Role of the Coronary Sinus in Maintenance of Atrial Fibrillation

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Coronary Sinus and Atrial Fibrillation. ***Introduction:*** **Bursts of tachycardia arising in the pulmonary veins may play an important role in perpetuating atrial fibrillation (AF). However, the role of the coronary sinus (CS) in the perpetuation of AF has been unclear. The aim of this study was to determine whether the CS plays a role in perpetuation of AF.**

Methods and Results: **Pulmonary vein isolation was performed by segmental ostial ablation with radiofrequency energy in 22 consecutive patients with paroxysmal AF. Bipolar and unipolar electrograms recorded in the left atrium and CS were analyzed during atrial pacing from the mitral annulus and during AF. There was a mean of 2.5 ± 0.5 electrical connections between the CS and the left atrium. The electrical connections between the left atrium and CS were ablated with a mean of 6.2 ± 2.7 minutes of radiofrequency energy applied along the atrial side of the inferior mitral annulus. During AF, episodes of intermittent tachycardia alternated between the left atrium and the CS. Among the 22 patients, sustained AF was still inducible in 9 after pulmonary vein isolation. After electrical disconnection of the CS from the left atrium, sustained AF was inducible in only 3 of these 9 patients.**

Conclusion: **The CS may be a source of rapid repetitive electrical activity during AF. The lower probability of inducible sustained AF after electrical disconnection of the CS from the left atrium suggests that the CS may play a role in perpetuating AF.** *(J Cardiovasc Electrophysiol, Vol. 14, pp. 1329-1336, December 2003)*

coronary sinus, atrial fibrillation, catheter ablation

Introduction

Muscle sleeves surrounding the pulmonary veins have been found to generate rapid electrical activity that may play a role in perpetuating atrial fibrillation (AF).[1,2] The coronary sinus (CS) also is covered with a myocardial sleeve, and muscular connections between this muscle sleeve and the left atrium have been demonstrated anatomically.[3-6] Focal atrial tachycardias originating in the musculature of the CS have been reported,[7,8] and the CS musculature may participate in a macroreentrant circuit that generates left atrial flutter.[9] Moreover, a recent study demonstrated that double potentials are recorded in the CS more often in patients with paroxysmal AF than in other patients and suggested that the CS may serve as a substrate for AF.[10]

The aim of this study was to investigate whether the CS plays a role in the perpetuation of AF. This was accomplished by assessing the AF cycle length within the CS and the inducibility of sustained AF after pulmonary vein isolation, before and after electrical disconnection of the CS from the left atrium.

Supported by the Ellen and Robert Thompson Atrial Fibrillation Research Fund.

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Manuscript received 30 April 2003; Accepted for publication 25 August 2003.

doi: 10.1046/j.1540-8167.2003.03222.x

Methods

Study Subjects

The subjects of this study were 22 consecutive patients (19 men and 3 women; mean age 47 ± 12 years) who underwent an electrophysiologic procedure for treatment of paroxysmal AF. AF was first diagnosed 6 ± 5 years prior to the procedure. None of the 22 patients had structural heart disease. Mean left ventricular ejection fraction and left atrial diameter were 0.56 ± 0.04 mm and 39 ± 6 mm, respectively.

Electrophysiologic Study

All patients provided written informed consent. A decapolar electrode catheter (Daig Corp., Minnetonka, MN, USA) with 2-5-2-5-2-5-2-5-2 mm interelectrode spacing was positioned in the CS such that the proximal electrode pair was just inside the CS ostium. Transseptal catheterization was performed and systemic anticoagulation was achieved to maintain an activated clotting time of 250 to 350 seconds. Venograms of the pulmonary veins were obtained. A deflectable decapolar catheter with a distal ring configuration (Lasso™ catheter, Biosense Webster, Diamond Bar, CA, USA) was used for ostial mapping. A deflectable, quadripolar 7-French catheter with 2-5-2 mm interelectrode spacing and a 4-mm distal electrode with an embedded thermistor (EP Technologies, Inc., Mountain View, CA, USA) was used for mapping and ablation. Bipolar and unipolar electrograms were filtered at bandpass settings of 30 to 500 Hz and 0.5 to 200 Hz, respectively, and were recorded digitally (EPMed Systems, Inc., West Berlin, NJ, USA). Electrograms were recorded from the CS catheter and the mapping catheter positioned along the inferior mitral annulus.

Pulmonary Vein Isolation

Pulmonary vein isolation was performed by segmental ostial ablation with conventional applications of radiofrequency energy, guided by pulmonary vein potentials, as described previously.[11,12] The left superior, left inferior, and right superior pulmonary veins were targeted in all patients. The right inferior pulmonary vein was targeted in 17 of the 22 patients. Applications of radiofrequency energy were delivered at a maximum of 35 W, with a target temperature of 52°C and duration up to 40 seconds. Elimination of all ostial pulmonary vein potentials and complete entrance block into the pulmonary vein were the endpoints of ostial ablation.[11,12]

Study Protocol

Among the 22 patients, 12 were in AF upon entry into the electrophysiology laboratory. In the other patients, AF was induced by 5- to 10-second bursts of atrial pacing at cycle lengths of 200 to 180 ms. Pacing was performed from a quadripolar catheter positioned within the CS. For the purposes of this study, an episode of induced AF that lasted >5 minutes was considered sustained. After pulmonary vein isolation, atrial pacing again was performed five times at cycle lengths of 200 to 180 ms, to assess the inducibility of sustained AF. Whenever AF was inducible, electrograms recorded in the CS and in the left atrium were digitally recorded for post hoc analysis. In patients with inducible sustained AF after pulmonary vein isolation, sinus rhythm was restored by transthoracic cardioversion after approximately 10 minutes.

In this study for the description of electrical connections between the CS and the left atrium, *attitudinally correct nomenclature* was used.[13,14] When accurately described, mitral annular sites commonly referred as lateral are *posterior,* posterior are *inferior,* anterior are *superior,* and medial are *paraseptal*.[13,14]

To identify electrical connections between the CS and the left atrium, the mapping catheter was positioned along the inferior mitral valvular annulus and atrial pacing was performed at twice threshold with this catheter. Pacing was first performed near the posterior annulus, adjacent to electrode 1 (distal) of the decapolar CS catheter. The mapping catheter then was sequentially positioned along the annulus at sites that were adjacent to other electrodes of the decapolar CS catheter, and pacing was repeated at these sites (Fig. 1).

Analysis of CS potentials was based on the unipolar electrograms recorded within the CS. When double potentials were present, the first component was considered a far-field potential attributable to left atrial activation, and the second component was considered a near-field potential with a rapid intrinsic deflection indicative of local CS activation (Fig. 2). Sites of earliest local CS activation during pacing at the mitral annulus were considered to be sites of electrical connections between the left atrium and the CS. A change in the CS activation sequence during atrial pacing from different mitral annular sites was considered indicative of multiple connections (Fig. 3). An electrical connection localized to one electrode was defined as a discrete connection, whereas a connection that spanned ≥2 electrodes was defined as a broad or nondiscrete connection.

Conventional applications of radiofrequency energy were delivered at sites along the inferior mitral valve annulus where there was evidence of an electrical connection. The applications were 30 seconds in duration, with a target temperature of 60°C and maximum power of 50 W. A change in the activation sequence of unipolar electrograms recorded within the CS during atrial pacing along the mitral annulus was considered indicative of successful ablation of an electrical

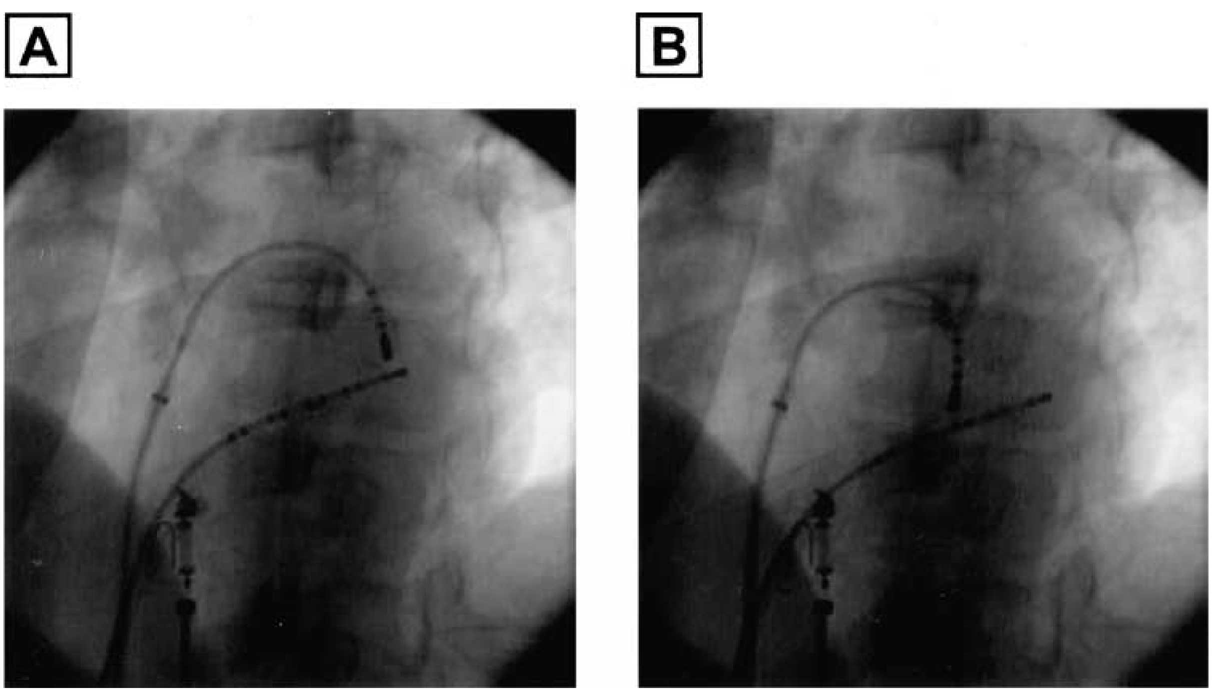

Figure 1. *Fluoroscopic image of catheter positions in the 45° left anterior oblique view. A decapolar catheter is positioned in the coronary sinus. Shown are examples of the mapping/ablation catheter within the left atrium positioned along the mitral valve annulus adjacent to electrode 2 (A) and electrode 6 (B).*

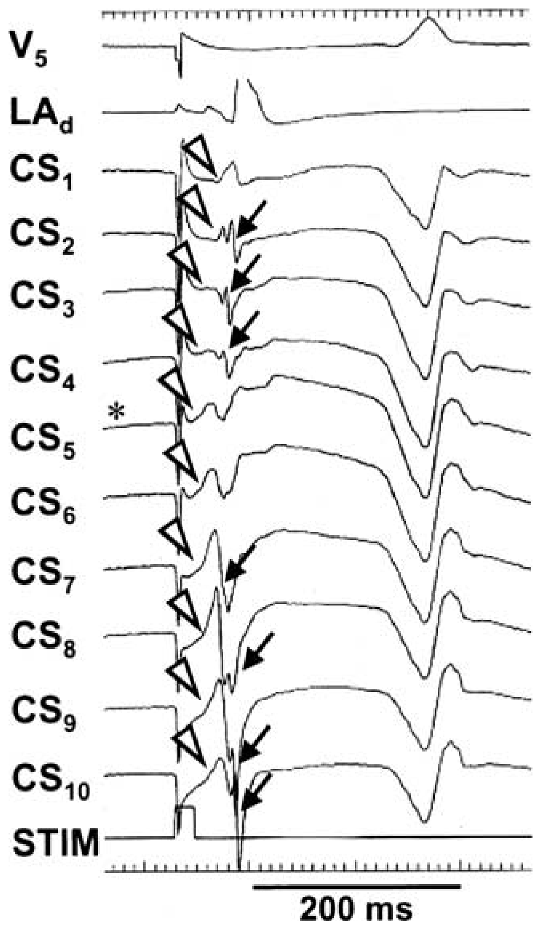

Figure 2. *Unipolar electrograms recorded by a decapolar catheter within the coronary sinus (CS). In this figure and in following figures, the most proximal electrode (CS_{10}) was positioned at the ostium of the CS. The unipolar electrograms were recorded during pacing from the inferior mitral valve annulus, adjacent to electrode 5 (asterisk) of the decapolar catheter. Double potentials are recorded by most of the electrodes: the first component is a far-field potential attributable to left atrial activation (open arrowheads), and the second component has a rapid intrinsic deflection and represents local CS activation (closed arrows). The earliest CS potential is recorded at CS_7, indicating the presence of a coronary sinus–left atrial connection adjacent to CS_7. LA_d = left atrial distal; Stim = stimulus channel.*

connection between the CS and the left atrium. After ablation of all identifiable electrical connections between the CS and the left atrium, rapid atrial pacing was again performed in the same manner as before ablation in all patients to determine whether sustained AF was still inducible. The total number of individual ablation sites that resulted in a change in the activation sequence within the CS was considered to indicate the number of electrical connections.

Analysis of Electrograms Recorded Within the CS

During AF, bipolar electrograms in the CS and the left atrium were recorded for at least 30 seconds and manually analyzed off-line to determine the AF cycle lengths. To account for fractionation and slow and fibrillatory conduction, only electrograms with an amplitude >10% of the maximum electrogram amplitude and separated by at least 50 ms were analyzed. Rapid electrical activity[1,2,15-17] within the CS was defined as a burst of electrical activity that had a cycle length shorter than in the adjacent left atrium (Fig. 4). Conversely, rapid electrical activity in the left atrium was defined as a burst of electrical activity that had a cycle length shorter than in the adjacent CS. To measure cycle lengths, electrograms recorded with the distal bipole of the mapping catheter positioned at the inferior mitral annulus and with the bipole of the CS catheter adjacent to the mapping catheter were analyzed.

Analysis of P Waves Before and After Disconnection of CS from Left Atrium

To determine the effect of CS disconnection from the left atrium on global atrial activation, the duration of the P wave recorded in lead II was measured using electronic calipers before and after CS disconnection.

Follow-Up

All patients were seen in an outpatient clinic 4 to 6 weeks after the ablation procedure and every 3 months thereafter. Patients who reported symptoms were provided with an event recorder to document the nature of these episodes. No patient was lost to follow-up.

Statistical Analysis

Continuous variables are expressed as mean ± 1 SD and were compared with a paired *t*-test. Categorical variables were compared by Chi-square analysis or with the Fisher's exact test. $P < 0.05$ was considered statistically significant.

Results

Pulmonary Vein Isolation

Among the 83 targeted pulmonary veins, 82 (99%) were successfully electrically isolated.

Inducibility of AF Before Disconnection of the CS

Before pulmonary vein isolation, sustained AF was inducible in all patients. After successful isolation of the pulmonary veins, sustained AF was still inducible in 9 (41%) of the 22 patients. In these 9 patients, the mean duration of episodes of sustained AF before transthoracic cardioversion was 11.9 ± 5.7 minutes. In the other 13 patients, inducible AF spontaneously converted to sinus rhythm in a mean of 1.1 ± 1.2 minutes (range 1 s to 3.8 min).

Electrical Connections Between Left Atrium and CS

A CS potential was recorded at a mean of 9 ± 1 electrodes of the decapolar catheter positioned within the CS. There was a mean of 2.5 ± 0.5 electrical connections between the CS and the left atrium. Among the 47 connections, 17 (36%) were located at the posterior or inferoposterior part of the mural aspect of the mitral annulus, 16 (34%) were located at the inferior portion of the mural aspect of the mitral annulus, and the remaining 14 (30%) were located at the paraseptal portion of the mural aspect of the mitral annulus. Among the 47 electrical connections, 17 (36%) spanned ≥2 contiguous electrodes (≥5 mm), and the remaining were discrete connections localized to 1 electrode (2 mm).

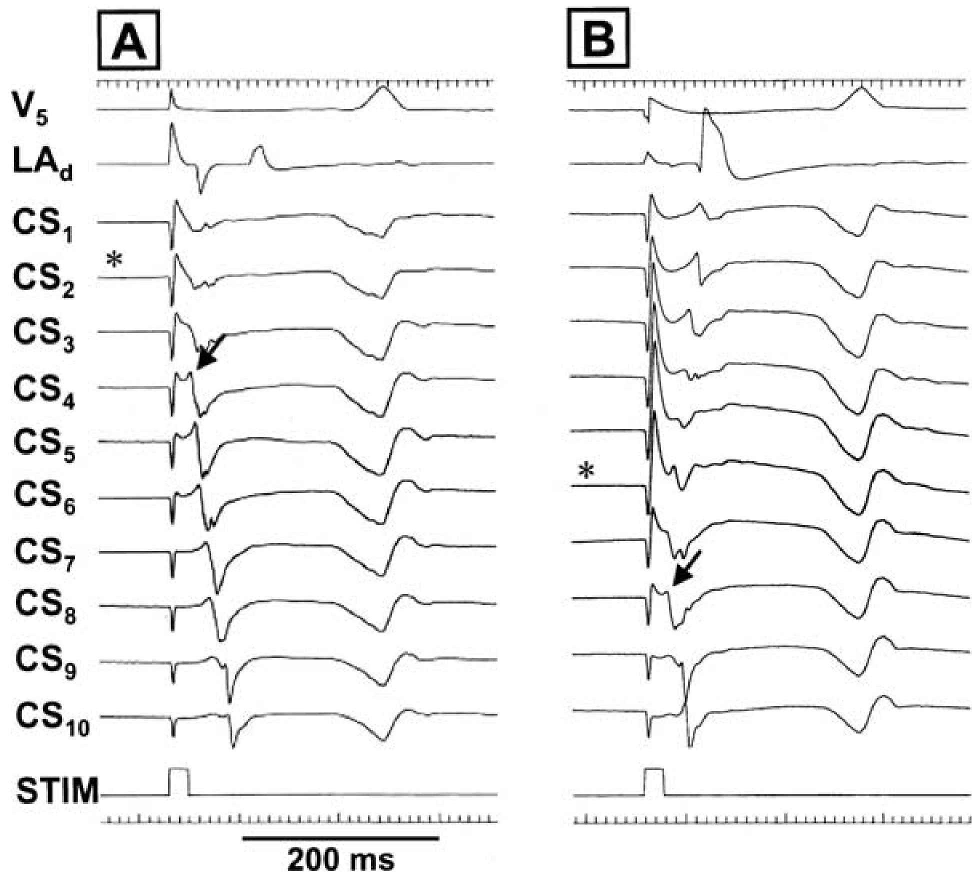

Figure 3. *Example of multiple connections between the coronary sinus (CS) and the left atrium. LA_d = left atrial distal; LA_p = left atrial proximal; Stim = stimulus channel. A: Activation sequence within the CS during pacing from the posterior mitral valve annulus, adjacent to electrode 2 (asterisk) of the CS catheter. Note that earliest activation of the CS (arrow) is recorded at electrode 4 of the decapolar catheter. B: When pacing was performed from the inferior annulus adjacent to electrode 6 (asterisk), there was a change in the activation sequence within the CS. Earliest activation within the CS (arrow) shifted to electrode 8. This is evidence of at least two electrical connections between the left atrium and CS.*

AF Cycle Length in CS and Left Atrium Before Disconnection of CS from Left Atrium

After pulmonary vein isolation, there was a mean of 4 ± 3 episodes per minute of rapid electrical activity in the left atrium; the mean duration of these episodes was 1,173 ± 420 ms, and their mean cycle length was 93 ± 19 ms, which was significantly shorter than the simultaneous cycle length in the CS (153 ± 42 ms, $P < 0.001$). In 17 (78%) of the 22 patients, there also was a mean of 19 ± 8 episodes of rapid electrical activity within the CS; the mean duration of these episodes was 1,471 ± 451 ms, and their mean cycle length was 83 ± 20 ms, which was significantly shorter than the simultaneous cycle length in the left atrium (177 ± 36 ms, $P < 0.001$).

Electrical Disconnection of the CS from the Left Atrium

Electrical disconnection of the CS was achieved with 11 ± 3 applications of radiofrequency energy that had a cumulative duration of 6.2 ± 2.7 minutes (Fig. 5). There were no complications related to catheter ablation in any of the patients.

Before electrical disconnection of the CS, a CS potential was recorded within the CS by a mean of 9 ± 1 electrodes of the decapolar catheter. After electrical disconnection of the CS from the left atrium, the number of CS electrodes at which a CS potential was recorded decreased to a mean of 3 ± 1 electrodes ($P < 0.01$) in 17 of the 22 patients. In the remaining 5 patients, no residual CS potentials were recorded within the CS after electrical disconnection of the CS from the left atrium.

When residual CS potentials were present after electrical disconnection of the CS, the stimulus to CS potential interval during atrial pacing along the mitral annulus increased from 30 ± 8 ms before ablation to 59 ± 9 ms after ablation ($P < 0.001$). Among 55 residual CS potentials, 26 (47%) were recorded in the proximal position of the CS by the electrodes closest to the ostium (Fig. 5).

Inducibility of AF After Disconnection of the CS

Among the 9 patients who had inducible sustained AF after isolation of the pulmonary veins, sustained AF was still inducible in only 3 after electrical disconnection of the CS from the left atrium ($P = 0.04$, Fig. 6).

Cycle Lengths Within the CS Before and After Electrical Disconnection

In patients who still had inducible AF after CS disconnection, regardless of whether the episode was sustained or nonsustained, there were fewer episodes of rapid electrical activity within the CS (3 ± 3 per minute) than before CS disconnection (19 ± 8 per minute, $P < 0.001$). During these episodes of rapid electrical activity, the cycle length recorded

Figure 4. *Example of rapid electrical activity within the coronary sinus (CS). All electrograms are bipolar recordings. CS_{1-2} was positioned adjacent to the posterior mitral annulus, and CS_{9-10} was positioned at the ostium of the CS. There is rapid electrical activity within the CS that has a mean cycle length of 95 ms, which is shorter than the mean atrial cycle length of 220 ms in the left atrium (LA), adjacent to CS_{9-10}.*

within the CS was longer after than before electrical disconnection of the CS (133 ± 34 ms vs 84 ± 23 ms, respectively, $P < 0.01$).

P Wave Duration

After disconnection of the CS from the left atrium, the P wave duration in lead II increased from a baseline value of 117 ± 27 ms to 129 ± 20 ms ($P < 0.01$).

Freedom from Recurrent AF

After a mean follow-up of 199 ± 35 days, 18 (82%) of the 22 patients with paroxysmal AF were free from recurrent episodes of AF in the absence of any antiarrhythmic drug therapy.

Discussion

Main Findings

The main findings of this study are as follows. (1) There are intermittent bursts of rapid electrical activity in the CS during AF that have a shorter cycle length than in the adjacent left atrium. (2) Electrical connections between the CS and the left atrium can be identified by conventional mapping techniques and reliably ablated. (3) Electrical disconnection of the CS from the left atrium reduces the likelihood of inducing sustained AF in patients who still have inducible sustained AF after pulmonary vein isolation. (4) Electrical disconnection of the CS form the left atrium in conjunction with pulmonary vein isolation results in freedom from recurrent episodes of AF in ∼80% of patients with paroxysmal AF.

These findings suggest that rapid repetitive electrical activity can occur within the muscle sleeve that surrounds the CS and may contribute to the maintenance of AF.

Role of the CS in AF

Bursts of rapid electrical activity were found to alternate between the left atrium and the CS up to 20 times per minute during AF. The observation that the cycle length at times was shorter in the CS than in the adjacent left atrium suggests that the bursts of rapid electrical activity were generated in the CS, as opposed to simply reflecting the electrical activity in the adjacent left atrium.

After electrical disconnection of the CS from the left atrium, sustained AF was inducible much less often than before disconnection. This suggests that the rapid electrical activity that originates in the muscular sleeves of the CS may play a role in the maintenance of AF. Of note is that intermittent bursts of rapid activity arising in the pulmonary veins previously have been demonstrated to play a role in perpetuating AF.[1,2] The results of the present study suggest that the CS may function to maintain AF in the same manner as the pulmonary veins.

Mechanism of Rapid Electrical Activity Arising in the CS

Focal atrial tachycardias probably caused by abnormal automaticity or triggered activity can originate in the CS musculature.[7,8] Furthermore, the complex spatial orientation of muscular fibers around the CS and their discrete insertion points in the left atrium may facilitate reentry within the CS.[5,18]

Abnormal automaticity with the CS musculature might be expected to persist even after electrical disconnection of the CS. Therefore, because the bursts of rapid electrical activity became less frequent and slower after electrical disconnection of the CS from the left atrium, abnormal automaticity is unlikely to be the mechanism of the rapid electrical activity.

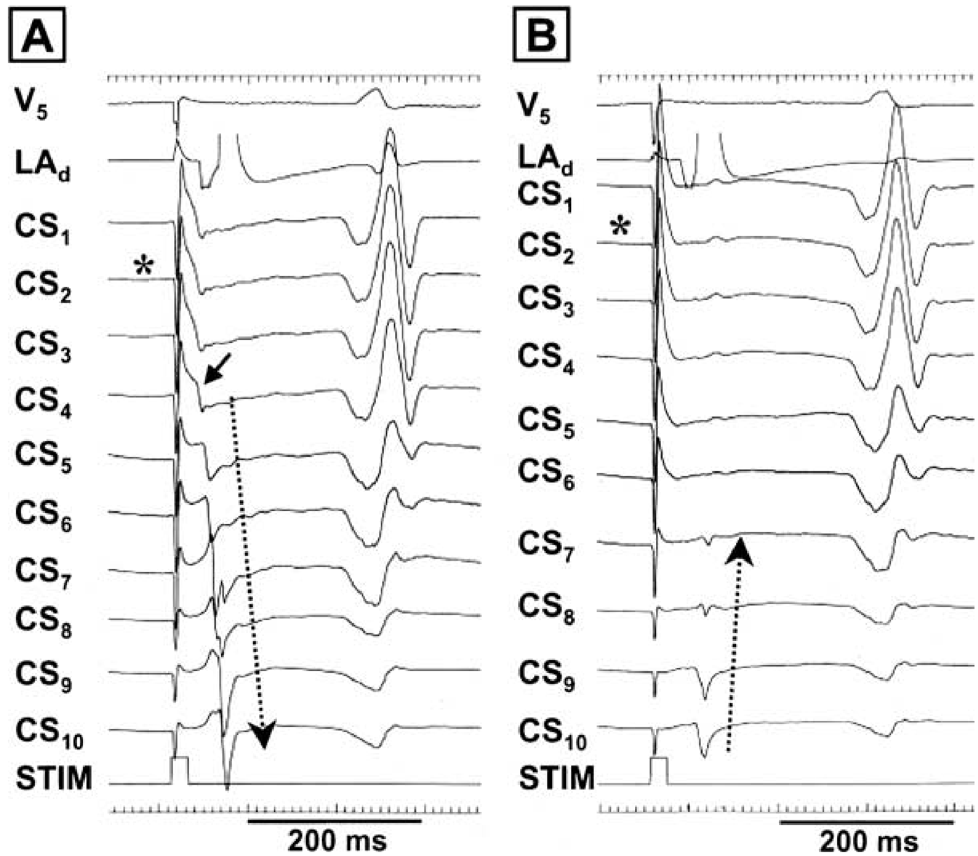

Figure 5. *Example of ablation of an electrical connection between the coronary sinus (CS) and the left atrium. Shown are unipolar recordings from a decapolar catheter positioned within the CS. A: Preablation, during pacing at the posterior mitral valve annulus adjacent to electrode 2 (asterisk), the earliest CS potential was recorded at CS_4 (arrow), indicating the presence of an electrical connection between the left atrium and CS at this site. B: After applications of radiofrequency energy at the inferior mitral valve annulus adjacent to electrodes 4 and 7, a CS potential was no longer present at electrodes 1–6 of the decapolar catheter and was still present at electrodes 7–10, which were closest to the ostium. In addition, the activation sequence (dashed line) within the CS during pacing adjacent to CS_4 changed, with the site of earliest CS activation shifting from CS_4 to CS_{10}. The shift in activation sequence within the CS reflects activation of the CS musculature only from the right atrium, consistent with electrical disconnection of the CS from the left atrium. Abbreviations as in Figure 2.*

As is the case with the muscle sleeves surrounding the pulmonary veins,[19,20] rapid electrical activity within the CS may be more likely to be caused by reentry or triggered activity in response to the rapid stimulation that occurs during AF or rapid atrial pacing. However, the mechanism of the rapid activity arising in the CS remains to be determined.

Electrical Connections Between CS and Left Atrium

The sites of electrical connections between the CS and the left atrium were identified by the activation sequence of unipolar electrograms recorded within the CS during pacing at different sites along the mitral annulus. A change in CS activation sequence after ablation confirmed that the presumptive sites of electrical connections had been correctly identified.

In a prior study, sites of electrical connections were identified by the analysis of double potentials during pacing from the proximal and distal CS and introduction of a premature stimulus.[18] However, in contrast to the present study, ablation was not performed in the prior study and, therefore, no validation of the results of the electrogram analysis was available.

Electrical Disconnection of the CS

In the present study, electrical disconnection of the CS from the left atrium was achieved by radiofrequency ablation along the endocardial atrial aspect of the mitral annulus. The electrical connections between the CS and the left atrium also might be ablated by applications of radiofrequency energy within the CS. However, this approach to ablation might be associated with a greater risk of perforation of the CS or injury to the coronary arteries. Furthermore, it may be easier to achieve effective disconnection by targeting the thinned-out muscular extensions of the CS on the left atrial side of the annulus.[21]

In the present study, the CS was electrically isolated from the left atrium, but no attempts were made to isolate the CS from the right atrium. Nevertheless, sustained AF usually was rendered noninducible. This is consistent with the results of prior studies that have indicated that the left atrium plays a more important role than the right atrium in generating AF.[22–27]

Applications of radiofrequency energy at the mitral valve annulus often resulted in the loss of CS potentials within the CS. In addition, the stimulus to CS potential interval lengthened significantly after ablation of the connections between

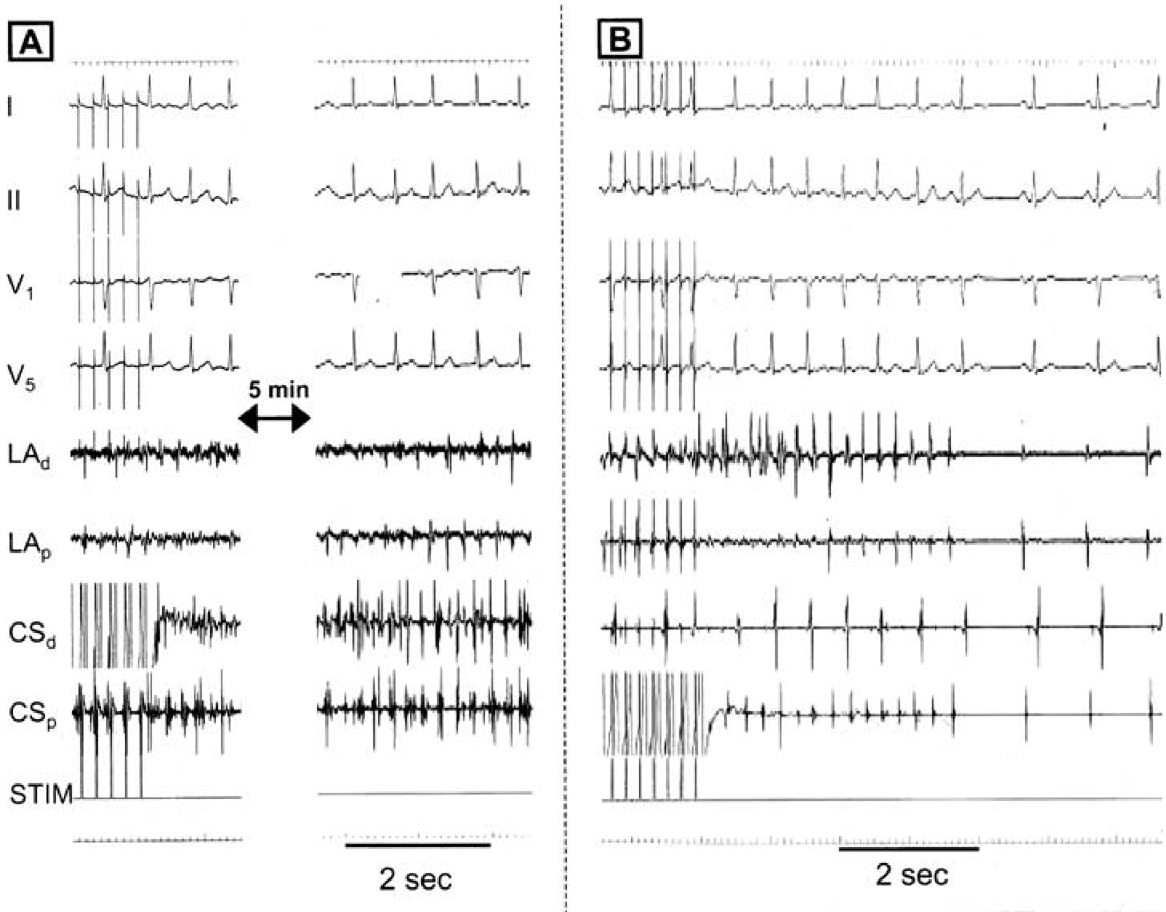

Figure 6. *Effect of electrical disconnection of the coronary sinus (CS) from the left atrium (LA) on inducibility of atrial fibrillation (AF). A: After isolation of the pulmonary veins, AF that persisted for more than 5 minutes was still inducible by atrial pacing at a cycle length of 180 ms. The mean cycle length within the CS was 105 ms. B: After electrical disconnection of the CS from the LA, sustained AF was no longer inducible. The induced AF lasted only 4 seconds, and the mean cycle length was 285 ms.*

the left atrium and CS. These effects of ablation on the CS potentials may have resulted from direct damage to the muscle fibers within the CS. In addition, similar to the muscle sleeves surrounding the pulmonary veins,[28] the electrical activity of the muscle fibers within the CS may be dependent on electrical input from the left or right atrium, and once this input is eliminated, they may become electrically silent. It also is possible that the muscle fibers surrounding the CS are electrically insulated from each other,[28] such that electrical disconnection of the CS results in elimination of CS potentials within a segment of the CS, while other segments may still have residual potentials. In this study, ~50% of all residual CS potentials were located near the CS ostium, consistent with input to the CS only from the right atrium.

Prior Studies

In a prior report of patients with valvular heart disease and AF, earliest activation during reinitiation of AF was found to occur around the ostium of the CS, and radiofrequency energy applications at the ostium resulted in the noninducibility of AF.[29] Therefore, in the present study, it is possible that connections between the CS and the right atrium were responsible for the episodes of sustained AF that were still inducible in 3 of 9 patients despite disconnection of the CS from the left atrium. In addition, other sources such as the left atrium itself, the superior vena cava, the ligament of Marshall, or the crista terminalis may have contributed to the persisting inducibility of AF in these patients.

Role of the CS in Global Atrial Activation

Previous studies have shown that the muscular sleeve of the CS serves as a major electrical connection between the left and right atria.[30,31] However, this is the first study to demonstrate that electrical disconnection of the CS from the left atrium results in prolongation of the P wave duration. Although it is possible that a conduction delay within the left or right atrium may result in prolongation of the P wave, the increase in P wave duration immediately after electrical disconnection, without any interventions in the atria, suggests that the interatrial conduction time lengthened. The P wave duration increased by only approximately 10%, perhaps because of persistent conduction through Bachmann's bundle and other interatrial connections.[30,31]

Study Limitations

A limitation of this study is that CS angiography was not routinely performed to define the anatomy of the CS and its branches. Therefore, the location of the CS to left atrial connections relative to landmarks such as the vein of Marshall cannot be specified.

Conclusion

The aim of the present study was to determine the feasibility of CS disconnection from the left atrium and its acute effect on the inducibility of AF. The study demonstrates that CS disconnection from the left atrium is feasible in a practical fashion and that the inducibility of AF lasting more than 5 minutes after pulmonary vein isolation is markedly attenuated by electrical disconnection of CS from the left atrium. A prior study demonstrated that the noninducibility of AF lasting more than 5 minutes after ablation was predictive of a successful clinical outcome in patients who underwent pulmonary vein isolation because of drug-refractory AF.[1] This provides a basis for concluding that the noninducibility of AF lasting more than 5 minutes after electrical disconnection of the CS from the left atrium also may have clinical significance.

The results of this study suggest that the CS may function as a fifth pulmonary vein in the maintenance of AF, perhaps accounting for recurrent AF in at least some of the 15% to 40% of patients who fail to respond to pulmonary vein isolation.[11,12,27] However, a larger-scale study comparing outcomes in patients who undergo pulmonary vein isolation with and without electrical disconnection of the CS is needed to establish the clinical value of CS disconnection.

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