ELECTROPHYSIOLOGY

Dispersion of atrial repolarization in patients with paroxysmal atrial fibrillation

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To study the role of the dispersion of atrial repolarization (DAR) in the genesis of atrial fibrillation (AF), monophasic action potentials (MAP) were recorded simultaneously from a catheter at the high lateral right atrium (HLRA) and a catheter moving around the high, middle and low lateral right atrium (RA) the high, anterior and posterior septal RA and the RA appendage in 15 patients with paroxysmal AF and 15 patients with atrioventricular nodal re-entry tachycardia (AVNRT) or concealed Wolf-Parkinson-White syndrome (WPW) without history of AF. After recordings during sinus rhythm (SR), MAPs were recorded during programmed stimulation (PS) via the HLRA catheter at a drive cycle length (CL) of 500 ms. Thus, MAPs were recorded simultaneously from 2 sites at a time and sequentially from 4 to 12 sites during SR, drive pacing and PS. Taking the MAP at the HLRA as reference, the dispersion of repolarization time (dispersion of RT) and its two components, the dispersions of activation time (dispersion of AT) and MAP duration (dispersion of MAP duration) among the 4 to 12 sites were calculated and taken as parameters of DAR.

Results During SR and PS, the maximal dispersion of RT was significantly greater in AF than in control patients, 113 ± 49 ms vs 50 ± 28 ms (P<0.001) and 114 ± 56 vs 70 ± 43 ms (P<0.05) respectively. The increased dispersion of RT in the AF group was caused by increases in both dispersion of MAP duration and dispersion of AT.

Conclusion During SR and PS, DAR increased in patients with paroxysmal AF due to increases in dispersion of MAP duration and dispersion of AT, which suggests the involvement of both repolarization and conduction disturbances in the development of paroxysmal AF.

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Key Words: Monophasic action potential, atrial fibrillation, repolarization, dispersion.

Introduction

Correlation between the increased dispersion of myocardial repolarization and the genesis of cardiac arrhythmia has been extensively studied both experimentally and clinically. However, most of these studies were concerned with the electrophysiology of the ventricles and ventricular arrhythmias[1-2]. Due to limitations in the available methods, repolarization of the atrium and its correlation with the occurrence of atrial fibrillation has not been well evaluated. Dispersion of the P wave has been used to evaluate the heterogeneity of atrial repolarization[3-5]. However, difficulties in the determination of the end of the P wave limited widespread use of this method. Furthermore the P wave does not represent the repolarization time course of the atrium. The present study used the monophasic action potential (MAP) recording technique, which could accurately reflect the time course of local myocardial repolarization, to analyze the dispersion of atrial repolarization in patients with paroxysmal atrial fibrillation and to evaluate its role in the genesis of atrial fibrillation.


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Methods

Patients

Thirty patients referred to the First Affiliated Hospital, Dalian Medical University, Dalian, China, or to the University Hospital, Lund, Sweden, for electrophysiological studies and/or radio-frequency catheter ablation of supraventricular tachyarrhythmias were recruited.

Of the 30 patients, 15 with clinically documented idiopathic paroxysmal atrial fibrillation comprised the atrial fibrillation group. Ten of these patients were male and five females, with a mean age of 53 ± 13 years (range: 34–74 years). The average history of atrial fibrillation was 6.8 ± 4.5 years (range: 1–14 years). The other 15 patients, 9 male and 6 female with a mean age of 42 ± 14 years (range: 19–62 years) had paroxysmal supraventricular tachycardias and comprised the control group. The clinical tachycardias of the control patients were atrioventricular nodal re-entrant tachycardia in seven cases, concealed Wolff–Parkinson–White syndrome in seven cases, and no arrhythmia in one case. None of the control patients had a history of spontaneous atrial fibrillation.

Paroxysmal atrial fibrillation was clinically diagnosed by documentation of the arrhythmia on electrocardiograms (ECG), and/or Holter ECG recordings. Idiopathic atrial fibrillation was defined as atrial fibrillation without any detectable organic heart disease or any other disease that could cause atrial fibrillation.

Before the procedures, physical examination, ECG, echocardiography and X-ray examination were routinely performed. No patients in the two groups had detectable organic heart disease.

Prior to the study, all antiarrhythmic drugs were withdrawn for at least five half-lives. There was no patient who received amiodarone treatment within 3 months prior to the study. Informed consent was obtained from all patients. The study protocol was approved by the local ethics committees at both hospitals and the electrophysiological procedures were in accordance with local institutional guidelines.

MAP recording

MAP recordings were performed before other electrophysiological examinations and/or catheter ablation. Two silver–silver chloride MAP recording/pacing combination catheters (7F, quadripolar, EP Technologies) were introduced percutaneously into the right atrium via the right femoral vein. One of the catheters was positioned in the high lateral right atrium as a reference MAP recording catheter and for pacing and programmed stimulation. The other one, the exploring MAP recording catheter, was positioned sequentially at the high, middle and low lateral regions, the high, anterior and posterior septal regions and the appendage in the right atrium.

When satisfactory MAPs were obtained from both the high lateral right atrium via the reference catheter and at one of the remote sites via the exploring catheter, these two MAPs were recorded during sinus rhythm and during the testing of the atrial effective refractory period through the catheter at high lateral right atrium using the extrastimulus technique at a drive cycle length of 500 ms.

After the first recording, the exploring catheter was moved to a new site. As soon as a stable MAP was obtained via the exploring catheter from the new site, the MAPs were again recorded during sinus rhythm and programmed stimulation, with the extra stimuli delivered through the reference catheter at coupling intervals 40 to 50 ms longer than the atrial effective refractory period and with 10 ms decrements until the atrial effective refractory period was reached. In this way, MAPs were recorded simultaneously from two sites at a time and from multiple sites sequentially during sinus rhythm, drive-train pacing and single programmed stimulation at coupling intervals close to the atrial effective refractory period (Fig. 1).

Drive-train pacing and programmed stimulation were performed at twice the diastolic threshold with pulse duration of 1.0 ms using a programmed stimulator (Medtronic or Biotronik).

The MAP signals were amplified using DC coupled differential amplifiers and isolated preamplifiers with filter bandwidths of 0 to 4000 Hz (Prucka Tech) or 0–0.01 to 1300 Hz (Bard Lab System), digitized at a sampling rate of 1000 Hz and recorded on optical disks for analysis. Twelve-lead surface ECGs were also recorded. Hard copies of the MAPs were printed at a recording speed of 100 mm·s⁻¹.

Definitions of terms

AT=activation time, the interval from the onset of the P wave on the body surface ECG during sinus rhythm, or from the stimulus artefact during pacing, to the time when the MAP upstroke reaches the 10% depolarization level.

MAP duration=MAP duration at 90% repolarization level.

RT=total repolarization time, the sum of the AT and MAP duration.

Dispersion of AT=the absolute value of the time difference between the ATs of the two simultaneously recorded MAPs. During pacing and programmed stimulation, this represents the conduction time from the stimulation point to the remote site.

Dispersion of MAP duration=the absolute value of the difference between the MAP duration of the two simultaneously recorded MAPs

Dispersion of RT=the absolute value of the time difference between the times of 90% repolarization on the two simultaneously recorded MAPs. This consists of dispersion of AT and dispersion of MAP duration.

Maximal dispersion of RT=the largest dispersion of RT at all the sampling sites in a patient.

Maximal dispersion of MAP duration=the largest dispersion of MAP duration at all the sampling sites in a
Patient (disregarding whether it was found at the site associated with maximal dispersion of RT).

Data analysis and statistics

Heart rate variation during sinus rhythm was calculated to monitor the potential influence of rate-dependent changes of MAP duration. The last drive-train in an atrial effective refractory period test was selected for the measurements during pacing so as to get the measurements close to steady state values.

Three main parameters, AT, MAP duration and RT, and their dispersions were measured manually from hard copies of the MAP recordings by two independent observers. During sinus rhythm and drive-train pacing, three consecutive MAPs were analyzed. During programmed stimulation, all the extra beats were analyzed. The maximal dispersion of RT and its two components, dispersion at AT and dispersion of MAP duration in the atrial fibrillation and control groups were analyzed and compared (Fig. 1). Differences in maximal dispersion of MAP duration between the two groups were also analyzed.

The mean level of phase 4 in two consecutive MAPs was taken as the baseline for MAP analysis. When the baseline disturbance was more than 10% of the plateau amplitude, the recording was excluded from analysis.
All data were expressed as mean ± 1 standard deviation in ms. Student’s *t*-test was used to assess the significance of the differences in parameters between the two groups. Within each group, the parameters during sinus rhythm, drive-train pacing and programmed stimulation were compared using two-way ANOVA analysis. To evaluate the influence of age on the electrophysiological properties, paired *t*-tests of age-matched comparison between 10 patients in each group were also performed. A *P*<0·05 was considered as statistically significant.

**Results**

The number of recording sites varied from 4 to 12 (6·6 ± 1·9 sites) in the patients, depending on the possibility of obtaining MAPs in the sampling areas and the time available for MAP recording. The amplitude of the MAPs was 4·31 ± 2·45 mV and the baseline disturbances were within 10% of the plateau amplitudes of the MAPs. In all patients, the heart rate variations were within 5% of the heart rate at the beginning of the study.

The maximal dispersion of RT and its two components dispersion of AT and dispersion of MAP duration during sinus rhythm, drive-train pacing and programmed stimulation are presented in Fig. 2. During sinus rhythm, the maximal dispersion of RT in atrial fibrillation patients was significantly larger than that in control patients. During programmed stimulation, maximal dispersion of RT was also significantly greater in the atrial fibrillation group than in the control group. Both components of the dispersion of RT, dispersion of AT and dispersion of MAP duration, contributed to the increase in the maximal dispersion of RT in patients with paroxysmal atrial fibrillation, as compared with control patients (Figs 2 and 3).

Within each group, dispersion of AT during drive-train pacing and programmed stimulation increased markedly, as compared with that during sinus rhythm. During programmed stimulation, the increase was 66·9% in the atrial fibrillation group, as against 33·1% in the control group (*P*<0·05). During drive-train pacing and programmed stimulation, dispersion of MAP duration became slightly shortened in the atrial fibrillation group, but was not significantly changed in the control group. As a result of the changes in its two components, maximal dispersion of RT did not change significantly in the atrial fibrillation group, but increased slightly in the control group during programmed stimulation.

Disregarding whether it was observed at the site associated with the maximal dispersion of RT or not, the value of maximal dispersion of MAP duration at all the recording sites (Fig. 1) was much greater in the atrial fibrillation group than in the control group during sinus rhythm and programmed stimulation, but during drive-train pacing the difference between the two groups was not statistically significant (Table 1).

There was no significant difference in age between the two groups (52 ± 13 years vs 42 ± 14 years in AF and control group respectively, *P*>0·05). Age matched comparison between 10 patients in each of the groups showed that the maximal dispersion of RT and dispersion of MAP duration during sinus rhythm were significantly larger in the AF group than that in controls (*P*<0·05). The same trend of differences between the two groups was also found in other parameters. However, these differences were not statistically significant. The left atrial diameter across the long axis of the left atrium was 39 ± 7 mm for the AF group and 37 ± 2 mm for the control group (*P*>0·05).

Three patients in the AF group had AF episodes within 24 h prior to the study. No arrhythmia other than short runs of atrial fibrillation (29 runs in the atrial fibrillation group and four runs in the control group) was induced. No complications were observed during or after the study.

**Discussion**

**Methodological aspects of evaluating atrial repolarization**

It is commonly accepted that multiple micro-re-entrant activities are related to the development and/or perpetuation of atrial fibrillation[6,7]. Increased dispersion of repolarization or refractoriness and disturbances in condition may create an electrophysiological environment favouring re-entry, and hence the genesis of tachyarrhythmias. Unlike the ventricle, atrial electrical activity has a lower amplitude and the repolarization phase overlaps with the ventricular depolarization making the atrial repolarization difficult to observe from body surface recordings.

In some studies *P* wave duration[4,5] or signal-averaged *P* waves[8] were measured from the surface ECG to predict the occurrence of atrial fibrillation and *P* wave dispersion was used to indicate the existence of non-uniform atrial electrical activity. Endocardial electrograms from multiple right atrial sites were markedly prolonged and fragmented in patients with paroxysmal atrial fibrillation but not in patients without a history of atrial fibrillation[9]. However, the time-course of the atrial repolarization could not be evaluated using the above-mentioned methods[10]. The fibrillation interval during atrial fibrillation was also measured to evaluate the dispersion of the atrial effective refractory period[11,12]. The atrial effective refractory period dispersion could also be measured sequentially from multiple atrial sites during sinus rhythm, although it is very time-consuming in practice. Moreover, refractoriness is not always in accordance with the time-course of repolarization[13].

MAP recording can accurately reproduce the time-course of local myocardial repolarization[14]. With the advantage of *in vivo* application, the MAP recording technique is now considered the method of choice for evaluating repolarization disturbances. Olsson *et al.* recorded atrial MAPs in patients with chronic atrial
fibrillation immediately after electrical cardioversion and reported markedly shorter MAP durations in those with atrial fibrillation which relapsed during follow-up\cite{19}. Brorson et al. recorded right atrial MAPs sequentially at 2 to 3 sites in healthy males and in patients with supraventricular arrhythmias, which made measurement of the dispersion of atrial repolarization possible\cite{16,17}. Simultaneous MAP recordings from 2 sites in the right atrium to evaluate dispersion of MAP duration were also reported recently\cite{18,19}. In the latter two studies, however, MAP was only recorded during sinus rhythm and/or constant pacing and only MAP duration analyzed. In the current study, we recorded MAPs from 4 to 12 sites during sinus rhythm, drive-train pacing and programmed stimulation analyzed not only MAP duration but also AT and RT so as to explore systematically repolarization disturbances of the right atrium in patients with atrial fibrillation and its role in the genesis of atrial fibrillation.

**Increased dispersion of atrial repolarization and atrial fibrillation**

Increased dispersion of repolarization or refractoriness is linked to the development of tachyarrhythmias, with relatively clearer evidence for ventricular arrhythmias\cite{1,2}, while in patients with atrial fibrillation, the available data are limited and controversial\cite{17-19}.

Diker et al. recently recorded two MAPs simultaneously from the right atrium and found that dispersion of MAP duration between the two sites was significantly greater in patients with paroxysmal atrial fibrillation than in normal subjects\cite{18}. However, Kamalvand et al. reported that dispersion of atrial effective refractory between two right atrial sites was significantly smaller in patients with chronic atrial fibrillation after electrical cardioversion than in control patients\cite{19}.

Our results in this study showed that during sinus rhythm and programmed stimulation, both maximal dispersion of RT and maximal dispersion of MAP duration were significantly greater in patients with paroxysmal atrial fibrillation than in controls. The value of maximal dispersion of MAP duration during sinus rhythm was 143\% larger in patients with paroxysmal atrial fibrillation than in control patients and 3.5 times greater than in normal subjects\cite{16}. We found also that the increase in maximal dispersion of RT in atrial fibrillation immediately after electrical cardioversion and reported markedly shorter MAP durations in those with atrial fibrillation which relapsed during follow-up\cite{19}. Brorson et al. recorded right atrial MAPs sequentially at 2 to 3 sites in healthy males and in patients with supraventricular arrhythmias, which made measurement of the dispersion of atrial repolarization possible\cite{16,17}. Simultaneous MAP recordings from 2 sites in the right atrium to evaluate dispersion of MAP duration were also reported recently\cite{18,19}. In the latter two studies, however, MAP was only recorded during sinus rhythm and/or constant pacing and only MAP duration analyzed. In the current study, we recorded MAPs from 4 to 12 sites during sinus rhythm, drive-train pacing and programmed stimulation analyzed not only MAP duration but also AT and RT so as to explore systematically repolarization disturbances of the right atrium in patients with atrial fibrillation and its role in the genesis of atrial fibrillation.

**Figure 2** Comparison of maximum dispersion of repolarization time (Disp RT; a) and its two components, dispersion of activation time (Disp AT; b) and dispersion of monophasic action potential duration (Disp MAPd; c) in sinus rhythm (SR), drive-train pacing (S1) and programmed stimulation (S2) between the atrial fibrillation (AF, ■) patients and control group (Control, □). The maximal Disp RT during SR and S2 were significantly larger in patients with AF than that in control patients, *P<0.05, **P<0.001. The Disp AT during SR and S2 were significantly larger in patients with AF than that in control patients, *P<0.05. No significant difference between the two groups was shown during S1. The Disp AT was increased when S1 and S2 were added, and was significantly larger during S2 than that in SR in both groups, #P<0.01, ##P<0.05. The Disp MAPd in SR was significantly larger in patients with AF than that in control patients, *P<0.001. No significant difference was shown during S1 and S2 between the two groups. The Disp MAPd was significantly shortened during S1 and S2 as compared with that in SR in AF group.
fibrillation patients was due not only to the increase in dispersion of MAP duration, but also partially due to an increase in dispersion of AT, i.e., during programmed stimulation, activation started at an incomplete repolarization level and its propagation was delayed (Figs 1 and 3). This was more marked in the atrial fibrillation patients and consequently dispersion of AT was further augmented. Thus, the increased dispersions in both MAP duration and AT may result in an electrophysiological status that favours the genesis and/or perpetuation of atrial fibrillation in patients with paroxysmal atrial fibrillation.

Our findings are consistent with those reported by Brorson et al.\(^\text{[17]}\) and Diker et al.\(^\text{[18]}\), while the magnitude of the dispersion of repolarization was more pronounced than in their studies. This magnitude difference may be related to the different electrophysiological substrates in our patients from theirs, but is more likely related to the fact that we recorded MAPs at 4 to 12 sites, whereas only at 2 sites in the previous studies. Thus, dispersion of repolarization may tend to be greater globally or in a relatively larger area than in small localized areas, as found in the ventricle\(^\text{[20]}\). The findings by Kamalvand et al.\(^\text{[19]}\) might have been influenced by the ‘memory’ phenomenon of electrical remodelling of the myocardium during chronic atrial fibrillation, since the recordings were performed within 15 min after electrical cardioversion and may also be influenced by the two randomly selected recording sites. The electrophysiological status of the myocardium as well as the DC shock itself might additionally have contributed to their findings.

**Figure 3** Simultaneously recorded monophasic action potentials (MAP) during sinus rhythm, one from the high lateral right atrium (HRA), one from the site with maximal dispersion of repolarization time (Disp RT). A tracing of surface electrocardiogram with the earliest P wave onset is also presented. (a): In a control patient, dispersion of activation time (Disp AT) was 38 ms, dispersion of MAP duration (Disp MAPd) 22 ms and dispersion of RT 60 ms. (b): In a patient with paroxysmal atrial fibrillation, Disp AT was 85 ms, Disp MAPd 55 ms and Disp RT 140 ms. Thus, the dispersion of atrial repolarization is markedly greater in the patient with atrial fibrillation than in the control patient. LLW=low lateral wall and LPW=low posterior wall.

**Table 1 Maximal dispersion of monophasic action potential duration in the two groups**

<table>
<thead>
<tr>
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<th>Sinus rhythm</th>
<th>Drive-train pacing</th>
<th>Programmed stimulation</th>
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<tbody>
<tr>
<td>PAF</td>
<td>119.5 ± 43.6**</td>
<td>89.2 ± 48.8</td>
<td>107.8 ± 52.1*</td>
</tr>
<tr>
<td>Control</td>
<td>49.1 ± 33.1</td>
<td>62.8 ± 21.7</td>
<td>59.5 ± 17.5</td>
</tr>
</tbody>
</table>

\(*=P<0.01\) and **=*P<0.001 compared with control group. PAF=paroxysmal atrial fibrillation.
In the current study, no difference in dispersion of RT was shown between the two groups during drive train pacing, which may be mainly due to the significant decrease in dispersion of MAP duration in the atrial fibrillation group. We have no clear explanation for this unexpected finding. As atrial pacing has been shown to be effective in prevention of AF[21,22], whether atrial pacing at an adequate rate could reduce increased dispersion of repolarization in patients with AF warrants further study.

**Limitations**

To obtain detailed information on the dispersion of atrial repolarization, MAP recordings from a sufficient number of sites are required. However, to record MAPs extensively is difficult in the clinical setting. In this study, we recorded two MAPs simultaneously and 4–12 MAPs sequentially from the right atrium. No recordings from the left atrium were obtained, although MAPs from septal sites may indirectly reflect the electrophysiological status of the left atrium. Furthermore, sequentially recorded MAPs are subject to the influence of dynamic changes in atrial repolarization. Such time-dependent changes have, however, been observed only in the ventricle[23]. We did not find any beat-to-beat changes in our atrial MAP recordings or P wave changes in the surface ECG. The consistent findings of dispersion of RT and dispersion of MAP duration within groups and significant differences between groups, in accordance with the findings in earlier studies[17,18], suggest that time-dependent changes had no significant influence on our results.

**Conclusion**

Due to increases in both dispersion of MAP duration and dispersion of AT, the dispersion of atrial repolarization during sinus rhythm and programmed stimulation was increased in patients with paroxysmal atrial fibrillation, suggesting the involvement of repolarization and conduction disturbances in the development of paroxysmal atrial fibrillation.

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**References**


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