The role of coronary sinus musculature in the induction of atrial fibrillation

Hiroshi Morita, MD,*† Douglas P. Zipes, MD, FHRS,* Shiho T. Morita, MD,*† Jiashin Wu, PhD*‡

*From the *Krannert Institute of Cardiology, Indiana University School of Medicine, Indianapolis, Indiana; †Department of Cardiovascular Therapeutics/Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan; ‡Department of Molecular Pharmacology and Physiology, University of South Florida, Tampa, Florida.*

BACKGROUND Coronary sinus (CS) musculature connects the right atria (RA) and the left atria (LA). However, the functional significance of the electrical junctions between the atria and the CS musculature is still unclear.

OBJECTIVE We investigated electrophysiological properties of the CS-atrial connections and their role in atrial fibrillation.

METHODS By using an optical mapping system, we mapped action potentials at 256 sites on the epicardial surface of 16 isolated and arterial-perfused canine atrial tissues containing the entire musculature of the CS, lower RA, posterior LA, left inferior pulmonary vein, and vein of Marshal. We paced from each of the above regions to measure electrophysiological properties and inducibility of atrial tachyarrhythmias.

RESULTS The CS musculature connected to the RA at the ostium of the CS and to the LA at proximal and distal CS sites. Electrical conduction across each of these CS-atrial junctions was slow ($P < .01$), but not decremental. Rapid pacing often induced entrance block at the CS-atrial junctions and resulted in sequential changes of activation sequence in the CS. Macroreentrant circuit involving the CS musculature and the CS-atrial junctions occurred in association with conduction block at these junctions. The reentrant circuit was usually unstable and resulted in atrial fibrillation–like electrocardiographic activity.

CONCLUSIONS The anatomical and electrical connections between the CS musculature and the RA and the LA caused conduction slowing and block in the CS musculature and its atrial junctions, which frequently initiated unstable macroreentry and atrial fibrillation.

KEYWORDS Coronary sinus musculature; Atrial fibrillation; Vein of Marshall; Optical mapping

ABBREVIATIONS **AF** = atrial fibrillation; **AT** = atrial tachycardia; **CL** = cycle length; **CS** = coronary sinus; **CSd** = distal coronary sinus; **CSos** = ostium of the coronary sinus; **CSp** = proximal coronary sinus; **ECG** = electrocardiogram; **LA** = left atrium; **PV** = pulmonary vein; **RA** = right atrium; **VOM** = vein of Marshall

(Heart Rhythm 2012;9:581–589)

Introduction

Coronary sinus (CS) is one of the thoracic veins that contain an atrial muscular sleeve.[1,2] The CS musculature connects the right atria (RA) and the left atria (LA) and is a part of the interatrial electrical connection as well as a part of Bachmann's bundle.[3] The muscular sleeves around the thoracic veins,[4] especially pulmonary veins (PVs) and superior vena cava,[5] are frequent sources of atrial fibrillation (AF). The CS musculature can also be a source of triggered activity[6] and atrial tachyarrhythmias.[7,8] For example, rapid repetitive electrical activity in the CS musculature caused focal atrial tachyarrhythmias and AF in some patients.[7] In addition to focal activity, the CS musculature may also contribute to arrhythmogenesis by providing an electrical connection between the RA and the LA for the formation of reentrant circuits.[6,9–11] Conduction delay within the CS musculature is also associated with increased propensity for reentrant circuits and atrial tachyarrhythmias.[12–14] However, the functional significance of atrial activation through the CS musculature and the electrical junctions between the atria and the CS musculature are still unclear. The purpose of this study was to clarify the electrophysiological properties of the CS musculature and its junctions with the atria. We hypothesized that the specific conduction properties of the CS musculature and its atrial junctions promote the initiation of atrial tachyarrhythmias.

This article was processed by a guest editor. **Address reprint requests and correspondence:** Dr Hiroshi Morita, MD, Department of Cardiovascular Therapeutics/Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-Cho, Okayama City, Okayama 700-8558, Japan. E-mail address: hmorita@cc.okayama-u.ac.jp.

Methods

Arterially perfused atrial tissue preparations

The investigation conforms to the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health (NIH Publication No. 85–23, revised 1996). We prepared tissues with procedures similar to those used previously.[15,16]

1547-5271/$ -see front matter doi:10.1016/j.hrthm.2011.11.041

We harvested hearts from 16 anesthetized (10,000 IU heparin followed 5 minutes later by pentobarbital sodium at ~30 mg/kg body weight) adult male mongrel dogs (25−30 kg) and immediately perfused the hearts through the aorta with a cardioplegic solution (Tyrode's solution [see below] with 15 mmol/L of KCl at 4°C). We isolated atrial tissue preparations that contained the CS musculature, the ostium of the CS (CSos), the ligament of Marshall, the left inferior PV and lower RA, and the posterior LA from the posterior portion of the atrium (Figure 1A). Each preparation contained the right coronary artery and the circumflex branch of the left coronary artery (diameter ~1−1.5 mm). We inserted into the left and right coronary arteries separate perfusion and pressure-monitoring cannulas. The tissues were mounted in a warmed chamber with the epicardial surface up, perfused with Tyrode's solution[15,16] at an arterial pressure of 40−50 mm Hg at (36.5 ± 0.5)°C, and immersed in the perfusion efflux.

We paced the tissue at a cycle length (CL) of 2000 ms from the RA during the tissue recovery and stabilization period before evaluating the conduction properties and arrhythmogenic mechanisms. Two silver electrodes were placed in the bath, 5 mm away from the tissue side of the LA (anode) and the RA (cathode), to register tissue electrocardiogram (ECG) (Figure 1A).

The tissue preparations were stained with di-4-ANEPPS (~4 mmol/L; Biotium, Inc, Hayward, CA) and immobilized with cytochalasin D (20−30 μmol/L; Fermentek Ltd, Jerusalem, Israel).[16] We evaluated the physiological conditions of the preparations before immobilization.[15,16] An optical mapping system with a 256-element (16 × 16) photodiode camera collected the fluorescence from a 31 × 31 mm^2 observation area on the tissue surface and converted it into 256 channels of electrical signals (action potentials).[15,16] We recorded action potentials and ECG sequentially after 10 pacing stimuli at the CLs of 2000, 1000, 500, 400, 300, 250, 200, 170, 150, and 120 ms (until 2-to-1 conduction at each of the pacing sites) by using a custom data acquisition system at 1000 samples/channel/s. We repeated the same pacing protocol and recordings from the proximal (CSp) and distal (CSd) portions of the CS, RA, LA, left inferior PV, and vein of Marshall (VOM). The sequences of baseline data recording were performed after tissue stabilization and verification (as the baseline control data) and then repeated after 20 minutes of stabilization following the addition of 10 μmol/L of pilsicainide (selective sodium-channel blocker; Asubuio Pharma, Tokyo, Japan). Pilsicainide slowed conduction and thus mimicked the conduction disturbances observed in patients with atrial tachyarrhythmias.

We analyzed conduction velocities and the shortest CL of 1:1 conduction at the CS, RA, LA, PV, and VOM as well as the action potential duration at the LA, RA, PV, and the CS musculature. We measured the conduction velocity at the following sites: the CS musculature in a proximal to

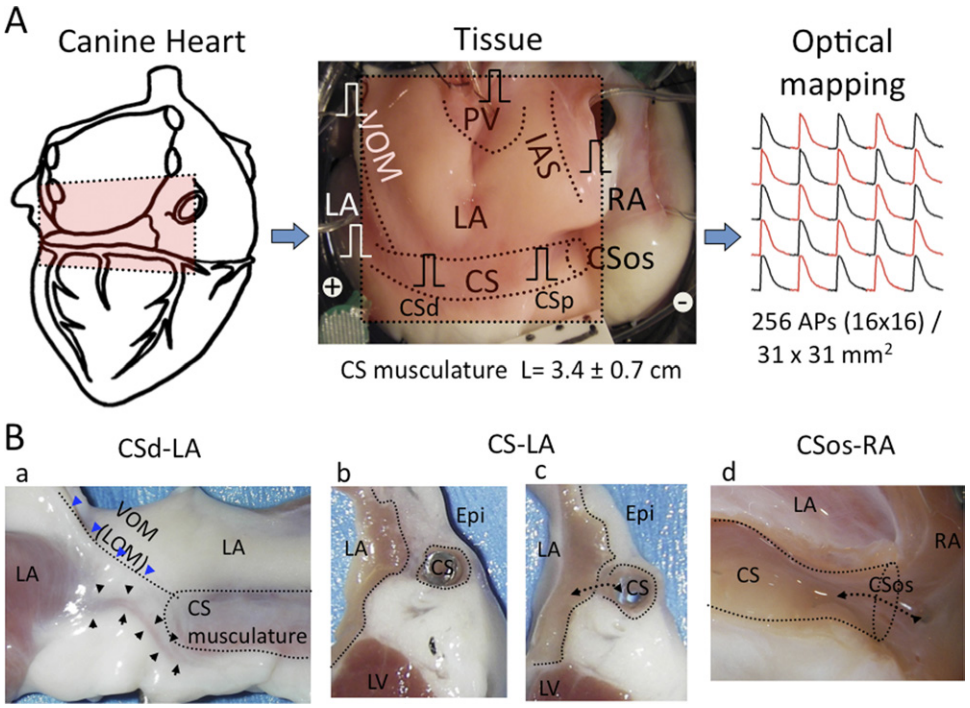

Figure 1 Tissue preparation and CS musculature. **A:** Method of tissue preparation. Posterior region of the atria that includes CS was perfused with Tyrode's solution. We optically mapped the epicardial surface of the tissues and recorded action potentials at 256 sites. We paced tissues at the RA, CSp, CSd, LA, left inferior PV, and VOM. The red square represents the mapping area. **B:** Connection between the CS musculature and atria. The VOM and discrete muscular bundle connected CS and LA at the CSd (a). The CS musculature connected to the LA from the proximal to the distal side of the CS (c), but connection at the CSd was interrupted by adipose tissue (b). The RA muscles extended into the CS at the CSos (d). CS = coronary sinus; CSd = distal CS; CSos = ostium of the CS; CSp = proximal CS; LA = left atrium; PV = pulmonary vein; RA = right atrium; VOM = vein of Marshall.