RESEARCH ARTICLE

Ventricular Repolarization Sequence During Right Ventricular Endocardial and Left Ventricular Epicardial Pacing: Monophasic Action Potential Mapping in Swine

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ABSTRACT. Previous studies have suggested that the sequence of ventricular repolarization follows that of activation during sinus rhythm and atrial pacing. However, the repolarization sequence during ventricular pacing is unknown. Using the CARTO mapping system on 10 healthy pigs, global monophasic action potentials (MAPs) were recorded from the left ventricular (LV) and right ventricular (RV) endocardium at 121 ± 35 sites during right atrial (RA) pacing, RV apex endocardial (RVEndo) pacing and LV laterobasal epicardial (LVEpi) pacing. The MAP mapping procedure of each pacing protocol was performed within 3 h. Local activation time (AT), MAP duration (MAPd) and end-of-repolarization (EOR) time were measured, and three-dimensional global maps of the AT and EOR were constructed. The results showed that 1) MAPd in both ventricles during RVEndo pacing was similar to that during RA pacing (p > 0.05), whereas MAPd during LVEpi pacing was significantly greater than that during RVEndo pacing (p < 0.05); 2) in all maps, there was a negative correlation between MAPd and AT and a positive correlation between EOR time and AT (p < 0.05–0.001); and 3) during RA pacing, the EOR sequence followed the AT sequence in both ventricles. Strikingly, the EOR sequence was also consistent with the AT sequence in both ventricles either during RVEndo pacing or during LVEpi pacing, even though the mapping was performed under abrupt changing of the pacing site. The ventricular repolarization sequence followed the activation sequence not only during RA pacing, but also during RVEndo pacing and LVEpi pacing, suggesting the importance of the activation sequence in governing repolarization patterns. Significant changes in repolarization from an altered activation sequence could happen within a few hours in vivo, implying that electrical remodeling of the ventricles may be rapidly induced by altered activation sequence.

KEYWORDS. repolarization sequence, activation sequence, ventricular pacing, monophasic action potential.

Introduction

Ventricular pacing has been widely used in patients with bradycardia, and recent studies have further highlighted the benefits of resynchronization therapy involving biventricular pacing for patients with congestive heart failure.1–3 In contrast to the extensive in vivo explorations of ventricular repolarization during sinus rhythm, however, the characteristics of repolarization during
ventricular pacing are poorly understood. Existing reports on the changes in ventricular repolarization under different pacing protocols have mainly been limited to in vitro studies and have mainly focused on ventricular electrical remodeling.

The global repolarization sequence is an important feature of ventricular repolarization. Recent studies have suggested that, contrary to the conventional concept that the repolarization sequence is in the direction opposite to that of the activation, the global sequence of repolarization follows that of activation during sinus rhythm. Moreover, previous data from in vitro ventricular preparations have suggested that the altered activation sequence could lead to changes in ventricular repolarization. How the global ventricular repolarization sequence is changed by an altered ventricular activation sequence, however, has never been evaluated in vivo.

The present study was designed to explore the patterns of global ventricular repolarization in vivo under ventricular pacing at two most commonly used ventricular pacing sites, endocardial pacing at the right ventricular (RV) apex and epicardial pacing at the lateral left ventricle, and to examine whether the altered activation sequence still governs the ventricular repolarization sequence.

Methods

Subjects and anesthesia

Ten healthy pigs weighing 46–52 kg were premedicated with pancuronium bromide (0.1 mg/kg), thiopental (5 mg/kg), and atropine (0.015 mg/kg). Anesthesia was maintained with an infusion of 10 ml/h of a mixture of 1 mg fentanyl and 10 mg of pancuronium bromide. Intubation and artificial ventilation of the pigs were performed during the study. Volume-controlled ventilation of 8 l/min, 20 breaths/min, positive end-expiration pressure of 5 cm H2O and FiO2 of 0.5 were used. The study was approved by the local ethics committee, and the electrophysiological procedures were in accordance with the guidelines of our local institution.

Pacing protocols

A temporary myocardial active fixation pacing lead (Model 646, Medtronic, Minneapolis, MN) was introduced through the right jugular vein and attached to the high lateral right atrium (RA) or the RV apex. For left ventricular (LV) epicardial pacing, a 4F pacing electrode was used. The electrode was relatively difficult to deliver due to the anatomy of the porcine coronary venous system, in which the great cardiac vein joins with a prominent left azygous vein at the posterolateral atrioventricular groove where it becomes the coronary sinus (Figure 1). In this study, a 6F lumen catheter was introduced into the coronary sinus through which the 4F pacing lead was delivered, avoiding going up to the left azygous vein, into the great cardiac vein, as far as possible until it stopped to allow a stable LV epicardial pacing. Thus, the pacing leads were located on the epicardial side at the laterobasal part of the LV (Figure 1). The pacing leads were connected to an external pacemaker (Model 30–77, St. Jude Medical, St. Paul, MN), with the output at twice the diastolic threshold and 0.4 ms pulse width.

In five pigs (Group I), endocardial monophasic action potentials (MAPs) were recorded from both right and left ventricles during RA pacing, and then during RV pacing at the RV apex (RVEndo). In the remaining five pigs (Group II), endocardial MAPs were recorded from both ventricles during epicardial pacing at a laterobasal site of the left ventricle (LVEpi) and then during RVEndo pacing. A period of sinus rhythm for more than 30 min was kept between the two pacing protocols. MAPs were always recorded after 30 min of atrial/ventricular pacing to reach the steady state. To avoid potential time-dependent changes, the mapping procedure of each pacing protocol was limited to 3 h or less. In addition, to avoid the influence of variations in heart rate and thereby the

Figure 1: The anatomy of the coronary sinus in swine. (a) Photograph showing A, coronary sinus; B, left azygous vein; C, great cardiac vein. (b) X-ray image showing the tip of left ventricular epicardial pacing lead (arrow).
capture of sinus beats, the pacing rate was set at 130 beats/min, 20–30 beats/min faster than the baseline rate, during the mapping.

**MAP recording using the CARTO system**

The electroanatomical mapping system (CARTO; Biosense Webster, Waterloo, Belgium) has been described in detail previously. In brief, the torso of the subject is covered by three magnetic fields of different frequencies. A location reference (Ref-Star, Biosense Webster) is fixed on the back of the subject, while a mapping catheter (Navi-Star, Biosense Webster) navigates within the cardiac chambers. The magnetic sensors present in the tip of the mapping catheter and the location reference continuously compare the intensities of the three magnetic fields, ensuring that the location of the mapping catheter can be accurately determined and displayed in real time. Three-dimensional maps of endocardial activation can be constructed from accurately localized electrograms recorded using the mapping catheter. The accuracy of spatial localization has been verified to be $\leq 0.7 \text{ mm in vivo}$.11

A modified-tip Navi-Star catheter (7F, Biosense Webster) was used in this study, which has a contact ball 0.5 mm in length and 1 mm in diameter at the end of the tip electrode to facilitate the recording of MAP signals. For LV mapping, the catheter was introduced into the left ventricle via the right carotid artery and/or the right femoral artery. For RV mapping, the catheter was introduced via the right jugular vein and/or the right femoral vein. A 7F long sheath (St. Jude Medical) was used to facilitate catheterization in some areas of the right or left ventricle whenever needed.

MAP signals were recorded between the 4-mm tip electrode (exploring electrode) and the 2-mm ring electrode 1 mm proximal to the tip (indifferent electrode) at a filter bandwidth of 0.05–400 Hz. A unipolar electrogram from the indifferent electrode was also recorded at a filter bandwidth of 0.5–120 Hz. When the amplitude and morphology of the MAP in the real-time monitor window of the CARTO system appeared satisfactory, it was captured in a sampling window for further inspection. The accepted signals were stored simultaneously at a sampling frequency of 1 kHz. Care was taken to place the mapping catheter perpendicularly against the endocardium and to avoid “ST segment” elevation, i.e. >20% amplitude of the ventricular deflection on the unipolar electrogram from the indifferent electrode. At least one MAP was recorded in an area of 2 cm² during the mapping.

Twelve-lead electrocardiogram (ECG) was simultaneously recorded with the MAP recordings at a filter setting of 0.5–120 Hz using the CARTO system, with the body surface electrodes being placed referencing to the electrode placement in humans.

**MAP analysis**

MAP analysis was performed off-line by an independent investigator using the double annotation feature of the CARTO system. The first annotation line was set at the maximum slope of the MAP upstroke, representing local activation, and the second was set at the intersection between the baseline and the tangent to the steepest slope on phase 3 of the MAP, representing local end of repolarization (EOR) (Figure 2). The two annotation lines were both manually set and carefully checked with display time scales of 200 mm/s and 100 mm/s.

The activation time (AT) was defined as the time interval from the earliest recorded ventricular activation to the local activation, the EOR time as that from the earliest ventricular activation to the local EOR, and the MAP duration (MAPd) as that from the local activation
to the local EOR. These three values were obtained at each site, taking the maximum slope or minimum value of the QRS complex in V4 on the surface ECG as time reference (Figure 2). Based on these values, three-dimensional maps of the AT and EOR were constructed under each pacing protocol.

Statistical analysis

All data are presented as mean ± 1 SD. Differences between the two groups and among the three pacing protocols were analyzed using the Mann–Whitney test. Linear correlation and regression analyses were used to study the relationship between the MAPd and AT and between the EOR time and AT. Thus, all MAPds and the EOR times in a map were plotted against AT, regardless of recording sites. A level of p < 0.05 was considered to be statistically significant.

Results

General data

MAPs were recorded from 112 ± 16 endocardial sites of both ventricles during RA pacing in five pigs (Group I), from 122 ± 23 sites during RV Endo pacing in all 10 pigs (Groups I and II), and from 126 ± 26 sites during LV Epi pacing in five pigs (Group II). The endocardial AT and MAPd of right and left ventricles were measured in each group during RA pacing; RV Endo pacing and LV Epi pacing, respectively (Table 1). Based on these data, the EOR times were calculated, and the three-dimensional maps of activation and repolarization under each pacing protocol were reconstructed in each pig. Thus, in total, 20 sets of ventricular maps were constructed.

In Group I, MAPd during RV Endo pacing, which was 228 ± 11 ms in LV and 220 ± 11 ms in RV, was similar to that during RA pacing, which was 222 ± 10 ms in LV and 213 ± 9 ms in RV (both p > 0.05). In Group II, however, MAPd during LV Epi pacing was 247 ± 12 ms in LV and 229 ± 10 ms in RV, which was significantly greater than that during RV Endo pacing (223 ± 8 ms in LV and 217 ± 13 ms in RV; both p < 0.05). During RV Endo pacing, no significant difference in MAPd was found between the two groups (p > 0.05), suggesting that in Group II the earlier LV Epi pacing did not have a significant effect on MAPd recorded during RV Endo pacing.

Activation sequence

During right atrial pacing (RAP), the activation started from the anteroseptum (n = 3) or midseptum (n = 2) of the LV, propagated to the RV septum and continued eccentrically toward the apex and anterior and posterior parts of both ventricles, finally ending in the left postero-lateral (n = 2) and right lateral basal areas (n = 3).

During RV Endo pacing, in both groups the activation started from the pacing site at the RV apex and propagated eccentrically toward the septum and the RV free wall. The LV breakthrough was observed at the apicoventricular area in five pigs (Figure 3a), at the midseptal area in three pigs, and both areas in two pigs (Figure 4a). After entering the LV, the activation spread eccentrically toward the apex and anterior and lateral wall of the LV. The latest activation was located at the lateral (n = 2) or posterolateral (n = 4) basal areas of the RV, and the posterolateral basal area of the LV (n = 4), respectively (Figure 5a).

During LV Epi pacing, the earliest activation started at the pacing site in the laterobasal area of the LV and propagated eccentrically toward the left anterior wall, apex, and septum. The activation broke into the LV at the midseptal (n = 1) or posteroseptal regions (n = 4) (Figure 6a) and propagated eccentrically from the septum to the apex, anterior and lateral wall, finally ending at the posterobasal (n = 1) and laterobasal (n = 4) areas of the RV (Figure 7a).

Repolarization sequence

During RA pacing, the EOR sequence was recognizable on all five maps, and it was similar to the AT sequence. The EOR started from the superior (n = 3) or midseptum (n = 2) of the LV, proceeded toward the RV septum, continued eccentrically to both ventricles, and ended in the posterolateral LV (n = 2) and the lateral basal RV (n = 3). In these maps, the longest MAPds were all recorded in or near the earliest activation areas, i.e. the septal/apical areas, whereas the shortest MAPds were recorded in or near the latest activation areas on all five maps.

Table 1: The activation times and MAP durations of right and left ventricles during RA, RV Endo and LV Epi pacing

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Activation time (ms)</th>
<th>MAP duration (ms)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>RV + LV</td>
<td>RV</td>
</tr>
<tr>
<td>RA Pacing (I)</td>
<td>5</td>
<td>28 ± 6</td>
<td>22 ± 6</td>
</tr>
<tr>
<td>RV Endo Pacing (I)</td>
<td>5</td>
<td>34 ± 8</td>
<td>23 ± 9</td>
</tr>
<tr>
<td>LV Epi Pacing (II)</td>
<td>5</td>
<td>43 ± 11</td>
<td>39 ± 11</td>
</tr>
<tr>
<td>RV Endo Pacing (II)</td>
<td>5</td>
<td>35 ± 9</td>
<td>24 ± 9</td>
</tr>
<tr>
<td>RV Endo Pacing (I + II)</td>
<td>10</td>
<td>34 ± 9</td>
<td>23 ± 9</td>
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</tbody>
</table>

Data are presented as mean ± 1 SD in ms. *MAP duration during LV Epi pacing was significantly greater than that during RV Endo and RA pacing (p < 0.05). MAP = monophasic action potential; RA = right atrial; RV Endo = right ventricular endocardial; LV Epi = left ventricular epicardial; I and II = Group I and Group II.

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During RV Endo pacing, the EOR sequence was recognizable in all five pigs from Group I and in four of the five pigs from Group II. In these nine pigs, the EOR followed similar sequences as the activation (Figure 5b). The earliest EOR started from the RV apical pacing site and proceeded eccentrically toward the septum and the

![Figure 3: Right anterior oblique views of activation (AT) (a) and end-of-repolarization (EOR) (b) sequences of the left ventricle (LV) during endocardial pacing at the right ventricular apex (RVEndoP) in pig 1. The LV breakthrough site is at the apicoseptal area. In the LV, the activation propagated eccentrically toward the apical, anterior, and lateral LV wall, and ended at the posterolateral basal area of the LV. The EOR sequence is very similar to that of the AT, including a similar breakthrough point at the apical septum.]

![Figure 4: Right anterior oblique views of activation (AT) (a) and end-of-repolarization (EOR) (b) sequences of the left ventricle (LV) during endocardial pacing at the right ventricular apex (RVEndoP) in pig 6. The left ventricular breakthrough sites are observed at both apicoseptal and midseptal regions. In the LV, the activation propagates eccentrically toward the apical, anterior, and lateral LV wall, and ends at the posterolateral basal area of the LV (not seen in this view). The EOR sequence also follows that of the AT, with similar breakthrough points at the midseptum and apical septum.]

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Figure 5: Bottom views of activation (AT) (a) and end-of-repolarization (EOR) (b) sequences of both right and left ventricles (RV and LV) during endocardial pacing at the RV apex (RV_EndoP) in pig 8. The activation starts from the pacing site at the RV apex, and propagates eccentrically toward the septum and the RV free wall. In the LV, the activation spread eccentrically toward the apex, anterior, and lateral wall. The latest activation is located at the posterolateral basal area of the LV. The EOR sequence follows that of the AT.

Figure 6: Left lateral views of activation (AT) (a) and end-of-repolarization (EOR) (b) sequences of the right ventricle (RV) during epicardial pacing at a laterobasal site of the left ventricle (LV_EpiP) in pig 9. The RV breakthrough site of the AT is located at the posterior septum, and the activation then propagates eccentrically from the septum to the apex and the anterior and lateral wall, finally ending at the right laterobasal areas. The EOR breaks into the RV also at the posterior septum, and follows a sequence similar to that of the AT.
RV free wall. Interestingly, in the LV, the earliest EORs were observed in similar regions around the activation breakthrough sites, which were at the apicoseptal area in six pigs (Figure 3b), at the midseptal area in two pigs, and at both areas in one pig (Figure 4b). In the LV, the EOR spread eccentrically toward the apex and the anterior and lateral LV wall. The latest EOR ended at the lateral (n = 2) or posterolateral (n = 2) basal areas in the RV, or at the posterolateral basal area of the LV (n = 5). On these nine maps, the longest MAPds were recorded in or near the earliest activation areas, whereas the shortest MAPds were recorded in or near the latest activation areas. The EOR pattern of the remaining pig was so complicated on the LV map that no EOR sequence was recognizable.

During LV_Epi pacing, the EOR sequence was recognizable in all five pigs of Group II, and the sequence of EOR followed that of activation. The earliest EOR started at the lateral pacing area, and proceeded eccentrically toward the anterior wall, apex, and septum in the LV. Similar to what was observed during RV_Endo pacing, the earliest EOR in the RV was located at the activation breakthrough areas, which were in the midseptal (n = 1) and posteroseptal regions (n = 4) (Figure 6b). The EOR then proceeded eccentrically from the septum to the apex and the anterior and lateral wall, and finally ended at the laterobasal areas (n = 5) of the RV (Figure 7b). The longest MAPds were recorded in or near the LV laterobasal pacing area in four of the five pigs. In two pigs, some of the longest MAPds were also observed around the septal/apical areas, although these MAPds did not affect the global repolarization sequence. The shortest MAPds were recorded in or near the latest activation areas, the laterobasal areas in the RV, in all five pigs.

**Linear correlation and regression analysis**

A negative correlation between MAPd and AT and a positive correlation between the EOR and AT were found in all maps regardless during RA, RV_Endo and LV_Epi pacing. The correlation was statistically significant in all of the maps (p < 0.05–0.001, Table 2). For the linear regression between MAPd and AT, the slope during LV_Epi pacing (−0.25 ± 0.09) had a trend to be less steep than that during RAP and RV_Endo pacing (−0.46 ± 0.13 and −0.32 ± 0.11, Figure 8), although the differences were not statistically significant (p > 0.05). For the linear regression between the EOR time and AT, the slope during LV_Epi pacing (0.54 ± 0.10) was similar to that during RAP and RV_Endo pacing (0.47 ± 0.11 and 0.51 ± 0.10, p > 0.05) (Figure 8, Table 2).

**Discussion**

**Relationship between activation and repolarization sequence**

The conventional view is that the repolarization sequence is in the direction opposite to that of the activation, which has been supported mainly by the ECG finding that the polarities of the T wave are concordant...
with those of the QRS complex. Experimental findings supporting the above concept were mainly based on evidence of transmural gradients, with the inner wall being more negative than the outer wall. Earlier clinical studies found a negative correlation between MAPd and AT in MAP recordings from 5 to 11 sites, and this was used to support the concept of opposite directions of activation and repolarization. In later in vitro studies using the optical mapping technique, the repolarization sequence was considered to be independent of activation sequence. This was based on the phenomenon that repolarization shows a relatively uniform pattern associated with ventricular fiber orientation when the pacing is altered from the epicardium to the endocardium in ventricular sheet preparations. Obviously, the relationship between activation and repolarization sequence has not been investigated in sufficient depth.

Recently, in a series of experimental and clinical studies from our institution, around 50 MAPs from the endocardium of the LV were recorded during sinus rhythm using the CARTO system. In spite of a significant negative correlation between the MAPd and AT, a positive correlation between the EOR time and AT was demonstrated, suggesting that the magnitude of the progressive shortening of MAPd was not enough to compensate for the progressive delay in the AT. As a result, the sequence of repolarization was similar to that of activation during sinus rhythm, as has also been supported by other studies. In the current study, a negative correlation between the MAPd and AT and a positive correlation between the EOR time and AT were also found during RA pacing. Interestingly, after changes in the activation sequence by RV Endo and LVEpi pacing, the repolarization sequence also changed to follow the activation sequence. These results are consistent with our previous findings of concordant sequences of the EOR and AT, and they strongly support the importance of the activation sequence in modulating the repolarization patterns. An earlier study by Lux et al lends experimental support to our conclusion. They recorded high-resolution arrays of unipolar electrograms from the canine epicardium and found that the repolarization “waves” propagated away from the pacing site, irrespective of its location, and replicated “collision” when multiple sites were paced simultaneously.

**Contribution of AT to the repolarization patterns**

Under normal ventricular activation, the repolarization follows the activation sequence, as also shown in an

### Table 2: Linear regression analysis of MAPd versus AT, and of EOR versus AT

<table>
<thead>
<tr>
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<th>n</th>
<th>sites</th>
<th>MAPd versus AT</th>
<th>EOR versus AT</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td>slope r</td>
<td>slope r</td>
</tr>
<tr>
<td>RAP</td>
<td>5</td>
<td>112 ± 16</td>
<td>-0.46 ± 0.13</td>
<td>-0.43 ± 0.18</td>
</tr>
<tr>
<td>RV EndoP</td>
<td>10</td>
<td>122 ± 23</td>
<td>-0.32 ± 0.11</td>
<td>-0.42 ± 0.08</td>
</tr>
<tr>
<td>LVEpiP</td>
<td>5</td>
<td>126 ± 26</td>
<td>-0.25 ± 0.09</td>
<td>-0.33 ± 0.10</td>
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MAPd = monophasic action potential duration; AT = activation time; EOR = end-of-repolarization time; RAP = right atrial pacing; RV EndoP = right ventricular endocardial pacing; LVEpiP = left ventricular epicardial pacing.

**Figure 8:** Linear correlation analysis from one of the pigs between monophasic action potential duration (MAPd) and activation time (AT), and between end-of-repolarization time (EOR) and AT during right atrial pacing (RAP) (a); right ventricular endocardial pacing (RV EndoP) (b); and left ventricular epicardial pacing (LVEpiP) (c), respectively. Under all these different pacing protocols, negative correlations were found between MAPd and AT, whereas positive correlations were found between EOR and AT.
earlier study of ours. In the current study, the repolarization followed the activation sequence even under RVEndo and LV_epi pacing. The mechanisms of modulation of repolarization by the activation sequence are still unclear. One of the mechanisms that has been proposed to explain the effect of the activation sequence on repolarization is electrotone interaction. Passive electrotonic coupling between cells can impose an electrical load on myocytes during propagation, and altered activation sequence may modulate action potential duration by altering the electrotonic load during repolarization. Action potential duration would be shortened in the direction of propagation as repolarized upstream cells may abbreviate repolarization of action potential plateau of downstream cells. In addition, the significant and persistent change in action potential duration demonstrated by other investigators suggested that many currents, such as Ito, are also being changed under such conditions, which could also be involved in the mechanisms of the repolarization changes.

In addition to these possible mechanisms, our in vivo data suggest that the relatively slow ventricular activation time during ventricular pacing may make an essential contribution to the sequence and pattern of ventricular repolarization. During RA pacing, impulse conducts quickly in the ventricles through the Purkinje system at around 3–4 m/s. During ventricular stimulation from the base of the LV and the apex of the RV, however, the activation does not spread along the Purkinje fibers, but goes slowly through the ordinary myocardial fibers at about 0.2–1 m/s, as also indicated by the relatively greater global AT of ventricles during ventricular pacing in this study. In addition, impulses conduct faster along the endocardial fibers and, as a result, the total activation time required for the activation is shorter under endocardial pacing than under epicardial pacing, which could explain the shorter total AT during RVEndo pacing than during LV_epi pacing in our study. Thus, the considerably delayed AT during ventricular pacing accounts more for the corresponding late EOR than does the progressive shortening of MAP with progressively later AT, which was evidenced by the less steep slope between the MAPd and AT during LV_epi pacing in this study. Moreover, the concordant sequence between activation and repolarization during LV_epi pacing in all pigs further supports the importance of slow impulse propagation in modulating the repolarization pattern during ventricular pacing.

Previous reports on the influence of altered activation sequence on ventricular repolarization have mainly been studies on cardiac memory, and the available data were generally obtained after the cessation of a period of altered ventricular activation. The repolarization changes that happen during alteration of activation sequence, especially those under abrupt sequence changes, were little known. In canine wedge preparations, Libbus and colleagues found that the transmural action potential duration could be changed significantly a few minutes after the pacing site was altered from the endocardium to the epicardium. In isolated rabbit heart preparations, Costard-Jackle et al observed a negative correlation between the AT and action potential duration during either RA pacing or 60–120 min of RV pacing, which is consistent with our results.

One may argue that in this study, the MAP sequentially recorded during the first few hours of ventricular pacing may have been influenced by the time-dependent changes, as observed in the isolated rabbit heart preparations, and that continuous ventricular pacing could produce slow changes of action potential duration. However, each corresponding set of AT, MAPd, and EOR time used for correlation analysis in our study was measured on the same recording from the same site, which has cancelled the potential time-dependent effect. Moreover, the MAPs were randomly recorded over the right and LV endocardium under each pacing protocol, which could also minimize the influence of the time-dependent changes, if any. In addition, previous studies have suggested that the action potential duration should reach steady state after approximately 15 min of activation sequence changes, which further supports the validity of our data acquired after at least 30 min of steady-state pacing for assessment of the modulation of the global repolarization under altered activation sequence. Importantly, the changes in repolarization during altered ventricular pacing protocols under in vivo conditions may be different from those during normal activation sequence, after the cessation of pacing in isolated heart preparations.

Study limitation

Myocardial repolarization is a complicated electrophysiological process and, in addition to endocardial repolarization gradients, epicardial and transmural gradients are important factors that influence the global sequence of repolarization. The current data, however, do not permit evaluation of the interaction of the endocardial, transmural, and epicardial gradients.

Previous studies on short-term cardiac memory have suggested that several hours of ventricular pacing can persistently modulate the ventricular repolarization sequence. Thus, the global repolarization maps obtained during the latter pacing protocol may have been influenced by the former, since the two pacing protocols were performed sequentially. However, all the MAPs were recorded after at least 30 min of steady-state pacing under each pacing protocol, which may help to
reduce the possible influence. In addition, the LV_Epi pacing did not show any significant effect on the MAPd during the consequent RV_Endo pacing in Group II, and there was a consistent correlation between both EOR and MAPd and AT in all the maps. These findings suggest that the short-term memory did not have any critical influence in this study.

**Conclusion**

Global sequences of ventricular repolarization under RV_Endo pacing and LV_Epi pacing were evaluated in vivo. The repolarization sequence not only followed the activation sequence during RA pacing, but also during RV_Endo pacing and LV_Epi pacing, suggesting that the activation sequence is of importance in governing patterns of ventricular repolarization. Significant changes in repolarization from an altered activation sequence could happen within a few hours in vivo, indicating that electrical remodeling of the ventricles may be induced rapidly by an altered activation sequence.

**References**


