Coronary Sinus Ablation Is a Key Player Substrate in Recurrence of Persistent Atrial Fibrillation

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Keywords

Atrial fibrillation · Coronary sinus · Radiofrequency ablation · Complex fractionated atrial electrograms

Abstract

Atrial fibrillation (AF) is the most frequent atrial arrhythmia. During the last few decades, owing to numerous advancements in the field of electrophysiology, we reached satisfactory outcomes for paroxysmal AF with the help of ablation procedures. But the most challenging type is still persistent AF. The recurrence rate of AF in patients with persistent AF is very high, which shows the inadequacy of pulmonary vein isolation (PVI). Over the last few decades, we have been trying to gain insight into AF mechanisms, and have come to the conclusion that there must be some triggers and substrates other than pulmonary veins. According to many studies, PVI alone is not enough to deal with persistent AF. The purpose of our review is to summarize updates and to clarify the role of coronary sinus (CS) in AF induction and propaga-

tion. This review will provide updated knowledge on developmental, histological, and macroscopic anatomical aspects of CS with its role as arrhythmogenic substrate. This review will also inform readers about application of CS in other electrophysiological procedures.

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Introduction

The coronary sinus (CS) is the largest cardiac venomuscular structure draining most of cardiac venous blood into the right atrium. The CS musculature is an extension of atrial myocardial fibers [1] providing not only an anatomical bridge between atria but an electrical connection as well [2]. For a long time, CS has only been considered a venous structure, but recently its role in the pathophysiology of atrial tachyarrhythmias has been recognized [3–10]. Knecht et al. [10] showed that focal tachyarrhythmia originates from CS and ablation within the CS eliminates the tachycardia.

An abstract of this study has been presented at 12th International Congress of Update in Cardiology and Cardiovascular Surgery, Antalya, March 2016, and published in *American Journal of Cardiology* (supplemental issue).

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Fig. 1. a Posterior view of the heart showing the coronary sinus (CS) connecting the right (RA) and left (LA) atrium. **b** Posterior aspect of the heart. Yellow arrow demonstrates the extension of atrial fibers on CS. RAA, right atrial appendage; RV, right ventricle; LV, left ventricle; dCS, distal coronary sinus, pCS, proximal coronary sinus; SCV, superior vena cava [16].

Catheter ablation of CS, at the endocardial and epicardial region, increases atrial fibrillation (AF) cycle length that is an indicator of AF termination [3]. The CS also provides percutaneous epicardial access for ablation, even in patients with previously failed endocardial radio-frequency (RF) ablation, which helps improve the outcome [11]. AF is a rapidly growing problem in routine clinical practice. To cope with this expanding health issue first, we need to know the exact substrate for AF. This review is an outline of the knowledge about relation of pathophysiology, mechanism of initiation, maintenance, and recurrence of AF with CS.

Macroscopic Anatomy of CS

The CS has a key role in myocardial venous drainage. About 60% of drainage is performed by CS, the remaining 40% by anterior and small cardiac veins. The CS receives four major tributaries: the great, middle, small, and posterior cardiac veins; the other two groups include anterior veins of the right ventricle also called anterior cardiac veins and the smallest group of cardiac veins named Thebesian veins that drain directly into the tributaries of the greater and smaller cardiac veins [12–14]. The CS is the continuation of the great cardiac vein that runs posteriorly in the left atrioventricular groove (Fig. 1). The anterior wall of the left ventricle and the interventricular septum are drained by the tributaries of the anterior interventricular vein, which collectively form the great cardiac vein on the annulus [4, 7, 13, 14]. The great cardiac vein joins the main posterior lateral vein to form CS. Remaining parts of the heart are drained by small cardiac veins into the ostium of CS [7]. Anatomically, CS starts from the ostium in the right atrium, positioned below the foramen ovale and above the inferior vena cava, and ends as a great cardiac vein [15] (Fig. 1).

CS lies in the coronary groove that is located on the diaphragmatic part of the heart (Fig. 1). Gray's anatomy describes “the coronary sinus as a wide venous channel, about 2.25 cm in length, situated in the posterior part of atrioventricular sulcus of the heart, usually covered by muscular fibers from the left atrium” and it has been considered as a part of the venous system for long time. In 2004, Barceló et al. [17] demonstrated that it is not a usual venous structure like other cardiac veins and also hypothesized that CS is a fifth small chamber of the heart with atrial myocardial characteristics [17].

Developmental Anatomy

Embryologically, the CS originates from the differentiation of the left sinus horn that is vital for the development of the complete venous system of the heart [18, 19]. Maturity and sexual dimorphism of the CS during antenatal period have an impact on its histological and electrophysiological features [20]. The CS and oblique vein of Marshall are both derivatives of sinus venosus. The muscular tissue around CS can be right atrial (RA) myocardial tissue continuation. Some of these muscular sleeve fibers join left atrial (LA) myocardial tissue that makes second most important connection between atria [21]. The proximal two-thirds of the CS have double muscular covering from the embryonic stage [10]. Muscular sheath is a derivative of the left sinus horn with some involvement from developing adjacent LA [21]. This double muscular covering of the CS plays an important role in interatrial connection [22]. The CS anomalies are classified by Mantini et al. [66], e.g. enlargement of CS, absence of CS, atresia of RA CS ostium, and hypoplasia of the CS [23]. These anomalies also affect the electrophysiological characteristics of CS. Ambrose et al. [24] reported the relationship between CS

ostium enlargement and supraventricular tachycardia in children. CS ablation can be done in patients with AF with CS anomalies even without prior PVs isolation [25].

Histological Features of CS

Barceló et al. [17] described three discrete layers including endocardium, myocardium, and epicardium similar to those of four cardiac chambers, which makes it different from other cardiac veins. In contrast to veins, the CS contains myocardial tissue, which is a continuation of left atrium muscles [21, 26], consisting of striated myofibrils like those of myocardium with intercalated discs; Jan Evangelista Purkyně was probably the first to discover this important fact [27]. On the posterior surface of CS, multiple Purkinje like cells with typical features like clear perinuclear halo, are present near the entrance of oblique Marshall veins [17]. In addition, cells similar to those of sinus node (P cells) with increased quantity of merged connective tissue were also found. Rossi [28] demonstrated that P-like cells were embryologically derived from primitive myocardial cells; the authors described multiple ganglionic neurons below the epicardial layer of the CS on the posterior aspect. Recently, Kugler et al. [29] discovered Purkinje-like cells in the myocardial layer of CS, which may be an important part of the mechanisms for AF initiation and maintenance due their conduction properties.

Clinical Significance of the CS

The CS is becoming an important subject of investigation in cardiac electrophysiological techniques; mainly, it provides access to the left heart for the implantation of biventricular pacing, epicardial mapping, and ablation techniques. It provides a route through epicardial surface to access atrial and ventricular accessory pathways [3, 30]. Total occlusion of left circumflex artery during ablation inside the CS can lead to life-threatening arrhythmias [31, 32]. Other complications like sudden cardiac death followed by ventricular fibrillation have been reported [31]. Due to its anatomic and electrophysiological relationship with atria, CS can be used to localize the origin of multifocal atrial tachycardia from either atrium by using electrophysiological mapping, where a high-frequency, higher-amplitude component indicates a near-field potential originating from the myocardial tissue of the CS, and a

low-frequency, lower-amplitude component indicates a far-field potential from the activation of the adjacent LA [33, 34].

Use of RF Ablation for CS

RF is the most common method currently used to ablate into the CS, usually with a three-dimensional anatomic guide system that allows detecting the areas to ablate. RF applications are delivered with maximum power set at 40–45 W and temperature control limited to 55–60°C using a standard, nonirrigated, 4-mm tip catheter. Recently, the use of catheters with irrigation and contact force has increased to deliver RF energy with higher efficacy and safety, with the irrigation rate ranging from 10 to 20 mL/min, maximum power set at 20–25 W and temperature control limited to 40–50°C.

Electrophysiological Features

The CS is a myocardial connection between right and left atria, and participates in simultaneous physiological contractions of both atria [21, 35]. As mentioned earlier, the muscular sleeve around the proximal 25–50 mm of its length [35] also connects two atria. These connections may play a role in arrhythmogenesis by acting as a trigger for AF and by forming a part of reentrant circuit [36]. The amplitude of the CS signal is an indicator of LA scarring, which is thought to be an important mechanism in AF maintenance [37]. The electrophysiological properties inside and outside the coronary ostium are completely different. The way of impulse generation in both areas is also variable. Impulse generation outside the CS does not need any force [38], while CS musculature needs external stimulus, even in response to catecholamines to generate impulse [39]. Action potential in CS is similar to atrial myocytes [39]. Norepinephrine enhances and acetylcholine decreases automaticity of the CS cells during spontaneous diastolic depolarization [39]. Resting potentials in CS atrial cells are >-80 mV and also show a plateau phase during repolarization, when the activity is regular. During decreased activity, the action potential also declines to <-70 mV [39]. Conduction block occurs due to a different nature of tissue, on the outside and inside of CS ostium. Habib et al. [42] showed in their study that CS musculature is capable of spontaneous depolarization and slow conduction, showing intrinsic automaticity [12, 40, 41]. Blood flow through CS becomes maximum dur-

Table 1. Summary of radiofrequency ablation for coronary sinus to treat atrial fibrillation

First author, year [Ref.]	Patients, <i>n</i>	Type of AF	Energy used to ablate	Complications	Percent free from AF at FU
Pambrun, 2019 [51]	10	Persistent AF	RF with 3.5-mm irrigated-tip catheter, temperature limited to 45°C; for each point, RF energy was delivered for 15–20 s with a power output of 20–25 W	n.a.	100% at 6 months
Fassini, 2005 [52]	Total 187 (CS ablation in 95)	126 paroxysmal 61 persistent	RF with irrigated-tip catheter with maximum power set at 20 W	1 transient ischemic attack 1 cardiac tamponade	71% at 1 year
Oral, 2003 [53]	Total 22 (CS ablation in 9)	22 paroxysmal	RF with standard 4-mm tip catheter, with applications 30 s in duration, with a target temperature of 60°C and maximum power of 50 W	n.a.	82% at 199±35 days
Haissaguerre, 2007 [3]	45	15 paroxysmal 30 persistent	RF with irrigated-tip catheter; power of 30–40 W endocardial; inside the CS, a maximal power of 25 W; temperature limited to 50°C	1 patient cardiac tamponade, 1 pulmonary edema	39 patients (12 of 15 ParAF, 27 of 30 PerAF) were arrhythmia free at 10 months

ing slow ejection and protodiastolic phases of cardiac cycle [21]. CS like other veins has compliance and is not influenced by other regulatory mechanisms of coronary vessels. Habib et al. [42] demonstrated clinical importance of connections between right and left atria which could be a source of arrhythmias, like AF [7, 42].

Role of CS in Inception and Propagation of AF

In 1907, Erlanger and Blackman [43] explained rhythmicity of CS. They cut atria into small slices and observed rhythmicity of those small pieces and interpreted results on an anatomical basis. AF may be triggered by the spontaneous firing of the CS cells [29, 42], and the main mechanism of its maintenance is re-entry phenomenon, and CS is involved in this re-entry mechanism as suggested by Morita et al. [45], where CS has an important role in triggering, maintenance, and recurrence of AF [36, 44]. The role of pulmonary veins in AF pathogenesis is well established [46] for paroxysmal AF, but pulmonary vein ablation is not sufficient to treat persistent AF. This failure to address persistent AF using pulmonary vein ablation demonstrates an additional re-entry mechanism, probably involvement of CS. Rotter et al. [47] published

a case of a 59-year-old patient, who underwent RF catheter ablation (RFCA) of PVIs even with modified substrate ablation including joining superior PVs and anterior mitral annulus. There was clinical improvement, but AF recurrences were evidenced; further mapping showed an independent localized source of AF originating from CS. After CS isolation, there was no more recurrence of AF. CS is the structure observed with focal origin of atrial tachycardia [48, 49].

Effects of CS Isolation on AF

CS is a well-developed interatrial connection. Interruption in the electrical activity of CS may improve the results of RFCA for AF because usually unstable re-entrant circuits appear in CS musculature and its atrial junctions [45]. This was demonstrated by Morita et al. [45] in their RFCA 3-step procedure of CS isolation with conduction monitoring during CS pacing. The first step was circular ablation of CS ostium to block electrical conduction between CS ostium and RA. Then in the second step, a 13.8 ± 7.5 mm linear ablation was performed between proximal CS and LA junction. After the first two steps, a connection was still found between distal CS and LA

junction in 12 tissues. Finally, the third step with a 8.3 ± 2.5 mm linear lesion was made by RF energy. After the first step of RFCA, RA activation was significantly delayed as before RFCA activation of both atria was direct during CS pacing. After the second step of RFCA, LA and RA activation was significantly delayed leading to a complete block after the third step of RFCA. But after complete isolation of CS, there were still some electrical signals from distal CS to LA junction associated with the vein of Marshall [45]. Recently, Yin et al. [50] reported that the frequency of AF was significantly higher in proximal CS and a lower distal CS/proximal CS ratio ($<67\%$) indicates better long-term outcome. Pambrun et al. [51] confirmed these data, showing that RF ablation of epicardium muscular bundles in CS is an important step to achieve the resolution of AF in a short time follow-up as mentioned in Table 1.

In this review, as well as the study by Mainigi et al. [54], it was suggested that CS might be an arrhythmogenic substrate and play a role in AF recurrence in post PVI patients. Di Biase et al. [55] recommend that for treatment of persistent AF, ablation of nonpulmonary vein triggers of AF including CS in addition to PVI, improves the long-term outcome of RFCA by decreasing the recurrences. Sanders et al. [56] have reported a successful electrical disconnection of CS from RA and LA where focal ablation inside CS was not successful.

Role of Complex Fractionated Atrial Electrograms in Termination of AF and Its Prevalence in CS

CS is recognized as a common area for fractionated electrograms and used as a target for ablation in persistent AF [5, 41, 57, 58]. Multiple factors are involved in the pathogenesis and recognition of AF substrate; the most common indicator is complex fractionated atrial electrograms (CFAEs) with short AF cycle length [58]. In 1997, Konings et al. [59] have for the first time explained fractionated electrograms, showing slow conduction areas in AF patients. Nademanee et al. [40] have for the first time demonstrated that CFAEs could be an ideal target for ablations in patients with AF. The targeted ablation of CFAEs has a great impact on long-term maintenance of the sinus rhythm in spite of LA enlargement [60]. In addition to PV ablation, CFAE ablation significantly improves results in persistent AF [61]. Forleo et al. [62] described the highest prevalence of CFAEs in distal CS, while Teh et al. [58] have demonstrated in their study that prevalence of CFAEs and short AF cycle length was high-

er in proximal CS, whereas the study by Boles et al. [63] suggested their presence in both the proximal and distal CS depending on whether they originated from RA or LA. Yoshida et al. [30] have suggested that the frequency and complexity of CS CFAEs might indicate the presence of AF sources and that dominant frequencies decrease within the CS might predict procedural success. Boles et al. [63] reported that CS CFAEs can predict the recurrence of AF after the ablation procedure. In conclusion, the high prevalence of CFAEs in CS and the good impact of CFAE target ablation on persistent AF suggest a role of CS in AF recurrence even after PV isolation.

Discussion

AF is the most common atrial arrhythmia in humans [46], which is increasing exponentially. The incidence increases with the advancing age. The PVs are common, and important structures are involved in the initiation of AF [46]. Since the last decade, one of the burning questions has been, "What is the underlying mechanism of AF or which part of the heart is responsible for initiation and maintenance of AF, especially recurrence after PV ablation." To achieve successful results in chronic AF, emphasis on non-pulmonary triggers is of utmost importance [55]. This is becoming very challenging these days especially with the arrival of novel ablation therapies in the field of electrophysiology, with high hopes of recovery from AF. Initially, these new ablation techniques showed promising results; however, after a short period physicians realized that even PV ablation was not very successful for persistent AF. This indicates that PVs are not the right ablation target for persistent AF. In order to find the right target for ablation, we have tried to systematically analyze the way of mapping and isolating PVs. New techniques of mapping the accessory pathways have allowed us to find answers to our question of failure to achieve significant outcomes with RF ablation. Several studies have provided sufficient evidence about the role of CS in AF maintenance, due to its connections with RA and LA. There is also embryological evidence that CS is involved in conduction and may be the origin of macro re-entrant circuits to maintain AF, even after PVIs. Interesting data come from CFAEs records, which demonstrate good clinical outcome after ablation of CFAEs to terminate persistent AF [64]. Ablation of drivers in CFAE has been found to be sufficient to terminate persistent AF in the majority of patients [65]. As reported earlier, CFAEs with short cycle lengths are suggestive of AF substrate [58], and several studies have identified them in

CS. The presence of CFAEs gives us a clue about arrhythmogenicity of CS and its significance that involves the evaluation of cycle length in persistent AF.

Conclusion

The CS is not only a vascular structure but rather a developmental, anatomical, and electrophysiological part of the cardiac electrical conduction system. The CS plays a

major role in maintenance and recurrence of AF. This knowledge may help in the management of therapeutic choices for persistent AF ablation.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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