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Deterioration of Interatrial Conduction in Patients with Paroxysmal Atrial Fibrillation: Electroanatomic mapping of the right atrium and the coronary sinus

Yunlong Xia, Eva Hertevig, Ole Kongstad, Erik Ljungström, Pyotr Platonov,
Magnus Holm*, Bertil Olsson, Shiwen Yuan.

Department of Cardiology, University Hospital, Lund, Sweden,
and *Biosense Webster Europe, Waterloo, Belgium

Short Title: Interatrial Conduction in Patients with and without Paroxysmal Atrial Fibrillation

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Correspondence to:

Shiwen Yuan, MD, PhD

Department of Cardiology

University Hospital

SE-221 85 Lund, Sweden

Tel: +46-46-173648

Fax: +46-46-157857

E-mail: Shiwen.Yuan@kard.lu.se

Abstract

Background: Interatrial conduction delay in atrial fibrillation (AF) patients has been reported. However, the localization of the interatrial conduction delay is still not clear. This study is aimed to analyze the velocities across the coronary sinus ostium (cross-CSo) and within the CS (intra-CS) in patients with and without paroxysmal AF, and estimate the interatrial conduction deterioration area in AF patients. **Methods:** Thirteen patients with paroxysmal AF and 10 control patients with atrioventricular nodal reentrant tachycardia or ectopic atrial tachycardia were enrolled in the study. Right atrial and CS mapping were performed using the CARTO electroanatomic mapping system during sinus rhythm and during distal CS pacing. The activation times and spatial distances of cross-CSo and intra-CS were measured between paired sites, from which the activation velocities of cross-CSo and intra-CS were obtained. **Results:** During sinus rhythm, the activation velocities of cross-CSo in the AF group (1.2 ± 0.2 m/s) were significantly slower than those in the control group (2.9 ± 1.6 m/s, $p < 0.05$). During distal CS pacing, the cross-CSo velocities of the AF group (1.0 ± 0.5 m/s) also appeared slower than those in the control group (1.4 ± 0.2 m/s, $p = 0.07$). However, no difference was found in intra-CS activation velocities between the two groups (2.8 ± 1.9 vs. 3.2 ± 2.2 m/s and 1.5 ± 0.3 vs. 1.4 ± 0.3 m/s, $p > 0.05$ during sinus rhythm and distal CS pacing, respectively). **Conclusion:** Interatrial conduction at the posteroparaseptal region across the CS ostium was significantly slower in our patients with paroxysmal AF than in control patients, which further supports the link between the interatrial conduction deterioration and paroxysmal AF.

Keywords: Atrial fibrillation, interatrial conduction, electroanatomic mapping, velocity.

Abbreviations

AF = atrial fibrillation

CS = coronary sinus

Cross-CSo = across the coronary sinus ostium

Intra-CS = within the coronary sinus

Introduction

The electrophysiologic mechanisms underlying atrial fibrillation (AF) are incompletely understood. Interatrial conduction disturbances have been implicated in the initiation and maintenance of AF (1-3). Although delayed conduction at the posteroparaseptal region in patients with paroxysmal AF has been reported and referred as a potential arrhythmogenic substrate (4), the exact localization of the interatrial conduction deterioration is still not clear. Several reports on conduction of atria and interatrial septum based on electroanatomic mapping and noncontact mapping have been published (5-9). However, these available data were merely conduction times that were likely to have been influenced by inter-individual variations in measurement distance. To the best of our knowledge, the velocities within the coronary sinus (CS) and across the CS ostium have never been analyzed.

In the present study in patients with and without paroxysmal AF, we measured the velocities within the CS and the interatrial conduction at the posteroparaseptal region across the ostium and along the long axis of the CS. The aim was to get more information about interatrial conduction, especially that across the CS ostium, and to estimate the deterioration area of interatrial conduction in patients with paroxysmal AF.

Methods

Study patients

The study included randomly selected patients, 13 with paroxysmal AF (the AF group, mean age 54 ± 8 years) and 10 patients with atrioventricular nodal reentrant tachycardia (N = 7) or ectopic atrial tachycardia (N = 3) without previous history of

AF (the control group, mean age 52 ± 12 years). Diagnosis was verified by evaluation of medical history, 12-lead ECG, documentation of the tachycardias and electrophysiology study. Patients with organic heart disease and systemic disorders were excluded. In AF group, the mean duration of paroxysmal AF history was 8 ± 4 years (range 2 to 11 years). All antiarrhythmic medication was terminated at least 5 half-lives before the electrophysiological study. No patient was taking amiodarone 3 months prior to the study. The study was approved by the local ethical committee and performed in accordance with the principles outlined in the Declaration of Helsinki. Informed consent was obtained from all patients.

Electroanatomic mapping protocol

The electroanatomic mapping system (CARTO, Biosense, Waterloo, Belgium) has previously been described in detail (9,10). In this study, we used the system for right atrium and CS mapping during sinus rhythm and/or distal CS pacing. In brief, a 6F decapolar catheter was introduced into the CS and advanced to a distal position with the proximal electrode at the CS ostium verified by fluoroscopic and catheter techniques. The mapping was performed by a 7F Navistar catheter (Biosense Webster), with the location reference electrode fixed externally to the back of the patient. Right atrium and CS were mapped during sinus rhythm and/or distal CS pacing. The pacing was conducted at twice-diastolic threshold from the distal CS at a cycle length of 600 ms.

Bipolar electrograms were recorded via the mapping catheter. Caution was taken to avoid displacement of the reference electrode during the entire procedure, especially during the mapping of CS. At least 1 recording in an area of 2 cm^2 was obtained in the right atrium. Effort was made to acquire high density maps around the

CS ostium, in which at least 2 recordings were obtained in an area of 1 cm², by mapping the anterior, posterior, superior, and inferior parts at each side of the CS ostium. Similarly, within the CS, at least 5 mapping points around the CS wall were taken in each of the proximal, middle and distal CS.

Off-line data analysis of activation velocities

A bipolar atrial electrogram from the CS with maximum deflection was taken as time reference to calculate local activation time. Visual inspection, and if necessary, manual correction of the activation time at each point was performed. Recordings of premature beats were excluded. Local activation was defined as the time point of the maximal slope on bipolar electrograms. Color-coded, 3-dimensional activation sequence maps were reconstructed, with the red color identifying the earliest activation area and the purple the latest (Fig. 1). For quantitative analysis, the following regional conduction times and linear distances between at least 5 paired sites along the long axis of the CS were measured using the CARTO system during sinus rhythm and/or distal CS pacing: (1) from the posteroparaseptal right atrium around the coronary sinus ostium to the proximal CS (cross-CSo), representing interatrial conduction across the ostium of CS; (2) and between paired adjacent sites within the CS (intra-CS). Activation velocity between each paired measurement sites was calculated. To minimize the influence of using linear distance, rather than the real distance over the endocardial surface, of the CARTO system we (1) limited the distance of the paired measurement sites to ≤ 30 mm, and (2) measured the distance between recording sites on the same plane of the right atrium and the CS, and between recording sites inside the CS, i.e., avoiding measurement along oblique lines.

Additionally, mean velocity of cross-CSo and that of intra-CS were obtained in each patient by averaging the activation velocities between paired sites for final analyses.

Statistical analysis

The variables are presented as mean \pm 1 standard deviation and were compared using the Mann-Whitney test. A value of $p < 0.05$ was considered as statistically significant.

Results

General data

Mapping procedures were successful both in the right atrium and CS in all patients. In the AF group, the right atrial and CS mapping were performed at 88 ± 21 and 93 ± 22 sites during sinus rhythm and distal CS pacing, respectively. Altogether 17 three-dimensional maps were obtained with 7 during sinus rhythm and 10 during distal CS pacing, i.e. 4 of the 13 patients were mapped during both sinus rhythm and distal CS pacing (Fig.1). During sinus rhythm, the mean velocities of cross-CSo activation were measured between 9 ± 2 paired sites and those of intra-CS activation between 6 ± 1 paired sites. During distal CS pacing, the mean velocities of cross-CSo and intra-CS activation were measured between 8 ± 2 paired sites and 6 ± 1 paired sites, respectively (Table 1).

In the control group, the right atrial and CS mapping were performed at 92 ± 22 and 98 ± 23 sites during sinus rhythm (Fig. 2) and distal CS pacing, respectively. There were 8 maps acquired during sinus rhythm and 4 during distal CS pacing, i.e. 2 of the 10 patients were mapped during both sinus rhythm and distal CS pacing. The mean velocities of cross-CSo activation were measured between 8 ± 2 paired sites and

those of intra-CS activation between 6 ± 1 paired sites during sinus rhythm. During distal CS pacing, the mean velocities of cross-CSo and intra-CS activation were measured between 8 ± 2 paired sites and 7 ± 2 paired sites, respectively. (Table 1)

Differences in activation velocities between patients with and without AF

During sinus rhythm, the distances of the paired sites between the two groups were not significantly different ($p > 0.05$). Additionally, the activation velocities of intra-CS between the two groups have no significant difference (2.8 ± 1.9 vs. 3.2 ± 2.2 m/s, $p > 0.05$). However, the activation velocities of cross-CSo in the AF group (1.2 ± 0.2 m/s) were significantly slower than those in the control group (2.9 ± 1.6 m/s, $p < 0.05$, Table 1).

During distal CS pacing, the distances between the paired sites were also not significantly different between the two groups ($p > 0.05$). The activation velocities of intra-CS between the two groups showed no significant difference (1.5 ± 0.3 vs. 1.4 ± 0.3 m/s, $p > 0.05$). For the conduction across the CS ostium, the activation velocities appeared slower in the AF group (1.0 ± 0.5 m/s) than those in control group (1.4 ± 0.2 m/s), but the difference was not statistically significant ($p = 0.07$, Table 1).

Differences in activation velocities between sinus rhythm and distal CS pacing

Activation velocities during sinus rhythm and distal CS pacing were also compared. In the AF group, the cross-CSo activation velocities during sinus rhythm were similar to those during distal CS pacing ($p > 0.05$). The intra-CS activation velocities during sinus rhythm showed a great range (1.1-5.8 m/s) with a tendency of being faster (2.9 ± 1.6 m/s) than those during distal CS pacing (1.4 ± 0.2 m/s, range 1.0-1.6 m/s), but the difference was not statistically significant.

In the control group, the cross-CSo and intra-CS activation velocities during sinus rhythm both displayed a higher variation, and tended to be faster than those during distal CS pacing (1.4-5.8 vs. 1.1-1.6 m/s and 1.1-6.0 vs. 1.1-1.7 m/s). However, neither the cross-CSo nor the intra-CS activation velocities during sinus rhythm was significantly different from those during distal CS pacing (Table 1).

Discussion

Anatomic and electrophysiological examination of human and animal hearts suggested that atrial muscle bundles, such as Bachmann's bundle (11,12), the rim of the fossa ovalis (13), and the CS (14), form preferential conduction routes between the right and left atria. However, our knowledge of the exact location and function of interatrial conduction routes is still incomplete, and the preferential conduction routes seem to vary with different original pacing sites (3, 5-9). In addition, previous studies have repeatedly reported that the inter- and intra-atrial conduction disturbances, especially the delayed interatrial conduction, are linked to the occurrence and/or perpetuation of AF, including AF of focal origin (1-3, 15,16). Nevertheless, the exact deteriorated conduction areas are still not clear. Fiber connections between the two atria around the CS ostium have been highlighted to play an important role for interatrial conduction (3,9,17).

Activation velocity as a parameter of interatrial conduction

Most of the previous studies have evaluated the inter- and intra-atrial conduction properties using conduction times between remote sites. The accuracy of these evaluations therefore must have been influenced by the inter-individual variance of measurement sites. Velocity should be a better parameter of conduction properties

than conduction times. However, activation velocity has scarcely been used probably due to difficulties in measuring the distance accurately between recording sites.

Electroanatomic mapping techniques have been used to delineate the propagation of intra-atrial and interatrial conduction (5-9). These techniques allow precise correlation of electrical signal with its anatomical origin on 3-dimensional maps of the cardiac chambers, and thus allow accurate measurements of distance, activation time, and activation velocity between two recording sites. Compared to conduction times, activation velocity is a more precise parameter of conduction properties. Using the CARTO system, Luo *et al.* measured the conduction velocities of different right atrial areas and compared them in patients with and without paroxysmal AF (18). However, to our knowledge, no data of conduction velocity across the CS ostium have been reported. In the present study, we constructed the activation maps of the right atrium and the CS both during sinus rhythm and distal CS pacing, and used activation velocity, instead of activation time, to evaluate the interatrial conduction across the CS ostium.

Deterioration of interatrial conduction during distal CS pacing in AF patients

Interatrial conduction have been conventionally evaluated through right atrial mapping during CS or left atrial pacing. This is partially due to the technical and ethical limitations for mapping in left atrium, and also due to the recent finding that ectopic activities in the left atrium are important factors for the development of AF. Using the CARTO mapping system, different activation patterns of the right atrium during pacing from the distal CS have been observed, with most right atria presenting a single transseptal breakthrough near the CS ostium (9, 17). In addition, using the Ensite 3000 noncontact mapping system, O'Donnell *et al.* observed similar

preferential inter-atrial conduction route during pacing in the left upper pulmonary vein (3). These findings suggested that the preferential conduction route during distal CS pacing should mostly be through the posterior region near the CS ostium.

In the present study, the activation velocities of cross-CSo and intra-CS during distal CS pacing were measured. These measurements should represent the actual conduction velocities since the preferential conduction route during distal CS pacing is along the long axis of the CS as observed previously (9, 17) (Fig 3). We found that the activation velocities of intra-CS were similar in the two groups, whereas the cross-CSo activation velocities in the AF group appeared slower than those in the control group. These data support the previous finding that the interatrial conduction delay in patients with paroxysmal AF is located in the posteroparaseptal region around the CS ostium (4, 18).

Deterioration of interatrial conduction during sinus rhythm in AF patients

Compared to the relatively clear interatrial conduction routes during distal CS pacing, the routes during sinus rhythm are more complicated. In the majority of published data, the dominant role of Bachmann's bundle for interatrial conduction has been emphasized. Conduction through other connections between the right and left atria, such as posterior interatrial conduction, was thought to be limited to local region and do not significantly contribute to left atrium activation in canine models (19), or in normal human atria (6). However, technical limitations for mapping the left atrium might have diminished the accuracy of mapping in the posteroparaseptum of the left atrium (20). Some anatomic studies have shown that there have been variable connections between the right and left atrium, and the importance of Bachmann's bundle as interatrial conduction was questionable (21, 22). Furthermore, a recent

study has shown that multiple connections capable of right-to-left atrial conduction exist, and that the posterior communications appeared to play a major role (7).

In the present study, the cross-CSo activation velocities during sinus rhythm were significantly slower in the AF patients than those in the control group. The interpretation of this finding is more complicated, compared to that during distal CS pacing. The activation velocity represents the speed of interatrial conduction provided the conduction crosses the CS ostium along the long axis of the CS. When the interatrial conduction is through other preferential routes, however, the activation time used to calculate the activation velocity across the CS ostium is actually the activation time difference between the posteroparaseptal right atrium and the proximal CS, with the former activated by wave front from the lateral wall and the latter by that from other interatrial connections (Fig 3). In this study, the markedly slower cross-CSo activation velocities during sinus rhythm in the AF patients may suggest either the cross-CSo conduction is delayed, or more probably that the conduction through other preferential routes is delayed as suggested by earlier studies in patients with AF (3, 23). As a result, the proximal CS of AF patients are activated later than that of the control patients. In other words, the relatively slow cross-CSo activation velocities during sinus rhythm in patients with AF represent mostly true conduction velocities across the CS ostium, while the faster cross-CSo activation velocities in the control group may be a result of almost concurrent activations of the posteroparaseptal right atrium and the proximal CS through two different conduction routes. A similar postulation could also be used to explain the faster intra-CS activation velocities during sinus rhythm. The fact that the activation velocities measured during sinus rhythm are all, except the cross-CSo activation velocities in patients with AF, faster than those during distal CS pacing (Table 1), and even faster than the normal

conduction velocities of atrial fibers, which is around 1 m/s (24), lend further support to this hypothesis. In addition, the greater range of activation velocities from 1 to 6 m/s also suggests more complex interatrial conduction routes during sinus rhythm, in contrast to the relatively clear interatrial conduction route during distal CS pacing.

Study Limitations

The activation of the left atrium has only been evaluated within the CS in the present study. Ideally, a detailed right and left atrial mapping including the CS could provide clear evidence on the propagation routes and the area of conduction delay. Such data is difficult to obtain from patients due to clinical and ethical reasons. Therefore, we concentrated on the activation velocities across the CS ostium and the difference within these parameters between patients with and without paroxysmal AF. In addition, a limitation of the CARTO system is that only direct linear distance between two sites is available. As a result, the distance between two remote sites is shorter than the true distance over the endocardial surface, and thereby activation velocity is underestimated. To minimize the influence of the CARTO algorithm of distance measurement, we measured the distance longitudinally along the CS and between adjacent sites over the surface of the right atrial endocardium in the same plane, and calculated each regional activation velocity by averaging multiple measurements. Moreover, the activation velocity was calculated using the same algorithm for both groups. Therefore we believe that the significant differences in activation velocities between the two groups are objective findings and bear important clinical implications.

Conclusion

The deterioration of interatrial conduction across the CS ostium during distal CS pacing in patients with paroxysmal AF is presented in this study. Conduction delay at the posteroparaseptal region across the CS ostium and/or over other conduction routes during sinus rhythm in the AF patients is indirectly suggested by our findings. These data further support the link between interatrial conduction deterioration at the posteroparaseptal region and paroxysmal AF.

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Table 1: The distances and activation velocities of cross-CSo and intra-CS measured during sinus rhythm and distal CS pacing in AF group and control group.

		Cross-CSo		Intra-CS	
		AF	Control	AF	Control
Sinus Rhythm	Paired sites (n=)	9±2	8±2	6±1	6±1
	Distance (mm)	23.0±2.8	20.4±3.2	15.8±3.9	15.1±3.9
	Velocity (m/s)	1.2±0.2*	2.9±1.6	2.8±1.9	3.2±2.2
CSd pacing	Paired sites (n=)	8±2	8±2	6±1	7±2
	Distance (mm)	19.8±3.1	17.5±2.1	15.7±4.0	21.6±2.6
	Velocity (m/s)	1.0±0.5†	1.4±0.2	1.5±0.3	1.4±0.3

Mean ± 1 SD, CS: coronary sinus, AF: atrial fibrillation. CSd: distal CS. Cross-CSo and Intra-CS: Across the CS ostium and within the CS. * $p < 0.05$, compared between AF group and control group. † $p = 0.07$, compared between AF group and control group. $p > 0.05$ in all the other comparisons between the two groups.

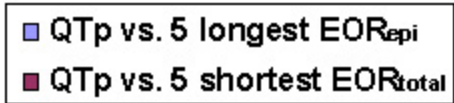
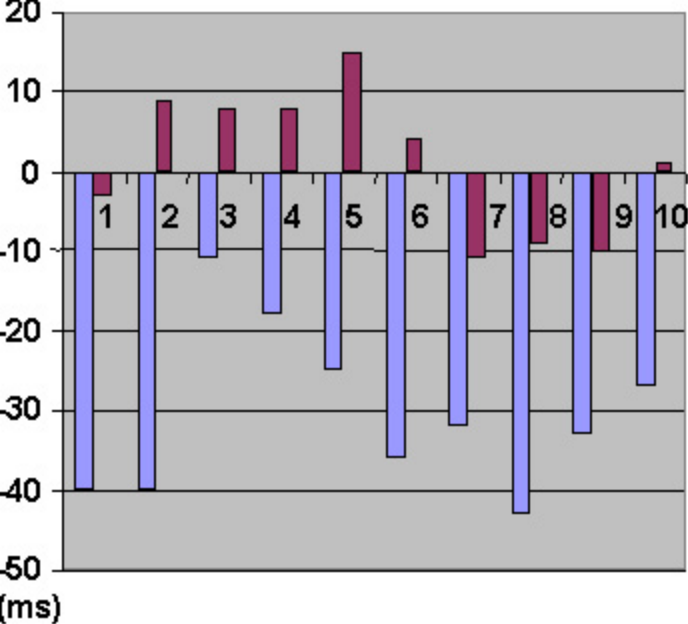
Legends of figures

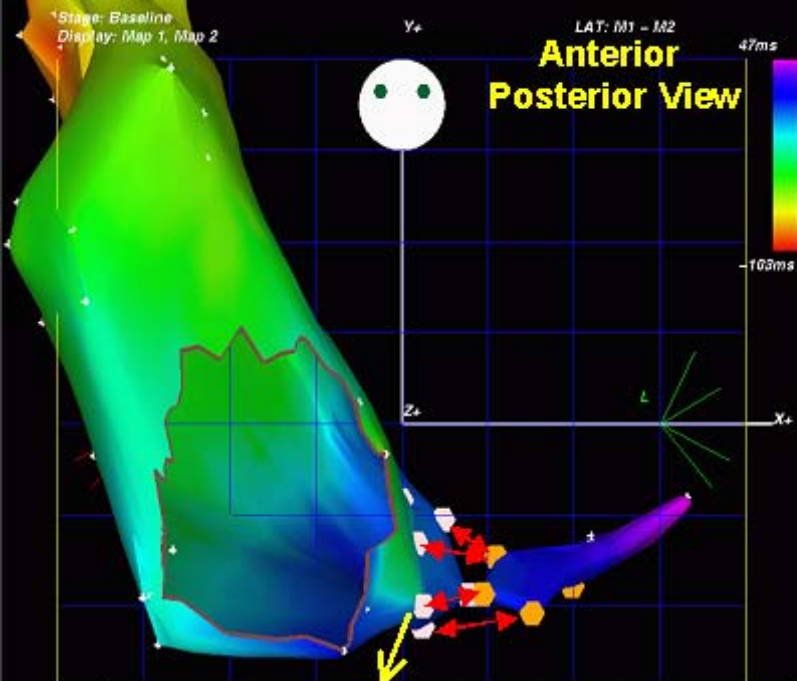
Figure 1: Right atrium and coronary sinus (CS) maps during distal CS pacing in a patient with paroxysmal atrial fibrillation. The mean velocity across the CS ostium is 0.7 m/s, which was calculated from 8-paired sites between the posteroparaseptal right atrium and proximal CS. **Left.** Posterior-anterior view, showing 3 paired sites (double-arrow lines) between the posteroparaseptal right atrium and posteroinferior proximal CS. The distance, conduction time and velocity between one of the paired sites were automatically measured as 12.16 mm, 14 ms and 0.87 mm/ms, respectively, using CARTO system. **Right.** Left anterior oblique view, showing additional paired sites across the CS ostium.

Figure 2: Right atrium and coronary sinus (CS) maps during sinus rhythm in a patient with atrioventricular nodal reentrant tachycardia. The mean velocity across the CS ostium is 1.5 m/s, calculated from 8-paired sites between posteroparaseptal right atrium and proximal CS. **Left.** Anterior-posterior view, showing 3 paired sites (double-arrow lines). The distance, conduction time and activation velocity between one of the paired-sites were 10.26 mm, 9 ms and 1.14 mm/ms. **Right.** Cranial view, showing additional paired sites across the CS ostium.

Figure 3: Schematic diagram of the activation velocity measurements. Open arrows indicate possible interatrial conduction routes and solid arrows indicate propagation of activation wave fronts. **Left.** During distal coronary sinus (CS) pacing, the conduction across the CS ostium is along the long axis of the CS, and thus the calculated activation velocity between the two stars (*), with left one indicating a right atrial site and the right one indicating a proximal CS site, may represent true conduction velocity across the CS ostium. **Right.** During sinus rhythm, when the conduction is across the CS ostium along the long axis of the CS, the measured activation velocity between the two stars (*), with the left one indicating a right atrial site and the right one indicating a proximal

CS site, represents the true interatrial conduction through the CS ostium. However, when the interatrial conduction is via other routes, the conduction route across the CS ostium is then not a preferential route. As a result, the right atrial site by the CS ostium and the site at the proximal CS are activated by different wave fronts. Thus, the calculated activation velocity would be overestimated as seen in some control patients in this study (see discussion for details).





Distance

Point #

The distance between point #54 and point #52 is: 10.26 (mm)
 Difference in LAT: 9 (ms)
 Conduction Velocity: 1.14 (mm/ms)

