

New challenges in arrhythmology

Edited by

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New challenges in arrhythmology

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Editorial: New challenges in arrhythmology

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KEYWORDS

atrial fibrillation, device, mapping, ablation, electrophysiology

Editorial on the Research Topic New challenges in arrhythmology

This Research Topic presents a cohesive collection of contributions that touch the full translational spectrum of cardiac electrophysiology—from mechanistic exploration and technological advancement to clinical applicability and therapeutic innovation. Together, these studies form a mosaic that not only highlights the dynamism of the field but also offers practical insights for shaping next-generation patient care.

At the heart of these innovations is the aim to personalize therapy improving safety, efficacy, and access to care. This editorial invites readers to consider each article as interconnected pieces that advance our understanding and capabilities in arrhythmia management.

The studies included in this Research Topic represent not only technological progress but a paradigm shift in how we understand and manage cardiac arrhythmias. Device therapy, as demonstrated by [Russo et al.](#), is now focused not merely on extending life, but on enhancing quality of life and reducing long-term procedural risk. This indicates a more nuanced, patient-centered approach in clinical decision-making.

Electroanatomical mapping studies by [Chen et al.](#) and [Drago et al.](#) show how electrophysiology is evolving into the acquisition of a real-time spatial data to predict outcomes and tailor procedures. Their work underscores how technical innovation can deepen physiological insight.

The advent of pulsed field ablation, covered by [Zhai et al.](#) and [Ma et al.](#), brings safety and specificity into focus. This energy source represents a fundamental change in ablation philosophy—offering cardiac-specific effects with reduced risk to other structures. Such transformation opens new possibilities for treating arrhythmias also in anatomically sensitive locations.

The analysis of arrhythmogenesis, discussed by [Hytting et al.](#), [Ou et al.](#), and [Henson et al.](#), demonstrate how arrhythmias are not purely electrical events but reflections of endocrine, metabolic, and pharmacologic imbalances. These insights advocate for a broader, integrative view in arrhythmia diagnosis and prevention.

[Menichetti et al.](#)'s work on cardiac contractility modulation invites readers to reconsider the role of device therapy—not just as an endpoint but as a tool for recovery and transition. This vision opens doors to new therapy for advanced heart failure patients. This editorial is a trip inside articles that collectively point toward the future of cardiac electrophysiology. Readers will find in these studies not only innovation but also a roadmap for what the electrophysiology can become when engineering, clinical insight, and translational science meet.

The reader should not only explore each article, but see the connections among them. This Research Topic reflects a push toward integrated, tailored, and safer care across patient populations. The synergy among mapping, ablation, device therapy, and systemic understanding will improve more and more physicians in a comprehensive taking care of their patients.

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MN: Writing – review & editing, Writing – original draft. LV: Writing – review & editing, Supervision, Validation.

Conflict of interest

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Preclinical evaluation of reversible pulsed electrical field: electrophysiological and histological assessment of myocardium

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Background: Pulsed field ablation, as a non-thermal ablation modality, has received increasing attention. The aim of this study is to explore whether a reversible pulsed electric field (RPEF) can temporarily inhibit electrical conduction and provide a novel method for precise ablation of arrhythmia.

Methods: RPEF energy was delivered from an ablation catheter to the atrium of six dogs, followed by a series of electrogram and histology assessments.

Results: RPEF ablation of ordinary myocardium resulted in an average reduction of 68.3% (range, 53.7%–83.8%) in electrogram amplitude, while 5 min later, the amplitude in eight electrograms returned to 77.9% (range, 72.4%–87.3%) of baseline. Similarly, the amplitude of the sinoatrial node electrograms reduced by an average of 73.0% (range, 60.2%–84.4%) after RPEF ablation, but recovered to 84.9% (range, 80.3%–88.5%) of baseline by 5 min. No necrotic change was detected in histopathology. Transient third-degree atrioventricular block occurred following the ablation of the maximum His potential sites with RPEF, the duration of which was voltage dependent. The histopathological results showed necrosis of the myocardium at the ablation sites but no injury to His bundle cells.

Conclusions: RPEF can be applied to transiently block electrical conduction in myocardial tissues contributing to precise ablation.

KEYWORDS

precise ablation, electroporation, reversible pulsed electric fields, critical isthmus sites, para-Hisian arrhythmia, sinus node modification

1 Introduction

Pulsed field ablation (PFA), is a non-thermal ablation modality, which leverages a continuous microsecond-level high-voltage electric field to induce irreversible electroporation (IRE), thereby disrupting cell membrane stability and ultimately leading to cell death (1). Of note, PFA has been preclinically and clinically confirmed to have certain tissue specificity, for ablating myocardium with little effect on some adjacent non-cardiac tissues (e.g., the esophagus and phrenic nerve) (2–8). PFA has attracted great attention because of its potential safety and has been used in some clinical trials to treat atrial fibrillation (AF) (9–14).

Different from the irreversible electroporation of PFA, a low intensity pulsed electric field (PEF) can reversibly electroporate cells (1, 15, 16). Attenuated pulses can affect the

transient permeability of the cell membrane without impacting dielectric breakdown of the cell membrane and cell death, which contributes to introducing various biomaterials (such as impermeable drugs and genetic materials) into cells (17–21). Deliberately applying such sublethal electric pulses to the myocardium can induce temporary changes in the electrical properties of the myocardium without causing permanent injury to the myocardium.

Accordingly, we hypothesized that reversible PEF (RPEF) can temporarily change the electrical properties of local myocardium and transiently suppress electrical conduction, then it can be changed to irreversible PEF ablation for accurate ablation—once critical isthmus sites of arrhythmia are confirmed. To verify this hypothesis, we studied the effect of RPEF on canine atrial tissue and we also probed into its impacts on sinoatrial node (SA) and His bundle.

2 Materials and methods

The animal experiments were approved by the Animal Experiment and Experimental Animal Welfare Committee of Capital Medical University (Ethics number: AEEI-2023-325). The experiments involved six male Labradors (30–40 kg), and included equipment from APT Medical [Shenzhen, China (Figure 1)], encompassing the following: Cardiac Pulsed Field Generator, Contact Force Sensing PFA Catheter, Radiofrequency Ablation Generator, Radiofrequency Catheter, Cardiac 3D Navigation System, and so forth. The non-saline perfusion pressure-sensing pulse ablation catheter was of 7.5 F size, with four equally spaced electrodes at the tip, D-2 discharge, unidirectional

180° bending, and equipped with a magnetic sensor. The tip was equipped with a pressure sensor (fiber-optic sensing mode). The main application scenarios were point-by-point, linear ablation.

2.1 Preparation before experiment

After an overnight fast, Labradors were injected intravenously with Zoletil® 50 (Virbac, Carros, France; Tiletamine hydrochloride and Zolazepam hydrochloride at 1:1 ratio, 0.05–0.1 ml/kg) and were further injected intramuscularly with atropine (0.05 mg/kg). After intubation and the use of artificial ventilators, propofol was injected intravenously at a dose of 1 ml/min. Access to bilateral femoral veins was established.

2.2 Experimental procedure

2.2.1 Preclinical experiment 1 (atrial myocardium)

Intracavitary echocardiography (10F SOUNDSTAR 3D Diagnostic Ultrasound Catheter, Biosense Webster, Irvine, CA, USA) was used only to guide the atrial septal puncture. Post a single atrial septal puncture, an adjustable curved sheath tube was inserted into the left atrium (LA) under the guidance of fluoroscopy. Intravenous administration of heparin maintained an active coagulation time of 300–350 s. The pressure at the tip of the pulse ablation catheter was maintained at 10–15 g, and the experiment was performed by an experienced electrophysiologist.

Under the guidance of electroanatomic mapping, the right and left atria of six Labradors were ablated by RPEF at select sites. After each ablation, the tip of the catheter was held in place in a

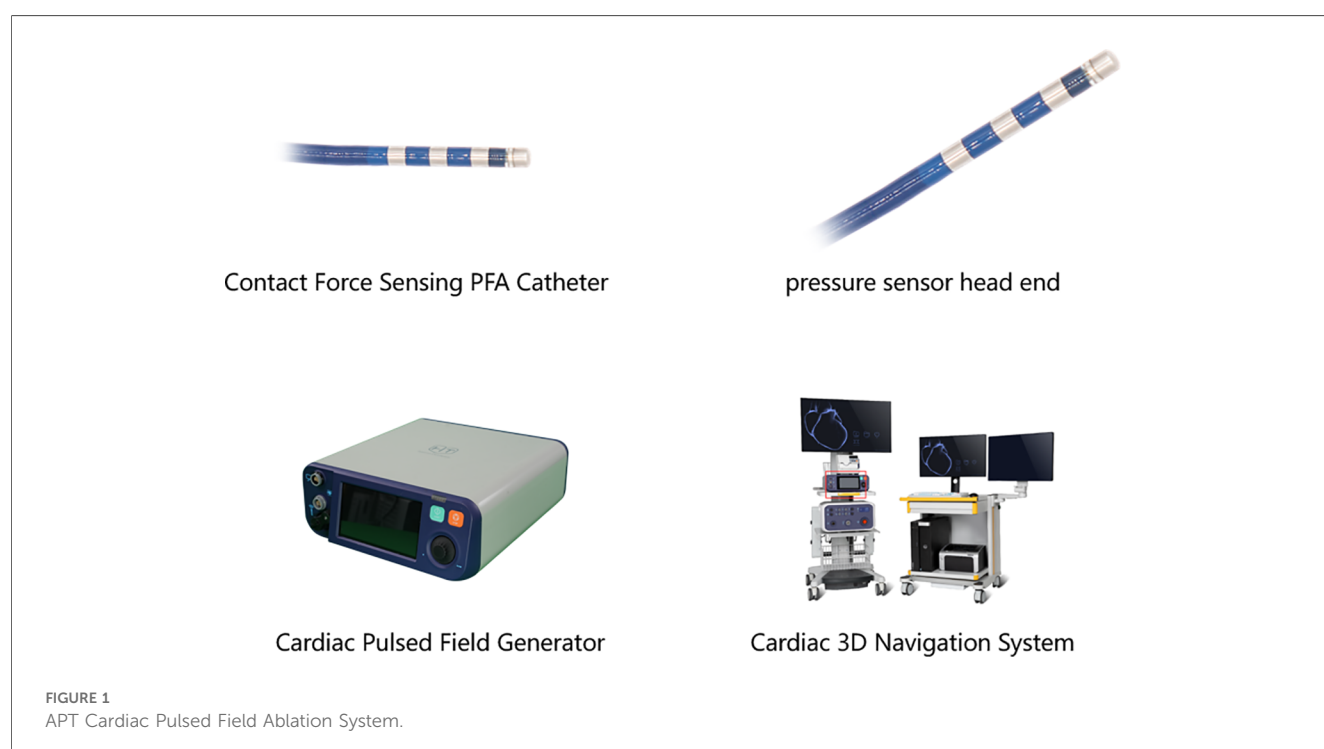


FIGURE 1
APT Cardiac Pulsed Field Ablation System.

stationary manner, and bipolar electrograms were continually recorded. The electrogram was measured continuously from the beginning of the RPEF ablation to 5 min after ablation. Electrograms before and after ablation were selected for amplitude analysis. Pacing threshold at 2 ms pulse width was evaluated at the same sites.

RPEF was applied between two discrete radiofrequency ablations (RFA lesions were formed 30 W, 30 s by radiofrequency catheter ablation) for identification of RPEF ablation sites at autopsy (Figure 2). The dogs were euthanized with intravenous injection of potassium chloride at a dose of 1–2 mEq/kg under basal anesthesia after 24 h. Then the hearts were extracted and stained with triphenyl tetrazolium chloride, following which all chosen sites were carefully examined and the selected tissue specimens underwent histopathological assessment. After formalin fixation, the tissues were processed and stained with hematoxylin and eosin in addition to Masson trichrome.

2.2.2 Preclinical experiment 2 (His bundle)

Under the guidance of electroanatomic mapping, the pulsed ablation catheter was sent into the right atrium (RA) to establish the right atrium model. All His bundle potentials were marked and the maximum His potential was labeled. The maximum His potential was applied with RPEF ablation which was of micro-second pulsed width, with biphasic wave, in bipolar fashion, and one dog was ablated with one voltage to regulate the pulse electric field intensity (to avoid cumulative effect interference) (Figure 3). The recovery time of complete atrioventricular block, atrial–His (AH) interval and His–ventricular (HV) interval before ablation, and AH interval and HV interval immediately after atrioventricular block recovery were recorded.

The His bundle region was removed by anatomical localization (as described in the following) and underwent histological analysis. Discrete continuous sections were processed, and stained with hematoxylin and eosin as well as Masson trichrome.

2.2.3 Preclinical experiment 3 (sinoatrial node)

The earliest exciting point of right atria, the sinus node, was marked under the guidance of the three-dimensional electroanatomic mapping system, and later ablated with RPEF (Figure 4), and bipolar electrograms were continuously recorded. The function of the sinus node was assessed before and after RPEF.

After euthanasia, tissue blocks of 1 cm × 2 cm were taken from the sinus node area (as described in the following). The tissue was sliced continuously along the long axis and then stained with hematoxylin and eosin, and Masson trichrome.

2.3 Statistical analysis

Continuous variables are expressed as mean ± standard deviation or the median of the quartile interval, and categorical variables are described by counts and percentages. Two-group comparison was performed using the paired t-test. A value of $P < 0.05$ was considered statistically significant. SPSS 26.0 (IBM, New York, USA) software was used for statistical analysis.

3 Results

3.1 Preclinical experiment 1 (atrial myocardium)

In the six dogs, eight RPEF ablation sites were detected in the posterior wall of LA ($n = 4$), the free wall of RA ($n = 2$), the RA septum ($n = 1$), and the right atrial appendage (RAA) root ($n = 1$). The baseline of electrogram amplitude was 8.1 ± 2.6 mV (range, 6.4–10.7 mV), and after ablation with RPEF, the electrogram amplitude decreased to 2.4 ± 1.5 mV (range, 1.2–3.9 mV), with a mean reduction of 68.3% (range, 53.7%–83.8%). As shown in Figure 5, the amplitude gradually recovered to 77.9% of baseline (range, 72.4%–87.3%) 5 min after RPEF ablation on eight

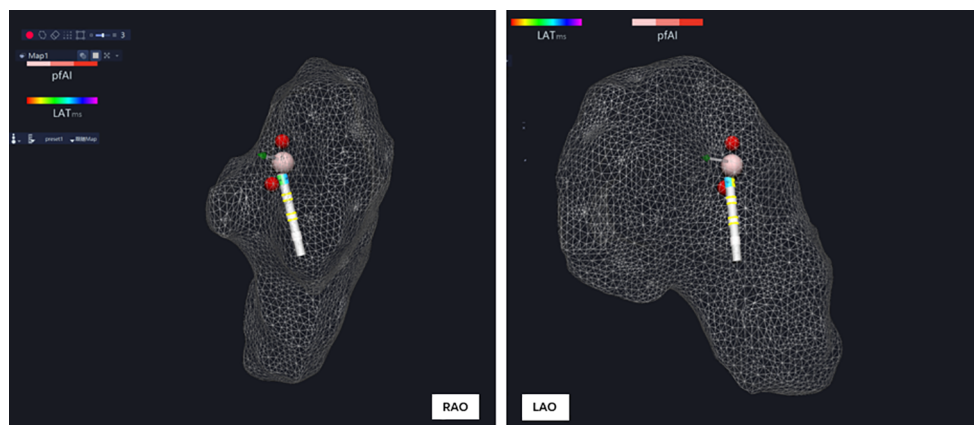


FIGURE 2

A single reversible PFA was placed between two discrete RFA lesions for identification of the RPEF lesion.

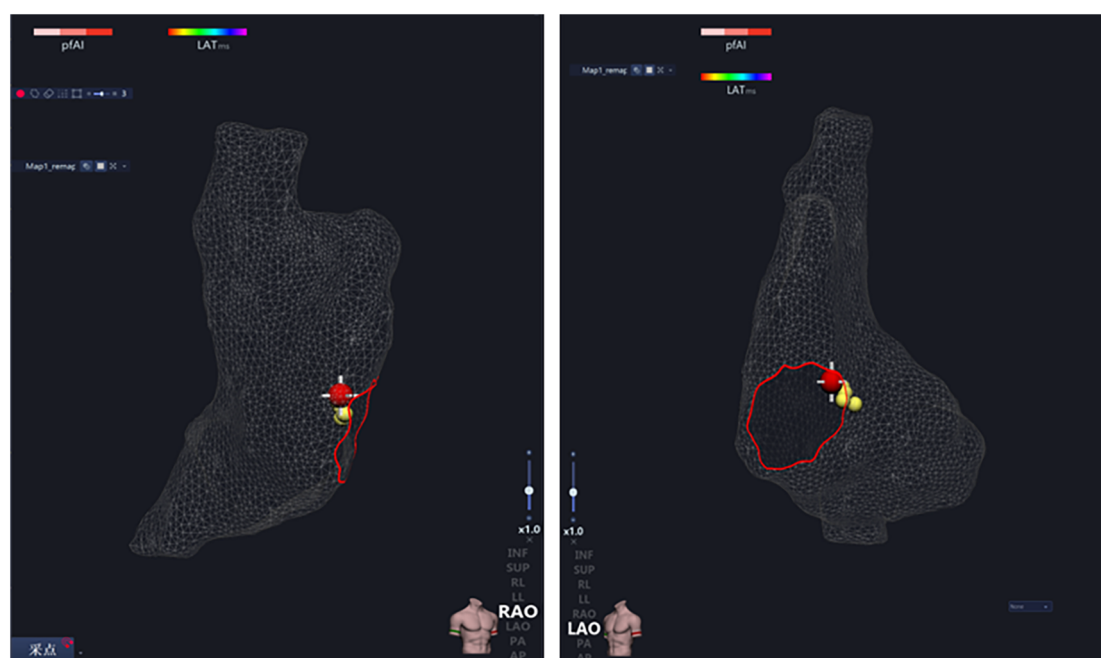


FIGURE 3

After the right atrium modeling, all His potential locations (yellow ball) were marked, and the maximum His potential location (red ball) was ablated.

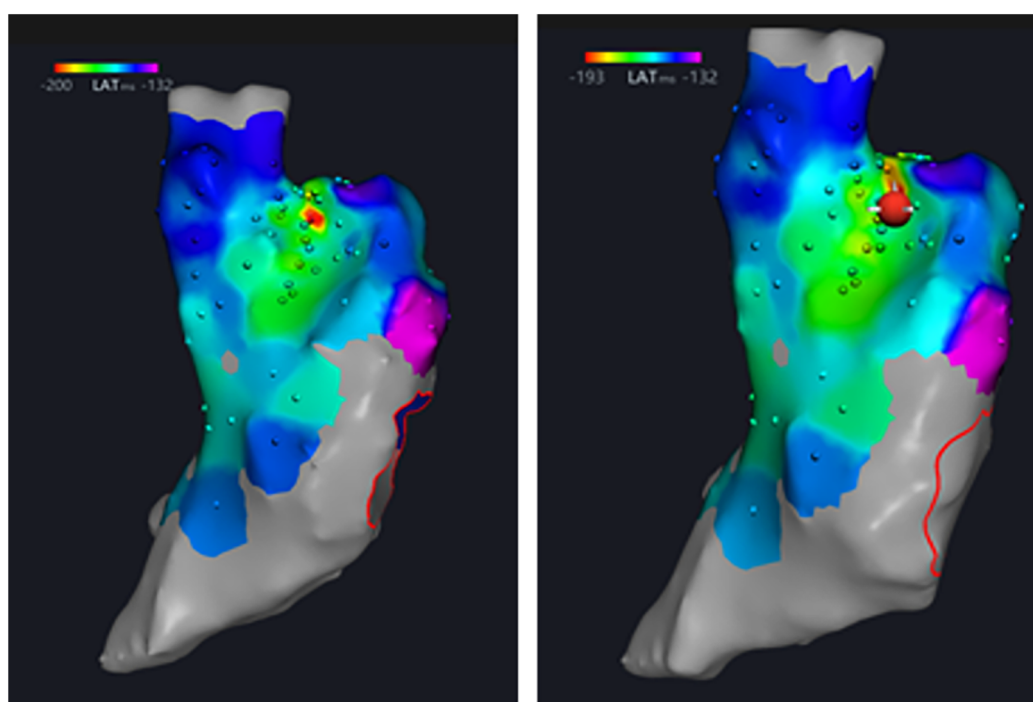


FIGURE 4

The earliest point of right atrial activation, the sinus node, was marked under the guidance of three-dimensional electrical anatomical mapping, and then was ablated with RPEF.

electrograms. In **Figure 6**, we analyzed the electrogram amplitude per minute within 5 min after ablation at four RPEF sites and found that the total electrogram amplitude gradually recovered after a sharp

decline. The electrical anatomical mapping did not reveal any bipolar low voltage (<0.1 mV) region at the RPEF ablation site. The pacing threshold was 1.1 ± 0.2 mA (range, 1.0–1.2 mA) before

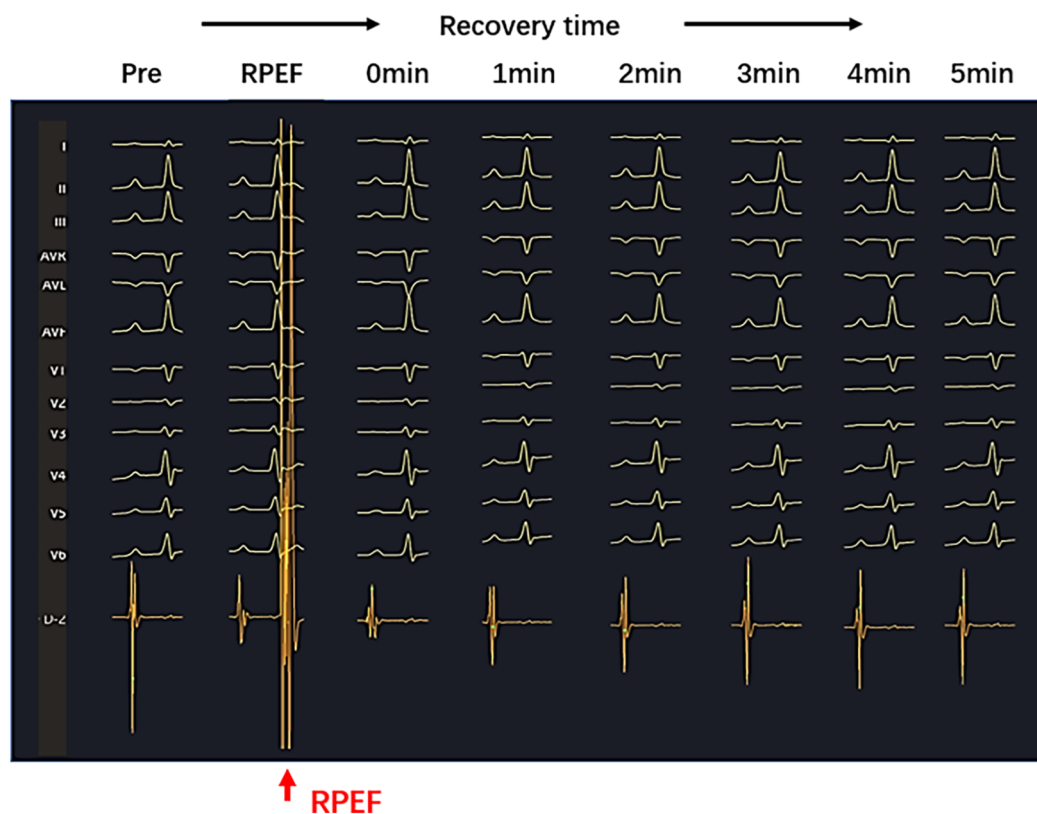


FIGURE 5

Sharply reduced electrogram (red arrow) was observed on the PEF pressure catheter after RPEF ablation. The amplitude of the electrogram decreased immediately and gradually recovered over time.

ablation, 3.7 ± 2.1 mA (range, 2.0–5.8 mA) immediately after ablation, and returned to 2.3 ± 1.3 mA (range, 1.3–3.0 mA) 5 min after ablation.

The pathological examination of the tissue between the two radiofrequency lesions (Figure 7) displayed mild to moderate degenerative changes between the two radiofrequency ablation lesions.

3.2 Preclinical experiment 2 (His bundle)

In the six canines, RPEFs at different voltage intensities ablated the maximum His potential locations. The baselines of AH interval and HV interval were 55.7 ± 3.9 ms (range, 52.3–59.3 ms) and 35.0 ± 1.4 ms (range, 33.8–36.3 ms), respectively. After RPEF ablation and the immediate recovery of third-degree atrioventricular blocks, AH interval was 65.7 ± 5.6 ms (range, 59.0–70.3 ms) and HV interval was 36.0 ± 2.8 ms (range, 33.8–38.0 ms). Statistics showed that the AH interval was prolonged before and after the atrioventricular blocks ($P < 0.05$), while the HV interval remained unchanged ($P > 0.05$). All six dogs presented transient third-degree atrioventricular blocks after ablation, which subsequently recovered. Under the condition that other parameters were constant, the greater the ablation voltage of RPEF was, the longer the recovery time it resulted in, reflecting the voltage-dependent characteristic.

The dogs were euthanized after interventional operation, and the position of the superior vena cava (SVC) was determined. The right atrium was incised along the superior vena cava. There is a triangular area called Koch triangle along the inner margin of the ostium of the coronary sinus (CSO), the margin of the tricuspid valve (TV), and the Todaro tendon, and the atrioventricular node area was approximately 1 cm upward along the ostium of the coronary sinus. Above the Koch triangle, the thinnest and transparent region was visible, through which the His bundle passed. The His bundle was cut out by means of local anatomy (Figures 3, 8A). Histopathological results revealed necrosis of ordinary cardiomyocytes at the ablation site, and His bundle cells were generally normal without obvious injuries.

3.3 Preclinical experiment 3 (sinoatrial node)

The electrogram amplitude at baseline was 5.8 ± 1.0 mV (range, 4.8–6.5 mV), and RPEF caused a decrement in the electrogram amplitude to 1.5 ± 0.7 mV (range, 1.0–2.0 mV), with a mean reduction of 73.0% (range, 60.2%–84.4%), which gradually recovered to 4.9 ± 0.7 mV (range, 4.2–5.4 mV) and returned to 84.9% (range, 80.3%–88.5%) within 5 min (Figure 9). Sinus node recovery time (SNRT) before ablation

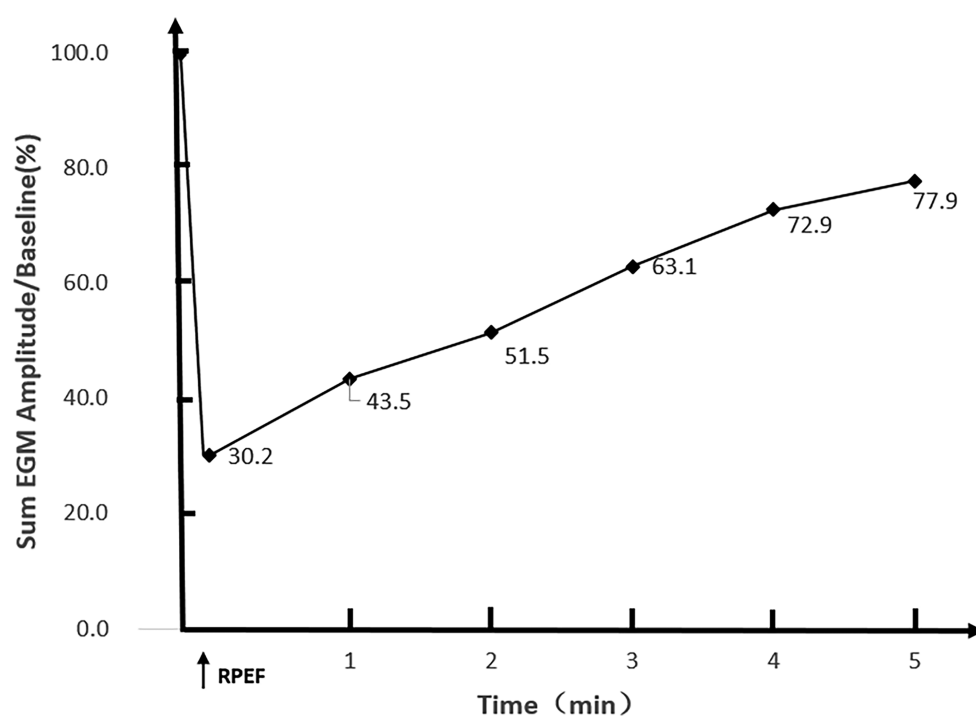


FIGURE 6

The total electrogram amplitude decrease was observed immediately after RPEF in the atrial myocardium of Labradors ($n = 4$ RPEF ablations). A sharp drop was determined in the amplitude of the electrogram followed by a gradual recovery (the horizontal axis represents time in minutes; the vertical axis shows the percentage of overall ECG amplitude recovery).

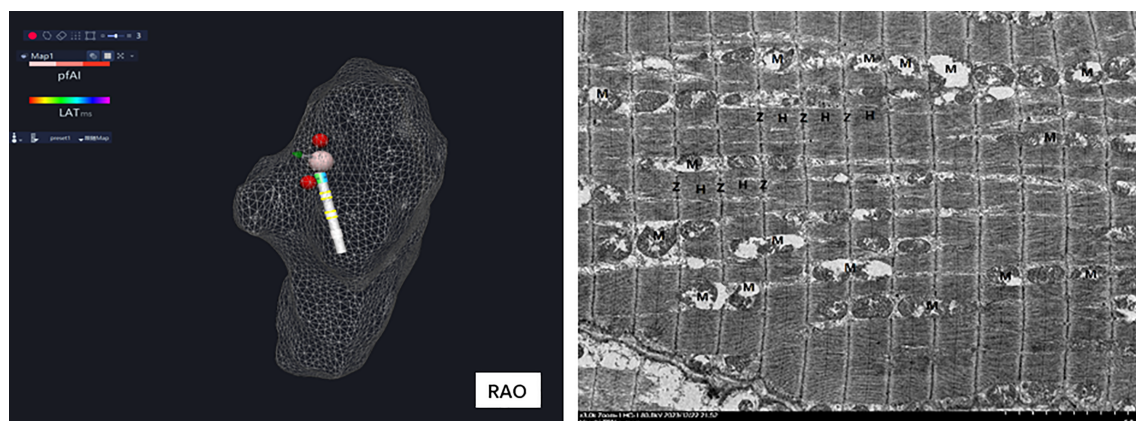


FIGURE 7

Histopathological results showed normal mild to moderate degenerative changes between two RFA lesions.

was $1,410.5 \pm 28.6$ ms (range, 1,388.3–1,445.5 ms) and became $1,377.8 \pm 31.6$ ms (range, 1,349.3–1,400.0 ms) after ablation for 5 min ($P > 0.05$). The corrected sinus node recovery time (CSNRT) before ablation was 635.7 ± 20.2 ms (range, 618.3–654.0 ms) and became 633.2 ± 16.7 ms (range, 623.8–644.0 ms) after ablation for 5 min ($P > 0.05$).

The positions of the SVC and RAA were determined. The junction of the root of SVC and RAA was the sinus node (Figures 4, 10A), where tissues of $1\text{ cm} \times 2\text{ cm}$ were obtained. Then the tissues were sliced continuously along the long axis.

The histopathological results unveiled that the structure of SA node cells was generally normal with no obvious injury.

4 Discussion

4.1 Reversible effect of pulsed electric field

When RPEF energy was delivered to canine atrial tissue, the biphasic electrogram amplitude dramatically diminished by

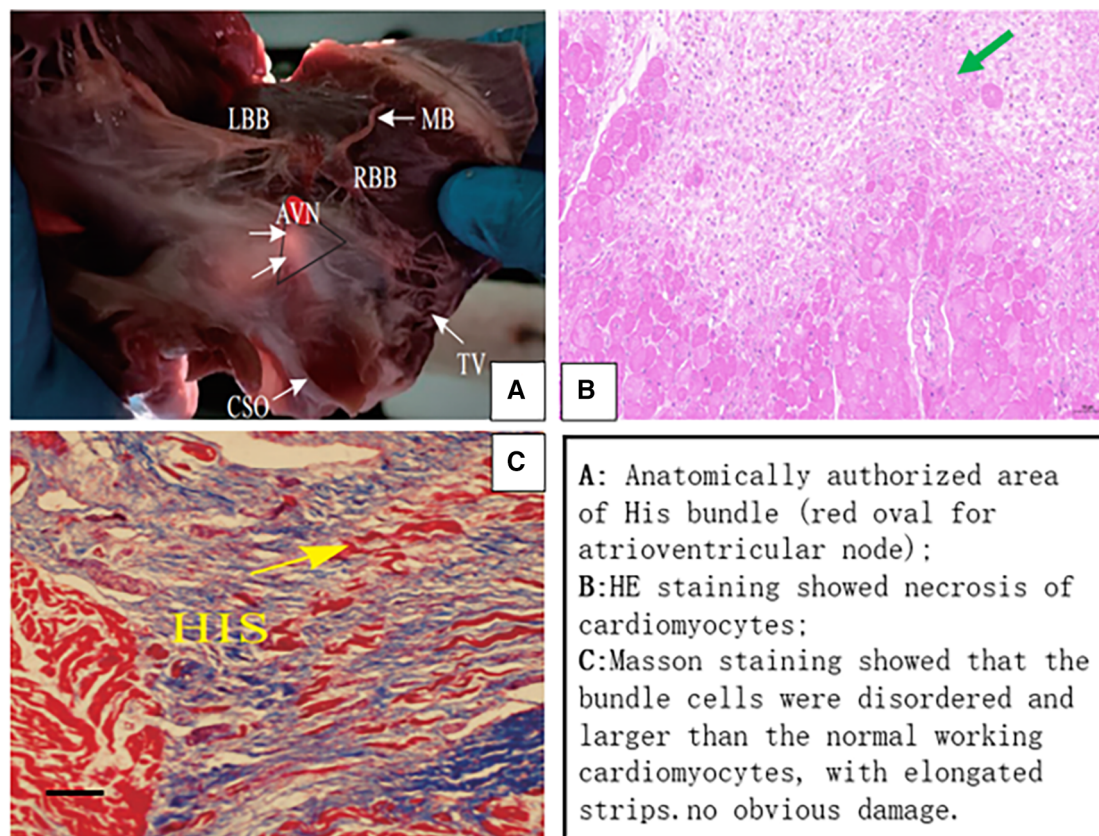


FIGURE 8

(A) Gross anatomical location of the His bundle and histopathology. HE staining showed local myocardial necrosis (B), and Masson staining exhibited normal cell structure of His bundle (C). AVN (red oval area), atrioventricular node; LBB, left bundle branch; RBB, right bundle branch; CSO, coronary sinus ostium; TV, tricuspid valve; MB, moderator band; HIS, His bundle.

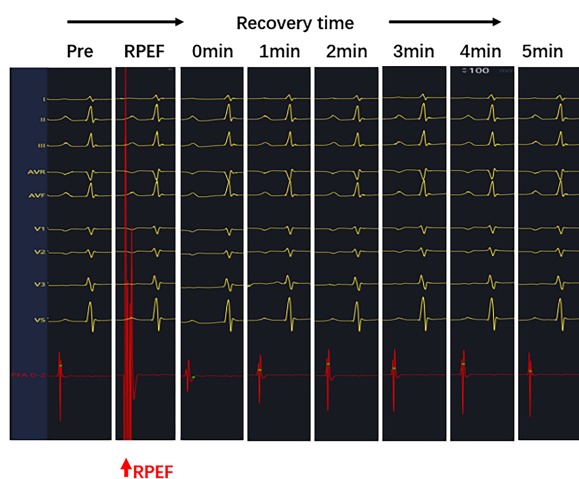


FIGURE 9

After RPEF ablation of the SA node, the amplitude of pulsed ablation catheter electrogram decreased immediately and recovered gradually over time.

approximately 70%, followed by a gradual recovery to about 80% of baseline within 5 min. The results of the pathological analysis showed that the ablation site was nearly normal myocardium

without lesion. Before arrhythmia ablation, partially reversible pulses can be delivered to potential targets to help identify critical isthmus sites. It manifests that RPEF can act on potentially important sites to terminate tachycardia, and thus contributes to identifying critical isthmus sites prior to ablation. Nowadays invasive electrophysiological mapping is widely performed in tachycardia patients. Mapping techniques such as excitation and entrainment are often used to map arrhythmia loops and identify critical isthmus sites for catheter ablation. However, these techniques fail to provide the precise location of ablation. In general, the putative target can only be determined based on whether the ablation lesion terminates the tachycardia. A lack of localization specificity results in the radiofrequency energy to possibly ablate cardiac tissue unrelated to arrhythmia.

4.2 Histiocytic selectivity of PEF

It has been documented that the electroporation thresholds of PEF differ greatly among different cell types (Table 1) (22–28), and PEF is particularly suitable for cardiac ablation since cardiomyocytes have the lowest electroporation threshold of all tissues (29). The difference in sensitivity between cardiomyocytes and other non-target tissues may reduce the risk of collateral

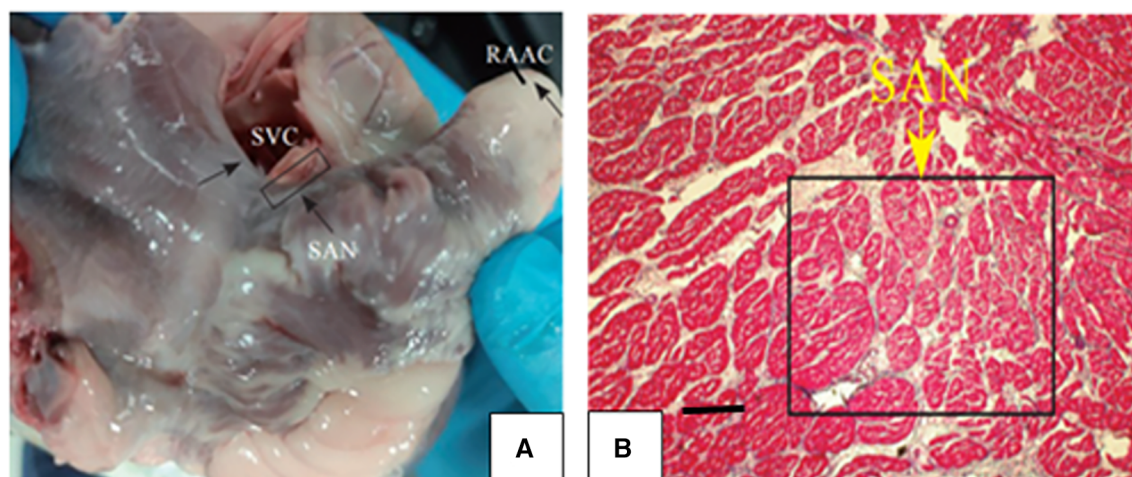


FIGURE 10

(A) The junction of the roots of SVC and the RAA was the sinoatrial node. (B) Histopathological results showed that the sinoatrial node cells were smaller and denser than the surrounding ordinary cardiomyocytes, presenting an irregular oval shape, disorderly arrangement, clumpy distribution and no clear boundary with ordinary cardiomyocytes.

TABLE 1 IRE thresholds for various cell types.

Tissue	IRE threshold (V/cm)	References
Nerve	3,800	Li et al. (22)
VSMC	1,750	Maor et al. (23)
RBC	1,600	Bao et al. (24)
Liver	700	Sano et al. (25)
Kidney	600	Neal et al. (26)
Pancreas	500	Arena et al. (27)
Myocardium	400	Kaminska et al. (28)

VSMC, vascular smooth muscle cell; RBC, red blood cell.

damage to the esophageal and phrenic nerves, while other thermal ablation methods, such as radiofrequency and cryoballoon ablation, may damage the esophageal and phrenic nerves. The exact mechanism that makes cardiomyocytes more sensitive to lower PEFs is not fully understood, but may be related to cell size, orientation, membrane properties, and sensitivity to non-specific cation entry (30). Acute kidney injury due to hemoglobinuria after pulsed electric field ablation has also been studied. More than 70 applications seem to have better sensitivity and specificity to predict hemolysis (31–34). However, a maximum of four applications per dog were performed and the PEF intensity was reversible, considering the low likelihood of causing hemoglobinuria and acute kidney injury associated with hemolysis.

Experimental studies regarding the impact of PEF on animals have indicated that there are marked differences in the effects of PEF on different cardiomyocyte types under the same pulse parameters. A monophasic pulse wave with a voltage of 1,000–1,500 V was used to ablate the bilateral ventricular septum, which was the initial distribution of His, left and right bundle branches. It was found that 63% of experimental animals developed transient third-degree atrioventricular blocks, with a dose-dependent duration and severity, 38% had right bundle branch block, and histopathological results confirmed that Purkinje's

nucleus and ultrastructure remained intact (35). In addition, a study on the isolated Langendorff model of canine heart has confirmed that the ablation mode was set with monophasic wave, 750~2,500 V voltage, 90 μ s pulse width, and 10 increments in voltage to release PEF, which could achieve irreversible damage to Purkinje's potential. The voltage required for the left bundle branch potential block was 2,000 V, whereas 2,500 V voltage only caused a few seconds of His bundle potential block (36). In our experiment, the maximum His potential was ablated with PEFs at different voltages. Transient third-degree atrioventricular blocks occurred in all dogs with biphasic wave, voltage of 600–1,800 V, the duration of which was significantly dose dependent. The structure of His bundle cells remained intact, while local ordinary cardiomyocytes were necrotic.

4.3 PEF ablation of para-His arrhythmia

When PEF was applied to the maximum potential of His bundle within a range of voltages, acute His injury and transient complete atrioventricular blocks appeared, and the higher the voltage, the longer the recovery time. The results of the pathological analysis showed that ordinary cardiomyocytes were necrotic at the ablation site, while the cells of His bundle were almost normal. Before ablation of para-His tachyarrhythmia, delivering PEF with safe voltages to the critical sites of para-His tachyarrhythmia can help determine the risk of a potential atrioventricular block, suggesting that PEF at safe voltages applied to important anatomic sites can facilitate the identification of potential risk of atrioventricular blocks prior to ablation. When patients with para-His arrhythmia receive invasive electrophysiological mapping, they are often treated simultaneously with titration ablation therapy. When electrophysiological examination confirms that there is obvious

bundle potential or the ablation therapy is ineffective at the right heart target site, a femoral artery puncture is required to retrograde into adjacent sites, such as the non-coronary cusp and right coronary cusp for targets mapping, then the ablation catheter is sent to the corresponding target site for ablation. Some patients need combined ablation for the femoral artery access of the left heart and femoral vein access of the right heart. However, these ablation therapies can only be performed anatomically as far away from the His bundle as possible. In general, the risk of ablation can only be observed by the presence of atrioventricular blocks. The absence of advance prediction on ablation risk results from the energy that may injure His bundle and thus cause the conduction block.

4.4 Sinus node modification

Our study verified that PEF ablation with a certain voltage could cause reversible injury to the electrical conduction of the SA node, and the histopathological results showed that the SA node cell structure was normal without obvious injury. Accordingly, when the sinus node is ablated close to the target heart rate in sinus node modification, RPEF ablation can be chosen to prevent excessive ablation and avoid severe SA node dysfunction. SVC isolation can be achieved with a segmental ablation approach at the level of the SVC–RA junction in paroxysmal AF patients with non-pulmonary vein (PV) triggers arising from SVC (37). The sinoatrial node was ablated only once per dog and the pulse electric field intensity was reversible, so the possibility of SVC isolation was slim. In addition, studies have shown that PEF can be performed without damaging the phrenic nerve or causing vascular stenosis (38–41). Consequently, phrenic nerve injury and superior vena cava syndrome can be avoided when PEF is chosen as the energy modality in the sinus node modification.

4.5 Limitations

Nevertheless, there is still room for improvement in this study. This study only evaluated the effect of RPEF on myocardial tissue in healthy dogs, and only obtained preliminary exploratory findings. The energy intensity that can be applied to preclinical and clinical arrhythmias still needs further exploration. In addition, the sample size of this study is small, and further studies are needed to verify the completely reversible energy intensity. The limited observation periods (<5 min) after RPEF precluded an understanding of the time duration needed for complete recovery of electrogram amplitude, pacing thresholds, and AH interval. Furthermore, because PFA can be altered with even minor changes to delivery parameters, these results cannot be regarded to be applicable to other PFA systems. Other preclinical and clinical studies reported data regarding PFA systems using different parameter compositions and catheter electrode designs are needed.

5 Conclusion

This study demonstrated that PEF could be transmitted in a reversible manner *in vivo*, and its transient effects on cell excitability contributed to elucidating the physiological mechanism of the tachycardia circuit. We also studied acute SA node injury and acute His injury, providing new strategies for SA node modification and para-His arrhythmia ablation. Collectively, RPEF provides a novel route to accurately ablate arrhythmias.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The animal study was approved by Animal Experiments and Experimental Animal Welfare Committee of Capital Medical University. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

ZZ: Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. YL: Data curation, Formal Analysis, Resources, Software, Writing – original draft, Writing – review & editing. YW: Investigation, Project administration, Writing – original draft, Writing – review & editing. LS: Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. XL: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Conflict of interest

YL was employed by Shanghai HT Co. Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Oral theophylline corrects sinus node dysfunction in acute on chronic lithium toxicity: case report and systematic review of lithium-induced Sinus node dysfunction

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Introduction: Lithium is a well-known agent to cause systemic toxicity with its narrow therapeutic window. Toxic cardiac effects are known but seldomly reported and can manifest as sinus node dysfunction (SND) ranging from delayed conduction to sinus arrest with the potential to induce asystole. Theophylline a positive chronotropic agent has been previously used for correction of sinus node dysfunction but never been utilized for the correction of lithium-induced SND. We report the first successful use of Theophylline for rate/rhythm correction of SND in a patient presenting with acute lithium toxicity along with a review summarizing the clinical features of all published literature regarding lithium-induced SND.

Methods: Case report and systematic review of the literature are presented. Three independent scientific databases were queried for reports of lithium-induced SND. A clinical compendium was then generated detailing associated clinical data and descriptive statistics were performed.

Results: 1,117 reports were initially retrieved with full-text review yielding a cohort of 49 unique, independent studies. (61.4%) of patients presented with a supratherapeutic lithium level, 12 (21.1%) were normotherapeutic, and 11 (19.3%) were subtherapeutic. EKG findings varied but most commonly described sinus node dysfunction with a variable degree of sinoatrial block with sinus bradycardia (54.39%) and sinus arrest (29.82%) predominating. Twelve patients (21.1%) required inotrope or vasopressor support. 10 (17.5%) of patient required temporary pacing while 7 (12.3%) required permanent pacemaker implantation. In the majority of cases no significant permanent sequelae were reported as 50 (87.7%) patients recovered, 2 (3.5%) patients had persistent sinus node dysfunction, and 2 (3.5%) patients expired as a result of acute lithium toxicity.

Discussion & conclusion: In this review we report the most up-to-date and comprehensive clinical compendium of lithium-associated sinus node dysfunction along with describing a novel treatment methodology to rapidly correct lithium-induced cardiac toxicity in a patient with long-standing bipolar disorder on chronic lithium treatment. We have reviewed the available literature and provide a comprehensive summary detailing symptomatology of presentation, treatments utilized, electrocardiographic findings and patient

prognoses. We have concluded that under the presumptive conditions that transient sinus node dysfunction will resolve with elimination of toxic concentrations of lithium, temporary chronotropic support provided by theophylline administration would be preferable to more invasive measures such as hemodialysis, temporary pacing, or implantation of a permanent pacemaker.

KEYWORDS

lithium, lithium toxicity, sinus bradycardia, sick sinus syndrome, sinus node dysfunction, arrhythmia, temporary pacing, hemodialysis

Introduction

Sinus node dysfunction (SND), also known as sick sinus syndrome (SSS), refers to a distinctive set of arrhythmogenic bradycardias with particular electrocardiographic patterns. Clinically, sinus node dysfunction can manifest on electrocardiogram (EKG) as either a regular or irregular bradycardia with heart rate <60 beats per minute (bpm) and present with symptoms of fatigue, dizziness, chronotropic incompetence, and syncope (1). Diagnosis requires a combination of clinical symptoms and EKG findings (2, 3). SND or sinoatrial block is similar to atrioventricular block (AV) in that it has varying classifications ranging in degree of severity, from Type I manifesting as delayed depolarization and conduction to Type III resulting in long sinus pauses maintained by junctional or idioventricular escape rhythms, or leading to complete sinus arrest. Pathophysiological disruptions of this intracardiac sinoatrial circuit can be caused by a multiplicity of pathologies causing direct damage to the sinus node ranging from acute myocardial infarction, embolization of the sinoatrial node artery, cardiomyopathy, diabetes, hypertension, metabolic derangements, to polypharmacy (2–6). Lithium, a common agent utilized in the treatment of chronic psychiatric conditions, including bipolar and schizoaffective disorders, is a known but seldomly reported pharmacological mediator of sinus node disruption. Lithium has been reported to disrupt intrinsic sinus node pacemaker activity through interaction with pacemaker (HCN) channels (7) and/or the sodium-calcium exchanger (8) thereby impairing pacemaker activity of the SA nodal cells which govern the complex physiological mechanism of cardiac pacing (8–10). Lithium, with its therapeutic window [0.8–1.2 mmol/L] has been shown to not-only induce sinus node dysfunction at supratherapeutic concentrations but, in some reports, at both therapeutic and subtherapeutic levels. Various treatment modalities have been utilized in acute lithium toxicity, ranging from simple observation to emergent hemodialysis, temporary pacing, and permanent pacemaker implantation, but the use of positive chronotropic agents for the treatment of acute lithium-induced SND has never been reported.

Theophylline, a methylxanthine known to have positive chronotropic effects, has been suggested for off-label use for patients with sinus node dysfunction or sick sinus syndrome (SSS) (11–13). In a comparative retrospective study evaluating the efficacy of theophylline vs. cilostazol for treatment of SSS in patients who refused pacemaker implantation, theophylline

increased heart rate from baseline by 12.0 ± 16.3 bpm by sphygmomanometry, ($p < 0.001$), by 8.4 bpm ± 12 by EKG recording ($p < 0.001$), and was shown to be non-inferior to cilostazol, ($p = 0.338$). Symptomatic improvement in chest discomfort, dyspnea, syncope, and palpitations was noted after administration of both medications, with improvement in dizziness being superior in the theophylline group ($p < 0.003$) (11). In another study of patients with SSS, theophylline decreased the frequency of sinus pauses from 256 ± 230 to 23 ± 62 pauses per 24 h and decreased the duration of the longest pauses from 4.7 ± 1.8 s to 2.2 ± 0.97 s after one month of treatment, with disappearance of subjective symptoms associated with cardiac pauses in 16 of 17 patients (12). Lastly, in the treatment of acute COVID-19 induced sinus bradycardia, theophylline has been shown to rapidly improve heart rate, induce reversion to normal sinus rhythm, and cause complete resolution of lightheadedness and dizziness (13). It is with these presuppositions we aim to describe the first reported use of theophylline for rapid correction of lithium-induced SND while simultaneously presenting the most up-to-date and comprehensive clinical compendium of the associated literature.

Case report

In this report we describe the first successful use of theophylline to correct lithium-induced sinus node dysfunction in a patient on long-term lithium maintenance therapy. We present the case of a 73-year-old female with long-standing comorbid schizophrenia and bipolar disorder who presented to our emergency department in November of 2023 with complaints of confusion, progressive fatigue and global weakness that had developed over the prior few months, as well as a symmetric fine-motor tremor of the bilateral upper extremities. The patient had a past medical history of insulin-dependent diabetes and hypertension. Home medications included neutral protamine Hagedorn (NPH) insulin 30 units administered twice daily, lisinopril 2.5 mg once daily, risperidone 3 mg once daily, and lithium 300 mg once daily. Her initial vitals were significant for bradycardia with normotensive pressures, a heart ranging from 31 to 56 and systolic blood pressure ranging from 108 to 131. Initial EKG Figure 1(s) obtained upon presentation showed evidence of sinoatrial block with junctional escape rhythm.

She was given 1 mg of atropine IV with response of heart rate to around 60 beats per minute. Initial lithium level was assessed

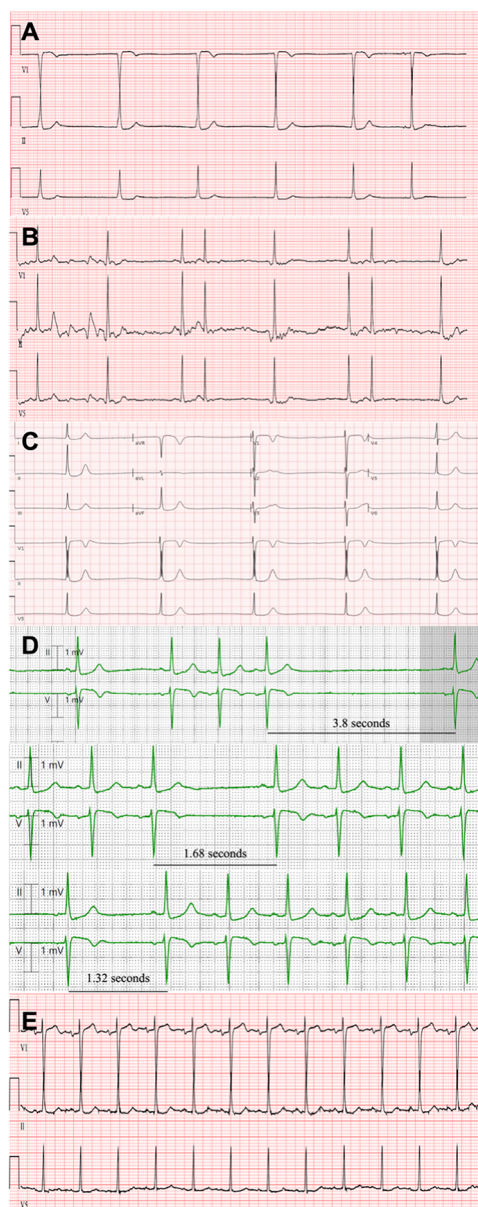


FIGURE 1

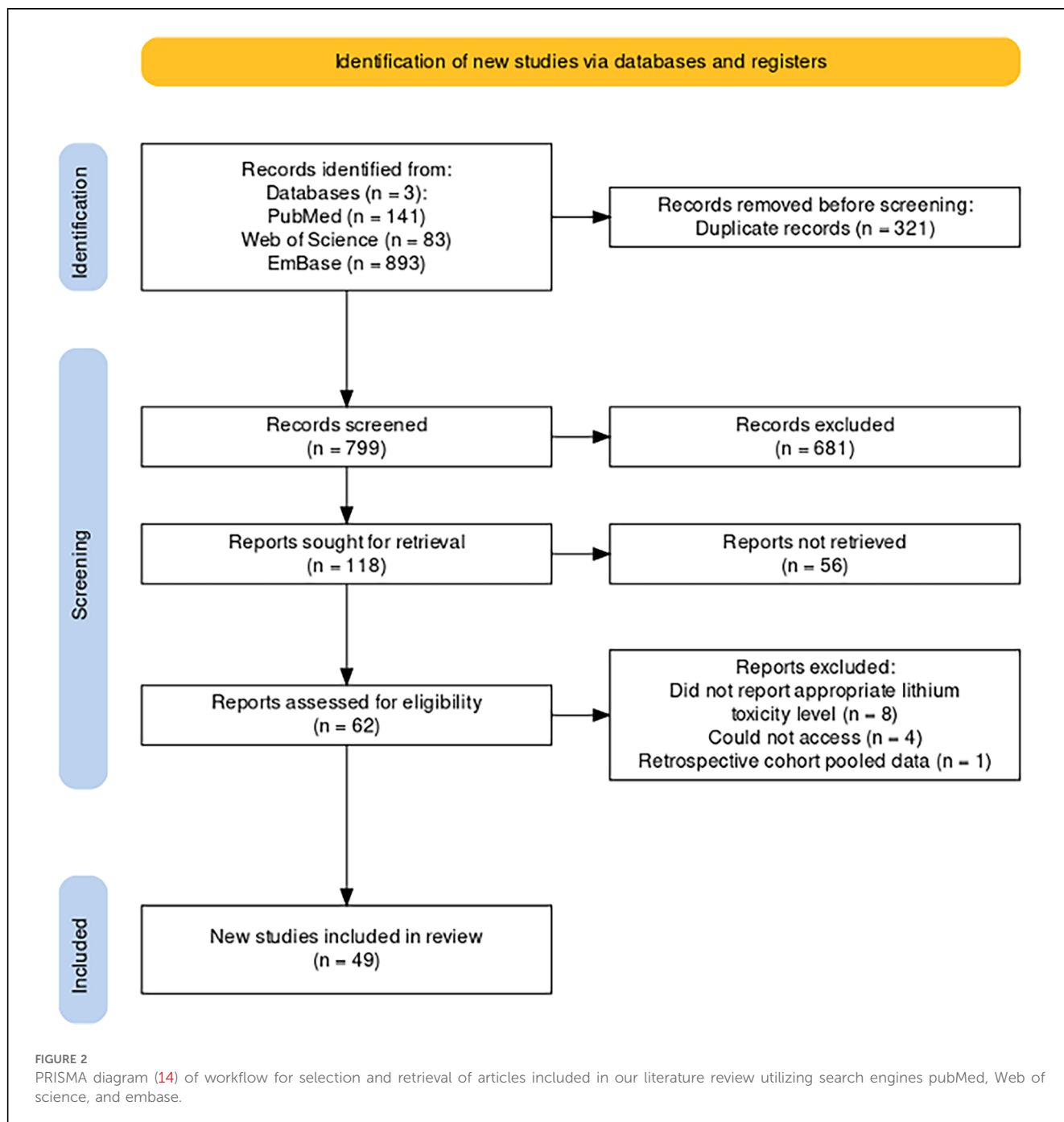
(A) Initial EKG at obtained in the emergency department at time of patient presentation with evidence of junctional escape rhythm and noted absence of p-waves indicative of sinoatrial dysfunction in all but the last sinus complex. (B) Repeat EKG 30-minutes after administration of atropine showing normal sinus rhythm with emergence of p-waves and bigeminal premature atrial complexes indicative of sinus node and atrial conduction recovery. There is noted lead misplacement of V1 indicated by only positive deflection of QRS complexes not consistent with antecedent and subsequent studies. (C) Repeat EKG obtained 12-hours after atropine administration revealing complete dissipation of sinus node recovery with re-emergence junctional escape rhythm and noted absence of p-waves indicative. (D) Sequential progression of telemetry-capture approximately 12-hours after initial Theophylline dose revealing progressively shortening sinus pauses ranging from sinus arrest of 3.8 s to a briefer pause of 1.12 s to eventual complete resolution of SND with return to normal sinus rhythm. (E) EKG obtained approximately 24 h after theophylline administration with evidence of sustained normal sinus rhythm and regular p-waves with normal sinoatrial conduction pattern.

and found to be 2.2 mmol/L [0.6–1.2 mmol/L]. Repeat EKG (Figure 1B) after the administration of atropine exhibited slight recovery of sinus function with emergence of p-waves and bigeminal premature atrial complexes indicative of improvement in atrial conduction.

At the time of presentation, the patient also exhibited an acute kidney injury (AKI) with creatinine of 2.6 mg/dl due to poor oral intake. TSH was checked and found to be within normal limits with a value of 3.77 uIU/ml. Other significant lab findings were a mild leukocytosis of 11.22 K/ml, and hyperkalemia of 6.6 mmol/L for which she was treated with calcium gluconate for myocardial stabilization. Multiple teams, including psychiatry, nephrology, and toxicology, were consulted for coordination of care in the setting of this complex presentation. The patient described in this case did not exhibit capacity during initial presentation and the patient's spouse desired to avoid invasive measures at all possible costs including escalation to a higher level of care. Given these limitations it was determined that the best course of action would be to proceed with judicious fluid resuscitation while monitoring continued response to atropine while the patient remained hemodynamically stable. She was admitted to the cardiology service and continued on normal saline at a rate of 150–200 (ml/hr) along with close surveillance and serial monitoring of lithium level every two hours. Pending decompensation, the patient's spouse was agreeable for transfer to the medical intensive care unit (ICU) for initiation of renal replacement therapy.

Although it appeared that atropine provided satisfactory heart rate recovery for multiple hours, sustained sinus node recovery was not observed. Approximately 12 h after atropine administration, the patient suffered deteriorating sinus node function with redevelopment of junctional bradycardia with a ventricular rate of 31 bpm (Figure 1C). Given that the patient remained hemodynamically stable albeit severe sinus bradycardia, it was decided that an alternate therapy would be best tried prior to escalation of care and initiation of chronotropic agent infusion which would require ICU transfer. Theophylline 300 mg was trialed. 12-hours subsequent to theophylline dosing, telemetry-capture (Figure 1D) revealed progressively shortening sinus pauses from sinus arrest of 3.8 s to a briefer pause of 1.32 s to eventual complete resolution of SND with return to normal sinus rhythm. The following morning, a repeat EKG (Figure 1E) was obtained that confirmed the patient had reverted to normal sinus rhythm, with a heart rate of 74 bpm—an increase of 43 bpm from the prior EKG.

The patient was maintained on telemetry throughout the remainder of her admission and did not experience anymore recorded telemetric events that evidenced sinus bradycardia or SND. She was monitored for an additional 24-hrs and given a second dose of Theophylline 300 mg the following morning. She was subsequently discharged with antihypertensive dose adjustment for improved blood pressure control and instructions for appropriate outpatient psychiatric follow-up for initiation of an alternate psychiatric medication regimen. Her Lithium was held at discharge.



Systematic review methods

A systematic review was conducted to summarize and gain a better understanding of the treatment methodologies that currently exist as standard of care for lithium induced sinus node dysfunction and to explore in this context the associated patient outcomes (Figure 2). Query was performed utilizing three comprehensive scientific research databases (Pubmed, Embase, and Web of Science) to assess lithium induced sinus node dysfunction and to catalog the treatments and patient outcomes available in clinical literature using the search terms [(“Lithium”) AND (“Sinus Node Dysfunction” OR “Sick Sinus Syndrome” OR

“Sinoatrial Block”)] which resulted in 1,117 reports. This query was then deduplicated using reference software Zotero resulting in 799 unique independent reports. From this cohort, initial abstract screen was performed with further exclusion of 681 reports resulting in 118 records that were sought for retrieval. Subsequently, inclusion and exclusion criteria were applied thereby resulting in further exclusion of 56 articles. Articles reporting sinus node dysfunction or lithium-induced bradyarrhythmia as a result of any form of toxicity (acute vs. acute on chronic vs. chronic) were included in initial abstract screen. Secondary screening consisted of evaluation for records with documented electrocardiographic evidence of sinus node

dysfunction, or sinoatrial block along with a documented recording of initial lithium level at presentation (both subtherapeutic, therapeutic, and supratherapeutic). On final abstract screen the following inclusion criteria were applied: retrospective or prospective studies, case reports, case series, randomized controlled trials, age >18 years old. Exclusion criteria included lithium-associated other tachy- or bradyarrhythmia (i.e., ventricular arrhythmias or AV block), meta-analyses, review articles, animal studies, <18 years old, articles not in English. Lastly, 62 articles then underwent full-text review for resulting in further exclusion of 13 studies for the following reasons: $n=8$, did not report appropriate lithium toxicity level or have electrocardiographic evidence of sinus node dysfunction, $n=4$, article unavailable to be retrieved, $n=1$ retrospective cohort with pooled data and inappropriate reporting of outcomes. This resulted in a final cohort of 49 unique, independent studies included in our review (Table 1).

Results

The number of individual patients included in our review totaled 57 with a mean age of 57.42 years aging from 21 to 82 years. As a distinct classification scheme for lithium toxicity is not well defined, for the purposes of this study we defined our classification of lithium toxicity as follows; acute toxicity is differentiated as either an intentional overdose or presentation of toxicity upon new initiation of lithium therapy regardless of initial lithium level, acute on chronic refers to patients with toxic symptomatology and supratherapeutic lithium levels that have been previously stable on long-standing lithium treatment, and chronic toxicity is defined as patients with toxic symptomatology with normo- or subtherapeutic lithium levels. Three patients (5.2%) were classified as acute, thirty-five were classified as acute on chronic (61.4%), and nineteen (33.3%) were classified as chronic. Of our included cases, (63%) reported treatment duration. Average treatment duration classified by type of toxicity are as follows: acute—5 days, acute on chronic—7.77 years, and chronic—7.0 years. The initial lithium level at presentation ranged from 0.2–5, with a mean of 1.73, and standard deviation of 1.05 with 32 (61.4%) of patients being supratherapeutic, 12 (21.1%) normotherapeutic, and 11 (19.3%) subtherapeutic. Repeat lithium level was reported in 22 (38.6%) of cases ranging from 0.02–1.6, with a mean of 0.78 and a standard deviation of 0.48. The most common reported symptom was syncope (19.30%), followed by dizziness (12.28%), and fatigue (10.53%). EKG findings varied but most commonly described sinus node dysfunction with a variable degree of sinoatrial block with sinus bradycardia (54.39%) and sinus arrest (29.82%) predominating. Regarding the various treatment regimens utilized, the majority of patients underwent simple observation 22 (38.6%) as compared to 7 (12.3%) who required urgent hemodialysis in the acute setting. Twelve patients (21.1%) required inotrope or vasopressor support. In regard to the use of pacing for symptomatic bradycardia, 10 (17.5%) patients required temporary pacing while 7 (12.3%) required permanent

pacemaker implantation. In the majority of cases no significant permanent sequelae were reported as 50 (87.7%) patients recovered, 2 (3.5%) patients had persistent sinus node dysfunction as evidenced by subsequent EKG, and 2 (3.5%) patients expired as a result of lithium toxicity.

Discussion

In this case report and systematic review, we herein demonstrate the first successful reported use of a novel treatment methodology to rapidly correct lithium-induced cardiac toxicity in a patient with long-standing bipolar disorder on chronic lithium treatment while also generating the most up-to-date and comprehensive clinical compendium of lithium-associated sinus node dysfunction (15–17). The administration of theophylline can be understood to be the primary factor attributing to sinus node recovery and improvement in bradycardia in our patient, as a careful analysis of the temporal sequence of events, and the patient's response to interventions strongly supports the primary role of theophylline. At presentation, the patient exhibited both lithium toxicity of 2.2 (mmol/L) and significant hyperkalemia of 6.6 (mmol/L), both of which can contribute to significant bradyarrhythmias and EKG abnormalities. The initial EKG changes, particularly the absence of p-waves could indeed be attributed to a combined effect of such significant electrolyte aberrancies, however the subsequent clinical course provides compelling evidence for the specific efficacy of theophylline in this case. The temporal association between interventions and clinical response is crucial to our interpretation in support for the case of theophylline (Figure 3). Despite initial management, including the administration of atropine and correction of electrolyte imbalances, there was only a transient improvement in the patient's cardiac rhythm with subsequent decline. Notably, even though the patient's potassium levels normalized rapidly, decreasing from 6.6 (mmol/L) to 4.4 (mmol/L) within two hours, and a significant improvement of renal function with a decrease of creatinine from 2.6 (mg/dl) to 2.0 (mg/dl) within 6 h, the patient still experienced a recurrence of junctional bradycardia with absence of p-waves approximately 12 h after admission as evidenced in Figure 1C. This temporal evidence of persistent SND in the setting of corrected metabolic derangements and improved renal function can be most likely attributed to the supratherapeutic levels of lithium. It points to a more direct and lasting effect on sinus node dysfunction which is consistent with the known pharmacodynamics of lithium with accumulation in cardiac tissues. This tissue deposition of lithium can likely continue to affect sinus node function even as serum levels begin to normalize (20).

Furthermore, the administration of theophylline marked a clear turning point in the patient's clinical course. Theophylline is thought to increase intracellular cAMP levels in cardiac tissue through phosphodiesterase inhibition (21), which given the temporal association with sinus node improvement is the likely mechanism of improved sinus node automaticity we observed in this case. Within 12 h of theophylline administration, telemetry

TABLE 1 Data compendium compiled from literature review of lithium-induced sinus node dysfunction.

Author (s)	Patient age	Classification of lithium toxicity	Duration of lithium treatment	Initial lithium level	Repeat lithium level	Home meds (excluding lithium)	Presenting symptoms	EKG findings	Treatment	Outcomes
Akhigbe et al.	67	Acute on Chronic	n/a	1.8	Not reported	Lisinopril	Syncope	Junctional escape rhythm with retrograde p-waves	Observation	Not reported
Ataallah et al.	42	Acute on Chronic	n/a	0.55	Not reported	Not reported	Dizziness and fatigue	Sinus bradycardia with non-specific t-wave inversions	Observation	Recovered
Ben Fredj et al.	35	Acute	7 days	0.3	Not reported	Valproic acid, haloperidol, lorazepam	Asymptomatic bradycardia	Sinus bradycardia	Observation	Recovered
Bogin et al.	61	Acute on Chronic	n/a	2.57	Not reported	Lisinopril	Dyspnea, confusion, and fatigue	Sinus bradycardia with escape capture bigeminy	Observation, inotropic support	Recovered
Bravo et al.	68	Acute on Chronic	12 years	1.67	0.92	Carbamazepine, pipamperone, zopiclone, mirtazapine, rofecoxib	Tremor, hypokinesia	Sinus bradycardia, sinus arrest, and intermittent complete av block	Observation, vasopressor support	Recovered
Chen et al.	76	Acute on Chronic	5 years	5	1.3	Losartan, perphenazine	Ataxia, anorexia	Sinus bradycardia with ventricular escape rhythm, non-specific st-t segment changes	Hemodialysis	Recovered
Dahan et al.	61	Chronic	9 years	1.2	0.7	Venlafaxine cr, clonazepam, risperidone,	Global weakness, tremors	Sinus bradycardia with non-specific t-wave inversions	Pacemaker (permanent)	Recovered
Demirtas et al.	82	Acute on Chronic	20 years	1.3	0.02	Quetiapine, ramipril, levodopa/benserazide, ibandronic acid	Weakness, fatigue, di, palpitations	Sinus bradycardia	Pacemaker (temporary)	Recovered
Farag et al.	75	Acute on Chronic	20 years	2.13	Not reported	Not reported	Syncope and collapse	Narrow-complex junctional bradycardia	Observation	Recovered
Goldberger	43	Acute on Chronic	> 1 year	3.64	0.41	Naproxen, amitriptyline, mirtazapine	Hypothermia	Sinus bradycardia and type ii sa block sinoatrial block with an intermittent 2:1 conduction pattern, with non-specific t-wave flattening	Hemodialysis	Recovered
Gupta et al.	55	Acute on Chronic	n/a	2.1	Not reported	Ramipril, aspirin, clopidogrel, carbamazepine	Nausea, vomiting, syncope	Junctional escape rhythm with sinus arrest	Pacemaker (temporary)	Recovered
Hagman et al.	75	Chronic	2 years	0.3	Not reported	Levopromazine, thioridazine, digoxin	Fatigue, repeated syncope	Sinus bradycardia, sinus arrest, and junctional escape rhythm, non-specific t-wave changes, st segment abnormalities	Observation	Recovered
Hagman et al.	63	Chronic	6 years	1.1	Not reported	Chlorpromazine, haloperidol	Repeated syncope	Sinus bradycardia, episodes of asystole without junctional escape rhythm	Observation	Recovered
Hussain et al.	81	Acute on Chronic	n/a	2.7	1.2	None	Syncope and collapse	Sinus bradycardia and pvc's with conversion to atrial fibrillation, t-wave inversion in inferior leads	Inotropic support, pacemaker (temporary)	Recovered

(Continued)

TABLE 1 Continued

Author (s)	Patient age	Classification of lithium toxicity	Duration of lithium treatment	Initial lithium level	Repeat lithium level	Home meds (excluding lithium)	Presenting symptoms	EKG findings	Treatment	Outcomes
Khalid et al.	68	Acute on Chronic	n/a	2.04	Not reported	Aspirin, enalapril, atorvastatin, haloperidol, lithium, trihexyphenidyl, valbenazine, and levothyroxine	Decreased po intake, dysphagia, lethargy	Sinus bradycardia and junctional escape rhythm with right bundle morphology	Observation	Recovered
Kumar et al.	48	Chronic	20 years	1.16	Not reported	Risperidone	Dizziness and syncope	Sinus bradycardia, sinus arrest, and junctional escape rhythm	Atropine, inotropic support, mechanical ventilation, pacemaker (temporary)	Recovered
Lahmeyer et al.	56	Acute on Chronic	9 years	2.2	Not reported	None	Altered mental status, lethargy, hypotension, unresponsiveness	Sinus bradycardia, diffuse st elevations in inferior and anterior leads, and qt prolongation	Pacemaker (temporary)	Recovered, persistent diabetes insipidus, and dyskinesia
Lai et al.	42	Acute on Chronic	> 2 years	3.86	0.15	Carbamazepine, clonazepam, trazodone, moperone, bethanechol, trihexyphenidyl	Tonic-clonic convulsion, loss of consciousness, diarrhea for 1-week, dizziness, ataxia, tremor, frequent falls, and drowsiness for 3-days	Sinus bradycardia, sinus arrest, and inverted t-waves with prominent u-waves	Hemodialysis	Recovered
Maddala et al.	77	Acute on Chronic	30 years	2.6	0.9	Losartan, metoprolol, levothyroxine	Dizziness, bilateral hand tremor	Junctional rhythm	Pacemaker (temporary)	Recovered
Martinez et al.	69	Acute on Chronic	n/a	2.32	Not reported	Olmesartan-amlodipine, venlafaxine, lamotrigine	Dizziness, asthenia, adynamia, repeated syncope	Second-degree type ii sa block, t-wave flattening	Observation	Not reported
Mehta et al.	54	Acute on Chronic	n/a	3	1.2	Amitriptyline, quetiapine, zolpidem	Confusion, insomnia, agitation	Junctional escape with premature bigeminy complexes, brugada pattern, and non-specific t-wave flattening	Observation	Recovered
Montal-ESCOT et al.	56	Chronic	12 years	0.8	0.1	Not reported	Dizziness, dysmetria, disequilibrium, mild dyspnea	Sinus bradycardia, and depression of t-waves in posterior segments	Atropine, pacemaker (temporary)	Recovered
Musfeldt et al.	61	Acute on Chronic	n/a	1.51	0.54	Not reported	Lightheadedness, dizziness, weakness, fatigue	Sinus bradycardia, and junctional escape rhythm	Observation	Recovered
Nagamine et al.	78	Acute on Chronic	3 months	2.04	0.51	Clonazepam	Repeated syncope	Junctional escape rhythm, and av disassociation	Observation	Recovered
Nakamura et al.	36	Acute	1 week	0.61	Not reported	Olanzapine, paliperidone, eszopiclone	Exacerbation of schizophrenic symptoms	Sinus bradycardia with partial fusion idioventricular escape rhythm	Observation	Recovered
Narayan et al.	37	Acute on Chronic	n/a	3.7	0.55	Not reported	Unresponsiveness	Sinus bradycardia, junctional escape rhythm, t-wave inversion, qt prolongation	Mechanical ventilation, inotropic support, hemodialysis	Recovered
Numata et al.	39	Chronic	6 years	0.9	Not reported	Not reported	Dizziness, chest discomfort	Sinoatrial block, and sinus arrest	Observation	Recovered

(Continued)

TABLE 1 Continued

Author (s)	Patient age	Classification of lithium toxicity	Duration of lithium treatment	Initial lithium level	Repeat lithium level	Home meds (excluding lithium)	Presenting symptoms	EKG findings	Treatment	Outcomes
Numata et al.	58	Chronic	2 years	0.7	Not reported	Not reported	Syncope	Sinus bradycardia, and sinus arrest with frequent pvc's	Observation	Recovered
Nykiel et al.	61	Acute on Chronic	n/a	1.51	Not reported	Not reported	Lightheadedness, weakness, fatigue	Sinus bradycardia with junctional escape rhythm	Atropine, inotropic support, pacemaker (chronicity not specified)	Recovered
Oudit et al.	64	Chronic	11 years	0.72	Not reported	Not reported	Presyncope	Sinus arrest with idioventricular escape rhythm	Atropine, observation	Recovered
Palileo et al.	61	Chronic	1 year	0.75	Not reported	Not reported	Repeated syncope	Sinus bradycardia, sinus arrest, and junctional escape rhythm	Pacemaker (permanent)	Recovered, persistent sinus node dysfunction
Pavuluri et al.	45	Acute on Chronic	n/a	3.31	Not reported	Lisinopril, furosemide	Altered mental status, diarrhea, unresponsiveness	Sinus bradycardia with prolonged qrs and prolonged qt followed by pulseless wide-complex bradycardia and asystole	Acls code, sustained low-efficiency dialysis (sled)	Deceased
Rector et al.	60	Chronic	9 months	0.8	Not reported	Diuretic (unspecified), methyl dopa	Asymptomatic	Sinus bradycardia, and second-degree type i (wenckebach) sa block	Pacemaker (permanent)	Not reported
Riccioni et al.	74	Acute on Chronic	6 months	2	1.27	Not reported	Confusion, ataxia, syncope	Alternating sinus bradycardia, supraventricular tachycardia, and junctional rhythm	Atropine, vasopressor support, observation	Recovered
Rijal et al.	37	Acute on Chronic	n/a	3.7	1.2	Lamotrigine, lisinopril, levothyroxine, metformin, glipizide	Vomiting, decreased po intake, tremor	Sinus bradycardia with sinus pauses, junctional rhythm with escape-capture bigeminy	Hemodialysis	Recovered
Rodney et al.	59	Acute on Chronic	2 years	1.3	0.1	Not reported	Asymptomatic	Junctional rhythm with ventricular bigeminy	Atropine, observation	Recovered, persistent sinus node dysfunction
Roose et al.	69	Chronic	10 years	1.1	Not reported	Triiodothyronine	Dyspnea on exertion, chronotropic incompetence	Sinus pauses with junctional escape rhythm	Pacemaker (permanent)	Recovered
Roose et al.	75	Acute on Chronic	9 years	1.8	1.5	Not reported	Ataxia, choreiform movements of fingers and hands	Sinus bradycardia with junctional escape rhythm, lbbb, and t-wave inversions	Observation	Recovered
Roose et al.	53	Chronic	3 months	1	Not reported	Not reported	Asymptomatic	Sinus pauses with junctional escape rhythm	Observation	Recovered
Sabharwal et al.	27	Acute	1 day	<0.2	Not reported	Unspecified psychiatric medications	Dizziness with confusion	Sinus bradycardia with right rbbb	Atropine, observation	Recovered
Sarangi et al.	74	Chronic	5 years	0.6	Not reported	Lisinopril, indomethacin, terazosin, furosemide, metoprolol, aspirin, vitamin c	Dizziness	Sinus bradycardia with prolonged pr interval, rbbb, and left anterior fascicular block	Pacemaker (permanent)	Recovered

(Continued)

TABLE 1 Continued

Author (s)	Patient age	Classification of lithium toxicity	Duration of lithium treatment	Initial lithium level	Repeat lithium level	Home meds (excluding lithium)	Presenting symptoms	EKG findings	Treatment	Outcomes
Shetty et al.	46	Chronic	15 years	0.7	Not reported	Not reported	Dizziness	Sinus arrest with junctional escape rhythm	Observation, pacemaker (temporary)	Recovered
Snipes et al.	60	Acute on Chronic	n/a	3.3	1.6	Atorvastatin, baclofen, carbamazepine, carvedilol, clonazepam, levetiracetam, mirtazapine	Altered mental status, diarrhea	Sinus bradycardia and non-specific interventricular conduction delay	Atropine, glucagon, inotropic support, pacemaker (temporary)	Recovered
Steckler	56	Acute on Chronic	3 years	2.05	1.21	Carbamazepine	Ataxia	Sinus bradycardia, sinus pauses	Observation	Recovered
Steckler	26	Acute on Chronic	n/a	1.5	Not reported	Carbamazepine, perphenazine, propranolol	Syncope	Sinus arrest and junctional bradycardia	Observation, vasopressor support	Recovered
Steckler	53	Acute on Chronic	5 months	1.66	Not reported	Haloperidol, cogentin, carbamazepine	Syncope	Sinus arrest and junctional bradycardia	Observation	Recovered
Steckler	75	Acute on Chronic	n/a	1.32	Not reported	Haloperidol, carbamazepine	Nausea, vomiting	Sinus arrest with junctional escape rhythm	Observation	Recovered
Steckler	40	Chronic	n/a	0.96	Not reported	Not reported	Mania, nausea, vomiting	Sinus bradycardia with prolonged pr interval with junctional and ventricular fusion escape beats, complete heart block	Observation	Recovered
Talati et al.	58	Chronic	n/a	1.1	Not reported	Levothyroxine, glyburide	Generalized weakness, fatigue	Sinus bradycardia with junctional escape rhythm	Atropine, observation	Recovered
Terao et al.	56	Chronic	6 years	0.7	Not reported	Valproic acid, haloperidol, levomepromazine, flunitrazepam	Syncope, mania	Sinus bradycardia with ventricular escape beats, sinus arrest	Observation	Recovered
Tuman et al.	42	Acute on Chronic	8 years	1.8	0.4	Not reported	Syncope	Sinus bradycardia, and a-fib with slow ventricular response	Pacemaker (permanent)	Recovered
Venkatarathnamma et al.	21	Chronic	n/a	0.8	Not reported	Haloperidol, trihexyphenidyl	Vomiting, respiratory failure	Sinus bradycardia, st segment depression and t-wave inversion in anterior and inferior leads	Mechanical ventilation, inotropic support	Deceased
Weintraub et al.	60	Acute on Chronic	5 years	1.25	Not reported	Not reported	Non-specific chest pain	Sinus bradycardia with non-specific t-wave inversions	Atropine, observation	Not reported
Wellens et al.	56	Chronic	6 years	1	Not reported	Not reported	Syncope, dizziness, fatigue	Irregular sinus rhythm, sinus arrest	Observation	Not reported
White et al.	54	Acute on Chronic	n/a	2.84	Not reported	Atenolol, gabapentin	Lethargy, chest discomfort, presyncope	Sinus arrest with irregular junctional escape rhythm	Atropine, pacemaker (temporary), hemodialysis	Recovered
Woods et al.	70	Acute on Chronic	n/a	2.3	0.6	Glargine, prophylactic heparin	Altered mental status, hypotension	Sinus bradycardia, sinoatrial block, and junctional escape rhythm	Observation, vasopressor support	Recovered
Worthley et al.	52	Acute on Chronic	5 years	3	Not reported	None	Cardiac arrest requiring cardioversion	Sinus bradycardia with non-specific t-wave flattening, prolonged qt interval, frequent ectopic ventricular beats	Observation, repeat cardioversion, vasopressor support, magnesium infusion	Recovered

Data Trend of Lithium Level and Metabolic Derangements

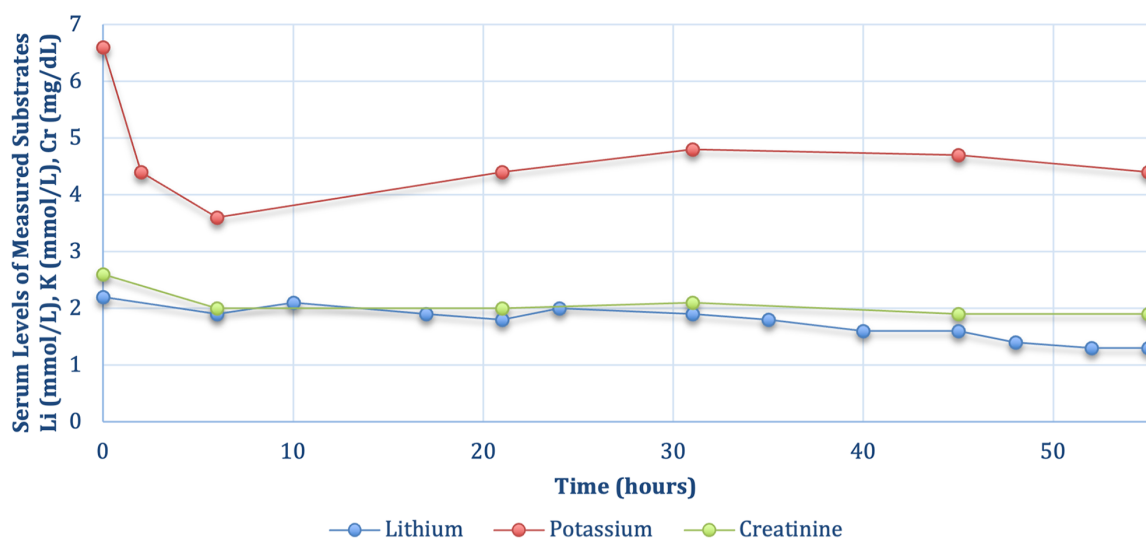


FIGURE 3

Timeline of monitoring for serial lithium levels potassium, and creatinine as a marker of renal function over the course of the patient's hospital admission.

capture revealed a progressive shortening of sinus pauses, from an initial arrest of 3.8 s to brief pauses of 1.32 s, culminating in a complete resolution of SND and return to normal sinus rhythm. This rapid and sustained response to theophylline, occurring when both lithium and potassium levels were closer to normal, strongly suggests a direct effect of theophylline on sinus node function consistent with prior reports in the clinical literature establishing the efficacy of theophylline in treating sinus node dysfunction (22, 23).

Symptomatology of acute lithium toxicity is fairly consistent at mild concentrations with presentations of dizziness, tremor, lethargy, nausea and vomiting at moderate to severe concentrations symptoms can progress to confusion, agitation, delirium, tachycardia and hypertonia (15–17). Cardiac symptomatology can present over a wide range of lithium concentrations with exposure ranging from acute to chronic with evidence of QTc prolongation, t-wave flattening, sinus node dysfunction, and life-threatening arrhythmias. The mainstay of treatment for acute lithium toxicity is judicious fluid resuscitation, but primarily driven by the degree of symptoms. If the patient demonstrates signs and symptoms of severe lithium poisoning or is having a renal failure due to its small volume of distribution and marginal protein binding, hemodialysis should be considered for rapid elimination (17, 18).

Cardiotoxic effects of lithium intoxication typically resolve with proper elimination, but if severely acute as in the case of profound bradycardia, the use of temporary pacing or permanent pacemaker implantation may be required. In non-lithium-associated sinus node dysfunction, methylxanthines (theophylline

and aminophylline) are an accepted treatment choice given their positive chronotropic effects (4). The majority of data supporting the efficacy of these medications has been evaluated primarily in the setting of either spinal cord injury or post-heart transplant patients, although there are reports of successful theophylline use in other etiologies of SND (13, 19). Under the presumptive conditions that transient sinus node dysfunction will resolve with elimination of toxic concentrations of lithium, temporary chronotropic support would be preferable to more invasive measures such as temporary pacing, hemodialysis, or implantation of a permanent pacemaker.

In conclusion, this case highlights the potential of theophylline as an effective treatment for lithium-induced SND, particularly in cases where the dysfunction persists despite correction of other contributing factors. The rapid and sustained response to theophylline observed in this patient, supported by extensive literature on its efficacy in treating sinus node dysfunction, provides a compelling argument for its use in similar clinical scenarios. Given the summary of findings regarding patient prognosis as described in our report, it can be postulated that theophylline may be potentially non-inferior to other treatment methodologies albeit this is not represented by comparative statistical analysis. We propose that further studies are needed before theophylline comparing the efficacy of theophylline to other treatment modalities in lithium-induced SND before theophylline can be recommended as a treatment specifically for lithium-induced sinus node dysfunction. Given the findings that our report provides, initial clinical utility for the use of Theophylline in rapid correction of lithium-induced sinus node dysfunction is evident.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

JCH: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. LM: Data curation, Investigation, Writing – original draft, Writing – review & editing. JH: Investigation, Writing – original draft. NW: Data curation, Writing – original draft. HP: Conceptualization, Resources, Supervision, Writing – review & editing.

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Case Report: Ethanol ablation of the Marshall vein as the first step for left atrial tachycardia ablation

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Electroanatomic mapping guides complex atrial tachycardia ablations; however, challenges may emerge after pulmonary vein isolation. 3D mapping systems can reveal the mechanism of tachycardia and critical areas that need to be ablated. Sometimes, however, these areas may be located deep inside, to the extent that they cannot be successfully reached by endocardial ablation. In this study, we present a unique case of a patient in whom vein of Marshall (VOM) ethanol ablation, a conventional secondary intervention, promptly terminated a Marshall bundle-related atrial tachycardia without further endocardial radiofrequency application, suggesting VOM ethanol ablation as a potential primary strategy.

KEYWORDS

alcohol ablation, atrial fibrillation, atrial tachycardia, electroanatomic mapping, vein of Marshall (VOM)

Introduction

Electroanatomic mapping plays a pivotal role in facilitating ablation procedures for complex atrial tachycardias (ATs). However, prompt understanding of the tachycardia mechanism remains crucial for achieving successful ablations. After pulmonary vein isolation (PVI) ablation, approximately 20% of unexpected left-sided atrial tachycardias may manifest, involving epicardial connections that cannot be effectively ablated from the endocardial side (1). The vein of Marshall (VOM) represents a branch within the coronary sinus (CS) venous system, situated in the epicardial aspect of the mitral annulus, typically terminating between the left atrial appendage (LAA) and the left superior pulmonary vein (LSPV) (2). The ablation strategy targets the Marshall bundles (MBs) located at the end of the VOM, which may be associated with tachycardia. When endocardial ablation fails for these ATs, alcohol ablation of the VOM is often utilized as a complementary strategy. In addition, Vlachos et al. showed that ethanol ablation may be related to a better long-term outcome (1). In this report, we present a case of a patient in whom initial VOM alcohol ablation promptly terminated an epicardial AT, rendering it non-inducible without the need for subsequent endocardial radiofrequency application.

Patient information

A 49-year-old male patient was admitted to our center with a palpitation of 3 months' duration. He had no other cardiac symptoms. His heart rate was 115 beats/min, blood pressure was 105/72 mmHg, and oxygen saturation rate was 97% in the air room. He

was a non-smoker and had neither comorbidities nor structural heart disease predisposing to the arrhythmia. He had undergone three previous left atrial ablations, namely PVI, posterior wall box isolation, and cavotricuspid isthmus ablation. Upon admission, the patient was prescribed rivaroxaban, amiodarone, metoprolol, and ramipril to manage his high heart rate. A full timeline of the patient's history is given in [Table 1](#).

Diagnostic assessment

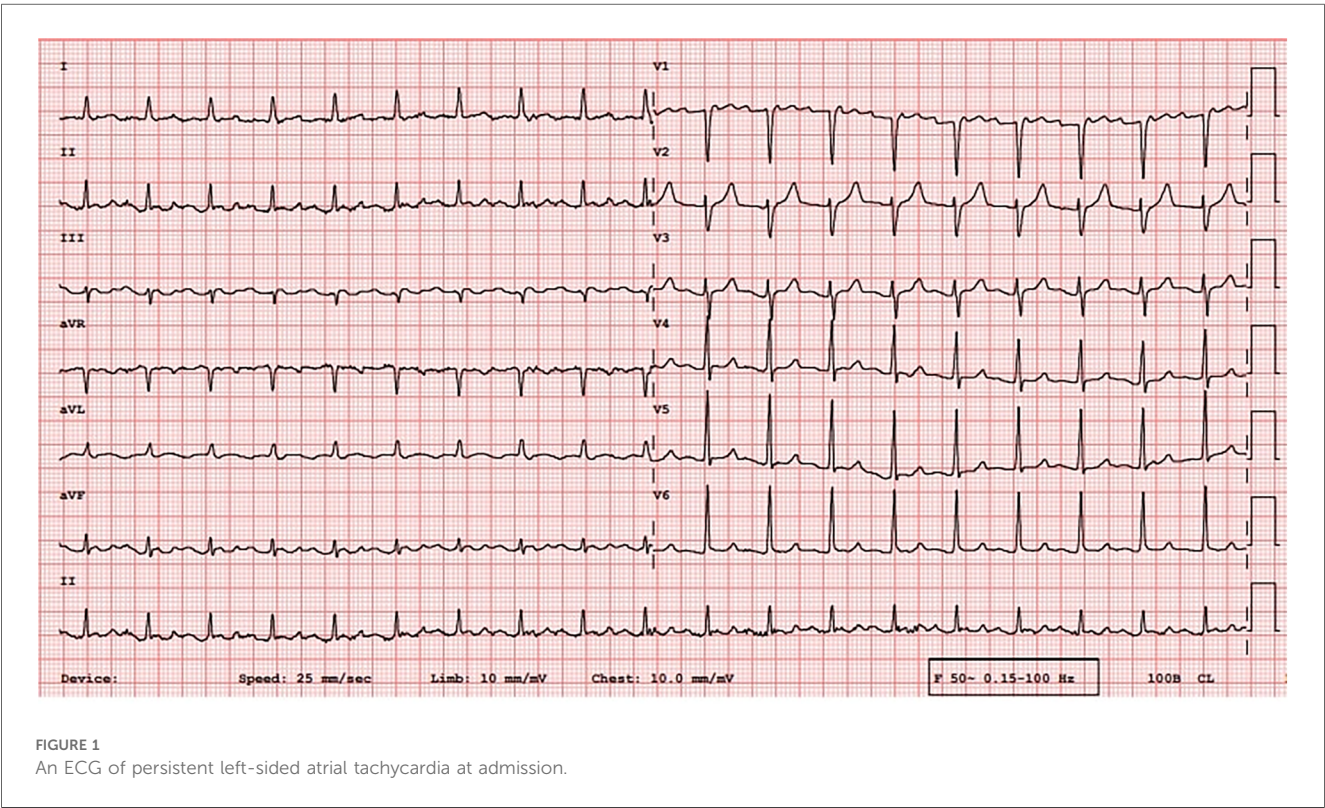
An electrocardiogram (ECG) was quickly performed and an atrial tachycardia was observed ([Figure 1](#)). All blood test results

were in normal range and there was no sign of infection. Then, echocardiography was performed and the left ventricle's ejection fraction was measured at 52% with normal cardiac structures. Next, an electrophysiological study (EPS) was conducted. The tachycardia cycle length (TCL) of the AT was found to be 285 ms, and CS activation was eccentric and compatible with left atrial origin. The LA was electroanatomically mapped using a CARTO 3D mapping system (Biosense Webster, Diamond Bar, CA, USA) with a high-density mapping catheter (Pentaray). The local activation time (LAT) map demonstrated that all pulmonary veins and the posterior wall were already isolated. A local reentry was detected between the LSPV and the LAA, and wavefront collision was seen on the anterior wall consequent to activation mapping, and therefore, no perimitral AT was suspected. This could have been easily excluded by performing consecutive entraining maneuvers at the CS proximal and distal regions, and these should be done when the mechanism of tachycardia cannot be understood. However, these maneuvers were not performed in this patient because of the fear of unwanted termination of the tachycardia and because the activation map clearly showed no perimitral AT. This area also harbored low-amplitude fragmented diastolic electrograms (EGMs) compatible with the critical region. However, 17% of the tachycardia circuit was found to be missing in the LAT histogram, suggesting another yet-unmapped site, i.e., the epicardial surface ([Figure 2](#)). Given the typical proximity of the Marshall bundle to this area, an element of suspicion arose regarding the direct participation of the MB in the tachycardia circuit.

TABLE 1 A timeline of the patient's history.

Date	Patient's history
March 2019	Paroxysmal atrial fibrillation was started when high-frequency episodes of arrhythmia occurred
September 2020	Pulmonary vein isolation with radiofrequency ablation
February 2021	Onset of persistent atrial fibrillation
March 2021	Failed electrical cardioversion in three attempts
August 2021	Redo pulmonary vein isolation (there were electrical connections in the right superior pulmonary vein) Posterior box isolation Anterior line ablation (between the right superior pulmonary vein and the mitral annulus) Cavotricuspid isthmus ablation
September 2022	Onset of drug-resistant persistent atrial tachycardia
December 2022	Vein of Marshall alcohol ablation
July 2023	6-month follow-up without any tachycardia episode

Bold text is the last and most curative procedure for this patient.



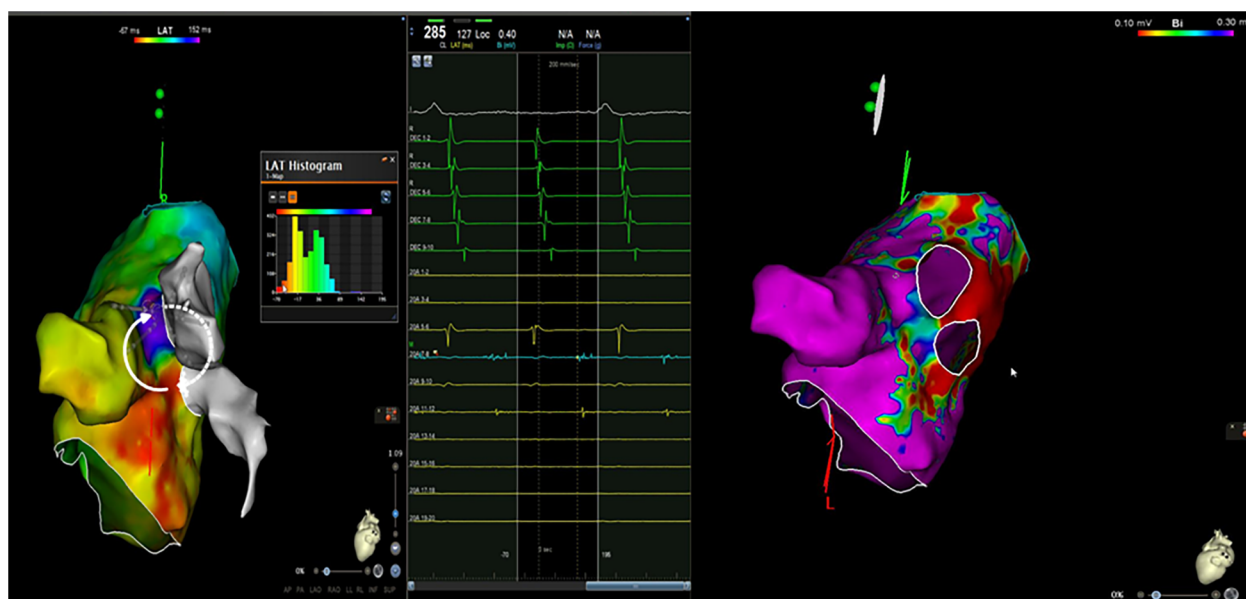


FIGURE 2

An electroanatomic mapping of the left atria and histogram of the LAT mapping during a tachycardia event and a bipolar map of the left atrium before ethanol ablation of the VOM (the propagation of the local reentry of the tachycardia is shown in the form of white arrows. The white arrows with dots show epicardial activation through the Marshall bundle).

Therapeutic intervention

Ethanol ablation for the VOM is typically performed after the failure of endocardial radiofrequency (RF) ablation as a complementary approach in persistent perimitral atrial tachycardias and not as a first option (3–5). But because we suspected direct involvement of the epicardial tissues in the AT mechanism, we opted for ethanol ablation of the VOM as the initial intervention after direct visualization of the VOM as a suitable target. An over-the-wire balloon (2 mm × 15 mm) was placed at the ostium of the VOM and the administration of 3 cc of ethanol was started. The AT promptly slowed down and terminated during the initial phase of the first ethanol infusion (around 1.5 cc). All planned ethanol infusions were completed. After the injections, we repeated VOM venography to demonstrate contrast staining of the affected myocardium (Figure 3). Following the alcohol infusion, a LA voltage map was re-created, which revealed no voltage over critical endocardial sites (Figure 3). Because no tachycardia could be induced, we did not apply any RF endocardially. In addition, because we already excluded a perimitral AT by activation mapping and therefore determined that the mitral isthmus was not involved in the circuit, we ultimately did not aim to achieve a bidirectional mitral block.

Follow-up and outcomes

The patient was followed up for 6 months, and during this period, he did not experience any symptoms or tachycardia. At the 3rd and 6th month visits, a 72-hour ambulatory ECG monitoring was performed and no arrhythmia was detected.

Discussion

Electroanatomic mapping utilizing 3D electroanatomic mapping systems significantly facilitates ablation procedures. However, accurate interpretation and annotation of the correct signals are pivotal for precise cardiac mapping (6). In instances where the LAT histogram fails to encompass the entire tachycardia cycle length, consideration must be given to alternative cardiac chambers potentially associated with the tachycardia, such as the epicardial space.

Prudent interpretation of intracardiac signals holds paramount importance in ablation procedures. Particularly crucial are mid-diastolic atrial signals spanning the entire period for pinpointing areas specifically linked to tachycardia. In the case of the patient in this study, the detection of presystolic and late mid-diastolic low-amplitude long-fragmented EGMs between the LAA and the LSPV was notable. The absence of early diastolic signals on the endocardial map suggested possible tachycardia-related sites within both the myocardium and the epicardium. In addition, the unipolar recording in this region demonstrated an rS pattern, signifying a breakthrough originating from an epicardial site (1). Therefore, considering the presumed critical site proximity to the lateral side of the left atrium, we suspected direct involvement of the MB, an epicardial structure.

Different centers adopt varied VOM ethanol administration techniques. Sang et al. employed a protocol involving two 2 ml ethanol infusions (2). In another study, authors administered 6–10 ml ethanol infusions (7). Our clinical experience



FIGURE 3
Vein of Marshall venography to demonstrate contrast staining of the affected myocardium and a bipolar map of the left atrium after ethanol ablation of the VOM.

suggests that lower ethanol amounts are likely to be associated with recurrences. Thus, despite terminating the tachycardia after a 1.5 cc ethanol infusion in our patient, we administered a 3 cc ethanol infusion each time and repeated it three more times. Margato et al. previously conducted successful ethanol ablation of the VOM in a similar patient case (8). Building on this evidence, we opted for exclusively performing ethanol ablation first, successfully terminating the tachycardia and rendering in non-inducible without additional endocardial radiofrequency application.

Alcohol ablation of the VOM is typically a complementary approach after radiofrequency ablation failure. However, in select patients in whom tachycardia is highly presumed to be MB-related, the aforementioned approach can serve as an initial option avoiding unnecessary subsequent endocardial radiofrequency ablations.

Take-home messages

Electroanatomic mapping has transformed ablation procedures for complex ATs. In patients in whom endocardial ablation fails, alcohol ablation of the VOM offers a complementary strategy. In this study, we presented a case of a patient in whom initial VOM alcohol ablation promptly terminated an epicardial AT, avoiding the need for further endocardial intervention. This underscores the potential of VOM alcohol ablation as an effective first-line option in select patients, particularly when epicardial involvement is suspected, potentially sparing patients from unnecessary endocardial procedures.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary Material](#), further inquiries can be directed to the corresponding author.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

MO: Writing – review & editing, Writing – original draft. ID: Writing – review & editing. EB: Writing – review & editing. AL: Writing – review & editing. BC: Writing – review & editing, Supervision.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fcvm.2024.1431736/full#supplementary-material>

SUPPLEMENTARY VIDEO 1

Propagation mapping of left atrium during tachycardia.

SUPPLEMENTARY VIDEO 2

Termination of tachycardia during alcohol infusion.

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Lipid-lowering drugs, circulating inflammatory factors, and atrial fibrillation: a mediation Mendelian randomization study

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Background: Previous studies have shown an association between lipid-lowering drugs, circulating inflammatory factors, and atrial fibrillation (AF), but the specific effects of lipid-lowering drugs on AF and whether they can be mediated by circulating inflammatory factors remain unclear.

Methods: We collected 10 genetic variants encoding lipid-lowering drug targets (LDLR, HMGCR, PCSK9, NPC1L1, APOB, APOB, ABCG5, ABCG8, LPL, APOC3, and PPARA) and AF based on genome-wide association study (GWAS) summary statistics. Drug target Mendelian randomization (MR) was used to explore the causal relationship between lipid-lowering drugs and AF. In addition, we performed a mediation analysis of 91 circulating inflammatory factors to explore potential mediators. Sensitivity analyses were performed to verify the reliability of the MR Results by MR-Egger intercept test, Cochran's Q test and leave-one-out test.

Results: The results of IVW method showed that LPL agonist had a protective effect on AF (OR = 0.854, 95%CI: 0.816–0.894, $P = 1.844 \times 10^{-11}$). However, the other nine lipid-lowering drug targets had no significant effect on AF. Notably, we found a mediator role of Fibroblast Growth Factor 5 (FGF5) in the protective effect of LPL agonist on AF with a mediator ratio of 9.22%. Sensitivity analyses supported the robustness of our findings, indicating a possible mediating pathway by which LPL agonists affect the risk of AF.

Conclusion: Our study provides new insights into the complex interactions among lipid-lowering agents, circulating inflammatory factors and AF, and also identified a potential mediating role of FGF5 in the pathogenesis of AF. Our findings highlight the potential of LPL agonists and targeting specific inflammatory factors for therapeutic intervention in AF, providing promising avenues for future research and clinical strategies for the management and prevention of AF.

KEYWORDS

lipid-lowering drugs, LPL agonist, atrial fibrillation, circulating inflammatory factors, fibroblast growth factor 5, drug treatment, Mendelian randomization study

Abbreviations

LPL, lipoprotein lipase; TG, triglyceride; FGF5, fibroblast growth factor 5; AF, atrial fibrillation; LDL-C, low-density lipoprotein cholesterol; CHD, coronary heart disease; MR, Mendelian randomization; IVW, inverse variance weighted; WME, weighted median; SNP, single nucleotide polymorphisms; NSNP, number of single nucleotide polymorphisms; POS, position; CHR, chromosome; SE, standard error; OR, odds ratio; CI, confidence interval.

1 Introduction

Atrial Fibrillation (AF), as one of the most common arrhythmias in clinical practice, has the characteristics of high disability rate and high mortality, and can cause a series of complications such as stroke, heart failure, cognitive dysfunction, which poses a serious threat (1–4). Although many studies have identified a variety of risk factors for atrial fibrillation, including age, hypertension and cardiac structural abnormalities, the pathogenesis of AF is still not fully understood, and the efficacy and safety of existing treatments are limited.

In recent years, abnormal lipid metabolism and inflammatory response have been considered to be important factors in the pathogenesis of AF. Elevated blood levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG), as well as inflammatory factors such as C-reactive protein (CRP) and interleukin-6 (IL-6), are associated with an increased risk of AF (5–10). And, several studies have indicated that dyslipidemia may further lead to inflammation (11, 12). Furthermore, it has been reported in some studies that in addition to their lipid-lowering properties, various lipid-lowering drugs may also exhibit anti-inflammatory and immunomodulatory effects, effectively reducing the incidence of AF (13, 14). However, some prospective studies have presented conflicting evidence regarding the correlation (15–18). Currently, the specific relationship between lipid-lowering drugs, circulating inflammatory factors and AF is not clear, especially the mediating role of inflammatory factors in the causal relationship between lipid-lowering drugs and AF. Therefore, it is crucial to explore the effects of lipid-lowering drugs and circulating inflammatory factors on AF.

Drug-target Mendelian randomization (MR) is a new research approach specifically designed for drug repurposing, finding new therapeutic targets, and revealing the harm of drugs. Compared with the traditional observational study, MR can effectively avoid the interference of external factors and potential confounding factors, being regarded as a natural randomized controlled trial that is more cost-effective. We explored the causal relationship between LDL-C (ABCG5, ABCG8, APOB, HMGCR, LDLR, NPC1L1 and PCSK9) and TG (LPL, APOC3 and PPARA) lowering targets and AF, as well as the mediating role of circulating inflammatory factors. We hypothesize that drugs lowering LDL-C and TG levels may indirectly reduce AF risk by dampening the inflammatory response. In this way, we hope to reveal the feasibility and effectiveness of lipid-lowering drugs as potential drug targets for AF, reveal the underlying biological mechanisms, and provide more precise therapeutic strategies for the prevention and treatment of AF.

2 Article types

Original Research

3 Materials and methods

3.1 Study design

In this study, single nucleotide polymorphisms (SNPs) from the GWAS data were used as instrumental variables (IVs) for

MR Analysis. The selection of SNPs for MR Analysis is based on three core assumptions (19): (1) SNPs must be strongly associated with the exposure variables; (2) SNPs should be independent of any potential confounders; and (3) SNPs influence the outcome solely through the exposure variables. This study was reported following the Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization (20, 21) (STROBE-MR). The specific process of this study is illustrated in Figure 1.

3.2 Genetic instruments for lipid-lowering drugs

In this study, we selected commonly used lipid-lowering drugs and the latest treatment methods, such as statins, ezetimibe, PCSK9 inhibitors, bile acid sequestrants, mipomersen, fibrates, and antisense oligonucleotides targeting apolipoprotein C-III (APOC3) mRNA. Utilizing the DrugBank database, we have identified the genes responsible for encoding the pharmacological targets of these drugs. These target genes can be further categorized into those that reduce LDL-C (such as LDLR, HMGCR, NPC1L1, PCSK9, APOB, ABCG5, and ABCG8) and those that reduce TG (including LPL, APOC3, and PPARA). LDL-C serum levels and TG serum levels are reliable downstream biomarkers of lipid-lowering drugs, so we simulated the effect of lipid-lowering drugs by obtaining SNPs within ± 100 kb of the drug target sites associated with LDL-C or TG levels to estimate the downstream effect of lipid-lowering drugs on AF risk.

Summary data on LDL-C (accession number: ieu-b-110), consisting of 440,546 Europeans and 12,321,875 SNPs, and summary data on TG (accession number: ieu-b-111), consisting of 441,016 Europeans and 12,321,875 SNPs, were obtained from the UK Biobank (UKBB). Richardson TG et al. (22) conducted a GWAS of circulating non-fasted lipoprotein lipid traits in the UKBB for low-density LDL-C, TG, and apolipoprotein B to identify lipid-associated SNPs. We first screened SNPs that were strongly associated with LDL-C or TG levels under the condition of $P < 5E-08$. Secondly, in order to ensure the independence of IVs, we excluded the interference of linkage disequilibrium (LD). For screening SNPs, $R^2 < 0.3$ was used as the criterion if more than three SNPs were identified. If fewer than three SNPs were obtained, $R^2 < 0.4$ was applied to ensure the MR Analysis's reliability. In addition, only SNPs with an effect allele frequency (EAF) > 0.01 were considered. Finally, in order to avoid the interference of potential confounding factors, LD trait tool was used to find and remove possible confounding factors, such as obesity, body mass index, smoking, hypertension, and diabetes (23).

3.3 Genetic instruments for circulating inflammatory factors

The GWAS data set for circulating inflammatory factors is available in the GWAS Catalog from a genome-wide protein quantitative trait locus study (accession number: GCST90274758

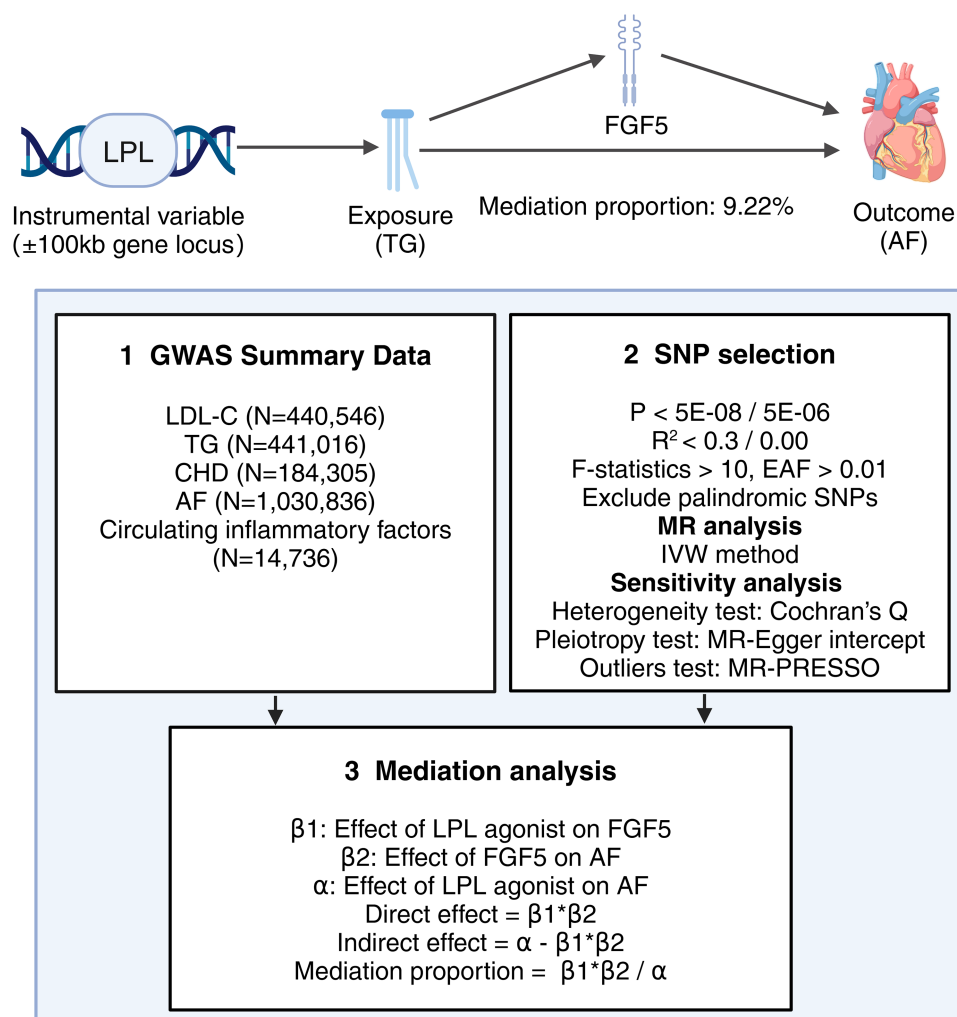


FIGURE 1
Overview of the research workflow employed in this study.

to GCST90274848). Zhao JH et al. (24) performed genome-wide pQTL mapping for 91 plasma proteins measured using the Olink Target Inflammation panel in 11 cohorts totaling 14,824 European-ancestry participants. To obtain a sufficient number of SNPs to ensure the reliability of the MR Analysis, we screened SNPs that were significantly associated with circulating inflammatory factors under the condition of $P < 5\text{E-}06$, and then excluded the interference from LD ($R^2 < 0.001$, $\text{KB} = 10,000$) to ensure the independence of IVs.

3.4 Source of results

The GWAS data for AF in this study are available on the IEU open GWAS database (accession number: ebi-a-GCST006414). Nielsen JB et al. (25) tested association between 34,740,186 genetic variants and AF, comparing a total of 60,620 cases and 970,216 controls of European ancestry from six contributing studies (HUNT, deCODE, MGI, DiscovEHR, UK Biobank, and the AFGen Consortium). As lipid-lowering drugs have been approved

for the treatment of coronary heart disease (CHD), CHD was selected as a positive control to validate our chosen lipid-lowering drug instrument in this study. The GWAS data for CHD were obtained from CARDIoGRAMplusC4D (accession number: ieu-a-7). Nikpay M et al. (26) assembled 60,801 cases and 123,504 controls from 48 studies for a GWAS meta-analysis of coronary artery disease. All the datasets included in this study were sourced from European populations to maintain demographic consistency.

3.5 Mediation analysis

First, we conducted separate assessments of the total causal effect of each of the 10 lipid-lowering drug targets on AF (α) and the causal effect of the lipid-lowering drug targets that were significantly associated with AF on circulating inflammatory factors (β_1). Second, we analyzed the causal relationship between circulating inflammatory factors that were significantly associated with lipid-lowering drugs and AF (β_2). In this MR Analysis, we excluded SNPs in the MR Analysis of lipid-lowering drug targets

and AF. Finally, we utilized the coefficient product method to calculate the indirect effect ($\beta_1 \times \beta_2$) and mediating proportion $[(\beta_1 \times \beta_2)/\alpha]$ of circulating inflammatory factors on the causal relationship between lipid-lowering drugs and AF.

3.6 Statistical analysis

Inverse variance weighted (IVW) was used as the main analysis method, and weighted median (WME) and MR Egger’s method were used for supplementary analysis. The strength of instrumental variables was evaluated using the F-statistic, with a value greater than 10 indicating no weak instrument bias (27). Heterogeneity was assessed using Cochran’s Q statistics based on IVW and MR Egger methods (28). In cases of heterogeneity, the inverse variance weighted multiplicative random effects (IVW-MRE) model was employed for MR Analysis (29).MR-Egger intercept test was used to detect pleiotropy, MR-PRESSO was used to identify and remove outliers, and leave-one-out sensitivity test was used to assess whether individual SNPs had a significant effect on the overall results. All statistical analyses were performed using R 4.3.2 and the R package (TwoSampleMR, VariantAnnotation, ieuGWAS, gwasglue, and MR-PRESSO). To correct for bias caused

by multiple comparisons, *P*-values were adjusted through Bonferroni correction (30).

4 Results

4.1 Positive control analysis

We identified causal relationships between various lipid-lowering drug targets and CHD, and as expected, the results of the IVW showed that, all 10 lipid-lowering drugs significantly reduced the risk of CHD [Bonferroni-corrected *P*-value threshold = 0.005 (0.05/10)] (Figure 2 and Supplementary Table S1).

4.2 MR analysis between lipid-lowering drugs and AF

The IVW results showed that LPL agonist had a significant effect on AF [Bonferroni-corrected *P*-value threshold = 0.005 (0.05/10)] (OR = 0.854, 95% CI: 0.816–0.894, *P* = 1.844E-11) (Supplementary Tables S2 and S3). However, there was no significant effect of other targets on AF (Figure 3).

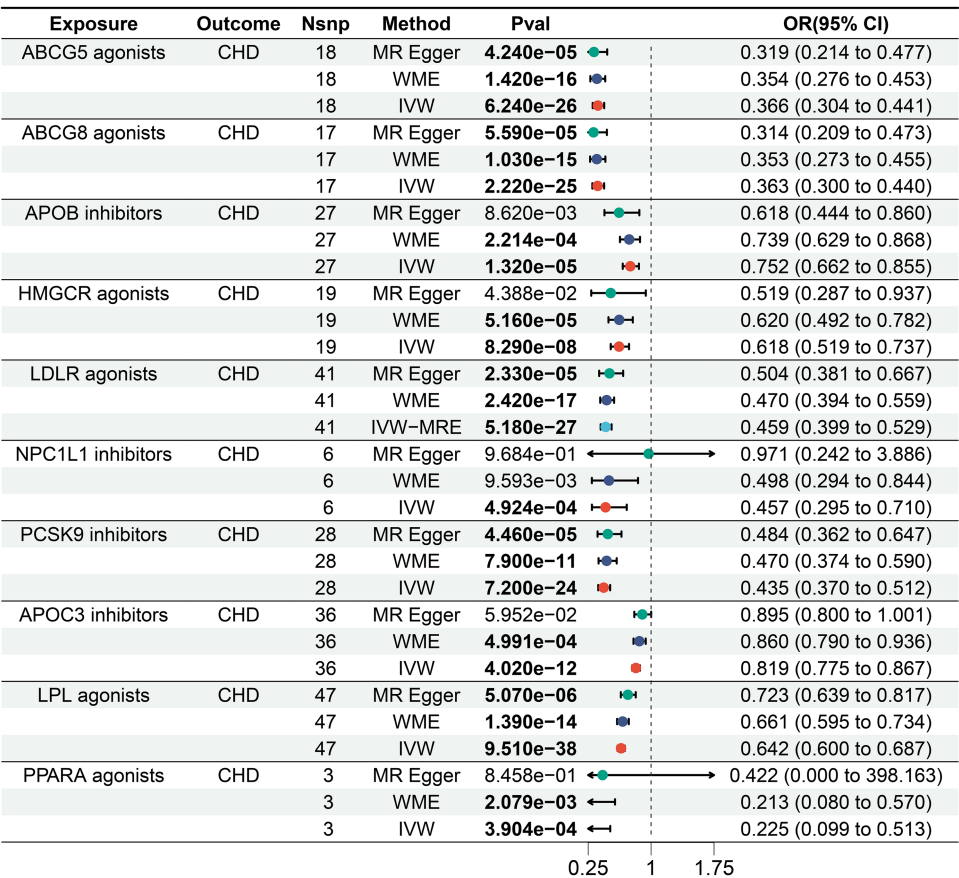


FIGURE 2 Forest plot of the results of the MR analysis between lipid-lowering drugs and coronary heart disease.

4.3 MR analysis between lipid-lowering drugs and circulating inflammatory factors

We assessed the impact of LPL agonist on 91 circulating inflammatory factors. According to IVW results, we observed a causal association between LPL agonist and reduced levels of six circulating inflammatory factors after Bonferroni correction [Bonferroni-corrected P -value threshold = $5.495\text{E-}04$ ($0.05/91$)] (Figure 4). Specifically, The results showed that LPL agonist was associated with decreased levels of Fibroblast growth factor (FGF) 19 (OR = 0.847, 95% CI = 0.777–0.924, P = $1.861\text{E-}04$), FGF5 (OR = 0.817, 95% CI = 0.745–0.896, P = $1.781\text{E-}05$), IL-6 (OR = 0.834, 95% CI = 0.765–0.909, P = $3.800\text{E-}05$), Matrix metalloproteinase-1 (MMP-1) (OR = 0.837, 95% CI = 0.764–0.918, P = $1.534\text{E-}05$), Oncostatin-M (OR = 0.836, 95% CI = 0.756–0.925, P = $5.092\text{E-}04$) and Tumor necrosis factor (TNF) (OR = 0.836, 95%CI = 0.760–0.921, P = $2.630\text{E-}04$) (Supplementary Tables S4 and 5).

4.4 MR analysis between circulating inflammatory factors and AF

Based on the IVW results, the MR analysis revealed a significant causal association between elevated FGF5 levels and an increased risk

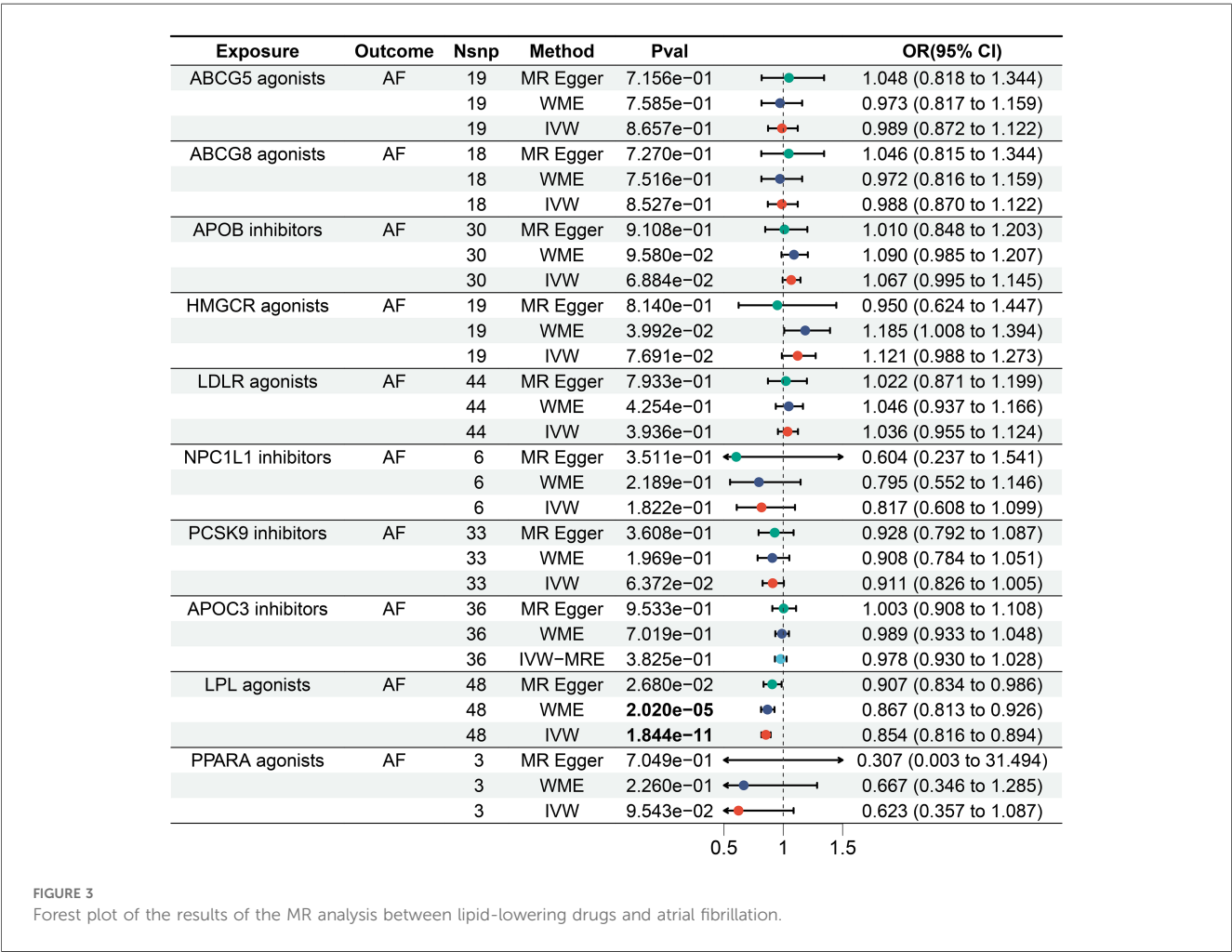
of AF [Bonferroni-corrected P -value threshold = $5.556\text{E-}03$ ($0.05/9$)] (OR = 1.075, 95% CI = 1.047–1.103, P = $6.436\text{E-}08$) among the six LPL agonist related circulating inflammatory factors (Figure 5). However, there was no evidence of a significant causal relationship between the other 5 circulating inflammatory factors and AF.

4.5 Mediating role of circulating inflammatory factors in the causal relationship between lipid-lowering drugs and AF

We further investigated the mediating role of FGF5 levels in the causal relationship between LPL agonist and AF. Our findings suggest that LPL agonist may reduce the risk of AF by lowering FGF5 levels. Using the product of coefficient method, we calculated that LPL agonist is associated with a 9.22% reduction in FGF5 levels related to AF risk.

4.6 Results of sensitivity analysis

The MR-Egger intercept test indicated no horizontal pleiotropy in any of the results in this study. The Cochran Q-test showed



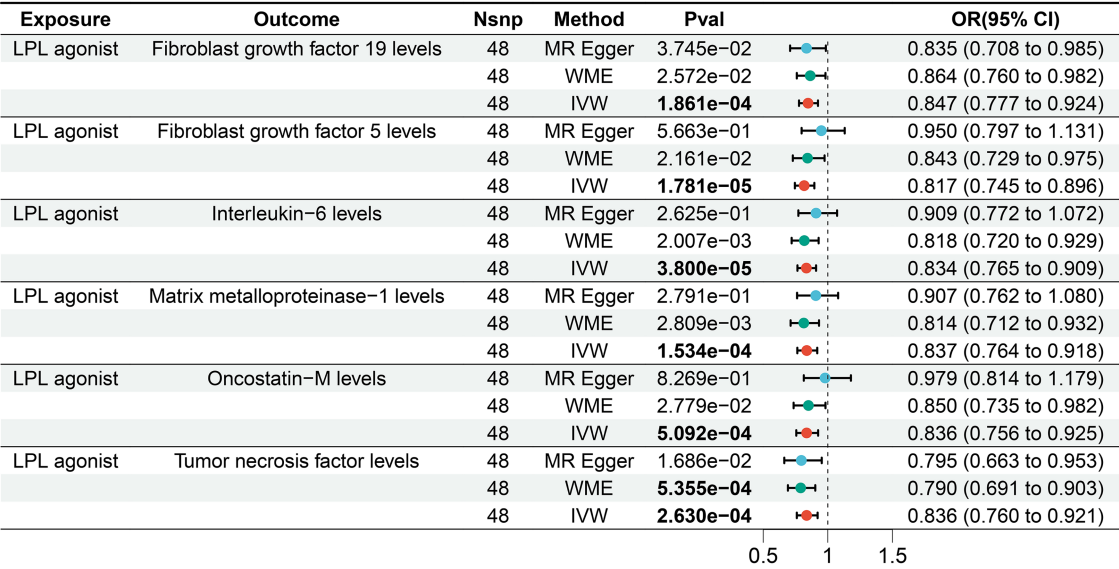


FIGURE 4
Forest plot of the results of the MR analysis between lipid-lowering drugs and circulating inflammatory factors.

heterogeneity in the MR Analysis between LDLR agonists and CHD, so we performed the MR Analysis using the IVW-MRE method to eliminate the bias caused by heterogeneity. In addition, an outlier (rs73015007) was identified in the MR Analysis between LDLR agonists and CHD. After removing this outlier, we repeated the MR Analysis to ensure result robustness. However, no heterogeneity or outliers were detected in the remaining MR Analyses (Supplementary Tables S7–S10). The results of leave-one-out method showed that there was no significant effect of individual SNP on the overall results in all the MR Analyses. In conclusion, the MR Results of this study are robust.

5 Discussion

In this study, we conducted a comprehensive exploration of the intricate relationship between LPL agonist, circulating inflammatory factors, and AF using the MR Method. The reliability of our findings was ensured through multiple sensitivity analyses and Bonferroni correction. Our study revealed a significant protective effect of LPL agonist against AF and highlighted the pivotal role of FGF5 in this process.

Through the analysis of the causal relationship between 10 lipid-lowering drug targets and AF, we discovered that LPL agonist exhibited a significant protective effect on AF. Subsequently, we conducted further investigation into the impact of LPL agonist on 91 circulating inflammatory factors. Our findings revealed that LPL agonist was significantly correlated with reduced levels of six inflammatory factors, including IL-6, TNF, and MMP-1, which was consistent with the conclusion that lipid-lowering drugs may have certain anti-inflammatory effects proposed in previous studies. LPL is an important lipid metabolic enzyme in the body, which can degrade TG in

Triglyceride rich Lipoproteins (TRLs) and release free fatty acids (FFA) for the body to use (31–34). LPL agonist is a class of drugs that can reduce blood lipid levels by activating lipoprotein lipase (LPL) and accelerating the hydrolysis of TRLs.

In recent years, the association between TRLs and inflammation has been extensively studied. Moreno-Vedia et al. (35) have shown that TRL concentration and composition have a significant effect on the subclinical inflammatory state of patients with lipid metabolism disorders. Cesena et al. (36) found different patterns of association between TRL subparticles and inflammatory markers through cross-sectional analysis of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) which supports the hypothesis that TRL may induce a low-grade inflammatory environment. A large number of previous studies have shown that inflammation plays an important role (37) in the occurrence and development of AF. Inflammation may increase the risk of AF by promoting atrial fibrosis, electrical remodeling, and causing endothelial dysfunction. Therefore, we suggest that LPL agonist may play a protective role in AF by accelerating the hydrolysis of TRLs, reducing the deposition of lipids in vascular endothelial cells, and reducing the activation and inflammatory response of endothelial cells.

However, conflicting evidence exists regarding the relationship between lipid levels and AF. A recent meta-analysis (38) found no significant correlation between TG levels and AF occurrence. This discrepancy may stem from the influence of age-related declines in TG levels or fluctuations due to dietary changes, which complicates the understanding of TG's long-term effect on AF. In contrast to simple blood lipid measurements, our study focuses on lipoprotein lipase (LPL) agonists, which dynamically regulate lipid metabolism and inflammation, offering a more comprehensive perspective on their potential protective role in AF. Therefore, while elevated TG levels may not be directly

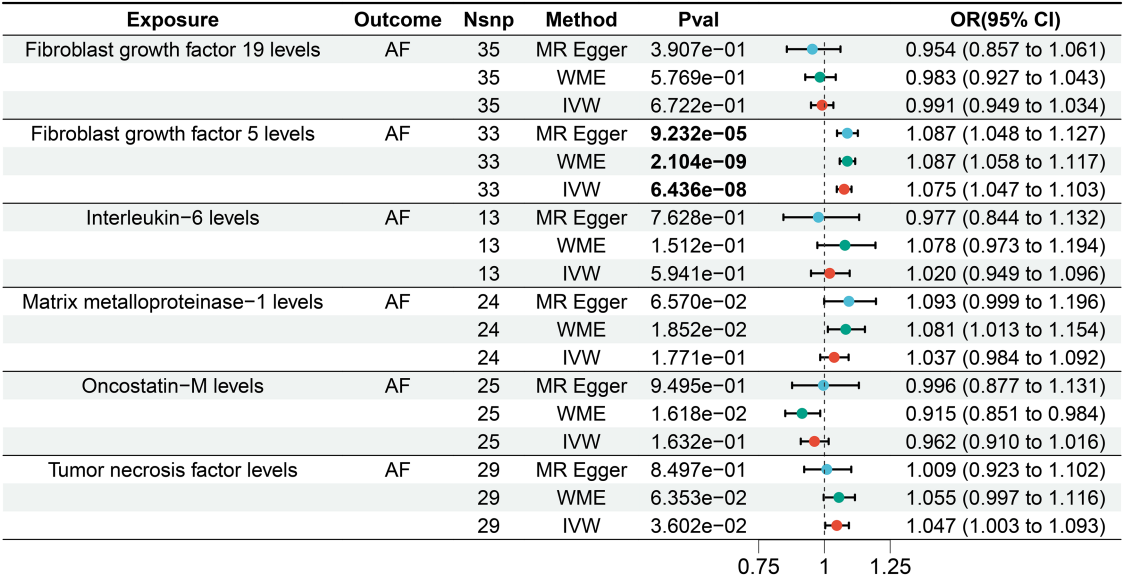


FIGURE 5 Forest plot of the results of the MR analysis between circulating inflammatory factors and atrial fibrillation.

linked to AF, LPL agonists might confer protective effects through mechanisms that extend beyond lipid levels alone.

Due to the intricate nature of the LPL regulation mechanism, as well as the challenge of developing high specificity and selectivity for the target and the complexity of clinical trials, current understanding of LPL activation as the core mechanism for drug effects is still in its developmental stage (39). In this study, we found the protective effect of LPL agonist on AF using drug-target MR Method, which provides a theoretical basis for larger-scale research of LPL agonist in the future.

FGF5 is a member of the FGF family, which is mainly involved in cell proliferation, differentiation, survival and tissue repair (40). Previous studies have found that FGF5 is mainly associated with cancer and hair growth (41–44). Recent studies have indicated that FGF5 also plays a significant role in cardiovascular conditions such as hypertension and coronary artery disease (CAD) (45–48). Vatner SF et al. (49) demonstrated that FGF5 has the ability to inhibit cell apoptosis, induce cardiomyocyte hypertrophy and proliferation, ultimately leading to an increase in myocardial mass and myocardial wall thickening. Additionally, Hu et al. (50) established a causal relationship between FGF5 and Cardiac Remodeling using MR method. In addition, FGF5 also plays an important role in promoting tissue fibrosis. Hiromi H et al. (51) discovered that FGF5 was implicated in the progression of liver fibrosis and suggested that FGF5 could potentially serve as a therapeutic target for liver fibrosis in non-alcoholic steatohepatitis. In the present study, we identified a significant causal relationship between elevated levels of FGF5 and an increased AF risk. While there is no direct evidence linking FGF5 to AF, our findings suggest that this causal relationship may be attributed to the ability of FGF5 to induce cardiomyocyte hypertrophy and promote myocardial fibrosis.

These effects ultimately lead to structural remodeling of the atrium, providing a potential mechanistic basis for the observed association (52, 53).

Through mediation analysis, we found that LPL agonist reduced the risk of AF by reducing the level of FGF5. The results of the mediation analysis indicated that changes in FGF5 levels accounted for 9.22% of the reduction in AF risk associated with LPL agonist treatment. This suggests that FGF5 plays a partial mediating role in the mechanism of action of LPL agonists in preventing AF. Previous studies have suggested that the protective effect of LPL agonists on AF may be linked to chronic inflammation and myocardial fibrosis, while FGF5 may increase the risk of AF through myocardial fibrosis and structural remodeling of the atrium. Therefore, it is possible that FGF5 mediates the causal relationship between LPL agonists and AF. Our study provides genetic evidence supporting the idea that FGF5 may mediate the protective effects of partial LPL agonists against AF. However, it is important to note that while our findings suggest a potential mediating association, further experimental studies are needed to confirm causality as well as to determine if other factors also play a role.

To the best of our knowledge, this is the first study to utilize MR analysis in examining the correlation between lipid-lowering drugs, circulating inflammatory factors, and AF in the general population. Our study provides new targets and strategies for the targeted treatment of AF, and points out the direction for future research. In terms of clinical implications, our findings suggest that LPL agonists could serve as novel therapeutic agents for AF prevention and management by targeting both lipid metabolism and inflammation. By reducing key inflammatory factors and influencing lipid dynamics, LPL agonists may address fundamental aspects of AF pathogenesis. Furthermore, identifying FGF5 as a

mediator offers a new therapeutic target, potentially allowing for more effective interventions to prevent atrial remodeling and fibrosis associated with AF. From a research perspective, our study underscores the value of integrating genetic association studies with drug development processes. Utilizing MR analysis provides genetic evidence that supports causal relationships, aiding in the prioritization of drug targets. This approach is consistent with recent frameworks that advocate for leveraging human genetics to identify druggable targets for AF (54).

At the same time, this study also has certain limitations. First, all the data in the study were from persons of European ancestry. This reduced bias due to ethnic and regional differences but also limited the generalizability of the findings to other ethnic groups. Second, although we used a variety of sensitivity analyses in our study, potential horizontal pleiotropy may still exist. Therefore, future studies should further explore the role of LPL agonist and FGF5 in different populations and clinical settings, and verify the potential for practical application of these biomarkers in the prevention and treatment of AF.

6 Conclusion

In conclusion, this study supports the genetically predicted association between LPL agonist, circulating inflammatory factors, and AF. Specifically, FGF5 levels mediate the protective effect of LPL agonist against AF. These findings provide genetic evidence for the mechanism by which LPL agonists reduce the risk of AF and may inform future mechanistic and clinical studies.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/[Supplementary Material](#).

Ethics statement

Ethical approval was not required for the studies involving humans because all data used in this study were obtained from publicly available databases; further ethical approval was not required. The studies were conducted in accordance with the local legislation and institutional requirements. The human samples used in this study were acquired from The datasets supporting this study are available from EMBL's European Bioinformatics Institute, GWAS Catalog and the UK Biobank database. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

GO: Writing – original draft, Writing – review & editing, Conceptualization, Methodology. YZ: Conceptualization, Writing – original draft. HC: Data curation, Writing – review & editing. KY: Methodology, Writing – original draft. ZQ: Methodology, Writing – original draft. YC: Formal Analysis, Writing – original draft. YY: Visualization, Writing – original draft. QC: Writing – review & editing, Methodology, Conceptualization, Visualization. XC: Funding acquisition, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fcvm.2024.1446610/full#supplementary-material>

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Transcatheter ablation of atrioventricular nodal reentry tachycardia in children and congenital heart disease in the era of 3D mapping

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Atrioventricular nodal reentrant tachycardia (AVNRT) is a common supraventricular tachycardia in children and congenital heart disease (CHD) patients. Nowadays, in large enough children, chronic treatment for symptomatic and recurrent AVNRT episodes relies on transcatheter ablation. Indeed, many three-dimensional (3D) mapping strategies and ablation techniques have been developed and it helped to increase success rates and to reduce complications. Therefore, this study aimed to perform an updated comprehensive review of the available literature regarding contemporary management of AVNRT in children. A literature search was performed using Google Scholar, PubMed, Springer, Ovid, and Science Direct. We found that in recent times many investigations have demonstrated that 3D mapping systems allow to localize more precisely the ablation substrate, with minimal use of fluoroscopy. The most frequently employed mapping strategies are the low-voltage bridge strategy together with the search for the SP potential and the Sinus Rhythm Propagation Map with the identification of areas of Wave Collision or Pivot Points. For transcatheter ablation in pediatric settings, radiofrequency (RF) ablation was first used in the 1990s, while cryoablation was introduced in 2003 and nowadays represents the most used energy for AVNRT ablation in this population. Indeed, its specific features, such as reversible cryomapping, cryoadhesion and the precision in lesion delivery, made this technique very appealing to decrease complications and fluoroscopy time. As regards AVNRT in CHD patients, it represents the third most common form of arrhythmia in children with CHD. However, in this subgroup ablation remains challenging and experience limited, since anatomy may be atypical and the areas of ablation less predictable or less accessible.

KEYWORDS

atrioventricular nodal reentry tachycardia, 3D mapping, transcatheter ablation, children, congenital heart disease

1 Introduction

Atrioventricular nodal reentrant tachycardia (AVNRT) is a common, regular, narrow complex QRS tachycardia in children, accounting for 13%–34% of supraventricular tachycardias (SVT) in this population (1–4). Its incidence increases with age, being extremely rare in infants younger than 2 years of age (1%–10% of SVT) and almost as

frequent as atrioventricular reentry tachycardia (AVRT) in females older than 12 years (up to 44% of SVT) (4–6). Pediatric patients present with various and often atypical symptoms, and the diagnosis is achieved through ECG and electrophysiology study (EPS) (7).

As for AVNRT in adults, the most common type of AVNRT uses the so-called slow nodal pathway (SP) as the anterograde limb of the reentrant circuit and the so-called fast pathway (FP) as the retrograde limb (“slow-fast” or typical AVNRT). More rarely, the reentry circuit is reversed (“fast-slow” AVNRT) or uses nodal pathways with “intermediate” electrophysiological properties; all these tachycardias are referred to as atypical AVNRT (7–11).

In recent years, three-dimensional (3D) mapping systems allowed to localize more precisely the SP, with minimal use of fluoroscopy. In addition, new ablation strategies focused on improving success rates and reducing complications. In this article, we provide an updated summary of AVNRT mapping and ablation in pediatric and CHD patients based on an extensive review of the literature.

2 Anatomy and histology of the nodal conduction system

In the era of 3D mapping and transcatheter (TC) ablation, appropriate knowledge of the atrioventricular node (AVN)

anatomy has become imperative for appropriate invasive treatment of AVNRT.

Morphologically, the AVN can be subdivided into three zones: the lower nodal bundle (LNB), the compact node (CN), and the inferior extensions (INE), namely the right inferior nodal extension (RINE) and the left inferior nodal extension (LINE) (Figure 1). Moreover, in the area between the AVN and the adjacent working myocardium, special cells called “transitional cells” surround the proximal margins of the CN and, more extensively, the inferior extensions towards the ostium of the coronary sinus and Eustachian ridge. These cells exhibit an intermediate morphology between the cells of the CN and those of the working myocardium (12–16).

Interestingly, the composition of the nodal structures has been reported to change with growth, such that the modifications already are notable in pediatric patients. Indeed, fibrofatty tissue gradually increases in the CN, creating a looser texture, and the gradual expansion of the muscular AV septum determines a CN more or less “glued” to the right crest of the septum with a more fusiform shape. Moreover, the RINE and LINE become significantly longer in young adults than in infants; therefore, their position changes from relatively close together in very young children to quite distant in adolescents and young adults. In addition, the intensity of contacts between the transitional cells and the AVN diminishes considerably, especially in the anterior parts. This, together with the modifications in length and relationships of the INE, may “set the scene” for AVNRT

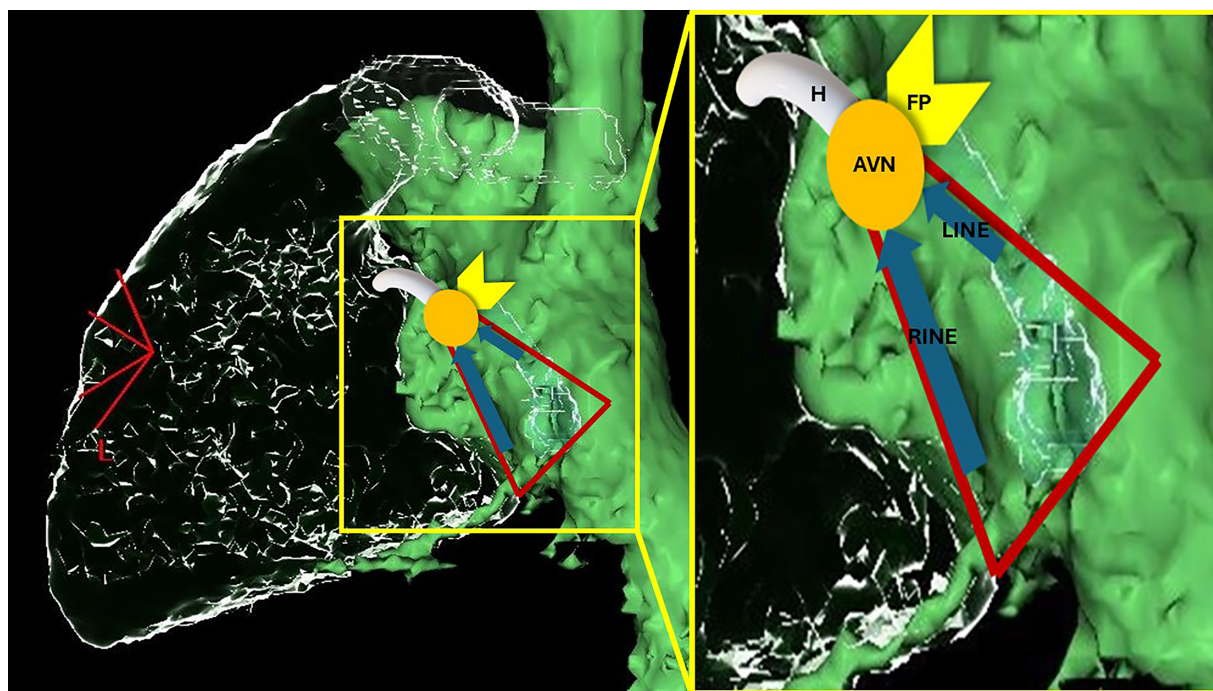


FIGURE 1

Schematic representation of AV nodal structures superimposed on a computed-tomography reconstruction of the right cardiac chambers from a left lateral view (the green chamber is a reconstruction of right atrium, inferior and superior vena cava; the glass structures represent right ventricle, pulmonary artery and coronary sinus). The triangle of Koch is marked in red. RINE, right inferior nodal extension; LINE, left inferior nodal extension; AVN, atrioventricular node; FP, fast pathway; H, His.

and could explain why this condition is more frequent in young adults than in infants. Indeed, it is thought that with increasing age, the non-uniform, anisotropic activation in the Koch's triangle (KT) increases, thus enhancing the probability of reentry in case of appropriately timed extrasystoles (13–15, 17).

After puberty and especially in adulthood, the LNB occupies the anterior portion of the AVN and is composed of large cells oriented parallel to each other, whilst the CN is an oval structure composed of smaller, densely packed, irregularly shaped cells located at the apex of KT, with distinct cellular histology, and fewer intercellular connections. As regards its INE, the RINE runs close to the annular attachment of the septal tricuspid valve leaflet, extends to the level of the ostium of the coronary sinus, and is connected anteriorly with both the compact AVN and the LNB. The LINE is positioned superiorly to the RINE at the level of the roof of the CS and diverts leftward toward the central fibrous body and the mitral annulus. The LINE is usually much shorter than the RINE, and the 2 extensions merge proximally to form the base of the compact AVN. Of note, in some individuals, the LINE is not present (14, 15, 17–19).

According to experimental, electrophysiology and anatomical studies, the INE, particularly the RINE and its surrounding transitional cells, have been perceived as the substrate of the slow pathway (SP) in humans, as discussed in the following chapter (12, 17, 19).

In the approach of pediatric patients, it has also to be highlighted that the length of KT is correlated with age, body surface area and the dimensions of the tricuspid valve (while in adults it poorly correlates with these parameters). For example, KT has been reported to be, on average, 7.8 mm in patients less than one year of age, 11.1–15.6 mm for BSA 0.8 m², 17.9 mm in adolescents aged >12 (13, 20, 21).

Congenital heart disease (CHD) patients may present with AVNRT at any age and more frequently when pressure or volume overload of the right heart exists, probably because of cellular electrophysiological alterations and intercellular fibrosis with consequent anisotropic conduction in the nodal/peri-nodal tissue (22, 23). In addition, in children affected by CHD, the AVN location is less predictable, and landmarks for KT can be distorted in some conditions (24).

3 Clinical presentation and ECG features

Pediatric patients suffering from AVNRT may present with palpitations, either at rest or with faster than normal heart rate during exercise, dizziness, syncope, chest pain, shortness of breath, sensation of pulsations in the throat. Infants and non-verbal toddlers may exhibit signs of poor feeding, profuse sweating with feeding, fast breathing and/or they can appear generally ill. Signs/symptoms usually have sudden onset and termination and can be brief but can also last for several hours (7, 9, 10).

Baseline ECG is usually normal (Figure 2A). During tachycardia, most often it shows a regular, narrow complex QRS

tachycardia; heart rate may be higher than 250 bpm, especially in younger children, but the heart rate strongly depends on the adrenergic tone (9, 10, 25). Rarely, the tachycardia may present with functional bundle branch block (as a wide QRS complex tachycardia) or AV conduction may be blocked in a 2:1 ratio (7, 11, 26) (Figure 2D).

In AVNRT, typically the retrograde P waves are hidden in the terminal portion of the QRS. However, in the typical form, sometimes they create a pseudo-r' in lead V1 or a pseudo-s wave in the inferior leads. In these cases, the RP interval is very short, less than 70 ms; therefore, typical AVNRT is classified as a short-RP tachycardia. In atypical forms, the P waves are visible at the end of or just after the T waves (long RP tachycardia) and have a negative polarity in the inferior leads, thus mimicking atrial tachycardias arising in the posteroseptal region or AVRT mediated by posteroseptal accessory pathways (8, 10, 11, 25).

There are no specific triggers for AVNRT; nonetheless, it is often associated with increased adrenergic tone. It is common for children to have their first (and subsequent) episodes of AVNRT during sporting events. Unfortunately, once a patient has been diagnosed with AVNRT there is a high recurrence rate, affecting the quality of life. On the other hand, episodes of AVNRT are usually self-limiting and do not result in tachycardia-induced cardiomyopathy (8–10, 25).

4 Electrophysiological properties

Several forms of AVNRT and possible circuits have been described. However, mapping and ablation strategies in children largely overlap and may differ slightly only between typical and atypical AVNRT (VA <60–70 ms and VA >60–70 ms, respectively) (27, 28).

The diagnosis of AVNRT in the electrophysiology (EP) lab may be slightly less obvious in children than in adults. Indeed, it usually relies on:

- The evidence of dual AVN physiology. During programmed atrial stimulation, the finding of an “AH jump”, that is a ≥ 50 ms increase in A2-H2 time with a 10 ms decrement in A1-A2 paced interval. During decremental atrial stimulation, a PR interval greater than or equal to RR (“Kay sign”) (Figure 2B).
- SVT features: VA relationship with V = A, VA <70 ms, concentric atrial activation (in typical forms).
- Responses to pacing maneuvers: “AH response” to ventricular overdrive pacing; a post-pacing interval minus tachycardia cycle length (PPI–TCL) following entrainment from the RV apex of more than 115 ms; an absolute “preexcitation index” greater than 100 ms (11, 27, 29). Importantly, no single pacing maneuver is 100% sensitive/specific for certain SVT (for instance, false positive ventricular pacing maneuver can be seen with a bystander, concealed nodo-fascicular/nodo-ventricular accessory pathway in a case of AVNRT) (30); however, a more detailed description of diagnostic pacing maneuvers goes beyond the purpose of this review and is presented elsewhere.

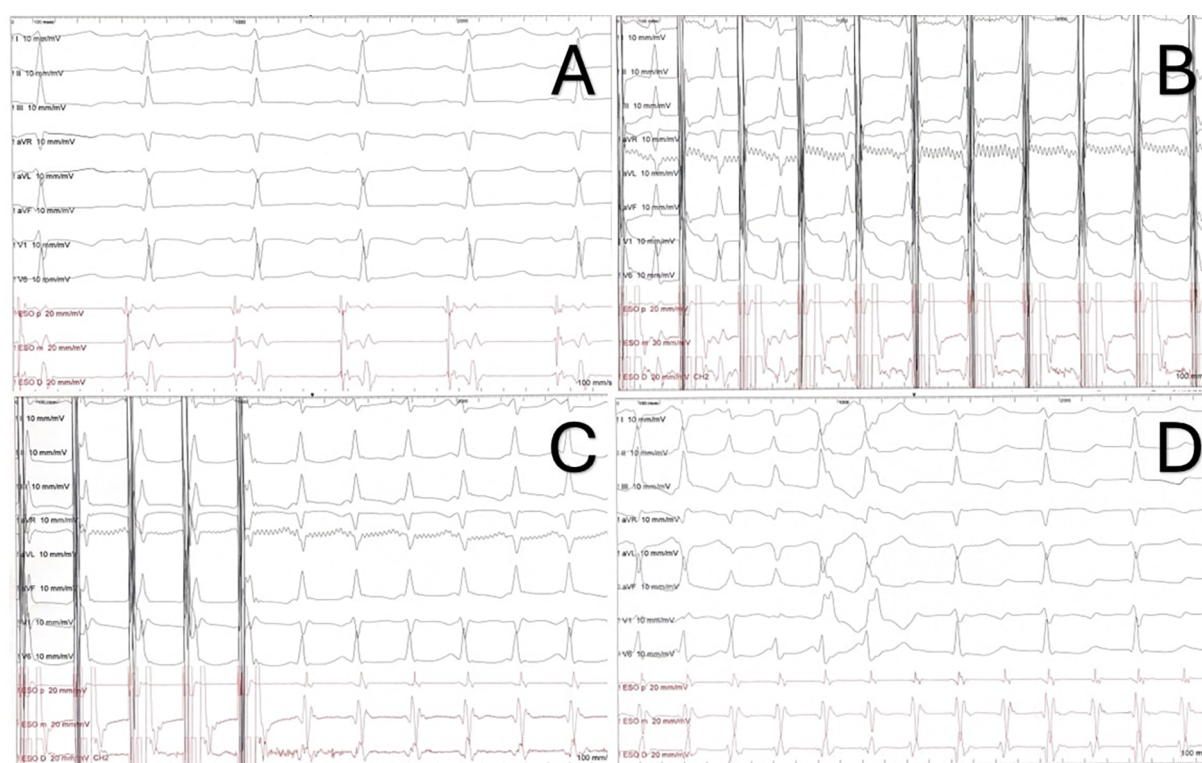


FIGURE 2

ECG and electrophysiology properties of AVNRT. (A) ECG and transesophageal electrograms in sinus rhythm. (B) Decremental atrial stimulation showing a Kay sign. (C) Induction of typical AVNRT through decremental atrial stimulation. Note the short RP (and VA) with pseudo-r' in lead V1. (D) Same patient from the recordings in panel (A–C). 1:1 AV conduction in the first part of the strip, followed by intraventricular conduction with right bundle branch block (two beats) and 2:1 AV conduction.

However, in the pediatric setting, the clinical tachycardia may not be inducible during the EP study, because general anesthesia is usually required (especially in younger children) and it diminishes overall tachyarrhythmias inducibility (31). Moreover, the AH jump and the Kay sign are less common than in adults (26, 27, 32–34). In detail, an AH jump is reported to be present in 42%–64% of pediatric AVNRT patients vs. 30% of pediatric patients without AVNRT; the maximum AH achieved is overall longer but with a large overlap between AVNRT and non-AVNRT children; a Kay sign is present in almost 2/3 of AVNRT patients vs. a minority of controls (26, 33, 35, 36). In fact, due to a more rapid nodal conduction in children, a 35–40 ms jump or a discontinuity in A2-H2 time is considered enough by some EP labs to establish the diagnosis of dual AVN physiology (25).

Additionally, in children a minimally invasive EP study can be obtained by transesophageal atrial pacing (TAP, Figure 2). Over the years, it has proven to be a highly accurate in diagnosing and characterizing various SVT in pediatric patients (37–40). Indeed, through atrial stimulation it is possible to study the AV conduction and to induce SVTs. Furthermore, TAP can be helpful in differential diagnosis of these tachycardias: in typical AVNRT, the VA interval <60–70 ms, with a P wave in lead V1 either not discernible or negative/biphasic and simultaneous with the atrial EGM (Figure 2C); in atypical AVNRT the VA interval

>60–70 ms, the P wave is positive in D1 and the P wave in V1 occurs before esophageal atrial EGM (28, 41, 42).

5 Mapping strategies

In the recent years, mapping strategies for AVNRT in pediatric patients have evolved to a fluoroscopy approach using 3D mapping systems (43–45). Even though only one recent trial (46) focused on direct comparison of 3D mapping vs. conventional fluoroscopic approach in children, data suggest that safety/efficacy of AVNRT ablation have improved in the 3D mapping era. Indeed, with 3D mapping systems almost all studies report 100% acute success rate and very low recurrences; moreover, permanent AV block was never described, even when RF was used (see Table 1). On the other hand, a meta-analysis on studies published before 2014 revealed that the mean acute procedural failure rate was 3.1% for cryoablation and 2.2% for RF ablation, and the mid-term failure (>2 months) was 9.7% for cryoablation and 3.8% for RF ablation; in addition, permanent AV block incidence was 0.75% for fluoroscopic RF ablation (57).

All strategies described in children rely on electro-anatomical maps of the KT area during sinus activation and the direct recording of SP potentials (43, 46, 49–58).

TABLE 1 Outcomes of transcatheter ablation in the era of 3D mapping systems.

Author	Journal	Year	Patients number	Age	Mapping strategy	Ablation energy	Acute success	Recurrence
Malloy (47)	Pediatr Cardiol	2014	28	15	LVB	CRYO	100%	14.2%
Bearl (48)	C Heart Dis.	2015	28	15.3	LVB	CRYO (first) + RF	96%	3.5%
Reddy (46)	HR	2017	71	14.3	LVB	CRYO	98.5%	0
Drago (49)	Europace	2018	35	12.1	LVB + SP potential	CRYO	100%	0
Drago (50)	Europace	2020	184	13	LVB + SP potential	CRYO	99.2%	2.7%
Drago (51)	JICE	2021	21	13	LVB (HD grid)	CRYO	100%	0
Drago (43)	PACE	2023	14	6.5	LVB + SP potential	CRYO	100%	0
Van Aartsen (52)	JICRMM	2017	39	15	Wave collision	CRYO	100%	2.8%
Fogarty (53)	JICRMM	2023	52	15	Wave collision	CRYO	-	-
Tseng (54)	HR	2023	36	16.5	Wave collision + LVB	CRYO	100%	5.6%
O’Leary (55)	JICE	2023	13	15.7	OT pivot point LVB Peak f>340 Hz	Random RF + CRYO	100%	7.6%
Howard (56)	JCE	2022	46	14	RIPPLE MAP	CRYO	100%	0
Total							99.2%	3.3%

Indeed, for both typical and atypical AVNRT, the ablation target is the SP. In this regard, Jackman and Haissaguerre first described the characteristics of atrial electrogram of SP in patients with AVNRT (59, 60). The “Jackman potential” (JP) (59, 61) is characterized by a low-frequency, low-amplitude component followed by a large-amplitude, high-frequency component (“hump and spike” pattern). The “Haissaguerre potential” (HP) (60) is a slow, hump, rounded potentials at the mid or posterior septum, anterior to the coronary sinus ostium, usually at two-thirds anterior-one-third posterior of the area between the His bundle and the coronary sinus ostium. This potential is more anterior in the right atrial septum compared to the JP, where the A:V ratio is approximately 0.7–0.8.

In his work, Jackman et al. explained the conduction properties of the SP in patients who had retrograde conduction over this pathway. Selective retrograde conduction over the SP was obtained by inducing either an atypical AVNRT or single echo beats that used the SP for retrograde conduction or by techniques of ventricular pacing that resulted in retrograde block in the FP. The earliest atrial activation during such conduction was recorded and located by mapping the right atrial septum and the coronary sinus. The sites of earliest atrial activation during retrograde SP conduction were located in the posterior septum, near the coronary sinus ostium. As mentioned, EGMs at these sites in SR showed a small atrial potential with the “hump and spike” feature and a large ventricular potential. The high-frequency atrial component generally has a late timing during sinus rhythm, while it represents the first retrograde atrial potential during fast-slow AVNRT. This potential was used to identify the presumed atrial insertion of the SP, and thus, as an ablation target in Jackman’s study.

The authors also suggested the presence of either multiple atrial insertions of the SP or multiple SPs in some patients since they sometimes observed that conduction over the SP was affected by energy delivered at two to four different sites.

In contrast to the SP location, they also provided evidence that the atrial insertion of the FP is usually located in the anterior septum, close to the His bundle.

Similarly, Haissaguerre et al. attempted to map the FP and the SP in patients with AVNRT. They recorded slow, hump, rounded potentials at the mid or posterior septum, anterior to the coronary sinus ostium, usually at two-thirds anterior-one-third posterior of the area between the His bundle and the coronary sinus ostium. In addition, they described that these potentials show a typical response to increasing atrial rates: a strong decline in amplitude and slope, an increase in duration, and a separation from preceding atrial potentials until the disappearance of the EGM.

Haisaguerre et al. usually performed ablation at a site where these hump-like potentials were preceded by spiky atrial EGM, which is more anterior in the right atrial septum compared to the JP, where the A:V ratio was approximately 0.7–0.8.

In the following years, hybrid EGMs with characteristics of both these signals, recorded in slightly different locations within the KT, were reported, mainly in adults (61, 62). However, many studies in the following years targeted the SP potential in the mid/posterior part of the KT, where a JP could be registered (44, 49, 51, 63–65).

Other studies, using optical mapping, showed that the presence of two distinct components of the local atrial EGM could possibly be explained by two different mechanism: (1) rounded, low-amplitude slow potentials correlate with the activation of the transitional and/or nodal cells in the context of INE, whereas relatively sharp spiky potentials may represent the insertion of the atrial myocardium into the SP atrio-nodal interface; (2) in the transmural re-entrant circuit, the sharp potential would represent the superficial atrial/transitional cells at the perinodal interface, whereas the low-amplitude slow potentials would correspond to the deeper cells of the INE itself (66–68).

5.1 Low-voltage bridge (LVB) strategy

All these findings suggested that the nodal/peri-nodal structures implied in the re-entrant circuit could be visualized

during 3D mapping. This is the basal concept of the so-called LVB strategy in mapping and ablation of SP, where the LVB is thought to be the direct visualization of the SP in the area of KT using voltage gradient mapping.

Indeed, after a 3D reconstruction of the endocardial geometry of the right atrium, mapping the voltage of the area of Koch's Triangle, AVN appears as a low-voltage area at the anterior superior tricuspid annulus in the expected anatomic position and the SP associated LVB is observed to connect the high-voltage region at the CS ostium to the AV nodal region. In the first study by Bailin (58), which enrolled mostly adults, 90% of the patients had a discrete LVB that connected the high-voltage region of the coronary sinus ostium to the high-voltage region of the AV node/His. These discrete connections were defined as type I LVB connections. In a minority of patients, the SP-associated LVB had a narrower area and was labelled as type II LVB.

The evidence that the LVB, located within the Koch's Triangle, represented the SP was supported by the following observations: (1) mapping within KT results in a loss of LVB when the SP refractory period is reached, (2) the lack of AVNRT inducibility following successful ablation is correlated with the disappearance of LVB connections, and (3) persistence of an isolated AVN echo beat is associated with incomplete LVB ablation or the presence of a second, separate, and distinct LVB.

The advantage of this novel ablation approach is the ability to visualize the SP within the KT and provide a definitive endpoint for ablation. This can reduce or eliminate the risk of iatrogenic AVB, as the catheter is placed on the LVB rather than on an empirical anatomical location or a location with a characteristic EGM.

Malloy (47) and then Bearl et al. (48) first validated the presence of LVB in children with AVNRT. In these studies, LVB strategy was found to reduce the procedural time, but it needed a learning curve and an "idealization" of the voltage map (increasing high- and low-voltage parameters) in patients for whom a LVB is not immediately obvious. So, in the Bearl's study, the ideal voltage range for each patient stratified by age or weight was reported.

Drago et al. later described a 3D mapping strategy using LVB slightly different from the others. Indeed, it takes into account the presence of the so called "hump and spike" potential to confirm the site of SP associated LVB (44, 49, 51) (Figure 3).

In their work, 3D mapping is achieved through the EnSite mapping systemTM (Abbott Medical) and usually a deflectable quadripolar (2-5-2 mm) catheter maintained as parallel as possible to the endocardial surface.

After performing the voltage mapping of the right atrium (RA), a very high-density voltage map is created for the interatrial septum (IAS) within the KT. Point collection of at least 130–150 points within the KT is performed, whenever feasible. Interpolation is set at 7 mm, and the interior/exterior projection at 7 mm.

The voltage color bar is then individually adjusted for each patient to highlight a LVB, if present, starting from a voltage range of 0.1–2 mV. Voltage data below the lowest value are shown as grey, whilst those above the upper limit as purple. The values between the two thresholds are displayed as green, yellow, and red. Both high- and low-voltage values are modified until a

voltage bridge becomes evident. This adjustment is necessary because of voltage variability in each patient.

Once substrate mapping of the IAS and KT is completed, the width of the voltage color bar (color low and high) is reduced as much as possible (usual range 0.1–1 mV) in order to obtain the most accurate electro-anatomical delimitation of the LVB defined as an area of low voltage, along the base of the KT, that protrudes into the KT connecting high-voltage areas of tissue (Figure 3A). Then, the color bar range (color low and high) is expanded again to highlight those previously identified areas with intermediate voltage, branching off from the LVB area, which could be involved in the slow conduction (Figures 3B,C).

LVBs identified are classified as follows: (1) a type I LVB (a clear, rather large area of low voltage between the CS ostium and the AV node with the base on the edge of the tricuspid annulus) or (2) a type II LVB (a narrow and small area of low voltage between adjacent normal-voltage regions with the base on the edge of the tricuspid annulus). LVB are generally detected with a voltage ranging from 0.12 ± 0.2 to 1.13 ± 0.5 mV.

During voltage mapping the SP potential is searched and its position is analyzed in relation to the area of the LVB. Using this electrophysiologically guided LVB strategy the SP potential is searched to confirm the exact site of LVB in the area of KT.

Using this mapping technique in children with any type of AVNRT, at least one LVB can be found in about 90% of the patients and two LVBs in the others with a higher prevalence of type I LVB in comparison with type II (60 vs. 40%). Interestingly, in atypical AVNRT, Type II seems to be more prevalent than type I, and in children having both types of AVNRT, two LVBs can be found in a higher proportion compared to those with only typical AVNRT. The SP associated double potential can be within the LVB in all children.

In the first study by Drago et al. (49) using this methodology, the new strategy of AVNRT mapping with a combination of 3D mapping (LVB) and electrophysiologically guided mapping (search for JP) ensured 100% mid-term success (1-year FUP).

Results were later confirmed on a large cohort of children (51), with acute procedural success of 99.2% and overall recurrence rate of 2.7%. In this study, type II LVB was found more frequently in children with atypical AVNRT and the presence of two LVBs was found to be much more frequent in patients with both typical and atypical re-entry. In addition, in patients with atypical AVNRT and more than one LVB, there was an increased recurrence rate during mid-term follow-up, suggesting that complex substrates can be more arrhythmogenic. Those results are similar to the findings of a North American multicenter pediatric study, in which the LVB cryoablation strategy was compared with the conventional strategy, showing a similar short-term success rate (LVB 98.5% vs. control 92%) but a considerably lower recurrence rate (LVB 0% vs. control 11%, $P = 0.006$) (46).

However, some authors reported that: (1) the LVB strategy is not so specific to children with AVNRT, and (2) SP potential seems to offer the highest combination of sensitivity and specificity (0.73 and 0.77, respectively) as a marker of AVNRT even in comparison to the others electrophysiological AVNRT characteristics (AH or HA jumps, echo beat, etc.) (69). Actually,

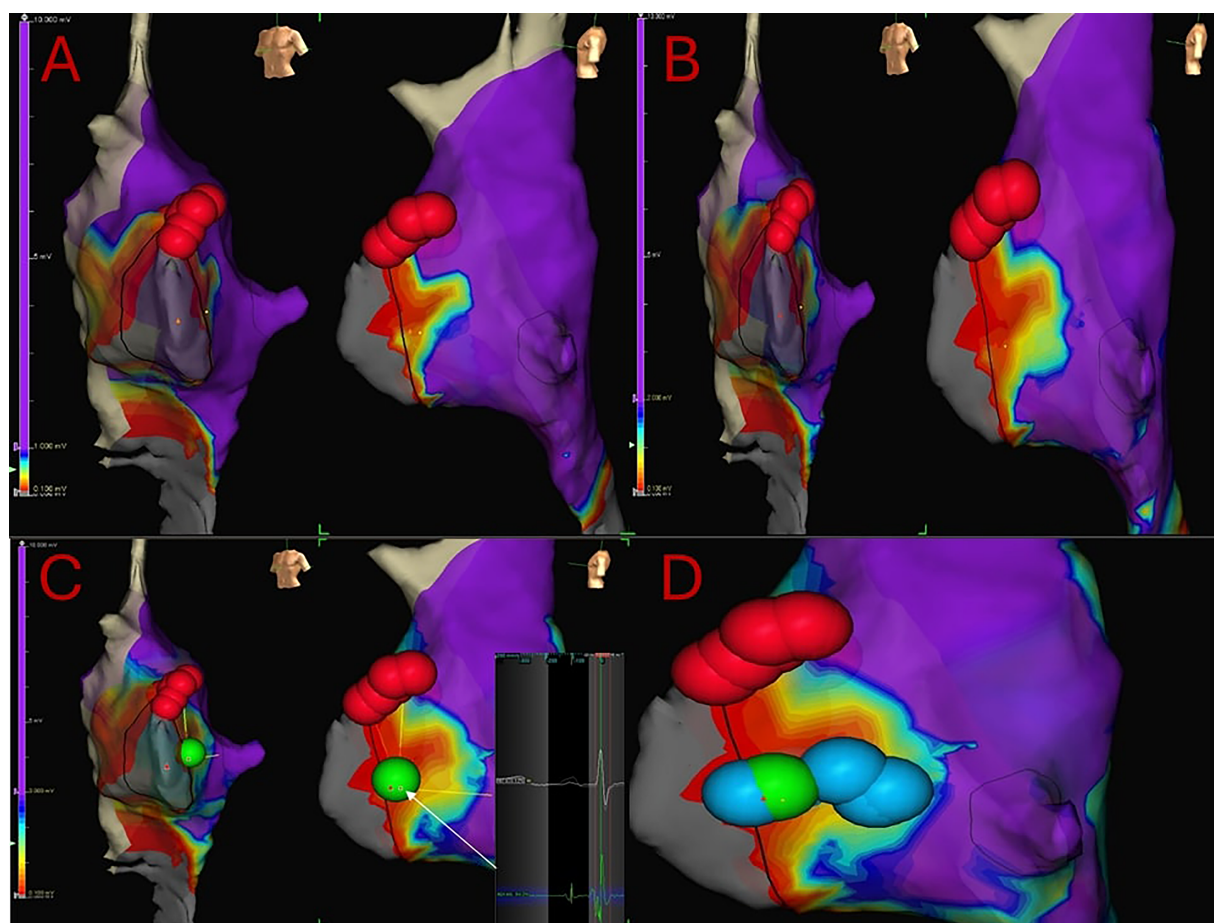


FIGURE 3

7 years-old, 24 kg girl suffering from both typical and atypical AVNRT refractory to medical therapy. Electrophysiologically guided low-voltage bridge (LVB) strategy, through 3D mapping of the Koch's triangle and the search for the typical "hump and spike" electrograms. Subsequent "linear lesion" cryoablation. (A) 3D mapping of the Koch's triangle; voltage bar range of 0.1–1 mV. A type 1 LVb is immediately visible. Red dots: His location. (B) Expanding voltage bar range to 0.1–2 mV, an even larger LVb is evident. (C) Voltage bar range to 0.1–3 mV. First and successful cryoablation (green dot) delivered in the exact location where the hump and spike electrograms were detected. (D) Due to the presence of residual nodal echo beats, a linear lesion cryoablation is delivered in the Koch's triangle to cover the entire LVb.

these data highlight the validity of the approach by Drago et al., that uses voltage gradient mapping together with the search of the SP potential.

Notably, mapping with a quadripolar deflectable catheter can be "difficult, operator-dependent and time-consuming". To solve this problem a multi-polar HD multipolar mapping catheter can be used (44, 50). In this way, HD mapping becomes faster, with higher spatial resolution and definition.

HD voltage mapping with HD GridTM multipolar catheter can the catheter can collect four times the number of points in half the time in comparison with conventional quadripolar 3D mapping. Moreover, in some patients, at the setting of the voltage color bar with which LVbs are clearly visible in the HD mapping, these latter are not visible in conventional mapping. Unfortunately, but rarely, HD mapping can be somewhat traumatic and children, especially the small ones, can experience transient iatrogenic block (44).

Regarding small children (<25 Kgs) (43, 63), LVb, always associated with the peculiar SP EGM, can be clearly visualized using the same voltage range as that one used in older pediatric

population and appeared more defined probably due to the absence of acquired low voltage areas in these very young patients. Especially in this population of patients, after the voltage mapping of KT, if the voltage color bar is completely opened, it can be visualized a definite LVb coming from the area of CS ostium to the area of AVN, in which it is possible to appreciate the JP in the proximal part and the HP in the even more proximal part very close the area of AVN. Then, reducing the voltage range as much as possible to obtain the most accurate electro-anatomical delimitation, it is possible to see that the LVb, as defined above, represents the proximal zone where the JP is present.

5.2 Sinus rhythm propagation mapping

Another described strategy for 3D mapping of the SP is the so-called Sinus Rhythm Propagation Mapping with the identification of Wave Collision or Pivot Point (Figure 4).

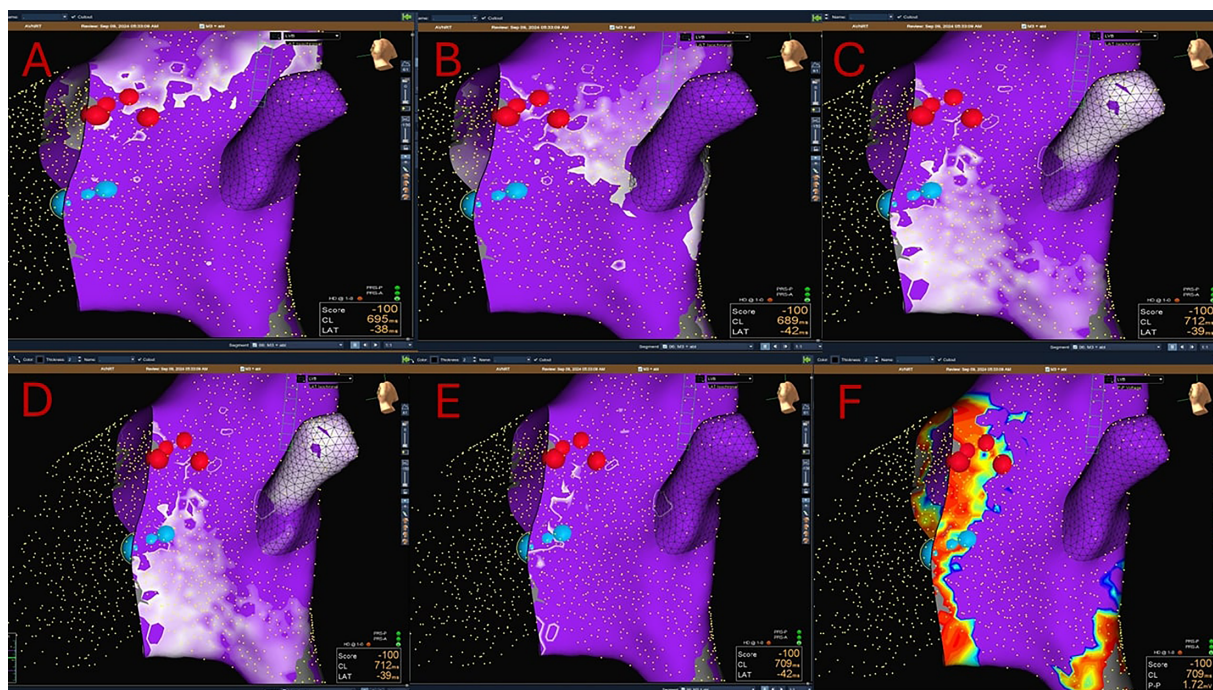


FIGURE 4

A combined Sinus rhythm propagation mapping and low-voltage bridge (LVB) strategy to guide cryoablation in AVNRT (red dots: His location; blue dots: cryoablation). The wavefront travelling in the inferior-superior direction (via slow pathway) is seen pivoting in the mid-posterior Koch's triangle and colliding with the wavefront moving in the superior-inferior direction (via fast pathway). In the area of collision, a type 2 LVB is identified. Successful cryoablation is performed in this site.

Sinus propagation is performed by creating a map of the atrial impulse in the sinus rhythm. Maps are created using a steerable diagnostic catheter with focused data collection within the KT and excluding from analysis ectopic beats. All 3D mapping systems (i.e., EnSite mapping systemTM by Abbott Medical, CARTOTM 3 by Biosense Webster Inc, Rhythmia HDxTM by Boston Scientific) can be used (52, 53, 61).

Sinus impulse in AVNRT patients typically splits in two wavefronts that reach separately the area of the KT. One wavefront moves superiorly around the ostium of the SVC and the other along the lateral wall toward the crista terminalis. Then, the two wave fronts enter in the KT moving in opposite directions: one, entering KT from the superior-inferior direction (via the fast pathway), proceeds anterogradely by activating the His bundle (Figure 4A) and retrogradely (superior-inferior direction), colliding with the wavefront coming from the inferior-superior direction (via the SP) (Figures 4B–D).

The area of collision correlates with the location of the SP (52, 53) (Figure 4E). The reason of this is still unclear and it is most likely a surrogate marker.

The *wave collision point* occurs in the mid or posterior-septal portion of the KT, where a SP potential is recorded in most patients. In addition, a marked conduction delay and fractionated, low amplitude potentials are present in this area (52–70).

The presence of *pivot points* is usually found in electroanatomic activation maps of the KT (displaying activation vectors

superimposed on standard isochronal local activation maps). It is defined as a marked change in activation direction, in the area of presumed collision of the FP and the SP. Remarkably, after pivoting, the vectors move back to the AV node (55, 70).

Fogarty et al. (53) with the wave collision mapping strategy reported a reduction in the median number of ablations needed to achieve SP modification, but no significant difference in the total number of ablations and longer total procedural times.

Since the LVB and the Sinus Rhythm Propagation Mapping techniques are not mutually exclusive, some authors reported their combined use for AVNRT mapping (54, 55) (Figure 4).

In a study by Van Aartsen et al. (52), the relationship of the propagation maps to both the voltage maps and the successful site of ablation in patients who underwent ablation for AVNRT were retrospectively evaluated. They found low-voltage areas and a wave collision in all patients. The successful ablation lesion was located over a LVB, usually within 4 mm of the wave collision within the KT and superior to it.

Tseng et al. (54) showed comparable procedural times and 100% efficacy both for the study group (propagation map and voltage map) and the control group (anatomic-based approach); however, the number of the cryoapplications and the recurrence rate were lower in the 3D mapping group, suggesting a more precise procedure. Moreover, this strategy was particularly advantageous in patients with multiple SPs. Indeed, in this study if multiple collision points were present, all were marked, and progressively targeted from the furthest to the closest to the His

region. Lastly, they also reported that in approximately 30% of patients no LVB was found or the LVB did not correspond to the final successful ablation site.

5.3 Other strategies

The omnipolar mapping technology, a new mapping tool available in EnSite™ X EP system (Abbott Medical) can be also used to better localize the SP in patients with AVNRT (55). Omnipolar EGMs are calculated at cliques of 3 electrodes (3 unipoles, 2 orthogonal bipoles) on a multipolar HD-grid catheter, simultaneously analyzing single depolarizations from multiple directions and providing activation direction and voltage. However, omnipolar voltage maps by definition generate the highest EGM amplitude independent of wavefront direction; therefore, it can be less accurate in defining LVBs because low voltage zones in the KT in AVNRT patients are theorized to represent nonuniform anisotropic conduction or collision resulting in atrial EGM fractionation and diminution.

In detail, this technique enables to obtain a more accurate activation vector pivot (pivot point), defined as a ≥ 45 -degree change in activation direction within the KT. Moreover, it allows the use of an algorithm that distinguishes near-field EGMs (high-frequency) from far-fields (low-frequency). Indeed, the “peak frequency analysis”, which is an automated identification of high frequency EGMs, can be used create a voltage map restricted to a peak frequency >340 Hz, which in turn can identify precisely the successful ablation site for AVNRT. Probably, it represents the atrial or transitional cells' EGMs connecting the inferior input to the SP and not the true SP (right inferior nodal extension) (55, 71). However, the target of ablation of the SP can also be the site that displays a relatively lower peak frequencies, within the range of 180–210 Hz, that actually is a pseudo far field potential, related to the presence of cells with slow upstroke of action potential and low conduction velocity, typical of the cells of the right inferior extension of the AV node (SP) (72).

O'Leary et al. (45) used both the bipolar and the omnipolar mapping technology and found that, omnipolar activation vector pivot (pivot point) had the highest positive (81%) and negative predictive values (100%) for identifying AVNRT cases and had a median distance of 1 mm from the effective ablation site. The authors also showed that conduction velocity within the TK was significantly slower in patients with AVNRT than those without AVNRT, but it was not useful in identifying the successful ablation site, leading to the conclusion that globally reduced KT conduction velocity may represent a marker of AVNRT substrate without necessarily identify precise ablation sites. Moreover, they found that the bipolar voltage restricted to a peak frequency >340 Hz had an optimal discriminatory performance to identify successful ablation sites.

Another proposed strategy for AVNRT mapping relies on the Ripple mapping software (CARTO™ 3, Biosense Webster Inc) (56, 73). It is obtained with a multipolar mapping catheter, used to collect points along the right septum during sinus rhythm or

during atrial pacing to increase the density of atrial activation. Atrial signals with voltages greater than 0.06–0.08 mV are utilized for the creation of the map. This software displays each EGM at its 3D coordinate as a bar changing in length according to its voltage–time relationship. This allows prolonged, low-amplitude signals to be displayed entirely, helping recognize propagation in low-voltage areas. A benefit of this technology is that manual annotation or interpolation are not needed. Howard et al. (56) compared this strategy to the standard electro-anatomical mapping in children and found that it helped to better localize the exact location of the SP (successful ablation lesion in $\approx 90\%$ of cases within 4 mm of the predicted site, reduced variability in number of test lesions until success).

5.4 Fluoroscopy minimization with new mapping systems

As mentioned above, the new available technologies in mapping systems play a key role not only in guiding precise substrate ablation but also in minimizing/eliminating fluoroscopy, which is of particular importance in children.

In a study by Reddy et al., authors demonstrated a reduction in fluoroscopy use in the 3D mapping group, along with a slight improvement in acute success rate and a significant reduction of recurrences (46).

Similarly, in the studies by Drago et al., zero fluoroscopy or near-zero fluoroscopy was achieved with the use of a 3D mapping strategy (43, 44).

Moreover, in another single-center study by Topalović et al., zero-fluoroscopy ablation of AVNRT in the pediatric population was found a feasible, effective and safe treatment option, with a 100% acute success rate and a 98.7% chronic success rate (74).

Cui et al., using a 3D mapping system demonstrated that fluoroscopy exposure in children can be completely avoided without affecting the safety and efficacy of RF ablation (75).

Lastly, in a recent meta-analysis on zero/minimal fluoroscopic approaches during SVT ablation in both children and adults, it was demonstrated that this approach reduces radiation exposure and ablation time without compromising the acute and long-term success or complication rates (76).

5.5 Role of intracardiac echocardiography (ICE)

In challenging cases, the use of ICE has been found to improve outcomes of AVNRT ablation, since it provides real-time visualization of intracardiac structures and the ablation catheter. Indeed, data in adult patients proved that it can reduce mapping and ablation time, radiation exposure, and RF deliveries (77, 78).

Although widely used in adult EPS, ICE utilization in pediatric patients raised concerns for complications such as valvular and vascular injuries. On the other hand, when dealing

with complex anatomic structures, such as in repaired CHD patients, ICE may be a valuable tool to directly visualize cardiac suture lines, baffles, and conduits. In this setting, it can be used to guide trans-baffle and trans-conduit puncture and provide precise localization of remote arrhythmic substrates. Moreover, it helps to monitor lesion formation and facilitate rapid diagnosis of complications (79).

In a recent study by Headrick et al. including 335 pediatric and CHD ablations, the use of ICE was safe and reduced procedure duration, fluoroscopy exposure, and arrhythmia recurrence compared to no-ICE control group; in detail, in AVNRT cases, it significantly reduced procedure duration without negatively affecting success rates (80).

6 Transcatheter ablation

In recent years, transcatheter ablation of AVNRT has become the treatment of choice in large enough children (i.e., >15 kg) and in patients with CHD; indeed, as discussed, technological improvements have made this procedure highly safe and successful. In recent guidelines catheter ablation is recommended for symptomatic, recurrent AVNRT patients. Chronic medical therapy, either with non-dihydropyridine calcium channel blockers (in patients without left ventricular dysfunction) or with beta-blockers, should be considered when ablation is not desirable or feasible (7, 81). As regards smaller children, catheter ablation is rarely used and is recommended when medical therapy is either not effective or associated with intolerable adverse effects (7).

Radiofrequency (RF) ablation was first used in the 1990s, while cryoablation was introduced in 2003 (82–84) and nowadays represents the most used energy for AVNRT ablation in pediatric patients (2, 44, 46, 49, 85). Indeed, its specific features, such as reversible cryomapping, cryoadhesion and the precision in lesion delivery, made this technique very appealing to decrease complications and fluoroscopy time in pediatric patients (86).

6.1 Cryoablation

Cryoablation is usually performed using a steerable cryoablation catheter (FreezorTM, Medtronic Cryocath LP, Montreal, Quebec, Canada, 4–8 mm tip size catheters). As regards tip sizes, 4 mm tip catheters are usually chosen for patients weighing <30 kg or with very small KT dimensions.

As mentioned, the use of cryoenergy allows the use of cryomapping, and different types of mapping have been described.

“Fixed cryomapping” is performed by reducing the tip temperature to -30°C for a maximum of 60 s; “step-by-step cryomapping” is performed by progressively decreasing the tip temperature by 10°C every 5 s from -30 to -70°C .

During cryomapping, repeat extrastimulus testing or ramps can be performed using the diagnostic catheter placed in the high right atrium to assess tachycardia inducibility or the absence of AV nodal SP conduction. If cryomapping is effective (i.e., no AH

jump, no re-entry beats, and no inducibility of tachyarrhythmia), the tip temperature can be further reduced to create a permanent lesion. In contrast, if cryomapping produces unwanted effects (e.g., transient high-degree AV block, lengthening of the PR interval), cryoapplication can be discontinued to allow tissue rewarming and reversibility of electrical function loss. Subsequently, the cryocatheter is repositioned to another target site, and cryomapping repeated. As a result, permanent AV node damage has never been reported with this energy source.

Several techniques have been described for cryoablation as well.

The focal lesion technique consists of delivering a single cryoablation at -75°C – -80°C for 4–8 min followed by one or more cryoenergy applications (cryobonus) in the same spot to consolidate and slightly enlarge the cryolesion (Figure 5). Importantly, after each delivered cryoablation, repeated extrastimulus testing or ramps may be conducted to reassess tachycardia inducibility or the absence of SP conduction.

In this regard, Drago et al. demonstrated that 8-min cryoapplications together with the use of cryobonuses improve the chronic success rate, maintaining an excellent safety profile (63).

Alternatively, the extended focal lesion strategy relies on a single lesion followed by one or more cryoenergy applications delivered slightly anterior and posterior to the first successful or apparently successful lesion.

Another option is the linear lesion technique (or 3D-guided “high-density linear lesion” [HDLL] (Figure 2D). It is carried out delivering multiple overlapping cryolesions from the ventricular to the atrial side of the tricuspid annulus, with a final cryolesion at least 10 mm long, obtaining an overlapping of 3D spheres/lesions of at least half of their diameter or at least 2 mm.

The extended HDLL is produced when extending the lesion anteriorly and posteriorly to the original HDLL to achieve successful cryoablation of the arrhythmia (49, 87–92).

In a study by Czonek et al., linear lesion cryoablation improved procedural outcomes and recurrence rates compared to single-lesion methods (92).

It has also been reported that cryoablation with a 6-mm tip catheter provides higher acute and chronic success rates than 4-mm tip catheters, and 8-mm tip catheters may further reduce the risk of recurrence in children with AVNRT, while maintaining an excellent safety profile. However, with the widely used Medtronic cryocatheters, the 8-mm tip does not provide the cryomapping feature (93, 94).

Also, double and triple freeze-thaw cycles (FTC) have been reported to diminish recurrences in AVNRT patients, probably because of the larger lesion volumes achieved. However, issues regarding transient AV block and possible coronary artery injuries have been raised (95, 96).

From its introduction in 2003, the use of cryoenergy for AVNRT ablation increased and, with growing experience using this technique, outcomes have improved.

Indeed, in the early era, when 3D mapping systems were not widely available and used, cryoablation of SP substrates was reported to carry higher recurrence rates than RF (87, 89, 97, 98).

However, in the following years several studies regarding cryoenergy use for AVNRT ablation showed acute success rates

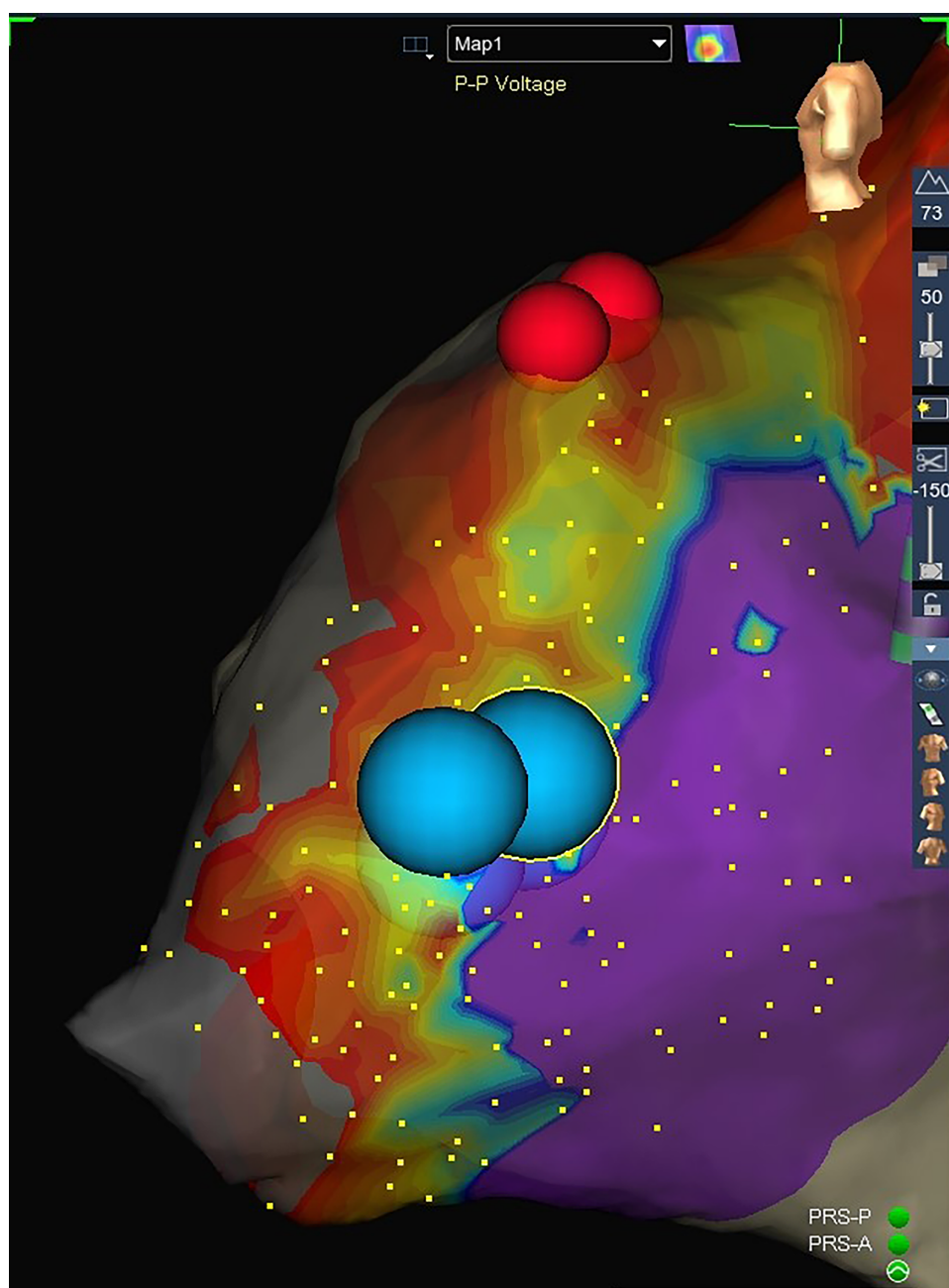


FIGURE 5
Single cryoablation followed by cryobonus.

of >95% and comparable recurrence rates to RF, even though with an increased variability among the studies (8% recurrence rate, range 0%–23%), probably related to different catheter tips and protocols (number, duration, and extension of cryolesions) (47, 49, 92–94, 99–101).

Finally, in the era of 3D mapping systems, cryoablation of AVNRT substrates has been reported to produce chronic success rates >95% (Table 1).

For example, in the multicentric MAP-IT registry (2), cryoenergy was most commonly used for AVNRT ablation (53% of cases) and no differences in acute success as compared to RF

were reported (acute success 99% for both energy sources; success at FUP 95% for cryo and 92% for RF).

In the EUROPA registry (1), even though cryoenergy was used in a minority of patients, its procedural success and tachycardia recurrence were comparable to RF. Therefore, it was suggested as a possible primary energy source for the ablation of tachycardia substrates near the cardiac conduction system, such as AVNRT.

Regarding monocentric studies, Drago et al. showed their growing experience and improved results with cryoablation, reaching chronic success rates at mid/long-term FUP $\approx$ 100% (43, 44, 49, 51, 88–91).

Similarly, two large monocentric studies (46, 85) demonstrated that the combined use of cryoenergy and non-fluoroscopic 3D mapping systems ensured acute success rates of 100% and recurrences ranging from 0% to 4.4%.

6.2 RF ablation

RF energy is another available option of trans-catheter ablation of AVNRT. It is delivered and guided by monitoring the temperature at the catheter tip, which is usually limited to a maximum of 55°C–60°C with a preset maximal power of <55 Watts (usually 20–40 W according to patients' body weight and operators' choice) (97, 102–104).

When RF is applied in the area of the SP, an accelerated junctional rhythm (<120 bpm) typically occurs, and RF energy is stopped if VA prolongation/block with junctional rhythm occurs. In addition, the RF current is terminated immediately in the event of an increase in impedance, displacement of the ablation catheter, or prolongation of the PR interval. If junctional beats are not evoked, RF delivery is usually interrupted, and the catheter is repositioned. Otherwise, RF deliveries are applied from 30 s to 60 s (105, 106).

RF is mostly delivered through non-irrigated-tip catheters; however, in the recent MAP-IT trial, irrigated tip RF catheters were used in 25%–30% of patients, with a 99% success rate and no reported complications (2).

In the early era of catheter ablation in children, the main multicenter studies focused only on the outcomes of RF ablation. In particular, the Pediatric Radiofrequency Catheter Ablation Registry (PCAR) (107) reported a success rate for AVNRT ablation of 95%–99%, with an improvement across the years, and a complication rate of 3%–5%. Similarly, in the Prospective Assessment after Pediatric Cardiac Ablation (PAPCA) (108), the registry success rate was 97% and the complication rate 2.9%–4.2%, with 2.15% for AV block.

In the PAPCA registry, the recurrence rate was 4.8% at 1-year FUP (108). In concomitant monocentric studies, results were comparable: acute success rate slightly above 95% and recurrence rate of 5%–10%, with a non-trivial occurrence of AV block (98, 109).

In recent years, a large Chinese registry concerning RF use in the treatment of arrhythmias in pediatric patients (110) showed that the acute and long-term success rates of AVNRT ablation were 99.3% and 95.0%, respectively. However, AVNRT was the most likely substrate to have serious complications, which occurred in 29 patients (0.6%), with 7 complete AV blocks (6 of them requiring permanent pacemaker implantation).

A remote magnetic navigation system to deliver RF has also been described as an ablation tool in children with AVNRT. The remote magnetic navigation ablation catheter has a flexible, magnetically enabled distal tip; therefore, a magnetic force can be used to navigate toward and hold the catheter with high stability in the ablation area (111, 112). This strategy had already demonstrated improved lesion formation and superior safety compared to manual RF ablation; moreover, in a study by Noten et al. (113), it was compared to other catheter ablation strategies

and proved to reduce recurrences compared to both manual-guided RF ablation and cryoablation.

It must be highlighted that, regardless of the type of energy used, some issues remain.

First, recurrences remain not negligible and a relevant part of them can occur very late, >5 years post ablation (100, 114). In this regard, many have tried to predict the risk of recurrence; however, neither the presence of jump nor a single echo beat after catheter ablation have demonstrated to be reliable predictors (26, 115). However, more extensive data on very long-term follow-ups is lacking.

Secondly, some authors pointed out that over a very long-term follow-up, the risk of late pacemaker implantation after AVNRT ablation is low but significantly higher than that in the general population. In addition, this risk is even higher than the risk of acute, periprocedural pacemaker implantation (114, 116). However, consistent data on this topic is still lacking.

All considered, a reasonable option for children is to perform SP modulation instead of complete SP ablation, especially when multiple ablation lesions are needed, and RF is used. In these particular cases, the presence of single nodal echo beats in the absence of sustained SP conduction is an acceptable endpoint (7, 117).

7 Special considerations in CHD

AVNRT may develop in patients with different types of CHD at any age and represents the third most common form of arrhythmia in children with CHD (after atrioventricular reentry tachycardia and macro-reentrant atrial tachycardia) (23).

AVNRT ablation in these patients is even more valuable than in normal hearts, since the tachycardia may be detrimental to already fragile hemodynamic status and antiarrhythmic drugs have limited efficacy and more side effects than in patients with structurally normal hearts. However, catheter ablation may be challenging, and experience remains limited (22, 118).

In CHD patients, special considerations relate to the localization of the specialized conduction system, which may be atypical and less predictable or less accessible. The former problem occurs more frequently in patients with AV septal defects, CC-TGA, heterotaxy syndromes, tricuspid atresia and double inlet ventricles and implies lower success rates and higher risks of AV block during ablation. The latter mainly occurs in D-TGA patients after Mustard or Senning operation and in patients with Fontan circulation. Indeed, accessing to the conventional SP region is complex in these cases as it most often requires a trans-baffle puncture for a direct antegrade approach. Moreover, in Mustard/Senning operation, SP ablation occasionally may require additional ablations to its 'left-sided' atrio-nodal input from the systemic venous aspect (24, 119, 120).

In general, ablation outcomes in CHD patients are poorer than in normal hearts, with acute success rates around 80% and major complications in 4%–5% (119, 121).

In addition, as demonstrated by Papagiannis et al, the complexity of the CHD influences electrophysiological

characteristics and ablation results. Indeed, patients affected by complex CHD have more frequently atypical AVNRT and are usually ablated at younger ages. Furthermore, ablation success rate is significantly lower (82% vs. 97% in simple CHD), recurrences higher (18% vs. 10%) as well as complications, with AV block requiring pacing in 10% (only with RF ablation) vs. 0% in simple CHD (22).

As regards specific CHD: CC-TGA is usually characterized by the abnormal location of AV conduction tissue and a marked fragility of it, which warrants a supreme care to avoid AV block and obviate the need for a permanent pacemaker. The compact node generally occupies a more anterior location, outside of the KT. In CC-TGA with situs inversus (I,D,D) ablation is usually performed in the left side, while in situs solitus (S,L,L) in the right side; for both, usually in the mid/posterior septum, even though cases of ablation in the anterior septum or even in a superior location medial to the right atrial appendage have been described (22, 24).

In D-TGA after Mustard or Senning operation the intra-atrial baffle prevents direct entrance to the KT from a femoral venous approach. Therefore, either a retrograde trans-aortic approach to the pulmonary venous side of the baffle or a trans-baffle approach are required (22, 122).

In patients with AV canal defects, the connecting AV node is displaced to an inferior location in the KT or even inferiorly to the KT, between the atrial sinus septum and the inlet of the muscular ventricular septum. The non-branching and branching bundles are typically exposed by the defect, i.e., not covered by valvular tissue, making them more susceptible to damage. Therefore, RF is not recommended by most authors, while the use of cryoenergy has been described more extensively (22, 24, 119, 123).

In patients with Single Ventricle Physiology (included those after Fontan operation) the reported outcomes are the worst, because of the uncertainty of the nodal/perinodal tissue and the lack of conventional landmarks of the KT, especially in heterotaxy and unbalanced AV canal defects, in which there is no KT to assist with AV node localization (22, 24). Furthermore, in dextrocardia or heterotaxy syndrome, the AV node may also be left-sided and rarely duplicated. Also, a conventional femoral approach may be inadequate due to venous anomalies (inferior vena cava absence in left atrial isomerism) (124). In addition, in patients with Fontan circulation, a trans-baffle puncture is required and carries the risks of potentially catastrophic consequences, such as intrathoracic hemorrhage (24, 119, 124).

In patients with tricuspid atresia, successful SP ablation may be sometimes achieved from the left side of the atrial septum, thus through a trans-septal or retrograde approach.

In Ebstein anomaly right atrial dilation and tricuspid valve displacement can distort the KT anatomy, but usually the sites of successful SP ablation are conventional (24).

8 Conclusion

AVNRT is a common SVT in children and its invasive management has deeply evolved in recent years. Mapping strategies in pediatric patients have significantly improved, leading to a more precise localization of the ablation substrate, with minimal use of fluoroscopy. It enabled us to perform fewer ablation lesions, reducing complications, and to avoid unnecessary radiologic exposure in growing human beings. Catheter ablation itself has now become extremely safe and effective, with reduced AV block rates after the spread of cryoenergy. However, overall risk of AV block and long-term consequences of catheter ablation in the pediatric age remain open issues. Moreover, in CHD patients ablation remains challenging and experience limited. Therefore, even with improved technologies and expertise, caution should be exercised in children, and a risk-benefit evaluation should be considered.

Author contributions

FD: Supervision, Validation, Writing – original draft, Writing – review & editing. FF: Conceptualization, Methodology, Resources, Visualization, Writing – original draft. CR: Data curation, Writing – original draft. CP: Supervision, Validation, Visualization, Writing – review & editing.

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Conflict of interest

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Multipath joint ablation strategy for focal atrial tachycardia originating from patent foramen ovale: a case report

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Introduction: Focal atrial tachycardia (FAT) is predominant in the pediatric population. Recent research has identified cases of sustained FAT originating from the interatrial septum (IAS); a subset of cases presents a unique challenge, with foci originating from the peri-patent foramen ovale (peri-PFO), requiring specialized management during catheter ablation. Here, we present a rare case of peri-PFO-associated FAT that resulted in tachycardia-related cardiomyopathy and propose a comprehensive multipath joint strategy for the successful treatment of PFO-associated FAT.

Case presentation: A 10-year-old boy presented with refractory cardiomyopathy associated with incessant atrial tachycardia, unresponsive to metoprolol. A 12-lead electrocardiogram revealed a narrow QRS complex tachycardia with a rate of 157 beats per minute and a prolonged RP relationship. Echocardiography indicated a severely reduced ejection fraction of 22%. Subsequent electrophysiological study findings identified the tachycardia as originating from the anterior limbus of the PFO. Radiofrequency ablation was performed at the earliest activation site and surrounding structures, encompassing the right atrial septum, non-coronary sinus of Valsalva, and the left atrium peri-PFO. Post-procedure, the patient remained free from arrhythmia and showed restored normal cardiac function and was prescribed a low-dose β -blocker for 1 month. Remarkably, the patient continued to be well without the need for any medications for the subsequent 3 months.

Conclusion: The structure of the PFO brought significant challenges in performing successful ablation. The multipath strategy was beneficial in managing peri-PFO-associated FAT based on its anatomical vicinity of the target.

KEYWORDS

atrial tachycardia, catheter ablation, tachycardia associated cardiomyopathy, patent foramen ovale, managing strategy, case report

Introduction

Supraventricular tachycardia (SVT) represents a diverse group of arrhythmias originating at or above the His bundle and is commonly encountered in pediatric cases (1). In adults, atrial fibrillation is often the most prevalent form of SVT, while in children, atrioventricular nodal reentrant tachycardia (AVNRT), atrioventricular reentrant tachycardia (AVRT), and focal atrial tachycardia (FAT) predominate (2). Prolonged episodes of SVT, particularly FAT, can lead to tachycardia-induced

cardiomyopathy, compromising cardiac function over time. While pharmacological therapy is typically employed to terminate or convert these arrhythmias, FAT can sometimes be resistant to drug-based treatments. For cases of symptomatic FAT in pediatric patients, catheter ablation has become an increasingly viable option. This procedure targets specific arrhythmogenic foci, which may be located in various anatomical sites such as the atrioventricular ring, crista terminalis, coronary sinus (CS) ostium, or a pulmonary vein (PV), offering a more definitive treatment (2, 3).

Recent studies have reported cases of sustained focal atrial tachycardia (FAT) arising from the interatrial septum (IAS), a rare phenomenon due to the IAS's predominant composition of connective tissue with minimal myocardial involvement (4). Ablating arrhythmogenic foci within the IAS presents notable challenges, especially when the focus is unilateral, which can lead to radiofrequency ablation failure (5). Consequently, bilateral ablation may be considered for FAT originating from the IAS. A particularly challenging subset of cases involves arrhythmic foci in the peri-patent foramen ovale (peri-PFO) region, which requires specialized management during catheter ablation procedures (6, 7). The dynamic motion of the valve of foramen ovale and the anatomical complexity of the peri-PFO tissue may compromise catheter stability, potentially reducing ablation success rates.

In this report, we describe a rare case of peri-PFO-associated FAT that progressed to tachycardia-induced cardiomyopathy. We detail the electrophysiological identification of peri-PFO FAT and propose a comprehensive, multi-path strategy for the effective termination of this arrhythmia.

Case presentation

Ethic approval

The study was approved by the ethics committee of the West China Second Hospital of Sichuan University (approval number: 2021-069). We also obtained written informed consent from the patient's parents prior to performing whole exon sequencing (WES) and for the inclusion of the patient's clinical and imaging details in this publication.

Clinical presentation

We present the case of a 10-year-old male patient [weight 39 kg, body mass index (BMI) 18 kg/m²] who was admitted to our cardiac intensive care unit following a two-year history of progressive exertional dyspnea. He reported reduced tolerance for physical activity, palpitations, and pallor. His parents denied any additional symptoms such as fainting, cyanosis, fever, seizures, edema, vomiting, or abdominal discomfort. There was no history of chest pain, syncope, or recent viral infection. The patient had been suspected of having dilated cardiomyopathy and incessant sinus tachycardia a year prior and was treated with metoprolol, an angiotensin receptor neprilysin inhibitor, furosemide, and spironolactone.

Physical examination revealed a chronically ill appearance with marked diaphoresis and fatigue. Tachycardia was noted, with a heart rate of 150–160 beats per minute, along with irregular premature beats. Blood pressure was normal across all four extremities. Respiratory auscultation revealed coarse breath sounds and diffuse wheezing in both lungs, while the cardiac apex was displaced to the left lower quadrant, suggesting an enlarged heart. The heart rhythm was irregular with occasional premature beats, but no murmurs were detected. The abdomen was soft with no splenomegaly, and muscle strength and tension were normal in all limbs. No pathological signs were present, nor were there any signs of meningeal irritation.

The patient's past medical history was otherwise unremarkable, with no family history of cardiovascular disease, hypertension, or coronary artery disease. The absence of significant risk factors for cardiovascular conditions further complicated the clinical picture, prompting a detailed workup to determine the underlying cause of his symptoms.

Laboratory and imaging examinations

The initial laboratory evaluation revealed normal results for routine blood cell counts, blood gas analysis, and hepatic and renal function tests. However, B-type natriuretic peptide (BNP) levels were significantly elevated at 4,356.8 pg/ml (normal range: <60 pg/ml), suggesting significant cardiac stress, although cardiac troponin I (cTnI) remained within normal limits. Screening for rheumatic disease, autoimmune conditions, and thyroid dysfunction was negative, and viral testing for pathogens such as SARS-CoV-2, Coxsackievirus, adenovirus, influenza, rhinovirus, and respiratory syncytial virus yielded negative results.

The 12-lead electrocardiogram (ECG) revealed a narrow QRS complex tachycardia at 157 beats per minute (bpm) without discernible *P* waves, but notable high-peaked *T* waves (Figure 1A). Echocardiography indicated severe systolic dysfunction with a left ventricular ejection fraction of 22%, an enlarged left atrium measuring 35 mm, and a dilated left ventricle measuring 57 mm (Figure 1B), with a patent foramen ovale (PFO) confirmed (Figure 1B'). The right atrium and ventricle appeared normal. Cardiac MRI supported the findings of left ventricular dilation but did not show evidence of myocardial fibrosis, ruling out the diagnosis of dilated cardiomyopathy (Figure 1C). After initiation of amiodarone therapy, ECG showed a reduction in the atrial rate to 124 bpm with the development of a Wenckebach block, resulting in a slower ventricular rate of approximately 82 bpm (Figure 1D). The biphasic *P* wave in lead V1 (−/+), along with positive, pointed *P* waves in leads I, II, III, and aVF and negative *P* waves in lead aVR (Figure 1D), pointed to a focal origin in the high right atrium, such as the superior vena cava or right atrial appendage. This pattern raised suspicion for inappropriate sinus tachycardia, though the atrial tachycardia persisted during hospitalization.

To further exclude a diagnosis of dilated cardiomyopathy, whole exome sequencing (WES) was performed to detect potential genetic variants. No cardiovascular-related mutations, particularly those affecting ion channels, were identified in the

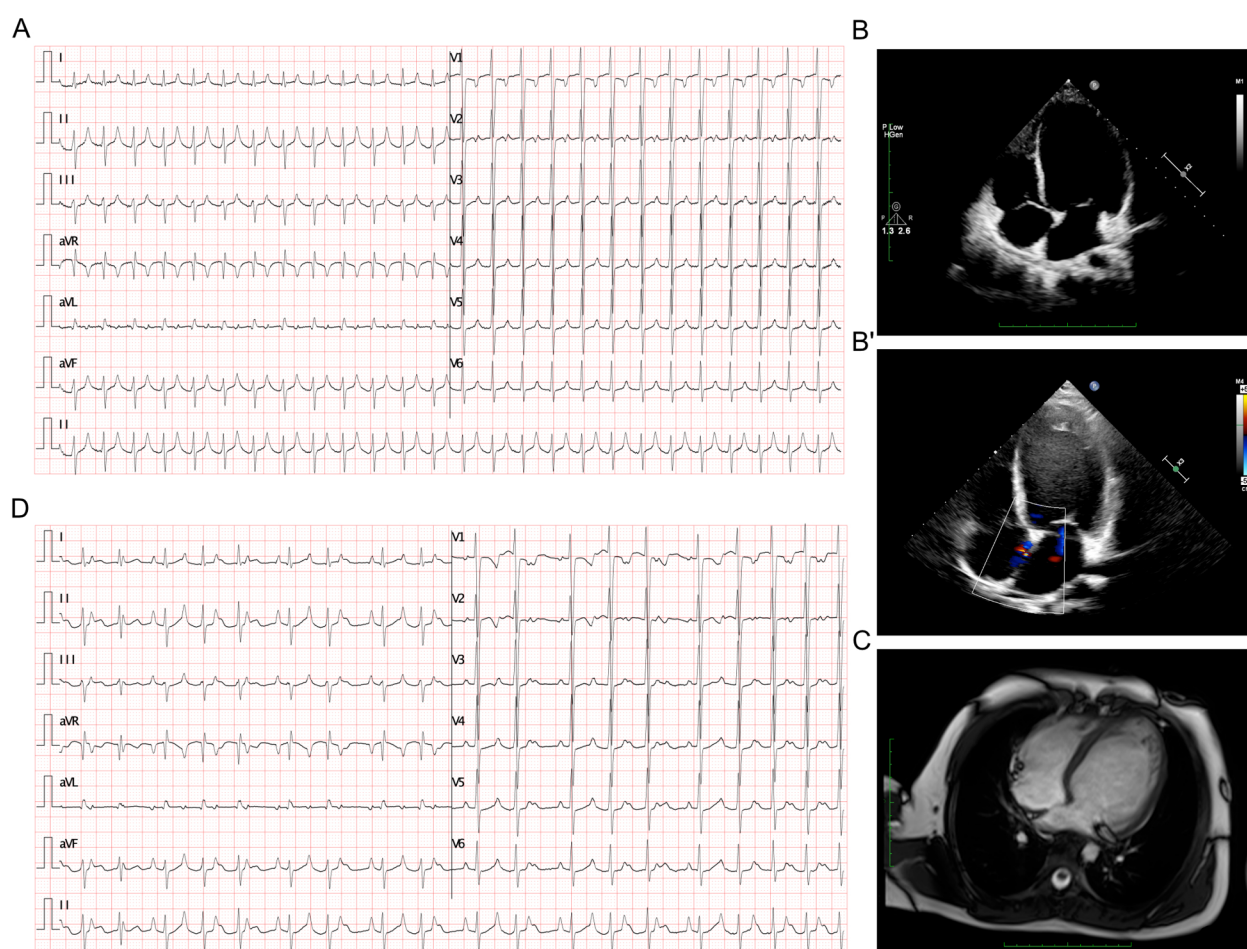


FIGURE 1

ECG and imaging presentation of the patient. (A) ECG presented a tachycardia at rate of 157 bpm. (B–B') Echocardiography presented enlarged left atrium of 35 mm and left ventricle of 57 mm (B), and a PFO (B'). (C) Cardiac MRI presented a dilated left ventricle which was absent from any signaling myocardial fibrosis against the diagnosis of dilated cardiomyopathy. (D) ECG demonstrated an atrial rate of 124 bpm after amiodarone treatment, and Wenckebach block was identified which lead to a slower ventricular rate at about 82 bpm.

proband or his parents. Due to the severity of clinical symptoms and the failure of pharmacological conversion, the patient underwent an electrophysiological study with subsequent catheter ablation.

Electrophysiologic study and ablation

The patient underwent the entire procedure under general anesthesia by inhaling 2%–3% sevoflurane continuously after initial anesthetic induction with propofol (2 ug/kg) and fentanyl (2 mg/kg). Diagnostic catheters [Inquiry™ Steerable Diagnostic Catheter (Abbott Corp., St. Paul, MN, USA) for the coronary sinus, Supreme Electrophysiology Catheter for the His potential and Inquiry™ Electrophysiology Catheter (Abbott Corp., St. Paul, MN, USA) for the right ventricle) were placed in the coronary sinus, the bundle of His, and the right ventricle, respectively, after successful puncture of both femoral veins and heparinization (100 U/kg). Initially, an incessant

atrial tachycardia was underlined, and the earliest atrial signal appeared to be on the His catheter with an atrial cycle length of 350–420 ms with 1:1 conduction to the ventricle. Changes in the ventricular-atrial interval were observed which suggested the tachycardia was a kind of FAT. Fine mapping was performed with an irrigated ablation catheter (TactiCath™ Contact Force Ablation Catheter, Sensor Enabled™, Abbott Corp., USA) through an SR0 sheath (Fast-Cath™ Guiding Introducer SR0™, Abbott Corp., USA) to identify the earliest atrial electrograms. The earliest atrial signals were 65 ms ahead of the surface P wave with QS unipolar electrograms and appeared to be an anterior limbus of PFO (Figure 2A). Radiofrequency energy was used at 30–40 W and 30 cc/min flow for 30–60 s per lesion at the earliest site with lesion size index (LSI) values of 3.5–4.0. During the ablation procedure, the tachycardia cycle length (TCL) extended to 460 ms. However, due to the anatomical characteristics of the mobile limbus of the PFO, optimal catheter-tissue contact was challenging to maintain, with contact force readings remaining

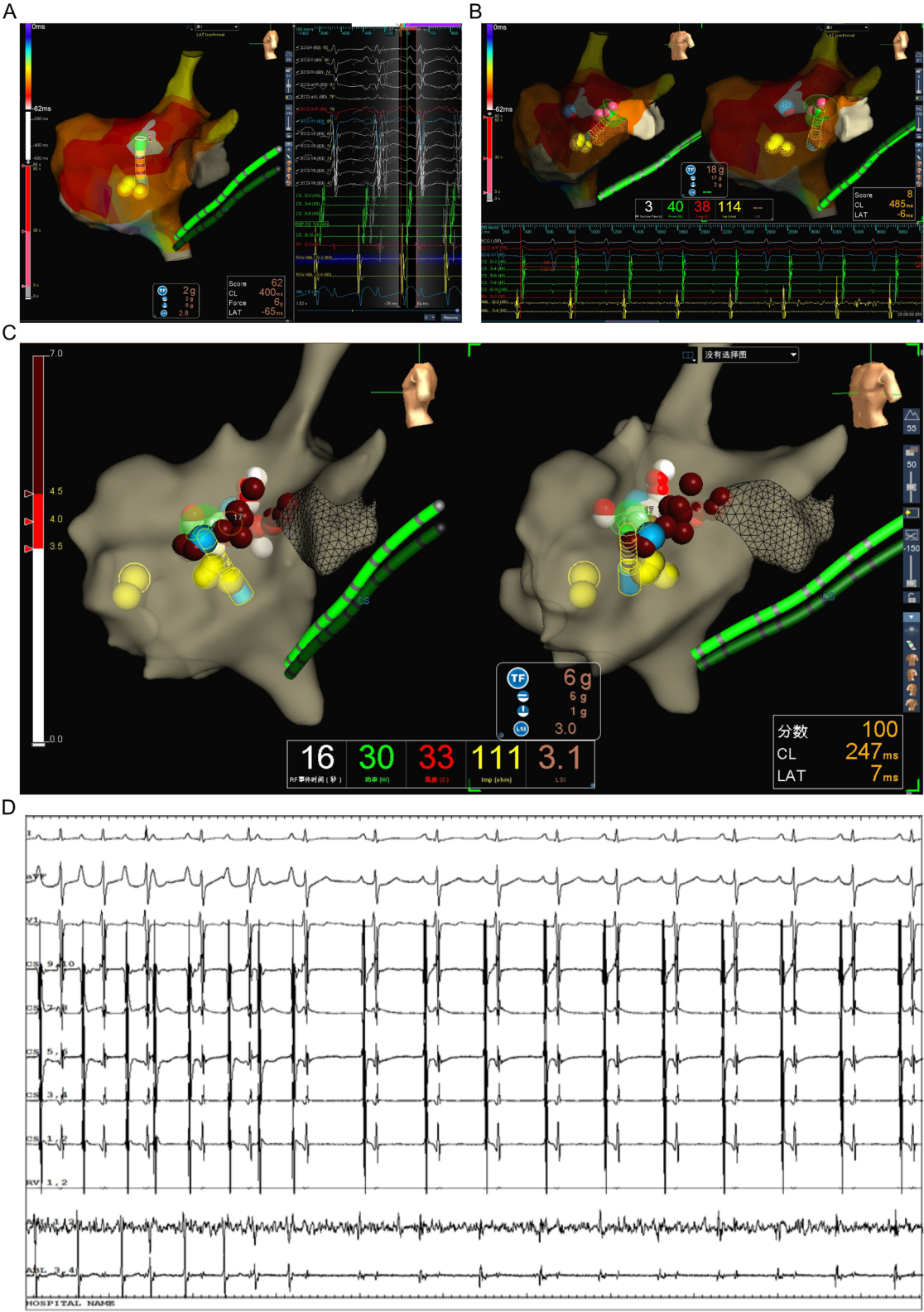


FIGURE 2 Identifying the originating of FAT in the patient. (A) Activating mapping suggested the earliest site at the interatrial septum in right atrium on left lateral view with EnSite Velocity system. (B) The catheter slipped into the left atrium through PFO and ablation performed at the anterior wall of left atrium. (C) The catheter retreated into the right side to continue the procedure at the vicinity of the earliest site along the limbus of PFO. (D) The tachycardia had been terminated and converted to sinus rhythm when ablation performing at the limbus of PFO.

suboptimal at 1–2 g (Figure 2A). Attempts to increase contact force resulted in inadvertent catheter displacement through the PFO into the left atrium. Next, we performed the procedure with the contact force for 10–20 g at 30 W and 30 cc/min flow for 30 s per lesion at the anterior wall of the left atrium opposite to the earliest site on the right side with LSI values of 4.0–4.5 (Figure 2B). The TCL was further extended to 480–500 ms during ablation on the left side. After that, we retreated the catheter into the right side to continue the procedure at the vicinity of the earliest site along the limbus of the PFO. Tachycardia was eventually terminated and converted to sinus rhythm (Figures 2C,D). Furthermore, additional lesions around this region that had been identified as the foci of FAT, including the opposite side of the earliest site in the non-coronary aortic sinus of Valsalva (Figures 3A,B) also received radiofrequency at a force of 10–20 g at 30 W and 30 cc/min flow for 30 s per lesion with LSI values of 4.0–4.5 to ensure enhanced treatment efficacy via multipath strategy. Then, standard atrial and ventricular stimulation protocols with single and double extra stimuli (S1S2 400/300 ms and S1S2S3 400/300/300 ms) and burst pacing (S1S1 200–300 ms) were used, and isoproterenol was repeatedly administered. The ablation electrode was ultimately positioned at the anterior limbus of the PFO, while the right ventricular electrode, serving as a high right atrial reference, demonstrated that the electrical signals at the high right atrium preceded those at the ablation target site (Figures 4A,B). Multiple stimulation protocols failed to induce any additional arrhythmias. The total procedure duration was 132 min, with a cumulative radiation exposure of 20 mGy. Activation mapping comprised 300 sampling points, predominantly concentrated in the RA. A total of 26 ablation lesions were delivered: 13 lesions surrounding the earliest activation site in the RA, 8 lesions in the left atrium (LA), and 5 lesions in the NCC following tachycardia termination.

Final diagnosis and follow-up

The patient was diagnosed with focal atrial tachycardia FAT originating from the peri-PFO region, resulting in tachycardia-induced cardiomyopathy. Following successful catheter ablation, the patient was initiated on a medical regimen comprising clopidogrel (0.5 mg/kg/day once daily) for antiplatelet therapy, along with heart failure management including metoprolol (1 mg/kg/day divided twice daily), sacubitril/valsartan (2 mg/kg/day divided twice daily), and spironolactone (1 mg/kg/day divided twice daily) to address left ventricular dysfunction and chamber dilation. At his 6-month follow-up, the patient reported resolution of his prior symptoms. A 12-lead electrocardiogram confirmed normal sinus rhythm at 80 beats per minute. Echocardiography demonstrated an improvement in left ventricular function, with the ejection fraction normalized to 60%, and the left ventricular end-diastolic diameter reduced to 46 mm. The patient's medication regimen was subsequently discontinued. At 6 months post-ablation, repeat ECG and echocardiographic evaluations remained within normal limits. There was no complication and adverse event observed for the follow-up period.

Discussion

FATs can arise from various locations within both atria, with up to 63% originating from structures in the right atrium, including the tricuspid annulus, crista terminalis, and CS ostium. Conversely, 37% have been identified to emerge from left atrial structures such as the pulmonary veins, mitral annulus, and CS body (8). In rare instances, FAT may have its origin in the atrial appendage, IAS, and/or the non-coronary cusp (9, 10). Various tachycardias may lead to TIC, marked by cardiac enlargement, decreased cardiac function, and the onset of heart failure. Pediatric patients, in particular, warrant screening for secondary

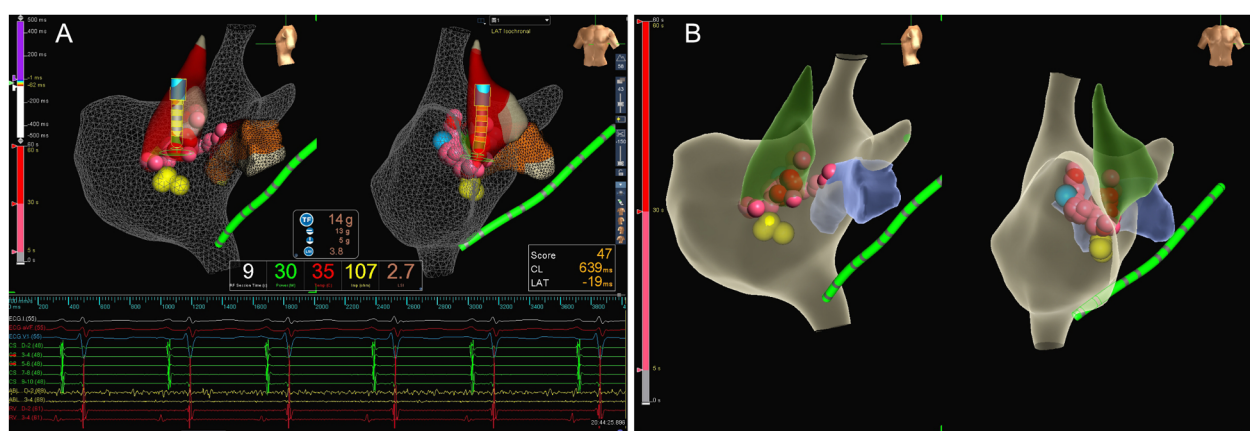
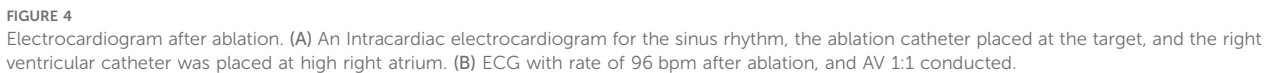


FIGURE 3

Multipath ablation strategy in the patient. (A) Ablation performed additional lesions in the non-coronary aortic sinus of Valsalva near to the earliest activate site in the right interatrial septum. (B) All ablation lesions for this patient, as the gray region is part of right atrium, the blue region is part of left atrium, and the green is part of noncoronary cusp.



A PFO represents a persistent fetal interatrial communication resulting from incomplete fusion of the septum primum to the septum secundum, typically in the posteroinferior portion of the medial atrial wall. The prevalence of PFO is estimated to be approximately 25%–30% within the population (4). Detection of PFO can be challenging with transthoracic echocardiography

(TTE) alone, as this method exhibits limited sensitivity. Specifically, TTE using color flow Doppler has a sensitivity of 21.4%, whereas the use of bubble contrast increases sensitivity to 53.8% for detecting PFO (12). In our patient, PFO was identified through TTE, and subsequent 3D electroanatomical mapping confirmed it to be the origin of atrial tachycardia. Embryologically, the central region of the foramen ovale typically consists of a membranous structure predominantly composed of thin fibrotic tissue devoid of action potential, with myocardial fibers and automaticity being either scattered or absent (13, 14). The presence of PFO is recognized as a significant risk factor for cryptogenic stroke, particularly in young adults where paradoxical embolism serves as a primary mechanism. This risk may be heightened during procedures involving peripheral venous access, including radiofrequency catheter ablation (RFCA) (15, 16). Based on current guidelines and the patient's asymptomatic status, we implemented a conservative management strategy with systematic follow-up, deferring PFO closure. Recent advancements in 3D electroanatomical mapping have confirmed these histological characteristics (17). Despite the rarity of arrhythmias originating from this central area owing to the lack of myocardial fibers, adjacent atrial muscle bundles may still exert an arrhythmogenic effect. Focal mapping using a multielectrode diagnostic catheter could enhance the accuracy of localizing the site of the arrhythmogenic focus during catheter mapping and likely reduce the duration of the whole procedure. Ablation around the unclosed foramen ovale poses challenges, particularly in placing the catheter to the limbus of the PFO, which may be free. This may be the reason for the extended TCL after our first attempt. Ablation performed in the anatomical vicinity of the target could potentially increase the success rate of the ablation procedure. We performed radiofrequency in our patient by using a combined strategy in applying ablation in the RA, LA, and NCC through arteriosus and venous routine for the values of LSI for ablation at the right septal lower than that at the other positions. As known, the LSI, similar to ablation index (AI), is a dimensionless contact force parameter that allows for an accurate estimation of lesion volume in real time by integrating contact force (grams), duration (seconds) and power (watts), and the value of LSI or AI could predict successful ablation of various arrhythmias (18–20).

FAT originating from the IAS is more commonly observed in adult patients, with approximately half of these cases associated with structural abnormalities, including atrial septal defects and PFO (4). Septal AT can originate from either side of the septum, presenting distinct ECG manifestations that require careful differentiation. The *P* wave polarity in lead V1 has been shown to accurately predict the side of origin within the IAS (4). Literature demonstrates that the prevalence of atrial arrhythmias, particularly AF and AFL, associated with atrial septal defects (ASDs) increases with age. In unoperated adults, the estimated incidence of atrial arrhythmias is approximately 10% in patients under 40 years of age, increasing to at least 20% in older patients with pulmonary arterial hypertension and systemic hypertension (5, 21, 22). Paradoxically, ASD closure has been associated with a significant increase in atrial arrhythmia incidence. Among patients older than 40 years, approximately 40%–60% develop atrial arrhythmias within 10 years post-ASD closure (5). While

ASD closure is associated with a higher prevalence of arrhythmias, no significant changes in arrhythmia prevalence have been observed in PFO patients between pre- and post-closure periods. Notably, there is no conclusive evidence suggesting an increased risk of ventricular arrhythmias in patients with either ASDs or PFOs, and no sudden cardiac death has been reported in this population. Mechanistically, it is believed that left-to-right shunting promotes cardiac remodeling secondary to chronic hemodynamic overload, resulting in focal interstitial fibrosis that creates a substrate for unsustainable or minimal reentry circuits, ultimately leading to atrial arrhythmias (23, 24). Consequently, closure is recommended for patients with non-reversible atrial arrhythmias.

Management of new-onset post-procedural arrhythmias is crucial (25). In PFO patients, a subset experiences transient arrhythmia during the initial days to weeks following the procedure, primarily attributed to local tissue irritation (26). Notably, up to two-thirds of these patients experience resolution of arrhythmias within one-year post-procedure. Due to the limited number of PFO patients requiring surgical repair, data regarding associated complications remains sparse. In contrast, surgical treatment of ASDs has been shown to increase the incidence of atrial arrhythmias through atriotomy-related electrophysiological remodeling (27, 28). Importantly, persistent arrhythmias may be directly related to the closure device itself. A significant consideration is that the defect itself represents a pre-existing potential central barrier of non-conduction for reentrant circuit formation (29). Additionally, device-related inflammation and scarring warrant careful monitoring.

The use of deflectable introducers can enhance catheter-tissue contact at the PFO limbus or ASD, particularly in post-device closure cases (30, 31). However, given the complex anatomical considerations, multiple-site ablation may be necessary to achieve optimal therapeutic outcomes. Various approaches exist to address these challenges, with transesophageal echocardiography or intracardiac echocardiography (ICE) proving particularly valuable in device closure patients (32), especially for pre-procedure onset arrhythmias. In our experience, the jugular approach may present operational challenges and increased procedural risks, particularly in pediatric cases. Recent technological advances in AF ablation, including PFA and very high-power short-duration (vHPSD) radiofrequency ablation, may improve success rates for ATs arising from PFO (33). ICE can enhance target visualization while reducing radiation exposure. A minimally fluoroscopic approach (MFA) should be pursued to minimize potential long-term adverse effects of radiation exposure, particularly in pediatric populations (34).

Our report has some limitations. The new mapping after TCL changed for the first ablation attempt to distinguish whether there were any other potential sites for ATs. Furthermore, we failed to carry out electrophysiological studies before the NCC ablation, which might have increased the procedure risk and prolonged the duration of x-ray exposure. In addition, we had not use ICE because we had no smaller size ICE catheter such as 8F ICE, but the 10F catheter we had may injure the child's femoral vein seriously.

Conclusion

Our report presents a rare case of TIC in a pediatric patient, driven by incessant FAT originating from the peri-PFO. Catheter ablation proved to be an effective treatment strategy, offering the potential for long-term resolution without the need for antiarrhythmic medication. However, the unique anatomical structure of the PFO presented significant technical challenges during the ablation procedure. Based on this experience, we propose a multipath approach to the management of peri-PFO-associated FAT, emphasizing the importance of targeting the anatomical vicinity for successful ablation.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Ethics statement

The studies involving humans were approved by the ethics committee of the West China Second Hospital of Sichuan University (approval number 2021-069). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

FL: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources,

Visualization, Writing – original draft. YL: Conceptualization, Formal Analysis, Investigation, Methodology, Resources, Supervision, Visualization, Writing – review & editing. SY: Data curation, Investigation, Methodology, Writing – original draft. LL: Data curation, Formal Analysis, Investigation, Methodology, Writing – original draft. KZ: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing. YH: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Prevalence of abnormal thyroid hormone levels in acute new-onset atrial fibrillation

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Introduction: Known risk factors for new-onset atrial fibrillation/flutter (NOAF) include thyrotoxicosis and subclinical hypothyroidism. While prior research has predominantly explored the link between thyrotoxicosis and NOAF, the presence of subclinical hypothyroidism among patients presenting with acute NOAF in the emergency department (ED) remains an underexplored area of inquiry. This study aimed to assess the prevalence of undiagnosed thyrotoxicosis and subclinical hypothyroidism in patients with acute NOAF diagnosed in the ED.

Methods: This registry-based cohort study was conducted in the ED at Vrinnevi Hospital in Sweden during the years 2018, 2020, and 2022, with a 1-year follow-up period. Patients ≥ 18 years diagnosed with NOAF in the ED, with no ongoing thyroid hormone substitution or previous documented thyroid abnormality within the past 2 years, were included. The primary outcome was the diagnosis of thyrotoxicosis or subclinical hypothyroidism either in the ED or during a 1-year follow-up period.

Results: 486 patients with NOAF were included in the study (43.6% females). 329 (67.7%) underwent thyroid function testing in the ED or by the end of the 1-year follow-up. In total, 16 (4.9%) patients presented with subclinical hypothyroidism while 4 (1.2%) patients presented with clinical or subclinical thyrotoxicosis.

Discussion: This study found that subclinical hypothyroidism was more prevalent (4.9%) than thyrotoxicosis (1.2%) among patients presenting with acute NOAF. These findings contrast with previous research that has predominantly linked thyrotoxicosis with acute NOAF, suggesting the need for further studies including both subclinical hypothyroidism and thyrotoxicosis in patients with NOAF.

KEYWORDS

atrial fibrillation, acute new-onset atrial fibrillation, thyroid testing, thyrotoxicosis, subclinical hypothyroidism, hyperthyroidism, emergency department

Introduction

Atrial fibrillation/flutter (AF) is the most frequent cardiac arrhythmia among patients worldwide (1, 2). The true prevalence of AF is unknown, as many patients remain undiagnosed due to asymptomatic disease (3, 4). AF increases the risk of ischemic stroke, heart failure, sudden cardiac death, and cardiovascular (CV) mortality (1, 2). Various risk factors contribute to the development of AF such as genetic predisposition,

advanced age, male sex, overweight, increased alcohol consumption, smoking, CV disease (CVD), and thyroid disease (5, 6). In patients with acute AF, spontaneous conversion is observed in up to 70% of cases. This occurrence depends on factors such as atrial size, concomitant heart failure, previous AF episodes, elevated heart rate, and the presence of a reversible thyrotoxic state (7, 8).

Normal thyroid function is particularly important for maintaining normal cardiac function. Thyroid dysfunctions are common and affects approximately 3.8% of the European population, with an annual incidence of 0.23% for hypothyroidism and 0.05% for hyperthyroidism (9). Clinical thyrotoxicosis, subclinical thyrotoxicosis, and subclinical hypothyroidism are established risk factors for new-onset AF (NOAF) and acknowledged in recent guidelines from the European Society of Cardiology (ESC) (10–13). Accordingly, the ESC recommends thyroid hormone testing in cases of NOAF.

Previous studies have primarily focused on the association between thyrotoxicosis and NOAF, reporting a prevalence ranging from 2.7% to 5.5% in the general NOAF population. In comparison, subclinical hypothyroidism—with an approximate prevalence of 5.7% in the general NOAF population—has received considerably less attention in the literature (14–18). Furthermore, there are few studies evaluating the prevalence of thyroid dysfunctions in patients diagnosed with acute NOAF in the ED. In regard of thyrotoxicosis, one study involving a mixed population of AF patients found that its prevalence was as high as 10.8% (19). However, this study relied solely upon thyroid stimulating hormone (TSH) levels to differentiate thyroid dysfunctions. This method could result in diagnostic issues since TSH profiles can overlap across various thyroid conditions that are not pertinent to AF. In regard of subclinical hypothyroidism, there are to the best of our knowledge, no studies investigating its prevalence in patients with acute NOAF diagnosed in the ED.

The aim of this study was to evaluate the prevalence of clinical and subclinical thyrotoxicosis as well as subclinical hypothyroidism in patients with acute NOAF diagnosed in the ED.

Materials and methods

Study design and participants

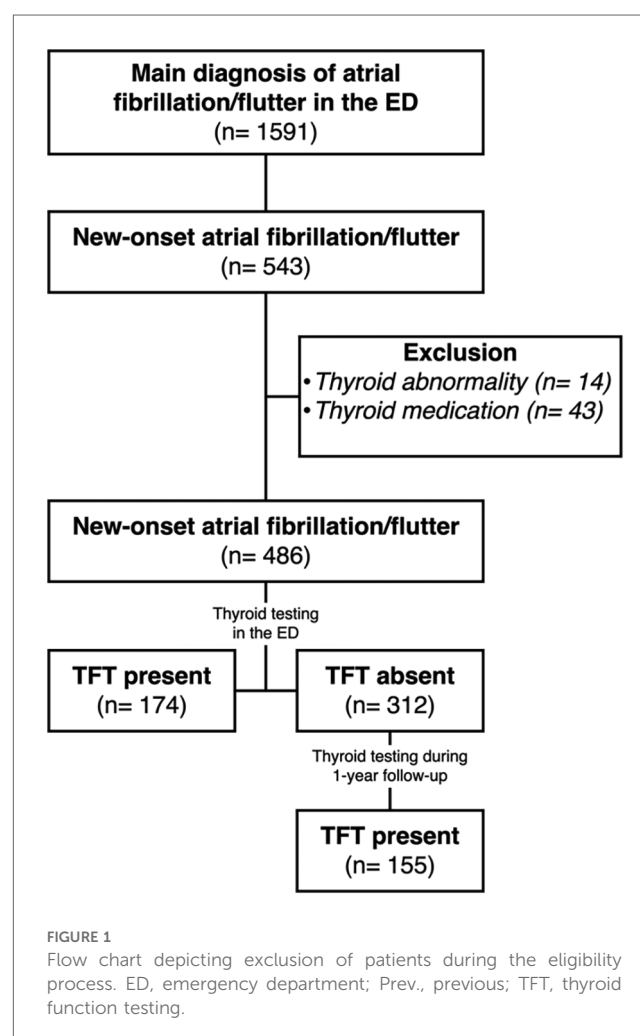
This was a single-center, registry-based, cohort study including all patients aged 18 years or older diagnosed with acute NOAF [International Statistical Classification of Diseases and Related Health Problems (ICD) –10 I48] visiting the ED during the years 2018, 2020, and 2022 at Vrinnevi Hospital, Norrköping, Sweden (catchment area of 180,000 inhabitants). A review of medical records was performed to confirm acute NOAF diagnosis by interpretation of electrocardiograms (ECGs) (obtained in the ED or in the ambulance). Patients with prior AF, thyroid dysfunction within two years before the ED visit, or those currently prescribed thyroid hormone replacement therapy were excluded. For patients who had multiple emergency

department visits during the study period, data from their initial admission was included, while information from any subsequent re-admissions was excluded, (Figure 1).

The study was approved by the Swedish Ethics Review Authority (2021-05963-01) and adhered to the principles of the Declaration of Helsinki. According to Swedish legislation, patients registered in healthcare quality registers are not required to provide written informed consent for their data to be used in healthcare research or publication (20).

Data sources

Data were obtained by Region Ostergötland decision support and follow-up system (REBUS) and medical records using the unique national identification number assigned to every Swedish resident at birth or at residency. Personal identification numbers given at birth or residency indicate the assigned sex by the penultimate number. Data collected from REBUS included date of visit at the ED, diagnosis (ICD 10), age, sex, date of discharge, and date of death. Data at the time of AF diagnosis regarding: CV risk factors (CVRf) [smoking, obesity (body mass index BMI ≥ 30 kg/m²)] and comorbidities [heart failure (ICD-10 I50),



ischemic heart disease (I20-I25), diabetes mellitus (E10), hypertension (I10)] were recorded. Additionally, heart rhythm (from ECG) and lab results [high sensitivity Troponin T (hsTnT), N-Terminal pro-B-type Natriuretic Peptide (NT-proBNP), hemoglobin, C-Reactive Protein (CRP), and blood glucose] were extracted from the medical records.

Thyroid testing and interpretation

TSH and free thyroxine (fT4) levels were obtained from medical records at the ED visit, as well as those lab results recorded within two years prior to the ED visit. Since the regional guidelines for thyrotoxicosis recommend initial testing with only TSH and fT4 in patients with a suspicion of hyperthyroidism, we did not have information regarding triiodothyronine (fT3) levels. Furthermore, for patients who had not undergone a thyroid function test either previously or in the emergency department, TSH and fT4 levels were evaluated during a 1-year follow-up period through their medical records.

Thyroid dysfunctions were classified according to local reference values (TSH 0.3–4.2 mIE/L and fT4 12–22 pmol/L), (Supplementary Table S1) (21–23). Thyroid function tests were analyzed with electrochemiluminescence immunoassay using Cobas e601 and e602 (Roche, Basel, Switzerland).

Outcome

The primary outcome was the detection of clinical or subclinical thyrotoxicosis as well as subclinical hypothyroidism in patients diagnosed with NOAF in the ED.

Statistical analysis

Baseline data is presented for the entire cohort and then divided into two groups: patients who received thyroid tests and patients who did not. The Kolmogorov-Smirnov test was used on continuous variables to determine whether data followed normal distribution. Continuous data, where normal distribution was not rejected, were presented with mean and standard deviation (SD). Continuous data with skewed distribution were presented with median with interquartile range (IQR). Categorical data were presented as number (*n*) and percent (%). Between-group differences regarding qualitative data were tested for statistical significance using the chi-squared test. If more than 20% of cells had a frequency <5 Fisher's exact test was used. The two sample *t*-test was used for comparison of normally distributed variables between two groups of independent samples, and the Mann-Whitney *U*-test was used on continuous variables that had a skewed distribution.

For statistical analysis, IBM SPSS, Statistics, 28.0 (Armonk, NY, USA) was used. A value of $p < 0.05$ was set as level of statistical significance.

Results

The study included 1,591 patients with AF during the years of 2018, 2020, and 2022. Of these, 486 patients [median age 73.1 years (IQR 62.6–79.8) and 43.6% female] were eligible for analysis, (Figure 1). Comorbidities were common, including hypertension (63.2%), obesity (34.8%), heart failure (16.9%), ischemic heart disease (18.9%), and type 2 diabetes mellitus (14.7%). Baseline characteristics are presented in Table 1.

Out of the 486 patients diagnosed with acute NOAF, 174 (35.8%) underwent thyroid function testing in the ED (43.6% females). During the 1-year follow-up, an additional 155 patients were tested (49.0% females), bringing the total to 329 (67.7%) patients who underwent thyroid testing within the first year of their NOAF diagnosis (46.2% females), (Figure 1). For all the tested patients, the median TSH level was 1.7 (1.2–2.9) mIE/L and fT4 level was 16.4 (15.0–18.1) pmol/L.

Overall, 31 patients (9.4%) with NOAF were found to have previously undiagnosed thyroid hormone abnormalities. Among them, 16 patients (4.9%) had subclinical hypothyroidism, and 4 patients (1.2%) had clinical or subclinical thyrotoxicosis. Regarding subclinical hypothyroidism, 11 patients (3.3%) were diagnosed in the ED, while an additional 5 patients (1.6%) were diagnosed during the 1-year follow-up. Regarding thyrotoxicosis, no cases of clinical or subclinical thyrotoxicosis were diagnosed in the ED, while 1 patient (0.3%) was diagnosed with clinical thyrotoxicosis and 3 patients (0.9%) were diagnosed with subclinical thyrotoxicosis during the 1-year follow-up, (Figure 2). No patients with confirmed thyroid dysfunction received Amiodarone prior to their thyroid function testing, 1 patient diagnosed with subclinical hypothyroidism later received Amiodarone in an outpatient setting. Additionally, 4 patients diagnosed with subclinical hypothyroidism and 1 patient with overt thyrotoxicosis later presented with normalized thyroid function within the follow-up period (re-evaluation occurred within 1–5 months after the initial testing for all but one patient, where it occurred within 9 months). Furthermore, 8 patients diagnosed with subclinical hypothyroidism and 2 patients with subclinical thyrotoxicosis had no re-evaluation within the 1-year follow-up, (Supplementary Table S2).

Patients screened for thyroid dysfunction in the ED were significantly younger (median age 69.3 vs. 75.0 years) than those who were not tested ($p < 0.001$), had a lower incidence of hypertension (56.3% vs. 67.0%, $p = 0.019$), and were less likely to have undergone previous thyroid testing (17.8% vs. 31.4%, $p = 0.001$) compared to those not tested. Differences were also observed in CRP levels between the groups ($p = 0.023$), although the median CRP level for both groups was the same at 2.5 mg/L, (Table 1). Additionally, patients tested and then diagnosed with clinical thyrotoxicosis, subclinical thyrotoxicosis, or subclinical hypothyroidism did not significantly differ in clinical characteristics when compared to those with normal thyroid function, (Table 2).

TABLE 1 Demographic and clinical characteristics of 486 patients with new-onset atrial fibrillation/flutter in the emergency department at Vrinnevi hospital Norrköping, Sweden in 2018, 2020, and 2022.

<i>n</i> (% of total)	Total 486	Thyroid testing in the ED 174 (35.8)	No thyroid testing in the ED 312 (64.2)	<i>p</i> -value
Female, <i>n</i> (%)	212 (43.6)	76 (43.6)	136 (43.6)	0.985
Median age, years median (IQR)	73.1 (62.6–79.8)	69.3 (56.4–76.8)	75.0 (66.5–80.9)	<0.001
Age groups, <i>n</i> (%)				<0.001
<60 years	98 (20.2)	54 (31.0)	44 (14.1)	
61–70 years	98 (20.2)	36 (20.7)	62 (19.9)	
71–80 years	175 (36.0)	57 (32.8)	118 (37.8)	
≥80 years	115 (23.7)	27 (15.5)	88 (28.2)	
Comorbidities and CVRF, <i>n</i> (%)				
Heart failure	82 (16.9)	25 (14.4)	57 (18.3)	0.271
Ischemic heart disease	91 (18.7)	32 (18.4)	59 (18.9)	0.888
Diabetes mellitus type 2	72 (14.8)	19 (10.9)	53 (17.0)	0.071
Hypertension	307 (63.2)	98 (56.3)	209 (67.0)	0.019
Smoking ^a	61 (13.9)	23 (14.2)	38 (13.7)	0.889
Obesity (BMI >30 kg/m ²) ^b	146 (34.8)	59 (38.8)	87 (32.6)	0.198
1-year mortality, <i>n</i> (%)	42 (8.6)	14 (8.0)	28 (9.0)	0.727
Heart rate, beats/min mean (SD)	124 (30)	127 (29)	122 (31)	0.064
ECG rhythm, <i>n</i> (%)				
Atrial fibrillation	400 (82.3)	138 (79.3)	262 (84.0)	0.245
Atrial flutter	84 (17.3)	36 (20.7)	48 (15.4)	
Pacemaker rhythm	2 (0.4)	0 (0)	2 (0.6)	
Laboratory findings				
hsTnT, ng/L median (IQR) ^c	17 (9–28)	16 (9–25)	18 (9–28)	0.257
NT-pro-BNP, ng/L median (IQR) ^d	1,825 (658–4,143)	1,410 (485–3,982)	2,030 (840–4,235)	0.168
TSH, mIE/L median (IQR)	–	1.7 (1.2–2.9)	–	na
fT4, pmol/L median (IQR)	–	16.4 (15.0–18.1)	–	na
Hemoglobin, g/L median (IQR) ^e	144 (133–154)	146 (136–154)	143 (132–154)	0.078
CRP, mg/L median (IQR) ^f	2.5 (2.5–10)*	2.5 (2.5–14)*	2.5 (2.5–8)*	0.023
Creatinine, μmol/L median (IQR) ^e	81 (69–97)	79 (67–95)	83 (71–99)	0.056
Blood glucose, mmol/L median (IQR) ^g	6.3 (5.4–7.0)	6.3 (5.5–6.9)	6.1 (5.3–6.8)	0.928
Previous thyroid testing, <i>n</i> (%)	129 (26.5)	31 (17.8)	98 (31.4)	0.001

P-values are presented for the groups: thyroid testing in the ED vs. no thyroid testing in the ED. ED, emergency department; ECG, electrocardiography; CVRF, cardiovascular risk factors; BMI, body mass index; hsTnT, high sensitivity Troponin-T; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; TSH, thyroid stimulating hormone; fT4, free thyroxine hormone; CRP, C-reactive protein; n, numbers; SD, standard deviation; IQR, interquartile range; na, not applicable.

Data missing for:

^a47 patients.

^b67 patients.

^c72 patients.

^d330 patients.

^e3 patients.

^f43 patients.

^g266 patients.

*For analytical purposes, CRP levels below the lower level of detection (i.e., values <5) were assigned the value of 2.5.

Discussion

Abnormal thyroid hormone levels are an established risk factor for NOAF and recently subclinical hypothyroidism has been highlighted as a clinically relevant disturbance in patients with NOAF (13, 24). The findings in the current study are, to the best of our knowledge, the first to show that subclinical hypothyroidism might be more prevalent than thyrotoxicosis in patients with acute NOAF diagnosed in the ED, with a prevalence of 4.9% compared to 1.2%.

Thyroid dysfunctions are sparsely studied in acute NOAF diagnosed in the ED, and studies have primarily focused on thyrotoxicosis. Buccelletti et al. (19) found by analyzing TSH levels solely that thyrotoxicosis was common, suggesting a prevalence as

high as 10.8% vs. 1.2% in the current study. This discrepancy may be attributed to various factors, such as differences in diagnostic thresholds and laboratory assays when diagnosing thyrotoxicosis as well as differences in populations and geographic variations in thyroid disease prevalence. It should be noted that there are differences in the annual incidence of hyperthyroidism in Sweden compared to i.e., northern Italy (0.03% vs. 0.08% respectively), which may account for some of the observed difference (25, 26). Furthermore, when differentiating thyroid disorders, it is essential to understand that TSH levels alone are insufficient for distinguishing between clinical thyrotoxicosis, subclinical thyrotoxicosis, non-thyroidal illness, and central hypothyroidism, as well as between clinical and subclinical hypothyroidism. To improve accuracy and decrease the risk of overestimating non-significant thyroid

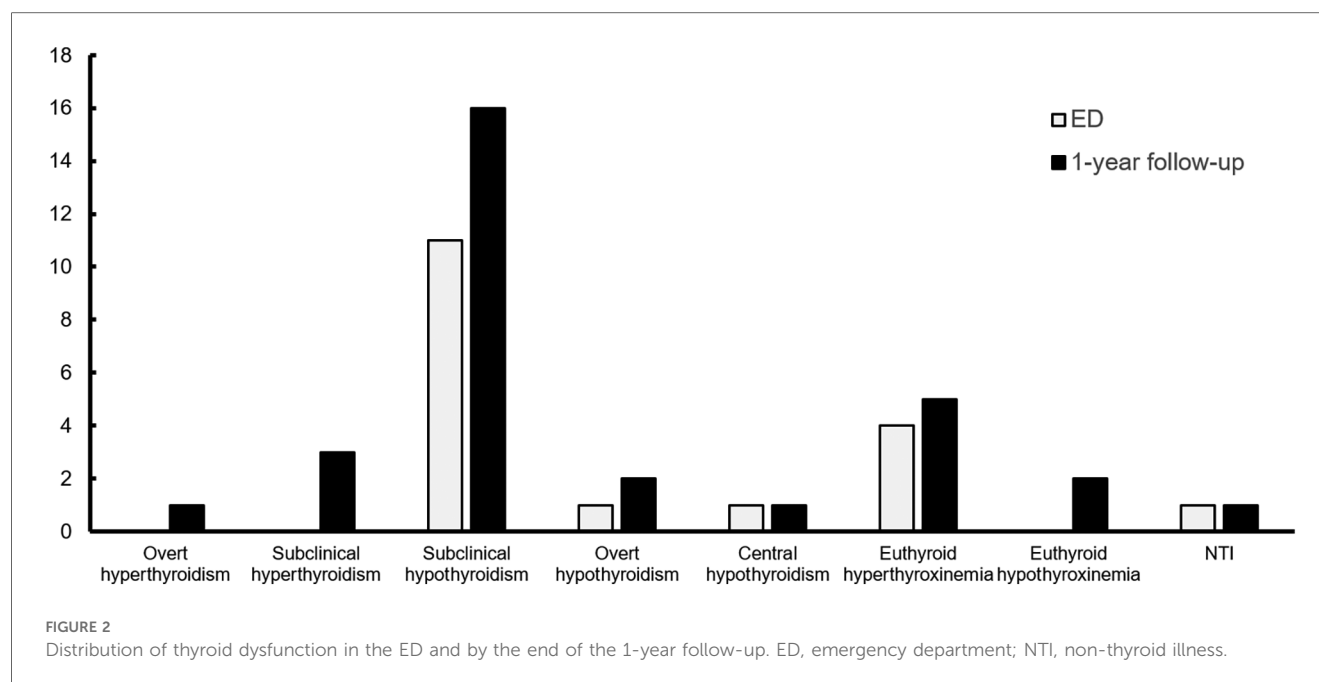


TABLE 2 Demographic and clinical characteristics of patients with normal thyroid function and thyroid dysfunctions associated with new-onset atrial fibrillation/flutter diagnosed in the emergency department at Vrinnevi hospital Norrköping, Sweden in 2018, 2020, and 2022.

<i>n</i> (% of total)	Normal thyroid function 298 (93.7)	Thyroid dysfunctions* 20 (6.3)	<i>p</i> -value
Female, <i>n</i> (%)	133 (44.6)	12 (60.0)	0.182
Median age, years (IQR)	72.0 (61.0–78.0)	74.5 (58.25–81.0)	0.468
Comorbidities and CVRF, <i>n</i> (%)			
Heart failure	51 (17.1)	4 (20.0)	0.741
Ischemic heart disease	55 (18.5)	3 (15.0)	0.673
Diabetes mellitus type 2	36 (12.1)	1 (5.0)	0.488
Hypertension	191 (64.1)	15 (75.0)	0.323
Smoking ^a	38 (12.8)	3 (18.8)	0.573
Obesity (BMI >30 kg/m ²) ^b	93 (31.2)	7 (41.2)	0.628
1-year mortality, <i>n</i> (%)	19 (6.4)	1 (5.0)	1.000
Heart rate, beats/min mean (SD)	125 (30)	127 (34)	0.790
ECG rhythm, <i>n</i> (%)			
Atrial fibrillation	242 (81.2)	16 (80.0)	1.000
Atrial flutter	56 (18.8)	4 (20.0)	
Pacemaker rhythm	0 (0)	0 (0)	
Laboratory findings			
hsTnT, ng/L median (IQR) ^c	16 (10–25)	24 (16–40)	0.037
NT-pro-BNP, ng/L median (IQR) ^d	1,730 (620–3,828)	4,520 (390–6,070)	0.309
Hemoglobin, g/L median (IQR) ^e	144 (134–153)	145 (131–153)	0.974
CRP, mg/L median (IQR) ^f	2.5 (2.5–9.0)**	6.0 (2.5–32)**	0.200
Creatinine, μmol/L median (IQR) ^e	81 (68–95)	77 (67–93)	0.558
Blood glucose, mmol/L median (IQR) ^g	6.1 (5.4–6.9)	7.0 (5.6–7.4)	0.287
Previous thyroid testing, <i>n</i> (%)	76 (25.5)	5 (25.0)	0.960

ED, emergency department; ECG, electrocardiography; CVRF, cardiovascular risk factors; BMI, body mass index; hsTnT, high sensitivity Troponin-T; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; TSH, thyroid stimulating hormone; fT4, free thyroxine hormone; CRP, C-reactive protein; n, numbers; SD, standard deviation; IQR, interquartile range; na, not applicable.

Data missing for:

^a21 patients.

^b35 patients.

^c44 patients.

^d194 patients.

^e1 patient.

^f27 patients.

^g163 patients.

*Clinical thyrotoxicosis, subclinical thyrotoxicosis, and subclinical hypothyroidism.

**For analytical purposes, CRP levels below the lower level of detection (i.e., values <5 mg/L) were assigned the value of 2.5.

dysfunctions, additional factors like the clinical context and biomarkers such as fT4 should be included (23).

Conversely, the prevalence of thyroid dysfunctions in the general NOAF population has been extensively studied, but the focus has primarily been on thyrotoxicosis, while subclinical hypothyroidism has often been overlooked. However, a study by Selmer et al. (12) employed a comprehensive diagnostic approach that included both TSH and fT4 levels and presented data on thyrotoxicosis as well as subclinical hypothyroidism, an approach adopted in the current study. Selmer et al. reported a prevalence of 2.7% for thyrotoxicosis and 5.7% for subclinical hypothyroidism, findings that align with the current study. Furthermore, Boriani et al. showed a similar prevalence of thyrotoxicosis (3%) in the general NOAF population. Additionally, Boriani et al. (16) included cases of hypothyroidism but did not differentiate between subclinical and clinical cases. Krahn et al. (15) reported a higher prevalence of thyrotoxicosis (5.4%) in the general NOAF population; however, they did not account for subclinical hypothyroidism and relied on TSH levels for diagnosis. As previously noted, this approach may lead to an overestimation of thyrotoxic cases. The above findings, in synthesis with the findings in the current study, suggest that the prevalence of significant thyroid dysfunctions in acute NOAF diagnosed in the ED is similar to that observed in the general NOAF population.

This study used data from high-quality patient registers with low dropout rates. Nevertheless, studies based on registers and patient medical records invariably encounter issues such as selection bias, confounding variables, measurement inaccuracies, and reporting biases. The hospital houses the only ED in the catchment area, providing a comprehensive real-life population of all NOAF patients diagnosed in the ED within the region. However, even though this study covers the total population of NOAF in the catchment area, the cohort size is limited. While the cohort size is similar to Buccelletti et al. (19), it is smaller than in recent studies of the general NOAF population (16, 17, 19). Within this cohort, only a third underwent thyroid testing in the ED and two thirds totally during the 1-year follow-up which may limit the generalizability of the results. Furthermore, it should be acknowledged that those with newly detected thyroid abnormalities during follow-up may not have had a thyroid dysfunction at the time of admission to the ED, and previous studies have found that NOAF is an independent predictor of subsequent thyrotoxicosis (17, 27). The 1-year follow-up in this study introduces a potential risk of overestimating the prevalence of thyrotoxicosis in the ED; nonetheless, the observed prevalence was notably lower than previously reported. Given that NOAF serves as a risk factor for subsequent thyrotoxicosis and considering the lower prevalence in this study compared to previous studies, the 1-year follow-up might not introduce a significant weaknesses in the study design. Subclinical hypothyroidism has been shown to resolve spontaneously in a majority of cases, suggesting that the follow-up could lead to an underestimation of its prevalence (28). The prevalence of subclinical hypothyroidism tends to increase with age, and the median age of 73 years in the current study may have contributed to the higher prevalence observed compared to thyrotoxicosis.

This age-related trend highlights the importance of considering demographic factors when interpreting differences in prevalence between these conditions (29). Additionally, the absence of fT3 levels in the current study is a limitation. However, it does not significantly impact the findings, as the comprehensive use of TSH and fT4 levels still provides a robust assessment of thyroid function.

The clinical implications of these findings are yet to be determined, and the effects of treating subclinical hypothyroidism in patients with NOAF needs further inquiry (24, 30). As recently reviewed, most guidelines recommend treatment for subclinical hypothyroidism only for patients exhibiting symptoms of hypothyroidism, or for those with TSH levels exceeding 10 mIE/L (31). Observational data have suggested a potential CV benefit from active treatment but randomized trials are needed for any firm conclusions to be drawn (32). Whether NOAF should be considered a symptom of subclinical hypothyroidism remains uncertain but cases of AF resolution have been documented following the treatment of subclinical hypothyroidism (33, 34). Larger multicenter studies involving diverse populations seem to be needed to confirm the prevalence rates of subclinical hypothyroidism and thyrotoxicosis in acute NOAF patients. Exploring geographic and demographic variations could identify populations at higher risk and inform targeted interventions to increase adherence to ESC guidelines regarding thyroid hormone testing. Furthermore, younger age and the absence of previous thyroid function testing were factors associated with a higher frequency of thyroid testing in NOAF. However, these factors did not significantly differentiate between those with a diagnosed thyroid disease and those without. This suggests that while certain demographic and clinical factors may influence the decision to conduct thyroid testing, they are not reliable indicators of underlying thyroid pathology in acute NOAF.

Conclusion

In conclusion, subclinical hypothyroidism was more frequently prevalent than thyrotoxicosis (4.9% vs. 1.2%) in patients diagnosed with acute NOAF, suggesting it may play a more significant role than previously recognized. These findings suggest that there is a need for further studies including both thyrotoxicosis as well as subclinical hypothyroidism in acute NOAF and further research into the clinical implications of subclinical hypothyroidism in this population.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Swedish Ethics Review Authority DNR: 2021-05963-01. The studies were

conducted in accordance with the Swedish legislation and institutional requirements. Written informed consent for participation was not required from the participants' or their legal guardians/next of kin because the study was registry-based. According to Swedish legislation, patients registered in healthcare quality registers are not obligated to provide written informed consent for their data to be used in healthcare research or for the publication of research findings.

Author contributions

JH: Conceptualization, Formal Analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. SC: Methodology, Project administration, Writing – review & editing. LB: Methodology, Project administration, Writing – review & editing. PM: Writing – review & editing. CD: Writing – review & editing. AW: Writing – review & editing. MW: Formal Analysis, Methodology, Writing – review & editing. MS: Formal Analysis, Methodology, Writing – review & editing. LH: Conceptualization, Formal Analysis, Funding acquisition, Methodology, Project administration, Resources, Writing – review & editing.

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Conflict of interest

MW has served on advisory boards and/or lectured for Astra Zeneca MSD, Lilly, Novo Nordisk and Sanofi, and has organized a professional regional meeting sponsored by Lilly, Rubin Medical, Sanofi, Novartis and Novo Nordisk. LH reports unrelated modest consultation fees from Astellas, Bayer, and Orion Pharma.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fcvm.2024.1518297/full#supplementary-material>

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The relationship between the 3D electroanatomical mapping parameters of the left atrial posterior wall and the recurrence of paroxysmal atrial fibrillation

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Background: Pulmonary vein isolation (PVI) remains the cornerstone of catheter ablation in paroxysmal atrial fibrillation (PAF). However, the recurrence of AF after PVI needs further investigation. The left atrial posterior wall (LAPW) is embryologically related to the pulmonary vein and plays an important role in the initiation and maintenance of AF. This study aims to explore the relationship between the 3D electroanatomical mapping parameters of the LAPW and recurrence in patients with PAF.

Methods: A retrospective analysis was conducted on patients with PAF who underwent PVI. Both clinical and procedural characteristics from the enrolled subjects were collected before PVI. 3D electroanatomical mapping anatomical and electrical parameters were measured and calculated in the CARTO system. Intergroup comparisons and multivariate logistic regression analysis were performed to demonstrate the relationship between the parameters of LAPW and AF recurrence. A combined prediction model for AF recurrence was constructed in this study.

Results: A total of 120 patients were included in the final analysis. Among procedural characteristics, compared with Group 1 (no recurrence), there was a significantly larger posterior wall surface area (PWSA) ($p = 0.013$) and a percentage of very low-voltage area (PVLVA) ($p < 0.001$) in Group 2 (recurrence). Further analysis revealed that there was a significant difference between the two groups in terms of the distribution of VLVA ($p = 0.026$). Subsequently, in a multivariate logistic regression analysis, both PWSA and PVLVA were found to be independent risk factors for AF recurrence [odds ratio (OR): 1.457, 95% confidence interval (CI): 1.037–2.049, $p = 0.030$; OR: 1.059, 95% CI: 1.013–1.107, $p = 0.012$, respectively]. Finally, a prediction model that combined the PWSA with the PVLVA for AF recurrence was constructed to draw the receiver operating characteristic curve. The area under the curve of this model was 0.900 (0.827–0.973) ($p < 0.001$). The result, evaluated by using the Hosmer–Lemeshow goodness-of-fit test, showed that $\chi^2 = 4.643$ ($p = 0.796$).

Conclusions: This study demonstrates that both PWSA and PVLVA were independent risk factors for AF recurrence. Moreover, we proposed a model that combined the PWSA with the PVLVA to predict the recurrence of AF, which may provide an approach for screening patients with PAF who may require attention for the LAPW.

KEYWORDS

paroxysmal atrial fibrillation, left atrial posterior wall, 3D electroanatomical map, pulmonary vein isolation, recurrence

Introduction

Atrial fibrillation (AF) is an arrhythmia with increasing global incidence and prevalence (1, 2). AF is associated with serious adverse events and increased mortality (3–5). More and more evidence has shown that catheter ablation is an important approach for rhythm control in patients with paroxysmal AF (PAF) (6, 7), which also leads to a lower risk of adverse cardiovascular outcomes (8) and improvement in quality of life (9). Nowadays, pulmonary vein isolation (PVI) remains the cornerstone of catheter ablation in AF (7, 10). However, AF recurrence after catheter ablation remains a clinical concern (11, 12), which eventuates excess suffering in, and economic burden on, patients (13).

The left atrial (LA) posterior wall (PW) has been shown to contribute to the initiation and maintenance of AF (14, 15). As a consequence, ablation in the LAPW has evolved as a strategy in surgery (16). Notably, the LAPW and the esophagus are adjacent anatomically (16). This may be the leading lesion to the esophagus when catheter ablation, especially radiofrequency ablation (RFA), is performed in the LAPW. Disastrous consequences may occur when LA-esophageal fistula forms (17). Accordingly, the option of PW isolation should be exercised with caution (18).

Presently, research studies on LAPW ablation mostly focus on non-PAF (19, 20), but still traces of recurrence can be found in patients with PAF due to the triggering and maintenance mechanisms associated with the PW (21). It is worth studying how to identify these patients.

Currently, wide antral circumferential ablation of PVI is considered to be an effective measure to reduce AF recurrence (22), as the myocardium in the expansive area is thicker, resulting in a decrease in the first-pass isolation rate and an increase in the number of gaps (23). These are likely followed by a prolongation of operation time and an increase in complication rates. There is no unified standard ablation strategy for determining power, pressure, and duration time for PVI when targeted in the LAPW. The selection of a different ablation index (AI) would vary according to the degree of pain experienced by patients and concerns for the occurrence of LA-esophageal fistula. Hence, it is worth considering which patient is more suitable for wide antral ablation and for selecting an increased AI in the LAPW.

A three-dimensional (3D) electroanatomical model reconstructed by the CARTO-3 mapping system (version 6.0, Biosense Webster, Inc.) with non-fluoroscopy displays a very realistic model (24),

which is in excellent concordance with CT (25). The area and the voltage of the LAPW can be determined in the CARTO system. This study aims to detect the relationship between the parameters of the LAPW in the 3D electroanatomical map and recurrence in patients with PAF.

Methods

Research subjects

A single-center, retrospective cohort method was performed in this study. Patients with PAF admitted to the Changzhou Hospital of Traditional Chinese Medicine from January 2021 to August 2023 and scheduled to undergo RFA were enrolled in this research. Inclusion criteria were as follows: (1) older than 18 years old; (2) diagnosis of PAF (defined as a sustained episode lasting <7 days or chemical and/or electrical cardioversion <7 days); (3) sinus rhythm when mapping; (4) patients who had received PVI alone; (5) complete basic information, procedure, and follow-up data. Exclusion criteria included: (1) severe organic heart disease (such as severe mitral regurgitation or stenosis, severe aortic regurgitation or stenosis, hypertrophic obstructive cardiomyopathy, etc.); (2) history of previous cardiac surgery; (3) patients with incomplete clinical and follow-up data. This study adhered to the Helsinki Declaration and received approval from the Scientific Ethics Committee of Changzhou Hospital of Traditional Chinese Medicine (2023-LL-0171); it was already registered in the Chinese Clinical Trial Registry (ChiCTR2300079137).

Catheter ablation

Catheter ablation was carried out in the CARTO system. All procedures were performed without interruption of anticoagulant therapy and off antiarrhythmic medications. The high-density multielectrode mapping catheter [PentaRay (Biosense Webster, Inc.)] and irrigated contact force sensing ablation catheter [Thermocool SmartTouch ST or STSF (Biosense Webster, Inc.)] were introduced into the left atrium with transseptal puncture.

PentaRay reconstructed the electroanatomical map of the left atrium, including the main part of the left atrium, the left atrial appendage (LAA), and the pulmonary veins (PVs) after excluding the inspiratory phase through fast anatomical mapping (FAM). Then, ST or STSF examined the true boundary of the

map further through contact force. Thus, a more realistic LA model could be revealed.

Ablation was performed with ST or STSF at a power of 35 W. The discharge time was determined according to the AI at each tag, with an intertag distance ≤ 6 mm. A target AI of 480–530 for the roof, anterior, and ridge; 420–450 for the inferior; and 360–380 for the posterior were recommended. PVI was defined by PV entrance and exit block.

Clinical baseline indicators

Clinical baseline indicators of patients were collected, including gender, age, body mass index (BMI), duration of AF, CHA₂DS₂-VASc score, and medical history [including heart failure (HF), hypertension, diabetes mellitus (DM), and stroke or transient ischemic attack (TIA)].

Laboratory indicators [including urea nitrogen, creatinine, and N-terminal precursor protein brain natriuretic peptide (NT-proBNP)], and echocardiographic indicators [including the left atrial diameter (LAD), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), and left ventricular ejection fraction (LVEF)] were collected.

Acquisition of anatomical and electrical parameters in the electroanatomical map

Anatomical and electrical parameters were measured in the 3D electroanatomical map of the CARTO system. All parameters were obtained from the maps before ablation.

Because of the embryonic homology between the PW and the PVs, the area of the PV ostia was also measured in this study. A new map was saved (Map 1) after obtaining the initial map. In Map 1, we drew a short line along the axial direction of PVs from the superior, inferior, anterior, and posterior orientation to assist us in the next step (Figure 1). Then, we utilized the function of “clipping plane” to make a vertical section at the PV ostia [the right superior pulmonary vein (RSPV), the right inferior pulmonary vein (RIPV), the left superior pulmonary vein (LSPV), and the left inferior pulmonary vein (LIPV), respectively]. The measurement would be merged in the common pulmonary vein, and the accessory pulmonary vein was also measured if it resembled the main bifurcation. Subsequently, the diameters of the long axis (a) and the short axis (b) of each PV were measured separately (Figure 1). According to the calculation formula ellipse area = $\pi \times (a/2) \times (b/2)$, the PV ostia area was obtained. The total area of the right PV (RPV) and left

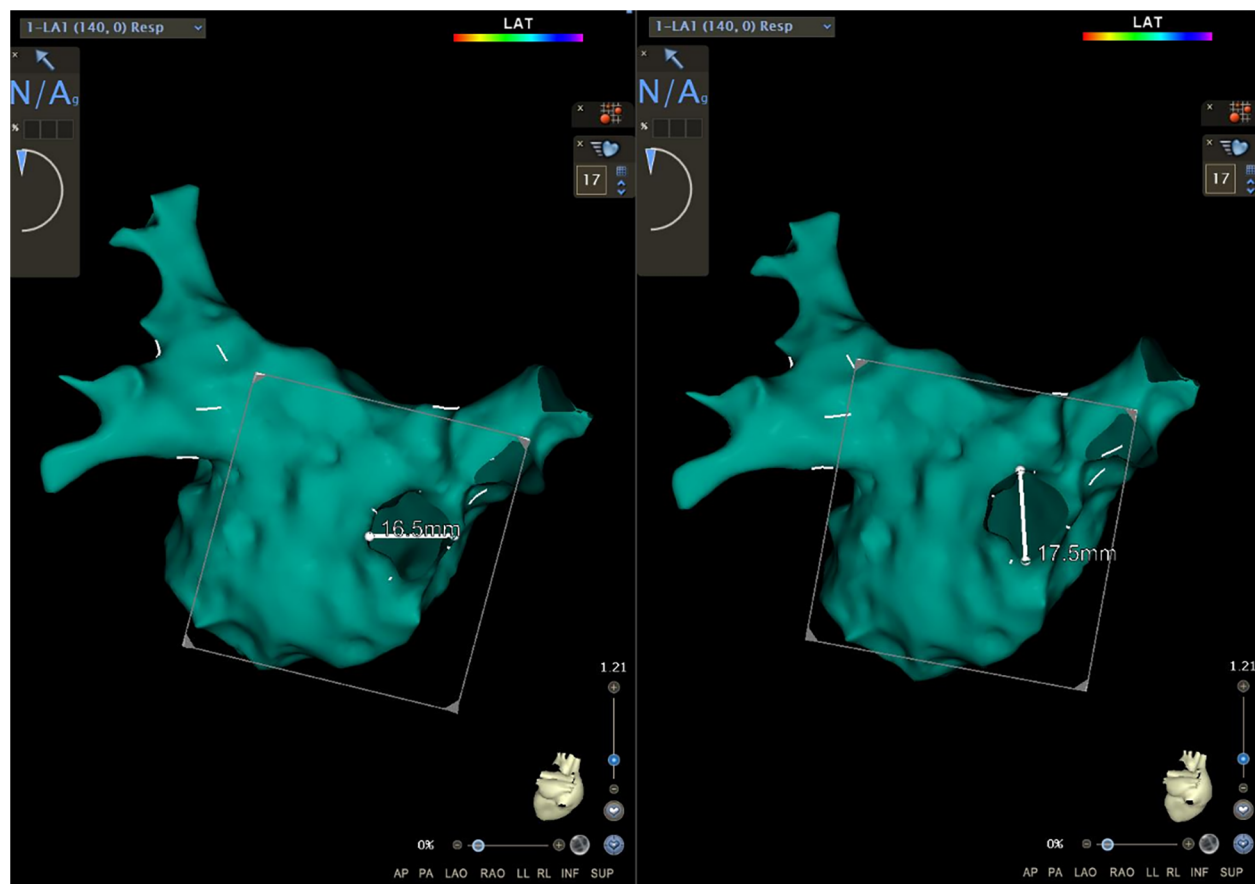


FIGURE 1

The function of the “clipping plane” was used to measure the diameters of the long axis and the short axis of each PV separately. RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein.

PV (LPV) was added up by each bifurcation. All parameters were measured independently by two researchers and an interobserver agreement was reached.

A map was saved again (Map 2) after completing this step. In Map 2, we drew another short line at the roof and the bottom of the PW. The inferior line was defined as a line located at the lowest margin between the RIPV and the LIPV in the posterior view (Figure 2a). The superior line was defined as a line that connected the middle of the LSPV and RSPV ostia in the superior view (SUP) (Figure 2b). The PW surface area (PWSA) was composed of the area delineated by the superior and inferior line and 0.5–1 cm outside the PV ostia. Then, the function of “area measurement” was used to measure and calculate the area (Figure 3).

The next step was to copy activation mapping points in the PW area to another map (Map 3) (Figure 4). In Map 3, after switching the bipolar map, we sorted all copied points by voltage (Figure 5). A very low-voltage area (VLVA) in the electrogram was defined as an amplitude of ≤ 0.1 mV. We subsequently counted the points with voltage ≤ 0.1 mV and calculated the percentage of the VLVA (PVLVA) in the LAPW (Figure 5).

In this study, we divided the distribution of the VLVA in the LAPW into two parts, namely, the connection of PVs and the LAPW (PV ostium in the PW) and the intra-atrial region in the PW (Figures 6a,b).

Follow-up

Procedural success was defined as freedom from recurrent atrial arrhythmias lasting longer than 30 s after an initial 3-month blanking period. Recurrent arrhythmias were classified as being AF, atrial tachycardia, or both. Patients underwent a clinical review and 24 h Holter monitoring at 3, 6, and 12 months.

Statistical analysis

Statistical analysis was performed using SPSS Statistics Software version 26 (IBM, Inc.). Measurement data that followed a normal distribution pattern are expressed as mean $\pm$ standard deviation ($x \pm s$). In cases where these data had a mildly skewed distribution, the median was used. Either an independent sample *t*-test or the Kruskal–Wallis test was performed in intergroup comparisons. Counting data were presented as a percentage, and intergroup comparisons were conducted using the chi-square test or Fisher's precision probability test. A univariate logistic regression analysis assessed the association of different factors and AF recurrence. After collinearity analysis (tolerance < 0.1 or variance inflation factor > 10 meant multicollinearity between variables), a multivariate logistic regression analysis was employed to evaluate which factor

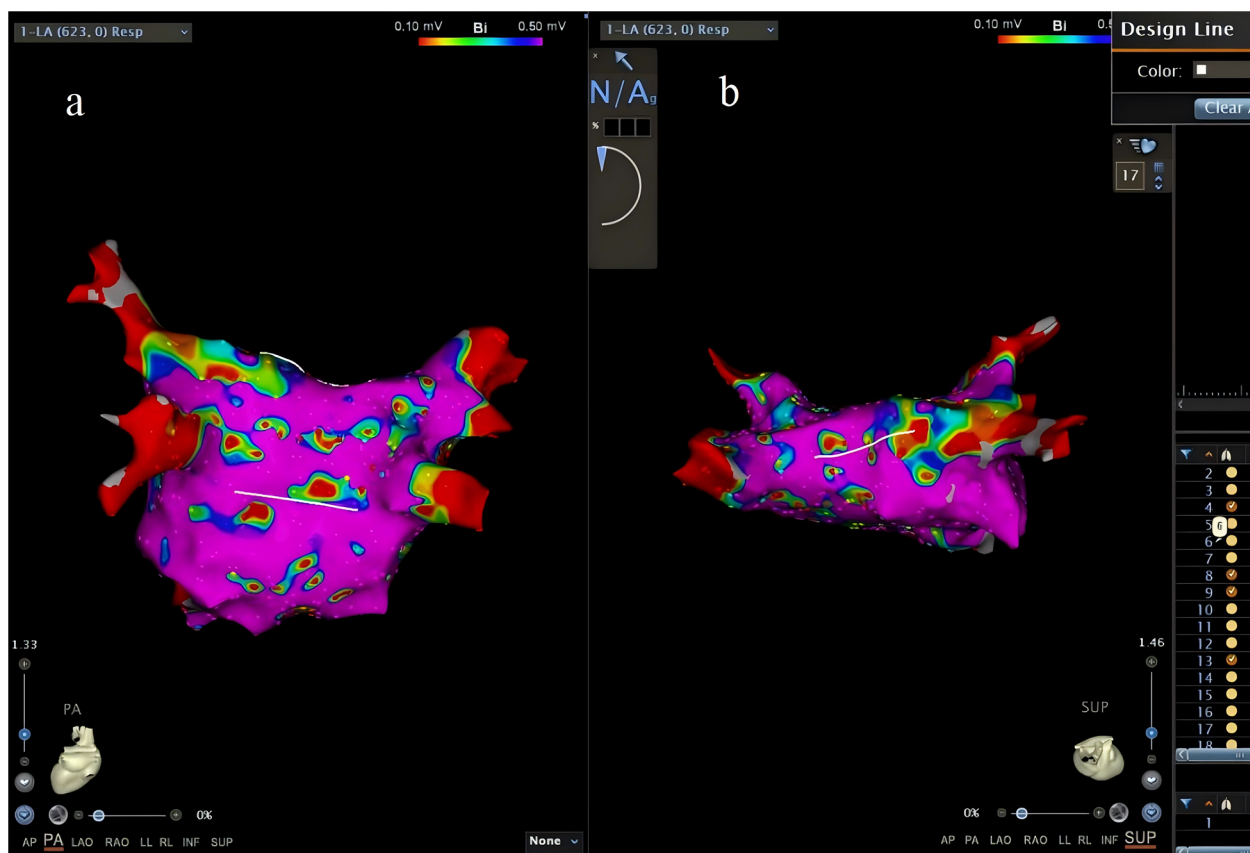


FIGURE 2
The inferior line (a) and the superior line (b) were drawn.

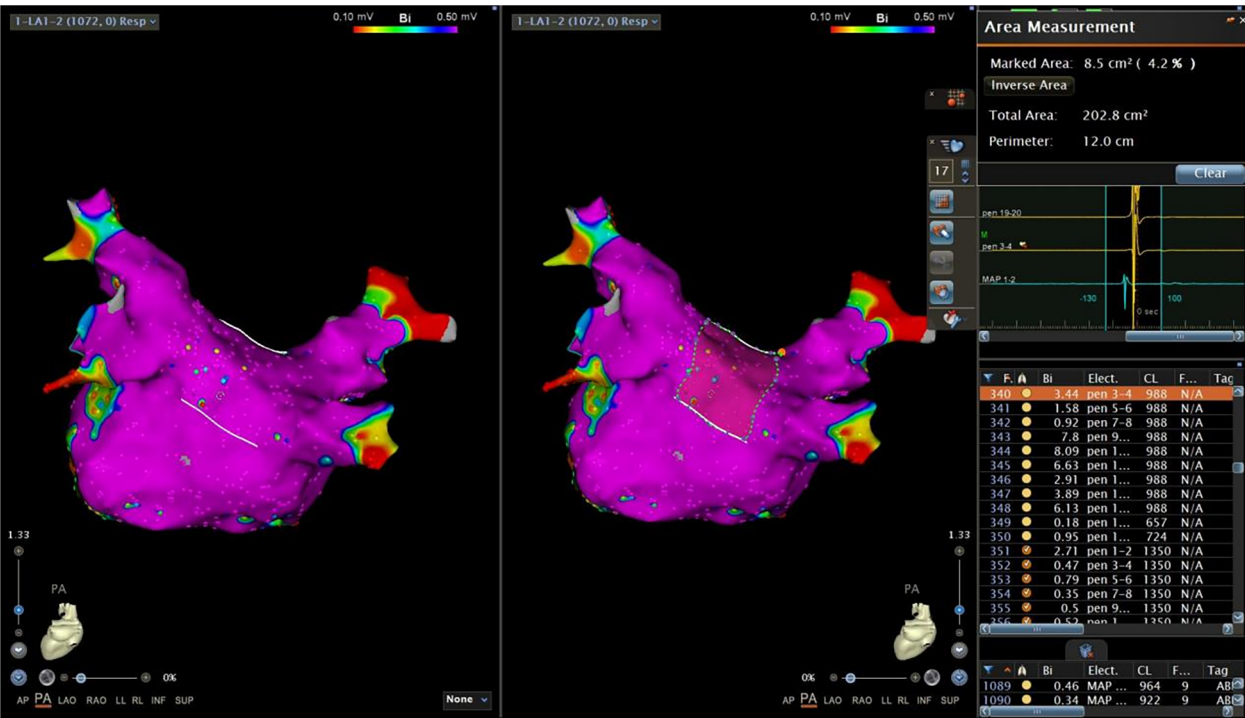


FIGURE 3
The function of “area measurement” was used to measure and calculate the PWSA. PWSA, posterior wall surface area.

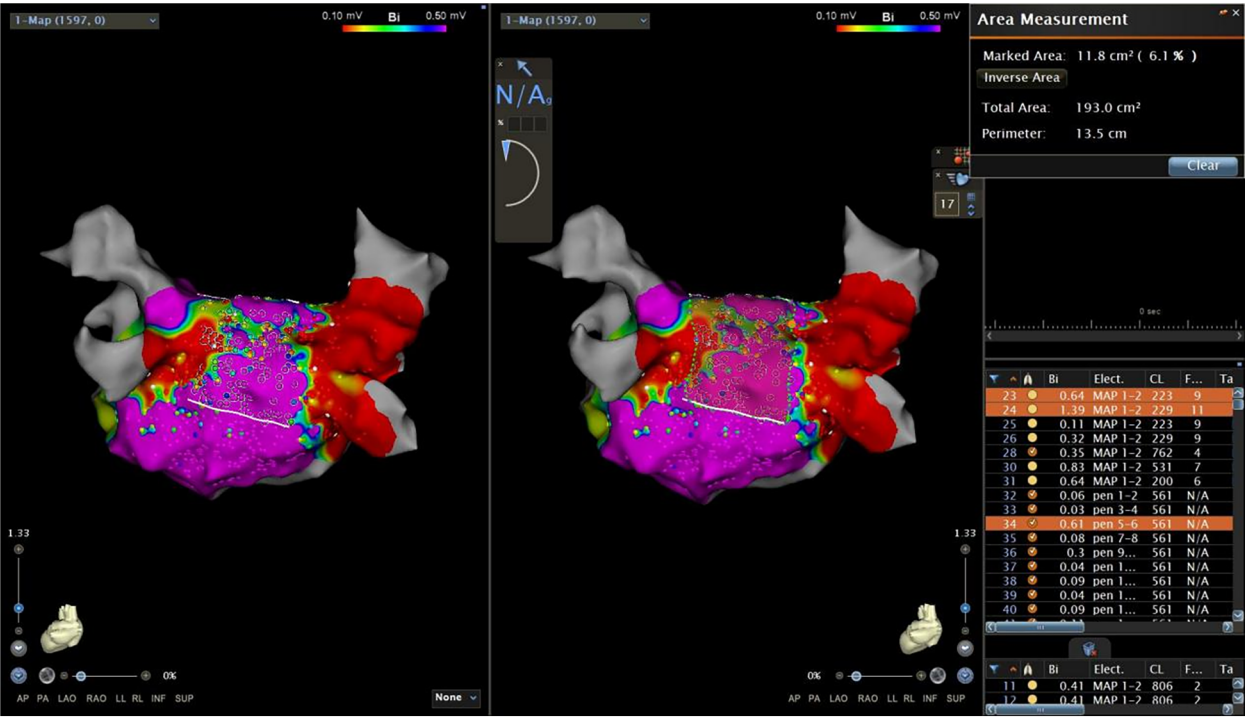


FIGURE 4
Copied activation mapping points in the PW area. PW, posterior wall.

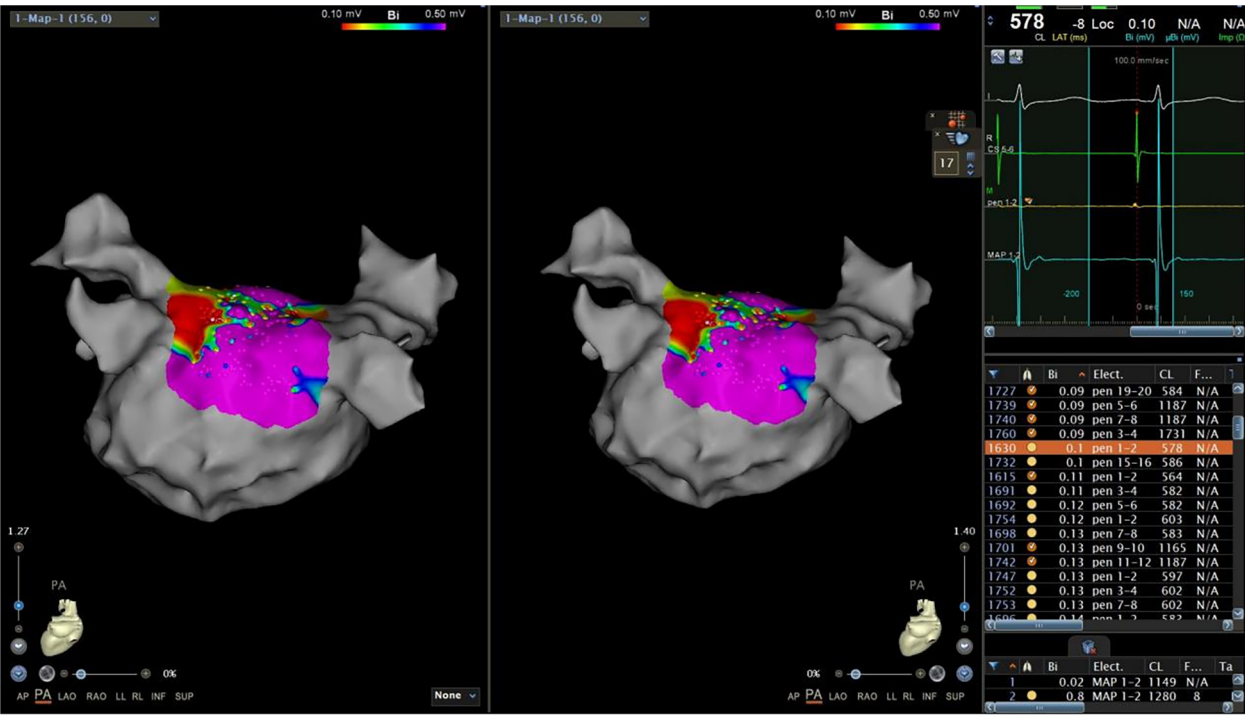


FIGURE 5 Copied points to another map and sorted all copied points by voltage.

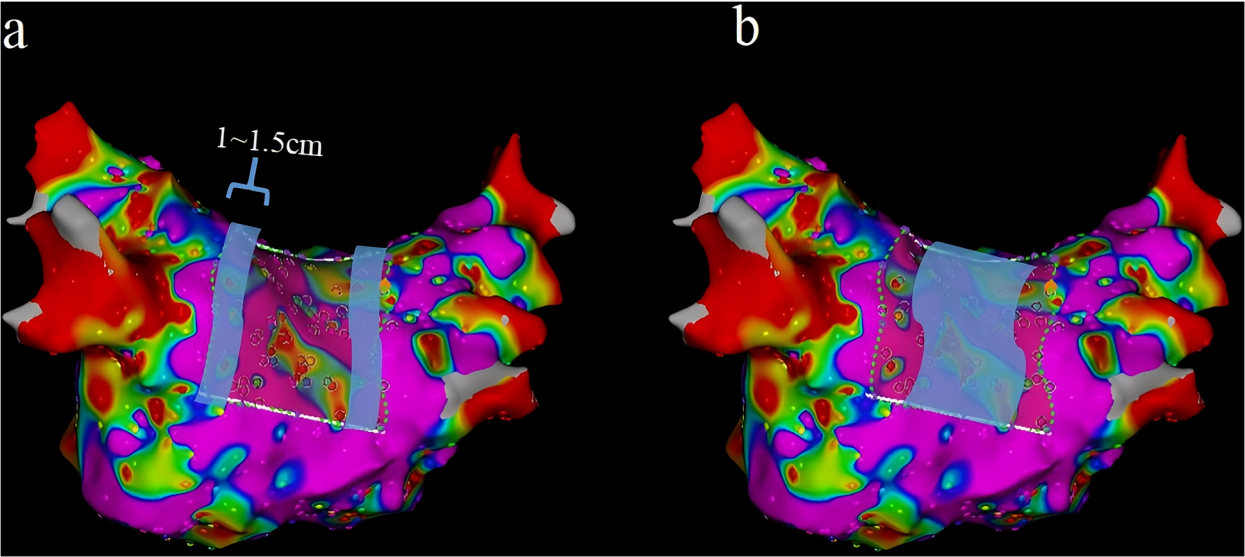


FIGURE 6 Two parts of the LAPW: PV ostium in the PW (the width was 1~1.5 cm) (a) and the intra-atrial region in the PW (b) LAPW, left atrial posterior wall; PV pulmonary veins.

was an independent risk factor for AF recurrence. A p -value <0.05 was considered statistically significant. If a covariate that changed the estimates of AF recurrence had a significant association ($p < 0.10$) in the univariate logistic regression analysis, it would be included as a potential confounding factor in the multivariate

logistic regression analysis. A receiver operating characteristic (ROC) curve was used to construct the combined prediction model for AF recurrence. If the area under the curve (AUC) was greater than 0.75, it indicated better predictive ability. A Hosmer–Lemeshow goodness-of-fit test was performed to evaluate the

calibration ability of the prediction model, and a p -value >0.05 was considered a good fit of the model.

Results

Baseline characteristics

According to the inclusion and exclusion criteria, a total of 128 patients were enrolled in this study. Of the initial participants, eight were excluded from the final analysis (including six incomplete data and two lost to follow-up) (Figure 7). Consequently, the baseline characteristics of 120 patients are presented in Table 1. According to the occurrence or non-occurrence of recurrent arrhythmias, these patients were divided into Group 1 (no recurrence) and Group 2 (recurrence). Group 1 comprised 49 males and 60 females, averaging 67.66 ± 12.60 years. Group 2 was composed of four males and seven females, averaging 67.18 ± 13.23 years. There was no significant difference between the two groups in terms of gender, age, BMI, duration of AF, CHA₂DS₂-VASc score, history of hypertension, DM and stroke, or TIA, except for a history of HF ($p = 0.028$). There was also no statistical difference in terms of urea nitrogen, creatinine, NT-proBNP, LAD, LVEDD, LVESD, and LVEF (Table 1).

Procedural characteristics

Procedural characteristics are presented in Table 2. The areas of the PV ostia (RPV and LPV, respectively) and the PWSA and the

PVLVA were measured and calculated. The complications were recorded. Among the procedural characteristics, patients in Group 2 were found to have a significantly larger PWSA ($p = 0.013$) and PVLVA ($p < 0.001$) (Table 2).

Analysis of the distribution of the VLVA

In patients with the VLVA in the LAPW, the proportions of distribution of the VLVA in the PV ostium in the PW, the intra-atrial region in the PW, and the mixed areas (contained both) were 60.0%, 20.0%, and 20.0%, respectively, in Group 1 and 12.5%, 12.5%, and 75.0%, respectively, in Group 2 ($p = 0.026$) (Table 3).

Univariate logistic regression analysis of the baseline and procedural characteristics with AF recurrence

AF recurrence was used as the dependent variable and baseline and procedural characteristics as independent variables. A univariate logistic regression analysis was performed to identify the potential factors associated with AF recurrence. The result showed that the BMI [odds ratio (OR): 0.839, 95% confidence interval (CI): 0.682–1.032, $p = 0.096$], HF (OR: 3.831, 95% CI: 1.080–13.585, $p = 0.038$), PWSA (OR: 1.369, 95% CI: 1.056–1.775, $p = 0.018$), and PVLVA (OR: 1.064, 95% CI: 1.025–1.103, $p = 0.001$) were potential factors related to AF recurrence ($p < 0.10$) (Table 4).

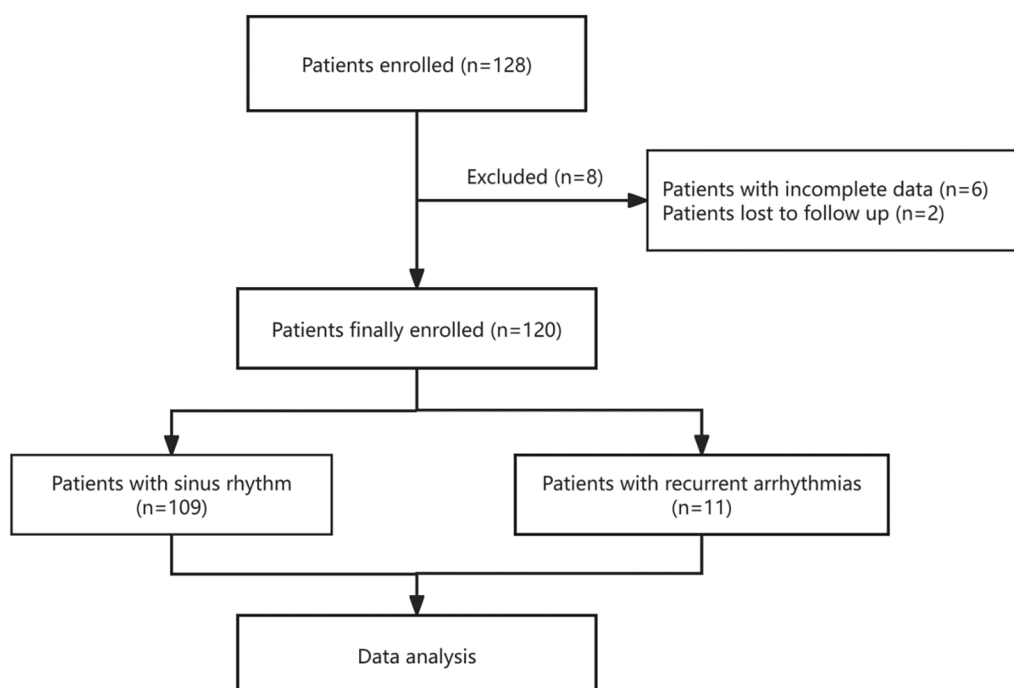


FIGURE 7
Flowchart of the study.

TABLE 1 Baseline characteristics.

	Group 1 (no recurrence)	Group 2 (recurrence)	<i>p</i> -value
<i>N</i> (cases)	109	11	
Female (%)	60 (55.0)	7 (63.6)	0.585
Age (years)	67.66 ± 12.60	67.18 ± 13.23	0.905
BMI (kg/m ²)	23.97 ± 3.19	22.16 ± 5.03	0.094
Duration of AF (months)	6 (1–36)	12 (2–72)	0.065
CHA ₂ DS ₂ -VASc			0.270
0 (%)	13 (11.9)	1 (9.1)	
1 (%)	19 (17.4)	1 (9.1)	
≥2 (%)	77 (70.6)	9 (81.8)	
Comorbidity			
HF, <i>n</i> (%)	26 (23.9)	6 (54.5)	0.028*
Hypertension, <i>n</i> (%)	63 (57.8)	8 (72.7)	0.337
DM, <i>n</i> (%)	25 (22.9)	2 (18.2)	0.719
Stroke or TIA, <i>n</i> (%)	7 (6.4)	0 (0)	0.386
Laboratory indicators			
Urea nitrogen (mmol/L)	6.32 ± 2.03	6.68 ± 2.47	0.586
Creatinine (μmol/L)	71.24 ± 21.87	68.30 ± 18.68	0.668
NT-proBNP (ng/ml)	420.06 (192.31–900.13)	1,033.90 (226.30–3,463.10)	0.063
Echocardiographic indicators			
LAD (mm)	40.28 ± 4.84	41.18 ± 5.93	0.567
LVEDD (mm)	47.91 ± 5.00	46.55 ± 4.08	0.384
LVESD (mm)	31.53 ± 5.50	30.91 ± 4.28	0.716
LVEF (%)	62.44 ± 8.56	60.64 ± 5.80	0.496

BMI, body mass index; AF, atrial fibrillation; CHA₂DS₂-VASc, stroke risk score of AF patients; HF, heart failure; DM, diabetes mellitus; TIA, transient ischemic attack; NT-proBNP, N-terminal precursor protein brain natriuretic peptide; LAD, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction.

**p*-value < 0.05.

TABLE 2 Procedural characteristics.

	Group 1 (no recurrence)	Group 2 (recurrence)	<i>p</i> -value
RPV ostia area (cm ²)	4.90 ± 1.61	5.68 ± 2.20	0.144
LPV ostia area (cm ²)	3.11 ± 1.30	3.31 ± 0.85	0.636
PWSA (cm ²)	10.13 ± 2.51	12.13 ± 2.48	0.013*
PVLVA (%)	0.00 (0.00–4.12)	11.56 (0.00–35.21)	<0.001*
Complications (%)	6.42	9.09	0.735

RPV, right pulmonary vein; LPV, left pulmonary vein; PWSA, posterior wall surface area; PVLVA, percentage of a very low-voltage area.

**p*-value < 0.05.

Multivariate logistic regression analysis of potential factors on AF recurrence

Although the *p*-value of the LAD was >0.10 in the univariate logistic regression analysis, it was a common influencing clinical factor, which was also included in the multivariate logistic regression analysis. The collinearity analysis of the BMI, HF, LAD, PWSA, and PVLVA were performed at first. The results showed that there was no linear relationship between these variables (Table 5). Then, a multivariate logistic regression analysis of potential factors demonstrated that both the PWSA

TABLE 3 Analysis of the distribution of the VLVA.

	Group 1 (no recurrence)	Group 2 (recurrence)	<i>p</i> -value
VLVA in the PV ostium (%)	60.0	12.5	
VLVA in the intra-atrial region (%)	20.0	12.5	
VLVA in the mixed area (%)	20.0	75.0	
Fisher's precision probability test			0.026*

VLVA, very low-voltage area; PVs, pulmonary veins.

**p*-value < 0.05.

TABLE 4 Univariate logistic regression analysis of baseline and procedural characteristics with AF recurrence.

Covariate	OR	<i>p</i> -value
Female, <i>n</i> (%)	1.429 (0.395–5.167)	0.586
Age (years)	0.997 (0.950–1.047)	0.904
BMI (kg/m ²)	0.839 (0.682–1.032)	0.096*
Duration of AF (months)	1.003 (0.995–1.010)	0.471
CHA ₂ DS ₂ -VASc	1.143 (0.803–1.629)	0.458
HF, <i>n</i> (%)	3.831 (1.080–13.585)	0.038*
Hypertension, <i>n</i> (%)	1.947 (0.490–7.742)	0.344
DM, <i>n</i> (%)	0.747 (0.151–3.683)	0.720
LAD (mm)	1.039 (0.913–1.182)	0.564
RPV ostia area (cm ²)	1.003 (0.999–1.006)	0.146
LPV ostia area (cm ²)	1.001 (0.997–1.006)	0.643
PWSA (cm ²)	1.369 (1.056–1.775)	0.018*
PVLVA (%)	1.064 (1.025–1.103)	0.001*

BMI, body mass index; AF, atrial fibrillation; CHA₂DS₂-VASc, stroke risk score of AF patients; HF, heart failure; DM, diabetes mellitus; LAD, left atrial diameter; RPV, right pulmonary vein; LPV, left pulmonary vein; PWSA, posterior wall surface area; PVLVA, percentage of very low-voltage area.

**p*-value < 0.10.

TABLE 5 Collinearity analysis.

Variables	Tolerance	VIF
BMI (kg/m ²)	0.751	1.332
HF, <i>n</i> (%)	0.723	1.382
LAD (mm)	0.591	1.693
PWSA (cm ²)	0.832	1.201
PVLVA (%)	0.879	1.138

BMI, body mass index; HF, heart failure; LAD, left atrial diameter; PWSA, posterior wall surface area; PVLVA, percentage of very low-voltage area.

Tolerance < 0.1 or VIF > 10 meant multicollinearity between variables.

and the PVLVA were independent risk factors for AF recurrence (OR: 1.457, 95% CI: 1.037–2.049, *p* = 0.030; OR: 1.059, 95% CI: 1.013–1.107, *p* = 0.012, respectively) (Table 6).

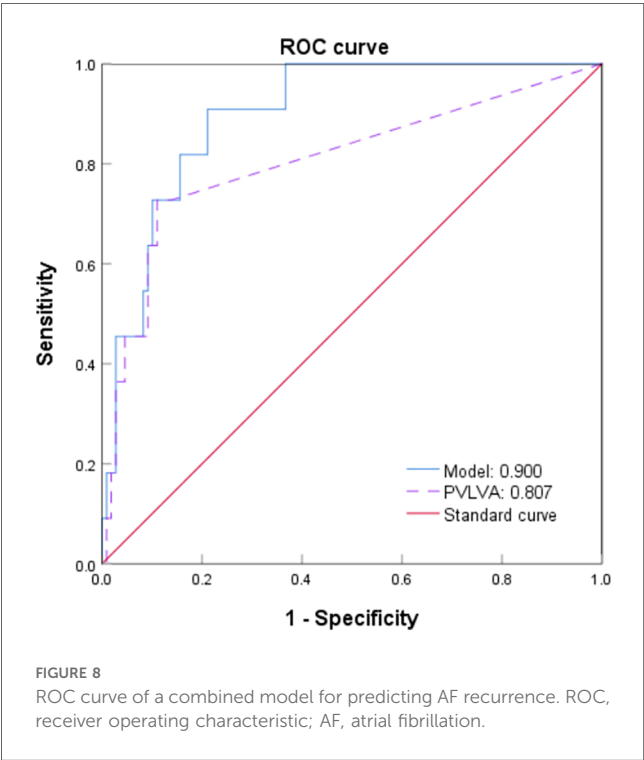
ROC curve and curve fitting

According to the logistic regression analysis of this study, the HF, LAD, PWSA, and PVLVA were included to construct the combined prediction model for AF recurrence and to draw the ROC curve (Figure 8). The equation was Logit (*P*) = −0.057 + 1.296 × HF − 0.175 × LAD + 0.342 × PWSA + 0.066 × PVLVA. The finding revealed that the AUC of this model was 0.900

TABLE 6 Multivariate logistic regression analysis of potential factors for AF recurrence.

Variables	OR	<i>p</i> -value
BMI (kg/m ²)	0.848 (0.648–1.110)	0.230
HF, <i>n</i> (%)	2.953 (0.478–18.235)	0.244
LAD (mm)	0.897 (0.725–1.100)	0.318
PWSA (cm ²)	1.457 (1.037–2.049)	0.030*
PVLVA (%)	1.059 (1.013–1.107)	0.012*

BMI, body mass index; HF, heart failure; LAD, left atrial diameter; PWSA, posterior wall surface area; PVLVA, percentage of very low-voltage area.
**p*-value < 0.05.



(0.827–0.973) ($p < 0.001$) (Figure 8). The Hosmer–Lemeshow goodness-of-fit test was performed to evaluate the calibration ability of the prediction model (Figure 9). The result suggested that there was no statistical difference between the predicted value of the model and the observed value ($\chi^2 = 4.643$, $p = 0.796$).

Discussion

The main findings of this study revealed that for patients with PAF who underwent PVI potential risk factors for AF recurrence could be discovered through the 3D electroanatomical map in the CARTO system. The area of the LAPW and the PVLVA may be associated with PAF recurrence.

Spontaneous trigger activity and rotors in the LAPW have been reported previously (26). In structurally normal hearts, focal discharges from the PVs and the LAPW are important initiating factors of AF (27). Recurrent PAF after one year is partly due to LAPW triggers (28). For patients with PAF who underwent PVI

alone, the recurrence was observed to involve the reentry of PVs and non-PV triggers. The recovery of PV ostium potential in the PW and other triggers within the intra-atrial region in the PW that were not ablated are recurrent factors associated with the LAPW. This may be elucidated from an anatomical standpoint. The LAPW is embryologically related to the PV (29). There is some interplay between the PVs and the LAPW musculature (30), resulting in conduction delay histopathologically and functionally (31). Non-contact mapping has also demonstrated significant conduction abnormalities in the LAPW in patients with PAF during sinus rhythm (32). Consequently, a part of recurrent foci of patients with PAF are derived from the LAPW, which is supported by numerous anatomical and electrical foundations.

Currently, research on LAPW triggers is primarily focused on non-PAF, with the most common intervention method being PW isolation (such as endocardial box isolation) (18, 19). There are only a few studies focusing on the PW in PAF. In this study, we measured the PWSA and the VLVA of patients with PAF before PVI in the CARTO system. The result demonstrated that there was a wider PWSA ($p = 0.013$) in recurrent patients. The PWSA was an independent risk factor for AF recurrence (OR: 1.457, 95% CI: 1.037–2.049, $p = 0.030$). However, there was no significant difference between the two groups in the LAD and the area of PV ostia. The lack of significant differences in LA size and AF burden among these patients may account for these results. In addition, the mild degree of LA structural remodeling may contribute to the outcomes. This indicated that the increase in the PWSA may not be due to the overall expansion of the left atrium. As AF persists and progresses, there would be a gradual expansion in both LA volume and PV opening area. The larger the LAPW, the broader the range of heterogeneity that can potentially occur, thereby increasing the likelihood of triggering foci in the PW.

The magnitude and conduction time of the electrical potential serve as indicators for cardiomyocyte health (33). Atrial fibrosis can impact the extracellular matrix, thereby influencing both electrical and mechanical functioning of the LA (34). The extent of atrial fibrosis is closely linked to AF recurrence (35, 36). Low-voltage or non-voltage electrograms and slow conduction are often considered manifestations of scar tissue or fibrosis (33, 37). The normal range of bipolar voltage of the LA is usually 0.3–1.0 mV (38). The region where a voltage <0.5 mV is typically considered is the low-voltage zone (39). Therefore, we defined the region with amplitude ≤ 0.1 mV as the VLVA in this study. The result showed that the recurrence group had a greater range of VLVA ($p < 0.001$). The PVLVA was also an independent risk factor for AF recurrence (OR: 1.059, 95% CI: 1.013–1.107, $p = 0.012$). Compared with Group 1, the VLVA of Group 2 exhibited a more extensive distribution, primarily within the mixed area ($p = 0.026$). This observation may suggest an increased presence of potential triggering foci in the PW or a greater complexity in heterogeneity at the junction between the PW and the PVs in these patients. The complexity may also include a significant anisotropy of crista terminalis and the subendocardial fiber around the septopulmonary bundle (30, 32). Anatomically, certain patients

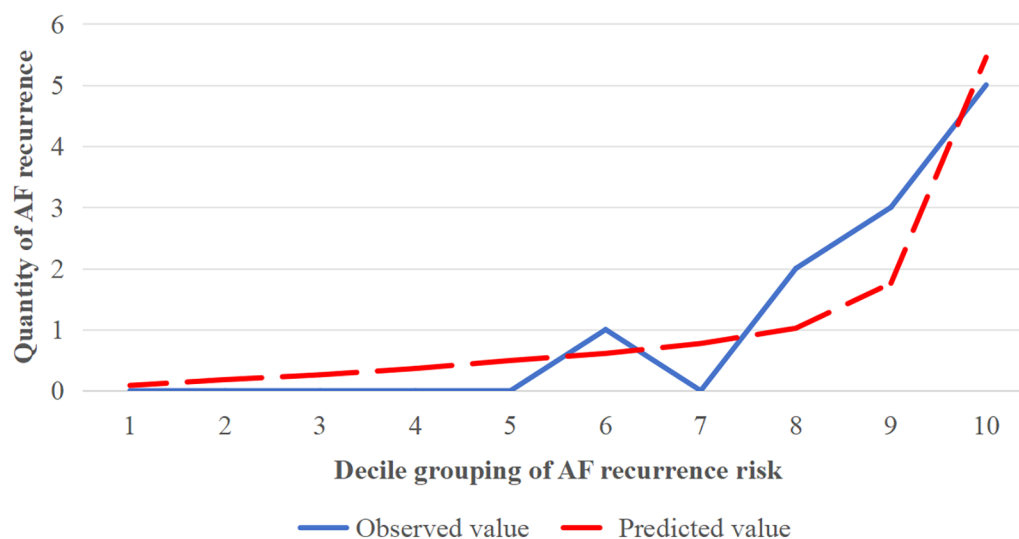


FIGURE 9
Hosmer–Lemeshow goodness-of-fit test (curve fitting).

exhibit a layer of adipose tissue that separates the septopulmonary bundle from the atrial myocardium, which impedes the penetration of radiofrequency energy. Consequently, this barrier allows for the persistence of epicardial conduction through the septopulmonary bundle, preventing the achievement of a true conduction block, which related to AF recurrences (40). Because of the early stage of AF, most patients with PAF exhibit a relatively healthy myocardium, with fewer conduction abnormalities or low-voltage areas. This underscores the significance of early detection of abnormal myocardial electrical activity.

Although there are many prediction models, the accuracy of predicting the recurrence of AF was not high enough (41). These prediction models predominantly include variables such as age, BMI, category of AF, LAD, LVEF, current smoking habits, and estimated glomerular filtration rate. The majority of these models have an AUC below 0.75. One potential explanation for this could be that these variables are almost entirely derived from non-invasive evaluations of the patient, with limited data on the electrical and anatomical characteristics of the patient's atria, which are frequently associated with AF recurrence. In this study, the prediction model that the PWSA combined with the PVLVA for AF recurrence was constructed by potential clinical factors and prior analysis. The AUC of the model achieved a moderate efficacy of 0.900 (0.827–0.973) ($p < 0.001$) in predicting AF recurrence after RFA, which was verified by using the Hosmer–Lemeshow goodness-of-fit test ($p > 0.05$). The advantage of this predictive model lay in its specific focus on the LAPW, encompassing both PV ostium in the PW and the intra-atrial region in the PW, while simultaneously considering the area of the PW and the degree and distribution of abnormal conduction.

At present, ongoing efforts are focused on achieving permanent PVI by techniques during an initial RFA (42). However, given the

anatomical and electrophysiological significance of the LAPW, as well as the potential complications associated with inappropriate ablation, determining the optimal ablation depth for this region during PVI is a question worthy of careful consideration. The latest study indicated that during ablation in the LAPW, selecting the strategy of 50 W/>10–15 s, as opposed to 40 W/10–15 s and 90 W/4 s, facilitated a more effective transmural lesion and resulted in a more durable block (43). Furthermore, for patients with PAF exhibiting an abnormal PW matrix, selecting ablation strategies for other regions of the PW beyond PVI also warrants further investigation.

Limitations

There were several limitations in this study. First of all, this study was a single-center, retrospective cohort study, with a relatively small sample size. Second, there was still a possibility of residual confounding factors in the multivariate logistic regression model. Moreover, although activation mapping points were considered as uniformly as possible on the map, it still could not completely represent the real situation of voltage distribution. Finally, the mechanism between the PWSA and the PVLVA with AF recurrence is currently unknown. Therefore, more research is needed to clarify the specific pathophysiological mechanism.

Conclusions

In summary, this study provided a method for predicting recurrence in patients with PAF, utilizing parameters related to

the LAPW based on the CARTO system, prior to undergoing PVI. The analysis demonstrated that both PWSA and PVLVA were independent risk factors for AF recurrence. Moreover, we proposed a model that combined the PWSA with the PVLVA to predict the recurrence of AF, which may provide an approach for screening PAF patients who may require attention for the LAPW.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Scientific Ethics Committee of the Changzhou Hospital of Traditional Chinese Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YC: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. JZ: Conceptualization, Data curation, Formal Analysis, Writing – original draft, Writing – review & editing. XL: Data curation, Formal Analysis, Writing – original draft. CZ: Data curation, Formal Analysis, Investigation, Writing – original draft. XC: Conceptualization, Formal Analysis, Investigation, Writing –

original draft. ZX: Conceptualization, Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. XF: Conceptualization, Formal Analysis, Investigation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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Clinical performance of subcutaneous vs. transvenous implantable defibrillator in patients with ischemic cardiomyopathy: data from Monaldi Rhythm Registry

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Introduction: Subcutaneous ICD (S-ICD) is an alternative to a transvenous implantable cardioverter-defibrillator (TV-ICD) system in selected patients not in need of pacing or resynchronization. Currently, little is known about the effectiveness and safety of S-ICD in patients with ischemic cardiomyopathy (ICM). The aim of our study was to describe the clinical features and the drivers of S-ICD implantation among patients with ICM, as well as the clinical performance of S-ICD vs. TV-ICD among this subset of patients during a long-term follow-up.

Materials and methods: All ICM patients with both S-ICD and TV-ICD implanted and followed at Monaldi Hospital from January 1, 2015, to January 1, 2024, were evaluated; among them, only ICD recipients with no pacing indication were included. We collected clinical and anamnestic characteristics, as well as ICD inappropriate therapies, ICD-related complications and infections.

Results: A total of 243 ICM patients (mean age 63.0 ± 11.0 , male 86.0%) implanted with TV-ICD ($n: 129$, 53.1%) and S-ICD ($n: 114$, 46.9%) followed at our center for a median follow-up of 66.9 [39.4–96.4] months were included in the study. Kaplan–Meier analysis revealed no significant difference in the risk of inappropriate ICD therapies (log-rank $p = 0.137$) or ICD-related complications (log-rank $p = 0.055$) between S-ICD and TV-ICD groups. TV-ICD patients showed a significantly higher risk of ICD-related infections compared to those in the S-ICD group (log-rank $p = 0.048$). At multivariate logistic regression analysis, the only independent predictors of S-ICD implantation were female sex [OR: 52.62; $p < 0.001$] and primary prevention [OR: 17.60; $p < 0.001$].

Conclusions: Among patients with ICM not in need of pacing or resynchronization (CRT), the decision to implant an S-ICD was primarily influenced by female gender and primary prevention indications. No significant differences in inappropriate ICD therapies and complications were found; in contrast, the S-ICD group showed a numerically reduced risk of ICD-related infections.

KEYWORDS

subcutaneous ICD (S-ICD), transvenous ICD, complications, infections, inappropriate shock therapy, ischemic cardiomyopathy

Introduction

Ischemic cardiomyopathy (ICM) is currently defined a myocardial disease characterized by impaired systolic left ventricle ejection fraction (LVEF) in the setting of obstructive coronary artery disease (CAD) and represents the most common cause of heart failure (1). Implantable cardioverter defibrillator (ICD) is effective for the primary prevention of sudden cardiac death (SCD) among ICM patients (2). Subcutaneous ICD (S-ICD) is an alternative to a transvenous implantable cardioverter-defibrillator (TV-ICD) system in selected patients not in need of pacing or CRT (3–10).

Currently, no sub-analysis of randomized clinical trials including ICM patients are available and real-world data comparing the effectiveness and safety of S-ICD in this clinical setting are lacking (11). The aim of our study was to describe the clinical features and the drivers of S-ICD implantation among patients with ICM, as well as the clinical performance of S-ICD vs. TV-ICD among this subset of patients during a long-term follow-up.

Materials and methods

This is a single-center, retrospective observational study. Data for this study were sourced from Monaldi Hospital Rhythm Registry (NCT05072119), which includes all patients who underwent ICD implantation and followed up at our Institution through both outpatient visits, every 3–6 months, and remote device monitoring. During the follow-up, the occurrence and the causes of inappropriate and appropriate ICD therapies, and ICD-related complications were assessed and recorded in the electronic data management system. For the present analysis, we selected all consecutive patients with ICM who received subcutaneous (S-ICD Group) and transvenous (TV-ICD Group) in primary or secondary prevention, from January 1, 2015 to January 1, 2024, according to the European guidelines and recommendations available at the time of implantation (12, 13). Only patients not in need of pacing or CRT that underwent TV-ICD implantation were included in the analysis. At our center, the choice between S-ICD and TV-ICD is guided by a shared decision-making process, which includes both implanting physician and patient preference. All S-ICDs were implanted under deep sedation and using the intermuscular two-incision technique (14, 15). The local institutional review boards

approved the study (ID 553-19), and all patients provided written informed consent for data storage and analysis.

ICD programming

The programming of the parameters for the detection of ventricular tachycardia (VT) or ventricular fibrillation (VF) was done according to the guideline's recommendations at the time of the implant. We routinely activate for primary prevention only one VF zone (30 intervals at 250 bpm) and for secondary prevention two windows of detection (VF: 30 intervals at 250 bpm; VT2: 30 intervals at 187 bpm or 10–20 bpm < VT rate) with shocks and up to three anti-tachycardia pacing (ATP) and eight shocks in VT2 zone. S-ICD devices were programmed with a conditional zone, between 200 and 250 bpm, and a shock zone > 250 bpm. The programmed sensing vector was primary (60.3%) or secondary (37.5%) for most patients and alternate in small percentage of cases (2.2%).

Outcomes

The primary study endpoints were ICD inappropriate therapies, defined as ATP and/or shocks for conditions other than VT/VF (Figure 1); ICD-related complications, defined as peri-procedural implantation complications, pulse generator or lead-related complications, infections which required complete removal of the system. The secondary endpoints were the clinical variables associated to S-ICD implantation.

Statistical analysis

Categorical data were expressed as number and percentage, whereas continuous variables were expressed as either median [interquartile range (IQR)] or mean $\pm$ standard deviation (SD), based on their distribution. Between-group differences for categorical variables were assessed using the chi-square test, with Yates' correction applied where appropriate. Continuous variables were compared using either the parametric Student's *t*-test or the nonparametric Mann–Whitney *U* test, depending on their distribution. Kaplan–Meier analysis was performed to evaluate the main outcomes of interest, stratified by ICD type, with survival curves compared using the log-rank test. Cox

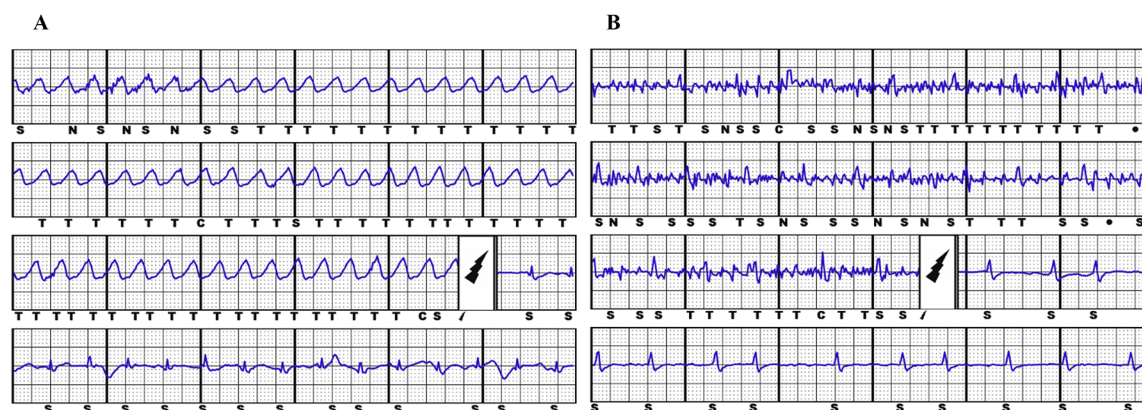


FIGURE 1

Example of appropriate S-ICD shock due to ventricular fibrillation (panel A) and inappropriate S-ICD shock due to muscular noise (panel B).

proportional hazards univariate and multivariate regression was used to assess the relationship between the variables of interest and the risk of adverse outcomes. Additionally, univariate and multivariate logistic regression analysis was conducted to identify baseline characteristics associated with S-ICD implantation. All analyses were performed using RStudio software (RStudio, Boston, MA).

Results

Study population

A total of 243 ICM patients (mean age 63.0 ± 11.0 , male 86.0%) with TV-ICD ($n: 129$, 53.1%) and S-ICD ($n: 114$, 46.9%) followed at our center for a median follow-up of 66.9 [39.4–96.4] months were included in the study. The indication for ICD implantation was primary prevention in 189 patients (77.8%) and secondary prevention in 54 patients (22.2%). S-ICD patients were younger (61.0 ± 11.0 vs. 65.9 ± 10.5 years, $p < 0.001$) and showed less frequently hypertension (61.4% vs. 81.4%, $p < 0.001$) and diabetes (19.3% vs. 41.9%, $p < 0.001$). The baseline clinical characteristics of the study population are summarized in Table 1. At multivariate logistic regression analysis, the only independent predictors of S-ICD implantation were female sex [odds ratio (OR): 52.62; 95% confidence interval (CI) 20.23–136.83; $p < 0.001$] and primary prevention [OR: 17.60; 95% CI 5.30–58.38; $p < 0.001$] (Table 2). Regarding S-ICD group, no patients required device extraction due to the need for pacing or CRT.

Clinical outcomes

Among our study population, ICD inappropriate therapies were experienced by 6 patients (2.5%); of them, 2 (1.6%) in S-ICD group and 4 (3.5%) in the TV-ICD group ($p = 0.327$) (Table 3).

The annual incident rate of ICD inappropriate therapies over 5 years was 0.4%. The Kaplan–Meyer analysis did not show a

significantly different risk of inappropriate ICD therapies between the two subgroups (log-rank $p = 0.319$) (Figure 2). At Cox multivariate analysis no patients' clinical characteristic, including S-ICD, was associated with inappropriate ICD therapies (Supplementary Table S1).

ICD related complications requiring surgical revision occurred in 9 patients (3.7%), of them, 2 (1.8%) in S-ICD group and 7 (5.4%) in the TV-ICD group ($p = 0.131$) (Table 3). S-ICD complications were exclusively attributed to PG malfunctions, whereas all TV-ICD complications were associated with lead-related issues. The Kaplan–Meyer analysis did not show a significantly different risk of ICD related complications between the two subgroups (log-rank $p = 0.137$) (Figure 3). At Cox multivariate analysis no patients' clinical characteristics, including S-ICD, was associated with ICD complications (Supplementary Table S2).

ICD-related infections occurred in 8 patients (3.3%), of them, 1 (0.9%) in S-ICD group and 7 (5.4%) in the TV-ICD group ($p = 0.048$) (Table 3). The Kaplan–Meyer analysis did not show a significantly different risk of ICD-related infections between the two subgroups (log-rank $p = 0.055$) (Figure 4).

All infected TV-ICD patients underwent lead extraction and subsequent S-ICD implantation; in two cases, a combined pacemaker leadless implantation was performed. The infected S-ICD patient was not re-implanted due to the absence of indication at clinical re-assessment after extraction.

At Cox multivariate analysis, a history of stroke/TIA [hazard ratio (HR) 7.77; 95% CI: 1.39–43.42; $p = 0.020$] and previous valve replacement (HR: 5.84; 95% CI: 1.25–27.28; $p = 0.025$) were independently associated with ICD infections, whereas S-ICD implantation was not (Supplementary Table S3).

Discussion

The main findings of our study are as follows: (1) Among patients with ICM, no significant differences were observed in inappropriate ICD therapies or ICD-related complications

TABLE 1 Baseline characteristics of the study population divided according to the ICD type.

Variable	Overall (n = 243)	S-ICD group (n = 114)	TV-ICD group (n = 129)	p
Age, y, mean (SD)	63.0 ± 11.0	61.0 ± 11.0	65.9 ± 10.5	<0.001
Male gender, n (%)	209 (86.0%)	101 (88.6)	108 (83.7)	0.274
NYHA I, n (%)	7 (2.9)	7 (6.1)	–	0.019
NYHA II, n (%)	111 (45.7)	47 (41.2)	64 (49.6)	0.191
NYHA III, n (%)	94 (38.7)	41 (36.0)	53 (41.1)	0.412
NYHA IV, n (%)	14 (5.8)	2 (1.8)	12 (9.3)	0.011
LVEF (%), median [IQR]	30 [25.0–35.0]	30 ± 8	30.0 [25.0–35.0]	0.085
History of CAD, n (%)	208 (85.6)	100 (87.7)	108 (83.7)	0.370
Recent MI, n (%)	191 (78.6)	98 (86.0)	93 (72.1)	0.008
Previous CABG, n (%)	43 (17.7)	23 (20.2)	20 (15.5)	0.340
Previous PTCA, n (%)	139 (57.2)	60 (52.6)	79 (61.2)	0.173
PAD, n (%)	29 (11.9)	11 (9.6)	18 (14.0)	0.303
Previous stroke/TIA, n (%)	11 (4.5)	4 (3.5)	7 (5.4)	0.470
Previous valve replacement, n (%)	15 (6.2)	6 (5.3)	9 (7.0)	0.570
AF history, n (%)	65 (26.8)	38 (33.3)	27 (20.9)	0.020
Hypertension, n (%)	175 (72)	70 (61.4)	105 (81.4)	<0.001
Diabetes, n (%)	76 (31.3)	22 (19.3)	54 (41.9)	<0.001
COPD, n (%)	62 (25.5)	32 (28.1)	30 (23.3)	0.780
CKD, n (%)	57 (23.5)	26 (22.8)	31 (24.0)	0.820
Primary prevention, n (%)	189 (77.8)	107 (93.9)	82 (63.6)	<0.001
Secondary prevention, n (%)	54 (22.2)	7 (6.1)	47 (36.4)	<0.001
Follow-up months, median [IQR]	66.9 [39.4–96.4]	70.7 [36.1–101.4]	60.5 [24.2–91.0]	0.694

ICD, implantable cardioverter defibrillator; S-ICD, subcutaneous implantable cardioverter defibrillator; TV-ICD, transvenous implantable cardioverter defibrillator; SD, standard deviation; LVEF, left ventricular ejection fraction; MI, myocardial infarction; CAD, coronary artery disease; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; PAD, peripheral artery disease; TIA, transient ischemic attack; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; ATP, anti-tachycardia pacing; PG, pulse generator.

TABLE 2 Univariable and multivariable logistic regression model for S-ICD implantation choice.

Variable	Univariable analysis				Multivariable analysis			
	OR	95% CI		p	OR	95% CI		p
Age	0.97	0.95	0.99	0.027	1.01	0.97	1.06	0.595
Sex								
M	1				1			
F	39.96	19.01	84.00	<0.001	52.62	20.23	136.83	<0.001
Primary prevention	8.76	3.77	20.39	<0.001	17.60	5.30	58.38	<0.001
Secondary prevention	0.11	0.05	0.27	<0.001				
NYHA class >2	0.62	0.41	0.93	0.022	0.50	0.23	1.05	0.066
LVEF	0.98	0.95	1.01	0.288				
Hypertension	0.36	0.20	0.65	<0.001	0.90	0.33	2.47	0.837
Diabetes	0.33	0.19	0.59	<0.001	0.52	0.49	1.44	0.210
COPD	1.29	0.72	2.29	0.391				
CAD history	1.04	0.52	2.06	0.917				
Previous CABG	1.38	0.71	2.67	0.342				
Previous PTCA	0.72	0.43	1.20	0.202				
History of stroke/TIA	0.63	0.18	2.22	0.476				
PAD	0.66	0.30	1.46	0.304				
CKD	0.93	0.52	1.69	0.822				
AF history	1.89	1.06	3.36	0.030	1.62	0.51	5.15	0.538
Previous valve replacement	0.74	0.26	2.15	0.581				

ICD, implantable cardioverter defibrillator; S-ICD, subcutaneous implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; TIA, transient ischemic attack; PAD, peripheral artery disease; CKD, chronic kidney disease; AF, atrial fibrillation.

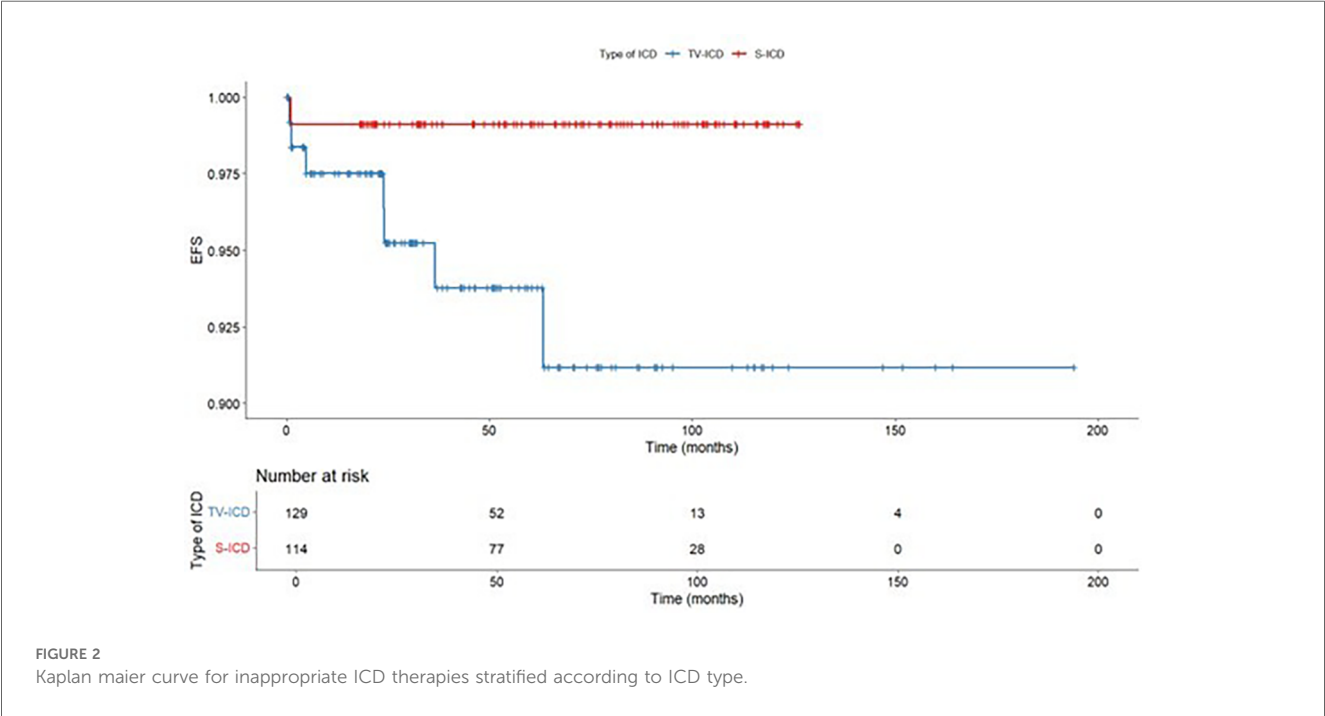
between S-ICD and TV-ICD. However, TV-ICD was associated with a numerically higher, though not statistically significant, rate of ICD-related infections during follow-up compared to S-ICD. (2) Female gender and primary prevention were the only clinical

factors independently associated with S-ICD implantation in ICM patients. S-ICD is an established therapy for SCD prevention and an alternative to TV-ICD system in selected patients (1, 2). S-ICD

TABLE 3 Clinical outcome events among study population.

	Overall (n = 243)	S-ICD group (n = 114)	TV-ICD group (n = 129)	p
Appropriate therapies, n (%)	21 (8.6)	3 (2.6)	18 (13.9)	0.002
ICD shock, n (%)	13 (5.3)	3 (4.3)	10 (7.7)	
ATP, n (%)	8 (3.3)	–	8 (6.2)	
Inappropriate therapies, n (%)	6 (2.5)	2 (1.8)	4 (3.1)	
Atrial fibrillation, n (%)	4 (1.6)	1 (0.9)	3 (2.3)	
T wave oversensing, n (%)	1 (0.4)	–	1 (0.8)	
Air entrapment, n (%)	1 (0.4)	1 (0.9)	–	0.327
ICD-related complications, n (%)	9 (3.7)	2 (1.8)	7 (5.4)	0.131
PG malfunction, n (%)	2 (0.9)	2 (1.8)	–	
Lead complications, n (%)	7 (3.1)	–	7 (5.4)	
ICD-related infections, n (%)	8 (3.3)	1 (0.9)	7 (5.4)	0.048

ICD, implantable cardioverter defibrillator; ATP, anti-tachycardia pacing; PG, pulse generator.



showed a non-inferiority vs. TV-ICD for device-related complications or inappropriate shocks in patients with an indication for defibrillator therapy and not in need of pacing or CRT (3–10). Recently, two real-world registries showed S-ICD may be a valuable alternative to TV-ICD in patients with cardiomyopathies (16) and in those with heart failure (17); however, the potential risk of IAS, mainly due to non-cardiac oversensing, was not negligible.

Among different studies comparing the efficacy and safety of S-ICD vs. TV-ICD, the percentage of patients with ICM ranged from 27% to 67% (5, 9). No sub-analysis of randomized clinical trials including this subset of patients are currently available. In the EFFORTLESS registry (13), which included 28.1% of S-ICD patients with ICM, the ischemic etiology was an independent predictor of treated episodes for monomorphic ventricular tachycardia at five years. In a single-center retrospective study by

Willy et al. (18) which included 45 patients with ischemic heart disease and S-ICD for primary or secondary prevention, no change to transvenous ICDs for anti-tachycardia pacing delivery was necessary, moreover, no surgical revision was required, and no system-related infections were reported during a mean follow-up of 2.5 ± 8.3 months. In an international observational study on 1,698 patients, of whom 31.7% had ischemic cardiomyopathy, no differences emerged between ischemic and non-ischemic patients regarding ICD appropriate shocks and device-related complications. However, ischemic patients showed a reduced risk of inappropriate ICD therapies (19).

Our data confirms in a large population the previous findings about the safety of S-ICD in patients with ICM. Among our study population, the cumulative incidence of inappropriate therapies was lower than previously reported (19, 20), mainly due to our strategy to optimize the TV-ICD programming at

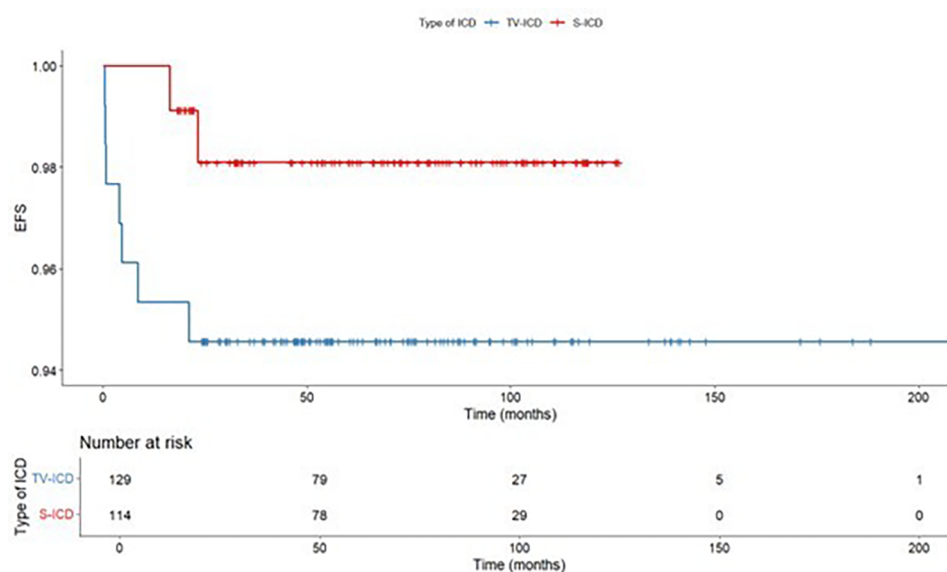


FIGURE 3
Kaplan maier curve for ICD related complications stratified according to ICD type.

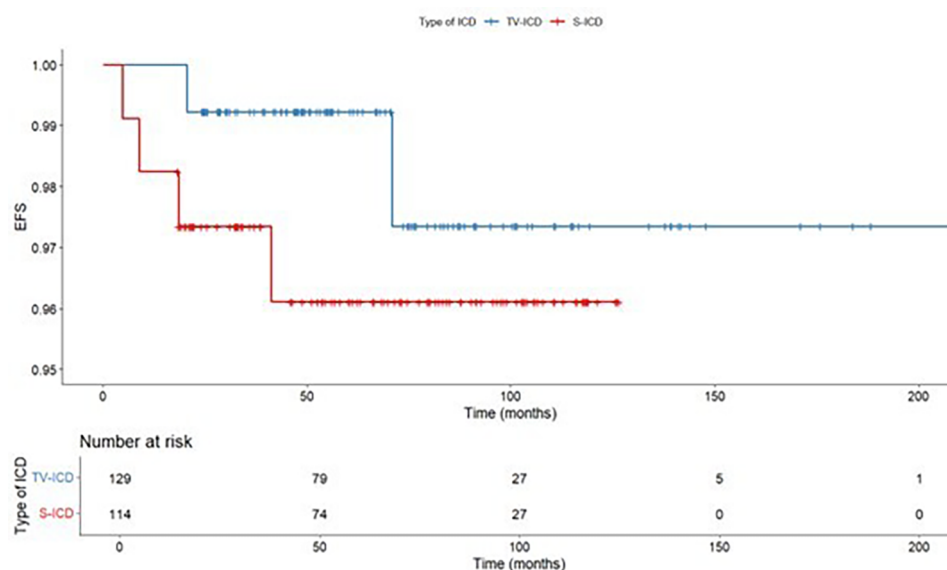


FIGURE 4
Kaplan maier curve for ICD related infections stratified according to ICD type.

each follow-up visit or based on remote monitoring reporting. Moreover, the generation S-ICD systems implanted at our Institution have an additional high-pass filter to the sensing methodology, called SmartPass (SP), designed to reduce the inappropriate therapies (21, 22).

Among S-ICD patients, the air entrapment has been recently described as undetected cause of inappropriate therapies in the early post-procedural period (23–25). Regarding the complications, we observed a numerically reduction of overall

ICD-related complications in the S-ICD group, mainly driven by less frequent lead-related complications. The low annual rate of ICD infections at our Institution confirms the reduced number of infections in high implantation volume centers (26); as we expected, the TV-ICD group showed a numerically higher incidence compared to the S-ICD group. These data may be explained by the multipronged strategies we apply to reduce the cardiovascular implantable electronic device (CIED) infection, including the proper patients' selection, the basic preparation of

the operating theater; the efforts to reduce hematoma formation; the use of an antibiotic-impregnated mesh envelope or antimicrobial solution during implantation in high-risk individuals. This evidence is of pivotal importance since systemic infections represent an important predictor of death for all causes, regardless of the result of the extraction procedure (27).

Among ICM patients, our data suggest a tendency to consider S-ICD the preferred choice for female patients and those in primary prevention. No data are available about the gender impact on the choice of ICD type. However, previous studies support for gender disparities in quality of life among ICD patients, with female patients reporting poorer mental health and more anxiety (28–31).

This preference for S-ICD in female patients may be explained by efforts to reduce the aesthetical impact of the TV-ICD wound in the anterior subclavian position, preferring instead for the more posterior and cranial placement of the S-ICD, where it minimally interferes with the position of the bra (32). Female S-ICD recipients experienced less likely appropriate ICD therapy, with similar risk of device-related complications compared to males; moreover, they were more likely to be at a low-risk of ventricular arrhythmias conversion failure (33).

Among our study population, the history of stroke/TIA and previous valve replacement were independently associated with ICD infections. According to the current guidelines, patients with prosthetic heart valves are considered at high risk of infective endocarditis (IE) and those receiving a CIED are considered at an intermediary IE risk (34). The combination of undergoing an prosthetic valve replacement and having or getting a CIED may result in an even higher risk of IE, independently from the timing of the CIED implantation (35).

The evidence that previous stroke/TIA is a risk factor for CIED infection might be related to the type and magnitude of loss of function following the acute event. In a systematic review by Martino et al. the dysphagia occurs in 37%–78% of stroke patients and increases the risk for pneumonia 3-fold and 11-fold in patients with confirmed aspiration (36). In addition, a stroke may lead to an induced immunodepression, a systemic anti-inflammatory response that is related to susceptibility to infection (37, 38).

In clinical practice, the use of S-ICD in patients with ICM who do not require pacing or CRT remains challenging. This is primarily due to concerns about the potential for sustained VT that may require ATP or the risk of incident bradyarrhythmias that could necessitate pacing (39). However, it should be noted that only 15–20% of patients experienced a high rate of monomorphic VT during the first year after the implant with a subsequent risk is 1.8%/year; moreover, the proportion of both monomorphic VT and successful ATP was comparable between patients with ischemic and non-ischemic cardiomyopathy (40). Finally, no studies have still addressed whether the efficacy of ATP translates into hard outcomes such as mortality benefits, prevention of inappropriate shocks, and risks of pro-arrhythmias (41). Patients with ischemic cardiomyopathy had significantly less inappropriate therapy compared to patients with non-ischemic cardiomyopathy and appear to be appropriate patients

for this type of device (39, 40). Moreover, patients with ischemic heart disease are particularly exposed to the risk of CIED-related complications due to their multiple comorbidities. This highlights the need for a patient-centered, tailored approach to device selection, rather than relying solely on the etiology of cardiomyopathy (ischemic vs. non-ischemic). Such an approach should consider not only the potential mechanisms of ventricular arrhythmias but also other patient-specific factors, including susceptibility to systemic infections, the concomitant use of other cardiac devices (42) and the risk of long-term device-related complications.

In the clinical context of TV-ICD explanation, S-ICD has proven to offer a viable alternative for both infection and lead failure, since the S-ICD recipient mortality did not appear to be correlated with the presence of a prior infection, S-ICD therapy (appropriate or inappropriate), or S-ICD complications but rather to worsening of HF or other comorbidities (43, 44). Moreover, advancements in modular pacing-defibrillator systems offer promising solutions for patients requiring antitachycardia or bradycardia pacing. A recently developed system combines a leadless pacemaker with a subcutaneous ICD, enabling wireless communication to provide both pacing modalities. Early data have demonstrated freedom from major complications related to the leadless pacemaker and its communication with the S-ICD. Furthermore, at six months, the majority of patients achieved adequate pacing thresholds, with a pulse width of 0.4 ms and a pacing voltage of up to 2.0 V (30). This innovation underscores the potential for further improving outcomes in this complex patient population by combining the benefits of S-ICD with advanced pacing technologies (45).

Study limitations

Our results should be interpreted considering the limitations related to the study's retrospective, observational, and single-center nature; however, it is the largest study evaluating the clinical performance of S-ICD vs. TV-ICD among patients with ischemic cardiomyopathy not in need of pacing or CRT. The findings of our study may be influenced by the high level of experience in ICD implantation and management at our center. The follow-up duration is relatively short, approximately 65 months; however, it remains the longest observational study including this subset of patients. Additionally, no data on pharmacological therapies or biomarkers were collected at the time of outcome events (46). An additional limitation is the small number of patients undergoing ventricular tachycardia ablation (4 in the TV-ICD group and 1 in the S-ICD group), which precluded meaningful analysis of its impact. This contrasts with findings from Schiavone et al., who reported improved long-term outcomes, including reduced arrhythmic events and cardiovascular mortality, in S-ICD carriers undergoing ablation (47). Furthermore, the associations between female sex and primary prevention as independent predictors of S-ICD implantation warrant further investigation in a multicenter study, ideally including comparisons with patients with non-ischemic

cardiomyopathy, to better assess their broader applicability and clinical significance.

Conclusions

In our clinical practice, the decision to implant an S-ICD in ICM patients was mainly driven by female sex and primary SCD prevention. No significant difference in inappropriate ICD therapies or ICD-related complications has been observed between TV-ICD and S-ICD; even if these latter showed a numerically lower risk of ICD-related infections. Our findings suggest that S-ICD may be a viable alternative to TV-ICD in ICM patients; however further prospective randomized studies are needed to confirm these results and explore their broader applicability.

Data availability statement

The data that support the findings of this study are available on reasonable request from the corresponding author.

Ethics statement

The studies involving humans were approved by University of Campania “Luigi Vanvitelli”, Azienda Ospedaliera Universitaria, “Luigi Vanvitelli”, Azienda Ospedaliera di Rilievo Nazionale “Ospedale dei Colli”; approval ID 553-19. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

VR: Writing – original draft, Writing – review & editing. AC: Writing – original draft, Writing – review & editing. VB: Writing – review & editing. AR: Writing – review & editing. EA: Writing – review & editing. AP: Writing – review & editing. ND: Writing – review & editing. AG: Writing – review & editing. AM: Writing – review & editing. AD: Writing – review & editing. PG: Writing – review & editing. ED: Writing – review & editing. GN: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Intraprocedural activated clotting time and heparin dosage in pulsed field ablation of paroxysmal atrial fibrillation

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Aims: Whether the intraprocedural anticoagulation regimen and activated clotting time (ACT) in pulsed field ablation (PFA) for atrial fibrillation (AF) are the same as those for radiofrequency catheter ablation (RFCA) is currently unknown.

Methods and results: Our retrospective study included 51 paroxysmal AF patients who underwent PFA (PFA group) and were matched with paroxysmal AF patients who underwent RFCA. Nearest-neighbor propensity score matching was performed at a 1:1 ratio (no tolerance to anticoagulant regimens and a tolerance of 0.02 on the CHA₂DS₂-VASc score, left atrial diameter, and left ventricular ejection fraction). Compared with the RFCA group, the PFA group had a significantly shorter procedure time but a longer fluoroscopy time. In both groups, an initial heparin dose of 110 U/kg was given. The 30-min ACT in the PFA group (240 ± 95.5 s) was shorter than that in the RFCA group (294.4 ± 82.3 s, *P* = 0.003). The 60-, 90-, and 120-min ACTs were significantly longer in the PFA group. The percentage of 30 min-ACTs in the therapeutic range in the RFCA group (33.3%) was greater than that in the PFA group (15.7%, *P* = 0.038). The time to achieve the target ACT was longer in the PFA group. There were no differences in the incidence of periprocedural thromboembolism or bleeding events between the two groups.

Conclusions: Compared with RFCA, PFA was associated with longer intraprocedural ACTs, shorter initial ACTs, fewer initial ACTs in the therapeutic range, and longer times to achieve the target ACT.

KEYWORDS

radiofrequency catheter ablation, pulsed field ablation, activated clotting time, atrial fibrillation, anticoagulant

1 Introduction

Atrial fibrillation (AF) is the most common type of arrhythmia worldwide, and its incidence and prevalence are increasing (1). AF is associated with a 2.4-fold increased risk of stroke and high healthcare costs and expenses for patients, according to previous studies (2). Moreover, the increased risk of heart failure in patients with AF also contributes to the high healthcare burden.

Currently, oral anticoagulants (OACs) and catheter ablation (CA) are the main treatments for patients with AF. OAC is the essential treatment for AF and has been

shown to decrease the lifetime risk of stroke (3). Non-vitamin K antagonist oral anticoagulants (NOACs) have become the main drugs used to treat patients with nonvalvular AF. Numerous randomized controlled trials (RCTs) and research involving large registries have revealed that CA is more effective than antiarrhythmic drugs in maintaining sinus rhythm (4, 5). Radiofrequency (RF) has become the main energy source for CA since the pulmonary vein was recognized to play a dominant role in AF in 1998. Cryoablation is an alternative for PVI. Cryoablation and RF ablation are comparable in terms of their effects, degrees of cellular damage, inflammatory response, and thromboembolic risk (6, 7). Notably, patients who undergo CA procedures for AF are at increased risk of stroke and thromboembolism. Periprocedural thromboembolic events (1.0%) and asymptomatic cerebral embolism (5%–15%) are notable complications and are sometimes life-threatening. Therefore, periprocedural anticoagulation management is essential to reduce the risk of thromboembolism, facilitate hemostasis and prevent intra- and postoperative bleeding. Uninterrupted anticoagulation with unfractionated heparin (UFH) to maintain the activated clotting time (ACT) in the safe range during the procedure is the current consensus. Most evidence on UFH and the intraprocedural target ACT (300–350 s) during ablation procedures for AF is derived from studies involving patients undergoing VKA and RFCA procedures (8).

Currently, pulsed field ablation (PFA) is another promising method for PVI in the treatment of AF (9). Unlike RF ablation or cryoablation, PFA is a nonthermal ablation procedure that causes irreversible and selective cardiac electroporation. PFA may not result in collateral damage to noncardiac tissues (10, 11). During PFA, electrical pulses delivered to cardiac cells disrupt the integrity of the cell membrane, causing cell death and replacement fibrosis. Currently, there are few early preclinical and clinical studies supporting the implementation of PFA in clinical practice. Whether PFA is better suited for periprocedural management of CA in patients with AF is unknown because of limited evidence. Whether intraprocedural anticoagulation management and periprocedural thromboembolic risk differs between PFA and RFCA are unknown. Currently, the protocol for intraprocedural anticoagulation management for PFA is the same as that for RFCA. It is uncertain whether the current intraprocedural UFH dosing regimen and target ACT values (300–350 s) are appropriate for PFA. Nevertheless, few studies focusing on the heparin dosage in AF patients who undergo PFA have been reported. We hypothesized that the intraprocedural anticoagulation management and periprocedural thromboembolic risk of PFA would differ from those of RFCA.

We compared the intraprocedural ACTs, time required for the ACT to reach the therapeutic range, actual percentages of measurements at the target ACT, heparin dosage, and incidence of periprocedural thromboembolic and bleeding events between

AF patients who underwent PFA and those who underwent RFCA to determine whether the current intraprocedural heparin dosing regimen is appropriate for PFA.

2 Methods

2.1 Study design

This study was a retrospective, single-center clinical trial involving patients with paroxysmal AF who underwent PFA and RFCA in our center from 1/02/2023–30/06/2024. This trial was approved by the Ethics Committee of the First Affiliated Hospital of Dalian Medical University.

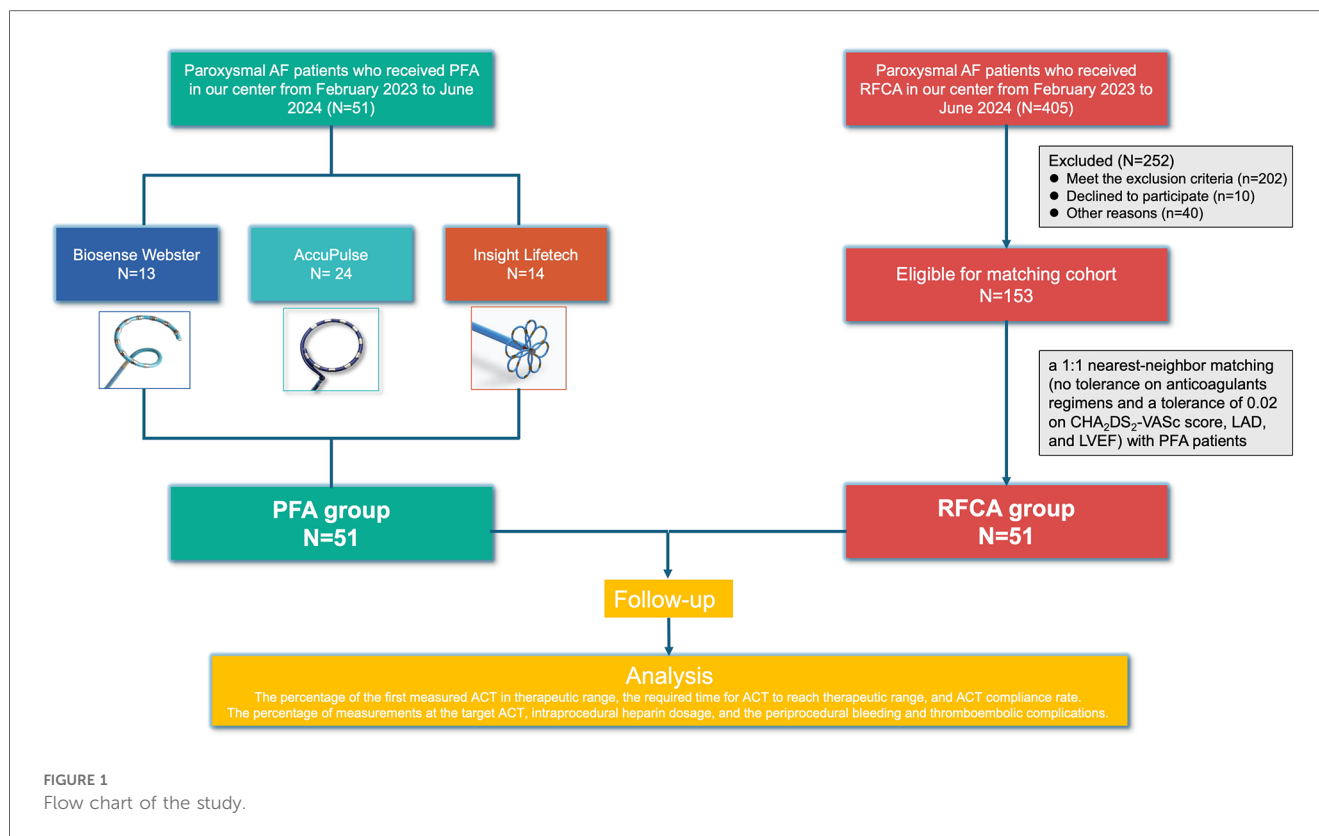
2.2 Study subjects

Patients with paroxysmal AF who underwent PFA and RFCA at our center from 1/02/2023 to 30/06/2024 were retrospectively included. Patients with a history of cardiac ablation, cardiac surgery, or cardiovascular implantable electronic devices; severe hepatic/renal insufficiency; cerebrovascular disease within the last 3 months (including stroke and transient ischemic attack); or contraindications to anticoagulants were excluded. Patients with severe cardiac dysfunction [a left ventricular ejection fraction (LVEF) $\leq 40\%$ or NYHA cardiac function grade III–IV] or a left atrial diameter (LAD) ≥ 55 mm were also excluded. Patients who refused to participate in this trial and were lost to follow-up were not included (Figure 1).

The patients in the PFA group were collected from the three prospective studies conducted in our center to evaluate the safety and effectiveness of PFA in paroxysmal AF: study A: the AFIRE study (a prospective, multicenter, single arm study with performance goals designed to evaluate the safety and effectiveness of a multielectrode circular IRE catheter and multichannel IRE generator in the treatment of paroxysmal AF, NCT05552963); study B: the PF-Beat-AF Trial [a study of pulse field ablation (PFA) for the treatment of paroxysmal atrial fibrillation, AccuPulse Medical Technology]; and study C: the Comparison of PFA vs. RFA in Patients with Symptomatic Paroxysmal Atrial Fibrillation (NCT06014996, Insight LifeTech). Patients in the RFCA group underwent RFCA at our center at the same time as those in the PFA group underwent PFA. PFA patients were matched 1:1 with RFCA patients via nearest-neighbor propensity score matching with no tolerance of anticoagulant regimens and a tolerance of 0.02 for the CHA2DS2-VASc score, LAD, and LVEF. Aside from the parameters mentioned above, weight, age, hepatic and kidney function, past medical history, date of procedure, and the operator were also considered during the matching process.

Abbreviations

ACT, activated clotting time; AF, atrial fibrillation; AFL, atrial flutter; CA, catheter ablation; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; NOAC, nonvitamin K antagonist oral anticoagulant; OAC, oral anticoagulants; PV, pulmonary vein; RCT, randomized controlled trials; RFCA, radiofrequency catheter ablation; SD, standard deviation; TIAs, transient ischemic attacks.



2.3 Preprocedural anticoagulant

All patients were treated with NOACs preoperatively, and atrial thrombosis was excluded by computed tomography or transesophageal echocardiography of left atrial appendage in female patients with CHA₂DS₂-VASc scores ≥ 3 and male patients with CHA₂DS₂-VASc scores ≥ 2 within 48 h before the ablation procedure.

2.4 Catheter ablation

The CA procedure was performed under general anesthesia. A bolus of 110 U/kg of heparin was administered immediately after right femoral vein puncture. A decapolar catheter was positioned in the coronary sinus for atrial pacing and signal reference. Transseptal puncture was performed via a modified Brockenbrough technique.

In the PFA group, ablation was performed via the following three specialized PFA generators and PFA catheters: (1) the Multi-Channel Irreversible Electroporation (IRE) generator and Multi-Channel Circular IRE catheter (Biosense Webster, Irvine, USA); (2) the AccuPulse PFA generator and circular-shaped PFA catheter [AccuPulse Medical Technology (Suzhou) Co. Ltd.; Jiangsu, China]; and (3) the PFA generator (Insight Lifetech, Shenzhen, China), a proprietary lotos-shaped PFA catheter (LotosPFA, Insight Lifetech), and a customized steerable sheath to navigate and position the PFA catheter.

In the RFCA group, a PV mapping catheter (Pentaray NAV ECO High Density Mapping Catheter, Biosense Webster, Irvine,

USA, or Advisor HD Grid Mapping Catheter, Abbott Laboratories, Chicago, IL) and a saline-irrigated ablation catheter (Thermocool SMART TOUCH SF, Biosense Webster, Irvine, USA, or TactiCath Contact Force Ablation Catheter) were used for mapping and ablation via the CARTO 3 V6 electroanatomic mapping system (Biosense Webster, Irvine, USA) or Ensite Precision Cardiac Mapping System (Abbott Laboratories, Chicago, IL).

The final stage of the CA procedure was complete electrical isolation of the PV, which was confirmed by the absence of PV potentials or PV-left atrium conduction; notably, no tachycardia was induced by the electrophysiologic study (EPS).

2.5 Intraprocedural heparin administration and ACT monitoring

The initial dosage of heparin was administered immediately after right femoral vein puncture. The amount of supplemental heparin used was determined by the operator to maintain the ACT between 300 and 350 s based on our previous study (12). An additional dose of heparin was not given if the ACT was ≥ 350 s. If ACT was 150–300 s, a heparin dose of 800 U was added, if ACT < 150 s, a heparin dose of 1,000 U was added. An additional dose of heparin was not given if the ACT reached the target or was ≥ 300 s. If severe bleeding complications occurred, heparin was discontinued immediately, and then protamine sulfate was administered.

The ACT was measured every 30 min with an optical coagulation analyzer (OCG-102, Wondfo Biotech, Guangzhou, China). ACT

compliance was defined as at least one intraprocedural ACT in the therapeutic range. The intraprocedural ACTs at each 30-min interval (30 min-ACT, 60 min-ACT, 90 min-ACT, 120 min-ACT, and 150 min-ACT), average percentage of measurements at the target ACT, percentage of initial ACTs (i.e., 30 min-ACT) in the therapeutic range, time required for the ACT to reach the therapeutic range, intraprocedural heparin dose, ACT compliance rate, and total amount of heparin administered were collected and analyzed.

2.6 Follow-up

The incidence rates of periprocedural bleeding and thromboembolic complications were recorded and analyzed. The periprocedural complications were defined as adverse events that occurred within 30 days after the procedure. The primary endpoints were the percentage of initial ACTs in the therapeutic range, time required for the ACT to reach the therapeutic range, and ACT compliance rate. The secondary endpoints were the percentages of measurements at the target ACT, intraprocedural heparin dosage, and periprocedural bleeding and thromboembolic complications.

2.7 Statistical analysis

SPSS version 27.0 (SPSS Inc., Chicago, USA) was used for all analyses. Continuous variables are expressed as the mean $\pm$ standard deviation (SD) if normally distributed; the median and the 25%–75% interquartile range were used for skewed data. An unpaired *t* test or one-way analysis of variance was performed for measurement data. For non-normally distributed measurement data, the Mann–Whitney *U* test was performed for comparisons between two groups. The Kruskal–Wallis *H* test with Bonferroni correction was used for comparisons between multiple groups. For categorical variables, chi-square tests or Fisher's exact tests were used for comparisons between two groups. The ACTs and actual percentages of measurements at the target ACT were compared between the RFCA group and the PFA group. A 2-tailed *P* value < 0.05 indicated statistical significance.

3 Results

3.1 Baseline characteristics

A total of 102 AF patients [59.9 $\pm$ 9.1 years; 58 (56.9%) males] were included in this study. There were 51 patients in the PFA group and 51 patients in the RFCA group. The mean LAD and LVEF were 36.8 $\pm$ 3 mm and 59 $\pm$ 1.5%, respectively. The mean CHA₂DS₂-VASc score was 1.4 (0 in 21 (20.6%) patients, 1 in 38 (37.3%) patients, 2 in 24 (23.5%) patients, 3 in 16 (15.7%) patients, 4 in 2 (2%) patients and 5 in 1 (1%) patient). There was no significant difference between the two groups in terms of age, sex, comorbidities, renal function, hemoglobin, concomitant antiplatelet therapy, CHA₂DS₂-VASc score, left ventricular diameter, etc. Compared with the RFCA group, the PFA group

had significantly shorter procedure times (105.8 $\pm$ 33.3 min vs. 155.8 $\pm$ 40.2 min, *P* < 0.001) but longer fluoroscopy times (16.2 $\pm$ 7.5 min vs. 6.7 $\pm$ 2 min, *P* = 0.024). The baseline clinical characteristics of the two groups are summarized in Table 1.

3.2 Intraprocedural ACTs

During the RFCA procedure, each patient underwent 2.4 $\pm$ 1 ACT measurements, and patients in the PFA group underwent 2.3 $\pm$ 1 ACT measurements (*P* = 0.556). The ACTs at 30-min intervals are shown in Figure 2A and Table 2. The 30-min ACT in the PFA group (240 $\pm$ 95.5 s) was shorter than that in the RFCA group (294.4 $\pm$ 82.3 s, *P* = 0.003). The 60 min-ACT, 90 min-ACT, and 120 min-ACT were significantly longer in the PFA group than in the RFCA group (Table 2). The average percentage of measurements at the target ACT in the PFA group (33% [0,50%]) was greater than that in the RFCA group (20% [0,50%], *P* = 0.565), but the difference was not statistically significant.

There was no significant difference in the ACT compliance rate between the two groups (58.8% in the PFA group vs. 51% in the

TABLE 1 Baseline characteristics of the patients.

	Overall (<i>n</i> = 102)	PFA group (<i>n</i> = 51)	RFCA group (<i>n</i> = 51)	<i>P</i>
Age (years)	59.9 $\pm$ 9.1	60.1 $\pm$ 8.6	59.6 $\pm$ 9.7	0.35
Male	58 (56.9%)	28 (54.9%)	30 (58.8%)	0.689
Weight (kg)	75.3 $\pm$ 12.3	75.8 $\pm$ 12.8	74.7 $\pm$ 12.8	0.666
Coronary artery disease	7 (6.9%)	4 (7.8%)	3 (5.9%)	0.999
Hypertension	43 (42.2%)	25 (49%)	18 (35.3%)	0.16
Diabetes mellitus	7 (6.9%)	4 (7.8%)	3 (5.9%)	0.999
Heart failure	0	0	0	-
Stroke/TIAs	0	0	0	-
Ccr (ml/min)	67.4 $\pm$ 14.3	67.6 $\pm$ 13.9	67.2 $\pm$ 14.7	0.89
Hemoglobin (g/L)	141.1 $\pm$ 14.4	140.6 $\pm$ 15	141.6 $\pm$ 13.8	0.707
Thrombocyte (10 ⁹ /L)	215.3 $\pm$ 55.8	218.9 $\pm$ 55.8	211.6 $\pm$ 56.1	0.514
Alanine aminotransferase	24 (17, 31.3)	23 (16, 31)	24 (17, 31.5)	0.361
Aspartate aminotransferase	23 (20, 29.3)	23 (20,29)	24 (20,30)	0.809
CHA ₂ DS ₂ -VASc score				0.211
0	21 (20.6%)	9 (17.6%)	12 (23.5%)	
1	38 (37.3%)	18 (35.3%)	20 (39.2%)	
2	24 (23.5%)	14 (27.5%)	10 (19.6%)	
3	16 (15.7%)	8 (15.7%)	8 (15.7%)	
4	2 (2%)	2 (3.9%)	0	
5	1 (1%)	0	1 (2%)	
LAD (mm)	36.8 $\pm$ 3	36.8 $\pm$ 2.7	36.9 $\pm$ 3.4	0.896
LVEF (%)	59 $\pm$ 1.5	58.8 $\pm$ 1.3	59.2 $\pm$ 1.6	0.175
Anticoagulants (<i>n</i>)				
Edoxaban	16 (15.7%)	8 (15.7%)	8 (15.7%)	
Rivaroxaban	86 (84.3%)	86 (84.3%)	86 (84.3%)	
Concomitant antiplatelet therapy	0	0	0	-
Procedure time (min)	142.3 $\pm$ 44.3	105.8 $\pm$ 33.3	155.8 $\pm$ 40.2	<0.001
x-ray time (min)	14.6 $\pm$ 7.8	16.2 $\pm$ 7.5	6.7 $\pm$ 2	0.024

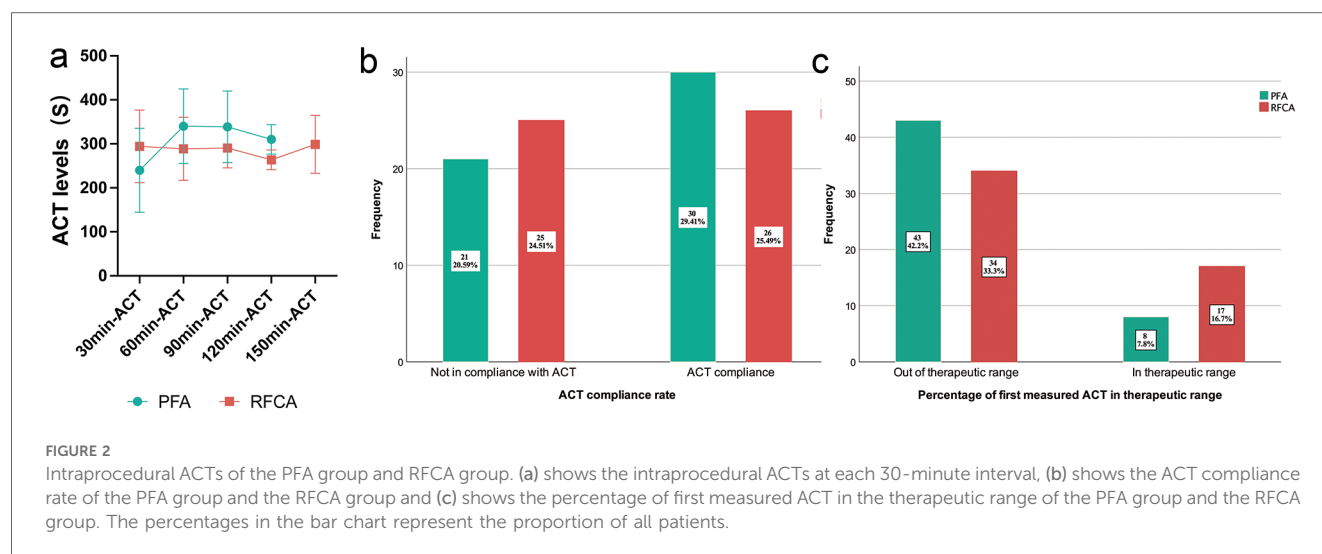


FIGURE 2

Intraprocedural ACTs of the PFA group and RFCA group. (a) shows the intraprocedural ACTs at each 30-minute interval, (b) shows the ACT compliance rate of the PFA group and the RFCA group and (c) shows the percentage of first measured ACT in the therapeutic range of the PFA group and the RFCA group. The percentages in the bar chart represent the proportion of all patients.

TABLE 2 Intraprocedural ACTs.

ACT (s)	Overall (n = 102)	PFA group (n = 51)	RFCA group (n = 51)	Difference (95% CI)	P
30 min-ACT	267.2 ± 92.8	240 ± 95.5	294.4 ± 82.3	−54.4 (−89.4 to −19.4)	0.003
60 min-ACT	314.1 ± 82.3	340 ± 84.9	288.9 ± 71.9	51.1 (16.8 to 85.5)	0.004
90 min-ACT	314.1 ± 69	338.8 ± 81.4	290.6 ± 45.2	48.2 (5.8 to 90.5)	0.027
120 min-ACT	288.7 ± 36.8	310.1 ± 33.5	263.6 ± 22.5	46.5 (10.9 to 82.1)	0.015
150 min-ACT	298.6 ± 65.9	-	298.6 ± 65.9	-	-
Percentage of measurements at the target ACT (%)	25% [0,50%]	33% [0,50%]	20% [0,50%]	0 (0 to 8%)	0.565
Percentage of initial ACTs in therapeutic range (%)	25 (24.5%)	8 (15.7%)	17 (33.3%)	−17.6% (−34% to −1.3%)	0.038
ACT compliance rate (%)	56 (54.9%)	30 (58.8%)	26 (51%)	7.8% (−11.4% to 27.1%)	0.426

RFCA group, $P = 0.426$; Figure 2B). However, the percentage of initial ACTs (30 min-ACT) in the therapeutic range in the RFCA group (33.3%) was markedly greater than that in the PFA group (15.7%, $P = 0.038$), indicating that the ACT in the RFCA group reached the target more quickly with the same initial dose of heparin (shown in Figure 2C).

Figure 3A,B show the number of ACT measurements and the percentage of ACTs in or out of the therapeutic range throughout the whole procedure. In the PFA group, 10 patients did not undergo a second ACT measurement, as the procedure was already complete. Thirty-one patients underwent two ACT measurements, representing 64.7% (31/51) of all PFA patients. The patients in the PFA group needed more time to achieve the target ACT than did the patients in the RFCA group (Figure 3C).

In the subgroup analysis of the PFA group, no significant differences in 60 min-ACT, 90 min-ACT or 120 min-ACT were detected among A, B, or C, as shown in Table 3 and Figure 4A. No difference in the average percentage of measurements at the target ACT, ACT compliance, or percentage of initial ACTs in the therapeutic range was detected between the types of PFA (Table 3 and Figure 4B,C).

3.3 Heparin dosage

The required heparin dosage to achieve the target ACT, including the initial, additional, and total dose of heparin, was

similar between the PFA group and the RFCA group (Table 4). The proportion of patients (78.4%) who needed an additional dose of heparin in the RFCA group was greater than that in the PFA group (56.9%, $P = 0.02$).

3.4 Bleeding and thromboembolic complications

There was no significant difference in the incidence of bleeding or thromboembolic complications between the two groups (Table 5). Two inguinal hematomas were observed in the PFA group, and three inguinal hematomas (including one arteriovenous fistula) were observed in the RFCA group. No hematuria/hemoglobinuria was detected in the two groups.

4 Discussion

In the present study, we retrospectively collected and analyzed the intraprocedural ACTs, periprocedural bleeding and thromboembolic complication rates, and heparin dosages in paroxysmal AF patients who underwent PFA at our center. The significant findings of our study were as follows: (1) PFA was more effective in terms of ablation and a longer fluoroscopy

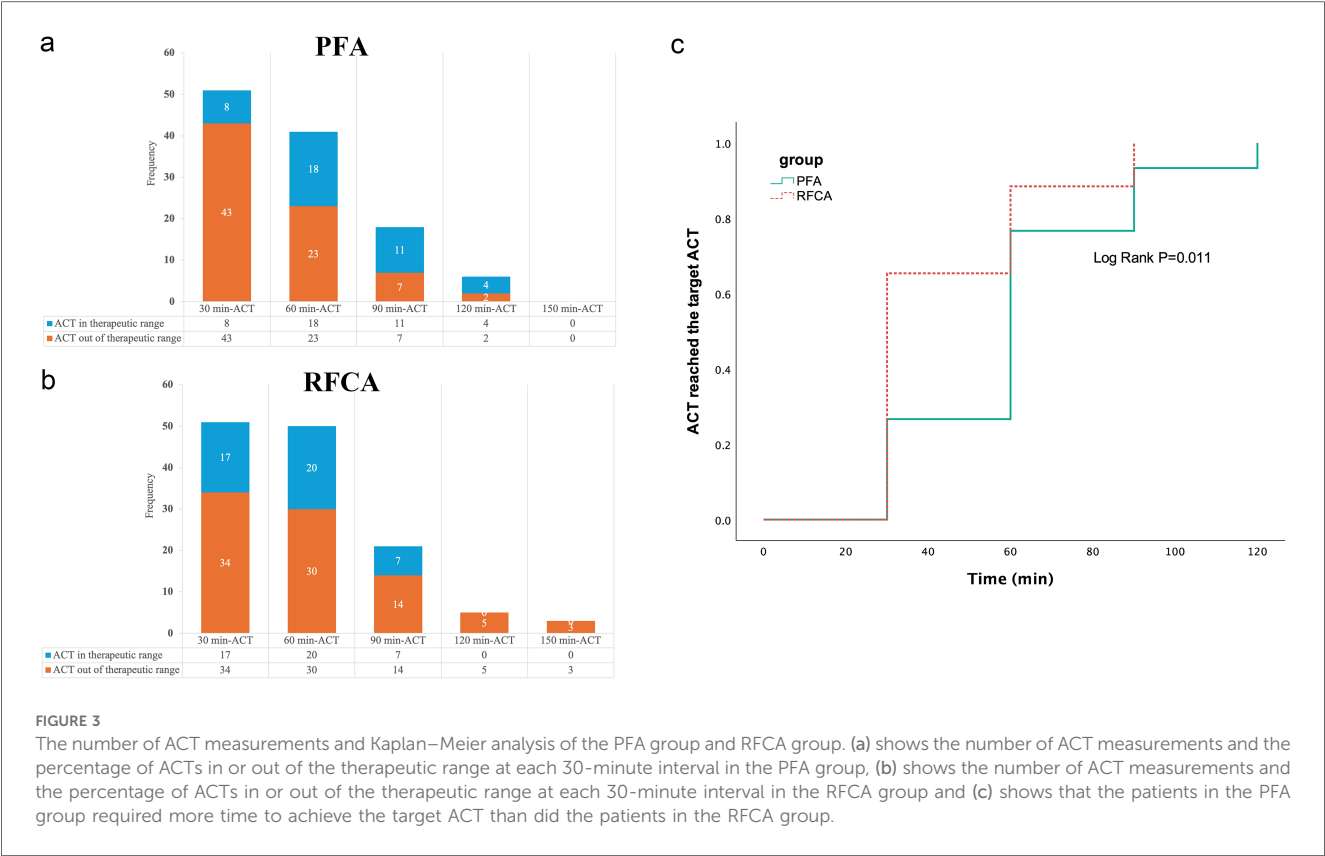


FIGURE 3 The number of ACT measurements and Kaplan–Meier analysis of the PFA group and RFCA group. (a) shows the number of ACT measurements and the percentage of ACTs in or out of the therapeutic range at each 30-minute interval in the PFA group, (b) shows the number of ACT measurements and the percentage of ACTs in or out of the therapeutic range at each 30-minute interval in the RFCA group and (c) shows that the patients in the PFA group required more time to achieve the target ACT than did the patients in the RFCA group.

TABLE 3 Subgroup analysis of intraprocedural ACTs in the PFA group.

ACT (s)	A (n = 13)	B (n = 24)	C (n = 14)	P	PA-B	PA-C	PB-C
30 min-ACT	257.4 ± 118.6	201.7 ± 81.1	289.5 ± 69.3	0.015	0.076	0.355	0.005
60 min-ACT	377.6 ± 87.5	332.2 ± 84.9	298.4 ± 61.4	0.096	0.128	0.038	0.33
90 min-ACT	370.1 ± 94.5	307.1 ± 42.9	277	0.147			
120 min-ACT	316.8 ± 37.1	309	278	0.663			
Percentage of measurements at the target ACT (%)	25% [0,67%]	33% [0,67%]	0 [0,50%]	0.465	1.000	1.000	0.65
Percentage of initial ACTs in therapeutic range (%)	2 (15.4%)	3 (12.5%)	3 (21.4%)	0.882			
ACT compliance rate (%)	9 (69.2%)	15 (62.5%)	6 (42.9%)	0.354			

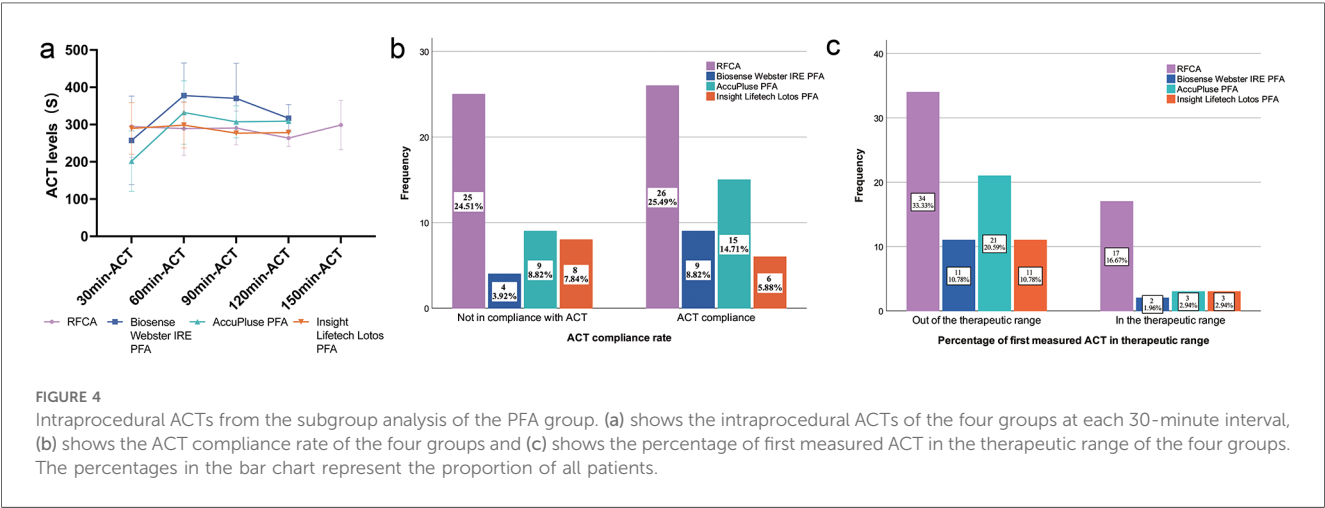


FIGURE 4 Intraprocedural ACTs from the subgroup analysis of the PFA group. (a) shows the intraprocedural ACTs of the four groups at each 30-minute interval, (b) shows the ACT compliance rate of the four groups and (c) shows the percentage of first measured ACT in the therapeutic range of the four groups. The percentages in the bar chart represent the proportion of all patients.

TABLE 4 Intraprocedural heparin.

	Overall (<i>n</i> = 102)	PFA group (<i>n</i> = 51)	RFCA group (<i>n</i> = 51)	Difference (95% CI)	<i>P</i>
Initial heparin	8,199 ± 1,538	8,486.3 ± 1,342.7	7,911.8 ± 1,675.4	574.5 (−22 to 1,171)	0.059
Added heparin	2,405.8 ± 1,295.6	2,456.5 ± 1,295.1	2,363.5 ± 1,310.6	103 (−531.9 to 737.9)	0.747
Total heparin	9,826.5 ± 1,934.8	9,888.2 ± 1,802.8	9,764.7 ± 2,074.5	123.5 (−640 to 887.1)	0.749
Numbers of added heparin	69 (67.6%)	29 (56.9%)	40 (78.4%)	−21.6% (−39.2% to −3.9%)	0.02

TABLE 5 Bleeding and thromboembolic complications.

Complications (<i>n</i>)	PFA group	RFCA group	<i>P</i>
Thromboembolic complications (<i>n</i>)	0 (0)	0 (0)	N/A
Stroke/TIAs	0 (0)	0 (0)	N/A
DVT	0 (0)	0 (0)	N/A
PE	0 (0)	0 (0)	N/A
Bleeding complications (<i>n</i>)	2 (3.9%)	3 (5.9%)	0.843
Cardiac tamponade	0 (0)	0 (0)	N/A
Pericardial effusion	0 (0)	0 (0)	N/A
Retroperitoneal hemorrhage	0 (0)	0 (0)	N/A
Hemoglobin drop ≥ 4 g/dl	0 (0)	0 (0)	N/A
Blood transfusion required	0 (0)	0 (0%)	1.000
Inguinal hematoma	2 (3.9%)	3 (5.9%)	0.843
Hematuria/Hemoglobinuria	0 (0)	0 (0)	N/A

time, with no significant difference between the types of PFA catheters; (2) compared with RFCA, PFA was associated with longer intraprocedural ACTs, shorter initial ACTs, and fewer initial ACTs in the therapeutic range, independent of the type of PFA catheter; (3) the time to achieve the target ACT was longer in patients who underwent PFA than in those who underwent RFCA; and (4) the additional dose of heparin needed to achieve and maintain the target ACT was similar in patients who underwent PFA to those in patients who underwent RFCA. To our knowledge, this is the first study investigating the differences between PFA and RFCA in terms of intraprocedural ACTs and periprocedural bleeding and thromboembolic complication rates.

PVI has been considered essential in CA for AF since PV potentials have been confirmed to trigger paroxysmal AF and the monitoring of PV potentials has been proven paramount (13). Thermal ablation, predominantly RFCA, has been the main treatment method for CA of AF in the last two decades. However, some thermal-related complications, such as atrioesophageal fistula, esophageal perforation, and adjunctive nerve injury, may be severe or immediately life-threatening and may require emergency management. PFA is a novel and promising procedure (14, 15). Although data for PFA are still limited, the existing evidence indicates that the incidence of adverse extracardiac effects is expected to be significantly lower due to electroporation into cardiomyocytes (16).

Stroke and asymptomatic acute cerebral lesions are serious periprocedural thromboembolic events with an incidence of 0.1%–0.5% and 5%–30%, respectively, that cannot be ignored and have lifelong consequences (17). The incidence of MRI-detected brain lesions after thermal ablation of AF was nearly 30% (18, 19). In contrast to the significant decrease in the incidence of adjunctive tissue damage, the incidence of periprocedural thromboembolic events associated with PFA did

not decrease significantly (20). The analysis of the neurological assessment subgroup in the ADVENT trial, which compared the cerebral impact of thermal and PFA ablation in treating PAF, revealed a comparable incidence of silent cerebral events (SCEs) and silent cerebral lesions (SCLs) following PVI ablation between PFA and RFCA (21). Therefore, safe and adequate intraprocedural anticoagulation management is also essential for PFA of AF. However, there is no consensus on the intraprocedural heparin dosing regimen and the target ACT for PFA, and few studies have focused on this issue.

The present intraprocedural anticoagulation protocol for PFA procedures is in accordance with the established guidelines for RFCA (22). The intraprocedural target ACT for PFA maybe clear (23). However, the appropriateness of current intraprocedural heparin regimens for PFA and whether intraprocedural ACTs are dependent on the type of PFA are still unclear. Different energy generates different lesions, consequently leading to diverse formation of microthrombi (24–26). In our study, we found that the PFA was associated with a longer intraprocedural ACT. However, the initial ACT and number of initial ACTs in the therapeutic range in PFA patients were lower than those in RFCA patients, and the time required to achieve the target ACT was longer in PFA than in RFCA. This could be attributed to real-time heparinized saline irrigation shortening the time to reach the target ACT during RFCA. In the later stages of RFCA, the formation of thrombi and microthrombi may have resulted in less pronounced increases in the ACT. The prolonged subsequent intraprocedural ACT observed in the PFA cohort may be attributed to the higher additional heparin bolus administered. Furthermore, the intraprocedural ACTs were found to be correlated with the heparin dosing regimens. Previous studies have indicated that a modified heparin dosing regimen may improve the ACT compliance rate and the required time to reach the target ACT (27–29). The ACT compliance rate in these modified regimens was higher than that observed in the present study, indicating that a novel heparin dosing regimen is a crucial component of the PFA.

In our study, three PFA catheters that were shaped differently were used: two circular shapes (tending to adhere to the thrombus) and one lotos shape, the latter of which was flexible and resulted in better catheter adherence and energy delivery. We also found that the PFA catheter used for saline irrigation in study A (Biosense Webster IRE Catheter) may have prolonged the ACT. PFA catheters are available in a variety of shapes and irrigated configurations, which result in different intraprocedural ACTs. As PFA becomes more widely used in clinical practice and post-market applications, it is essential to consider the impact of this variability on periprocedural anticoagulation management.

In our study, although the total amount of heparin administered was not significantly different between the two groups, the number of additional units of heparin administered to the PFA group was fewer than that administered to the RFCA group. PFA is a short procedure and may have been completed before an additional dose of heparin was administered. The discrepancy in the total heparin dosage was attributable to the necessity of a 30-minute observation period during clinical studies in the PFA cohort, during which additional heparin was administered to mitigate the risk of embolization. Thus, we suggest a higher initial dose of heparin for PFA. Moreover, according to the latest study of 337 patients undergoing PFA for AF, PFA may redefine the blanking period of AF ablation (30). This offer more benefits to AF patients, such as the reduced necessity for post-procedure anticoagulation therapy.

This study has several limitations. This was a single-center retrospective study with a small sample of patients. Due to the low incidence of hemorrhagic event and no thrombotic complication, it was underpowered to detect differences in periprocedural bleeding or thromboembolic complication rates. The incidence of silent cerebral ischemia after ablation was not evaluated. Multicenter prospective RCTs with a larger sample of patients and MRI-detected SCLs are needed to verify this hypothesis. Moreover, few measurements were at the target ACT in this study. This study exclusively examined intraprocedural ACTs for PFA and RFCA, and did not evaluate intraprocedural ACT management and anticoagulation strategies for other emerging technologies, such as cryoablation or laser ablation. This was due to the limited procedural volume and technical constraints. In addition, the study concentrated on the peri-procedural management, and a long-term follow-up was not conducted.

5 Conclusion

Compared with RFCA, PFA was associated with longer intraprocedural ACTs, shorter initial ACTs, fewer initial ACTs in the therapeutic range, and longer times to achieve the target ACT.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by First Affiliated Hospital of Dalian Medical University. The studies were conducted

in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CM: Formal analysis, Investigation, Software, Writing – original draft, Writing – review & editing. XX: Conceptualization, Investigation, Writing – review & editing. QC: Data curation, Formal analysis, Writing – review & editing. WL: Software, Visualization, Writing – review & editing. ZW: Data curation, Methodology, Writing – review & editing. SD: Investigation, Writing – review & editing. YS: Investigation, Writing – review & editing. YX: Resources, Supervision, Validation, Writing – review & editing. LG: Conceptualization, Supervision, Validation, Writing – review & editing. XY: Conceptualization, Methodology, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Cardiac Contractility Modulation as bridge to recovery in a patient with advanced heart failure evaluated for left ventricular assist devices: a case report and review of literature

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This case report illustrates the effects of CCM as a bridge to recovery in a patient who has been a candidate for LVAD. After CCM the patient has become stable in NYHA class II, with no further acute HF episodes and a significant clinical and functional improvements. Consequently, the patient was no longer an LVAD candidate, as CCM had acted as a bridge to recovery, making the advanced HF designation no longer applicable. The ease of implantation, uneventful procedural recovery, extraordinary device longevity, and favorable risk profile all position CCM as an important tool in the treatment of advanced HFrEF patients candidate to LVAD therapy, serving as a bridge to recovery. Further large-scale randomized controlled trials are needed to confirm the long-term benefits of CCM therapy in this particular population subgroup, helping a better patient selection.

KEYWORDS

Cardiac Contractility Modulation (CCM), advance heart failure, bridge to recovery, left ventricular assist devices (LVAD), heart transplantation

Introduction

Up to 10% of patients with heart failure (HF) fail to respond to pharmacological treatments, leading to a clinical progression (1). The preferred therapeutic approach for patients with advanced HF is heart transplantation (HT) or alternatively the implantation of a left ventricular assist device (LVAD) (2). Cardiac Contractility Modulation (CCM) represents an emerging therapeutic strategy for patients with heart failure with reduced ejection fraction (HFrEF) and could benefit this specific population candidate to HT or LVAD.

The CCM therapy affects the epigenetic and proteomic scenery of cardiomyocytes, by applying non-excitatory electrical signals to the myocardium during the absolute refractory period of the action potential. The mechanisms underlying CCM's effects remain unclear but may partly involve improved calcium handling through upregulation of L-type Ca²⁺ channels and regulation of phospholamban activity (3); this leads to enhancing contraction without increasing oxygen consumption. The final result is an improvement of exercise tolerance and quality of life and a reduction of hospital admissions for patient with HF and CCM device implanted.

The FIX-HF-5C2 trial evaluated 60 patients with an ejection fraction (EF) between 25% and 45%, NYHA class III-IV symptoms despite optimal medical therapy, and a narrow QRS interval (<130 ms) without indication for cardiac resynchronization therapy (CRT). After six months of follow-up, CCM demonstrated a reduction in HF-related hospitalizations and an improvement in exercise capacity, quality of life and NYHA class (4).

Similarly, the CCM-REG registry analyzed outcomes of 140 patients with an EF between 25% and 45%, already implanted with CCM devices. The primary endpoint was a comparison between predicted survival by the Seattle Heart Failure Model (SHFM) to that observed through a follow-up of 3 years. While no significant difference in survival was observed both in the entire cohort and in the one with LVEF between 25% and 34%, patients with an EF between 35% and 45% exhibited a better survival compared to SHFM predictions (5).

Another registry, which included 68 NYHA class II–III patients with low EF and a QRS duration <130 ms, reported a significant reduction in mortality over a follow-up period of 4.5 years compared to SHFM-predicted mortality (6). This better survival was also observed in other registries (7, 8).

A recent case report suggested that CCM may be a viable bridge-to-transplant strategy in select end-stage HFrEF patients not adequately compensated by pharmacological therapy in which LVAD was contraindicated due to factors such as severe obesity (9).

Additionally, the management of systolic HF post-HT remains challenging due to drug interactions and renal insufficiency with subsequent limitations to optimal medical therapy. A case report documented the first use of CCM in a post-HT patient with refractory HF and narrow QRS (10).

This case report illustrates the effects of CCM as a bridge to recovery in a patient who was a candidate for LVAD. This clinical outcome may influence the approach for treating many patients with advanced-stage heart failure in any therapeutic phases.

Case presentation

We describe the case of a 74-year-old patient presenting to our Cardiology Department with worsening dyspnea at rest. The patient's medical history included dilated cardiomyopathy with severe left ventricular dysfunction and a dual-chamber ICD implanted for primary prevention 5 years before; ICD memory revealed an episode of appropriate therapy delivered by the ICD for ventricular fibrillation 2 years before. Despite receiving optimal medical therapy at the highest tolerated doses (sacubitril/valsartan 49/51 mg twice daily, bisoprolol 5 mg daily, and eplerenone 50 mg daily), severe left ventricular dysfunction persisted and the patient continued to experience NYHA class III symptoms. In the last 12 months, the patient was hospitalized several times due to HF recurrences, requiring increased home diuretic therapy. At an outpatient visit, we used echocardiographic speckle-tracking strain imaging (a non-Doppler and angle-independent technique) for

myocardial function assessment (11). This revealed an impaired global longitudinal strain (GLS −10.0%).

A cardiopulmonary testing confirmed severe functional impairment, with a peak oxygen uptake (VO₂ peak) of 11 ml/kg/min and a ventilation/carbon dioxide production slope (VE/VCO₂) of 36. After few weeks the patient was admitted for cardiogenic shock (CS). A severely depressed systolic function (LVEF 17% calculated with the biplane Simpson's formula) and widespread hypokinesia of the LV were documented. Right ventricular function was also severely impaired. The patient exhibited systolic blood pressure <90 mmHg for ≥30 min, refractory to fluid resuscitation, with laboratory findings consistent with end-organ dysfunction. The cardiac index (CI), assessed via FloTrac/Vigileo (12), was 1.9 L/min/m².

Given the marked functional impairment despite optimized therapy, the patient was evaluated for HT but excluded for age limits. Few week after hospital discharge, despite ambulatory pulsed levosimendan infusion, the patient experienced another episode of acute HF, requiring hospitalization and continuous inotropic support. The patient was subsequently evaluated for LVAD implantation. The efficacy of assist devices has been demonstrated in a randomized trial enrolling end-stage HF patients awaiting CT, with a significant survival and quality of life improvement by the use of an LVAD. However, only a quarter of patients survived to 2 years and complications of LVAD were frequent (13). Although fully magnetically levitated (centrifugal-flow LVADs are associated with better outcomes than axial-flow devices), infections related to the device frequently occur, limiting the actual indication (14). The patient's INTERMACS score (a commonly used measure of disease severity) at that time was 3 (stable continuous inotrope-dependent).

Considering the patient's small size, impaired right ventricular function and high risk of infection, device malfunction and pump thrombosis associated with LVAD in patients with pre-existing cardiac devices, CCM implantation was identified as the most feasible therapeutic alternative. Patient has been informed about the benefits, expectations, and potential complications of CCM implantation, both in writing and verbally.

Following informed consent on the benefits, expectations, and potential complications of CCM implantation, in December 2022 the patient underwent implantation of a two-lead CCM, consisting of an Optimizer Smart implantable pulse generator (Impulse Dynamics Inc. Orangeburg, NY, USA) located in the right infraclavicular fossa connected to 2 ventricular pacing leads placed in the interventricular septum (Figure 1). The target area is the lower part of the septal region of the right ventricle, maintaining at least 2 cm separation. Lead positioning is obtained with a Mond type stylet, designed with a primary J curve and a secondary posterior curve. Proper pacing and sensing parameters were confirmed, with no diaphragmatic or chest wall capture and no patient's complain of chest discomfort during high-output stimulation. The device was programmed in OVO-LS-CCM mode with a CCM train of 2 pulses of 7.5 V with a 22 ms duration and a CCM programmed dose of 8 h periods per day. The typical CCM ECG is with spike within QRS refractory period (Figure 2).

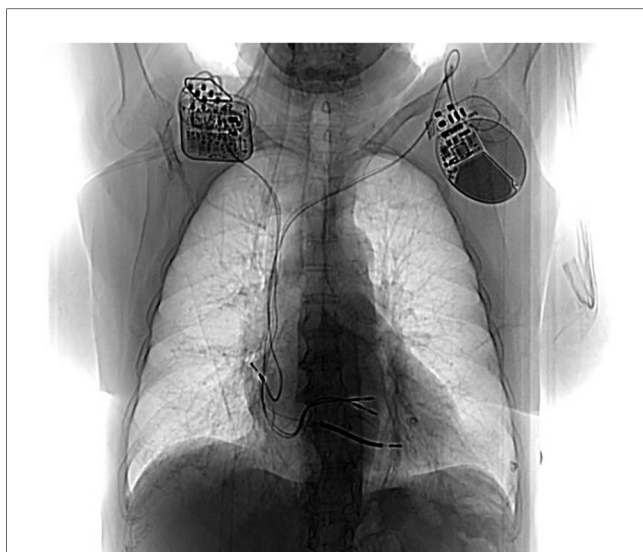


FIGURE 1

Post CCM implant chest X ray. Generator is located in the right infraclavicular fossa and it's connected to 2 ventricular pacing leads. On the left side the previous dual chamber ICD can be noted.

A innovating feature of the Optimizer Smart device is its rechargeable battery requiring the patient to charge it with a portable device for only 1 h per week. This rechargeable battery is guaranteed for 15 years of longevity. The patient has been educated about the importance of battery charge and the knowledge of appropriate actions to take in response to device alarms.

In the first two months post-implantation, no symptom improvement was observed and the patient required another hospitalization for acute decompensated heart failure. However, by the third month, gradual symptomatic improvement was observed, including enhanced NYHA class, six-minute walk test distance, echocardiographic parameters, and NT-proBNP levels.

The LV parameters also improved, with GLS reaching -42% (vs. -10%) and LVEF 35% (vs. 17%). Six months post-implantation walked 350 meters without desaturation at SMWT the patient and her MLWHFQ score improved to 51. A repeat cardiopulmonary test showed a VO_2 peak increase to 15.6 ml/kg/min (vs. 11 ml/kg/min) and a reduced VE/VCO_2 slope of 22 (vs. 36). Since low ventilatory efficiency is an important predictor of cardiovascular mortality in HF patients (15), these results highlight CCM's therapeutic impact on our patient. By December 2024, the patient was stable in NYHA class II, with no further acute HF episodes (Figure 3). The patient's INTERMACS score was unquantifiable due to significant clinical and functional improvements. Consequently, the patient was no longer an LVAD candidate, as CCM had acted as a bridge to recovery, making the advanced HF designation no longer applicable. Finally, the patient perspective has been a new restart provided by CCM.

Discussion

The management of advanced HF presents significant challenges. In patients without CRT indications, HT remains the gold standard but is limited by donor shortages, while LVAD therapy is often limited by HF patient comorbidities. The CCM therapy aims to enhance myocardial contractility and could be chosen as additional therapy for patients with severe HF.

Currently, no large-scale randomized trials have demonstrated mortality endpoints with CCM, so that therapy has not yet been implemented in the guidelines. However, the evidence supporting CCM is comparable with the one supporting the CRT, indeed both these therapies have not been yet showed benefit in survival endpoint. On the other hand, meta-analyses and clinical trials have shown significant improvements in cardiopulmonary function, suggesting it as a viable option for CRT-non-responsive patients with a wide QRS duration and patients with reduced LVEF and "narrow"

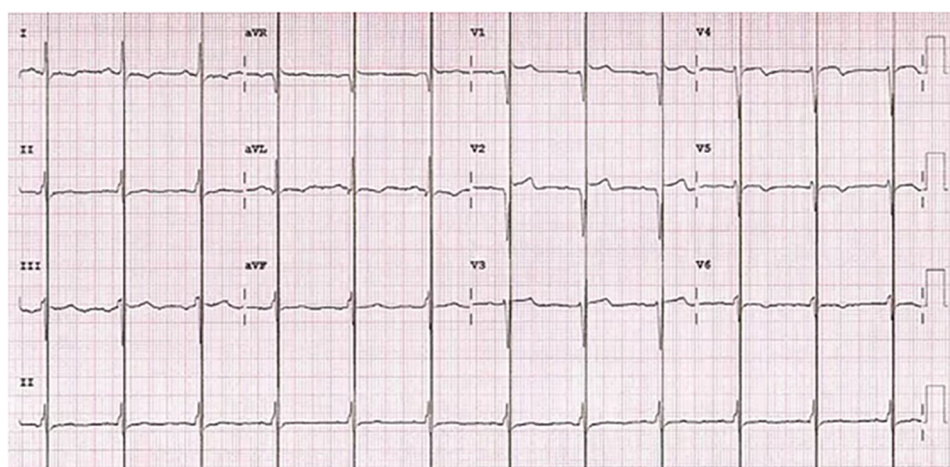


FIGURE 2

Electrocardiogram during cardiac contractility modulation treatment with typical spike within QRS refractory period.

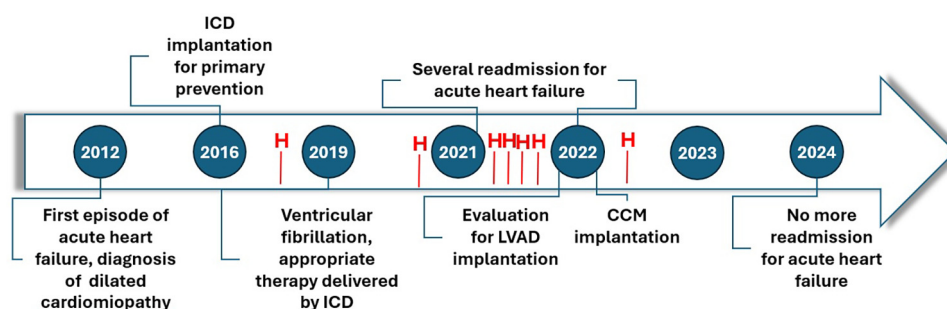


FIGURE 3

Timeline of patient's history. No further hospitalization (H) were observed for acute HF episodes after three months by CCM implant.

QRS (16–18). Notably, EF inclusion criteria (EF 25%–45%) for CCM encompass twice as many patients as are currently indicated for CRT. Furthermore, over 80% of CCM patients improve by at least one NYHA class and over 40% of CCM patients improve two classes. Although tricuspid regurgitation is a potential complication after the implantation of right ventricular electrodes, preliminary data suggest no significant worsening with CCM therapy (19). Finally recent advancements have led to the first successful implantations of devices integrating ICD and CCM functionalities (20). This new development is a promising area for ongoing research and may further expand the role of CCM.

Subgroup analysis from the FIX-HF-5 trial indicated limited benefit in patients with EF <25% (21); however, few effective therapies exist for this kind of patients and no worsening was observed in this group. Our patient belongs to this population subgroup with severely reduced LVEF and advanced heart failure so LVAD could have served as a bridge to HT and CCM does not seem to promise great benefit. However, CCM was chosen as an alternative therapeutic option and after its implantation the patient returned to NYHA class II, regained a quality of life in many daily activities and experienced significant improvements in echocardiographic and cardiopulmonary test data. Consequently, the patient was no longer an LVAD candidate, as CCM had acted as a bridge to recovery.

Nowadays a prospective worldwide registry is needed, with strong monitoring in specific populations and avoiding excessive reliance on mortality endpoints that could miss the real clinical benefits of CCM therapy.

Conclusion

This case highlights CCM therapy as a bridge to recovery in an advanced HFrEF patient initially considered for LVAD. The CCM therapy offers ease of implantation, minimal procedural risks, long device longevity, and a favorable safety profile, serving as a bridge to recovery in selected end-stage HFrEF patients. Further randomized controlled trials are necessary to establish the long-term benefits of CCM therapy and refine patient selection criteria.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

FM: Writing – original draft, Writing – review & editing. MS: Writing – review & editing. ES: Writing – review & editing. VG: Writing – original draft. TG: Writing – original draft. FV: Conceptualization, Writing – review & editing. AD: Supervision, Writing – review & editing.

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