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Association of Rate-Dependent Conduction Block between Eccentric Coronary Sinus to Left Atrial Connections with Inducible Atrial Fibrillation and Flutter

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Abstract

Background—We sought to describe the prevalence and variability of coronary sinus (CS) and left atrial (LA) myocardium connections, their susceptibility to rate-dependent conduction block, and association with atrial fibrillation (AF) and flutter (AFL) induction.

Methods and Results—The study cohort included 30 consecutive AF patients (age 63.3±10.5 years, 63% male). Multipolar catheters were positioned in the CS, high right atrium (HRA), and LA parallel to and near the CS. Trains of 10 pacing stimuli were delivered during sinus rhythm from each of the following sites: CS proximal (CS_p), CS distal (CS_d), LA septum (LA_s), lateral LA (LA_l), and HRA, at the following cycle lengths (CL): 1000, 500, 400, 300, and 250 ms, while recording from the other catheters. With the CS 9–10 bipole just inside the CS ostium, CS-LA connections were observed in 100% at CS 9–10, 30% at CS 7–8, 23% at CS 5–6, 23% at CS 3–4, and 97% at CS 1–2. Eighteen patients (60%) had AF/AFL induced. Rate-dependent conduction block of a CS-LA connection at CL ≥250 ms was present in 17 (94%) of those with versus none of those without AF/AFL induction ($P<0.001$).

Conclusions—Rate-dependent eccentric CS-LA conduction block is associated with AF/Flutter induction in patients with drug-refractory AF undergoing ablation. The presence of dual muscular CS-LA connections, coupled with uni-directional block in one limb, appears to serve as a substrate for single or multiple reentry beats and arrhythmia induction.

Keywords

atrial fibrillation; coronary sinus; rate-dependent conduction block; initiation

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The coronary sinus (CS) is a complex structure comprising a mesh of circumferential muscular fibers with connections to both atria.[1] Canine studies have pointed to the participation of CS musculature to left atrial (LA) connections in unstable macro-reentrant atrial tachycardia (AT) and atrial flutter (AFL) with degeneration to atrial fibrillation (AF).[2–5] Additionally, the CS is a source of focal triggered activity in 15% of patients with AF recurrence despite pulmonary vein isolation (PVI).[6] Ablation of endocardial and epicardial aspects of the CS has been shown to prolong the fibrillatory cycle length and terminate AF in selected patients.[3,7] Although clinically recognized, variations in distal CS musculature-LA myocardium (CS-LA) connections have not been systematically evaluated in patients with atrial arrhythmias. In addition, although the concept of rate-dependent conduction block between functional atrial components such as the crista terminalis and atrial arrhythmia has been demonstrated,[8] the association between rate-dependent unidirectional CS-LA conduction block with arrhythmia induction has not been examined. In this study, we sought to define the electrophysiological properties of the CS-LA muscular connections by describing a) the prevalence and variability of CS-LA connections, b) the susceptibility of CS-LA connections to unidirectional rate-dependent conduction block, and c) association of CS-LA connection characteristics with atrial arrhythmia induction.

Methods

Study Population

The study cohort included 30 patients with drug refractory paroxysmal or persistent AF undergoing catheter ablation at the Johns Hopkins Hospital from April to June 2016. Patients with prior history of peri-mitral ablation were excluded. Persistent AF was defined as AF lasting more than 1 week and paroxysmal AF was defined as AF that terminates spontaneously or with intervention within 7 d of onset according to the 2016 ESC and 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation.[9,10] Anti-arrhythmic drugs were not discontinued prior to catheter ablation. All participants provided written and informed Institutional Review Board-approved consent.

Pacing Protocol

Vascular access was established through femoral veins. Following administration of IV heparin (ACT goal > 350 seconds), the LA was accessed by double trans-septal punctures. Figure 1 is a schematic drawing demonstrating the location of catheters used in this protocol. Pacing and recording were performed using a decapolar catheter with 2-mm inter-electrode distance and 8-mm inter-bipole distance (Boston Scientific) in the CS, a quadripolar catheter with 2-mm interelectrode distance and 5-mm inter-bipole distance (St. Jude Medical) the high right atrium (HRA), and a duo-decapolar catheter with 2-mm interelectrode distance and 10-mm interbipole distance (St. Jude Medical) in the LA near the mitral annulus and parallel to the CS catheter. The pacing protocol was performed in sinus rhythm (SR) prior to any peri-mitral ablation. If the patient presented in, or developed AF during the pacing protocol, sinus rhythm was restored with cardioversion (n=6). Care was taken to place the CS 9–10 (proximal) bipole just inside the coronary sinus ostium based upon left anterior oblique (LAO) and right anterior oblique (RAO) views. A train of 10 pacing stimuli were applied from each of the following sites: CS proximal (CS_p), CS distal (CS_d), left atrium

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septum (LA_s), lateral left atrium (LA_l), and high right atrium (HRA), at the following circle lengths (CL): 1000, 500, 400, 300, and 250ms. Pacing was performed at twice diastolic capture threshold and pulse-width of 3 ms and interrupted if sustained AT/AF/AFL was induced. Intracardiac electrograms were filtered at 30 to 500 Hz, and were displayed at a paper speed of 100 mm/s (Prucka CardioLab System, General Electric Healthcare, Milwaukee, WI).

Ablation Procedure

Pulmonary vein isolation (PVI) was performed using radiofrequency (RF) applications, guided by a 3-dimensional (3-D) electroanatomic mapping system (CARTO 3, Biosense Webster, Diamond Bar, CA) as previously described.[11] The procedural end point was elimination of electrograms at the PV antra on a circumferential mapping catheter (Lasso, Biosense Webster) as well as demonstration of entrance block into the PVs. Linear ablation at the LA roof, mitral isthmus (MI), or cavo tricuspid isthmus (CTI) was performed after PVI in selected cases with persistent AF or AFL.

CS-LA Connections

Conduction patterns were measured using intra-cardiac electrograms and orthogonal LAO/RAO fluoroscopic images (Figure 1). Conduction patterns were derived from analysis of conduction direction following pacing. The order of activation was determined from the electrogram tracings by comparing electrogram timing at each bipole annotated at the first sharp peak following the pace stimulus. Rate-dependent conduction block was defined as a change in CS or the LA activation pattern during incremental pacing from a constant site. Cycle lengths (CLs) at which conduction block occurred between CS-LA were recorded. CS pivots and triggers during pacing were also recorded and analyzed. In a subset of 5 patients, high density LA mapping was performed using a multi-polar catheter (LASSO 2515 eco, Biosense Webster) during distal CS pacing at 100 ms faster than the basal cycle length. Eccentric CS-LA connection were targeted for ablation after PVI, at the discretion of the attending electrophysiologist, and if rate dependent block followed by AF/AFL induction was observed.

Statistical Analysis

Continuous variables were expressed as median and interquartile range (IQR). Categorical variables were expressed as numbers and percentages. Univariable comparisons were made by using the Wilcoxon-Mann-Whitney and Fisher's exact tests as appropriate. *P*-values < 0.05 were considered statistically significant. Analyses were performed using STATA version 12 (College Station, TX).

Results

Patient Characteristics

Of 30 patients in the study, 11 (37%) were female, and 6 (20%) had persistent AF. The median age was 66 (IQR 57 – 73) years. The median body mass index (BMI) was 28.9 (IQR 23.9 – 35.9) kg/m^2. Other patient characteristics have been summarized in Table 1.

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Electrophysiologic Study Findings

During the study pacing protocol, AF/AFL was induced in 18 (60%) patients. Evidence of CS pivot and arrhythmogenic triggers were found in 12 (40%) and 4 (13%) cases, respectively. Of these patients, 4/12 (33%) CS pivot and 1/4 (25%) triggers led to sustained AF/AFL (Figure 2).

Electrophysiological Properties of the CS-LA Connections

With the 9–10 bipole of the decapolar catheter positioned inside the CS ostium, we observed CS-LA connections at CS 9–10 in 30 (100%), CS 7–8 in 9 (30%), CS 5–6 in 7 (23%), CS 3–4 in 7 (23%), and CS 1–2 in 29 (97%) patients. Thus, CS-LA connections were significantly more common at the proximal and distal ends of the CS than other portions. A representative high density activation map of the LA during distal CS pacing, which demonstrates an eccentric CS-LA connection, is displayed in Figure 3. The CS-LA connections were bi-directional in most cases. Representative electrograms exhibiting the presence or absence of CS-LA connections at the middle and distal portions of the CS are displayed in Figure 4. Additionally, a detailed summary of CS-LA connection patterns is included in Table 2.

Rate-Dependent Conduction Block of CS-LA connections

Rate-dependent conduction block occurred in 17 cases (57%). Of these 17 patients, block occurred at a pacing CL of 500 ms in 9%, 400 ms in 14%, 300 ms in 36%, and 250 ms in 41% (Table 2). Three patients demonstrated at least 2 different conduction block CLs at different points along the CS. In the majority of cases (77%), rate-dependent conduction block was achieved at a pacing CL at or below 300 ms.

Rate-Dependent Conduction Block in CS and AF/AFL Induction

Rate-dependent conduction block was demonstrated in 17/18 (94%) patients with AF/AFL induction. None of the patients with non-inducible AF/AFL displayed conduction block at CL ≥250 ms ($P<0.001$). As summarized in Table 3, the positive and negative predictive values of rate-dependent conduction block in CS for AF/AFL induction are 100% (95% CI 80–100%) and 92% (95% CI 64–100%), respectively. Figure 5 displays representative electrograms of rate-dependent conduction block of CS-LA connections followed by arrhythmia induction during incremental pacing.

Ablation of CS-LA Connections

In 4 patients selected per electrophysiologist discretion, with AF/AFL induction following rate-dependent CS-LA conduction block, the connection site was targeted from the endocardial LA surface. These were distal CS to lateral LA connections. The CS-LA connection was successfully and safely ablated in all 4 cases. Repeating the identical pacing protocol following ablation failed to induce any arrhythmia in these cases. The position of the ablation catheter and electrograms of a representative case are displayed in Figure 6.

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Discussion

In this study, we examined the electrophysiological properties of CS-LA muscular connections. Rate-dependent CS-LA conduction block was readily demonstrable in 57% of AF patients referred for ablation, 77% of which occurred at a CL between 250 and 300 ms. The most important finding of the study was that rate-dependent CS-LA conduction block is closely associated with AF/AFL induction during pacing maneuvers. Importantly, anatomical surrogates of atrial remodeling were unassociated with rate-dependent conduction block of eccentric CS-LA connections. In a subset of patients, we also demonstrated the feasibility of targeted, rather than linear, ablation of distal CS-lateral LA connections.

Delayed conduction at the CS musculature and junctions between the CS and atria has been recognized as a source of triggered activity,[12] and substrate for macroreentry and AF in canine models.[2,13–15] Triggers and intra-CS reentry beats have been occasionally observed, consistent with the previously reported 3% incidence of triggers in AF patients.[16–18] The CS musculature may also contribute to arrhythmogenesis by providing a secondary conduction path between the RA and the LA potentially allowing the formation of reentrant circuits.[19,20] Conduction delay within the CS musculature has been demonstrated to correlate with increased propensity for reentrant circuits and atrial tachyarrhythmias.[13–15]

Our findings suggest that targeted ablation of CS-LA connections when rate-dependent conduction block is observed may reduce the propensity for AF/AFL induction. Previous studies have demonstrated the overall safety and feasibility of linear ablation at the endocardial and epicardial aspects of the CS.[7,21,22] However, linear CS ablation may increase procedure duration, and increase the likelihood of gap-dependent atrial flutters. In a small subset of patients, we demonstrated that targeted RFA can safely and efficaciously achieve eccentric CS-LA conduction block. Larger studies are needed to confirm the safety as well as benefits of targeted eccentric CS-LA connection ablation when rate-dependent CS-LA block is observed.

Clinical implications

Although, PVI has become the cornerstone for treatment of drug refractory AF, it has lower efficacy in the setting of persistent AF. Advances such as hybrid surgical procedures, complex fractionated atrial electrogram (CFAE) ablation, and rotor ablation may improve efficacy in some patients; however, outcomes remain suboptimal.[21–27] Endocardial and targeted ablation of eccentric CS-LA connections, when associated with unidirectional rate-dependent conduction block, may provide a novel ablation target for AF suppression.

Limitations

Our study is limited by its small sample size. However, the sample size was adequate to demonstrate substantial variability in CS-LA connections and the association of CS-LA connections with AF/AFL inducibility. Of all patient, 37% had undergone prior PVI. Thus, patients with AF refractory to PVI may have been oversampled, and the incidence of rate-dependent CS-LA conduction block in this study may not be generalizable to all AF

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patients. Larger prospective controlled studies are needed to study the overall incidence of eccentric CS-LA connections and of rate dependent conduction block, as well as the safety and efficacy of targeting such connections during catheter ablation. Although anti-arrhythmic drug use was not different among study groups, CS-LA conduction patterns may have been altered in their presence. Additionally, the resolution of mapping was limited to the inter-electrode spacing of the multipolar catheters utilized in the study. Future studies following anti-arrhythmic drug washout, and with higher density electrodes or a pair of decapolar catheters in the CS to record activation in both the roof and floor of the CS body may refine these results.

Conclusion

Rate-dependent CS-LA conduction block is associated with AF/AFL induction in patients with drug refractory AF undergoing ablation. The presence of dual CS-LA connections, coupled with unidirectional block in one connection, appears to serve as a substrate for single or multiple reentry beats and arrhythmia induction. Rate-dependent CS-LA conduction block may provide a novel ablation target to increase the efficacy of catheter ablation for AF.

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What is Known

- Canine studies have pointed to the participation of coronary sinus to left atrial connections in macro-reentrant atrial tachycardia and flutter with degeneration to atrial fibrillation.
- The coronary sinus has been recognized as a source of focal triggers for recurrent atrial fibrillation following pulmonary vein isolation.

What the Study Adds

- Rate-dependent eccentric coronary sinus to left atrial conduction block is associated with atrial fibrillation induction in drug-refractory atrial fibrillation patients undergoing ablation.
- The presence of dual muscular coronary sinus to left atrial connections, coupled with uni-directional block in one limb, appears to serve as a substrate for single or multiple reentry beats and arrhythmia induction.
- Endocardial and targeted ablation of eccentric coronary sinus to left atrial connections, when associated with unidirectional rate-dependent conduction block, may provide a novel ablation target for atrial fibrillation suppression.

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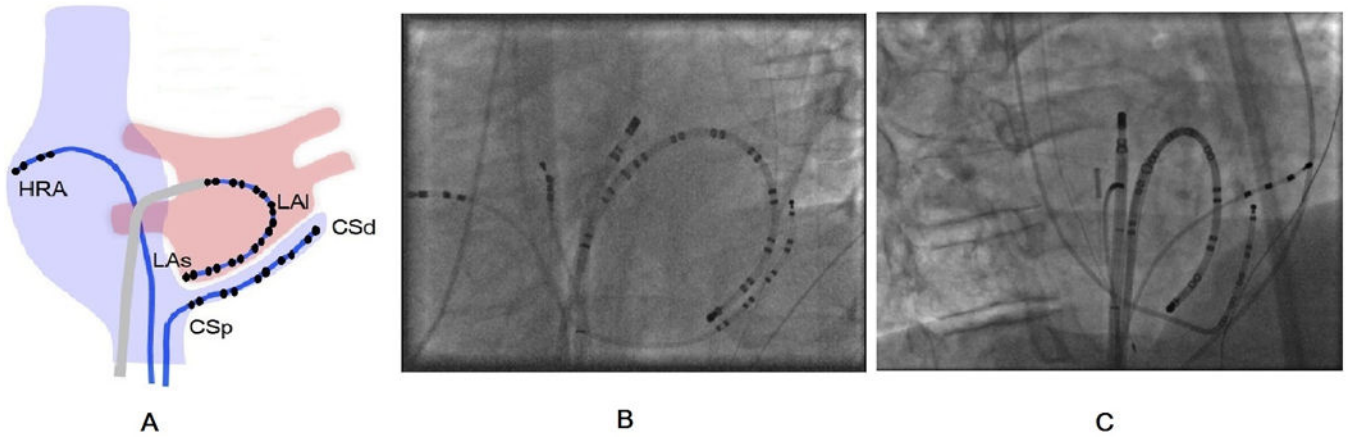

Figure 1.

Catheter placement for pacing and recording: (A) The schematic shows the positions of decapolar, quadripolar, and duodecapolar catheters in the coronary sinus (CS), high right atrium (HRA), and left atrium (LA), respectively; additional panels show a typical case with fluoroscopic (B) left anterior oblique and (C) right anterior oblique views. HRA: high right atrium; LA_s: left atrium septum; LA_l: lateral left atrium; CS_p: proximal coronary sinus; CS_d: distal coronary sinus

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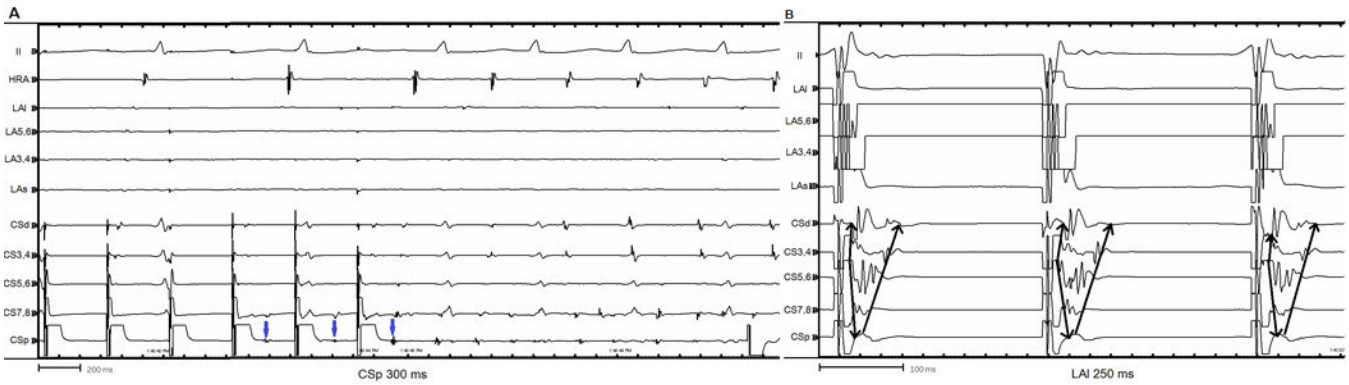

Figure 2.

Representative electrograms of CS trigger (A) and CS pivots (B). Panel A shows a CS trigger (blue arrow) that induced AF. Panel B displays CS pivots at CS_p during LA_l pacing with CL 250 ms. Note lack of electrograms on the adjacent LA catheter which confirms that the CS signals are not far-field.

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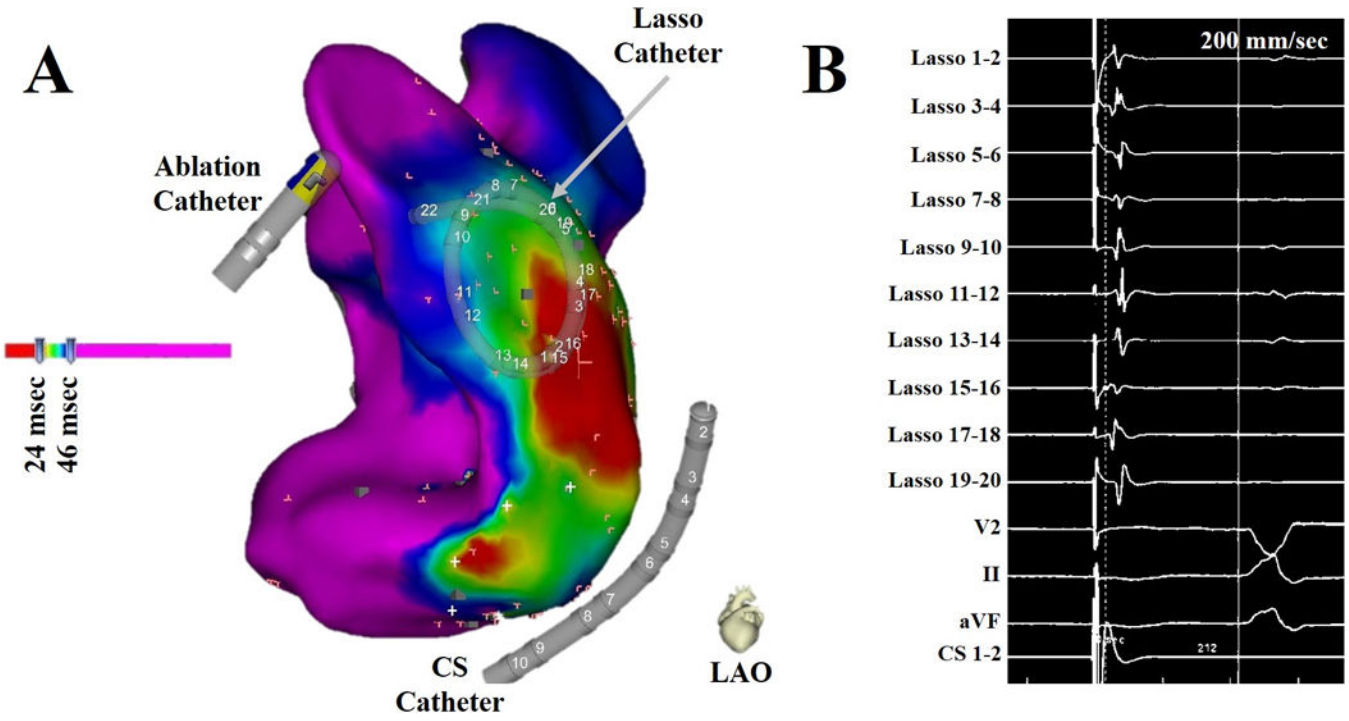

Figure 3.

Representative high density activation map of the LA (A) and electrograms (B) demonstrating CS-LA connections during low output distal CS pacing (CS 1–2). Panel A demonstrates 2 distinct sites of early activation in the LA overlying the distal CS and the proximal CS when pacing the distal CS at a cycle length of 900 ms. Panel B displays the earliest LA electrograms (Lasso 15,16 and 17–18 on panel A), which demonstrate delay compared to the stimulus and rule out direct LA capture. LAO: left anterior oblique; CS: coronary sinus

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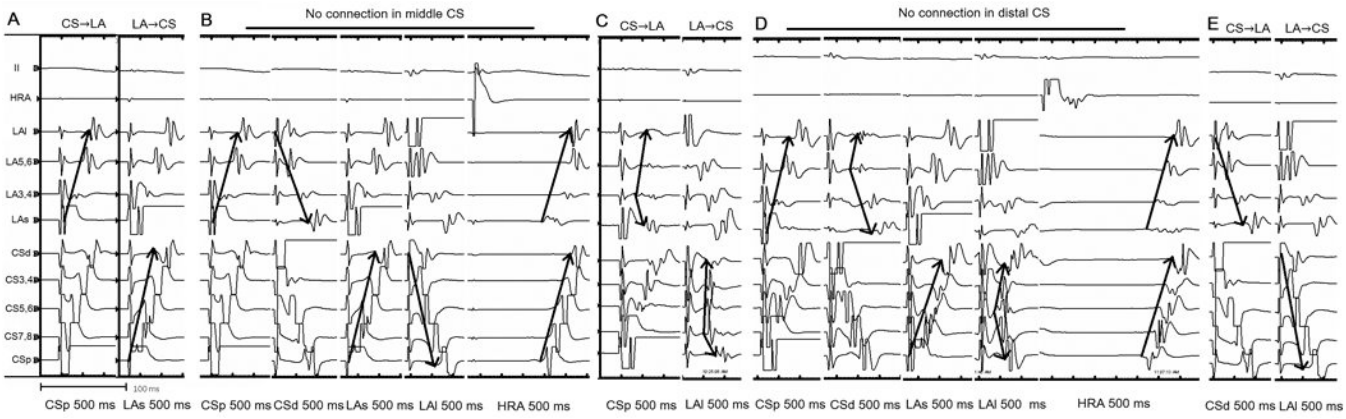

Figure 4.

Representative electrograms of CS-LA connection at the proximal (A), middle (C), and distal (E) CS, as well as absence of CS-LA connections at the middle (B) and distal (D) CS. The annotation at the bottom of each figure indicates the pacing location and CL. Panel A shows CS-LA connections at the proximal CS with bi-directionality of the conduction. Traces from 5 separate patients are displayed in figures A through E.

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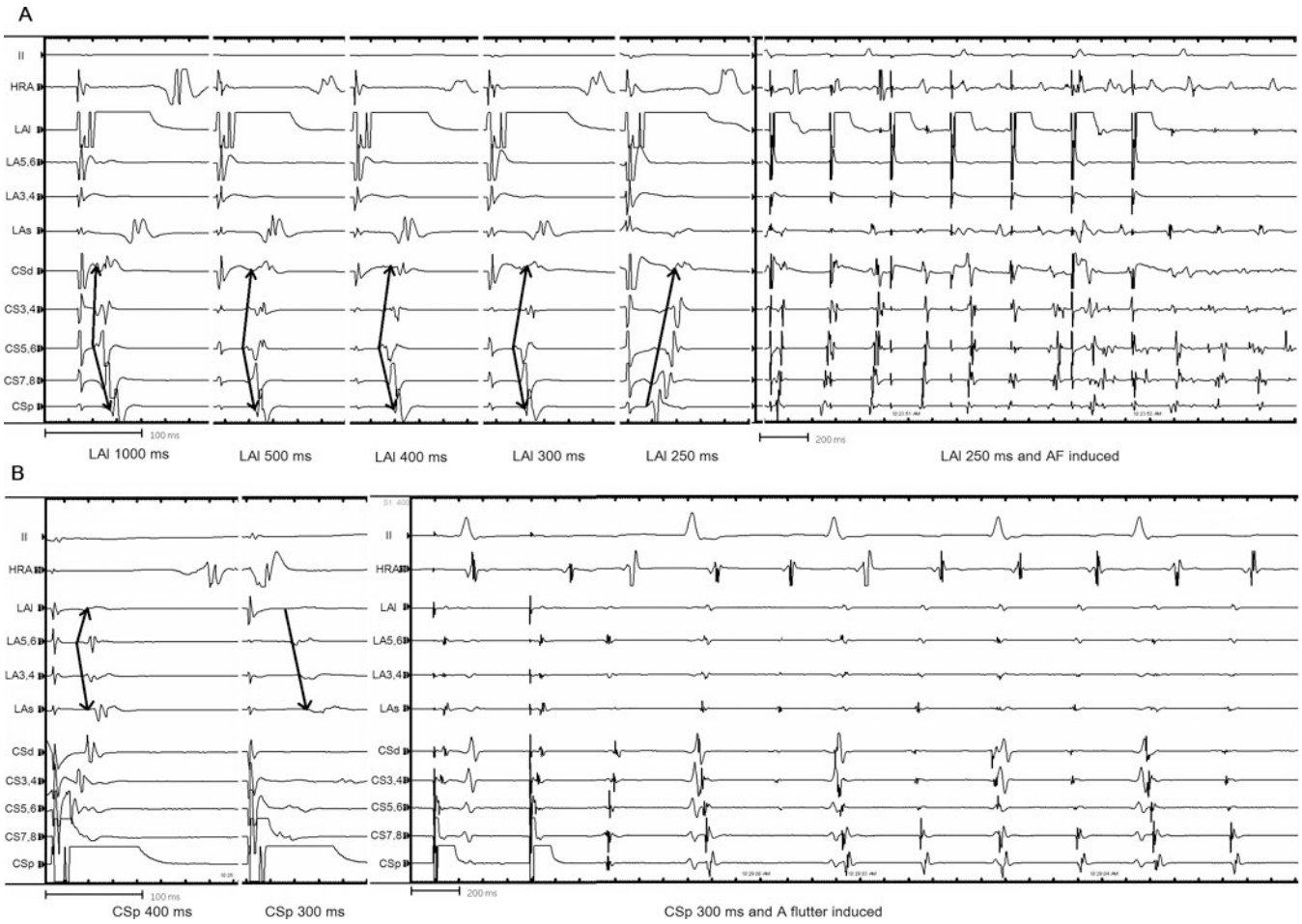

Figure 5.

The electrograms suggest rate-dependent conduction block of CS-LA connections followed by induction of AF (A) or AFL (B). Annotations below each tracing indicate pacing location and CL. Panel A shows pacing from the lateral LA with rate-dependent CS-LA conduction block at CS 7,8 at 250 ms followed by AFL induction and degeneration to AF within 6 beats. Panel B shows pacing from lateral LA with rate-dependent CS-LA conduction block at CS 1,2 at 250 ms, followed by AFL induction.

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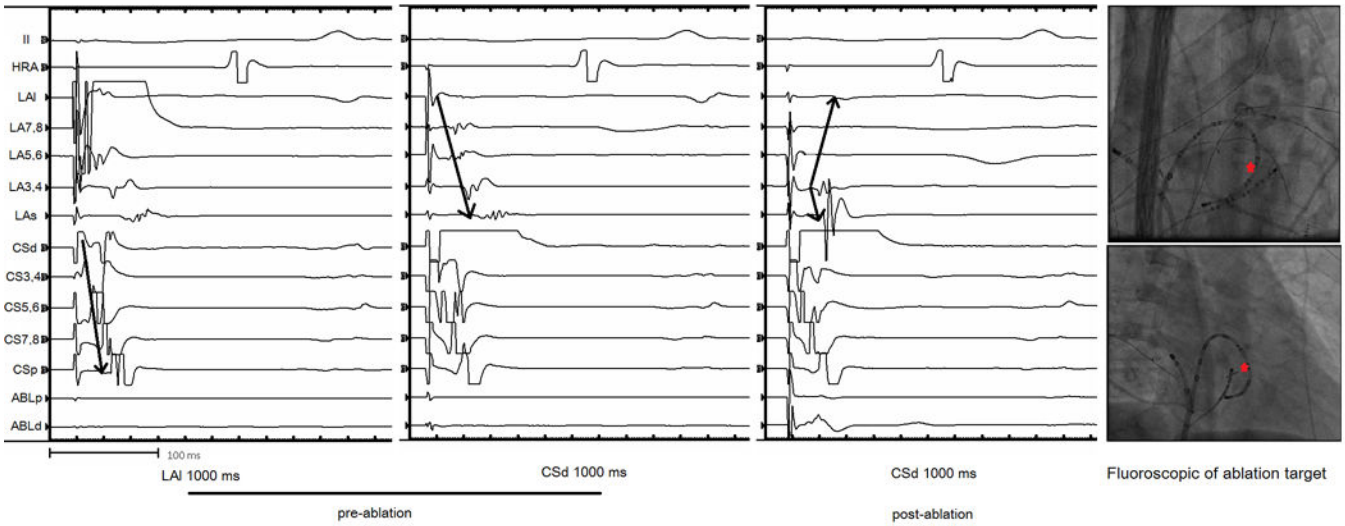

Figure 6.

The Figure displays a representative case of CS-LA connection ablation following AF induction. Annotations at the bottom of each electrogram indicate the pacing location and CL. After RFA at the CS_d-LA_l, LA_s activates earlier with only delayed and far-field activation of the LA_l. The position of the ablation catheter is marked with a red star on the fluoroscopic image.

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Table 1

Clinical characteristics of the study cohort*

	All Patients (n=30)	Patients with Rate-Dependent Conduction Block (n=17)	Patients without Rate-Dependent Conduction Block (n=13)	*P* Value
Mean Age, years	66 (57, 73)	69 (58, 73)	60 (57, 66)	0.240
Female, n (%)	11 (37)	8(47)	3(23)	0.260
Prior PVI, n (%)	11 (37)	7(41)	4(31)	0.708
AF Duration, years	4.5 (2, 8)	5 (2.3, 9)	3 (2, 5)	0.438
Persistent AF, n (%)	6 (20)	3(18)	3(23)	1.000
BMI, kg/m^2	28.9 (23.9, 35.9)	25.7 (23.5, 30.2)	32.2 (28.0, 36.0)	0.149
LA Diameter (cm)	4 (4, 4)	4 (4, 4)	4 (4, 4.5)	0.282
LA Volume (cm^3)	102.2 (87, 120.6)	101.2 (94.6, 122.0)	103.2 (86.5, 119.2)	0.754
Anti-arrhythmic Drugs, n (%)	26 (87)	15 (88)	11 (85)	1.000
AF Induced, n (%)	11 (37)	10(59)	1(8)	0.007
A Flutter Induced, n (%)	7 (23)	7(41)	0(0)	0.010
CS pivot, n (%)	12 (40)	7(41)	5(39)	1.000
CS Trigger, n (%)	4 (13)	3(18)	1(8)	0.613

*Values are reported as median and interquartile range or numbers and percentages.

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Table 2

Detailed summary of CS-LA connections

	CS-LA Direction of Conduction				n, (%)	Block Cycle Length (ms)					
	None	CS→LA	LA→CS	Both		1000	500	400	300	250	<250
CS 9,10	0	1	5	24	30 (100)	0	0	0	2	4	24
CS 7,8	21	1	5	3	9 (30)	0	0	1	2	1	5
CS 5,6	23	1	4	2	7 (23)	0	0	0	2	0	5
CS 3,4	23	3	1	3	7 (23)	0	0	0	0	0	7
CS 1,2	1	12	3	14	29 (97)	0	2	1	1	2	23

CS: Coronary sinus; LA: Left atrium; None: No conduction between CS-LA at this site; CS→LA: Unidirectional conduction from CS to LA at this site; LA→CS: Unidirectional conduction from LA to CS at this site; Both: Bidirectional conduction between CS and LA at this site

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Table 3

Diagnostic value of rate-dependent CS-LA conduction block for AF/AFL induction

Rate-dependent Conduction Block	Induced AF/AFL		Total
	+	–	
+	17	0	17
–	1	12	13
Total	18	12	30
Positive Predictive Value	100%, 95% CI * (80–100%)	Negative Predictive Value	92%, 95% CI (64–100%)
Sensitivity	94%, 95% CI (73–100%)	Specificity	100%, 95% CI (74–100%)

* CI – Confidence Interval