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 and atrial flutter (AFL) with degeneration to atrial fibrillation (AF).2–5 In addition, 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 (CL) 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 arrhythmias has been demonstrated,4 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 (1) the prevalence and variability of CS–LA connections, their susceptibility to rate-dependent conduction block, and association with atrial fibrillation (AF) and flutter induction.

**Methods**

**Study Population**

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 (CSp), CS distal (CSd), LA septum (LAS), lateral LA (LAL), and HRA, at the following cycle lengths: 1000, 500, 400, 300, and 250 ms, while recording from the other catheters. With the CS 9 to 10 bipole just inside the CS ostium, CS–LA connections were observed in 100% at CS 9 to 10, 30% at CS 7 to 8, 23% at CS 5 to 6, 23% at CS 3 to 4, and 97% at CS 1 to 2. Eighteen patients (60%) had AF/atrial flutter induced. Rate-dependent conduction block of a CS–LA connection at cycle length of ≥250 ms was present in 17 (94%) of those with versus none of those without AF/atrial flutter induction (P<0.001).

**Conclusions**

Rate-dependent eccentric CS–LA conduction block is associated with AF/atrial flutter induction in patients with drug-refractory AF undergoing ablation. The presence of dual muscular CS–LA connections, coupled with unidirectional block in one limb, seems to serve as a substrate for single or multiple reentry beats, and arrhythmia induction. (Circ Arrhythm Electrophysiol. 2017;10:e004637. DOI: 10.1161/CIRCEP.116.004637.)

Key Words: atrial fibrillation ■ atrial flutter ■ catheter ablation ■ coronary sinus ■ myocardium
WHAT IS KNOWN

- Canine studies have pointed to the participation of coronary sinus to left atrial connections in macroreentrant 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 unidirectional 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.

and 2014 AHA/ACC/HRS (American Heart Association/American College of Cardiology/Heart Rhythm Society) guideline for the management of patients with AF. Antiarhythmic drugs were not discontinued before catheter ablation. All participants provided written and informed institutional review board–approved consent.

Pacing Protocol

Vascular access was established through femoral veins. After the administration of intravenous heparin (activated clotting time goal >350 s), 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 interelectrode distance and 8-mm interbipole distance (Boston Scientific) in the CS, a quadripolar catheter with 2-mm interelectrode distance and 5-mm interbipole distance (St. Jude Medical) in 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 before any perimtrial 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 to 10 (proximal) bipole just inside the CS ostium based on left anterior oblique and right anterior oblique views. A train of 10 pacing stimuli was applied from each of the following sites: CS proximal (CSp), CS distal (CSd), left atrium septum (LAS), lateral left atrium (LAl), and high right atrium (HRA), at the following cycle lengths (CLs): 1000, 500, 400, 300, and 250 ms. Pacing was performed at twice diastolic capture threshold and pulse-width of 3 ms and interrupted if sustained atrial tachycardia/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

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

CS–LA Connections

Conduction patterns were measured using intracardiac electrograms and orthogonal left anterior oblique/right anterior oblique 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 after 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. 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 multipolar catheter (LASSO 2515 eco; Biosense Webster) during distal CS pacing at 100 ms faster than the basal CL. Eccentric CS–LA connection was 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. 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 of <0.05 were considered statistically significant. Analyses were performed using STATA version 12 (College Station, TX).

Figure 1. Catheter placement for pacing and recording. A, The schematic diagram shows the positions of decapolar, quadripolar, and duodecapolar catheters in the coronary sinus, high right atrium (HRA), and left atrium, respectively; additional panels show a typical case with fluoroscopic (B) left anterior oblique and (C) right anterior oblique views. CSs indicates distal coronary sinus; CSp, proximal coronary sinus; LAl, lateral left atrium; and LA, left atrium septum.
Table 1. Clinical Characteristics of the Study Cohort*

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=30)</th>
<th>Patients With Rate-Dependent Conduction Block (n=17)</th>
<th>Patients Without Rate-Dependent Conduction Block (n=13)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>11 (37)</td>
<td>8 (47)</td>
<td>3 (23)</td>
<td>0.260</td>
</tr>
<tr>
<td>Previous PVI, n (%)</td>
<td>11 (37)</td>
<td>7 (41)</td>
<td>4 (31)</td>
<td>0.708</td>
</tr>
<tr>
<td>AF duration, years</td>
<td>4.5 (2, 8)</td>
<td>5 (2.3, 9)</td>
<td>3 (2.5)</td>
<td>0.438</td>
</tr>
<tr>
<td>Persistent AF, n (%)</td>
<td>6 (20)</td>
<td>3 (18)</td>
<td>3 (23)</td>
<td>1.000</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.9 (23.9, 35.9)</td>
<td>25.7 (23.5, 30.2)</td>
<td>32.2 (28.0, 36.0)</td>
<td>0.149</td>
</tr>
<tr>
<td>LA diameter, cm</td>
<td>4 (4, 4)</td>
<td>4 (4, 4)</td>
<td>4 (4, 4.5)</td>
<td>0.282</td>
</tr>
<tr>
<td>LA volume, cm²</td>
<td>102.2 (87, 120.6)</td>
<td>101.2 (94.6, 122.0)</td>
<td>103.2 (86.5, 119.2)</td>
<td>0.754</td>
</tr>
<tr>
<td>Antiarrhythmic drugs, n (%)</td>
<td>26 (87)</td>
<td>15 (88)</td>
<td>11 (85)</td>
<td>1.000</td>
</tr>
<tr>
<td>AF induced, n (%)</td>
<td>11 (37)</td>
<td>10 (59)</td>
<td>1 (8)</td>
<td>0.007</td>
</tr>
<tr>
<td>A flutter induced, n (%)</td>
<td>7 (23)</td>
<td>7 (41)</td>
<td>0 (0)</td>
<td>0.010</td>
</tr>
<tr>
<td>CS pivot, n (%)</td>
<td>12 (40)</td>
<td>7 (41)</td>
<td>5 (39)</td>
<td>1.000</td>
</tr>
<tr>
<td>CS trigger, n (%)</td>
<td>4 (13)</td>
<td>3 (18)</td>
<td>1 (8)</td>
<td>0.613</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; BMI, body mass index; CS, coronary sinus; LA, left atrium; and PVI, pulmonary vein isolation.

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

Results

Patient Characteristics
Of 30 patients in the study, 11 (37%) were women and 6 (20%) had persistent AF. The median age was 66 years (interquartile range: 57–73 years). The median body mass index was 28.9 kg/m² (interquartile range: 23.9–35.9 kg/m²). Other patient characteristics have been summarized in Table 1.

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

Electrophysiological Properties of the CS–LA Connections
With the 9 to 10 bipolar of the decapolar catheter positioned inside the CS ostium, we observed CS–LA connections at CS 9 to 10 in 30 (100%), CS 7 to 8 in 9 (30%), CS 5 to 6 in 7 (23%), CS 3 to 4 in 7 (23%), and CS 1 to 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 bidirectional 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. In addition, 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

Figure 2. Representative electrograms of coronary sinus (CS) trigger (A) and CS pivots (B). A, A CS trigger (blue arrow) that induced atrial fibrillation. B, CS pivots at proximal coronary sinus (CSp) during lateral left atrium (LA) pacing with cycle length 250 ms. Note the lack of electrograms on the adjacent LA catheter, which confirms that the CS signals are not far-field.
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 of 18 (94%) patients with AF/AFL induction. None of the patients with noninducible 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% confidence interval, 80%–100%) and 92% (95% confidence interval, 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 after 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 after 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.

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 patients with AF 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

Figure 3. Representative high-density activation map of the left atrium (LA; A) and electrograms (B) demonstrating CS–LA connections during low output distal coronary sinus (CS) pacing (CS 1–2). A, Two 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. B, The earliest LA electrograms (Lasso 15, 16, and 17–18 on A), which demonstrate delay compared with the stimulus and rule out direct LA capture. LAO indicates left anterior oblique.

Figure 4. Representative electrograms of coronary sinus (CS)–left atrium (LA) connection at the proximal (A), middle (C), and distal (E) CS, as well as the 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 cycle length (CL). A, CS–LA connections at the proximal CS with bidirectionality of the conduction. Traces from 5 separate patients are displayed in A through E.
is closely associated with AF/AFL induction during pacing maneuvers. Importantly, anatomic 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 the 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 patients with AF.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.2,21,22 However, linear CS ablation may increase procedure duration, and increase the likelihood of gap-dependent AFLs. In a small subset of patients, we demonstrated that targeted radiofrequency ablation can safely and efficaciously achieve eccentric CS–LA conduction block. Larger studies are needed to confirm the safety and 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 the 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 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 patients, 37% had undergone previous 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 patients with AF. 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 antiarrhythmic drug use was not different among study groups, CS–LA conduction patterns may have been altered in their presence. In addition, the resolution of mapping was limited to the interelectrode spacing of the multipolar catheters used in the study. Future studies following antiarrhythmic 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.

Conclusions

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, seems to serve as a substrate for single or multiple reentry beats and
Eccentric CS–LA Conduction Block and AF Induction

Arrhythmia induction. Rate-dependent CS–LA conduction block may provide a novel ablation target to increase the efficacy of catheter ablation for AF.

Sources of Funding

The study was funded by a Biosense-Webster grant and National Institutes of Health (NIH) grants K23HL089333 and R01HL116280 to

Figure 5. The electrograms suggest rate-dependent conduction block of coronary sinus (CS)–left atrium (LA) connections followed by induction of atrial fibrillation (AF; A) or atrial flutter (AFL; B). Annotations below each tracing indicate pacing location and cycle length (CL).

A, 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. B, Pacing from proximal CS with rate-dependent CS–LA conduction block of an LA lateral connection at 300 ms, followed by AFL induction. HRA indicates high right atrium; LA\(_L\), lateral left atrium; and LA\(_s\), left atrium septum.

Figure 6. A representative case of coronary sinus (CS)–left atrium (LA) connection ablation after atrial fibrillation induction. Annotations at the bottom of each electrogram indicate the pacing location and cycle length. After radiofrequency ablation 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. CS\(_d\) indicates distal coronary sinus; HRA, high right atrium; LA\(_L\), lateral left atrium; and LA\(_s\), left atrium septum.
Disclosures

Dr Nazarian is principal investigator for research funding to Johns Hopkins University from Biosense Webster and has served as a scientific advisor to Biosense Webster, CardioSolv, and St Jude Medical, Inc. The other authors report no conflicts.

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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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