Further evidence of localized posterior interatrial conduction delay in lone paroxysmal atrial fibrillation

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Aims Prolongation of interatrial conduction time has been reported in patients with paroxysmal atrial fibrillation (PAF). The study objective was to localize the region of the conduction delay in patients with lone PAF.

Methods and Results Twenty-one patients with lone PAF and 23 patients with AV nodal re-entrant tachycardia ablation without history of PAF (control group) were recruited. Endocardial recordings were made during sinus rhythm and programmed atrial stimulation. The authors measured the interatrial conduction time, the ‘right-sided’ conduction time between the high lateral right atrium and the proximal coronary sinus (RA-CSp), and the ‘left-sided’ conduction time between the proximal and the distal coronary sinus (CSp-LA). During sinus rhythm, the interatrial conduction time was longer in the PAF group (103 ± 19 vs 86 ± 12 ms, P<0.01) due to delay of right-sided conduction (RA-CSp was 74 ± 20 vs 56 ± 10 ms, P<0.01). During programmed stimulation at the distal coronary sinus, the maximal RA-CSp time was also longer in the PAF group (110 ± 47 vs 69 ± 16 ms, P<0.05). No differences in CSp-LA time were observed.

Conclusion This study supports the role of posterior septal right atrial conduction disturbances in the genesis of lone PAF.

Key Words: Lone atrial fibrillation, interatrial conduction, electrophysiology.

Introduction

While atrial fibrillation (AF) currently remains the most common cardiac arrhythmia demanding therapy in society, its exact pathophysiological mechanisms are still incompletely understood. Although there is a growing pool of evidence for ectopic atrial activity causing paroxysms of AF in some patients[1–5], it is not at all clear how abundant this finding is in the entire AF population. Endocardial electrophysiological (EP) studies, performed during sinus rhythm on patients with paroxysmal AF (PAF), have repeatedly shown that disturbances of interatrial conduction are involved in the induction and maintenance of this arrhythmia[6,7]. Furthermore, dual-site right atrial[8], biatrial[9] or interatrial septal pacing[10,11], may prevent induction of AF, favouring the concept of primary conduction disturbances underlying the development of AF. It is, however, still not clear whether a homogenous deterioration of atrial conductive properties or a more localized abnormally conducting atrial tissue is responsible for the genesis of the arrhythmia.

The authors have previously published non-invasive evidence that localized posterior interatrial conduction delay is linked to a propensity for PAF[12]. Abnormalities of the configuration of the unfiltered signal-averaged P waves recorded in the orthogonal leads in patients with lone PAF suggested the conduction defect to be located in the posterior septal region. Therefore, the aim of this study was to explore, in a more exact way, possible correlation between intra- and interatrial conductive properties and the presence of lone PAF.

Material and methods

Twenty-one patients with lone PAF (15 males, six females, mean age 51.8 ± 10.4 years) were selected for study, and 23 consecutive patients with atioventricular
nodal re-entrant tachycardia admitted for radiofrequency catheter ablation without a previous history of AF (three males, 20 females, mean age 52.4 ± 12.5 years) were taken as a control group (Table 1). The electrophysiological sessions were performed as part of a clinically motivated examination. In the study group, the mean duration of the AF history was 7.9 ± 5.5 years (range 1–18 years). All patients had a history of multiple DC cardioversions. In 17 patients with a long history of arrhythmia (>1 year), more than three antiarrhythmic medications (including amiodarone, sotalol and propafenone) had failed substantially to reduce the frequency of AF paroxysms. All subjects enrolled in the study underwent transthoracic echocardiography. Left atrial diameters were measured in parasternal views. Patients were first involved in the study a minimum of five half-lives after ceasing antiarrhythmic drugs, and all gave their informed consent. Seven patients were treated with amiodarone before entering the study, and none of them was receiving the drug during the preceding 6 months. The study complied with the requirements of the Helsinki declaration.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Study population characteristics</th>
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<tr>
<td></td>
<td>PAF (n=21)</td>
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<tr>
<td>Male/female</td>
<td>15/6</td>
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<tr>
<td>Age (years)</td>
<td>51.8 ± 10.4</td>
</tr>
<tr>
<td>LA (mm)</td>
<td>45 ± 5*</td>
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<tr>
<td>Mean PAF history duration (years)</td>
<td>7.9 ± 5.5</td>
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*P<0.05 for comparison between the PAF and control groups. LA, left atrial diameter in the parasternal view; PAF, paroxysmal atrial fibrillation.

Definitions of the conduction times

Local activation was defined as a timing of (1) maximal absolute voltage for uni- and triphasic electrograms, or as (2) maximal derivative of the interphase transition for biphasic electrograms[13].

At the atrial sites, the activation time was defined as the time interval between the stimulus artifact or the earliest right atrial electrogram located in the sinus node region and the local bipolar electrogram.

Right-sided intra-atrial conduction was defined as activation times at the coronary sinus orifice and HSRA. When the multipolar catheter was not used, the quadripolar catheter placed at HLRA was used to record the right atrial local electrogram in the region adjacent to the sinus node.

Left-sided intra-atrial conduction was defined as the difference between the conduction times at HLRA and coronary sinus ostium, and the latest coronary sinus electrogram.

Interatrial conduction time was defined as the local activation time difference between the earliest signal in the right atrium and the latest in the coronary sinus.

Maximum values of conduction times were compared at the earliest coupled atrial premature extrastimuli preceding achievement of AERP.

Electrophysiological study protocol

The endocardial EP study protocol included programmed atrial stimulation at twice the diastolic threshold with a basic cycle length between 500 and 600 ms, which was shorter than the underlying sinus cycle length by at least 100 ms. Pacing was delivered to the high lateral right atrium (HLRA), the low lateral right atrium (LLRA) and the distal coronary sinus. It was followed by an extrastimulus with a coupling interval, which started from the basic drive cycle length and decreased in 10-ms decrements until the atrial effective refractory period (AERP) was reached. Registrations of atrial local activation in the HLRA, high septal right atrium (HSRA), His and coronary sinus areas were accomplished by standard positioning of 10-polar coronary sinus and quadripolar His catheters in all patients, and by placing 50-polar basket (3 PAF patients) or 20-polar Halo catheters (15 PAF and two control patients) in the right atrium. In the remaining control patients, two quadripolar catheters were used; one for pacing (at HLRA or LLRA) and the other for simultaneous recordings at HSRA. In order to explore conduction in the vicinity of the posterior interatrial septum, the coronary sinus catheter was placed under fluoroscopic guidance with its proximal pair of electrodes at the coronary sinus ostium. The positioning of all pacing and recording sites was documented by video-recorded fluoroscopic images and stored as printouts.

Statistics

Results were analysed using the non-parametric Mann–Whitney U-test for unpaired variables. All results are expressed as means ± standard deviations from the means. Statistical significance was indicated by a P value<0.05.

Results

Atrial dimensions and body size

The left atrial antero-posterior diameter measured by echocardiography in the parasternal view was significantly longer in patients with PAF (45 ± 5 vs 35 ± 4 mm, P<0.05). Body surface area (BSA) was also significantly greater in the PAF group (2.1 ± 0.3 vs 1.8 ± 0.2 m², P<0.01). Ratios of left atrial diameter to the BSA did not differ significantly between patients with PAF and controls.
Table 2  Right-to-left conduction during sinus rhythm and right atrial pacing

<table>
<thead>
<tr>
<th>Conduction time</th>
<th>Sinus rhythm</th>
<th>HLRA pacing</th>
<th>LLRA pacing</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>PAF</td>
<td>Control</td>
</tr>
<tr>
<td>IACT</td>
<td>86 ± 12</td>
<td>103 ± 19*</td>
<td>125 ± 25</td>
</tr>
<tr>
<td>RA-HSRA</td>
<td>19 ± 13</td>
<td>25 ± 15</td>
<td>64 ± 27</td>
</tr>
<tr>
<td>RA-CSp</td>
<td>56 ± 10</td>
<td>74 ± 20*</td>
<td>96 ± 20</td>
</tr>
<tr>
<td>HSRA-LA</td>
<td>72 ± 19</td>
<td>80 ± 12</td>
<td>75 ± 22</td>
</tr>
<tr>
<td>CSp-LA</td>
<td>26 ± 8</td>
<td>27 ± 10</td>
<td>32 ± 11</td>
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*P-value <0.01 for comparison between the control and PAF groups. HLRA, high lateral right atrium; LLRA, low lateral right atrium; IACT, interatrial conduction time; RA, right atrium; HSRA, high septal right atrium; LA, left atrium; CSp, proximal coronary sinus; PAF, paroxysmal atrial fibrillation. See text for definitions of conduction times.

Figure 1  Endocardial electrograms during sinus rhythm in a control patient without a previous history of atrial fibrillation (a) and a patient with lone paroxysmal atrial fibrillation (PAF) (b). Note the difference in the right-sided conduction time (RA-CSp) and interatrial conduction time (IACT) in the PAF patient. HLRA, high lateral right atrium; HSRA, high septal right atrium; CS, coronary sinus ostium; T n-m, electrode pairs from the 20-polar Halo catheter positioned in the right atrium.

not differ between the groups (21 ± 3 vs 20 ± 3 mm/m² for the PAF and control groups, respectively n.s.).

Atrial conduction during sinus rhythm

During sinus rhythm, there were significantly longer interatrial conduction times in the study group compared with the controls (103 ± 19 vs 86 ± 12 ms, \(P<0.01\)). Comparison of conduction times to the different septal sites showed that the activation time of the coronary sinus orifice was significantly longer in PAF patients (74 ± 20 vs 56 ± 10 ms, \(P<0.01\)), but no differences in left-sided conduction were seen (Table 2). Examples of different patterns of intra-atrial conduction are presented in Fig. 1.

Intra-atrial conduction during atrial pacing

While stimulation at the basic pacing drive delivered to HLRA and LLRA showed a tendency towards longer interatrial right-to-left conduction times and RA-CSp in PAF patients, this was not significant during right atrial pacing (Table 2).
Table 3  Left-to-right conduction during distal coronary sinus pacing

<table>
<thead>
<tr>
<th>Conduction time</th>
<th>Control</th>
<th>PAF</th>
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<tbody>
<tr>
<td>IACT (ms)</td>
<td>123 ± 19</td>
<td>140 ± 18</td>
</tr>
<tr>
<td>LA-HSRA (ms)</td>
<td>104 ± 15</td>
<td>107 ± 21</td>
</tr>
<tr>
<td>LA-CSp (ms)</td>
<td>48 ± 20</td>
<td>56 ± 23</td>
</tr>
<tr>
<td>HSRA-RA (ms)</td>
<td>33 ± 26</td>
<td>40 ± 24</td>
</tr>
<tr>
<td>CSp-RA (ms)</td>
<td>67 ± 21</td>
<td>90 ± 29*</td>
</tr>
</tbody>
</table>

*P value <0.05 for comparison between the control and PAF groups.

HLRA, high lateral right atrium; LLRA, low lateral right atrium; IACT, interatrial conduction time; RA, right atrium; HSRA, high septal right atrium; LA, left atrium; CSp, proximal coronary sinus; PAF, paroxysmal atrial fibrillation. See text for definitions of conduction times.

Pacing of the distal coronary sinus produced a response similar to right-sided pacing, with a tendency towards longer left-to-right conduction and significant prolongations of the conduction times between the coronary sinus orifice and HLRA in the PAF group (90 ± 29 ms vs 67 ± 21 ms, P<0.05, Table 3).

Effects of programmed atrial stimulation on intra-atrial conduction

There were no significant differences between the absolute values of the maximum conduction times in response to early-coupled extrastimuli during HLRA and LLRA pacing in the two groups. The maximum left-to-right conduction times between proximal CS and HLRA during programmed stimulation of the distal coronary sinus were greater in the PAF group than in controls (110 ± 47 ms vs 69 ± 16 ms, P<0.05).

Conduction in the proximal coronary sinus region

The authors also explored activation sequences within the coronary sinus during sinus rhythm and pacing at the HLRA or LLRA, which showed either unidirectional activation along the coronary sinus from its orifice to the distal part, or fusion of the two oppositely directed activation wavefronts (Fig. 2). In five PAF patients, collisions of the two wavefronts were demonstrated, while 16 PAF patients and all the control subjects showed unidirectional right-to-left activation spread along the coronary sinus.

Three patients from the PAF group showed a remarkable deterioration of conduction specifically located at the proximal coronary sinus area between CS 9-10 and CS 7-8 in response to early coupled extrastimuli at LLRA (Fig. 3). The maximum local activation time differences between the neighbouring electrode pairs (10 mm interelectrode distance) exceeded 50 ms. Conduction time on the left side from CS 7-8 was only slightly affected. The same findings were observed in one control patient who also developed non-sustained AF after LLRA programmed stimulation with single extrastimuli.

Discussion

This study provides further evidence for the localization of the intra-atrial conduction disturbance in patients with lone PAF. The pathophysiological mechanism is identified within the posterior septal right atrium as suggested previously from a series of examinations using unfiltered signal-averaged P-wave ECG[12].

Clinical assessment of interatrial conduction routes in humans

Electroanatomic right atrial mapping of left-to-right transeptal conduction performed in patients without structural heart disease has shown that the coronary sinus ostium is one of the three sites where right atrial activation breakthrough occurs (the others are Bachmann’s bundle and the fossa ovalis)[14]. Recently, right-to-left transeptal conduction in patients with patent foramen ovales was explored[15], showing that two main inputs (Bachmann’s bundle and the posterior septal region adjacent to the CS) provide the route for left atrial activation. The existence of electrical conduction between the two atria via the musculature of the coronary sinus has recently been experimentally confirmed[16].

Earlier studies of interatrial conduction in patients with PAF

A connection between prolonged interatrial conduction times and the presence of PAF has frequently been reported[6-7,17]. Although no specific area of deteriorated conduction responsible for the development of AF has been localized, some investigators believe that the induction and maintenance of AF are associated with abnormal conduction and a more enhanced dispersion of atrial refractoriness in the left atrium than in the right[1,18,19].

Invasive EP studies during sinus rhythm aimed at exploring the underlying mechanisms of AF have been performed in patients with structural heart disease[20,21], WPW syndrome[22,23], and idiopathic PAF[17,24-26]. In the majority of published reports, interatrial conduction times were studied during pacing or programmed stimulation at the right atrial appendage[17,23] or the high right atrium[27,28]. Registration of left atrial activity is routinely accomplished by recordings taken from the coronary sinus catheter. The interatrial conduction time was measured as the time difference between stimulus...
artifact at the right atrial appendage or high right atrium, and the beginning of the atrial electrogram at the distal coronary sinus\textsuperscript{[22,27]}.

**Main findings**

In agreement with the reports published previously, interatrial conduction times were longer in the PAF patients during sinus rhythm, as well as during pacing at any of the selected sites. The differences were statistically significant during sinus rhythm and distal coronary sinus pacing.

According to the present data, the differences in intra-atrial conduction times between the groups were observed almost exclusively in conduction between the sinus node area and the coronary sinus orifice. The differences were most prominent during sinus rhythm and programmed stimulation of the distal coronary sinus.

In contrast, none of the indices used for characterizing left-sided conduction (from the proximal coronary sinus and HSRA to the distal coronary sinus area) showed significant differences during either sinus rhythm or atrial stimulation.

No difference in right-to-left intra-atrial conduction was noticed between HLRA or LLRA and HSRA (at the putative insertion of Bachmann’s bundle), either during sinus rhythm or during pacing. At the same time, significant differences in conduction times between the HLRA and the coronary sinus ostium, discovered between the PAF and the control groups, highlight an important connection between the conduction delay in the right atrial part of the posterior interatrial conduction route and the presence of lone PAF.

These findings are in accordance with recently published reports which highlighted the role of conduction disturbances in the region of the proximal coronary sinus. It was known from clinical experience that atrial extrastimuli are more likely to induce AF when delivered from the high right atrium than from the coronary sinus\textsuperscript{[29]}. This phenomenon was studied by Papageorgiou et al.\textsuperscript{[30]} who suggested that non-uniform anisotropic properties, required for re-entry and initiation of AF, exist in the posterior triangle of Koch. More recently, it was shown that eliminating the conduction delay in the region of the proximal coronary sinus made it impossible to induce AF\textsuperscript{[31]}. The importance of this region for inducing AF is supported by Saksena et al.\textsuperscript{[32]}, who have demonstrated significant...
increases in conduction time in the posterior septal and proximal coronary sinus regions accompanying the induction of AF.

Studies with dual-site atrial pacing from the high right atrium and the coronary sinus ostium demonstrated the suppression of inducible AF or atrial flutter elicited after single-site high right atrial pacing in selected patients. Acute suppression was more likely to be observed in patients with greater dispersion of right atrial refractoriness between these two sites\[8\]. Jais et al. showed that during induced AF, the posterior intercaval and adjacent septal regions, as well as the septal, posterior and superior parts of the left atrium, exhibit complex atrial activity most of the time, which is significantly more disorganized than in other atrial regions\[13\].

The present findings are also in accordance with those reported by Lewalter et al.\[34\]. They showed, in a smaller number, that during low lateral pacing, conduction to the proximal coronary sinus is longer in patients with PAF than in controls, although no significant differences were demonstrated. Yu et al.\[35\], in their study evaluating effects of different atrial pacing modes on atrial electrophysiology, also showed that atrial conduction delay during HLRA pacing was more prominent in patients with PAF. However, the present finding of the delayed left-to-right conduction during distal CS pacing...
in patients with PAF is conflicting with their observations[3]. The authors believe that the present data, considered together with these recently published reports, support the role of the right atrial structures in the genesis of AF, and highlight one of the important directions of future studies of the EP mechanisms underlying this arrhythmia.

This study has also explored the activation sequence within the coronary sinus during sinus rhythm and pacing at the HLRA or LLRA, and documented either unidirectional activation along the coronary sinus or fusion of two oppositely directed activation wavefronts. The proximal positioning of the coronary sinus catheter used in this study favours the identification of this ‘fusion’ pattern, which may be explained by either a more superior location of the sinus node pacemaker (or HLRA pacing site) or by the presence of the delayed interatrial conduction via the posterior-inferior route in the septal region. Observation of the fusion pattern during LLRA pacing would support the presence of conduction disturbance. In fact, such a phenomenon was observed in five PAF patients during programmed stimulation of the LLRA, but was not observed in the control group.

Recent reports show that focal atrial activity, originating in the pulmonary veins and initiating AF, is also a very common finding, reported in about half of all patients with lone AF[4]. Therefore, it is not clear whether these two common pathophysiological mechanisms (focal activity and conduction disturbances) represent entirely different forms of AF or if they overlap each other producing an arrhythmogenic substrate.

**Limitations of the study**

Although the terminology ‘right-sided’ and ‘left-sided’ is used in this study, the technique of coronary catheter positioning did not allow verification the exact location of the proximal electrode pair. It is possible that catheter positioning under the fluoroscopic guidance might have influenced measurements of the intra-atrial conduction times. However, the same technique was used in both groups and the significant differences between the two groups suggest that the catheter positioning did not introduce errors into these measurements.

Since the proximal coronary sinus was the region of greatest interest in this study, the decapolar coronary sinus catheter was positioned in such a way that its proximal pair of electrodes was located near the coronary sinus ostium. In these circumstances, the registration sites may not have covered the entire length of the coronary sinus and, in particular, its distal region. Interatrial conduction times might, therefore, be underestimated. As mentioned above, this limitation would influence both groups equally and, therefore, only the variations of the coronary sinus lengths between the two groups could affect the observations, presumably to a limited extent.

Since the arrhythmia itself might produce anatomical and electrical atrial remodelling, the true logistic relation between these findings and the arrhythmia may be questioned. Nevertheless, localization of the conduction delay in the relatively limited region of the posterior interatrial septum in patients, who did not have chronic AF, indicates that atrial remodelling might be of less importance in the development of the localized conduction disturbance; this could be an underlying condition.

**Summary**

Predominant conduction disturbances within the right atrium causing a localized infero-posterior interatrial conduction delay were found in patients with PAF. No significant differences in left-sided intra-atrial conduction times between the PAF and control groups were found. These findings suggest that primary conduction disturbances between the proximal coronary sinus and the posterior interatrial septum result in interatrial conduction disturbances, which may be an important prerequisite for development of lone PAF in a group of patients. Further clarification of the role of these interatrial conduction disturbances in the genesis of lone PAF should be the subject of future studies.

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**References**


