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Case Report

Fractionated non-pulmonary vein triggers contribute to spontaneous activity and initiating and maintaining paroxysmal atrial fibrillation: A case report

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ABSTRACT

Pulmonary vein (PV) antrum isolation (PVAI) that involves electrically isolating PV foci is a useful treatment strategy for atrial fibrillation (AF). However, non-PV triggers during/after the PVAI are observed in approximately 30 % of AF cases, contributing to AF recurrence. We present the case of an 84-year-old woman who underwent ablation of recurrent symptomatic paroxysmal AF in our hospital. AF was easily induced following spontaneous activity (SA) from non-PV triggers even after completing the PVAI, left atrial posterior wall isolation with roof and bottom lines, and superior vena cava isolation. Interestingly, the area of the earliest activation site of the SAs initiating AF and that with a fractionation mapping score of ≥4 corresponded. AF was steadily terminated during ablation of this fractionated area, and the programmed stimulation could no longer induce any SA or AF. This case report demonstrated that the area with a score of ≥4 points on the fractionation mapping calculated by EnSite™ (Abbott, Abbott Park, IL, USA) during sinus rhythm may contribute to the initiation and maintenance of paroxysmal AF. In patients whose AF does not resolve during ablation, physicians may consider performing an additional targeted ablation of the area with a fractionation mapping score of ≥4, even in patients with paroxysmal AF.

Learning objective: The area with a fractionation mapping score of ≥4 calculated by EnSite™ during sinus rhythm might play an important role in producing spontaneous activities and initiating and maintaining paroxysmal atrial fibrillation (AF). Thus, if the AF does not terminate during ablation, physicians should consider performing an additional targeted ablation of the area with a fractionation mapping score of ≥4, even if it is paroxysmal.

Introduction

Pulmonary vein (PV) antrum isolation (PVAI) that involves electrically isolating PV foci is a useful treatment strategy for atrial fibrillation (AF). However, non-PV triggers during/after the PVAI are observed in approximately 30 % of AF cases, contributing to AF recurrence [1].

Case report

An 84-year-old woman underwent ablation of recurrent drug-refractory symptomatic paroxysmal AF at our hospital. She had undergone cryo-balloon ablation of paroxysmal AF 2 years previously. Thereafter, she had no symptoms or arrhythmias for 2 years. However, she began having repeated symptomatic AF episodes a few months before readmission. She had a history of heart failure, hypothyroidism, hypertension, and untreated sleep-disordered breathing (SDB) of apnea-hypopnea index 25.4 events/h and was taking medications including telmisartan 40 mg, hydrochlorothiazide 12.5 mg, bisoprolol 2.5 mg, levothyroxine 25 μg, and bepridil 50 mg once daily, and apixaban 2.5 mg twice daily. Her blood pressure was 126/66 mmHg, and her pulse rate was 60 beats/min and regular. Auscultation revealed normal cardiac and breath sounds. Her body mass index, B-type natriuretic peptide level, serum creatinine level, free thyroxine (fT4) (normal range, 0.70–1.48 ng/dl), and thyroid-stimulating hormone (TSH) (normal range, 0.61–4.23 mIU/L) levels were 29.8 kg/m^2, 45.4 pg/mL, 0.75 mg/dL, 1.07 ng/dL, and 4.78 uIU/mL, respectively. The 12-lead electrocardiogram evaluation showed sinus rhythm. Echocardiography revealed a

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normal left ventricular ejection fraction and an enlarged left atrium (LA) (42.4 mm). Her $CHADS_2/CHA_2DS_2$-VASc and direct-acting oral anticoagulants (DOAC) scores [2] were 3/5 and 7 points, respectively.

After a double transseptal puncture, the LA and PVs were reconstructed in detail by a three-dimensional mapping system (EnSite™, Abbott, Abbott Park, IL, USA), using a high-density mapping catheter (HDMC) (Advisor™ HD Grid catheter, Abbott), during sinus rhythm. During the mapping, AF was easily induced. We confirmed the absence of any remaining potentials inside or along the PVAI lines (complete entrance block). Further, exit block of the four PVs was confirmed by pacing in detail using an HDMC with an output of 10 V (complete exit block). In addition, we confirmed the absence of epicardial connections [3] inside the PVAI lines (Fig. 1A). Next, we added an LA posterior wall isolation with roof and bottom lines and a superior vena cava isolation, however, we did not confirm the arrhythmogenic properties of the LA posterior wall and superior vena cava before proceeding with their isolation. However, repeated bolus injections of isoproterenol (ISP) (5 μg) induced AF, following some spontaneous activities (SAs) observed near the His-bundle, and on a circular mapping catheter (Optima™, Abbott) positioned on the inter-atrial side of the LA free wall (white arrow in Fig. 1B and 2A). Finally, fractionation mapping was performed using an Advisor™ HD Grid catheter. The electrocardiogram recordings from the Advisor™ HD Grid catheter revealed fractionated potentials (Fig. 2B).

The fractionation mapping using an EnSite™ system [4] can map sites exhibiting discrete atrial complexes and a consistent activation sequence during sinus rhythm. The map parameters were standardized at internal and external projections of 7 mm, interpolation of 7 mm, and low-voltage identification of 0.1 mV. Fractionated signals were collected over 5 s using a high-density mapping catheter. To exclude background system noise, a low threshold of 0.05 mV was applied. Voltage peaks greater than this threshold but <0.1 mV were defined as scar tissue. The mapping catheter was held tangentially to the endocardial surface, enabling stable tissue contact. Electrograms of >5 mm from the geometry surface were automatically excluded. A fractionation map was created using combinations of the width (5–15 msec), refractory time (20–30 s), roving sensitivity (0.1 mV), and fractionation threshold (4, 6, 8, 12, 20). Based on the width, refractory period, and sensitivity, a fractionation score was assigned to each electrogram by the mapping algorithm. The areas with a fractionation score of ≥4 points, suggestive of a fractionated electrogram and indicated as a white-colored area on the map, were considered potential drivers of AF.

The area with a fractionation mapping score of ≥4 points (white arrow in Fig. 1C) and that with the earliest activation site of the SA

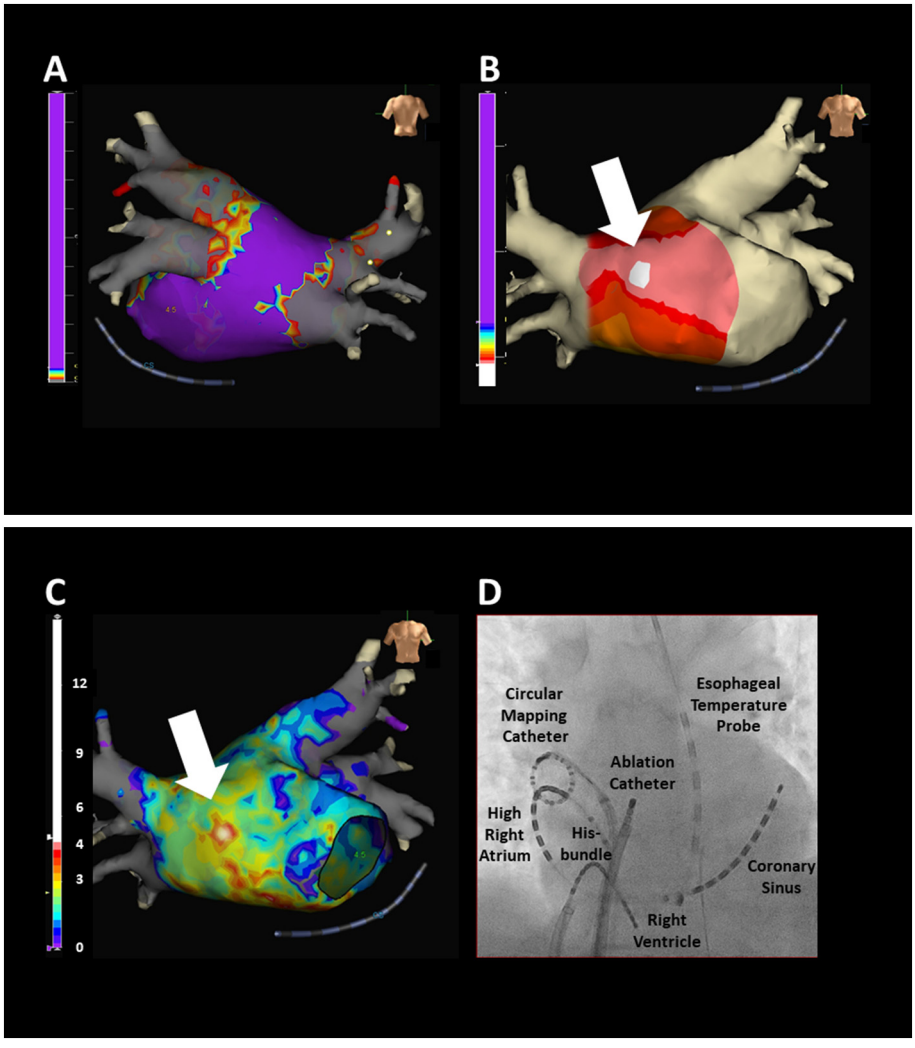


Fig. 1. Voltage map (A) viewed from the posteroanterior view, activation map (B) and fractionation map (C) constructed by EnSite™, and fluoroscopic image (D) viewed from the anteroposterior view. The white arrow in (B) indicates the earliest activation site of spontaneous activity (SA) initiating atrial fibrillation (AF). The area of the earliest activation site of SA initiating AF (white arrow in B) and that with a fractionation mapping score of ≥4 (white arrow in C) corresponded.

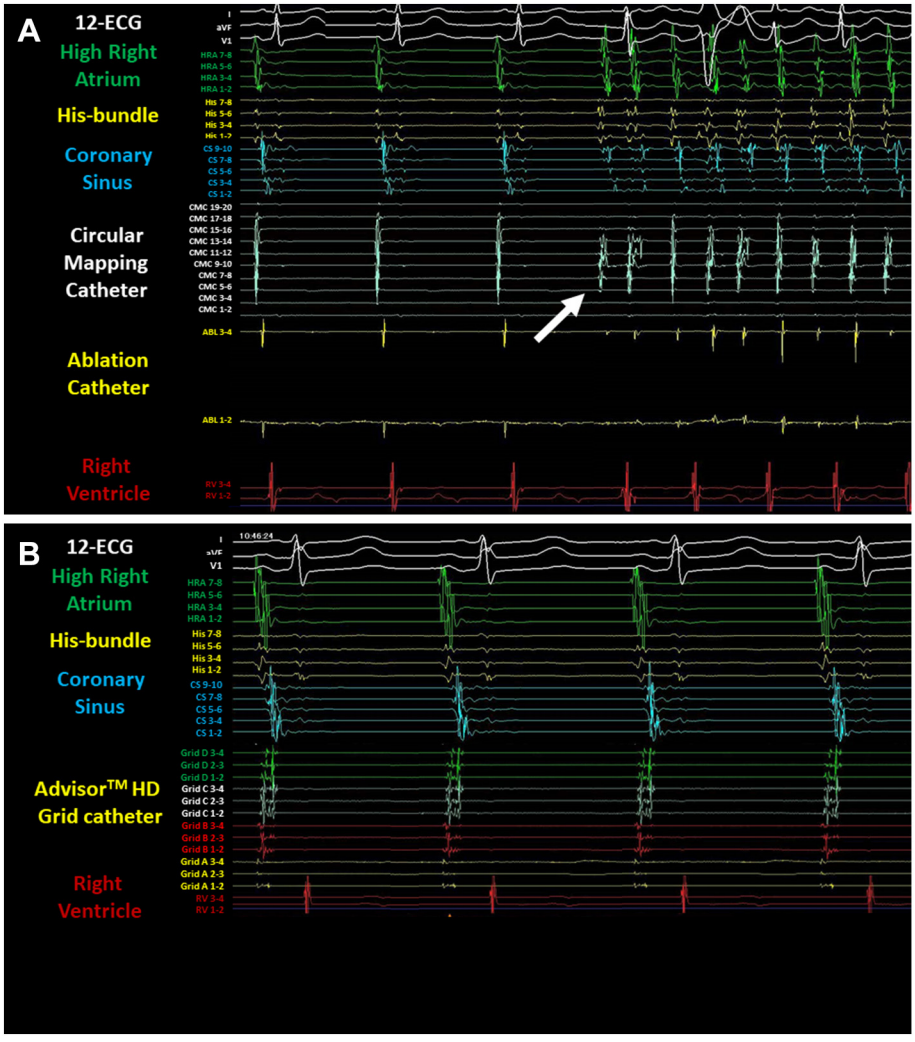
initiating AF (white arrow in Fig. 1B) corresponded. The electrocardiogram records from the tip of the ablation catheter revealed fractionated potentials (white arrows in Fig. 2C). During AF, the radiofrequency energy was delivered to this site with a maximum power of 30 W (green bar in Fig. 2D). Then, the AF became organized (yellow-green bar in Fig. 2D) and steadily terminated (white bar in Fig. 2D). Finally, the programmed stimulation, even under repeated bolus injections of ISP, could no longer induce any SA or AF. After the ablation of AF, continuous positive airway pressure therapy was introduced for her SDB. The 24-h Holter monitoring, which was conducted at the 3-, 6-,12–24-, and 36-month visits, revealed no recurrence of AF. Thus, apixaban was discontinued at the 6-month visit because of her high DOAC score of 7 points. In addition, the value of fT4 was within the normal range [5]. The patient has remained without any symptoms for >3 years after the ablation of these fractionated non-PV triggers.

Discussion

Recent reports have demonstrated that abnormal atrial electrograms recorded during sinus rhythm are related to atrial vulnerabilities such as repetitive atrial firing that induces sustained AF [6]. Ablation in the atrium outside the PVAI lines of these sites, so-called fractionated atrial muscle signal area, detected using Rhythmia™ (Boston Scientific, Marlborough, MA, USA) [6] during sinus rhythm may be among the effective treatment strategies in patients with *long-standing persistent* AF. These fractionated areas may be among the mechanisms contributing to AF recurrence in these patients [4,6,7]. However, no previous study has examined non-PV triggers using a fractionation mapping score of ≥4 points calculated by an EnSite™ system [4] during sinus rhythm in patients with *paroxysmal* AF.

In the present case with *paroxysmal* AF, repeated bolus injections of ISP could induce AF following the SAs from non-PV triggers after performing a stepwise ablation consisting of a PVAI, LA posterior wall isolation, and superior vena cava isolation. Interestingly, the area of the earliest activation site of the SAs initiating AF (white arrow in Fig. 1B) and that with a fractionation mapping score of ≥4 points (white arrow in Fig. 1C) corresponded. The AF steadily terminated after delivering the radiofrequency energy to that site, and programmed stimulation could no longer induce any SA or AF even under repeated bolus injections of ISP. Thus, an area with a fractionation mapping score of ≥4 points may contribute to the initiation and maintenance of *paroxysmal* AF. A previous study demonstrated that procedural termination of AF by ablation was significantly associated with an improved outcome of AF recurrence [8]. The patient remained without any AF recurrence for >3 years after the ablation. Thus, ablation of those fractionated non-PV triggers may be an important adjunctive treatment for AF. Therefore, if AF does not resolve, additional ablation of those fractionated areas may be recommended to help prevent AF recurrence, even in patients with the *paroxysmal* type.

A recent report demonstrated that non-PV triggers were observed in one-third of patients with paroxysmal AF after cryo-balloon ablation and that they were associated with AF recurrence [1]. However, if this were a true association, AF might have recurred earlier. This patient had no AF recurrence for 2 years after the first session. Although the mechanisms involved remain unclear, novel expression of fractionated



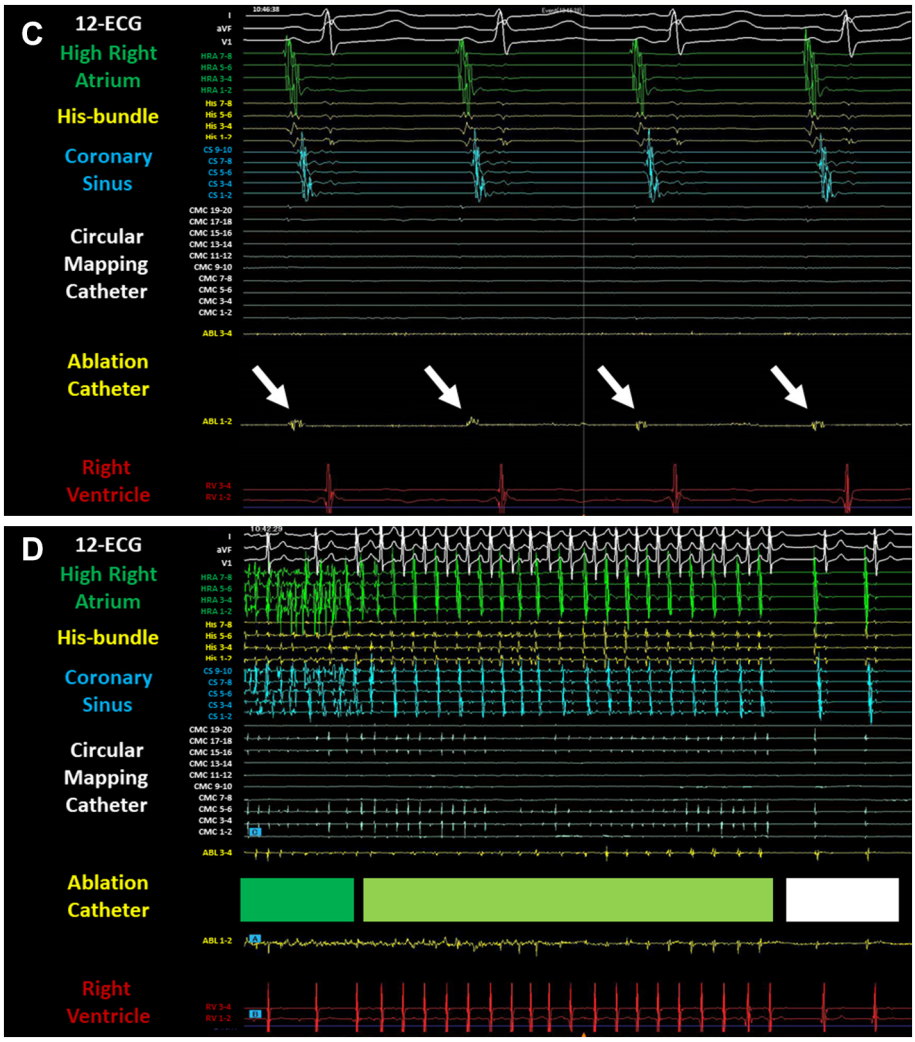


Fig. 2. A circular mapping catheter placed at the inter-atrial side of the left atrial free wall could detect the spontaneous activity that initiated atrial fibrillation (AF) (white arrow in A). During sinus rhythm, the electrocardiogram recorded from the Advisor™ HD Grid catheter (B) and the tip of the ablation catheter revealed fractionated potentials (white arrows in C). During AF, radiofrequency energy was delivered to that site (green bar in D). The AF became organized (yellow-green bar in D) and steadily terminated, and sinus rhythm was restored (white bar in D).

areas and non-PV triggers may be involved after the first session. This patient had several cardiovascular risk factors, including obesity (high body mass index), hypertension, and AF. These conditions may cause a progression of LA electrical and structural remodeling [9], which may accelerate the expression of the fractionated areas. This patient also had an untreated SDB. Obstructive sleep apnea, which is the most common form of SDB, is characterized by recurrent episodes of partial or complete upper airway obstructions resulting in intermittent hypoxia, hypercapnia, and intrathoracic pressure changes, triggering an autonomic nervous system imbalance, which activates LA inflammation, oxidative stress, and the renin-angiotensin system, accelerating LA degeneration. This cascade has been implicated in the initiation, progression, and recurrence of AF [10]. Thus, SDB may have contributed to the emergence of new fractionated areas in the present case. However, this single case may appear to lack evidence for this discussion. Future studies may determine whether SDB could accelerate the production of fractionated areas in the atrium of patients with AF.

In addition, this patient had hypothyroidism. A previous report demonstrated that, in euthyroid individuals, higher circulating fT4 levels, but not TSH levels, are associated with increased risk of incident AF [5]. Thus, the fT4 level was maintained within the normal range to prevent AF recurrence. Finally, apixaban was discontinued at the 6-month visit because of her high DOAC score [2] of 7 points, indicating an increased bleeding risk.

Conclusion

This case report demonstrated that the area with a score of ≥4 points on the fractionation mapping calculated by EnSite™ during sinus rhythm may contribute to the initiation and maintenance of *paroxysmal* AF. In patients whose AF does not resolve during ablation, physicians may consider performing an additional targeted ablation of the area with a fractionation mapping score of ≥4, even in patients with *paroxysmal* AF. However, to make this argument convincingly, future investigations should focus on how often fractionated areas are AF triggers and/or drivers in patients with *paroxysmal* AF.

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Consent statement

Written informed consent was obtained from the patient.

CRediT authorship contribution statement

All doctors were involved in case management. Drs Umemoto and Takemoto performed the ablation and wrote this manuscript.

Declaration of competing interest

None declared.

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