surface potentials. However, in order to provide a more definitive answer to EADs, the experimental protocol needs to be refined to record EADs by some other means (monophasic action potentials catheters or other action potential recordings), in addition to body surface potentials for 3DCEI and intra-cardiac mapping. This is beyond the scope of the current study and needs further investigation.

Conclusion

In conclusion, the present study suggests the capability of 3DCEI to dynamically characterize the 3D ventricular activation patterns and localize the origin of activation during ventricular arrhythmias with drug-induced QT prolongation, as evaluated by 3D intra-cardiac mapping in rabbit. The findings imply the potential application of 3DCEI to aid in studying the proarrhythmic effects of drug infusion and understanding the arrhythmia mechanisms associated with QT prolongation in the clinical setting.

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List of Abbreviations

3D	3-dimensional
3DCEI	3-dimensional cardiac electrical imaging
ECG	Electrocardiography
LV	Left ventricle
PVC	Premature ventricular complex
RV	Right ventricle
RVOT	Right ventricle outflow tract
TdP	Torsades de pointes
UFCT	Ultra fast computed tomography

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Figure 1.

(A) The drug infusion protocol. (B) Example of torsades de pointes. (C) The change of cycle length, QT interval, and rate-corrected QT (QT_c) interval during the drug infusion.

Figure 2.

Comparison between the measured and imaged activation sequences for two premature ventricular contractions (A) and (B) in rabbit 1. The activation sequence is color coded from red to blue, corresponding to earliest and latest activations. ECG lead I is shown with red boxes indicating the beats analyzed. The activation sequence is displayed on epicardial and endocardial surfaces, respectively, in an anterior view. The measured initial site and the estimated initial site of activation are marked by a black asterisk and a purple arrow.

Figure 3.

Comparison between measured and imaged activation sequences for a couplet (A) and (B) in rabbit 7. The epicardial and endocardial surfaces are displayed in a right anterior view for the beat in (A) and in a left top view for the beat in (B), respectively.

Figure 4. Comparison between measured and imaged activation sequences for a premature ventricular complex preceding ventricular asystole in rabbit 8. The epicardial and endocardial surfaces are displayed respectively in an anterior view.

Figure 5.

(A) Selected channels of ECG tracings (CH1-CH9) in body surface potential mapping for 3DCEI and ECG lead I for a ten-beat torsades de pointes (TdP) in rabbit 2. “L” indicates the initiation site located in the left ventricle and “R” indicates the initiation site located in the right ventricle. (B) Selected bipolar electrograms for the first two beats of this TdP. In the left column, red dots and letters from a to j represent the locations for the selected plunge-needle electrodes in the heart. In the middle and right columns, the activation time for each bipolar electrogram is displayed in red for the first two beats of this TdP. Panels (C), (D), and (E) show the comparison between measured and imaged activation sequences for beat 2, beat 7, and beat 9 of this TdP, respectively. The epicardial and endocardial surfaces are displayed in an anterior view.

Figure 6.

Comparison between measured and imaged activation sequences for a six-beat TdP in rabbit 3. Panels (A), (B), and (C) show the activation sequence for the first three beats, respectively. The epicardial and endocardial surfaces are displayed in an anterior view (A), a left anterior view (B), and a right posterior view (C) respectively.

Table 1
Ventricular arrhythmias induced during the infusion of clofilium and phenylephrine.

Rabbit No.	Sex	PVC	Couplet	TdP	Sites of Initiation	
					RVOT	LV
1	F	+	+	+	Basal anterior.	Basal anterior.
2	F	+	+	+	Basal inferior, basal lateral.	Basal anterior, apical inferior.
3	M	+	+	+	Basal lateral, basal anterior.	Basal anterior, middle inferior.
4	F	+	+	-	Basal anterior.	Middle antero-lateral, apical inferior.
5	F	+	+	+	Middle anterior, middle septum.	Apical lateral.
6	F	+	+	-	Middle anterior	Middle antero-septal, apical anterior.
7	F	+	+	-	Basal lateral	Basal antero-septal, basal anterior, basal infero-lateral.
8	F	+	-	-	Basal lateral.	Apex.

Note: PVC, premature ventricular complex; TdP, torsades de pointes; RVOT, right ventricle outflow tract; LV, left ventricle.