Isolation of Canine Coronary Sinus Musculature From the Atria by Radiofrequency Catheter Ablation Prevents Induction of Atrial Fibrillation

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Background—The junction between the coronary sinus (CS) musculature and both atria contributes to initiation of atrial tachyarrhythmias. The current study investigated the effects of CS isolation from the atria by radiofrequency catheter ablation on the induction and maintenance of atrial fibrillation (AF).

Methods and Results—Using an optical mapping system, we mapped action potentials at 256 surface sites in 17 isolated and arterially perfused canine atrial tissues containing the entire musculature of the CS, right atrial septum, posterior left atrium, left inferior pulmonary vein, and vein of Marshall. Rapid pacing from each site before and after addition of acetylcholine (0.5 μmol/L) was applied to induce AF. Epicardial radiofrequency catheter ablation at CS-atrial junctions isolated the CS from the atria. Rapid pacing induced sustained AF in all tissues after acetylcholine. Microreentry within the CS drove AF in 88% of preparations. Reentries associated with the vein of Marshall (29%), CS-atrial junctions (53%), right atrium (65%), and pulmonary vein (76%) (frequently with 2–4 simultaneous circuits) were additional drivers of AF. Radiofrequency catheter ablation eliminated AF in 13 tissues before acetylcholine (P<0.01) and in 5 tissues after acetylcholine. Radiofrequency catheter ablation also abbreviated the duration of AF in 12 tissues (P<0.01).

Conclusions—CS and its musculature developed unstable reentry and AF, which were prevented by isolation of CS musculature from atrial tissue. The results suggest that CS can be a substrate of recurrent AF in patients after pulmonary vein isolation and that CS isolation might help prevent recurrent AF. (Circ Arrhythm Electrophysiol. 2014;7:1181-1188.)

Key Words: atrial fibrillation ▪ catheter ablation ▪ coronary sinus ▪ optical Vm mapping

Radiofrequency catheter ablation (RFCA) is a common treatment of atrial fibrillation (AF). The pulmonary veins (PVs) are frequent sources of AF, and thus are major targets of RFCA.1 PVs contain muscular sleeves extending from the left atrial (LA) myocardium. Similar to PVs, the coronary sinus (CS) also has a muscular sleeve that connects the right atrium (RA) and LA.2,3 Atrial tachyarrhythmias can arise spontaneously from the musculature of the CS4,5 or after PV isolation by RFCA.6,7 In some patients, macroreentrant atrial tachycardia (AT) in association with the CS4,5 or by a focal atrial firing arising from the CS6,7 initiates and drives AF. Thus, the CS is a possible ablation target to eliminate recurrent AF.8–10

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The CS musculature can also be a source of triggered activity11 and delayed conduction at the CS musculature and junctions between the CS and both atria. Such conduction delay also provides substrates for macroreentrant activity.12–15 The vein of Marshall (VOM), which is a branch of the coronary veins connected to the LA and CS, is a substrate for reentrant circuit and foci of repetitive rapid responses.16 Recently, we showed that muscular junctions between the CS musculature (including VOM) and both atria contributed to initiation of the atrial tachyarrhythmias by rapid pacing.15 Rate-dependent conduction block in these pathways led to unstable reentry and AF-like activities.

Clinical and experimental observations indicate that isolation of the CS musculature from both atria by RFCA can be a secondary target for curing AF after completion of PV isolation.8,9,10,15,17,18 In the current study, we investigated the relationship of the CS musculature to persistent AF induced by rapid atrial pacing with acetylcholine administration and the effects of CS isolation on the induction and maintenance of AF.

Methods

Arterially Perfused Atrial Tissue Preparations

The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the National Academy of Sciences (8th edition, Washington DC, 2011) and follows in accordance with our institutional guidelines. We prepared tissues with procedures similar to those used previously.19
We harvested hearts from 17 anesthetized adult male mongrel dogs and isolated atrial tissue preparations that contained the ostium of the CS (CSos), the CS musculature, the ligament of Marshall, the left inferior PV and lower interatrial septum of the RA, and the posterior LA from the posterior portion of the atrium and removed the free wall of the RA (Figure 1A). Each preparation contained the right coronary artery and the circumflex branch of the left coronary artery (diameter, ≈1–1.5 mm), into which separate perfusion and pressure monitoring cannulas were inserted. The tissues were mounted in a warmed chamber with epicardial surface in the focal plane of the mapping camera and were perfused with Tyrode’s solution. Two silver electrodes were placed in the bath, 5 mm away from the LA (anode) and the RA (cathode) sides of the tissue, to register an ECG.15

The tissue preparations were stained with a voltage-sensitive fluorescent dye di-4-ANEPPS (Biotium, Inc, Hayward, CA, n=4 mmol/L) and immobilized with cytochalasin D (Fermentek Ltd, Jerusalem, Israel, 20–30 μmol/L), which does not influence canine atrial action potentials (APs).16 An optical mapping system with a 256-element (16x16) photodiode camera collected the fluorescence from a 33.6x33.6 mm² observation area on the tissue surface for general mapping and 19.5x19.5 mm² for detailed mapping of microreentry and converted it into 256 channels of electric signals. We recorded APs and ECG sequentially after 10 pacing stimuli at the coronary entry and converted it into 256 channels of electric signals. We determined the muscular connections at the LA, RA, and the musculature of the CS during pacing in these pathways. We also analyzed the distributions of AP duration for unpaired data and paired data, as appropriate. We verified normality of the continuous data. Ordinal data were analyzed with Kruskal–Wallis test. Fisher exact test was performed for the comparison of proportions among groups. Significance was defined as P<0.05.

Radiofrequency Catheter Ablation to Isolate the CS

After induction of sustained atrial tachyarrhythmia with acetylcholine, we performed RFCA at the junctions between the CS musculature and both atria (Figure 1B) with a 4-mm tip catheter (Medtronic Conductor, Medtronic, Minneapolis, MN). Radiofrequency current (Atakr; Medtronic, Minneapolis, MN) was delivered between the catheter tip electrode and an Ag–Cl pad (1.5x1.5 cm²) applied to edge of the tissue bath (5–10 W for 20–30 seconds; temperature ≤55°C).21 We first applied RFCA energy around the CSos to isolate the CS musculature from the RA, and then performed linear ablation along the CSP–LA junctions. We evaluated the activation patterns during CS pacing after each ablation step. We additionally ablated the Csd–LA junction, if the LA was activated from the Csd–LA junction or from VOM after blockade of the CSP–LA junction. After isolating the CS from the atria, we evaluated the recurrence of conduction across the CS–atrial junctions for 20 minutes. Any remaining conduction between the CS and atria was then eliminated with additional RFCA. We repeated the pacing protocol to induce atrial tachyarrhythmias with and without acetylcholine after isolating the CS from the atria. To avoid excessive heat around the catheter, we superperfused the tissue at the ablation site with 60 mL/min Tyrode’s solution (28–30°C) during RFCA.21

Statistics

Continuous data were expressed as mean±SD. Comparisons among mean values were performed with 2-way ANOVA coupled with Dunnett test. Comparisons of 2 groups were made with Student t test for unpaired data and paired data, as appropriate. We verified normality of the continuous data. Ordinal data were analyzed with Kruskal–Wallis test. Fisher exact test was performed for the comparison of proportions among groups. Significance was defined as P<0.05.

![Figure 1. Tissue preparation and musculature of the coronary sinus.](http://circep.ahajournals.org/Downloadedfrom/1182_CircArrhythmElectrophysiol_December2014)
Results
Anatomy and Electrophysiological Properties of the CS Musculature
The visible CS musculature from the CSos to the distal end was 31±6 mm long and the diameter of the CSos orifice was 7±1 mm (Figure 1A). Muscular connections from the RA extended into the CSos and LA musculature directly to the CSp. The ligament of Marshall contained veins within the musculature that connected to the CS musculature in all tissues.

There were no statistical differences in AP duration and morphology between the LA, RA, PV, and CS musculature. Rapid pacing abbreviated the AP duration (Figure 2A). There were no statistical differences in the shortest pacing CL for 1:1 conduction among atrial sites (CS, 121±29 ms; RA, 124±25 ms; LA, 121±17 ms; PV, 123±18 ms; and VOM, 123±14 ms; P=0.9770), indicating similar longest refractory periods. Acetylcholine abbreviated AP duration at all sites. These data suggested similar electrophysiological properties among these muscular structures.

Induction of AF
At baseline, rapid pacing induced unstable macroreentry in association with conduction block at the CS–atrial junctions (Figures 3A and 4), resulting in AF-like ECG activity for 4.0±2.8 seconds (range, 1.5–12.0; median, 2.6 seconds). The average pacing CL that induced AF was 130±21 ms. LA pacing frequently induced AF, but the difference compared with other pacing sites did not reach statistical significance (incidence of induced AF: CS pacing 71%, RA pacing 77%, LA pacing 88%, and PV pacing 82%; P=0.6209). During AF, the LA had the longest mean CL of local activation among all atrial sites (Figure 2B). Unstable reentry usually appeared in association with the CS musculature and its atrial junctions, the VOM, PV, and intra-atrial septum (Figure 4), and usually 1 to 2 reentrant circuits existed simultaneously. During pacing-induced AF episodes at baseline, reentrant circuits were frequently associated with the CS musculature and the left inferior PV (Figure 2C).

After administration of acetylcholine, all tissues had sustained AF (>8 minutes) that either was induced by rapid pacing (pacing CL, 137±26 ms; n=14) or occurred spontaneously (n=3; Figure 3B). Because of the continuation of induced AF after acetylcholine, we could not evaluate 1:1 conduction systematically at all pacing and induction sites (induced pacing sites: 5 tissues at LA, 4 at PV, 4 at CS, and 1 at RA). Mean CL of local activation during AF with acetylcholine was shorter than at the baseline (Figure 2B). Compared with the RA and LA, CS and PV had shorter CLs of local activation during AF. AF after acetylcholine treatment had similar (usually 2–4 simultaneous) unstable reentrant circuits as the AF at the baseline and was associated more frequently with microreentry within the intra-atrial septum, PV and VOM (Figures 2C, 4C–4F, and 5) than with macroreentry between the CS and atria using CS–atrial junctions (Figures 4A and 4B). Moreover, microreentry within the CS musculature appeared frequently during AF after acetylcholine treatment (Figures 4F and 5). All AF episodes terminated spontaneously 2.3±1.7 minutes (median, 1.7 minutes) after acetylcholine washout.

CS Isolation From Both Atria
We isolated the CS with 3 RFCA steps and evaluated conduction during CS pacing. First, we performed circular ablation of the CSos (8.4±1.0 applications of RF energy) to block electric conduction between the CSos and RA (step 1, ablation of CSos–RA junction). Then a 13.8±7.5-mm linear ablation (range, 7–27; median, 12 mm) was performed (4.2±1.3 applications) along the CSp–LA junctions from CSp to CSd on the epicardium (step 2, ablation of CSp–LA junction). After step 2, connection between the CSd and LA was found in 12 tissues. These tissues subsequently received 2.9±1.1 applications RF energy to the CSD junction, resulting in 8.3±2.5-mm linear lesion (range, 5–14; median, 8 mm; step 3, ablation of CSD–LA junction; Figure 1B). The CSD–LA junction usually existed in association with branching of the VOM from the CS. We concluded that there was successful separation of the CSD–LA junction from the CSP–LA junction when their

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**Figure 2.** Action potential (AP) and its conduction in the atrium. A, AP duration (APD) in the left and right atria (LA and RA) and coronary sinus (CS). There were no statistical differences in APDs among the LA, RA, and CS. Short pacing cycle length (CL; 200 ms) abbreviated APDs. Acetylcholine (ACh) shortened APD at all sites. **P<0.01 vs CL=500 ms. †P<0.01. B, Mean CL during induced atrial fibrillation (AF) at each site. RA had the longest CL during AF at baseline. Acetylcholine abbreviated AF-CLs. AF-CLs were shorter in the CS and pulmonary vein (PV) than in the atria. **P<0.01 and †P<0.05 vs CS. ‡P<0.01 vs. baseline. C, Reentry. At baseline, reentry usually occurred in association with CS and its atrial junctions. Acetylcholine increased microreentry in the PV, intra-atrial septum (IAS), vein of Marshall (VOM), and CS. D, Activation times of the RA and LA during CS pacing. Ablation prolonged atrial tachycardias (ATs) in both atria. **P<0.01 vs control. †P<0.01 vs RA (N=17). Comparisons were performed with 2-way ANOVA coupled with Dunnett test (A, B, and D). OS abl indicates ablation at ostium of CS; and P abl, ablation at proximal portion of CS.
ablation lines were ≥7 mm apart because single RFCA made a lesion of 3.8±0.9 mm diameter in these experiments.

Figures 2D and 6 show the changes in activation pattern in the RA and LA during CS pacing following each RFCA step. Before RFCA, excitation evoked by CS pacing propagated via the CS–atria junctions directly into both the RA and the LA (Figure 6A) with slightly earlier activation in the LA than in the RA (Figure 2D). After step 1 of RFCA, the RA was activated with significant delay via the interatrial septum (Figure 6B) from the LA, which was also delayed slightly. After step 2, the LA was activated from the CSp–LA junction. Both the LA and the RA activated significantly later than before step 2 (Figure 6C). Step 3 ablation fully isolated the CS, resulting in complete exit and entrance block (Figure 6D). Three tissues had reappearance of conduction at the CS–atrial junctions and required additional ablations to achieve electric isolation of the CS musculature.

Macroscopic observation after RFCA is shown in Figure 7. CS musculature connected directly to the LA at the upper side of the CS in CSp. Radiofrequency energy ablated the muscular connection of the CSp–LA junctions as well as the upper third of the CS musculature. At the CSd in which direct muscular connection was eliminated, small muscular bundles and VOM connected the CS and LA.

**Effect of Isolation of CS Musculature From Both Atria on Induction of AF**

We repeated electric stimulation after CS isolation. Although rapid pacing (CL, 132±22 ms) induced atrial tachyarrhythmias (≥0.5 seconds) in 4 tissues without acetylcholine, the duration of the tachyarrhythmias was significantly shorter than before RFCA (duration after RFCA, 0.4±0.8 seconds; range, 0–2.7 seconds; median, 0 second; P<0.01 versus before RFCA; Figure 3C). Short runs of reentrant tachycardia occurred in the interatrial septum (n=2) and left inferior PV (n=3).

Rapid pacing (CL, 128±18 ms) with acetylcholine induced atrial tachyarrhythmias (≥0.5 seconds) in 12 tissues. In contrast to the induced AF before RFCA, CS isolation organized the induced tachyarrhythmias into ATs having short durations (after CS isolation, 8.6±20.9 seconds; range, 0.9–81 seconds; median, 1.7 seconds; P<0.01 versus before RFCA; Figure 3D). Only 2 tissues had sustained AT (duration, 40 and 81 seconds, respectively) in association with the VOM and PV after RFCA. Residual reentry appeared in the left inferior PV (n=7; Figure 8A), intra-atrial septum (n=4; Figure 8B), and

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**Figure 3.** Atrial ECG characteristics of the induced atrial fibrillation (AF). A, Rapid pacing induced AF (duration: 1.9 s) at the baseline. B, After acetylcholine administration, rapid pacing induced sustained AF with finer waves than the baseline. C, After isolation of the coronary sinus (CS), rapid pacing induced only 1 to 2 echo beats. D, After isolation of the CS, administration of acetylcholine and rapid pacing induced short organized atrial tachycardia. Note these ECGs show atrial electrogram and do not include QRS complex.

**Figure 4.** Schematic drawings of the unstable reentry induced by rapid pacing. A, Induced macroreentry of proximal coronary sinus (CSp)—left atrium (LA)→right atrium (RA)→ostium of CS (CSos)→coronary sinus (CS)→CSp. B, Induced macroreentry of distal coronary sinus (CSd)→LA→CSos/CSp→CS→CSd. C, Reentry of vein of Marshal (VOM)→LA→CSd→VOM. D, Microreentry associated with intra-atrial septum. E, Reentry associated with intra-atrial septum. F, Microreentry within the CS musculature. These reentrant circuits were usually unstable, resulting in atrial fibrillation–like ECG activity.
VOM (n=2; Figure 8C). Intra-CS reentry did not sustain for ≥0.5 seconds after CS isolation. Additional ablation to the residual reentrant circuits eliminated ATs in 9 tissues.

Discussion

We observed that rapid pacing–induced unstable macroreentry was associated with conduction slowing in the CS musculature and its atrial junctions, consistent with our previous findings. New in this study, however, is that in addition to macroreentry, acetylcholine promoted microreentry involving the PV, VOM, and CS musculature and resulted in sustained AF. Importantly, microreentry within the CS musculature appeared only during AF induced by acetylcholine. Isolation of the CS musculature from both atria prevented induction of macroreentry in the CS musculature and organized AF into short-term ATs. Additional RFCA to the reentrant circuits associated with the ATs eliminated residual microreentry in the PV, VOM, and interatrial septum.

In addition to the initiation of AF from the PVs, the musculature of the CS also has inherent arrhythmogenicity and can be a source of AT/AF. The CS has been associated with initiation and maintenance of AF in 35% of patients.

Figure 5. Microreentry during atrial fibrillation (AF) induced by rapid pacing and acetylcholine. A, Activation time map of the AF and action potentials. Activation time map showed that 2 microreentry appeared in the vein of Marshal (VOM) and coronary sinus (CS) simultaneously. B, CS was activated by rapid figure-of-8 microreentry and propagated 2:1 to the atria. C, VOM was activated from the proximal to distal and then propagated to left atrium (LA). Mapping area: 33.6×33.6 (A), 19.5×19.5 (B and C) mm². ECGs represent atrial electrogram and do not include QRS complex. RA indicates right atrium.

Figure 6. Activation of the atria during coronary sinus (CS) pacing before and after stepwise ablation. A, Atrial activation before ablation (ABL). Right atrium (RA) and CS were activated from ostium of CS (CSos) and proximal CS (CSp) junctions, respectively. B, Atrial activation after CSos-ABL. RA was activated from ostium (CS) and then propagated to RA. C, Atrial activation after CSp-ABL. LA was activated from the distal CS (CSd; vein of Marshall) junction and then propagated to RA. D, Atrial activation after CS isolation. Activation during CS pacing did not propagate to both atria.
in whom AF remained after PV isolation. Macroreentrant and focal ATs within the CS have been observed in ≤25% of the patients after PV isolation for AF, and foci within the CS have been reported responsible for 1.4% to 27% of the extra PV foci. Several reports showed the effectiveness of CS-RFCA in eliminating AF after PV isolation, by

![Figure 7](image1)

**Figure 7.** Macroscopic observation of the coronary sinus (CS)-atrial junctions after ablation (ABL). A, Ablation lesion around the ostium of CS (CSos). Dotted area showed degeneration by ABL. CS was cut at epicardial ablation site longitudinally in the lower panel. Radiofrequency energy reached within CS. B, ABL lesion at the proximal CS (CSp). CS musculature connected to the left atrial (LA) muscles directly at the upper side of the CS. ABL degenerated the CS–LA junctions, LA muscles and upper a-third of the CS musculature. C, ABL lesion at the distal CS (CSd). CS was separated from the LA by adipose tissues but small muscular bundle connected the CS and LA (arrows). LV indicates left ventricle; and RA, right atrium.

![Figure 8](image2)

**Figure 8.** Microreentries after electric isolation of the coronary sinus. A, Microreentry around the left inferior pulmonary vein (LIPV). Counterclockwise reentry was induced by rapid pacing with acetylcholine after the coronary sinus (CS) isolation. B, Microreentry along with the vein of Marshall (VOM). Clockwise reentry was induced by rapid pacing with acetylcholine. C, Microreentry along the intra-atrial septum (IAS). Figure-of-8 reentry was induced by rapid pacing with acetylcholine n. Induced atrial arrhythmias were organized into atrial tachycardia after CS isolation. Note that ECGs represent atrial electrogram and do not include QRS complex. LA indicates left atrium; and RA, right atrium.
disconnecting the LA from the CS musculature or by eliminating rapid atrial activity within the CS. In long-term AF, complex fractionated atrial electrograms are another target for eliminating AF, and CS is one of the sites where complex fractionated atrial electrograms are frequently recorded after PV isolation.

Our study supports the mechanism and therapeutic option in patients with AT associated with CS. We induced AT/AF by rapid pacing with or without acetylcholine and showed that the CS musculature can be a part of a macroreentrant circuit and source of microreentry. Acetylcholine abbreviated atrial refractory periods, shortened reentrant circuits, reduced the incidence of macroreentry in the CS and its atrial junctions, and promoted smaller reentrant circuits. The shifting of reentrant circuits and simultaneous existence of multiple reentrant circuits resulted in AF. Microreentry and slow conduction within the CS and functional block at the CS–atrial junctions during AF can be sources of the rapid electric activity, such as complex fractionated atrial electrograms. Clinically, the importance of PVs on AF initiation and maintenance has been established, so the present model can be applied to instances of recurrent or residual AF after PV isolation.

The CS ablation procedures eliminated micro- and macroreentry associated with the CS musculature and organized the conduction of reentry associated with VOM, interatrial septum and PV. Similar multistep ablation, including PV isolation and linear ablation of the CS, increased the success of AF termination clinically. The microreentry within the CS was less frequent after RFCA in this study, possibly because of the ablation injury in the CS musculature.

Autonomic ganglia are another RFCA target for eliminating AF. Although this model of isolated tissue was separated from the central nervous system, acetylcholine release from local ganglia could still facilitate microreentry during AF. Epicardial RFCA to the CS–atrial junction or VOM would modify autonomic ganglia as well as disconnect the macro- and microreentrant circuits to terminate AF/AF.

Limitations of the Study
We only studied electric activity in the atrial epicardium. Foci and circuits certainly can exist in the endocardium as well, where the activation pattern may be different from what we found in the epicardium.

Application of radiofrequency energy created electric noise in the electrograms so we could not evaluate what step of the ablation procedure terminated AF.

We observed a greater incidence of microreentry in the CS as a driver of acetylcholine-induced AF (88%) than observed clinically. One potential explanation why our AF model differs from clinical AF is that the latter usually occurs after atrial remodeling while we used tissue from healthy canines. In addition, resection of left upper and right PVs in the tissue preparations reduced the electrophysiological substrate of PVs as a role of AF driver.

Conclusions
We showed the efficacy of CS isolation for eliminating AF in the isolated canine atrial model. Rapid pacing induced macroreentrant AF at CS–atrial junctions and microreentry at PV, VOM, and CS. Complete electric isolation of the CS from the atria eliminated reentries associated with the CS and organized AF into AT arising from the PV, intra-atrial septum, and VOM. Additional RFCA to these circuits of the ATs prevented arrhythmias in this model.

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Disclosures
None.

References

**CLINICAL PERSPECTIVE**

The significant points of this study are (1) the coronary sinus musculature is one of the sources driving atrial fibrillation and (2) isolation of the coronary sinus musculature from the atria converts fibrillatory conduction to organized reentry. Ablation of these residual reentry sites terminated atrial tachycardia/fibrillation. These observations are consistent with the recent demonstration that spiral reentry (rotors) and focal excitation can drive human atrial fibrillation, and catheter ablation of these sources (focal impulse and rotor modulation) can terminate atrial fibrillation and restore sinus rhythm. The reentrant circuits associated with the coronary sinus musculature, Marshall vein, pulmonary veins and atrial septum in this study are probably sources of rotors targeted by focal impulse and rotor modulation in human atrial fibrillation.

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