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

Running title: Morita et al.; Coronary sinus isolation by ablation

Hiroshi Morita, MD1,2; Douglas P. Zipes, MD1; Shiho T. Morita, MD1,2; Jiashin Wu, PhD1,3

1Krannert Institute of Cardiology, Indiana University School of Medicine, Indianapolis, IN; 2Department of Cardiovascular Therapeutics / Cardiovascular Medicine, Okayama University Graduate School of Medicine, Okayama, Japan; 3Department of Pharmaceutical Sciences, College of Pharmacy, Northeast Ohio Medical University, Rootstown, OH

Correspondence:
Hiroshi Morita, MD
Department of Cardiovascular Therapeutics
Okayama University Graduate School of Dentistry and Pharmaceutical Sciences
2-5-1 Shikata-Cho
Okayama, 700-8558
Japan
Tel: +81-86-235-7351
Fax: +81-86-235-7353
E-mail: hmorita@cc.okayama-u.ac.jp

Abstract:

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 (RFCA) on the induction and maintenance of 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 (RA), posterior left atrium (LA), left inferior pulmonary vein (PV) and vein of Marshal (VOM). Rapid pacing from each site before and after addition of acetylcholine (ACh: 0.5 μM) was applied to induce AF. Epicardial RFCA at CS-atrial junctions isolated the CS from the atria. Rapid pacing induced sustained AF in all tissues after ACh. Microreentry within the CS drove AF in 88% of preparations. Reentries associated with the VOM (29%), CS-atrial junctions (53%), RA (65%), and PV (76%) (frequently with 2-4 simultaneous circuits) were additional drivers of AF. RFCA eliminated AF in 13 tissues before ACh (p<0.01) and in 5 tissues after ACh. RFCA 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 PV isolation and that CS isolation might help prevent recurrent AF.

Key words: coronary sinus, atrial fibrillation, ablation, optical mapping, rotor, coronary sinus musculature
Introduction

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 CS\(^4,5\) or after PV isolation by RFCA\(^6,7\). In some patients, macro-reentrant atrial tachycardia (AT) in association with the CS\(^5\) or by a focal atrial firing arising from the CS\(^6,7\) initiates and drives AF. Thus, the CS is a possible ablation target to eliminate recurrent AF\(^8-10\).

The CS musculature can also be a source of triggered activity\(^11\) 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\(^8-10,15,17,18\). 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\textsuperscript{15}.

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 (LOM), 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 electrocardiogram\textsuperscript{15}.

The tissue preparations were stained with a voltage-sensitive fluorescent dye di-4-ANEPPS (Biotium, Inc., Hayward, CA, ~4 mmol/l) and immobilized with cytochalasin D (Fermentek Ltd, Jerusalem, Israel, 20-30 μmol/l), which does not influence canine atrial APs\textsuperscript{19}. 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 electrical signals. We recorded APs and ECG sequentially after 10 pacing stimuli at the CLs of 500 and 200 ms using a custom data acquisition system.15

The protocol for the experiments consisted of 5 parts and we examined all tissues during each part: 1) AF induction without acetylcholine, 2) AF induction with acetylcholine, 3) RFCA, 4) AF induction without acetylcholine after ABL, 5) AT/AF induction with acetylcholine after ABL. To induce atrial tachyarrhythmias, we paced the tissues with trains of 5-15 pacing stimuli, first at 180 ms CL and then repetitively with progressively abbreviated CLs in 10-ms steps until the occurrence of 2-to-1 conduction at each pacing site, including: the CS, RA, LA, left inferior PV and VOM. The above sequences of data recording were performed after tissue stabilization and verification (as the baseline control data) and then again after 10 min of stabilization following the addition of 0.5 µmol/l acetylcholine (Sigma-Aldrich, St. Louis, MO). Acetylcholine shortened AP duration, and thus mimicked vagally-induced AF in patients.20

We analyzed the shortest CL of 1:1 conduction at the CS, RA, LA, PV, and VOM, which indicated the longest refractory period in these pathways. We also analyzed the distributions of AP duration at the LA, RA and the musculature of the CS during pacing CLs of 500 and 200 ms. We determined the muscular connections between the CSos-RA and CS-LA as reported previously.2,3,15 For ease of reference, the proximal CS-LA (CSp-LA) junction was defined as the proximal or first half of the CS while the distal CS-LA (CSD-LA) junction was defined as the distal or second

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half of the CS.

We analyzed conduction patterns of sustained (≥0.5 sec) atrial tachyarrhythmias that were induced by rapid pacing from each site\(^{15}\). We defined AF as an atrial tachyarrhythmia with polymorphic changes of f waves in the electrocardiogram recorded between the RA and LA\(^{15}\).

While there are no standard definitions of microreentry and macroreentry, we separated them by diameter of the reentrant circuit: macro > 1 cm and micro ≤ 1 cm.

**Radiofrequency catheter ablation to isolate the coronary sinus**

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 cm\(^2\)) applied to edge of the tissue bath (5-10 W for 20-30 s, 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 min. 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 superfused the tissue at the ablation site with 60 ml/min Tyrode’s solution (28-30°C) during
Statistics

Continuous data were expressed as mean ± standard deviation. Comparisons among means were performed with 2-way ANOVA coupled with Dunnett’s test. Comparisons of 2 groups were made with Student’s t-test for unpaired data and paired data, as appropriate. We verified normality of the continuous data. Ordinal data were analyzed with Kruskal-Walis test. Fisher’s exact test was performed for the comparison of proportions among groups. Significance was defined as p<0.05.

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 LOM 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, 4), resulting in AF-like ECG activity for 4.0±2.8 sec (range 1.5-12.0, median 2.6 sec). The average pacing CL that induced AF was 130±21 ms. LA pacing frequently induced AF, but the difference compared to 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 RA 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 intraatrial septum (Figure 4), and usually 1-2 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 min) 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 to 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 intraatrial septum, PV and VOM (Figures 2C, 4C-F, 5) than with macroreentry between the CS and atria using CS-atrial junctions (Figures 4A, B).
Moreover, microreentry within the CS musculature appeared frequently during AF after acetylcholine treatment (Figures 4F, 5). All AF episodes terminated spontaneously 2.3±1.7 min (median 1.7 min) 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 electrical 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 ablation lines were ≥7 mm apart because single RFCA made a lesion of 3.8±0.9 mm diameter in this experiments.

Figures 2D and 6 showed 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 LA (Figure 6A) with slightly earlier activation in the LA than 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 CSd-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 electrical 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 electrical stimulation after CS isolation. Although rapid pacing (CL 132±22 ms) induced atrial tachyarrhythmias (≥0.5 sec) in 4 tissues without acetylcholine, the duration of the tachyarrhythmias was significantly shorter than before RFCA (duration after RFCA: 0.4±0.8 sec, range 0-2.7 sec, median 0 sec, p<0.01 vs. 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 sec) in 12 tissues. In contrast to the induced AF before RFCA, CS isolation organized the induced tachyarrhythmias into ATs having very short durations (after CS isolation: 8.6±20.9 sec, range 0.9-81 sec, median 1.7 sec, p<0.01 vs. before RFCA) (Figure 3D). Only 2 tissues had sustained AT (duration: 40 and 81 sec, respectively) in association with the VOM and PV after RFCA. Residual
reentry appeared in the left inferior PV (n=7) (Figure 8A), intraatrial septum (n=4) (Figure 8B), and VOM (n=2) (Figure 8C). Intra CS reentry did not sustain for ≥0.5 sec 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 lasting 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 in whom AF remained after PV isolation. Macroreentrant and focal ATs within the CS has been observed in up to 25% of the patients after PV isolation for AF, and foci within the CS have been reported responsible for 1.4-27% of the extra PV foci. Several reports showed the effectiveness of CS-RFCA in eliminating AF after PV isolation, by disconnecting the LA from the CS musculature or by...
eliminating rapid atrial activity within the CS\textsuperscript{10, 24}. In long-lasting AF, complex fractionated atrial electrograms (CFAEs) are another target for eliminating AF\textsuperscript{18}, and CS is one of the sites where CFAEs are frequently recorded after PVs isolation\textsuperscript{18}.

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\textsuperscript{2, 12, 15} can be sources of the rapid electrical activity, such as CFAEs. 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\textsuperscript{23}. Similar multi-step ablation, including PV isolation and linear ablation of the CS increased the success of AF termination clinically\textsuperscript{24}. The microreentry within the CS was less frequent after RFCA in this study, possibly due to 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\textsuperscript{25} as well as disconnect the macro and microreentrant circuits to terminate AF/AF.

**Limitations of the study**

We only studied electrical activity in the atrial epicardium. Foci and circuits certainly can exist in the endocardium as well,\textsuperscript{26} where the activation pattern may be different from what we found in the epicardium.

Application of radiofrequency energy created electrical 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.

**Conclusion**

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 electrical 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.

**Conflict of Interest Disclosures:** None
References:


Figure Legends:

**Figure 1**: Tissue preparation and musculature of the coronary sinus. A. Posterior region of the atria that includes coronary sinus (CS). B. The epicardial area of 256-channel mapping usually covers the entire CS musculature, right atrial side of intraatrial septum (IAS), left atrium (LA), left inferior pulmonary vein (PV), and vein of Marshall (VOM). C. Ablation points (red circles) electrically isolated CS from both atria in 3 steps: 1) circular ablation around ostium of CS (CSos), 2) linear ablation along the borderline between the CS musculature and LA, and 3) distal region of the CS in which VOM inserted to CS.

**Figure 2**: Action potential and its conduction in the atrium. A. Action potential 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) (200ms) abbreviated APDs. Acetylcholine 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 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, IAS, VOM and CS. D. Activation times of the RA and LA during CS pacing. Ablation prolonged 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’s test (A, B, D).
**Figure 3:** Atrial ECG characteristics of the induced AF. A. Rapid pacing induced atrial fibrillation (AF, Duration: 1.9 sec) at the baseline. B. After acetylcholine administration, rapid pacing induced sustained AF with finer waves than the baseline. C. After isolation of the CS, rapid pacing induced only 1-2 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 CSp→LA→RA→CSos→CS→CSp. B. Induced macroreentry of CSd→LA→RA→CSos/CSp→CS→CSd. C. Reentry of VOM→LA→CSd→VOM. D. Microreentry associated with left inferior PV. E. Reentry associated with intraatrial septum. F. Microreentry within the CS musculature. These reentrant circuits were usually unstable, resulting in AF-like ECG activity. CS: coronary sinus, CSd: distal CS, CSp: proximal CS, LA: left atrium, PV: left inferior pulmonary vein, RA: right atrium, VOM: vein of Marshall.

**Figure 5:** Microreentry during AF induced by rapid pacing and acetylcholine. A. Activation time map of the AF and action potentials. Activation time map showed 2 microreentry appeared in the VOM and CS simultaneously. B. CS was activated by rapid figure-of-eight microreentry and propagated 2:1 to the atria. C. VOM was activated from the proximal to distal and then propagated to LA. Mapping area: 33.6x33.6 (A), 19.5x19.5 (B and C) mm². ECGs represent atrial electrogram and do not include QRS complex.
**Figure 6:** Activation of the atria during CS pacing before and after stepwise ablation. A. Atrial activation before ablation (ABL). 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 LA via CSp junction. C. Atrial activation after CSp-ABL. LA was activated from the CSd (vein of Marshall) junction and then propagated to RA. D. Atrial activation after CS isolation. Activation during CS pacing did not propagated to both atria.

**Figure 7:** Macroscopic observation of the CS-atrial junctions after ablation. A. Ablation (ABL) 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).

**Figure 8:** Microreentries after electrical isolation of the coronary sinus. A. Microreeentry around the left inferior pulmonary vein (PV). Counterclockwise reentry was induced by rapid pacing with acetylcholine after the CS isolation. B. Microreeentry along with the vein of Marshall (VOM). Clockwise reentry was induced by rapid pacing with acetylcholine. C. Microreeentry along the intraatrial septum. Figure-of-eight reentry was induced by rapid pacing with acetylcholine. Induced atrial arrhythmias were organized into atrial tachycardia after CS isolation. Note that ECGs represent atrial electrogram and do not include QRS complex.
A. CSp-CSos

B. CSd-CSp/or CSos

C. VOM-LA-CS

D. PV

E. Intraatrial septum

F. Intra CS

----- Functional block line at the CS-LA junctions
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