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Insights in cardiac rhythmology 2023

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Editorial: Insights in cardiac rhythmology 2023

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Editorial on the Research Topic
Insights in cardiac rhythmology 2023

It has been a dense year worldwide, as geopolitical instability, economic uncertainty and effects of climate change are building up pressure on most societies. Similarly, the scientific World is faced by many upcoming challenges: an ageing population with increasing comorbidities, as much as the constant growth of new technologies whose economic costs are likely to burden on stretched sanitary budgets (1–3.) It is essential to respond to these challenges by strengthening the efforts to guarantee necessary treatments remain accessible and affordable to all patients (4).

In Cardiac Rhythmology, this year once again underscored the great interest in atrial fibrillation (AF) (Figure 1), with an expanding role for catheter ablation (CA) to reduce symptoms, recurrence and progression. As a result, the number of procedures is expected to rise steadily in the next years, also as a first line approach (5, 6).

Currently, CA demonstrates a high success rate and low incidence of complications (7), but trans-septal puncture (TSP) remains one of the most challenging steps of this procedure, also exposing the patients to an associated radiation risk (8). A retrospective analysis (Silva Cunha et al.) demonstrated the possibility to reduce fluoroscopy time by a single compared to a double TSP approach, with similar rates of efficacy and complications at follow-up.

CA outcomes are less satisfactory in patients with persistent AF (perAF) and extensive atrial remodeling. In the pre-pacific study (Limite et al.), patients with perAF who had a positive response to electrical cardioversion (ECV) were found to have less extended abnormal left atrial substrate at voltage mapping. A more aggressive approach beyond pulmonary vein isolation (PVI) in patients with ECV failure, displaying more advanced atrial remodeling, could therefore increase the success rate of CA (9). Convergent or hybrid AF ablation, that combines endocardial and mini-invasive epicardial approaches, has the potential to become a strategy to achieve rhythm control in these patients (10). When performed in experienced centers, the procedure was safe, with few and minor complications, as well as favorable in terms of rhythm control rates (Carpenter et al.)

Another recent innovation in the field of CA is represented by pulsed field ablation (PFA) (11). Interestingly, this technique has shown potential applications outside the field of AF. In a case report of a young man with repetitive episodes of orthodromic

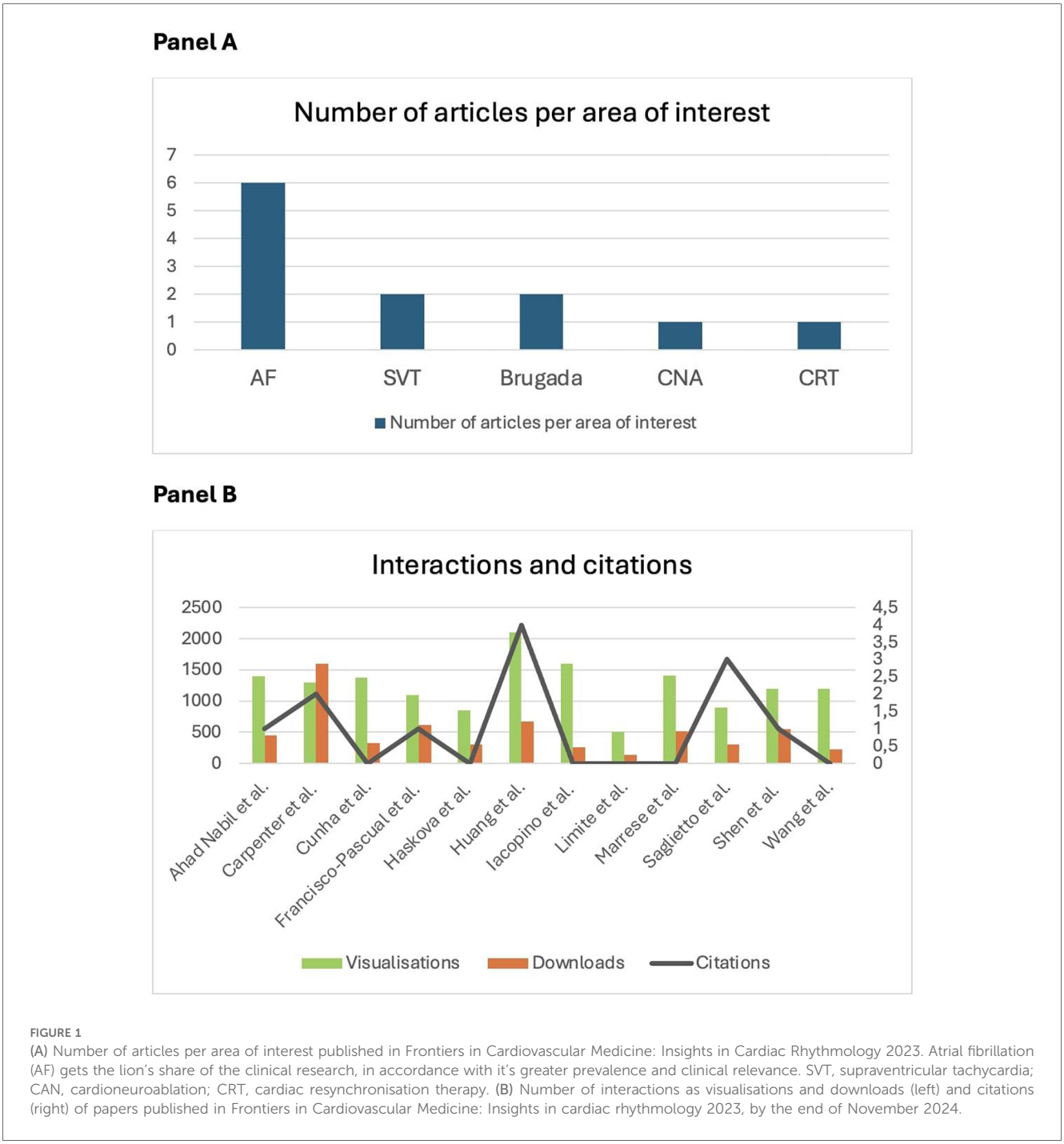

FIGURE 1
(A) Number of articles per area of interest published in Frontiers in Cardiovascular Medicine: Insights in Cardiac Rhythmology 2023. Atrial fibrillation (AF) gets the lion's share of the clinical research, in accordance with it's greater prevalence and clinical relevance. SVT, supraventricular tachycardia; CAN, cardioneuroablation; CRT, cardiac resynchronisation therapy. **(B)** Number of interactions as visualisations and downloads (left) and citations (right) of papers published in Frontiers in Cardiovascular Medicine: Insights in cardiac rhythmology 2023, by the end of November 2024.

atrio-ventricular re-entrant tachycardia (AVRT) refractory to previous endocardial ablation attempts, PFA was successfully adopted for accessory pathway ablation, avoiding epicardial access and the related higher risk of complications.

An increasing awareness of the role played by the autonomic nervous system (ANS) in both the development and persistence of AF is emerging (Huang et al.). Autonomic dysregulation altering the electrophysiological properties of the atrium, through direct effects on ion channel function and disrupted calcium handling, can lead to atrial tachyarrhythmias. Interestingly, an imbalance between sympathetic and parasympathetic activities from acute injury to central autonomic regions, such as the insular cortex, resulted in an increased risk of cardiovascular and arrhythmic complications. Despite the complexity of the brain-heart connection, these findings suggest that therapies targeting the central nervous system and upstream pathways may represent a breakthrough in the treatment of AF.

Also dietary patterns, such as the Mediterranean and DASH (Dietary Approaches to Stop Hypertension) diets, play a role in modulating AF risk and progression. Incorporating nutrients like omega-3 fatty acids, magnesium and antioxidants might reduce

incidence and progression of the arrhythmia, as part of a more holistic approach (Ahad Nabil et al.)

One of the most challenging aspects regarding AF is unfolding the relationship with cardioembolic ischemic events (12). Therefore, the possibility to identify a radiologic fingerprint to predict a cardio-embolic genesis of stroke would have a major impact on clinical practice, with a potential influence on secondary prevention strategies. Considering CA as an "*in vivo*" model of cardioembolic lesions, Saglietto et al. described core radiologic features supportive of a cardioembolic origin: cortical location in the territory of the middle cerebral artery, small dimensions (< 10 mm) and ubiquitarian distribution among lobes.

Shifting the attention from AF to bradyarrhythmias, cardioneuroablation (CNA) has emerged as a promising therapeutic option for young patients with recurrent cardioinhibitory syncopes that are unresponsive to conservative measures and in whom implantation of a permanent pacemaker is undesirable (13). Implementation of patients' selection (through head-up tilt test, atropine test and Holter-monitoring derived indexes such as heart rate variability and deceleration capacity), as well as the diffusion of techniques to accurately identify the ganglionic plexi location during the procedure have prompted the diffusion of the technique. However, the lack of long-term follow-up and randomized controlled trials leave uncertainties regarding the extension of ablation (whether directed towards only right or both atria) and the definition of procedural endpoints (Marrese et al.)

Focusing the attention on inherited disorders, stratification and management of arrhythmic risk still represents a major challenge, as unexpected triggers might lead to fatal events. In a recently published case-report, lacosamide (an anti-epileptic drug which acts as an enhancer of slow-inactivated state of neuronal voltage-gated sodium channels) triggered the development of ventricular fibrillation in a young Asian female with seizures. After the detection of a type 1 Brugada pattern during ajmaline test, genetic testing revealed the presence of a heterozygous mutation in the SCN5A gene.

Considering the role of depolarization abnormalities in arrhythmogenesis in Brugada syndrome (14, 15), combination of novel ECG markers (dST-Tiso interval—the interval between the onset of the coved ST elevation and its termination on the isoelectric line) and ECG imaging (ECGi) through CardioInsight (a non-invasive 3D mapping system) have been tested to stratify arrhythmic risk in a 48-year old patient with drug-induced type 1 Brugada pattern and an anamnesis of syncope (Iacopino et al.), unveiling the presence of a conduction block along the anterior wall of the right ventricular outflow tract during ajmaline infusion. A subsequent electrophysiological study resulted positive for induction of VF, leading to the implantation of a single chamber defibrillator. Despite requiring further validation, ECGi may be useful for non-invasive stratification of arrhythmic risk in such patients.

An interventional approach with CA has become the first-line treatment in patients with congenital heart diseases with supraventricular and ventricular arrhythmias, as antiarrhythmic drugs can be problematic in this category (Francisco-Pascual et al.). In such patients meticulous procedure planning is essential, taking into consideration the patient's specific anatomy to identify a suitable vascular access. Intraprocedural imaging techniques, as well as the fusion of electroanatomic mapping (EAM) with previous imaging testing can provide guidance for a successful intervention.

Eventually, there is a persisting effort to better predict response to well-established treatment, such as resynchronization therapy (CRT). In a prospective study (Wang et al.), lateral wall regional constructive work (CW) and septal wasted work (WW) were identified as independent determinants of reverse modelling, with a positive impact on clinical outcomes and a better performance than global parameters.

This year's research confirms that cardiac rhythmology is indeed a fascinating and ever-evolving field! Despite these exciting developments, many questions still lay unanswered as new evidence continuously emerge. We can only look forward to the next year being a turning one for the many unresolved issues, in and outside of the scientific world.

Author contributions

CG: Investigation, Writing – original draft, Writing – review & editing. SR: Investigation, Writing – original draft, Writing – review & editing. MA: Conceptualization, Writing – original draft, Writing – review & editing.

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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Generative AI statement

The authors declare that Generative AI was used in the creation of this manuscript. GPT-4o mini (ChatGPT Enterprise, OpenAI) was used to revise sections of the text, maintaining the original technical rigor while improving clarity, structure and overall flow. It had no role in the planning of work, research, choice of sources and in adding information.

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Research on atrial fibrillation mechanisms and prediction of therapeutic prospects: focus on the autonomic nervous system upstream pathways

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Atrial fibrillation (AF) is the most common clinical arrhythmia disorder. It can easily lead to complications such as thromboembolism, palpitations, dizziness, angina, heart failure, and stroke. The disability and mortality rates associated with AF are extremely high, significantly affecting the quality of life and work of patients. With the deepening of research into the brain-heart connection, the link between AF and stroke has become increasingly evident. AF is now categorized as either Known Atrial Fibrillation (KAF) or Atrial Fibrillation Detected After Stroke (AFDAS), with stroke as the baseline. This article, through a literature review, briefly summarizes the current pathogenesis of KAF and AFDAS, as well as the status of their clinical pharmacological and non-pharmacological treatments. It has been found that the existing treatments for KAF and AFDAS have limited efficacy and are often associated with significant adverse reactions and a risk of recurrence. Moreover, most drugs and treatment methods tend to focus on a single mechanism pathway. For example, drugs targeting ion channels primarily modulate ion channels and have relatively limited impact on other pathways. This limitation underscores the need to break away from the "one disease, one target, one drug/measurement" dogma for the development of innovative treatments, promoting both drug and non-drug therapies and significantly improving the quality of clinical treatment. With the increasing refinement of the overall mechanisms of KAF and AFDAS, a deeper exploration of physiological pathology, and comprehensive research on the brain-heart relationship, it is imperative to shift from long-term symptom management to more precise and optimized treatment methods that are effective for almost all patients. We anticipate that drugs or non-drug therapies targeting the central nervous system and upstream pathways can guide the simultaneous treatment of multiple downstream pathways in AF, thereby becoming a new breakthrough in AF treatment research.

KEYWORDS

atrial fibrillation, stroke, therapies, mechanism, forecast

Abbreviations

AF, atrial fibrillation; AFDAS, atrial fibrillation detected after stroke; KAF, known atrial fibrillaton; ANS, autonomic nervous system; BBB, blood-brain barrier; ICAM-1, intercellular adhesion molecule-1; PDGF, platelet derived growth factor; CMED, coronary microvascular endothelial dysfunction; MII, myocarditis infiltration; EA, electric acupuncture; GGA, geranylgeranylacetone; pAF, paroxysmal atrial fibrillation; cAF, chronic(persistent) atrial fibrillation; HFrEF-cAF, heart Failure with Reduced Ejection Fraction and chronic Atrial Fibrillation; POAF, postoperative atrial fibrillation.

1. Introduction

Atrial Fibrillation (AF) is the most prevalent clinical arrhythmia, characterized by irregular atrial activity and subsequent loss of mechanical function, making it the most severe atrial electrical activity disorder. The atrium loses its regular and orderly electrical activity, replaced by rapid and disorganized fibrillation waves (1). According to estimates from the 2010 Global Burden of Disease Study, the worldwide prevalence of AF is approximately 33 million people. The incidence of AF is higher in males, while females tend to have a higher mortality rate associated with AF. In countries such as Australia, Europe, and the USA, the prevalence of AF among adults ranges from 1% to 4%, but this figure rises to over 13% among individuals aged 80 and older. In the United States alone, there are an estimated 3–5 million people living with AF. With the aging of the population, it is projected that over 8 million people in the USA will be affected by AF by 2050. In Europe, the prevalence of AF is expected to increase from the current estimated 8.8 million to approximately 18 million by 2060. It is estimated that Japan has around 700,000 individuals with AF, and this number is projected to surpass 1 million by 2050. In China, approximately 3.9 million individuals aged 60 years or older have AF. However, by 2050, as China's population of individuals aged 60 years or older grows to 460 million, it is estimated that 9 million of them will have AF (2). In 2020, the domestic cardiovascular health and disease report conducted random sampling statistics of community residents in 2015. It found that the prevalence of AF among Chinese residents aged 35 and above was 0.7%, while it was 1.2% for rural Chinese residents aged 35 and above. Within this group, the prevalence was 0.1% for individuals aged 35–44 and 4.6% for those aged at least 75. The prevalence of AF did not differ significantly between genders (3). The most common comorbidities in AF patients include hypertension, followed by coronary heart disease and heart failure. Patients aged over 75 with AF are more likely to have coronary heart disease, hypertension, stroke, cognitive impairment, and chronic obstructive pulmonary disease (COPD).

Every year, there are 8 million cases of ischemic stroke worldwide. Among these, 20% of individuals have prevalent atrial fibrillation, a condition characterized by irregular heart rhythms. In the remaining 80% of patients without known atrial fibrillation (KAF), up to 24% can be newly diagnosed with atrial fibrillation after undergoing long-term electrocardiogram monitoring. Despite this, a significant number of cases still go undiagnosed due to inadequate monitoring (4). As research into the brain-heart axis and brain-heart syndromes continues to expand, scholars have unveiled a close relationship between the brain and the heart. Within this context, stroke-heart syndrome has emerged as a crucial branch of brain-heart research. While some studies suggest there may not be a direct causal relationship between stroke and atrial fibrillation, certain research findings indicate that stroke can act as both a cause and a consequence of atrial fibrillation, or that their interaction may involve more complex mechanisms (5–7). Consequently, an increasing number of studies have started to investigate the interplay between stroke and AF, categorizing AF into two groups: known atrial fibrillation (KAF) and newly discovered atrial fibrillation after stroke (AFDAS), using stroke as a baseline. KAF is primarily driven by structural changes in the heart, and therefore, it can be predominantly considered "cardiogenic." On the other hand, AFDAS is primarily linked to stroke and may be regarded as "neurogenic," or a combination of both.

2. Mechanisms of KAF

KAF is primarily cardiogenic, often stemming from underlying cardiac abnormalities, and has undergone extensive research (8). These mechanisms encompass atrial remodeling, altered autonomic function, changes in calcium channels and gap junctional proteins, inflammatory responses, and abnormal gene expression. When these underlying mechanisms trigger atrial fibrillation, the rapid and irregular activation of the atria during atrial fibrillation leads to electrical remodeling. This results in the shortening of the atrial refractory period and promotes reentry, creating a detrimental cycle known as "AF begets AF" (9, 10). AF is both a cause and a consequence of atrial heart disease. The pathogenesis of KAF is intricate. In this paper, we will provide a concise overview of the following six aspects (11):

- Electrical remodeling and structural remodeling
- Alterations in the autonomic nervous system
- Calcium-handling remodeling
- Gap-junction remodeling
- Inflammatory responses
- Abnormalities in gene expression

2.1. Atrial remodeling

Atrial remodeling primarily encompasses structural remodeling and electrical remodeling. Structural remodeling is recognized as a significant factor in the initiation and persistence of AF (12). It involves changes such as atrial enlargement, cardiomyocyte hypertrophy (13), depolarization, and atrial fibrosis. Research has indicated that fibrosis is frequently observed in AF patients, and the increased presence of fibroblasts, myofibroblasts, and elevated extracellular matrix deposition in fibrotic tissue disrupts the continuity of myocardial bundles and interferes with the gap junctions between cardiomyocytes. Endomyocardial biopsies in patients with isolated atrial fibrillation have revealed abnormal alterations, including myolysis, glycogen accumulation, mitochondrial changes, and signs of chromatin structure depolarization. These changes are characterized by the dispersion and disappearance of the sarcoplasmic reticulum, as well as degeneration and necrosis of atrial myocytes (14). In the right atrium of patients with persistent AF, micronodular content was found to be reduced, and myolysis with loss of cellular myogenic fiber structure was observed (15). Additionally, studies have shown that the activation of the renin-angiotensin-aldosterone system (RAAS),

particularly angiotensin II (Ang-II), also contributes to structural remodeling of the atria (16).

Electrical remodeling in AF pertains to alterations in electrophysiological properties induced by AF and is considered a compensatory mechanism to prevent intracellular Ca2+ overload. Calcium overload is implicated in the electrical and structural remodeling of the atria, leading to atrial fibrillation, impairment of cardiac cell vitality, and contractile dysfunction (12, 17). Yoo et al., using a novel gene therapy approach in a canine model of rapid atrial pacing, demonstrated that oxidative damage caused by NADPH oxidase 2 (NOX2) results in the upregulation of acetylcholine-dependent K-current (IKACh) activity. This mechanism is not only the origin but also a perpetuator of electrical remodeling in AF. Experimental evidence also indicated that rapid pacing of canine atrial myocytes is induced by oxidative damage through the induction of NOX2 and the production of mitochondrial reactive oxygen species. This suggests that oxidative damage may trigger electrical remodeling in AF by a mechanism involving the activation of protein kinase C epsilon, causing an upregulation of IKACh (18). Recent studies have also suggested the involvement of SK channels in atrial remodeling in experimental AF models. Cardiac SK channels functionally connect voltage-gated calcium ion channels and are activated during contraction, participating in cardiac action potential (AP) repolarization. Experimental research demonstrated that SK channel inhibition can have antiarrhythmic effects by directly blocking SK channels (19, 20). Channels in the K2P family, such as TWIK-1, TASK-1, and TASK-3, are background potassium channels, and research suggests that they can influence the duration of depolarization in ventricular muscle cells, potentially inducing arrhythmias. Upregulation of K2P currents can lead to APD shortening in chronic AF patients, and inhibition of channels like TWIK-1, TASK-1, and TASK-3 may potentially reverse AF-related APD shortening, thereby inhibiting atrial fibrillation occurrence and preventing electrical remodeling (21, 22).

2.2. Changes in autonomic function

Many animal and clinical studies have shown that imbalances in the cardiac autonomic nervous system (ANS) play a vital role in developing and maintaining AF, and that parasympathetic and sympathetic overactivity increase vulnerability to AF (23). The autonomic nervous system communicates extensively with the heart through external inputs and ganglionated plexi (GP) located on the epicardial surface (24). The ANS is closely associated with heart rate variability, and Agarwal et al. noted that impaired cardiac autonomic function, characterized by reduced resting heart rate variability, is associated with a higher incidence of AF (25). Activation of the autonomic nervous system can induce atrial tachyarrhythmias, including atrial tachycardia and AF, by inducing significant and heterogeneous changes in atrial electrophysiology (23). Research indicates that autonomic regulation has a significant impact on cardiac ion channels. Simultaneous activation of the sympathetic and parasympathetic nervous systems, for example, can lead to increased intracellular Ca2+ transients by the sympathetic nervous system and activation of IKAch by the parasympathetic nervous system, resulting in shortened APD (action potential duration) and larger and longer Ca2+ transients. Shortened APD and larger Ca2+ transients create conditions for early afterdepolarizations, which can trigger triggered activity and AF (26). Patterson et al. found that in canine pulmonary veins, rapid discharges and atrial fibrillation could be triggered by simultaneous stimulation of the parasympathetic and sympathetic nervous systems (27). Other studies have suggested that the autonomic nervous system not only contributes to the substrate for AF in normal hearts but also participates in the genesis of structural heart disease, with the parasympathetic system contributing to the maintenance of AF and the sympathetic system affecting the frequency characteristics of AF (28). As demonstrated by Arora, interactions between the vagus nerve and sympathetic nerve stimulation can create ectopic foci, making the autonomic nervous system a trigger for AF. Additionally, in structural heart disease, ANS forms a substrate for AF maintenance (29). Park et al. (30) experimentally demonstrated in a canine model that simultaneous sympathetic discharge was the most common trigger for paroxysmal tachycardia and AF. Chen et al. discussed the importance of autonomic nervous system activity in inducing PAF. They demonstrated that vagal denervation can enhance the efficacy of circumferential pulmonary vein isolation in preventing AF recurrence. Through heart rate variability analysis, they found that sympathetic and parasympathetic imbalances existed before the onset of PAF; sympathetic and vagal discharges occurred simultaneously prior to PAF onset in experimental animals (31). Gould et al. also suggested in their study of persistent AF patients that autonomic remodeling may be a part of the atrial substrate for AF (32). Zhang et al. (33) showed that the vagus nerve can regulate AF through the α7nAChR-mediated cholinergic anti-inflammatory pathway. To our knowledge, the sympathetic nervous system is typically associated with the adrenergic system, while the parasympathetic nervous system is typically associated with the cholinergic system. In the human body, the autonomic nervous system and the adrenergic/cholinergic systems interact to maintain balance. When the sympathetic nervous system is stimulated excessively or abnormally, it can lead to excessive release of adrenaline. Workman stated in their research that adrenergic stimulation by catecholamines can lead to AF in patients. Catecholamines can influence every electrophysiological mechanism of AF initiation and maintenance in human atria (34). In summary, the autonomic nerves inherent to the heart can act as the sole trigger for initiating AF. Furthermore, current research suggests that the autonomic nervous system is linked to other fundamental mechanisms of AF. Modulating the ANS through electrical stimulation has been considered a promising therapeutic strategy in clinical and research settings.

2.3. Calcium-handling remodeling

Intracellular calcium (Ca2+) overload and abnormal Ca2+ handling processes can contribute to the development and

persistence of AF. Research conducted in animal models and human cardiomyocytes isolated from atrial appendages has revealed that reduced mRNA and protein expression of L-type Ca2+ channels, along with altered phosphorylation and redox potential, result in decreased Ca2+ current density. A reduction in Ca2+ current density is a hallmark of AF (35). Chelu and colleagues discovered that abnormal ryanodine receptor 2 (RyR2) with enhanced calcium sensitivity in a mouse model of AF leads to excessive intracellular calcium release from cardiac myocytes. This, in turn, causes increased activity of calmodulin-dependent protein kinase II (CaMKII), which is a critical downstream effect in individuals susceptible to AF. In a comparison of patients with and without AF, Hove-Madsen et al. found that the development of AF was associated with increased spontaneous calcium release from the sarcoplasmic reticulum in atrial myocytes (36). Some studies have identified significant differences in electrical remodeling and calcium handling among different forms of primary atrial fibrillation (AF), such as paroxysmal AF (pAF), persistent AF (cAF), and persistent AF with heart failure (HFrEF-cAF). Their research demonstrated that abnormal Ca2+ handling promotes ectopic (triggered) activity and reentry through action potential duration (APD) shortening and heterogeneous conduction. These mechanisms are the primary causes of arrhythmia. Classic indicators of atrial electrical remodeling associated with AF primarily appear in cAF and HFrEF-cAF. Ca2+-dependent triggered activity forms the basis for atrial arrhythmias in pAF patients, primarily due to increased sarcoplasmic reticulum (SR) Ca2+ load and dysregulation of RyR2, leading to an increased incidence of spontaneous Ca2+ events (SCaEs), resulting in delayed afterdepolarizations (DAD) and triggered activity. Spontaneous cell activity in central atrial cardiomyocytes increases in pAF patients. In cAF patients' atrial muscle cells, higher spontaneous Ca2+ release events are observed, along with electrical remodeling characterized by APD shortening and membrane potential hyperpolarization, which promotes reentry. In cAF, the increased SR Ca2+ release is a result of increased RyR2 channel open probability (RyR2 Po) mediated by CaMKII due to excessive phosphorylation of RyR2, making RyR2 channels more sensitive to Ca2+. However, in pAF, there is primarily an increase in SR Ca2+ uptake, opposite to the decrease observed in cAF, and no increase in RyR2 phosphorylation is found, nor is atrial fibrillation-related electrical remodeling observed in pAF cardiomyocytes. Studies in HFrEF-cAF patients did not observe a decrease in connexin-43, but markers of fibrosis (collagen-1a, fibronectin, periostin) were expressed at higher levels. Myosin and RyR2 protein levels both decreased, but SERCA2a expression increased, leading to increased RyR2-Ser2814 phosphorylation, making RyR2 more sensitive to Ca2+ (10, 37, 38).

2.4. Gap-junction remodeling

Gap junctions represent a significant determinant of electrical impulse conduction in cardiac tissue (39). In the atria, the primary gap junction subunits are connexins40 and connexins43. Notably, there is substantial heterogeneity in the distribution of connexins throughout different regions of the heart. In a study on goats, it was discovered that the "gap junction remodeling" process is involved in the stabilization of atrial fibrillation. As the duration of atrial fibrillation increases, apart from the redistribution of Cx40, the overall levels of these gap junction proteins also significantly decrease (40). van der Velden et al. in their research indicated that local variations in the expression of connexin proteins (Cx40 or Cx43), whether upregulated or downregulated, may underlie conduction velocity heterogeneity (or dispersion), thereby creating conditions conducive to micro-reentry, which could lead to sustained atrial fibrillation (41). Therefore, Changes in connexins in AF may contribute to local conduction abnormalities and may facilitate the initiation and perpetuation of AF (17).

2.5. Inflammatory response

Inflammation and the associated immune response play a role in initiating and sustaining AF. Inflammatory signaling pathways are causally involved in the development of atrial electrical remodeling, calcium handling, and structural remodeling. These pathways can also influence neural growth and autonomic variations by affecting the heart's intrinsic cardiac nervous system (42). Research has demonstrated that AF can further exacerbate inflammation, and mediators of the inflammatory response can modify atrial electrophysiology and structural substrates, increasing susceptibility to AF. Postoperative atrial fibrillation (POAF) is a common complication following cardiac surgery, often peaking 2–4 days after the procedure. It typically manifests as newly developed atrial fibrillation immediately after surgery, with episodes being short in duration, paroxysmal, and asymptomatic. Evidence suggests that inflammation may be one of the complex mechanisms contributing to the occurrence of POAF. It is associated with inflammatory biomarkers such as IL-2, IL-6, and C-reactive protein (43). In their study, Fakuade and colleagues also found that abnormal calcium handling, primarily impaired SR calcium uptake, not only results in pre-existing atrial contractile dysfunction but also creates a substrate for atrial arrhythmias, making patients more susceptible to POAF (44). Subsequent research by Heijman and others revealed that patients who develop POAF exhibit clear abnormalities in calcium handling and activation of the NLRP3-inflammatory/CaMKII signaling pathway in atrial cardiomyocytes. These molecular substrates render cardiomyocytes sensitive to spontaneous calcium release and arrhythmogenic afterdepolarizations, particularly when exposed to inflammatory mediators (45). Furthermore, inflammation also regulates calcium homeostasis and connexins, which are linked to AF triggers and heterogeneous atrial conduction. Inflammatory pathways mediate myolysis, myocardial apoptosis, and fibrosis through fibroblast activation, transforming growth factor-β signaling, and matrix metalloproteinase activation, all contributing to structural remodeling of the atria (46, 47).

2.6. Abnormal gene expression

Early studies have indicated that a family history of AF is linked to a 70% increased risk of AF in offspring (48). Currently, AF genetics is an emerging focus in AF research (49), and microRNAs represent a significant target in genetic studies of AF-related genes that regulate cardiac electrophysiology, as well as the electrical and structural remodeling associated with AF. MicroRNAs, often referred to as miRNAs, are highly conserved noncoding RNAs that are abundantly present in microvesicles and exert control over gene expression at the transcriptional or post-transcriptional level. Some studies have unveiled the crucial role of miRNAs in the development and progression of cardiovascular diseases, including AF. To date, several miRNAs found in atrial tissue, such as miR-1, miR-21, miR-26, miR-29, miR-30a/b, miR-31, miR-328, and miR-208a/b, have been reported to be involved in atrial electrical and structural remodeling (50). Certain studies have identified gain-of-function and loss-of-function mutations in K-channel genes within families exhibiting rare "isolated" AF. Furthermore, in genome-wide association studies involving patients with "isolated" AF, common variants in genes associated with potassium (K) currents have been identified (51). Additionally, genome-wide association studies have identified the chromosome 4q25 locus as the most significant genome-wide association study locus influencing AF susceptibility in the general population to date. Several haplotypes on chromosome 4q25 have been independently linked to an increased risk of AF (52) (Refer to **Figure 1**).

3. Potential mechanisms of AFDAS

Recent studies have revealed that AFDAS represents a distinct clinical condition compared to KAF (53, 54). Approximately 5% of patients who had no previous history of AF may develop AF following an acute ischemic stroke. This newly occurring AF is referred to as newly detected AF or newly diagnosed AF and is typically characterized by being paroxysmal, brief in duration, and asymptomatic (55). The concept of AFDAS has recently been incorporated into the 2020 European Society of Cardiology guidelines for the diagnosis and management of AF (56).

Early detection of AFDAS following a stroke poses a diagnostic challenge, requiring extended electrocardiogram (ECG) monitoring and long-term ECG examination during the initial stages of stroke patients (53, 55). Studies have indicated that AF can be newly diagnosed in around 7%–10% of patients within the first 3–5 days after a stroke. The detection rate increases to 24% or more after cardiac monitoring spanning 6–12 months (7). It's worth noting that the early-detected symptoms of atrial fibrillation may not necessarily represent newly developed atrial fibrillation after a stroke; they could also signify pre-existing (yet asymptomatic) primary atrial fibrillation (5, 57, 58). Current research has attributed AFDAS to cardiogenic (primary), neurogenic (secondary), and mixed variants. Although the question of whether some AFDAS cases are neurogenic remains subject to debate, clinical evidence still supports the existence of a post-stroke neurogenic mechanism in patients with AFDAS.

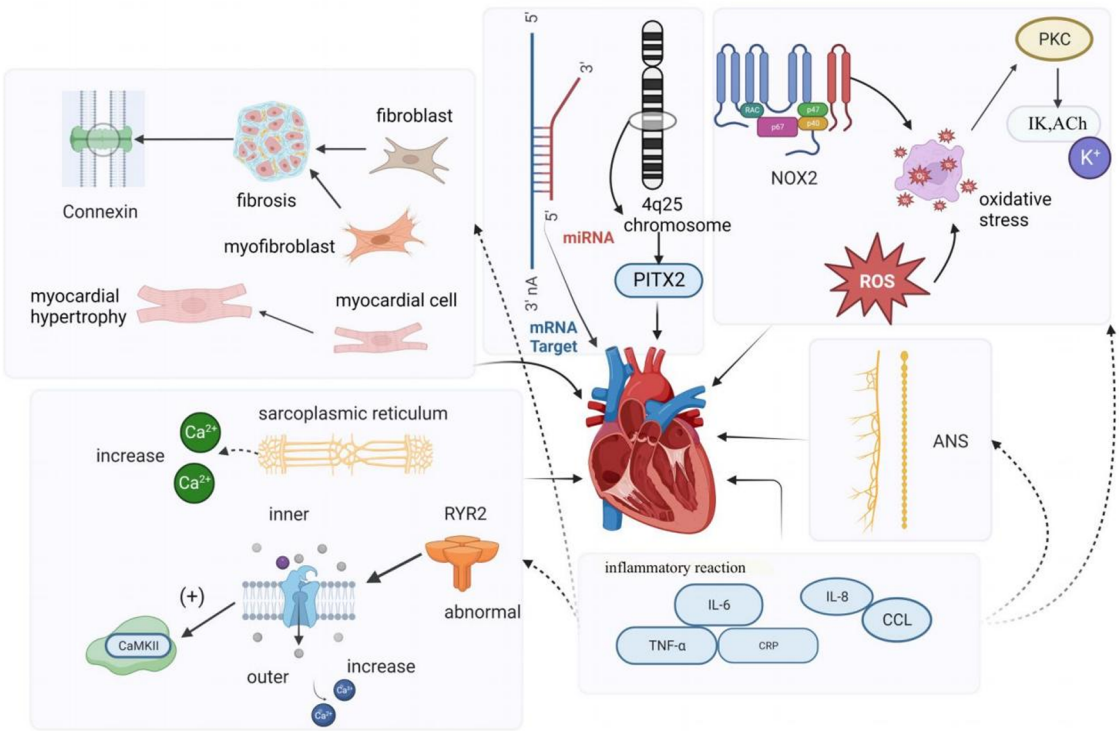

FIGURE 1
Simple mechanism of KAF.

In certain instances, AFDAS discovered following an acute ischemic stroke may be temporary and possibly intermittent, resulting from autonomic dysfunction and an immune-inflammatory response triggered by the stroke (6). The majority of recent studies concur that autonomic dysfunction and the immune-inflammatory response are the primary underlying mechanisms of AFDAS. These mechanisms are intricately connected to the insula region of the brain.

3.1. Autonomic nervous system

The central autonomic nervous system comprises neuronal groups within various cortical regions, including the insula, ventral medial prefrontal cortex, and anterior cingulate cortex, as well as subcortical regions like the amygdala and hypothalamus, along with the brainstem, including areas like the periaqueductal gray matter of the midbrain, the parabrachial nucleus, the Kölliker-Fuse region of the lateral pons, the solitary bundle nucleus in the medulla, the ventral lateral medulla oblongata, and the intermediate medullary reticular area. These structures regulate cardiovascular function via sympathetic preganglionic and parasympathetic postganglionic fibers collectively known as the exogenous cardiac nervous system. This system connects to the intrinsic cardiac nervous system, consisting of cardiac neurons located within the ganglion plexus found in peripulmonary venous adipose tissue. This intricate network receives impulses from the myocardium and pressure receptors, allowing for autonomic adjustments. Stroke-cardiac syndrome's diverse clinical manifestations are believed to stem from stroke-induced changes in the central autonomic network's function and structure, resulting in dysregulation of cardiac autonomic control. Notably, within the central autonomic network, which encompasses various brain structures, the insular cortex, prefrontal cortex, cingulate cortex, amygdala, hypothalamus, and hippocampus play vital roles in regulating cardiovascular function by modulating sympathetic input to the heart (7). The insular cortex, in particular, is a complex and highly interconnected structure with diverse functions, including interoception, multimodal sensory processing, autonomic regulation, and emotional guidance of self-awareness and social behavior. Research by Seifert et al. (59) suggests that reduced heart rate variability (HRV) indicators are more pronounced in patients with right insula involvement. This implies that the right insular cortex, right frontal cortex, right parietal cortex, as well as lesions in the right amygdala, basal ganglia, thalamus, and their proximity to the development of arrhythmias, are interconnected. Experimental studies have demonstrated that stimulating the left insular cortex tends to evoke a parasympathetic cardiac response, while stimulating the right insular cortex leads to a sympathetic response. Cerebrovascular lesions near the right insular cortex significantly impact heart function (60–62). According to Sposato et al. (11), the autonomic regulation of cardiac rhythm constitutes an integrated transmission system, with the highest control center residing in the cerebral cortex, particularly within the insular region. The occurrence of AF may result from an imbalance between sympathetic and parasympathetic activity, a common consequence following insula infarction, disrupting autonomic regulation and the brain's control of the heart's intrinsic autonomic nervous system. Likewise, Cerasuolo et al. (58) posited, based on heart neuroanatomy, that the heart's intrinsic autonomic nervous system consists of a ganglia plexus distributed along the ends of the pulmonary veins in the left atrium and within the pericardium. This system is highly regulated by the external autonomic nervous system. Therefore, damage to the insular cortex or its projection areas may trigger AFDAS within the ganglion plexus. Clinical studies conducted by Romano et al. (63) have revealed the critical role of the right insular cortex in autonomic control of cardiac function. Strokes confined to this region can lead to alterations in sympathetic balance. Hilz et al. (64) investigated the relationship between NIHSS scores and autonomic function, concluding that increased stroke severity corresponds to a progressive loss of overall autonomic regulation, reduced parasympathetic tone, heightened stress reflex sensitivity, and a gradual shift toward sympathetic dominance. Such changes within the autonomic nervous system increase the risk of cardiovascular complications and worsen prognosis in severe stroke patients. Additionally, Wang et al. (65) demonstrated that sympathetic overactivity following stroke results in a massive release of catecholamines, which directly overstimulate β-adrenergic receptors on cardiac nerves. This leads to abnormal Ca2+ handling in cardiomyocytes, triggering ectopic cardiac activity. Dorrance et al. (66) also highlighted the role of cerebral ischemia in the release of systemic catecholamines, leading to increased sympathetic tone. The surge in catecholamines overactivates β 1-adrenergic receptors, causing intracellular calcium overload, muscle rigidity, metabolic imbalance, and cell death. Furthermore, it overactivates α 1-adrenergic receptors, leading to coronary artery constriction and reduced myocardial blood flow.

3.2. Immuno-inflammatory response

In the acute phase of a stroke, brain injury triggers a localized inflammatory response, characterized by the proliferation of microglia and astrogliosis. This leads to a substantial release of cytokines and chemokines. Simultaneously, due to damage to endothelial cells, the blood-brain barrier (BBB) becomes more permeable, allowing pro-inflammatory molecules to enter the peripheral circulation through the compromised BBB. This process induces systemic inflammation (67).

It has been demonstrated that inflammatory mediators progressively alter atrial electrophysiology and structural substrates through various signaling pathways, increasing susceptibility to AFDAS (65). Research by Cerasuolo et al. has emphasized the critical role of systemic inflammation in AFDAS development, primarily through the autonomic cascade response and atrial myocarditis. The autonomic cascade response within the ganglion plexus may result from autonomic dysfunction caused by systemic inflammation following a stroke. Prolonged inflammatory responses can lead to atrial remodeling and perpetuate the effects of AF through atrial myocarditis, further

contributing to the pro-thrombotic state associated with AF. Furthermore, Sposato et al. (6) have suggested that inflammation triggering AF in the first days after an ischemic stroke may occur through the stimulation of inflammatory mediators on the intrinsic autonomic nervous system and direct damage to the atrial myocardium. Additionally, a study by Victoria et al. (68) has indicated that ischemic stroke patients with localized damage to the right insular cortex develop left atrial coronary microvascular endothelial dysfunction (CMED), myocarditis infiltration (MII), and fibrosis. Even 28 days after a stroke, left ventricular tissue exhibited prolonged fibrosis and B-lymphocyte infiltration. This supports Balint et al.'s findings (69), suggesting that CMED, MII, and fibrosis due to ischemic stroke in the left and right insula are pathological markers of arrhythmogenesis.

Various inflammatory cytokines can significantly affect changes in ion channel function and structural substrates. Studies by Liew et al. have shown that TNF-α overexpression leads to abnormal Ca2+ handling and electrical remodeling. Saba et al. (70) have demonstrated that TNF-α activation also stimulates mouse cardiac fibroblasts and increases matrix metalloproteinase two secretion through the transforming growth factor β signaling pathway. IL-6 promotes the synthesis of various inflammatory factors, including TNF-α, C-reactive protein, fibrinogen, and IL-1β, while also promoting ICAM-1 expression and activating matrix metalloproteinases in cardiac myocytes. This induces apoptosis and fibrosis (65). In mouse models, Liao et al. (71) have identified mast cells as critical mediators of allergic and immune responses, which are essential in the pathogenesis of AF in stressed mouse hearts. In contrast, platelet-derived growth factor (PDGF), primarily produced by fibroblasts and mast cells, is another inflammatory cytokine that affects both electrical and structural alterations in cardiac myocytes. PDGF-A promotes cell proliferation and collagen expression in mouse cardiac fibroblasts, leading to atrial fibrosis, increased susceptibility to AF, and electrical remodeling.

In summary, current research into the potential mechanisms of AFDAS has centered on the role of autonomic dysfunction, especially after insular damage. The inflammatory response in the heart is triggered by cerebral ischemia, although these mechanistic theories are still in the exploratory research stage. There is no definitive evidence to fully explain the pathophysiological mechanisms of AFDAS. However, the clinical incidence of AFDAS is rising, with studies suggesting that AF may be newly detected in nearly a quarter of stroke or transient ischemic attack patients and in around 5% of patients with no prior history of AF (55, 72). Paroxysmal AF is more common than persistent AF (73). AFDAS increases the risk of recurrent stroke, and mortality rates are 1.5 times higher in patients with AFDAS after a stroke compared to those without AF (74). According to current guidelines, oral anticoagulants are the preferred choice for early prevention and treatment of AFDAS. However, anticoagulants pose a bleeding risk and may not be suitable, especially for patients with hemorrhagic strokes. Therefore, the need for new alternative treatments for early prevention and management of AFDAS is pressing (Refer to **Figure 2**).

In this article, we have broadened the concept of KAF to encompass cardiogenic AF resulting from underlying cardiac abnormalities. This type of AF not only significantly elevates the risk of thromboembolism but is also associated with a higher prevalence of coronary artery disease, congestive heart failure, prior myocardial infarction, and a history of cerebrovascular events compared to AFDAS. Patients with KAF typically exhibit larger left atrial dimensions and lower left ventricular ejection

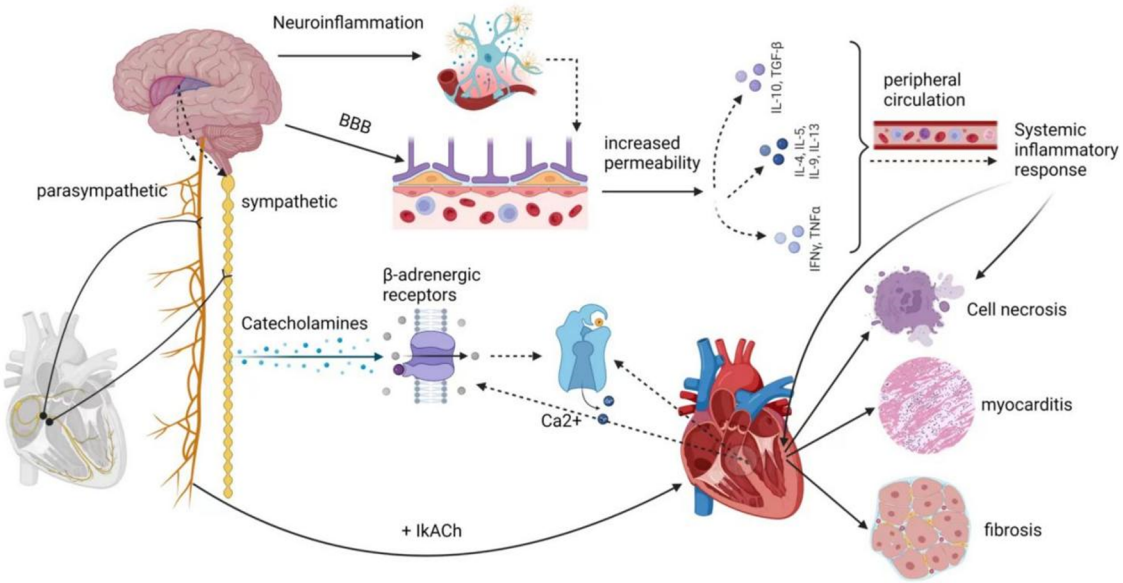

FIGURE 2
Potential mechanisms of AFDAS.

fractions than those with AFDAS. Moreover, patients with KAF face a heightened risk of stroke recurrence compared to AFDAS patients. It's worth noting that in clinical practice, there is a subtype of atrial fibrillation known as secondary atrial fibrillation (SAF), which shares some similarities with AFDAS. SAF is characterized by self-limiting and reversible clinical features and is often secondary to conditions such as surgery, acute infections, and myocardial infarction. Postoperative atrial fibrillation (POAF) is the most common form of SAF, especially following valve replacement surgery. Inflammation and the influence of the autonomic nervous system are key mechanisms in the development of POAF, somewhat resembling the potential mechanisms in AFDAS (75). Some studies suggest that SAF patients may have different stroke and bleeding risks compared to KAF patients. SAF patients have a higher bleeding risk than KAF patients, and this bleeding risk may even surpass their risk of stroke. This conclusion is drawn from observations that the use of anticoagulants does not effectively reduce the risk of ischemic stroke in newly diagnosed atrial fibrillation patients associated with acute coronary syndrome (ACS), acute pulmonary disease, and sepsis. Furthermore, a higher bleeding risk has been noted in patients with acute pulmonary disease, leading to the conclusion that anticoagulation therapy's benefits for SAF may be limited, offering no advantage in reducing stroke risk and potentially increasing the risk of bleeding (76). Additionally, research has shown that secondary atrial fibrillation patients face a lower average recurrence risk and a reduced risk of heart failure. However, this does not imply that we can disregard the risk of recurrence. Infection-induced secondary atrial fibrillation carries a thromboembolic risk twice as high as non-infection-induced atrial fibrillation and is associated with higher mortality and poorer treatment outcomes (77). For newly diagnosed and secondary atrial fibrillation patients, heightened vigilance for recurrent atrial fibrillation may be necessary. Nonetheless, the optimal monitoring and thromboembolic prevention strategies for SAF patients remain unclear at this time (78).

In summary, KAF, SAF, and AFDAS all pose significant clinical challenges in contemporary medicine, and early imaging, such as head CT or MRI, long-term electrocardiogram, cardiac monitoring, or Holter testing, should be conducted for early prevention and treatment.

4. Current therapeutic advances and limitations

Over the past decade, significant breakthroughs have occurred in understanding atrial fibrillation (AF), encompassing epidemiology, genetics, electrophysiology, and molecular cell biology. Concurrently, there has been a growing focus on research related to brain-cardiac syndrome and stroke-cardiac syndrome, strengthening the connection between brain function and cardiac health. This has accentuated the need to urgently address the clinical issues surrounding cardiac complications arising from strokes. In the 2020 guidelines by the European Society of Cardiology (ESC) for the diagnosis and treatment of AF, patients with AF are recommended to undergo a thorough evaluation based on four key criteria. These criteria encompass assessing stroke risk using the CHA2DS2VASc score, evaluating symptom severity with the EHRA Score, gauging the severity of AF burden (which includes self-termination, paroxysmal, persistent, and permanent forms), and assessing substrate severity, which takes into account factors like aging, comorbidities, and structural heart disease. These guidelines also propose a comprehensive A-B-C approach to treatment.

4.1. Stroke avoidance

In this context, "A" represents stroke avoidance, highlighting the role of anticoagulation therapy. While current clinical practice recommends oral anticoagulants as the primary treatment for AFDAS, it's important to note that the use of oral anticoagulants has been associated with an increased risk of bleeding, recurrent ischemic stroke, and mortality (79). Although the adverse risks associated with early anticoagulant use are lower compared to later stages of treatment (80), it's crucial to understand that this form of anticoagulation primarily aims to prevent and manage complications related to ischemic strokes rather than addressing the root cause of the condition.

4.2. Better symptom management

"B" represents better symptom management, emphasizing heart rate and rhythm control. Early rhythm control refers to prompt intervention with antiarrhythmic medications or AF ablation for patients with early atrial fibrillation and underlying cardiovascular diseases. A growing body of evidence supports the effectiveness of early rhythm control in high-risk patients, as it can reduce irreversible atrial remodeling, prevent adverse outcomes like AF-associated death, heart failure, and stroke, and potentially halt the progression of AF, sparing patients from years of symptomatic AF (80–82). Current clinical treatments for KAF involve both pharmacologic and non-pharmacologic approaches. First-line pharmacologic therapy primarily includes antiarrhythmic drugs, with amiodarone being one of the most commonly used and effective antiarrhythmic drugs. These drugs primarily target ion channels, although their efficacy in maintaining normal heart rhythm, especially as first-line drugs, is somewhat limited. Additionally, they come with various toxicity concerns (83), such as amiodarone, which can potentially lead to thyroid dysfunction, pulmonary fibrosis, skin disorders, and other minor adverse reactions (84). Some antiarrhythmic drugs even have proarrhythmic effects and an increased risk of death (85, 86).

Apart from antiarrhythmic drugs, modern clinical studies have introduced various innovative ideas and methods for AF treatment. For example, research by Wiedmann investigated the effectiveness of Doxapram in antiarrhythmic effects using large clinical animal models. They based their study on the significant upregulation of TASK-1 (K2P3.1) in AF patients, providing a basis for inducing

AF-related electrical remodeling. The study found that Doxapram could block the upregulation of atrial TASK-1 current and associated shortening of the action potential duration (APD), successfully inducing acute cardioversion in paroxysmal AF and rhythm control in persistent AF. This experiment served as a preclinical pilot study, demonstrating Doxapram's potential as a Class III antiarrhythmic agent, with further clinical trials needed to assess its impact on AF patients (87). Simultaneously, in another study, they also discovered that the TASK-1 inhibitor A293 could induce cardiac cardioversion in paroxysmal and persistent AF pig models, exhibiting antiarrhythmic effects (88, 89). Currently, the K2P3.1 channel has emerged as a novel strategy for treating atrial fibrillation. However, it's worth noting that some research indicates an association between the new gene KCNK3 and familial and idiopathic pulmonary arterial hypertension, potentially elevating pulmonary artery pressure (89, 90).

SK channels have also become a new target for AF treatment, similar to TASK-1, primarily expressed in the atria. Studies suggest that in the late phase of inducing atrial fibrillation action potentials, SK channels contribute to repolarization of atrial myocardial cells. By blocking SK channels, one can prolong the action potential duration of atrial myocardial cells, reduce their excitability, and aid in restoring normal rhythm (91). Diness and their team explored a novel SK channel inhibitor—AP14145 in their research. They demonstrated that AP14145 selectively prolonged the refractory period of the pig left atrium and shortened the duration of acutely induced AF, but it's important to note potential adverse effects such as vomiting. In another study, they evaluated the antiarrhythmic effects of three SK channel inhibitors, UCL1684, N-(pyridin-2-yl)-4-(pyridin-2-yl) thiazol-2-amine (ICA), and NS8593. These three drugs were found to prolong atrial effective refractory period without affecting the QT interval, effectively preventing or terminating AF, and were equally suitable for patients with paroxysmal AF and hypertension (92–94). However, SK channel blockers still need further testing in large-scale phase III trials.

The renin-angiotensin-aldosterone system (RAAS) plays a role in the development and progression of AF, with angiotensin II activating intracellular signaling cascades that lead to cardiomyocyte hypertrophy, apoptosis, and fibroblast proliferation. Li et al. (95) demonstrated that sacubitril/valsartan could improve atrial remodeling and ultimately reduce the occurrence and recurrence of AF by inhibiting RAAS activation and lowering blood pressure. However, this type of drug may be more targeted to patients with hypertension-induced AF, and its therapeutic scope may be relatively limited. Recent studies have suggested that elevated expression of Hsp27, a chaperone shock protein, observed in patients with paroxysmal AF, may help protect cardiomyocytes and limit the progression of persistent AF (96). Polyglutinyl acetone (GGA), a natural product extracted from licorice, is thought to have various biological activities such as anti-inflammatory, antioxidant, and anti-stress properties. Some studies have found that HSP induction can prevent remodeling induced by atrial tachycardia. Oral HSP inducer GGA has been shown to prevent AF in clinically relevant animal models, suggesting the use of HSP inducers as a novel approach to treating atrial fibrillation (97). Chloroquine, an anti-malarial drug, has shown promise in treating AF as it selectively blocks inwardly rectifying K+ channels (98–100). However, prolonged use of chloroquine is not without systemic effects. Vericiguat, a soluble guanylate cyclase agonist, has been investigated for its potential to treat AF by decreasing electrical and structural remodeling in rabbit models of AF. However, the specific mechanism of its effect on AF remains unclear, and the drug has not yet been widely validated, although it may hold potential value in AF treatment (101). Other studies have indicated that endoplasmic reticulum stress-induced autophagy is a crucial pathway in the progression of AF. Experimental evidence has shown that 4-phenylbutyrate can prevent electrical remodeling and slow the progression of AF by inhibiting autophagy activation and transient calcium loss, highlighting the potential therapeutic benefits of the endoplasmic reticulum stress inhibitor, 4-phenylbutyrate (102). Zhang et al. also suggested that histone deacetylase (HDAC6) has the potential to prevent AF-associated remodeling, indicating that HDAC6 could be a viable therapeutic target for clinical AF treatment. Ying et al. (103) demonstrated that colchicine could reduce AF recurrence by mitigating electrical remodeling in post-surgical AF. This effect is achieved through the inhibition of immune-related gene expression and the stabilization of microtubules. "IKur," an ultra-rapid delayed-rectifier K+ current, is exclusive to the atria, and several drugs have shown that effective IKur inhibition can terminate AF and prevent its recurrence (104). However, highly selective IKur blockers are not effective in prolonging atrial refractoriness and are downregulated in the human atria during persistent atrial fibrillation, raising questions about the relevance of IKur as a target for anti-fibrillation therapies (105, 106). A relatively low dose of galactomannan (GM CT-01), administered intravenously, demonstrated the ability to reduce both structural and electrical remodeling, as well as the burden of AF in a sheep model of persistent AF without comorbidities. However, it's important to note that Gal-3 inhibition did not lead to the long-term restoration of sinus rhythm (105). Among the protein family, Cx40 appears to be one of the most promising therapeutic targets because of its high expression in the atria while not being present in the ventricles. Shiroshita-Takeshita et al. (107) discovered that antiarrhythmic peptides improved gap-function conduction, with rotigaptide showing improved conduction velocity in several animal models. Although antiarrhythmic peptides hold potential benefits for AF, their effects may not be consistent throughout the atrium, possibly exacerbating the existing heterogeneity of atrial electrophysiology. This interaction could be influenced by factors such as fibrosis and ion channel remodeling in the atria. The G-protein-IP3-Ca2+ signaling axis has also been proposed as a potential target for AF treatment, acting by modulating intracellular calcium ion concentrations (108). However, doubts remain regarding its selectivity, as this axis is functionally active in many cellular processes and cell types, which could lead to potential adverse events in the heart and other organs. Consequently, no drugs targeting the G-protein-IP3-Ca2+ signaling axis have been tested for atrial fibrillation treatment in humans (105). Inflammation of atrial

tissue is implicated in arrhythmic remodeling and is considered a potential target for antiarrhythmic therapy. Corticosteroids, known for their potent anti-inflammatory effects, have been studied for their ability to prevent atrial fibrillation after cardiac surgery (109). However, their use is limited due to potential adverse effects, especially with long-term use.

In addition to Western medicine, traditional Chinese herbs have been explored for AF treatment. WenXin Granules, a Chinese medicinal preparation consisting of various herbs like Gan Song, Codonopsis, Panax Ginseng, Succinum, and Rhizoma Polygonati Odorati, has been used to aid in the treatment of cardiovascular diseases. It offers benefits such as improving blood circulation, reducing blood stasis, dilating blood vessels, and regulating cardiac function. Research has suggested that WenXin Granules might exhibit atrial-selective inhibitory effects on INa (110).

In addition to drug therapy, non-pharmacological treatments primarily encompass the following methods: electrical cardioversion, pulmonary vein electrical isolation, ablation, left atrial appendage occlusion, gene therapy, pacemaker implantation, low-level vagus nerve stimulation, and acupuncture. It's worth noting that His bundle ablation, cardiac pacing, and electrical cardioversion do not prevent the occurrence and progression of new AF and necessitate continued anticoagulation therapy. His bundle ablation, which disrupts the His bundle in the conduction system between the atria and ventricles to block abnormal electrical signaling and restore normal rhythm, traditionally requires continuous right ventricular pacing after interrupting ventricular conduction. This can potentially lead to a deterioration of cardiac function. However, modern physiological pacing strategies, such as LBB/LB area pacing, physiological rate-responsive pacing, multi-chamber pacing, and adaptive pacing, have emerged to address the issues associated with adverse reactions seen in traditional pacing. These strategies maintain synchronous contraction of the left and right ventricles, reducing adverse reactions and improving the effectiveness of cardiac treatment and patient quality of life (111). Nonetheless, it's important to recognize that not all patients may require or benefit from these modern physiological pacing strategies, and factors such as regular monitoring and economic costs also need consideration. Catheter ablation offers better efficacy in rhythm control compared to antiarrhythmic drugs but carries a significant rate of AF recurrence, particularly in patients with persistent AF, which may necessitate repeat procedures (112). There are numerous complications associated with catheter ablation, with vascular complications being the most common, followed by pericardial effusion, pericardial tamponade, and stroke or transient ischemic attack (86). Among the different types of catheter ablation, radiofrequency (RF) ablation is a procedure that disrupts abnormal rhythmic sources or conduction pathways using radiofrequency energy. However, RF ablation can lead to complications such as cardiac perforation, esophageal injury, and pulmonary stenosis. Cryoballoon ablation, which freezes abnormal rhythm sources or conduction pathways, can result in complications like phrenic nerve injury (113). In contrast, pulsed field ablation (PFA) is a novel non-thermal ablation method that selectively ablates cardiac tissue while preserving other anatomical structures, thus avoiding complications associated with thermal ablation (114). Studies have shown PFA to be a feasible and safe ablation method for mitral isthmus ablation in persistent atrial fibrillation patients, in addition to pulmonary vein isolation (PVI). However, some reversible and non-lethal adverse events were observed in experiments, such as coronary artery spasm and a 20% recurrence rate (115). Furthermore, studies comparing cell death induction between radiofrequency ablation, cryoballoon ablation, and PFA ablation have suggested that PFA ablation may offer faster, safer, and more tissue-selective ablation with less inflammation due to apoptosis-dominated cell death (116).

Left atrial appendage occlusion is a surgical treatment used to prevent AF-related thromboembolism. It does not directly target AF but rather avoids the potential risks and side effects associated with anticoagulants. However, this procedure is indicated for specific groups of patients, such as those at high risk of embolism, those unable to tolerate anticoagulant medications, or those experiencing complications from anticoagulant therapy. Gene therapy for AF is an emerging therapeutic approach aimed at treating or alleviating AF symptoms by modulating or repairing genetic variations associated with AF. These approaches include gene repair, gene-targeted therapy, and gene modulation. While preliminary studies and clinical trials have shown potential therapeutic effects, gene therapy is still in the research and experimental stage in the context of AF treatment. More studies and clinical trials are needed to determine its safety and efficacy before clinical application. Autonomic activity has been found to play a significant role in initiating and maintaining AF (23). Modulating autonomic function may help control AF, suggesting potential therapeutic tools such as ganglion plexus ablation, renal sympathetic denervation, cervical vagus nerve stimulation, pressure reflex stimulation, skin stimulation, novel pharmacological approaches, and biological therapies (23). Low-level vagus nerve stimulation is a recently introduced treatment for AF that involves stimulating the dominant auricular branch of the vagus nerve, located in the external acoustic canal and the skin of the auricle. It has been effective in reducing the incidence and burden of AF (117, 118). Studies have shown that low-level vagal nerve stimulation can help suppress paroxysmal AF by attenuating the inflammatory response through the activation of cholinergic anti-inflammatory pathways (119). Additionally, sustained low-level vagal nerve stimulation has been shown to suppress stellate ganglionic neural activity and reduce the incidence of paroxysmal atrial tachyarrhythmias (120). Acupuncture, as an effective non-invasive and safe treatment tool, has demonstrated the ability to significantly reduce the number and duration of symptomatic AF attacks. It also has a beneficial effect on maintaining sinus rhythm and converting AF to sinus rhythm in acute cases (121). Moreover, acupuncture has been shown to prevent recurrence in patients with persistent AF after cardioversion (122, 123). One of the mechanisms behind its effectiveness lies in the regulation of autonomic function. Based on current research, the effectiveness and potential mechanisms of acupuncture in AF treatment can be categorized into four

aspects: regulating anti-inflammatory factors, modulating ion channels and connexins, regulating the autonomic nervous system, and enhancing the ultrastructure of atrial muscle (124–126) (Refer to **Figure 3**).

4.3. Cardiovascular risk factor and comorbidity management

"C" represents cardiovascular risk factor and comorbidity management, emphasizing the importance of early preventive management of AF and its complications. This management primarily includes lifestyle changes, nutritional health treatment. Lifestyle changes entail adopting moderate exercise, improving physical fitness, and increasing exercise training, all of which can reduce the recurrence of AF and provide overall cardiovascular benefits. However, it's worth noting that intense exercise may elevate the risk of developing atrial fibrillation in individuals with the condition (127). Research has shown that both physical and mental exercises, such as yoga, tai chi, and qigong, have favorable effects on cardiac autonomic function, may alleviate symptoms in AF patients, normalize biomarkers of AF, and promote healthy aging. Nutritional therapy involves making dietary adjustments, ensuring balanced nutrition, and following a low-fat diet, all of which can help reduce the accumulation of body and visceral fat (128). Obesity is associated with an increased risk of developing AF (129), so strategies to avoid excessive weight gain are essential for preventing AF and its recurrences after the first episode. These measures also contribute to improving patient symptoms and enhancing their overall quality of life (130) (Refer to **Figure 4**).

5. Prospects and outlook

The development of AF is intricate, and it may involve multiple factors. Therefore, a single pathway of drug therapy may be suitable

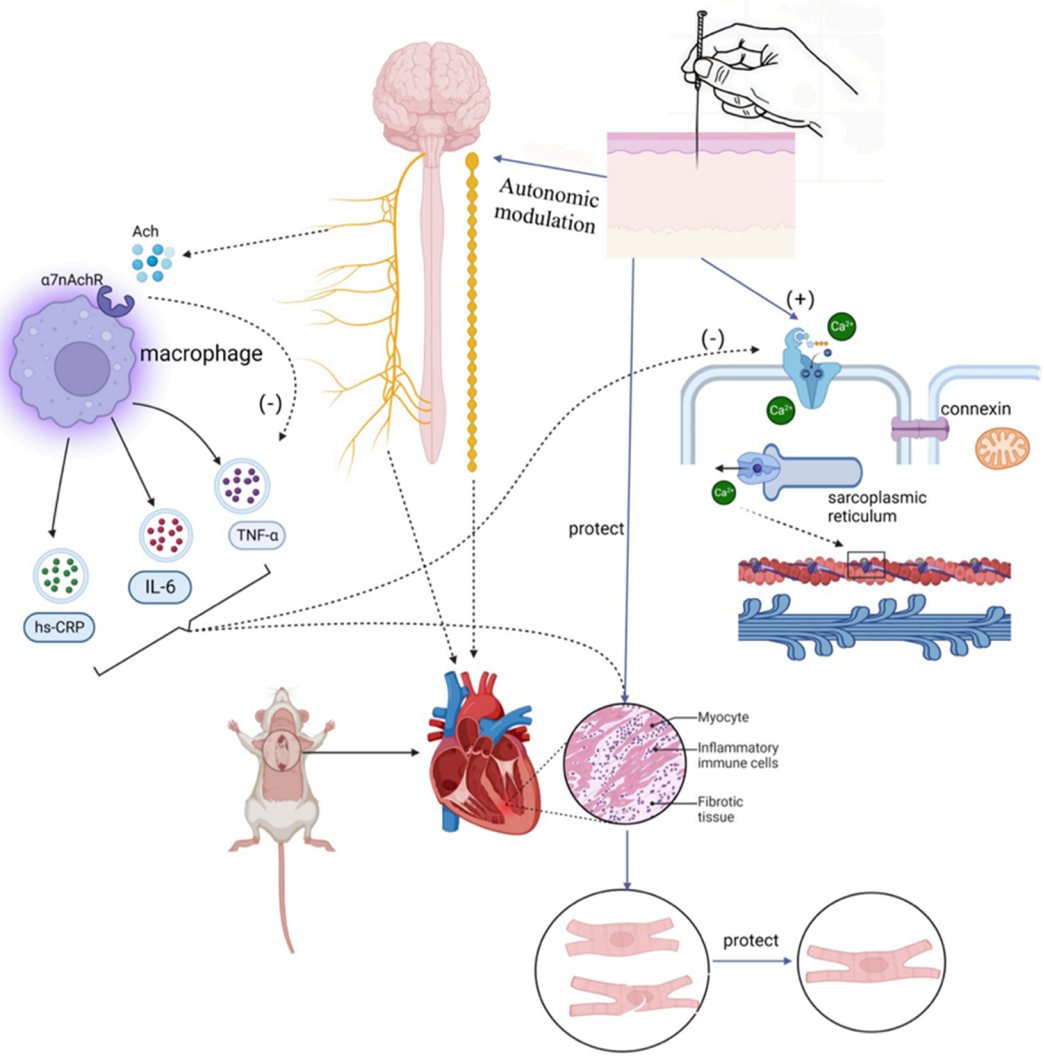

FIGURE 3
Mechanism hypotheses diagram of autonomic modulation in AF.

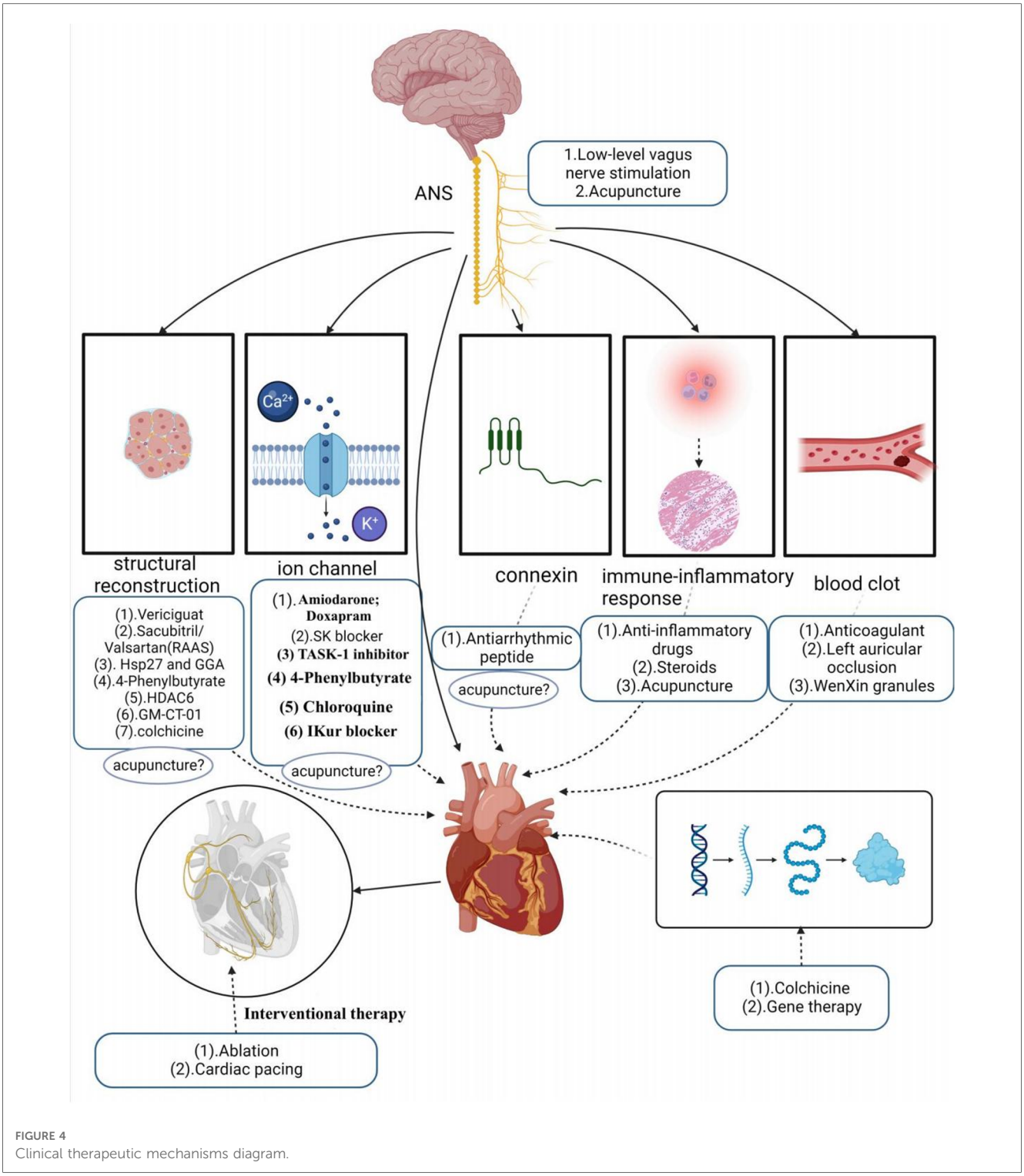

FIGURE 4
Clinical therapeutic mechanisms diagram.

for some patients but not for everyone. While the A-B-C pathway of integrated care may help compensate for the limitations of a single pathway, reduce some risks, and achieve a comprehensive and holistic approach to preventive treatment, most therapeutic interventions within each pathway still predominantly target the symptoms or single mechanisms of AF. Furthermore, the majority of therapeutic goals are directed toward downstream pathways, with limited impact on upstream pathways. We should contemplate how to predict new treatment strategies based on the diversity of AF mechanisms and upstream pathways.

Current research suggests that mechanism-based therapies for AF are still in their early stages, and the strong connection between the brain and the heart is gaining prominence as brain-heart syndrome research expands (7, 131). In this discussion, when summarizing the entire pathogenesis of AF briefly, it becomes apparent that the central nervous system, housing the

brain and autonomic nerves, plays a pivotal role in AF development. It not only directly regulates the heart but also acts as an upstream pathway influencing downstream pathways like cardiac structural remodeling, immune-inflammatory responses, ion channels and connexins, vasoconstriction, and thrombosis, ultimately affecting cardiac function. However, most current therapeutic approaches primarily target the downstream pathways and lack consideration for the central nervous system and upstream pathways. This limitation narrows the scope of action and increases the likelihood of recurrence. As our understanding of AF genetics, the brain-heart axis, vagus nerve stimulation therapy, and autonomic function modulation continues to grow, the range of targets for AF treatment will likely expand. It may be possible to effectively treat AF by focusing on the upstream pathway to guide the coordinated action of multiple downstream pathways. Predictably, central nervous system regulation will likely become a major focus of AF treatment in the future. However, this process will require extensive experimental studies and clinical validation to progress. With advancements in technology and increased comprehensive mechanistic exploration and integrated research efforts, we can gradually unravel the diversity and dynamic changes in AF mechanisms. This will pave the way for innovative approaches in both pharmaceutical and non-pharmaceutical treatments. While translating these novel mechanism-based therapeutic strategies into clinical applications poses significant challenges and demands interdisciplinary, large-scale, and sustained collaborative efforts, we maintain optimism about the future of atrial fibrillation treatment and research based on the current landscape.

Author contributions

JH: Writing – original draft, Writing – review & editing. BW: Writing – review & editing, Funding acquisition, Conceptualization. PQ: Investigation, Writing – review & editing. YC: Investigation, Writing – review & editing. ZZ: Resources, Writing – review & editing. YC: Resources, 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.

Publisher's note

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A simplified single transseptal puncture approach using high-density 3D voltage mapping for atrial fibrillation ablation: acute complications and long-term results

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Background: An ablation catheter and a circular mapping catheter requiring a double transeptal puncture (TSP) for left atrial access have been conventionally used for atrial fibrillation (AF) ablation. Recently, different operators have combined a single transseptal puncture technique with 3D high-density mapping catheters for pulmonary vein isolation (PVI).
Objective: This study aims to compare two strategies, single vs. double TSP, regarding the duration of the procedure, radiation time, complication rates, and outcomes.
Methods: Retrospective analysis of a large cohort of consecutive patients that underwent first PVI with radiofrequency energy (RF), using a point-by-point strategy, with a 3D mapping system, either with single or double TSP, according to the operator's choice.
Results: 285 patients with a mean age of 59.5 ± 11.6 years (36.5% female, 67.7% paroxysmal AF) underwent a point-by-point catheter ablation with RF between July 2015 and March 2020. The mean CHA2DS2-VASc score was 1.7 ± 1.3. Single TSP was performed in 115 (40.3%) patients and double TSP in 170 (59.6%). The operator's experience (≥5 years of AF ablation procedures) was equally distributed among the two groups. The average procedure time (133 ± 31.7 min vs. 123 ± 35.5 min, for single and double TSP, respectively) did reach a statistical difference between both groups ($p = 0.008$), but there was a substantial advantage regarding fluoroscopy time (13 ± 6.3 min vs. 19 ± 9.1 min, for single and double TSP, respectively; $p < 0.001$). Acute major complications present similar rates in both groups (2.6% vs. 2.3%, $p = 0.799$). At the 2-year follow-up, both groups had a similar sinus rhythm maintenance rate (76.5% vs. 78.8%, $p = 0.646$).

Conclusion: A simplified single-TSP technique using high-density multi-electrode 3D mapping is a safe and highly successful option for AF ablation. This approach yields a substantial reduction in fluoroscopy time, with the potential to avoid acute complications, compared to a conventional double-TSP strategy.

KEYWORDS

atrial fibrillation, catheter ablation, transseptal puncture, complications, safety

1. Introduction

In the past two decades, significant advancements have been made in managing atrial fibrillation (AF) through catheter ablation. Initially, the procedure focused on isolating pulmonary veins (PV) due to their role in AF initiation (1). So, complete PV isolation (PVI) became the foundation for catheter ablation in AF therapy (2) and circumferential ablation around the PV ostia has become a key element in AF ablation. Catheter ablation is now a routine procedure with a high success rate and a low incidence of complications (3–5). Randomised trials have shown its superiority over antiarrhythmic drugs when carefully selecting patients (6–12). As a result, PVI is widely performed as an effective treatment for AF ablation, with current ESC guidelines recommending it as a primary strategy for all AF patients undergoing ablation (13).

Radiofrequency (RF) point-by-point ablation guided by electro-anatomical mapping systems is standard in most electrophysiology laboratories. High-density mapping catheters with more electrodes and smaller distances between them have emerged (14), allowing for more precise and faster mapping and offering detailed insights into arrhythmia mechanisms (15, 16).

Transeptal (TSP) access to the left atrium (LA) remains a challenging step in the ablation procedure (17), with inherent risks and safety concerns, including the major complication of cardiac perforation and cardiac tamponade (18, 19). The original technique for TSP, introduced by Ross (20), is still the standard but demands a high level of operator skill and a steep learning curve.

In many centres, a standard approach for AF ablation involves two sequential TSP punctures (21). Double TSP access allows the insertion of two catheters simultaneously, aiding in real-time visualisation of PV electrograms without needing catheter changes. Another option is a simplified ablation strategy using a single TSP with the multipolar mapping catheter and the ablation catheter through a single sheath (one catheter at a time).

In this study, we assessed the feasibility, safety, and long-term outcomes of a single TSP technique using a high-density mapping catheter. We compared it with the traditional double TSP strategy for AF ablation.

2. Methods

2.1. Study population

We performed a retrospective analysis of a non-randomized cohort of 285 consecutive patients undergoing PVI procedures (without additional left atrial lesions) with point-by-point radiofrequency to treat paroxysmal or persistent AF. The database was registered at the local Institutional Review Board. The hospital ethics committee approved the study protocol (Ethics Committee approval number 974/2020). All participants provided written consent for data collection, and the analysis was conducted according to the Declaration of Helsinki guidelines.

We studied data from all patients over 18 years with AF diagnosis, refractory to at least one anti-arrhythmic drug agent, undergoing catheter ablation as a first procedure from July 2015 to March 2020. Patients with a left atrial flutter, undergoing AF ablation with a single-shot technique or repeated ablation (re-do) were excluded from the current study. AF ablation was performed using a 3-dimensional electroanatomic mapping system (CARTO, Biosense Webster, Inc., Diamond Bar, CA and EnSite NavX/Velocity, Abbott Laboratories, Abbott Park, IL).

Single TSP was performed in 115 patients, and double TSP in 170 cases. Information was collected regarding demographics, anthropometric data, baseline bleeding risk, anti-arrhythmic drugs, LA dimensions, left ventricular ejection fraction (LVEF), and structural heart disease. Regarding the comparison between both techniques, we considered the complication rates as a primary safety endpoint and, as a secondary efficacy endpoint, the freedom from any documented sustained atrial tachyarrhythmia (AF/AT) episode during a 2-year follow-up.

2.2. Ablation procedure

Every patient underwent a routine preprocedural transthoracic echocardiogram to evaluate LVEF and LA dimensions and to screen for structural heart disease. Computed tomography (with LA segmentation) was performed to assess LA anatomy and exclude the presence of intracardiac thrombi. Additionally, if the mentioned imaging study was obtained >48 h before the procedure, transesophageal echocardiography was performed on the day of the ablation to exclude thrombi. All patients underwent ablation with continued oral anticoagulation (at least four weeks before ablation), using warfarin to maintain an international normalised ratio between 2.0 and 3.0. If the patient was under direct oral anticoagulants (DOAC), the last dose was omitted on the day before the ablation.

All the procedures were carried out in conscious sedation and analgesia, using propofol infusion and fentanyl or under general anaesthesia. A deflectable decapolar catheter was positioned through the right femoral vein into the coronary sinus (CS) to guide the TSP, record, and pace the LA. Continuous monitoring

of oxygen saturation and ECG were maintained throughout the ablation. Three experienced operators (≥5 years of AF ablation procedures) performed all catheter ablation interventions, and the number of procedures carried out by each of the operators was similarly distributed in both the single and double TSP groups (operator 1 = 102, operator 2 = 87 and operator 3 = 96 total procedures respectively).

Power settings were at the individual operator's discretion within the 25–40 W range, depending on the LA segment (25–30 W posterior wall; 30–40 W anterior wall). Ablation Index (Biosense Webster, Inc, Diamond Bar, CA) (22) targets guided each lesion: 480 at the roof and anterior walls and 380 at the posterior and inferior walls and LSI (23, 24) (Abbott, Abbott Park, IL) with target LSI values at 4.5 and 4.0 for anterior and posterior walls, respectively.

2.2.1. Double transseptal—double sheath technique

Catheter access was performed using 7, 8 and 8.5 French (F) sheaths inserted in the right femoral vein. During TSP, a decapolar diagnostic catheter was placed in the CS for mapping reference and orientation. TSP was done using a needle system (89 cm, BRK transseptal needle, St. Jude Medical, St. Paul, MN, USA) and a non-deflectable 8 and 8.5 French sheaths SL-1 (Fast-CathTM Transseptal Guiding Introducer SwartzTM SL, Abbott, St. Paul, MN, USA) with fluoroscopic guidance. The 8 F sheath was introduced, and the needle was placed into the superior vena cava and then pulled down. Two movements are detected: the entrance into the right atrium and the fossa oval (FO). After FO identification, the puncture was performed (in the left anterior oblique view). After the first puncture, the same needle system and an 8.5 F introducer (8.5 F, Abbott, St. Paul, MN, USA) were used for the second TSP, performed the same as the described first transseptal puncture. After having both sheaths in the left atrium, a circular mapping catheter and an ablation catheter were inserted through the transseptal sheaths (**Figure 1A**).

Both sheaths were continuously irrigated with saline during the procedure. Heparin was administered intravenously as a bolus (100 U/kg of standard heparin) immediately after TSP, followed by an additional bolus to maintain an activated clotting time of ≥300 s. Three-dimensional mapping of the LA was performed with either the EnSite NavX/Velocity (Abbott Laboratories, Abbott Park, IL) or CARTO (Biosense Webster, Irvine, California) system. The mapping catheter used was Inquiry™ steerable (Abbott) or the Lasso® (Biosense Webster). Radiofrequency applications were performed using an open-irrigated-tip catheter (TactiCath Ablation Catheter®, Sensor Enabled or ThermoCool SmartTouch® _SurroundFlow, Biosense Webster) with point-by-point-lesions. To verify PVI, stimulation with 10 V outputs was delivered through all pairs of electrodes of the circular mapping catheter positioned beyond the ablation line (exit block). Also, pacing from close to the ablation line was performed to confirm electrical isolation (entrance block) (25). Additional applications were delivered if conduction gaps were identified. A successful procedure was defined by the absence of PVI-LA conduction at all pacing sites.

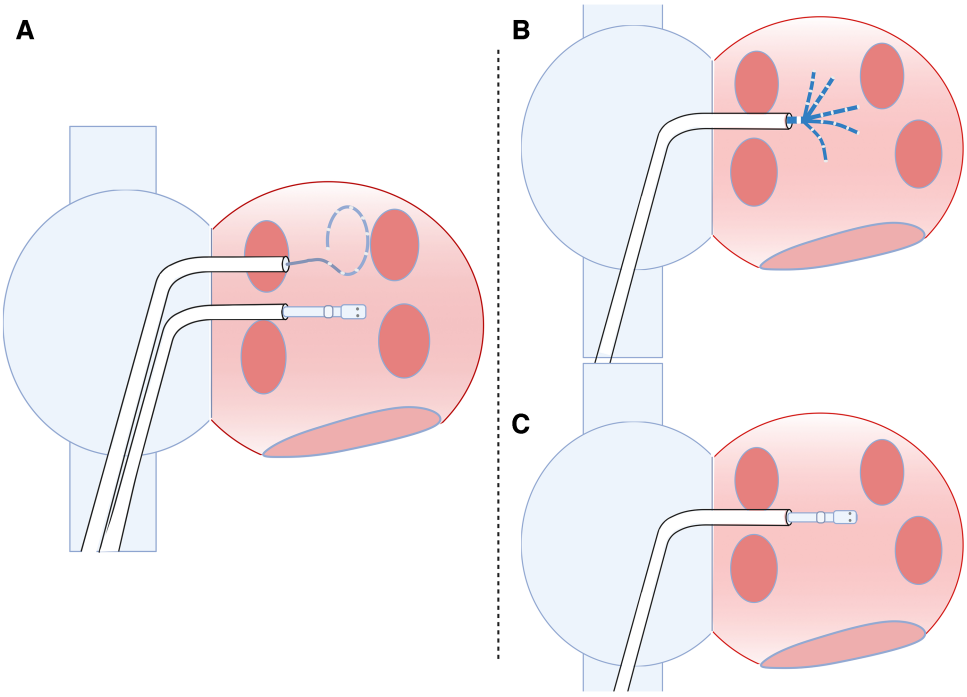

FIGURE 1
Types of punctures for LA access (double and single puncture). (A) Two punctures in the inter-atrial septum for left atrium access. (B) Single transeptal puncture with the mapping catheter used to create LA geometry and high-density voltage mapping. After completing the geometry and voltage map, the mapping catheter is removed, and the ablation catheter is introduced (C) by the same sheath.

2.2.2. Single transseptal—single sheath technique

Catheter access was performed by 7 and 8.5 French sheaths inserted in the right femoral vein. In addition, a decapolar diagnostic catheter was placed in the CS for mapping reference and orientation during TSP. A single TSP was done by fluoroscopic guidance using a needle system (98 cm, BRK transseptal needle, Abbott, St. Paul, MN, USA) and an Agilis NxT steerable introducer (8.5 F, Abbott, St. Paul, MN, USA), medium (22.4 mm) curl Dual-Reach™ Bi-directional.

Heparin was administered intravenously as described above. The Agilis sheath was continuously irrigated with heparinised saline during the whole procedure. The high-density mapping catheter (CARTO®PENTARAY®, Biosense Webster, Inc., Baldwin Park, CA, USA) was introduced into the LA through the Agilis sheath, and the 3D mapping system (CARTO®, Biosense Webster, USA) and used to create the LA geometry and a high-density voltage mapping. Mapping was done during sinus rhythm or distal CS pacing with the following settings: filtering cycle length: 550–650 ms, LAT stability: 5 ms, position stability: 5 mm, density: 1 mm, voltage scale: <0.2 mV.

After completing the geometry and voltage map, the mapping catheter was removed, and the ablation catheter was introduced by the same sheath (**Figures 1B,C**). RF ablation was performed using an open-irrigated SmartTouch catheter (Biosense Webster, Inc., Baldwin Park, CA, USA, 3.5 mm open-irrigated tip), by a point-by-point approach, with the catheter in a stable position and a numeric contact force value of ≥10 g. Maximum delivered RF energy did not exceed 40 W, provided by a 500 kHz ablation unit (Stockert EP shuttle, Biosense Webster, Inc., Baldwin Park, CA, USA). Next, remapping was performed to analyse signals, possible gaps and low-voltage areas. If so, the ablation of gaps was followed by remapping to confirm homogeneous low-voltage and PVI (**Figure 2**). A bi-directional block and low voltage homogeneity of PV and antrum proved PVI.

2.3. Post-ablation follow-up

After the ablation procedure, patients were discharged on AAD at the operator's discretion, together with oral anticoagulation. Patients were observed for routine follow-up in the outpatient clinic 1–3 months after the procedure and every six months (or earlier if symptoms) during the first two years post-ablation. At each visit, a standard 12-lead ECG was obtained. After the blanking period, patients were followed up with a 24 h Holter at each outpatient visit. AAD was continued for six months after CA and was withdrawn—except for beta-blockers—if the patients were free from arrhythmia-related symptoms. Oral anticoagulation was re-evaluated in the third month, and the decision to continue was based on the CHA2DS2-VASc score. In addition, clinical events occurring during the follow-up were evaluated. Atrial arrhythmia recurrence was defined as any documented episode of AF or atrial tachycardia (AF/AT) sustained for >30 s However, symptomatic and clinically typical sustained episodes were considered recurrences even without documentation.

3. Statistical analysis

Descriptive statistics summarised patients' characteristics, procedural data, safety, and follow-up. Continuous variables were expressed as mean ± SD, and categorical data as frequencies and percentages. Intergroup analysis was made using an unpaired *t*-test, and intragroup analysis using the Chi-square test. The Chi-square test was used for the comparison of nominal variables. The student *t*-test and one-way ANOVA were used to compare continuous variables. Comparisons were made using non-missing data only. The Kaplan–Meier model was used to

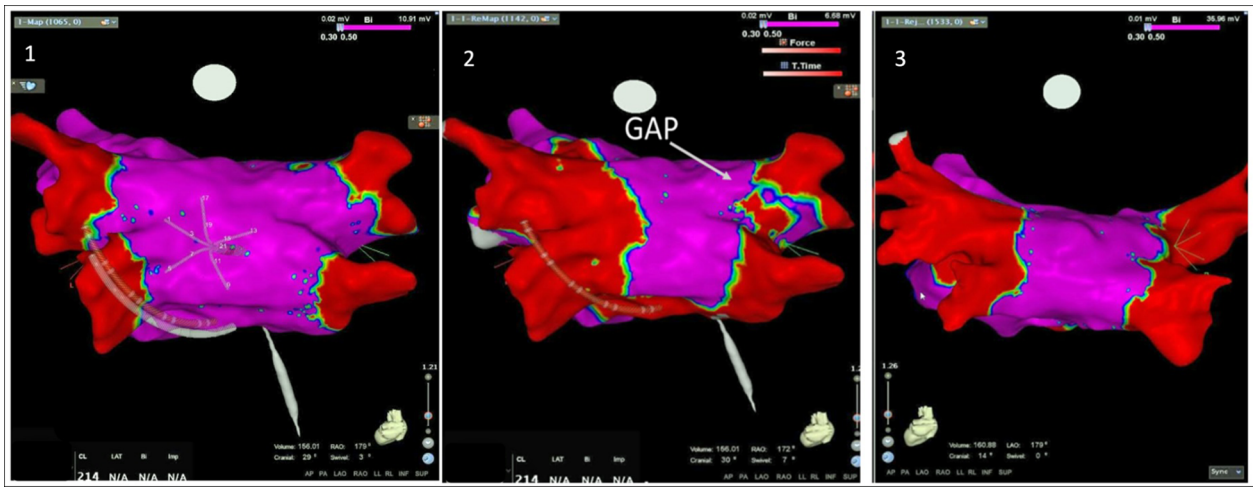

FIGURE 2
Electroanatomic mapping using a high-density mapping catheter. Posterior-anterior view of left atrial voltage map with CARTO 3-D mapping system. Panel 1: basal map collected with a high-density catheter (PentArray). Panel 2: second map, after the first pass ablation, with identification of a gap in the ablation line in the posterior aspect of the right superior pulmonary vein. Panel 3: map after the second pass of radiofrequency applications, showing complete isolation of both pairs of veins.

determine cumulative estimates of AF/AT recurrence following the 90-day blanking period through a 2-year follow-up, with between-group comparisons of cumulative event rates calculated using the log-rank test. All tests were two-sided, and a statistical significance was considered when $P < 0.05$. Analyses were performed using Stata, version 14.1 (StataCorp, College Station, TX).

4. Results

4.1. Baseline characteristics

We enrolled 285 consecutive patients who underwent catheter ablation utilising point-by-point radiofrequency (RF) energy at our institution. In this cohort study, the average age of the patients was 59.5 ± 11.6 years, and 36.5% were female (as indicated in Table 1). Among the patients, 193 (67.7%) had paroxysmal atrial fibrillation (AF); the mean CHA2DS2-VASc score was 1.7 ± 1.3 points. At the time of ablation, all patients were receiving oral anticoagulation therapy. Single transeptal puncture (TSP) was performed in 115 (40.3%) patients, while double TSP was performed in 170 (59.6%) patients. The double TSP group had a higher prevalence of paroxysmal AF. There were no statistically significant differences between the groups regarding age, body mass index, or gender. This procedure represented the initial ablation for all patients.

Regarding comorbidities (as displayed in Table 2), the groups did not exhibit significant differences concerning conditions such as hypertension, hyperlipidemia, diabetes mellitus, obstructive sleep apnea, chronic obstructive pulmonary disease (COPD), thyroid disease, cancer, heart failure, coronary disease, vascular disease (including stroke, peripheral artery disease, and aortic plaques), and hypertrophic cardiomyopathy. Furthermore, the left ventricular ejection fraction did not display statistically significant differences between the groups. The only variations between the groups were observed in the occurrences of hyperlipidemia and a history of previous stroke or transient ischemic attack, which are not expected to impact the interpretation of the results significantly. On the other hand, the CHADS-VASC score was higher in the single puncture group. As assessed through either echocardiography or CT scan (as shown in Table 3), atrial dimensions exhibited no significant differences between the groups.

Regarding the overall procedure duration (as presented in Table 4), the double TSP group had a slightly shorter duration ($p = 0.008$). However, the single TSP group substantially reduced fluoroscopy time and dwell time ($p < 0.001$).

In the single TSP group, 90% of the cases underwent a second endocardial map after the first pass point-by-point ablation, and 29% received a third map due to gaps. Regarding the number of points collected during mapping with the high-resolution catheter, the average number of points was: 1,020 (388–2,200) for

TABLE 1 Baseline sample characteristics.

Variable	Overall sample ($n = 285$)	Single puncture ($n = 115$)	Double puncture ($n = 170$)	*p*-value
Age (years)—mean ± SD	59.5 ± 11.6	60.8 ± 10.6	58.6 ± 12.3	0.111
Female, *n* (%)	104 (36.5)	41 (35.7)	63 (37.1)	0.809
BMI (kg/m^2)–median (IQR)	27.9 (5.6)	28 (6)	27.8 (5)	0.946
paroxysmal AF, *n* (%)	193 (67.7)	65 (56.5)	128 (75.3)	<0.001
persistent AF, *n* (%)	92 (32.3)	50 (43.5)	42 (24.7)	<0.001
CHA_2DS_2-VASC—mean ± SD	1.7 ± 1.3	1.9 ± 1.3	1.5 ± 1.2	0.035

BMI, body mass index; AF, atrial fibrillation.

TABLE 2 Study sample comorbidities and group comparison.

Variable	Overall sample ($n = 285$)	Single puncture ($n = 115$)	Double puncture ($n = 170$)	*p*-value
Hypertension, *n* (%)	166 (58.2)	74 (64.3)	92 (54.1)	0.086
Hyperlipidemia, *n* (%)	95 (33.3)	46 (40)	49 (28.8)	0.050
Diabetes mellitus, *n* (%)	20 (7)	7 (6.1)	13 (7.6)	0.613
Obstructive sleep Apnea, *n* (%)	38 (13.3)	12 (10.4)	26 (15.3)	0.236
Smoking, *n* (%)	31 (10.9)	17 (14.8)	14 (8.2)	0.082
COPD, *n* (%)	10 (3.5)	6 (5.2)	4 (2.4)	0.210
Thyroid disease, *n* (%)	32 (11.3)	15 (13)	17 (10.1)	0.445
Cancer, *n* (%)	14 (4.9)	4 (3.5)	10 (5.9)	0.357
LVEF < 35%, *n* (%)	11 (4.1)	7 (6.4)	4 (2.5)	0.128
LVEF < 50%, *n* (%)	36 (13.4)	18 (16.5)	18 (11.3)	0.221
Heart failure, *n* (%)	22 (7.7)	11 (9.6)	11 (6.5)	0.337
Coronary disease, *n* (%)	19 (6.7)	10 (8.7)	9 (5.3)	0.264
Vascular disease (stroke, PAD, aortic plaques), *n* (%)	21 (7.4)	11 (9.6)	10 (5.9)	0.243
Previous stroke/TIA, *n* (%)	13 (4.6)	9 (7.9)	4 (2.4)	0.028
Hypertrophic cardiomyopathy, *n* (%)	7 (2.5)	3 (2.6)	4 (2.4)	0.589

COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; PAD, peripheral arterial disease; TIA, transient ischemic attack.

TABLE 3 Echocardiography and computed tomography characteristics of the left atrium and group comparison.

Parameter	Overall sample ($n = 285$)	Single puncture ($n = 115$)	Double puncture ($n = 170$)	p-value
ECO LA diameter (mm)—mean ± SD	44 ± 8.5	44.8 ± 8.4	44.5 ± 6.8	0.819
ECO LA indexed volume ml/m^2—mean ± SD	39.5 ± 17.6	39.1 ± 12.6	39.4 ± 16.5	0.943
CT scan LA volume in ml—mean ± SD	115.9 ± 42.5	106.5 ± 33.3	101.2 ± 33	0.245

ECO, echocardiography; LA, left atrium; CT, computed tomography.

TABLE 4 Group comparison of procedure characteristics regarding time and complications.

Parameter	Overall sample ($n = 285$)	Single puncture ($n = 115$)	Double puncture ($n = 170$)	p-value
Procedure duration in minutes—mean ± SD	131 ± 33.9	133 ± 31.7	123 ± 35.5	0.008
Fluoroscopy time in minutes—mean ± SD	16 ± 8.4	13 ± 6.3	19 ± 9.1	<0.001
Dwell time in minutes—mean ± SD	118 ± 95.4	113.9 ± 32.5	120.2 ± 108.0	<0.001
Major complications rate—n (%)	7 (2.4)	3 (2.6)	4 (2.3)	0.799

the first map, 1,009 (244–2,617) for the second map and 399 (135–1,019) for the third map (including only PV with gaps).

4.2. Complications occurrence

When we examine the occurrence of complications, major complications show similar rates in both groups (2.6% vs. 2.3%, with a p-value of 0.799). Procedural and periprocedural minor complications were observed in 12 patients (2.6% vs. 5.2%, with a p-value of 0.154). Minor complications included 6 cases (2.1%) of minor hemorrhage at the access site, 2 cases (0.7%) of pseudoaneurysm formation, 1 case (0.3%) of temporary right phrenic palsy, 1 case (0.3%) of air embolism in the coronaries, 1 case (0.3%) of hemoptysis, and 1 case (0.3%) of transient asystole during the procedure (refer to Table 5).

4.3. Follow-up

The median follow-up period lasted 24 months, with a range from 12 to 48 months. At the 2-year follow-up mark, both groups displayed a similar rate of maintaining sinus rhythm (76.5% compared to 78.8%, with a p-value of 0.646). The assessments of atrial fibrillation recurrence over a 24-month follow-up in AF patients who underwent catheter ablation, stratified by transeptal puncture (single vs. double), revealed no distinction between the two approaches ($p = 0.704$) (Figure 3). Also, when examining the recurrence rates stratified by transeptal puncture (single vs. double) and the type of AF (paroxysmal vs. persistent), we observed no noteworthy differences between the groups (log-rank test, $p = 0.113$).

TABLE 5 Complication rates disaggregated by type of transeptal puncture.

Complication ($n = 12$)	Single puncture ($n = 3$)	Double puncture ($n = 9$)
Minor haemorrhage access site	2	4
Pseudoaneurysm	1	1
Temporary right phrenic palsy	0	1
Air embolism to the coronaries	0	1
Haemoptysis	0	1
Transitory asystole	0	1

5. Discussion

5.1. Safety and feasibility of the single transeptal puncture approach in AF ablation

The present study demonstrated the feasibility and safety of a simplified single TSP puncture using 3D high-density PVI mapping using a point-by-point RF approach in a large cohort of AF patients. In addition, we compared double-TSP catheterisation, used in many centres as a standard technique, with a single TSP technique, using a 3D high-density mapping catheter and the ablation catheter through a single sheath (each catheter at a time).

There was not a substantial distinction between the two approaches in terms of the overall procedure duration, although the single puncture strategy did result in a slightly lengthier procedure time (133 ± 31.7 compared to 123 ± 35.5, with a p-value of 0.008). However, the extent of this difference (10 min) may not hold clinical significance. We attribute this variance to the operators' initial learning curve, as it might be necessary to change catheters multiple times in the single puncture strategy, leading to a marginal increase in the total procedure time. Nevertheless, there was a notable reduction in dwell time in the single puncture group ($p < 0.001$).

It is crucial to emphasize that fluoroscopy times were significantly lower in the single transeptal puncture strategy. This substantial reduction in fluoroscopy time is important for patients and medical operators, as this decreased radiation exposure is linked to reduced risks (26).

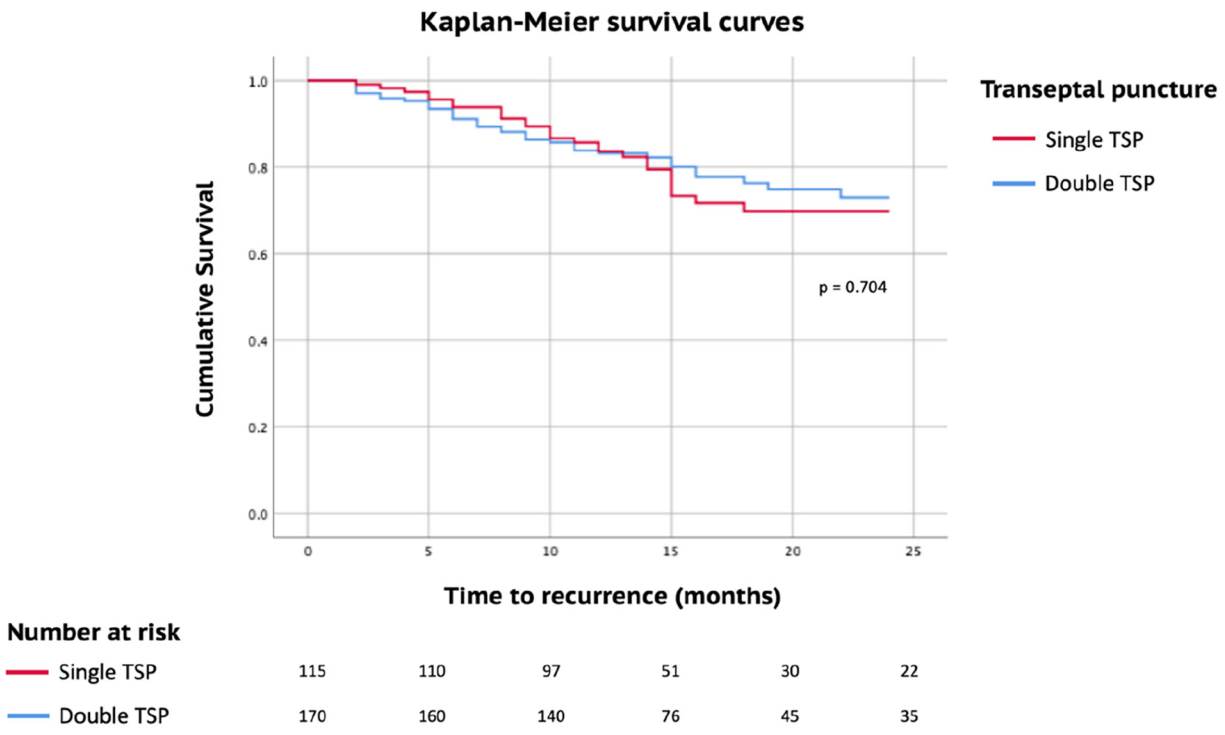

FIGURE 3
Kaplan meier survival curves estimates of AF recurrence during a mean follow-up of 24 months stratified by transeptal puncture: single vs. double (log-rank, $p = 0.704$).

The transeptal puncture (TSP) is a pivotal step in the atrial fibrillation (AF) ablation procedure. In theory, the double catheterization technique could introduce additional risks. The documented occurrence of pericardial effusion during catheter-based AF ablation varies between 0.5% and 4%, with cardiac tamponade observed in approximately 1% of cases (27, 28). A recently published meta-analysis of randomized clinical trials (29), which included patients undergoing their initial atrial fibrillation ablation procedure, revealed an overall complication rate of 4.5%. In this analysis, the incidence of severe procedure-related complications was 2.4%, which aligns with our findings.

Despite the need to exchange catheters a few times during the procedure, no stroke cases occurred in any group. Ischemic stroke complications can have dramatic consequences in AF ablation, with an incidence reported to be between 1% and 2% (30).

It's important to emphasize that the authors did not employ adjunctive tools for transeptal puncture (TSP). The use of intracardiac echocardiography and transesophageal echocardiography guidance could play a crucial role in reducing adverse events associated with TSP and facilitating challenging transseptal catheterization (31). These imaging tools theoretically could have prevented some of the adverse events observed in our study. Further investigations with larger sample sizes may provide more clarity on this matter.

The single TSP approach resulted in fewer minor complications than the double-TSP catheterisation patients (2.6% vs. 5.2%), although this difference did not reach statistical significance. However, apart from air embolisation, it's challenging to establish a clear correlation between the technique used to access the atrium and the occurrence of other complications. The absence of air embolisation complications in the single puncture group is noteworthy. It can be attributed to meticulous sheath irrigation throughout the procedure and careful aspiration during catheter changes.

Another aspect worth highlighting is that our centre did not have access to steerable sheaths that could be visualised using an electroanatomical mapping system when these procedures were conducted. Evidence indicates that this sheath type can substantially reduce fluoroscopy time (32).

5.2. Long-term outcome after AF catheter ablation

PVI, the cornerstone of any AF ablation procedure for paroxysmal and persistent AF, was the strategy therapy followed in this cohort. The AF/AT recurrence rate 24 months after the ablation was less than 30% for the entire cohort. In the current study, the AF/AT-free survival rate was slightly improved compared to other studies with long-term follow-up available in the literature. Kardos et al., in a study (33) comparing RF energy using contact force sensing and cryoballoon ablation for PVI in paroxysmal AF patients, showed freedom from AF/AT after a

24-month follow-up of around 66%. Ganesan et al.'s systematic review and meta-analysis included 6,167 patients with paroxysmal and non-paroxysmal AF from 19 studies undergoing AF ablation, with a mean follow-up of ≥24 months. They found freedom from AF/AT of 53% after one CA, with lower success rates for non-paroxysmal AF (3).

It should also be noted that both techniques have similar recurrence rates at 24 months follow-up. This comparable long-term outcome suggests that the single TSP technique is not sacrificing effectiveness for the sake of its other advantages. This is crucial for the overall success and sustainability of the ablation procedure.

Both groups equally distributed the operator's experience, with ≥5 years of AF ablation procedures. This equal distribution minimises the potential bias related to operator experience, making the comparison more reliable.

We would also like to point out that a steerable sheath was used in the single TSP group. In contrast to a non-steerable sheath, the use of steerable sheath technology enhances control over catheter manipulation. This advancement theoretically enables a broader spectrum of catheter orientations and improved stability, potentially leading to enhanced tissue contact and, consequently, more effective ablation lesions. One systematic review and meta-analysis that analysed the results of using both strategies found that the fluoroscopic and RF application times were comparable (34). Another recent meta-analysis (35) also considered comparing these two technologies for RF ablation of AF. It concluded that steerable sheaths can effectively reduce the recurrence rate of AF and the occurrence of acute PVs reconnection events. However, there is no advantage in shortening the total RF time, fluoroscopy time, total surgical time and reducing complications (35). Considering that our study aimed to evaluate the complications and long-term results, using the steerable sheath might influence the recurrence rate but not the other parameters reported in our results.

5.3. Study limitations

We wish to emphasise several limitations in our research. Firstly, this study was conducted as a non-randomized single-centre investigation. However, it's worth noting that both groups consisted of atrial fibrillation patients who were consecutively enrolled for point-by-point pulmonary vein isolation, which somewhat mitigates the absence of randomisation. Secondly, the significant advancements in 3D mapping systems and the increasing experience of the operators over the course of the study, which spanned five years, may have influenced the observed reduction in radiation exposure times. It's important to highlight that our primary objective was to assess the safety of catheter ablation, specifically focusing on single-transseptal puncture (TSP) and double-TSP approaches. Thirdly, the utilisation of 24 h Holter recordings, as opposed to 7-day recordings, could potentially lead to an underestimation of AF recurrence rates. Nevertheless, it is noteworthy that this assessment method has been employed by multiple researchers, and in our study, it was consistently applied to both groups, minimising the likelihood of introducing substantial bias. Fourthly, it is important to point out that a steerable sheath was used in the single TSP group, which may introduce some variance in the comparison between the groups.

Fifthly we did not perform pre- and post-catheter ablation cerebral magnetic resonance imaging in this study. Consequently, we could not evaluate the incidence of silent cerebral lesions (36), which could be significant, especially in catheter exchange within the single transeptal puncture group. Lastly, while our approach theoretically simplifies the catheter manipulation process, it is important to acknowledge that it may demand a longer learning curve than conventional techniques, which should be considered when implementing this method.

6. Conclusion

This retrospective analysis of a large cohort of consecutive patients highlights the viability, safety, and high success rate of employing a single transeptal puncture and a single sheath for catheter placement in the left atrium during atrial fibrillation ablation. This approach represents a valuable alternative to the conventional practice of using double transseptal catheterisation and double sheaths simultaneously. Moreover, it offers an option for operators seeking to reduce x-ray exposure and minimise potential complications associated with a second TSP procedure while delivering promising long-term results for paroxysmal and persistent AF.

In summary, the single TSP technique presents advantages such as reduced fluoroscopy time, the potential avoidance of acute complications, and comparable long-term outcomes. These findings indicate that the single TSP approach is feasible and preferable in certain aspects, contributing to the enhancement and optimisation of AF ablation procedures.

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 Comissão de Ética do Centro Hospitalar Universitário de Lisboa Central. 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

PS: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. BT: Formal Analysis, Investigation,

Writing – review & editing. SL: Formal Analysis, Writing – review & editing. GP: Resources, Writing – review & editing. BV: Resources, Writing – review & editing. AD: Resources, Writing – review & editing. MP: Resources, Writing – review & editing. AR: Data curation, Resources, Writing – review & editing. MB: Resources, Writing – review & editing. MC: Data curation, Resources, Writing – review & editing. MP: Methodology, Resources, Writing – review & editing. AL: Resources, Writing – review & editing. CG: Formal Analysis, Resources, Writing – review & editing. RF: Supervision, Writing – review & editing. MO: Data curation, Writing – original draft, Writing – review & editing.

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Conflict of interest

MO has served as a speaker for Medtronic and is a member of the European Advisory Board of Medtronic. MP and AR are employees of Biosense Webster, Portugal.

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.

Publisher's note

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MRI pattern characterization of cerebral cardioembolic lesions following atrial fibrillation ablation

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Background: Recognizing etiology is essential for treatment and secondary prevention of cerebral ischemic events. A magnetic resonance imaging (MRI) pattern suggestive of an embolic etiology has been described but, to date, there are no uniformly accepted criteria.
Aim: The purpose of the study is to describe MRI features of ischemic cerebral lesions occurring after transcatheter ablation of atrial fibrillation (AF).
Methods: A systematic review and meta-analysis of studies performing brain imaging investigations before and after AF transcatheter ablation was performed. The incidence of cerebral ischemic lesions after AF transcatheter ablation was the primary endpoint. The co-primary endpoints were the prevalence of the different neuroimaging features regarding the embolic cerebral ischemic lesions.
Results: A total of 25 studies, encompassing 3,304 patients, were included in the final analysis. The incidence of ischemic cerebral lesions following AF transcatheter ablation was 17.2% [95% confidence interval (CI) 12.2%–23.8%], of which a minimal fraction was symptomatic [0.60% (95% CI 0.09%–3.9%)]. Only 1.6% of the lesions (95% CI 0.9%–3.0%) had a diameter >10 mm, and in 20.5% of the cases the lesions were multiple (95% CI 17.1%–24.4%). Brain lesions were equally distributed across the two hemispheres and the different lobes; cortical location was more frequent [64.0% (95% CI 42.9%–80.8%)] while the middle cerebral artery territory was the most involved 37.0% (95% CI 27.3–48.0).
Conclusions: The prevailing MRI pattern comprises a predominance of small (<10 mm) cortical lesions, more prevalent in the territory of the middle cerebral artery.

KEYWORDS

stroke, imaging, cardioembolic, MRI pattern, atrial fibrillation, ablation

Introduction

Stroke is a leading cause of mortality and long-term disability (1); recognizing the underlying cause of stroke is relevant for treatment, prognosis, and secondary prevention (2). However, about 25% of strokes are defined "cryptogenic" because the etiology remains unknown in spite of exhaustive investigations (3). Hart et al. recently proposed to call these types of lesions "embolic strokes of undetermined source"

(ESUS) (4), considering that the vast majority recognizes an embolic etiology. Detecting a potential mechanism would, indeed, be relevant, when therapeutic options aiming at preventing recurrences are available, such as the initiation of oral anticoagulation in case of atrial fibrillation (AF) or percutaneous closure in case of suspected paradoxical embolism through a patent foramen oval (PFO).

With the development of computerized tomography (CT) and magnetic resonance imaging (MRI) techniques, a specific imaging pattern of brain lesions for every etiologic type of acute stroke has been hypothesized. A number of studies have concluded that in cardioembolic strokes, lesions are mostly multiple and cortical in location (5–7), but a systematic description of the neuroimaging features associated with a cardioembolic genesis of ischemic strokes is presently lacking. In the past two decades, silent cerebral lesions have been described at MRI following AF transcatheter ablation (8). These lesions have been carefully identified by comparing imaging before and after the procedure with MRI diffusion-weighted imaging (DWI) sequences, the most sensitive technique for the detection of acute cerebral ischemia (9).

Because during an uncomplicated transcatheter AF ablation the patient does not experience hemodynamic compromise, we hypothesize that the pathophysiological mechanism underlying brain lesions is embolic, and not related to hypoperfusive genesis. The major mechanisms involved include endothelium damage at transseptal puncture, conventional clotting (e.g., from the groin) and crossed emboli in the iatrogenic interatrial septum defect, and thermal thrombus formation in the left atrium (charring and gas embolism). In addition, during a transcatheter ablation the introduction of bulky devices, such as multielectrode catheters, and balloons carries a risk of air embolism (10).

In the present study we conducted a systematic review and meta-analysis to describe the neuroimaging features of newly formed cardioembolic lesions after AF transcatheter ablation.

Methods

This work was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (11).

Search strategy

Pertinent articles were searched in MEDLINE/PubMed with MeSH strategy, using the following terms: ((cerebral lesion* OR stroke OR silent cerebral lesion OR SCI embolism) AND cerebral MRI AND (Atrial fibrillation ablation OR Fib ablation OR AF ablation)). The search was ended on 30 January 2023.

Study selection and data extraction

Two independent reviewers (EB, MB) screened the retrieved citations through title and/or abstract. When potentially pertinent, the studies were appraised as complete reports according to the following inclusion/exclusion criteria:

- They reported the absolute number of new ischemic cerebral lesions that occurred after AF transcatheter ablation; this implies that the included studies were designed to perform cerebral MRI scan prior to and immediately after the ablation procedure.
- They reported at least one of the evaluated characteristics of the ischemic cerebral lesions (please refer to the following section regarding the specific study endpoints for detailed description of evaluated features).

Exclusion criteria were non-human setting; duplicate reporting (in which case, the manuscript reporting the largest sample of patients was selected).

Two independent, unblinded reviewers (EB and MB) abstracted the following data on prespecified forms: authors, journal, year of publication, baseline clinical and interventional features, cerebral MRI protocol, and neuroimaging features. Data collection was conducted by mutual agreement and all potential disagreement was resolved by a third reviewer (AS).

Study endpoints

The incidence of new cerebral ischemic lesions after AF transcatheter ablation was the primary endpoint. The co-primary endpoints were the prevalence of the following neuroimaging features regarding new cerebral ischemic lesions:

- Lesion dimension: size > 10 mm;
- Multiple lesions;
- Left vs. right hemisphere location;
- Cortical, subcortical (white matter and/or basal ganglia), or cerebellar location;
- Involved anatomical lobe: frontal, parietal, occipital, temporal;
- Involved vascular territory: anterior cerebral artery (ACA), middle cerebral artery (MCA), posterior cerebral artery (PCA), and border zone (BZ).

The secondary endpoint was the incidence of symptomatic cerebral ischemic events (stroke/transient ischemic attack).

Statistical analysis

The baseline characteristics of the pooled study populations were reported as median values and their interquartile ranges (IQRs). The meta-analysis of the proportions (crude incidence of new cerebral ischemic lesions and prevalence of the prespecified neuroimaging features) was performed using a generalized linear mixed models (12) under a random-effect framework and the results were reported together with the corresponding 95% confidence interval (CI). Cochrane I^2 test was used to investigate heterogeneity, with I^2 values of 25%, 50%, and 75% representing, respectively, mild, moderate, and extensive heterogeneity. Statistical analyses were performed with

R version 4.0.0 (R Foundation for Statistical Computing, Vienna, Austria) and *p*-values less than 0.05 were considered statistically significant.

Results

The initial search retrieved 125 studies. Among these, three studies were removed because of duplication, and one study was not assessed for eligibility because of the unavailability of the English translation. Given that 39 studies were not pertinent to the topic of the meta-analyses, 82 studies were assessed for eligibility, and 25 eventually included (13–37). Figure 1 reports the detailed PRISMA flowchart of the selection process. The resulting meta-analytic population encompassed 3,304 patients who had undergone AF transcatheter ablation and pre- and post-procedure cerebral MRI scans to detect new ischemic lesions. More details regarding the included studies, in particular concerning the adopted cerebral MRI protocol, the ablation technique, and the energy source are reported in

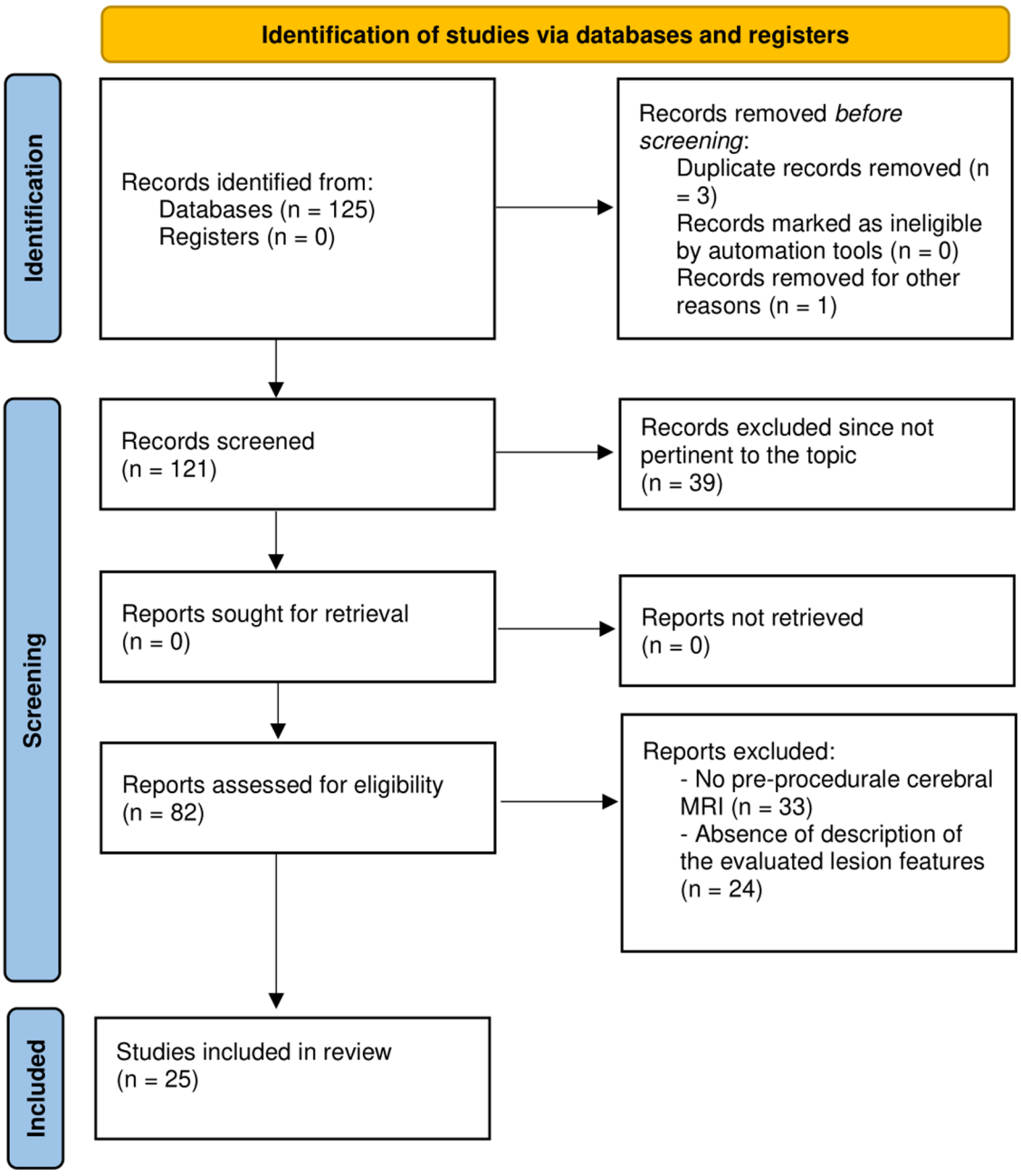

FIGURE 1
PRISMA flowchart of the study selection process.

TABLE 1 General characteristics of the included studies.

Study	Patients	Study-specific MRI definition of cerebral ischemic lesions	Number of lesions	Ablation details
Lickfett et al. (13)	20	DWI/FLAIR/TSE sequences	3	RF, point-by-point
Gaita et al. (14)	232	DWI EPI sequences	34	RF, point-by-point
Neumann et al. (24)	89	DWI EPI sequences	7	RF, point-by-point (49.4%)/Cryobaloon, single shot (50.6%)
Gaita et al. (31)	108	DWI/FLAIR sequences	36	RF, point-by-point (66.7%)/Cryobaloon, single shot (33.3%)
Deneke et al. (32)	86	DWI EPI sequences	119	RF, point-by-point
Siklódy et al. (33)	74	DWI EPI sequences	30	RF, point-by-point (68.9%)/Cryobaloon, single shot (31.1%)
Scaglione et al. (34)	80	DWI EPI sequences	7	RF, point by point
Rillig et al. (35)	70	FLAIR/DWI EPI sequences/T1	16	RF, point-by-point
Sramko et al. (36)	58	DWI sequences	1	RF, point-by-point
Herm et al. (37)	37	DWI sequences	56	RF, point-by-point
Verma et al. (15)	60	DWI sequences	1	RF, point-by-point
Martinek (16)	131	DWI EPI sequences	25	RF, point-by-point
Haeusler et al. (17)	37	DWI EPI sequences	22	RF, point-by-point
Deneke et al. (18)	88	DWI sequences	51	RF, point-by-point (46.6%)/Cryobaloon, single shot (22.7%)/ Laserbaloon, single shot (30.7%)
Di Biase et al. (19)	428	DWI EPI sequences	42	RF, point-by-point
Deneke et al. (20)	43	DWI sequences	26	RF, point-by-point
Wissner et al. (21)	86	DWI sequences	21	RF, point-by-point (25.6%)/Cryobaloon, single shot (23.2%)/ Laserbaloon, single shot (51.2%)
Von Bary et al. (22)	52	DWI/FLAIR sequences	54	RF, point-by-point (90.4%)/Cryobaloon, single shot (9.6%)
Bergui et al. (23)	927	DWI sequences	164	RF, point-by-point/Cryobaloon, single shot[a]
Nakamura et al. (25)	160	DWI/FLAIR sequences	64	RF, point-by-point/Cryobaloon, single shot[a]
Nagy-Balò et al. (26)	27	DWI/FLAIR sequences	11	RF, point-by-point
Miyazaki et al. (27)	256	DWI/FLAIR sequences	180	RF, point-by-point/Cryobaloon, single shot[a]
Keçe et al. (28)	70	DWI/FLAIR/TSE sequences	18	RF, point-by-point
Yu et al. (29)	55	DWI sequences	106	RF, point-by-point
Malikova et al. (30)	30	DWI/FLAIR sequences	3	RF, point-by-point

FLAIR, fluid attenuated inversion recovery; EPI, echo-planar imaging; RF, radiofrequency.
[a]Percentages not available.

Table 1. The AF type was paroxysmal in the majority of the patients (69%, IQR 59%–97%). The median age was 61 (IQR 58–63) years with a nearly 2:1 male-to-female ratio (males 68%, IQR 63–75).

The incidence of new ischemic cerebral lesions in patients that had undergone AF transcatheter ablation was 17.2% (95% CI 12.2%–23.8%; I^2: 93%) (Figure 2A). Among these lesions, only a minimal proportion had ischemic symptoms [0.60% (95% CI 0.09%–3.9%; I^2: 56%)] (Figure 2B).

Concerning the neuroimaging features of the new cerebral ischemic lesions, the size, reported in 16 studies (evaluating 778 lesions), had a diameter of above 10 mm in 1.6% (95% CI 0.9%–3.0%; I^2: 10%) of the cases (Figure 3A). Multiple lesions, described in 13 studies (464 lesions), were reported in 20.5% (95% CI 17.1%–24.4%; I^2: 0%) of the scans (Figure 3B). The pooled prevalence of left hemisphere location, reported in 14 studies (667 lesions), was 42.3% (95% CI 31.7%–53.7%; I^2: 83%) (Figure 3C). The cortical location (reported in 13 studies, 661 lesions) showed the highest pooled prevalence [64.0% (95% CI 42.9%–80.8%; I^2: 94%); Figure 3D] while lesions were, instead, subcortical (5 studies, 266 lesions) or cerebellar (12 studies, 627 lesions) in 25.5% (95% CI 7.1%–60.7%; I^2: 91%; Supplementary Figure S1) and 15.2% (95% CI 9.7%–23.1%; I^2: 75%; Supplementary Figure S2) of the cases, respectively. The pooled prevalence of frontal lobe location (13 studies, 627 lesions) was 19.7% (95% CI 14.3%–26.5%; I^2: 63%; Figure 3E), while parietal (12 studies, 595 lesions), occipital (12 studies, 593 lesions), and temporal (10 studies, 537 lesions) lobes were involved in 17.1% (95% CI 9.3%–29.5%; I^2: 87%; Supplementary Figure S3), 12.1% (95% CI 8.9%–16.1%; I^2: 29%; Supplementary Figure S4), and 8.6% (95% CI 3.5%–19.8%; I^2: 79%; Supplementary Figure S5) of the scans, respectively. The vascular territory of the MCA was the most commonly involved (3 studies, 81 lesions), reported in 37.0% (95% CI 27.3%–48.0%; I^2: 0%; Figure 3F) of the cases. ACA (3 studies, 242 lesions), PCA (3 studies, 242 lesions), and border zone (3 studies, 108 lesions) territories were involved in 28.5% (95% CI 23.2%–34.5%; I^2: 0%; Supplementary Figure S6), 28.1% (95% CI 22.8%–34.1%; I^2: 0%; Supplementary Figure S7), and 22.9% (95% CI 8.5%–48.8%; I^2: 81%; Supplementary Figure S8) of the scans, respectively.

Discussion

The main findings of the present analysis are as follows (Figure 4—Graphical Abstract):

- Among the proportion of patients presenting a cerebral ischemic lesion at cerebral MRI after AF transcatheter ablation (17%), 0.6% are symptomatic from a neurological standpoint.
- These cardioembolic cerebral lesions are generally balanced between the right and the left sides and are ubiquitously detected in all cerebral lobes; the lesions are typically small (diameter less

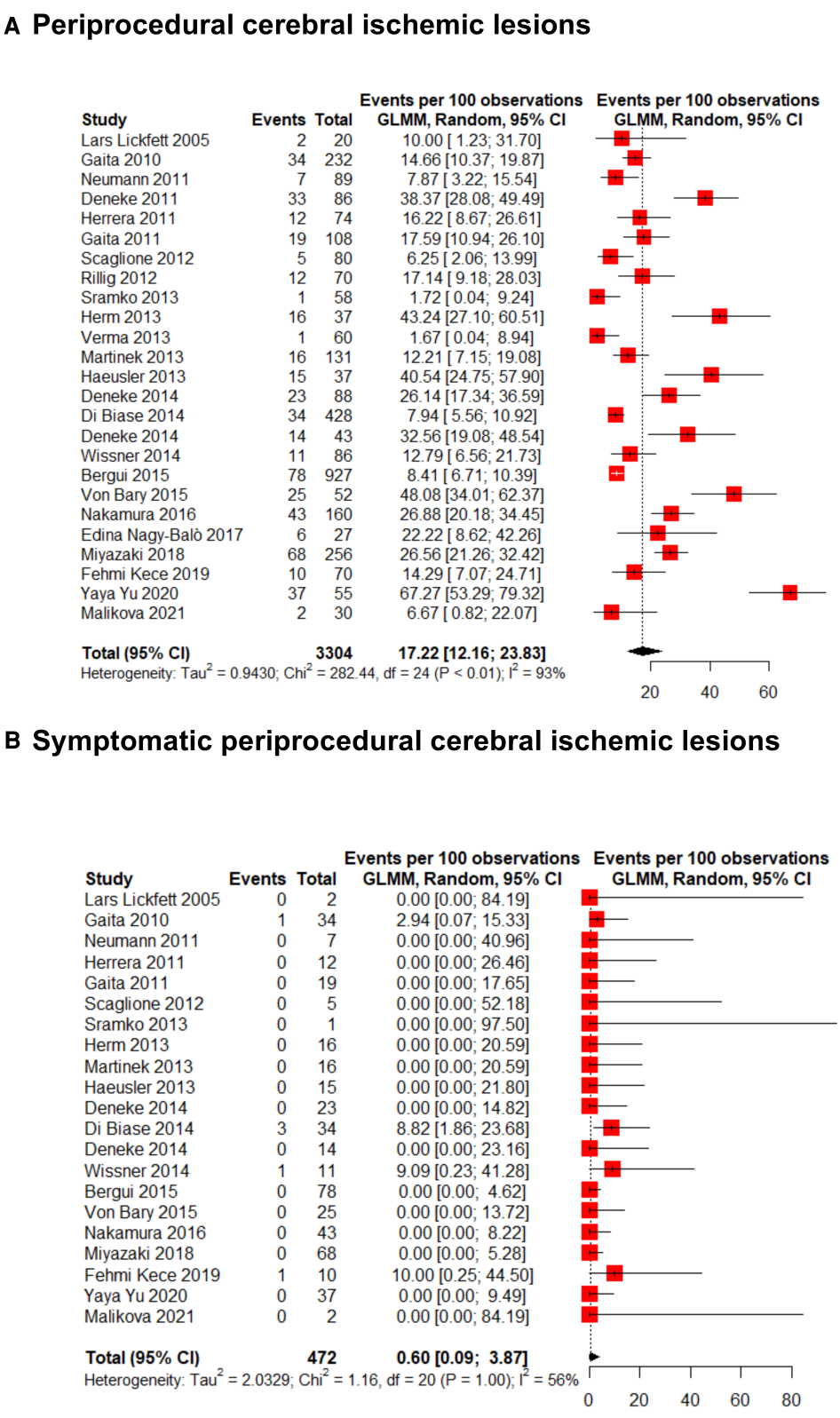

FIGURE 2
Forest plot for (A) overall and (B) symptomatic periprocedural cerebral ischemic lesions incidence.

than 10 mm), generally single (multiple only in about 20% of the cases), and they preferentially affect the cerebral cortex (in nearly two-third of the cases) of the MCA vascular territory.

Determining the underlying cause of an acute stroke is important not only to guide patient's immediate management but also to prevent new events, given that stroke recurrence is strongly

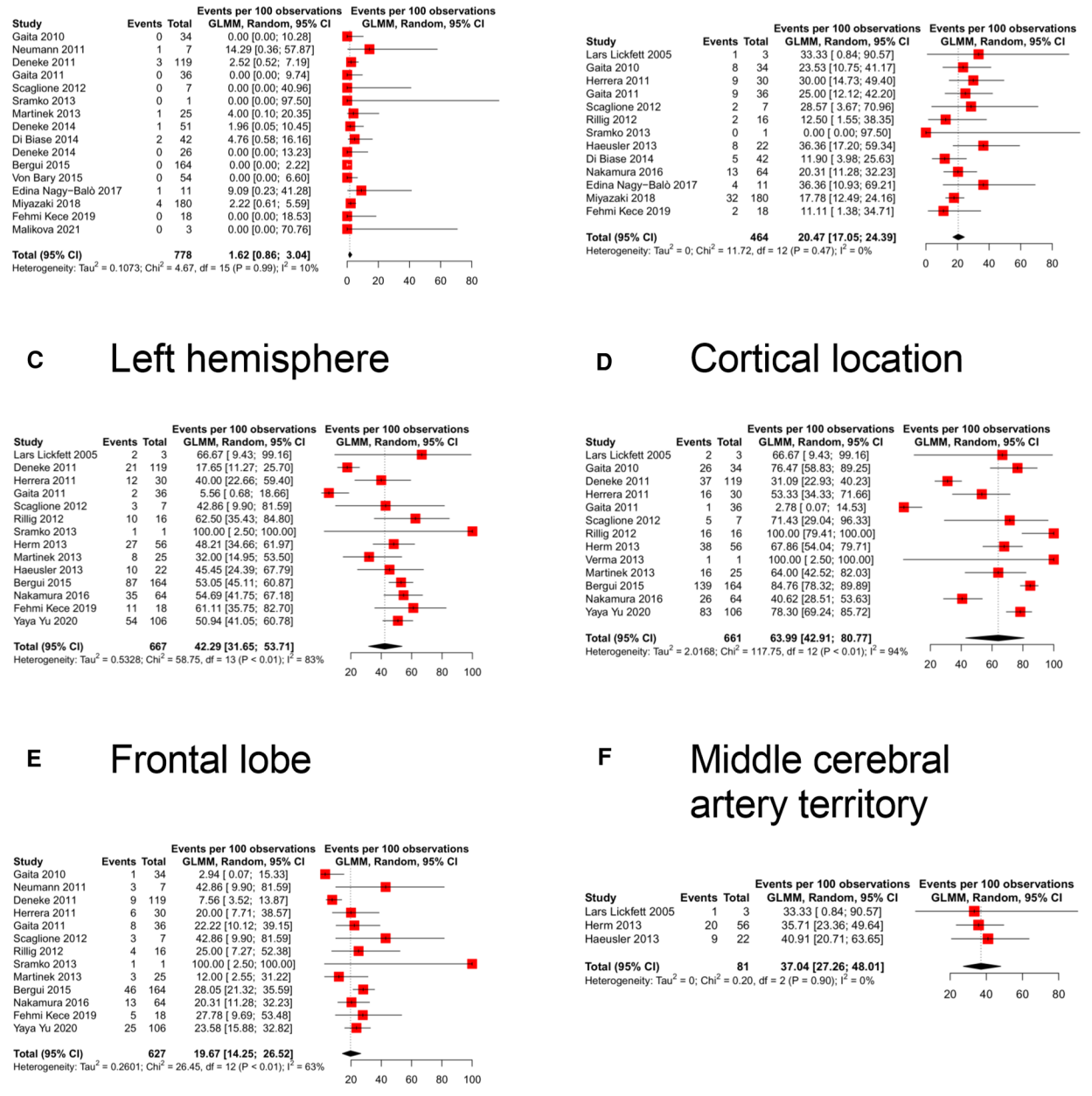

FIGURE 3
Forest plot of the different neuroimaging features: (A) diameter more than 10 mm, (B) multiple lesions, (C) left hemisphere location, (D) cortical location, (E) frontal lobe location, and (F) middle cerebral artery territory location.

related to its specific etiology (38–40). Imaging has a primary role in early diagnosis of strokes: in fact, some patterns of brain infarction may suggest a specific cause. In particular, regarding ESUS, early identification of a potential cause underlying the ischemic event might be of paramount importance, since it could expedite the clinical decision process leading to the adoption of therapeutic strategies, such as initiation of oral anticoagulation in case of an AF-related genesis. Moreover, considering that patients with AF frequently present asymptomatic cerebral lesions (41), keeping in mind that AF-related subclinical lesions might be due to several mechanisms (42–47), recognizing a certified neuroimaging pattern suggestive of subclinical AF-related lesions might even help prevent the occurrence of clinically relevant events.

Despite these potential benefits, a systematic description of the neuroimaging features associated with a cardioembolic genesis of ischemic strokes is presently lacking. For this purpose, AF transcatheter ablation can be regarded as an *in vivo* model of cardioembolic lesions, used to derive a neuroimaging

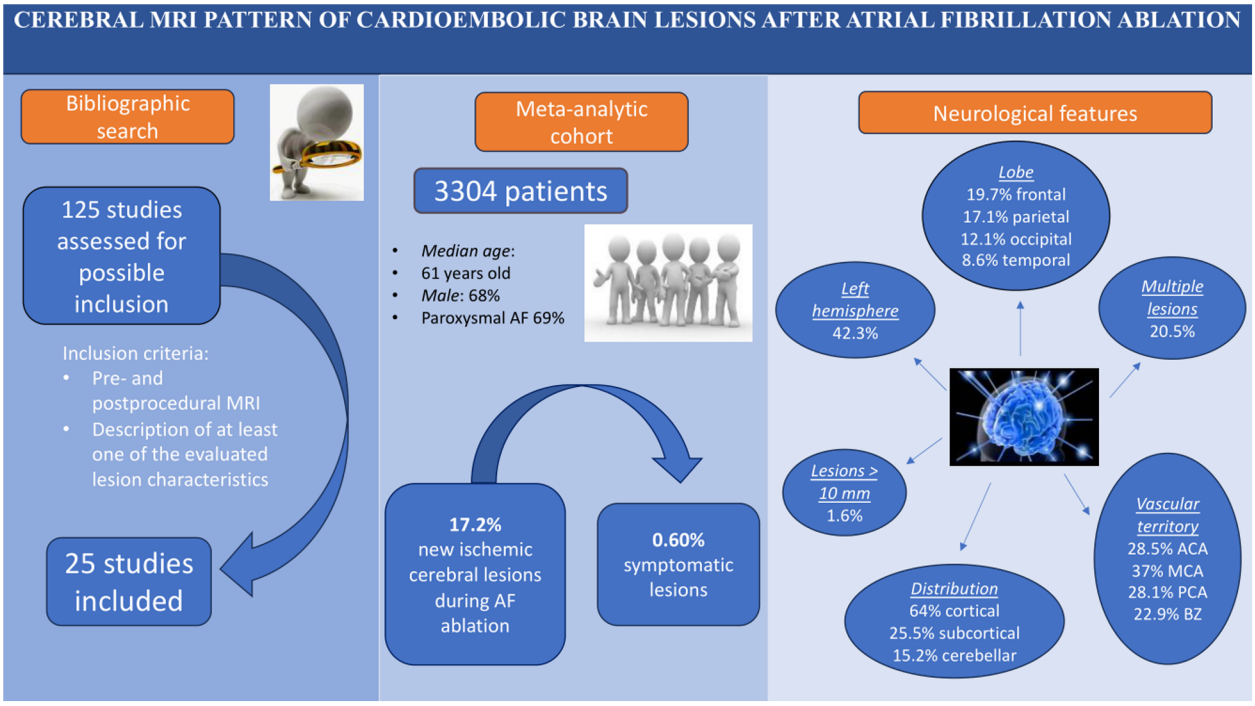

FIGURE 4
Graphical abstract.

"fingerprint" of typical cardioembolic lesions. In fact, during an uncomplicated transcatheter AF ablation the patient does not experience hemodynamic compromise, making a hypoperfusive genesis (due to transient reduction of cardiac output) of new cerebral ischemic lesions not plausible. Other cardioembolic models, such as cardiac surgery [during which hypotensive episodes might occur (48)] or transcatheter aortic valve replacement [the rapid ventricular pacing performed during valve deployment temporarily reduces cardiac output (49)], certainly do not share this feature.

The present analysis suggests that typical cardioembolic lesions, such as occurring during an AF ablation procedure, tend to be located at a cortical level and, particularly, in the vascular territory of the middle cerebral artery. Cerebral lesions related to a hypoperfusive genesis, instead, more commonly are subcortical and determine watershed infarcts (50–52). Watershed infarcts occur at the border between cerebral vascular territories where the tissue is furthest from arterial supply and thus most vulnerable to hypotension and hypoperfusion, or might exacerbate embolism-related damage (e.g., delayed embolism "washout," impaired perfusion of ischemic penumbra) (53). In any case, this neuroimaging "fingerprint" differs quite clearly from that of cerebral lesions related to a cardioembolic genesis.

Limitations

The analysis is limited by the inherent limitations of a meta-analysis. In particular, although all studies performed diffusion-weighted imaging sequences to detect new cerebral lesions, hidden technicalities across the different studies cannot be excluded. Moreover, the present results might apply prevalently to a population of paroxysmal AF patients undergoing catheter ablation. In addition, although we selected a cut-off value of 10 mm to distinguish between smaller and larger lesions, we cannot exclude that different cut-offs (e.g., 3 or 5 mm) might be more appropriate and provide different trends. Finally, we cannot directly exclude that the populations included in studies from the same Research Groups might present partial overlaps.

Conclusions

In conclusion, by thoroughly assessing incidence and neuroimaging features of cerebral ischemic lesions following AF transcatheter ablation, it emerges that in predominance they consist of small (<10 mm) cortical lesions, almost ubiquitous in all cerebral lobes and in both hemispheres, prevalent in the territory of the middle cerebral artery.

The present analysis supports the existence of an, at least, suspicious neuroimaging "fingerprint" of cardioembolic brain lesions. If confirmed in specifically designed studies, specific neuroimaging features in *de novo* cerebral lesions would rapidly prompt a tailored clinical management, shortening time to diagnosis of the underlying etiology, and, potentially, preventing recurrences.

Data availability statement

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

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 the institutional requirements.

Author contributions

AS: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Formal Analysis, Supervision. EB: Data curation, Methodology, Writing – original draft. MB: Data curation, Methodology, Writing – original draft. IF: Conceptualization, Data curation, Methodology, Writing – original draft. CR: Data curation, Methodology, Writing – original draft. FO: Conceptualization, Data curation, Methodology, Supervision, Writing – original draft. GDF: Data curation, Methodology, Supervision, Writing – original draft. MA: Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing – original draft.

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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.

The authors declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2024.1327567/full#supplementary-material

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Non-invasive cardiac activation mapping and identification of severity of epicardial substrate in Brugada Syndrome: a case report

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Introduction: It has recently been shown that electrocardiographic imaging (ECGi) can be employed in individuals undergoing an ajmaline test who have Brugada Syndrome (BrS), to evaluate the extent of substrate-involved arrhythmia in the right ventricular overflow tract (RVOT). For the first time, we stratify the risk of sudden cardiac death (SCD) in BrS during ajmaline testing using the dST-Tiso interval (a robust predictor of the inducibility of ventricular arrhythmias (VAs) in the presence of drug-induced BrS type-1 pattern) in combination with ECGi technology.

Case presentation: We studied a 48-year-old man with BrS ECG type-2 pattern and presence of J-wave without a family history of SCD but with a previous syncope. Transthoracic echocardiography and cardiac magnetic resonance imaging were performed, showing normal results. The ECG was performed to assess the novel ECG marker "dST-Tiso interval." The 3D epicardial mapping of the RVOT surface was performed with the support of a non-contact cardiac mapping system in sinus rhythm during ajmaline infusion. The examination of the propagation map unveiled the presence of multiple conduction blocks in this pathologic epicardial region, and the conduction blocks were identified within the central part and/or near the boundary separating the normal and slow conduction areas.

Conclusion: The dST-Tiso interval, which lies between the onset and termination of the coved ST-segment elevation and serves as a robust predictor of VA inducibility in cases of drug-induced BrS type-1 pattern, was utilized in conjunction with ECGi technology (employed for the non-invasive confirmation and identification of the pathological substrate area). This combined approach was applied to stratify the risk of SCD in BrS during ajmaline testing, alongside clinical scores.

KEYWORDS

non-invasive cardiac imaging, Brugada Syndrome, epicardial substrate, case report, Brugada Syndrome ECG type-2 pattern

1 Introduction

Brugada Syndrome (BrS) is a hereditary channelopathy linked to an increased risk of developing severe ventricular arrhythmias (VA) and sudden cardiac death (SCD) in individuals who are otherwise healthy (1). Nevertheless, in cases where patients continue to receive recurrent implantable cardioverter-defibrillator (ICD) shocks despite receiving the best available medical therapy, there is an alternative option—

radiofrequency transcatheter ablation of the arrhythmogenic substrate. This option has shown promising outcomes (2–4). While there is a general consensus that the pathologic substrate in BrS is primarily located in the right ventricular outflow tract (RVOT) epicardium, the precise origin or pathogenesis of BrS is still a subject of ongoing debate and research. Early theories attributed the propensity for developing VA to abnormal and non-uniform repolarization, leading to concealed phase-two reentry in the epicardium (5); however, more recent evidence suggests that depolarization abnormalities, including slow conduction, conduction blocks, and excitation failure, are thought to have a significant role in arrhythmogenesis in BrS. These abnormalities may result from subtle fibrosis in the RVOT epicardium and abnormalities in gap junctions (6). Sodium channel blockers like Ajmaline, Flecainide, and Procainamide can reveal or exacerbate these alterations, leading to well-documented electrogram (EGM) abnormalities during sinus rhythm. These EGM abnormalities may include low-amplitude epicardial EGMs (less than 1 mV) and/or late potentials (greater than 120 ms) with multiple components (three or more) (3). Today, the identification of complex cardiac arrhythmia sources requires precise substrate mapping, accurate determination of time signal activation, and assessment of propagating wavefronts. Recently, a novel ECG marker known as the "dST-Tiso interval" has been proposed as a predictor of VA inducibility in drug-induced BrS type-I patterns (7). Nonetheless, conventional bipolar signal recording comes with several limitations, and the innovative omnipolar mapping technology (OT) has demonstrated its value as a useful tool in complex mapping (8). OT can be a valuable tool in BrS ablation procedures. It provides immediate assessment and visualization of authentic signal voltage, including its direction and activation speed, with enhanced efficiency and reduced ambiguity compared with the conventional bipolar method. This information can assist in elucidating the disordered signal propagation and wave disruptions in BrS, leading to a clearer distinction between pathological and non-pathological regions when administering sodium channel blockers (9). Recently, it has been demonstrated that electrocardiographic imaging (ECGi) with CardioInsight (non-invasive 3D Mapping System technology, Medtronic Inc.) can be employed in patients with BrS during an ajmaline test to assess the severity of substrate-involved arrhythmia in the RVOT (10). We present a case where, for the first time, a suspected diagnosis of BrS was confirmed by two different non-invasive tests, including the dST-Tiso interval and RVOT activation map analysis using ECGi.

2 Case presentation

We studied a 48-year-old man with BrS ECG type-2 pattern and presence of J-wave (Figure 1, Panel A) without a family history of SCD but with a previous syncope. He was admitted to our clinic for risk stratification. In the previous days, during a non-competitive sport medical examination, the ECG occasionally revealed BrS type-2 pattern with J-waves. In the anamnesis, the patient reported repeated episodes of paroxysmal palpitations never documented (but associated with a sense of vertigo) and a syncope. Physical examination and laboratory results were normal. A 24-h Holter monitoring was unremarkable. The 12-lead ECG, with the right precordial leads in the fourth intercostal space, was suggestive of BrS type-2. It showed an ST-segment elevation of 2 mm in the fourth right precordial lead followed by a convex ST. Both transthoracic echocardiography and cardiac magnetic resonance imaging yielded normal results, with no evidence of late gadolinium enhancement in any areas.

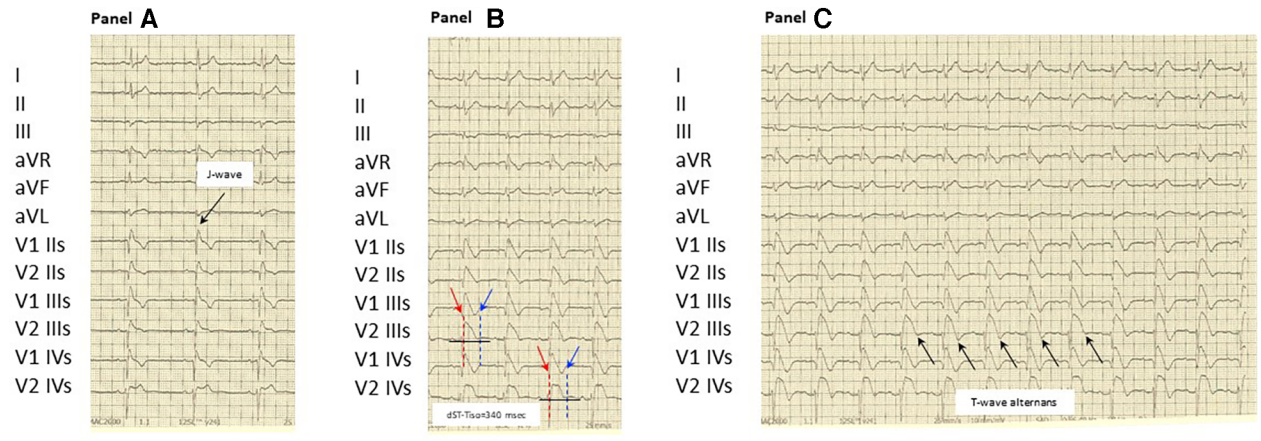

FIGURE 1
(**Panel A**) At baseline: show the spontaneous type 2 BrS pattern in IV intercostal space (ST-segment elevation of 2 mm in the right precordial leads followed by a convex ST) and presence of J-wave in II intercostal space. (**Panel B**) During ajmaline test: confirming the diagnosis of BrS during ajmaline infusion at 5 min and displaying a dST-Tiso of 340 ms. (**Panel C**) During ajmaline test: showing a T-wave alternans due to alternating activation during ajmaline infusion at 7 min (black arrows). (IIs-IIIs-IVs indicate chest electrodes position in basal condition and during ajmaline infusion: II-III-IV intercostal space). dST-Tiso is obtained measuring the interval between the onset of the coved ST-segment elevation and its termination at the level of the isoelectric line in V2 IIIs and V2 IVs leads.

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3 Diagnostic assessment

After gaining informed consent, the novel ECG marker denoted "dST-Tiso interval" was assessed and appeared to be 340 ms (Figure 1, Panel B). In our previous study, we demonstrated that the interval between the onset of the coved ST-segment elevation and its return to the isoelectric line in leads V1 and V2 (dST-Tiso interval >300 ms) serves as a robust predictor of VA inducibility when observing the drug-induced BrS type-1 pattern (7). The patient underwent ajmaline test. Also, a T-wave alternans due to alternating activation during ajmaline infusion at 7 min was documented (Figure 1, Panel C). The T-wave morphology in the patient with BrS, exhibiting multiple ajmaline-induced electrogram fluctuations, reveals a notable reliance on the strength of epicardial activation. According to the value of dST-Tiso interval, in order to assess the severity of the substrate, we decided to perform a programmed electrical stimulation (PES) and to study the activation maps using non-invasive ECGi. The 3D epicardial RVOT surface was performed with the support of a non-contact cardiac mapping system (CardioInsight). During the ajmaline test, activation maps were performed in sinus rhythm, under baseline condition (preajmaline infusion), during ajmaline infusion (1 mg/kg in 5 min), and during PES according to the protocols described by Brugada et al. and Priori et al. (11, 12). These protocols consisted of two drive cycles (600 and 400 ms, S1) and three extrastimuli (S2–S4). A minimum coupling interval of 200 ms was established for premature beats in the case of S2 and S3, and it was set to a refractoriness period for S4. During the PES, a VF was induced. At baseline, there were "no areas" exhibiting abnormal EGM readings on the anterior part of the epicardium in the RVOT. However, during ajmaline infusion, a BrS type-1 pattern became evident, and an area of slow activation developed along the anterior wall of the epicardial RVOT. The examination of the propagation map unveiled the presence of several instances of conduction block in this pathological epicardial region, indicating interruptions in electrical conduction. These conduction blockages were observed both in the central part and in close proximity to the border zone between the normal and slow conduction areas (Figure 2, Panels 1–6). Following that, we examined the baseline maps to compare the direction of conduction. It was observed that the line of conduction block that emerged after ajmaline infusion was not present in the baseline maps. It is interesting to observe the comparison between the activation map in the progress of ventricular fibrillation (VF) (Supplementary Video, Panel A) compared with the activation map at 7 min from the ajmaline infusion (Supplementary Video, Panel B). By observation, the 7-min propagation in sinus rhythm confirms the block areas and coincides with an "aborted" reentry mechanism (i.e., with block in entry and exit). In the case of the triggering of VF with three extrastimuli from RVOT, the antegrade activation front finds the same block area followed by a late activation with a reentry mechanism that leads to the VF triggering. Ultimately, a genetic test was required to identify the genetic alteration consistent with BrS, and subsequently, the patient successfully underwent transvenous single-chamber defibrillator implantation (SC-ICD). At the 6-month follow-up, the patient was asymptomatic, and infrequent ventricular extrasystole and non-sustained ventricular tachycardia (maximum three beats) were recorded.

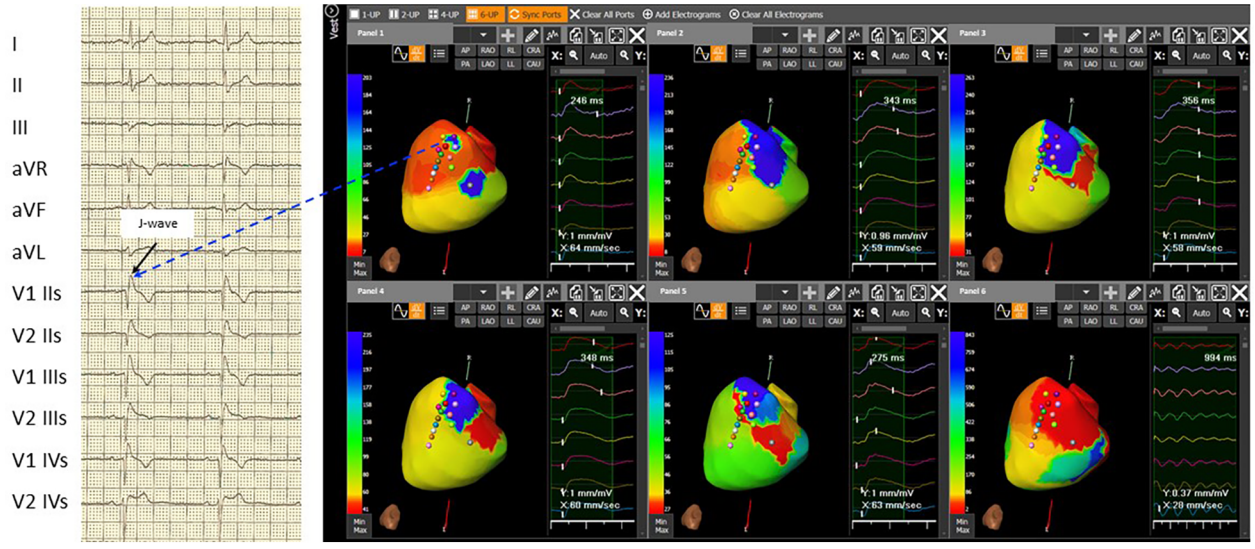

FIGURE 2
The 3D epicardial RVOT surface was performed with the support of a non-contact cardiac mapping system (CardioInsight) during ajmaline test. In basal conditions, the map shows not late RVOT but only small late areas (related to the presence of J-wave and right delay present on the basal ECG) (**Panel 1**). **Panel 2**, at 5 minutes after the ajmaline infusion, a delay appears on the RVOT in the antero-septal area. **Panel 3**, at 7 minutes after the ajmaline infusion, notice the maximum expression of the Brugada ECG pattern, extension of the delay in the entire anterior area of RVOT, and the appearance of functional block areas. A clear change in color between the later (blue area) and the earliest (red area) is observed in **Panel 4**: at 15 minutes after the ajmaline infusion, there is a reduction of the delayed zone in RVOT and persistence of the functional block area (green line). At 30 minutes after the ajmaline infusion, there is still a reduction of the late area in the RVOT and the disappearance (or clear reduction) of the block areas in **Panel 5**. The activation during induced ventricular fibrillation shown triggering zone (earliest) is depicted in **Panel 6** that coincides with the most late in sinus rhythm in Panel 3. Note: ECG: IIs, second intercostal space; IIIs, third intercostal space; and IVs, fourth intercostal space.

4 Discussion

In this case report, we stratified the risk of SCD in a patient exhibiting a BrS ECG type-2 pattern. We employed a combination of two non-invasive diagnostic exams—the dST-Tiso interval and ECGi technology—to unveil the presence of abnormal substrate. The outcomes were subsequently validated through invasive exams, including PES and induction of VF. In a brief historical overview, traditional substrate maps based on bipolar signals have been primarily influenced by the direction of a wavefront toward the mapping dipole. These bipolar maps do not supply the essential information needed for a comprehensive characterization of the ablation target. Recently, Porta-Sanchez et al. (13) conducted an evaluation using voltage maps obtained through an equally spaced electrode array and omnipolar mapping (OT) electrogram (EGMs) in the endocardium of 10 pigs. The results indicated that OT EGMs are more effective in distinguishing between infarcted and non-infarcted areas compared with traditional bipolar EGMs. Furthermore, achieving accurate refinement of the pathological borders in the RVOT can be important. Failure to ablate pathological areas could potentially lead to arrhythmic recurrences during the follow-up period (14). The voltage maps obtained with an evenly spaced electrode array and omnipolar EGM technology, used to characterize the epicardial substrate in BrS, better delineate areas of delayed conduction that give rise to wavefront fragmentation and lines of blocks. Utilizing an intracardiac non-contact mapping array and isochronal mapping during a ventricular S1–S2 stimulation protocol, Lambiase et al. discovered a notable conduction delay in the RVOT among individuals with BrS, a phenomenon not observed in healthy controls (14). Furthermore, these areas with delayed conduction exhibited wavefront fragmentation and lines of blockage, ultimately leading to polymorphic VT degenerating into VF in 5 out of 18 BrS patients (14). This arrhythmogenic behavior has also been recently documented by Haïssaguerre et al. (6). In this report, localized conduction blockages occur at multiple sites following a single premature stimulus or during sodium channel-blocker infusion. These blockages could potentially be responsible for the initiation of VF. Moreover, during ajmaline infusion we observed a large spectrum of T-wave morphologies (including monophasic and biphasic patterns) as described by Haissaguerre et al. (15). The morphologies and alternans of T-waves can be associated with abnormal tissue activation. More recently, ECGi has proven to be effective in elucidating the mechanisms underlying a wide range of cardiac arrhythmias, and it is essential to follow an optimal workflow to achieve the best clinical outcomes. In the ECGi procedure, it is crucial to manually verify the signals recorded by the system and included in the calculations to prevent errors associated with automatic processing. Signals of good quality with high amplitude yield maps of the highest accuracy, as demonstrated in our case. In addition, BrS presents as spontaneous variations in electrocardiographic markers, suggesting dynamic changes in the electrical substrate. The use of ECGi methodology in patients with unconfirmed BrS can be highly valuable in the risk assessment process. This is due to its non-invasive nature, making it painless, and its ability to provide additional information about the cardiac substrate and its severity. This remains true even in cases involving evaluations for ablation. When the effectiveness of ECGi methodology is demonstrated by rigorous studies, it may be possible to replace PES study and the induction of VF with the assessment of the ECGi substrate. This could streamline the management of asymptomatic patients with suspected Brugada Syndrome on ECG. Risk stratification for SCD in BrS remains a subject of ongoing debate. As a result, clinical predictors are an attractive and practical solution, especially when incorporated into risk assessment scores.

Sieira et al. (16) have recently introduced a dependable risk score model aimed at predicting the occurrence of SCD in this patient population. Likewise, the Shanghai score has been validated for SCD risk stratification. However, its predictive accuracy has been primarily demonstrated in patients who have not experienced a previous episode of VF (17). In the current guidelines (18) and in clinical practice, there is a lack of consensus on the most appropriate clinical management for patients who exhibit BrS induced by ajmaline. In summary of the data from this case report and supporting studies, the dST-Tiso interval (a robust predictor of VA inducibility in drug-induced BrS type-1 pattern) in combination with ECGi data from the CardioInsight System technology (used to confirm and identify the pathological substrate area non-invasively) could be employed for risk stratification of SCD in BrS during ajmaline testing, alongside clinical scores. Importantly, it is evident that this is a single case review, and the results should not be generalized without further research. Moreover, it is vital to follow the current guidelines (1) to diagnose the entirety of BrS and the subsequent steps, and additional studies with larger cohorts of patients need to be considered to confirm these findings. In particular, randomized studies are needed to assess the value of ECGi to improve the pathway of patients with BrS and to indicate the use of cardiac implantable electronic devices (CIEDs) or provide clear guidance on substrate ablation or, simply, a follow-up strategy.

5 Conclusions

This case described the use of two different non-invasive examinations to assess SCD risk. In this case review, both tests revealed an abnormal substrate; however, further large studies may assess the predictive value of a single test vs. the value of combined tests.

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

SI: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review and editing. PS: Visualization, Writing – review and editing. GC: Writing – review and editing, Data curation. GF: Writing – review and editing, Data curation. EF: Writing – review and editing. JC: Methodology, Writing – review and 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2024.1304404/full#supplementary-material

SUPPLEMENTARY VIDEO

Comparison between the map of activation in progress of ventricular fibrillation (VF) (VIDEO, Panel A) compared to the map of activation at 7 minutes from the administration of Ajmaline (VIDEO, Panel B). Note how the 7-minute propagation in sinus rhythm confirms the block areas and coincides with an "aborted" reentry mechanism, that is, with block in entry and block in exit. In the case of the triggering of VF with three extra-stimuli from RVOT; the antegrade activation front finds the same block area followed by a late activation with reentry mechanism that gives rise to the triggering of VF.

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Convergent approach to persistent atrial fibrillation ablation: long-term single-centre safety and efficacy

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Background: Efforts to maintain sinus rhythm in patients with persistent atrial fibrillation (PsAF) remain challenging, with suboptimal long-term outcomes.
Methods: All patients undergoing convergent PsAF ablation at our centre were retrospectively analysed. The Atricure Epi-Sense® system was used to perform surgical radiofrequency ablation of the LA posterior wall followed by endocardial ablation.
Results: A total of 24 patients underwent convergent PsAF ablation, and 21 (84%) of them were male with a median age of 63. Twelve (50%) patients were obese. In total, 71% of patients had a severely dilated left atrium, and the majority (63%) had preserved left ventricular function. All were longstanding persistent. Eighteen (75%) patients had an AF duration of >2 years. There were no endocardial procedure complications. At 36 months, all patients were alive with no new stroke/transient ischaemic attack (TIA). Freedom from documented AF at 3, 6, 12, 18, 24, and 36 months was 83%, 78%, 74%, 74%, 74%, and 61%, respectively. There were no major surgical complications, with five minor complications recorded comprising minor wound infection, pericarditic pain, and hernia.
Conclusions: Our data suggest that convergent AF ablation is effective with excellent immediate and long-term safety outcomes in a real-world cohort of patients with a significant duration of AF and evidence of established atrial remodelling. Convergent AF ablation appears to offer a safe and effective option for those who are unlikely to benefit from existing therapeutic strategies for maintaining sinus rhythm, and further evaluation of this exciting technique is warranted. Our cohort is unique within the published literature both in terms of length of follow-up and very low rate of adverse events.

KEYWORDS
hybrid, convergent, atrial fibrillation, ablation, AF

What's new?

- Successful maintenance of sinus rhythm in patients with longstanding persistent atrial fibrillation (AF) remains a significant challenge, with endocardial catheter ablation often suboptimal.
- Convergent AF ablation combines surgical epicardial ablation of the left atrial posterior wall followed by endocardial pulmonary vein isolation.

- Our single-centre real-world data show favourable rates of maintenance of sinus rhythm at 36 months, which is a longer follow-up period when compared with existing studies.
- Importantly, we describe excellent safety outcomes without major complications or mortality in our cohort.
- Convergent AF ablation could be a safe and effective option for those likely to have limited success with conventional endocardial ablation strategies.

Background

Catheter ablation (CA) of atrial fibrillation (AF) has been demonstrated to improve quality of life and symptoms in those with symptomatic AF (1–5). However, ablation of persistent AF (PsAF, defined as AF of continuous duration greater than 7 days) fares significantly worse in terms of medium- and long-term maintenance of sinus rhythm (6–8), likely related to progressive adverse remodelling of the atrial substrate (9).

Convergent (also known as "hybrid") AF ablation involves a combination of surgical epicardial and endocardial catheter ablation to deliver durable pulmonary vein isolation (PVI). A minimally invasive thoracoscopic approach allows epicardial delivery of transmural left atrial (LA) posterior wall ablation. Subsequent endocardial studies are then used to confirm posterior wall isolation and further radiofrequency endocardial lesions delivered to complete PVI. Though relatively new with few published studies, it seems to offer significant promise in treating PsAF (10–13), although a significant increase in periprocedural complications is reported compared with endocardial CA alone (10, 12–14).

We undertook a single-centre retrospective observational study to investigate the safety, efficacy, and associated patient experience of the convergent ablation procedure to treat PsAF.

Methods

The patients included in the study included all those undergoing the procedure from its inception locally and for a period of 18 months at our institution, a tertiary referral centre with electrophysiology and cardiac surgical expertise. Demographic, clinical, echocardiographic, and procedural data were collected. All patients undergoing convergent ablation over the time period were included. Left atrial (LA) and left ventricular (LV) echocardiographic data were recorded. LA dilatation was quantified by volume as non-dilated ($\leq$ 58 ml), mildly dilated (59–68 ml), moderately dilated (69–78 ml), or severely dilated ($\geq$ 79 ml). LV systolic function was assessed by Simpson's biplane ejection fraction (EF) using transthoracic echocardiography within 1 year preceding ablation.

Safety outcomes including perioperative complications, death, and stroke/transient ischaemic attack (TIA), as well as efficacy outcomes including freedom from documented or symptomatic AF, were collected at 3, 6, 12, 18, 24, and 36 months.

Obesity was defined as a body mass index (BMI) of $\geq$ 30. A positive smoking history was recorded as $\geq$20 smoking pack-years. The symptom burden was quantified using the AF symptom score established by the European Heart Rhythm Association (EHRA).

Surgical epicardial ablation

Surgical ablation was performed under general anaesthesia and by one of two designated experienced cardiac surgeons with training in the procedure. Abdominal incisions and insufflation allowed access to the pericardium via the central tendon of the diaphragm. A pericardial window was created to allow access via a port to the posterior pericardium, and a 5 mm endoscope was introduced to visualise the posterior wall of the LA from left to right pulmonary veins. The Epi-Sense® Coagulation (Atricure® Inc, USA) ablation device was used to deliver lesions to the posterior left atrial wall under direct endoscopic vision. The transmurality of lesions was judged using preset energy delivery and impedance drop targets (> 10% from baseline). The sensing port of the Epi-Sense® device was used to confirm local electrical isolation and informed procedure completion. Continuous pericardial irrigation and oesophageal temperature monitoring were undertaken throughout lesion delivery. All patients received direct-current cardioversion at the end of the procedure.

Endocardial catheter ablation

Catheter ablation was undertaken by experienced operators via femoral venous access, 6–12 weeks following surgical ablation. Either local or general anaesthesia was used according to individual patient factors and patient preference. Anticoagulation was uninterrupted. Trans-septal puncture was fluoroscopically guided, using trans-oesophageal (TOE) guidance where necessary. Electro-anatomical mapping of the LA was generated using the CARTO® software package (Biosense Webster, USA). Ablation consisted of PVI via a wide area circumferential ablation (WACA) strategy to isolate the pulmonary veins. Where required, further ablation including roof and/or floor lines, and more extensive ablation (complex fractionated atrial electrograms, mitral/tricuspid isthmus or coronary sinus ablation) was undertaken to achieve PV isolation. Where posterior LA wall isolation was incomplete as demonstrated by voltage mapping, these gaps were addressed with additional ablation and posterior wall isolation confirmed. PV isolation was confirmed by pacing to confirm the entrance and exit block. SmartTouch® (Biosense Webster, USA) contact-force sensing ablation catheters were used, and the force–time integral guided the lesion delivery.

Follow-up

Patients were seen in an outpatient setting at 3, 6, and 12 months following their final endocardial ablation procedure,

during which an office electrocardiogram (ECG) was performed. Further follow-up at 18, 24, and 36 months occurred either locally, in primary care, or at the referring local hospital. Further AF monitoring comprised symptom-led Holter recording at any point during follow-up. A team of specialised arrhythmia nurses facilitated enhanced patient education and provided a responsive and accessible point of contact for patients throughout the process.

Longstanding PsAF was defined as those suffering with AF episodes lasting for >1 year. AF freedom was defined as the absence of documented AF by office 12-lead ECG testing at follow-up. ECG AF documentation in primary care records or direct patient communication was included.

Statistical analysis

Statistical analysis was performed using GraphPad PRISM (GraphPad Software, USA). Data are presented as median ± interquartile range.

The study was approved by the institutional clinical audit and research department and received NHS Health Research Authority (HRA) approval.

Results

Baseline characteristics

Over an 18-month period, 24 patients underwent the convergent ablation procedure for longstanding PsAF. Patient baseline characteristics and arrhythmia data are displayed in Table 1. In total, 84% ($n = 21$) of patients were male, with a median age of 63 and median BMI of 30. A total of 36% ($n = 11$) of patients suffered from hypertension, 17% ($n = 4$) patients suffered from obstructive sleep apnoea (OSA), and 8% ($n = 2$) of patients suffered from diabetes. A total of 38% ($n = 9$) of patients exhibited a significant smoking history, and the median alcohol units consumed per week was 14. The median CHA_2DS_2VASc score was 1, with 71% ($n = 17$) of patients falling in the 0–1 bracket.

The majority of patients (71%; $n = 17$) had a severely dilated LA. The majority (63%; $n = 15$) of patients had preserved LV function (≥ 50%), 25% ($n = 6$) had mild impaired function (LVEF 40%–49%), and 13% ($n = 3$) suffering from significantly impaired function (LVEF < 40%), consistent with the 2016 ESC heart failure classification (15).

Arrhythmia data

All patients had longstanding PsAF, with AF duration exceeding 1 year, with 75% ($n = 18$) greater than 2 years, and 25% between 1 and 2 years. A total of 83% ($n = 20$) of patients had a "moderately disabling" EHRA symptom score, with 17%

TABLE 1 Baseline characteristics and arrhythmia data of patients with atrial fibrillation undergoing convergent ablation procedure.

Baseline characteristics	All patients, [*N* (%)] *n* = 24
Age	
Median (IQR)	63 (10) Range 42–71
<65	16 (67%)
65–74	8 (33%)
≥75	0
Male gender	21 (84%)
BMI	
Median (IQR)	30 (9) Range 26–41
≥30	12 (50%)
Hypertension	11 (46%)
Obstructive sleep apnoea	4 (17%)
Diabetes	2 (8%)
Smoking history (≥20 pack-years)	9 (38%)
Alcohol units per week [median (IQR)]	14 (16)
CHA_2DS_2VASc	
Median (IQR)	1 (2)
0–1	17 (71%)
2	5 (21%)
3	2 (8%)
4	0
≥5	0
Left atrial volume, ml [median (IQR)]	
Median (IQR)	99 (34)
Non-dilated, ≤58 ml	3 (13%)
Mildly dilated, 59–68 ml	2 (8%)
Moderately dilated, 69–78 ml	2 (8%)
Severely dilated, ≥79 ml	17 (71%)
Left ventricular ejection fraction (%)	
Mean (SD)	52 (6)
≥50%	15 (63%)
40%–49%	6 (25%)
<40%	3 (13%)
Arrhythmia history	
Duration of AF	
<1 year	0
1–2 years	6 (25%)
>2 years	18 (75%)
EHRA symptom score	
1 (none)	0
2a (mild)	0
2b (moderate)	20 (83%)
3 (severe)	4 (17%)
4 (disabling)	0
Symptom reported	
Breathlessness	18 (75%)
Fatigue/lethargy	16 (67%)
Reduced exercise tolerance	3 (13%)
Prior AF catheter ablation	
1 prior ablation	1 (4%)
≥2 prior ablations	1 (4%)
Rhythm-control medication	2 (8%)
Anticoagulation	
DOAC	20 (83%)
Warfarin	4 (17%)

IQR, interquartile range; BMI, body mass index; SD, standard deviation; AF, atrial fibrillation; EHRA, European Heart Rhythm Association; DOAC, direct oral anticoagulant.

($n = 4$) of patients having a "severely disabling" score. A total of 75% ($n = 18$) of patients reported breathlessness as a symptom, 67% ($n = 16$) reported fatigue or lethargy, and 13% ($n = 3$) reported reduced exercise tolerance. The observed overlap reflects the frequent multiple symptom burden in patients. Two patients had previously undergone AF catheter ablation, one of whom had undergone a single ablation and the other patient underwent three previous ablations. In total, 8% ($n = 2$) of patients were on rhythm-controlling medications at the time of work-up (flecainide, amiodarone). All patients were anticoagulated, with 83% ($n = 20$) of them on a direct oral anticoagulant (DOAC) and the remaining patients taking warfarin.

Procedural and outcome data

Full data are shown in Table 2. The median number of surgical lesions delivered was 25 (interquartile range of 12) with a minimum number of 13 lesions and a maximum of 41 lesions. The average number of lesions delivered seemed to increase over the study period: the first 12 patients had a mean of 21.6 lesions while the latter 12 patients had a mean of 26 lesions. However, this did not seem to correlate with any clear change in efficacy. The patients stayed in the hospital for a median of 2 days.

The endocardial ablation strategies used included PVI only (21%; $n = 5$), PVI plus roof line (21%, $n = 5$), PVI, roof line, and floor (42%, $n = 10$), and more extensive ablation (complex fractionated atrial electrograms, mitral/tricuspid isthmus or coronary sinus ablation) in 17% ($n = 4$) of patients. Figure 1 demonstrates a representative 3D anatomical left atrial voltage map showing the extensive scar on the posterior wall, as well as the subsequent endocardial ablation undertaken to complete the PVI.

Following the surgical ablation procedure, there were three (13%) minor wound infections, all treated successfully with oral antibiotics in the outpatient setting. There was a single occurrence of re-admission for postoperative pericarditic pain, and a single occurrence of a post-surgical incisional hernia. There were no major complications, significant pericardial effusion, bleeding, or infective endocarditis. There were no immediate endocardial catheter ablation complications. There was no post-procedural mortality.

There was no mortality recorded within the study population at 3, 6, 12, 18, 24, or 36-month follow-up. Similarly, there were no new diagnoses of stroke/TIA at 3, 6, 12, 18, 24, or 36-month follow-up.

Further re-do catheter ablation for AF was undertaken in four patients (17%), all undergoing a single further procedure within 12 months. Separately, one patient (4%) underwent a further catheter ablation procedure within 12 months for symptomatic atrial tachycardia.

The freedom from documented AF was 83% ($n = 20/24$) at 3 months, 78% ($n = 18/23$) at 6 months, 74% ($n = 17/23$) at 12 months, 74% ($n = 17/23$) at 18 months, 74% ($n = 17/23$) at 24 months, and 61% ($n = 14/23$) at 36 months. The survival plot is illustrated in Figure 2.

One patient was lost to follow-up before 18 months due to disruption related to the COVID-19 pandemic, although the mortality data were confirmed for all 24 patients.

TABLE 2 Procedural and outcome data of patients with atrial fibrillation undergoing convergent ablation procedure.

Procedural data	All patients, [*N* (%)] $n = 24$
No. surgical lesions delivered [median (IQR)]	25 (12) Range 13–41
Surgical inpatient days [median (IQR)]	2 (0.25)
Endocardial ablation strategy	
PVI only	5 (21%)
PVI + roof line	5 (21%)
PVI, roof line and floor	10 (42%)
PVI, roof, floor plus additional (CFAEs, mitral or cavo-tricuspid isthmus and/or CS)	4 (17%)
Further re-do endocardial procedures undertaken	
1 within 12 months for AF	4 (17%)
≥2 within 12 months for AF	0
Within 12 months for atrial tachycardia	1 (4%)
Outcome data	
Freedom from documented AF	
At 3 months	20/24 (83%)
At 6 months	18/23 (78%)
At 12 months	17/23 (74%)
At 18 months	17/23 (74%)
At 24 months	17/23 (74%)
At 36 months	14/23 (61%)
Safety data	
Mortality	
At 3 months	0
At 6 months	0
At 12 months	0
At 18 months	0
At 24 months	0
At 36 months	0
New diagnosis stroke/TIA	
At 3 months	0
At 6 months	0
At 12 months	0
At 18 months	0 (of 23 under follow-up)
At 24 months	0 (of 23 under follow-up)
At 36 months	0 (of 23 under follow-up)
Periprocedural complications	
Endocardial procedure complications	0
Post-surgical minor wound infection	3 (13%)
Admission for post-surgical pericarditic pain	1 (4%)
Post-surgical incisional hernia	1 (4%)
Significant bleeding	0
Pericardial effusion	0
Infective endocarditis	0
Other	0

Data are shown for procedural outcomes. IQR, interquartile range; PVI, pulmonary vein isolation; CFAE, complex fractionated atrial electrogram; CS, coronary sinus; AF, atrial fibrillation; TIA, transient ischaemic attack.

Discussion

Procedural outcomes and safety

A convergent approach to AF ablation has been described in several small studies (11, 13, 14, 16–19) as well as a recent meta-analysis (10) and randomised controlled trial (RCT) (12). They report very favourable rates of maintenance of

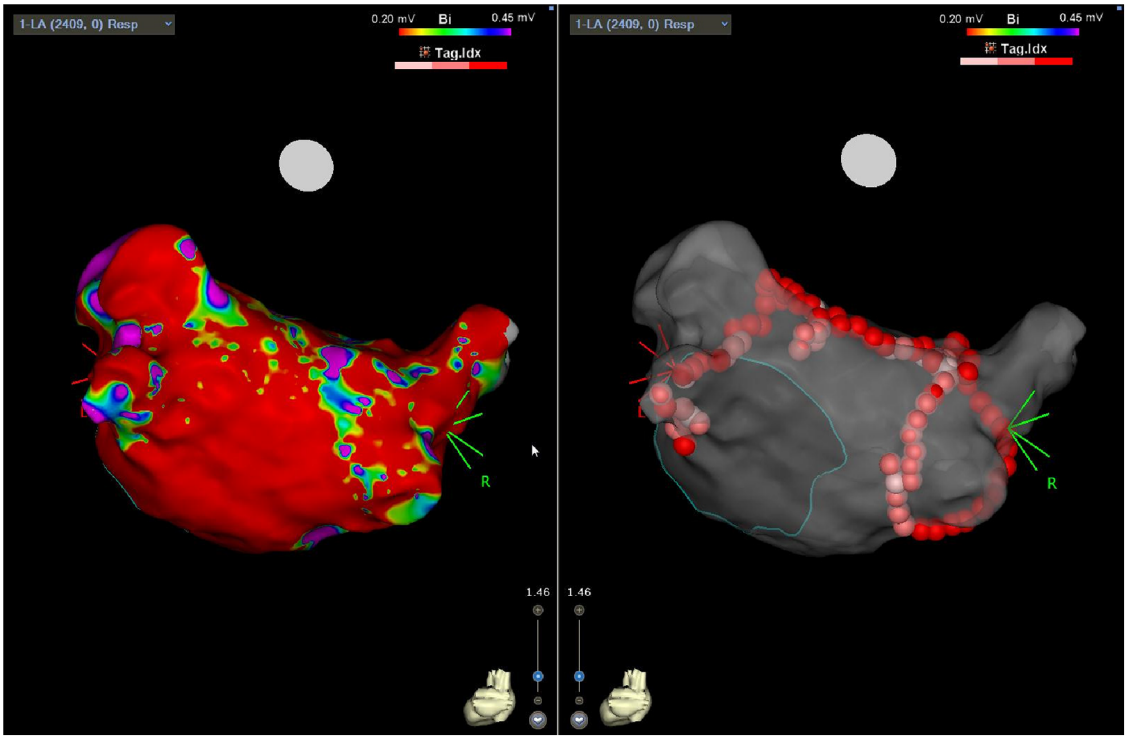

FIGURE 1
Three-dimensional electro-anatomical map showing posterior LA with diffuse regions of low voltage (left panel) following surgical epicardial ablation and subsequent endocardial PVI (right panel).

sinus rhythm in the medium and long term. However, they also report a significant burden of periprocedural complications with associated morbidity and mortality. Our small study shows that the convergent ablation approach can be undertaken safely. Our cohort found a low number of minor procedural complications, which consisted of wound infections, pericarditic pain, and a postoperative incisional hernia. All wound infections were successfully treated with oral antibiotics in the outpatient setting. The number of surgical lesions delivered seemed to increase throughout the study period, although without observable effect on efficacy.

Importantly, and in contrast to other reported studies, there were no major periprocedural complications and no stroke, TIA, or mortality observed periprocedurally or during follow-up. Thus, despite the findings of the recent RCT (12) and other published reports with larger patient cohorts, our data are novel both in terms of the very low rate of serious periprocedural complications and the follow-up data—longer than any other published cohort, at 3 years.

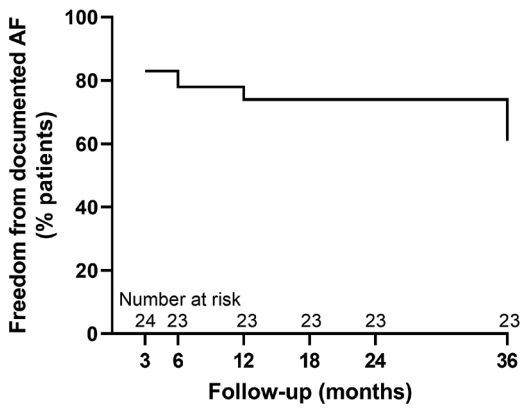

FIGURE 2
Survival plot showing single-procedure freedom from documented AF at 3-, 6-, 12-, 18-, 24- and 36-month follow-up.

Arrhythmia-free survival and quality of life

The rates of maintenance of sinus rhythm are favourable and in keeping with other published studies (1, 20) with 78% of patients maintaining sinus rhythm at 6 months, 74% at 12, 18, and 24 months, and 61% at 3 years, in a cohort of patients with longstanding PsAF and evidence of established remodelling.

There were a small number of re-do endocardial procedures within the study period (four re-do procedures for AF, one for focal atrial tachycardia). The use of repeat ablation procedures is common in real-world practise to promote sinus rhythm (21), allowing assessment of the PVI and further ablation to be delivered if required to address gaps, promoting durable block.

Our 36-month duration of long-term follow-up is unique within the literature and provides a useful insight into the long-term disease course of these patients.

Convergent AF ablation and arrhythmia mechanisms

Our study captures a cohort of patients undergoing ablation for longstanding PsAF which reflects real-life practise, with a high burden of reported symptoms and a significant duration of AF. Our cohort also reflects a group of patients with typical upstream AF disease drivers with significant rates of obesity, hypertension, and diabetes. These are individuals who are likely to experience a poor long-term outcome from conventional endocardial PsAF catheter ablation (6–8), and in whom satisfactory rhythm control for AF remains an ongoing unmet need. Indeed, 75% of patients in our cohort had an AF duration of greater than 2 years, and 71% of patients had a severely dilated LA. These individuals are likely to demonstrate established atrial remodelling and fibrosis. The mechanisms of failure of AF ablation in these types of individuals remain unclear, with increased difficulty in obtaining durable isolation of both PV (22, 23) and non-PV AF triggers (3, 24) likely playing a role. Indeed, repeated endocardial ablation procedures may indeed generate new non-PV triggers (23, 25), thus exacerbating the situation. However, extensive ablation in pursuit of such foci has failed to show any compelling benefit beyond PVI alone (7).

Convergent ablation offers the potential for durable posterior LA wall ablation. This is then confirmed at the time of endocardial ablation, and completed if required. PVI is then undertaken, at which point further ablation is performed if felt beneficial. This more extensive ablation lesion set may potentially recruit more PV as well as non-PV triggers, as there has been a suggestion that the posterior LA wall, and in particular localised atrial fat, may play an important role in persistent AF (26, 27). In addition, there may be some endocardial–epicardial dissociation contributing to arrhythmogenesis in those with persistent AF (28, 29), which is more effectively targeted by a convergent approach. The advent of novel ablation technologies such as pulsed field ablation (PFA) presents further opportunities for convergent AF ablation and merits further study.

Limitations

Our data are primarily limited by a lack of quantitative rhythm monitoring. The use of continuous rhythm monitoring such as with an implantable loop recorder (ILR) would have enhanced two aspects of the study: first, it would have enabled an accurate assessment of AF recurrence. Second, it would have allowed a quantitative assessment of AF burden before and after ablation. Indeed, the assessment of arrhythmia (as well as symptom) burden may be more important than binary absolute recurrence. A further limitation of the data was lack of consistently available procedural data as well as LA dwell time.

The low number of patients taking rhythm-control anti-arrhythmic medication may not be representative of the universal experience of patients with longstanding PsAF. However, it may be that medication intolerance or lack of efficacy was an influencing factor in the decision to pursue convergent ablation.

Conclusions

Convergent ablation offers favourable short- and long-term efficacy. Our study is the first to show that it can be undertaken safely without significant complications or mortality and with durable efficacy as far out as 36 months. As the technique continues to develop and experience with the procedure grows, we may see continued improvements in efficacy and safety.

Convergent ablation for persistent AF offers an attractive option for a patient group suffering with an atrial substate that has already undergone advanced remodelling. They are not well served by existing conventional endocardial ablation and this continues to represent an unmet need in a cohort with a high symptom burden. This new technique offers an exciting new approach to improve quality of life and would be well served by further comprehensive evaluation.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the clinical audit and research department at University Hospitals Bristol and received approval from the NHS Health Research Authority (HRA). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

AC: Writing – original draft, Writing – review & editing. LP: Writing – original draft. SR: Writing – review & editing. KM: Writing – original draft. CR: Writing – review & editing. FC: Writing – review & editing. ED: Writing – review & editing.

GT: Writing – review & editing. PB: Writing – review & editing. RB: Writing – review & editing. AN: Writing – review & editing.

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Conflict of interest

AC received an MRC Clinical Research Training Fellowship (MR/S021299/1). LP receives a BHF Clinical Research Training Fellowship (BHF/FS/CRTF/21/24122) for unrelated work. AMN has received consulting fees from Atricure. The funder had no involvement with any aspects of the study, including but not limited to study design, data collection and analysis, decision to publish or preparation of the manuscript. No other funding was received by any authors for the study. All authors declare no other conflicts of interest or funding sources.

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Clinical significance of regional constructive and wasted work in patients receiving cardiac resynchronization therapy

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Background: Previous studies have shown that global constructive work (CW) and wasted work (WW) predict response to cardiac resynchronization therapy (CRT). This study evaluated the predictive value of regional CW and WW for reverse remodeling and clinical outcomes after CRT.
Methods: We performed a prospective study involving 134 CRT candidates with left bundle branch block and left ventricular ejection fraction ≤35%. Global and regional CW and WW were calculated using pressure-strain loop analysis. CRT response was defined by reverse remodeling as a reduction of ≥15% in left ventricular end-systolic volume after six months.
Results: At six-month follow-up, 92 (69%) patients responded to CRT. Of the regional CW and WW measures, lateral wall (LW) CW and septal WW were most strongly and significantly correlated with reverse remodeling. At multivariate analysis, LW CW and septal WW were both independent determinants of reverse remodeling. When LW CW and septal WW were included in the model, global CW and WW were not independently associated with reverse remodeling. LW CW and septal WW predicted reverse remodeling with an area under the curve (AUC) of 0.783 (95% CI: 0.700–0.866) and 0.737 (95% CI: 0.644–0.831), respectively. Using both variables increased the AUC to 0.832 (95% CI: 0.755–0.908). Both LW CW ≤878 mmHg% (HR 2.01; 95% CI: 1.07–3.79) and septal WW ≤181 mmHg% (HR 2.60; 95% CI: 1.38–4.90) were significant predictors of combined death and HF hospitalization at two-year follow-up.
Conclusion: LW CW and septal WW before CRT are important determinants of reverse remodeling and clinical outcomes.

KEYWORDS

cardiac resynchronization therapy, myocardial work, constructive work, wasted work, reverse remodeling, survival, heart failure

Introduction

Cardiac resynchronization therapy (CRT) reduces morbidity and mortality in patients with heart failure (HF) and a wide QRS complex (1). However, a significant portion of patients who receive CRT do not respond favorably to the therapy (2). Several echocardiographic measures have been suggested to predict CRT response by analyzing

the timing of mechanical events (3–5). Although these time-delay parameters initially showed promise, randomized controlled trials have shown that these parameters are not reliable predictors of CRT response (6, 7). One possible explanation for these findings is that the mechanical dyssynchrony caused by primary electric dyssynchrony is the modifiable substrate for CRT (8). The problem with conventional time-delay indices of mechanical dyssynchrony is that they can also be caused by regional contractile disparities such myocardial ischemia, infarction, or scar, which are less likely to be amenable to CRT (8, 9). As an alternative, visual assessments of apical rocking, septal flash, and left bundle branch block (LBBB) contraction pattern are used to assess left ventricular (LV) mechanical dyssynchrony, potentially overcoming the limitations of previously suggested parameters (10, 11).

In a healthy heart, all LV segments contract synchronously and myocardial energy is used efficiently to eject blood into the aorta. However, when there is a delay in electrical conduction, segments that activate early and late contract at different times, leading to the wastage of myocardial energy in stretching opposing walls. Several studies have shown that non-invasive estimates of global constructive work (CW) or wasted work (WW) using pressure–strain loops predict reverse remodeling or mortality after CRT better than dyssynchrony indices do (12–15). The combined assessment of myocardial CW and WW involves evaluating the contractile reserve and wasted energy caused by LV dyssynchrony, providing a comprehensive approach to evaluate the mechanisms underlying the CRT response. However, the prognostic value of regional CW and WW in CRT candidates has rarely been defined (16). In addition, a recent study showed that the combination of work difference between the septum and lateral wall (LW) with septal viability can be used to predict CRT response (17). The study employed cardiac magnetic resonance imaging with late gadolinium enhancement to evaluate septal viability. The current study aims to assess the efficacy of combining regional CW and WW in predicting reverse remodeling and clinical outcomes of patients undergoing CRT.

Methods

Study population

This was a prospective single-center study. We assessed patients with HF and LBBB who were undergoing CRT. We excluded patients who had atrial fibrillation, severe heart valve disease, or poor apical acoustic window. All patients were receiving optimized medical therapy at the time of CRT. An ischemic etiology was defined as a history of myocardial infarction, coronary revascularization, or angiographic evidence of multi-vessel disease or single-vessel disease with >75% stenosis of the left main or proximal left anterior descending artery. The study was approved by the institutional review board and complied with the Declaration of Helsinki. All patients provided written informed consent to participate in the study.

Conventional echocardiographic analysis

All patients underwent transthoracic echocardiography using a commercially available ultrasound probe and device (M5S probe, Vivid E9, GE Healthcare, Horten, Norway) before and six months after CRT. Two dimensional and pulsed wave Doppler data were stored and analyzed offline. LV volumes and function were obtained using the modified Simpson's rule.

Speckle tracking analysis

The study used digital loops of two-dimensional LV images for offline speckle-tracking analysis with a commercially available software (EchoPAC, GE Vingmed Ultrasound, Horten, Norway). The gain settings and sector width were adjusted to optimize the image quality with frame rates of 50–90 Hz. Two-dimensional LV images were obtained at the apical four-chamber, two-chamber, and long-axis views for speckle-tracking strain analysis. To analyze LV longitudinal strain, the endocardial border was traced on an end-systolic frame, and the width of the region of interest was adjusted to include most of the LV myocardium. The software automatically tracked myocardial motion and generated six curves of segmental longitudinal strain for each apical view. Global longitudinal strain was computed as the average of peak systolic longitudinal strain of all LV segments.

Myocardial work assessment

The study utilized a vendor-specific software (EchoPAC version 202, GE Vingmed Ultrasound) to assess global and regional myocardial work. The peak LV pressure was assumed to be equivalent to the brachial systolic blood pressure, measured before the echocardiographic study. The software produced a previously validated noninvasive LV pressure curve that was adjusted based on the timing of ejection and isovolumic phases (18). These phases were defined by the timing of aortic valve and mitral valve opening and closing using spectral Doppler tracings. LV strain measured by speckle-tracking analysis and LV pressure curve were synchronized by aligning cardiac cycle phases and peak LV pressure. We quantified myocardial work by computing the rate of regional shortening via strain curve differentiation and multiplying this value by estimates of instantaneous LV pressure. Myocardial CW measurements quantified the amount of work performed during systolic shortening and the negative work performed while lengthening during isovolumic relaxation. Myocardial WW measurements quantified the amount of negative work performed while lengthening in systole and work performed while shortening in isovolumic relaxation. We computed regional CW and WW values for six regional walls (the inferior, posterior, lateral, anterior, anteroseptal, and septal walls) as the averages of the values for the basal- and mid-LV segments. We calculated the global values of CW and WW as the mean values for all LV walls.

Alternative approaches

Two experienced observers assessed the existence of septal flash, apical rocking, and LBBB contraction pattern before CRT. Septal flash was characterized as the thickening and thinning of the septum during the isovolumic contraction period, while apical rocking was described as the movement of the LV apical myocardium vertical to the LV long axis (10). The LBBB contraction pattern was recognized by analyzing longitudinal strain curves in the apical four-chamber view using three criteria (11). These criteria included: (1) early shortening of at least one basal- or mid-LV segment in the septum and early lengthening in at least one basal- or mid-LV segment in the LW; (2) early septal peak shortening occurring within the initial 70% of the ejection period; and (3) LW reaching peak shortening after aortic valve closure (11). The work difference between the LW and septum was calculated in the apical four-chamber view as the absolute difference between net myocardial work in the LW and septum (17).

Endpoints

The study's primary objective was to assess LV reverse remodeling, which was defined as a reduction in LV end-systolic volume (ESV) of ≥15% after six months of CRT. The secondary endpoint was the composite of all-cause death or hospitalization due to HF during a two-year follow-up.

Statistical analysis

Continuous data are presented as mean ± standard deviation and categorical data as number and percentage. Comparisons among continuous variables were examined using the Student's *t*-test. Comparisons among categorical data were performed using the chi-squared test. We evaluate the predictive performance of global and regional CW and WW for reverse remodeling by calculating receiver-operating characteristic cures and areas under the curve (AUCs). To identify CRT responders, we selected an optimal cut-off value that maximized the Youden index (sensitivity + specificity − 1). Pearson's correlation analysis was conducted to examine the association between values of CW and WW and the decrease in LV ESV following CRT. To assess the predictive value of variables for reverse remodeling, we employed logistic regression analysis. Variables that had a univariate p value of <0.05 were included in a multivariate model. We utilized a series of nested models by incorporating CW (global or lateral) and WW (global or septal) parameters. The incremental predictive ability of each model was assessed by comparing chi-square values at each stage. To determine the cumulative probabilities of all-cause death or HF hospitalization after CRT, we employed the Kaplan–Meier method, and between-group comparisons of cumulative event rates were calculated using the log-rank test. We evaluate the inter- and intra-observer agreement for CW and WW in 20 randomly chosen patients. A p-value of <0.05 was considered statistically significant. We conduced statistical analysis using a statistical package (SPSS ver. 22.0, IBM, Chicago, IL, USA).

Results

Table 1 summarizes the baseline characteristics of the 134 patients included in the study, with an average age of 69.0 ± 11.9 years, 54.5% of whom were male, and 37.3% had ischemic etiology. Five patients died before the six-month follow-up and were classified as non-responders. Of the remaining 129 patients, 92 achieved the primary endpoint of a reduction in LV ESV of ≥15%, resulting in a response rate of 69%. Responders exhibited a higher prevalence of non-ischemic etiology, less dilated LV, and a more preserved LV ejection fraction and global longitudinal strain than non-responders. Prior to CRT, there were significant differences in regional CW between responders and non-responders in the posterior, lateral, anterior, and anteroseptal walls. There were also significant differences in regional WW in the anteroseptal and septal walls. Figure 1 displays the segmental values of myocardial work, CW, and WW in a responder (Panel A) and non-responder (Panel B) before CRT and after six months. Prior to CRT, the responder had marked differences in myocardial work, CW, and WW between regional walls, with large septal WW, which was converted to large CW with CRT. On the other hand, the non-responder shows smaller variations in myocardial work, CW, and WW before CRT. After CRT, there was only a modest improvement of septal function with noticeable WW in the posterior wall (LV pacing site). Supplementary Table S1 shows the effects of CRT on LV function and myocardial work. At follow-up, responders showed a significant improvement in LV ejection fraction and global longitudinal strain, whereas non-responders did not experience any changes in these parameters. Responders also exhibited significant improvements in septal WW, global CW, global WW, and work difference after six months, whereas non-responders did not show any significant changes in LW CW, septal WW, and global WW at follow-up.

Predictive characteristics for reverse remodeling after CRT

Based on the binary definition of reverse remodeling, posterior wall CW, LW CW, anterior wall CW, anteroseptal WW, and septal WW had an AUC greater than that under the line of no information (Table 2). Of the regional CW values, the LW CW varied the most between responders and non-responders [AUC: 0.783, 95% confidence interval (CI) 0.700–0.866, cut-off value 878 mmHg%, sensitivity 72%, specificity 74%]. Of the regional WW values, septal WW varied the most between responders and non-responders (AUC: 0.737, 95% CI: 0.644–0.831, cut-off value: 181 mmHg%, sensitivity 88%, specificity 55%). Combining LW CW and septal WW increased the AUC to 0.832 (95% CI: 0.755–0.908). Figure 2 displays the response rates of patients whose regional CW and WW values met (true-positive rate) or did not meet (false-negative rate) the cut-off values. The

TABLE 1 Baseline characteristics of the entire population and based on CRT response.

	All patients ($n = 134$)	Responders ($n = 92$)	Non-responders ($n = 42$)	p-value
Age, years	69.0 ± 11.9	69.9 ± 11.4	67.1 ± 12.9	0.214
Male	73 (54.5)	45 (48.9)	28 (66.7)	0.056
Ischemic etiology	50 (37.3)	23 (25)	27 (64.3)	<0.001
Medications				
ACE-inhibitor/ARB	105 (78.4)	73 (79.3)	32 (76.2)	0.681
ARNI	12 (9)	10 (10.9)	2 (4.8)	0.251
Beta-blocker	119 (88.8)	84 (91.3)	35 (83.3)	0.175
Aldosterone antagonist	73 (54.5)	53 (57.6)	20 (47.6)	0.281
QRS duration, ms	161.9 ± 19.3	162.2 ± 19.4	161.3 ± 19.3	0.812
eGFR, ml/min/1.73 m^2	63.3 ± 31.1	65.1 ± 31.3	59.2 ± 30.8	0.309
QRS duration ≥150 ms	94 (70.1)	65 (70.7)	29 (69)	0.851
Systolic blood pressure, mmHg	120.1 ± 19.4	122.3 ± 19.4	115.4 ± 17.8	0.054
Diastolic blood pressure, mmHg	70.6 ± 12.0	71.2 ± 12.4	69.1 ± 10.8	0.343
NYHA class	2.8 ± 0.5	2.7 ± 0.5	2.9 ± 0.6	0.051
Mitral regurgitation	1.0 ± 0.7	1.0 ± 0.7	1.0 ± 0.7	0.787
LV EDV, ml	171.1 ± 67.6	160.0 ± 60.1	195.6 ± 76.8	0.004
LV ESV, ml	132.8 ± 62.6	122.4 ± 55.1	155.5 ± 72.0	0.004
LV ejection fraction, %	24.6 ± 7.5	25.6 ± 6.8	22.3 ± 8.5	0.020
GLS, %	−6.5 ± 2.9	−7.0 ± 2.9	−5.3 ± 2.7	0.001
Septal flash	90 (67.2)	75 (81.5)	15 (35.7)	<0.001
Apical rocking	97 (72.4)	80 (87.0)	17 (40.5)	<0.001
LBBB contraction pattern	88 (65.7)	75 (81.5)	13 (31.0)	<0.001
Work difference, mmHg%	953 ± 530	1,115 ± 498	596 ± 415	<0.001
Global CW, mmHg%	767 ± 346	846 ± 346	592 ± 277	<0.001
Global WW, mmHg%	279 ± 148	301 ± 149	230 ± 135	<0.001
Regional CW, mmHg%				
Inferior wall	636 ± 384	634 ± 383	642 ± 392	0.911
Posterior wall	1,103 ± 548	1,263 ± 525	752 ± 423	<0.001
Lateral wall	1,026 ± 493	1,175 ± 467	701 ± 381	<0.001
Anterior wall	853 ± 415	943 ± 406	655 ± 365	<0.001
Anteroseptum	486 ± 337	527 ± 364	396 ± 250	0.017
Septum	407 ± 302	402 ± 324	418 ± 249	0.779
Regional WW, mmHg%				
Inferior wall	261 ± 204	283 ± 203	215 ± 201	0.076
Posterior wall	313 ± 204	332 ± 202	272 ± 207	0.115
Lateral wall	255 ± 164	246 ± 151	273 ± 190	0.379
Anterior wall	182 ± 136	175 ± 121	197 ± 164	0.383
Anteroseptum	298 ± 286	341 ± 306	204 ± 212	0.003
Septum	407 ± 280	474 ± 278	261 ± 226	<0.001

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CW, constructive work; EDV, end-diastolic volumn; eGFR, estimated glomerular filtration rate; ESV, end-systolic volumn; GLS, global longitudinal strain; LBBB, left bundle branch block; LV, left ventricular; NYHA, New York Heart Association; WW, wasted work.
Data are shown as n (%) or mean ± standard deviation.

results show that LW CW was superior to the other regional CW measures and global CW, with a true-positive rate of 86% and a false-negative rate of 46%. Septal WW was superior to the other regional WW measures and global WW, with a true-positive rate of 81% and a false-negative rate of 32%. The AUCs for global CW and WW were 0.732 (95% CI: 0.639–0.825) and 0.692 (95% CI: 0.589–0.796), respectively. Combining the global CW and WW increased the AUC to 0.759 (95% CI: 0.669–0.850).

Variables associated with reverse remodeling

Multivariate analysis, using the significant variables from the univariate analysis (Supplementary Table S2) revealed that non-ischemic etiology and LV end-diastolic volume were independently associated with reverse remodeling, and they were thus included in the baseline model ($\chi^2 = 26.7$, Table 3). We then added the CW (lateral and global) and/or WW (septal and global) parameters to the model. The LW CW [odds ratio (OR) 1.26, 95% CI: 1.10–1.44 per 100-mmHg% increase] and septal WW (OR 1.33, 95% CI: 1.07–1.66 per 100-mmHg% increase) were both independently associated with reverse remodeling. Model power improved when LW CW (χ^2 difference: 24.4, $p < 0.001$) and septal WW (χ^2 difference 17.2, $p < 0.001$) were added to the model. In contrast, global CW and WW were not independently associated with reverse remodeling when LW CW or septal WW was included in the model. The addition of LW CW >878 mmHg% (OR 4.09; 95% CI: 1.44–11.62) and septal

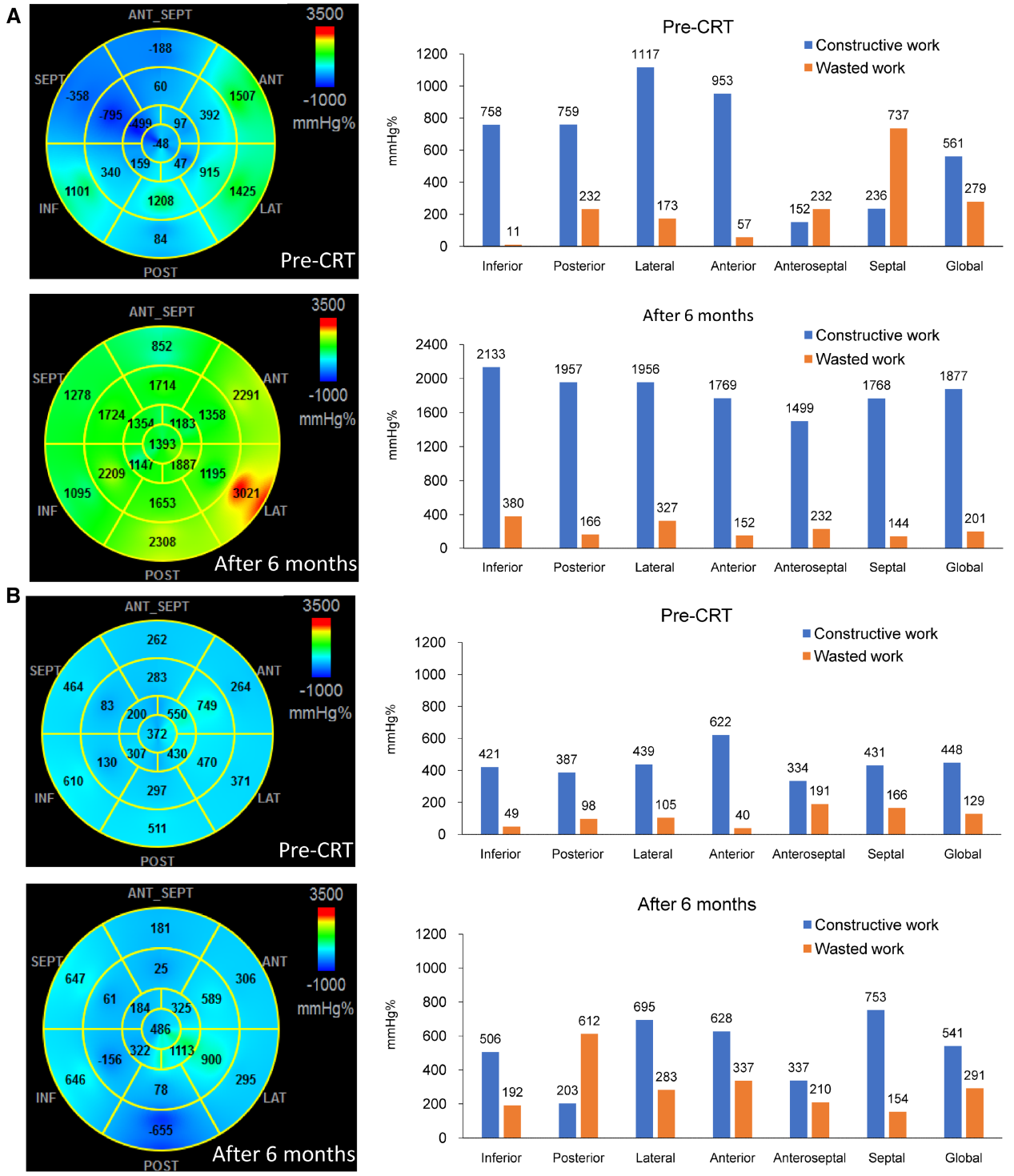


FIGURE 1
The bull-eye plots and bar charts showing the values of myocardial work, constructive work (CW) and wasted work (WW) before and 6 months after cardiac resynchronization therapy (CRT). In (Panel A), which represents a responder, high values of CW were observed in the lateral wall, while predominant WW was seen in the septum before CRT. Following CRT, there was a significant improvement in septal function, and the septal WW was converted to substantial CW. On the other hand, (Panel B), which represents a non-responder, showed lower values of lateral wall CW and septal WW compared to the responder. After CRT, there was only a moderate improvement in septal function, and noticeable WW was observed in the posterior wall.

TABLE 2 Predictive characteristics of regional constructive work and wasted work prior to cardiac resynchronization therapy.

	Versus ΔESV		Dichotomous reverse remodeling response			
	CC	*p*-value	AUC (95% CI)	Cut-off, mmHg%	Sensitivity, %	Specificity, %
Constructive work						
Inferior wall	0.01	0.950	0.507 (0.400–0.614)	488	67	46
Posterior wall	0.38	<0.001	0.774 (0.692–0.857)	1,052	65	76
Lateral wall	0.35	<0.001	0.783 (0.700–0.866)	878	72	74
Anterior wall	0.23	0.009	0.720 (0.624–0.816)	822	59	79
Anteroseptum	0.05	0.598	0.602 (0.502–0.702)	559	44	79
Septum	−0.14	0.118	0.557 (0.451–0.663)	333	64	55
Global LV	0.24	0.007	0.732 (0.639–0.825)	635	71	71
Wasted work						
Inferior wall	0.07	0.397	0.617 (0.510–0.724)	136	74	52
Posterior wall	0.11	0.206	0.619 (0.510–0.729)	236	66	64
Lateral wall	−0.11	0.196	0.529 (0.422–0.636)	232	57	53
Anterior wall	−0.06	0.532	0.514 (0.408–0.621)	132	64	46
Anteroseptum	0.24	0.005	0.650 (0.552–0.748)	172	64	67
Septum	0.33	<0.001	0.737 (0.644–0.831)	181	88	55
Global LV	0.18	0.039	0.692 (0.589–0.796)	222	71	67

AUC, area under the curve; CC, correlation coefficient; ESV, end-systolic volume; LV, left ventricle.

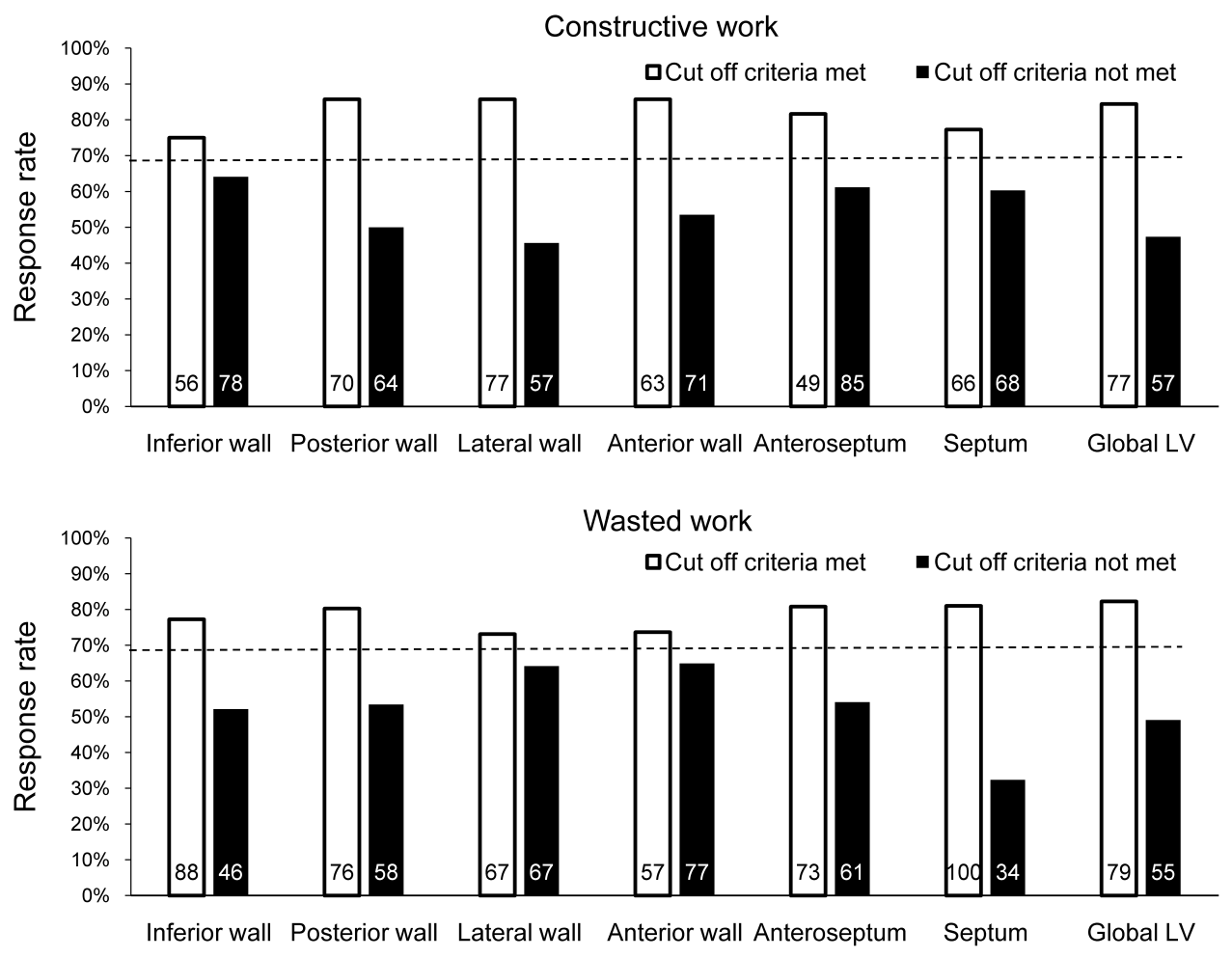


FIGURE 2
Response rate at 6 months after CRT by determining whether the cut-off value for each CW and WW parameter was met in all patients. The dashed line indicates the response rate observed when ignoring the parameter. The number of patients who met or did not meet the cut-off criterion for each parameter is shown inside each bar.

TABLE 3 Variables associated with CRT response in the baseline model and after addition of constructive work and wasted work parameters.

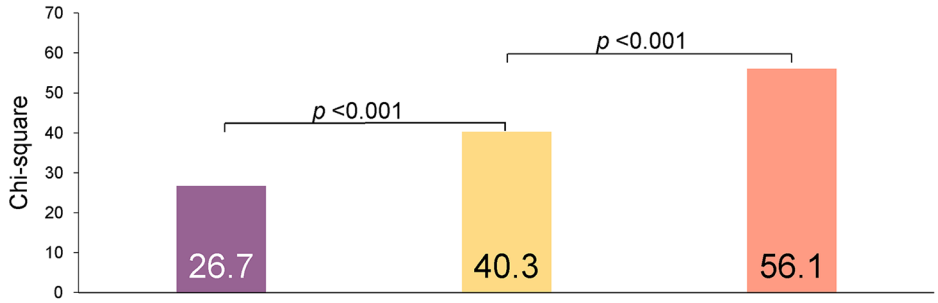
	Baseline model		Baseline model + global CW + global WW		Baseline model + global CW + LW CW		Baseline model + global WW + septal WW		Baseline model + LW CW + septal WW	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Non-ischemic etiology	5.76 (2.52–13.15)	<0.001	6.62 (2.67–16.41)	<0.001	6.65 (2.61–16.94)	<0.001	4.99 (2.06–12.12)	<0.001	5.64 (2.16–14.73)	<0.001
LVEDV, per 10 ml	0.92 (0.86–0.98)	0.008	0.97 (0.91–1.04)	0.433	0.98 (0.91–1.05)	0.486	0.91 (0.85–0.97)	0.005	0.96 (0.90–1.03)	0.293
Global CW per 100-mmHg%			1.32 (1.09–1.56)	0.005	0.89 (0.67–1.18)	0.399				
Global WW per 100-mmHg%			1.46 (1.00–2.13)	0.049			0.84 (0.50–1.42)	0.518		
LW CW, per 100-mmHg%					1.41 (1.15–1.72)	0.001			1.26 (1.10–1.44)	0.001
Septal WW, per 100-mmHg%							1.54 (1.17–2.04)	0.002	1.33 (1.07–1.55)	0.011

CI, confidence interval; CW, constructive work; LVEDV, left ventricular end-diastolic volume; LW, lateral wall; OR, odds ratio; WW, wasted work.

WW >181 mmHg% (OR 7.37; 95% CI: 2.64–20.63) to a baseline model including non-ischemic etiology and LV end-diastolic volume significantly increased model power (Figure 3). There were 66 patients (49%) with both LW CW >878 mmHg% and septal WW >181 mmHg%. Of this group, 29% ($n = 19$) showed ischemic cardiomyopathy, which was a significantly smaller proportion than was observed in the other group ($p = 0.044$). This presence of both LW CW >878 mmHg% and septal WW >181 mmHg% was associated with a high response rate (91%). There were 23 patients (17%) with both LW CW ≤878 mmHg% and septal WW ≤181 mmHg%. Their response rate was only 21%. The response rate in the 45 patients (34%) who had either LW CW >878 mmHg% or septal WW >181 mmHg% was 60%.

Event-free survival

Figure 4 displays the Kaplan–Meier curves dichotomized according to LW CW ≤878 mmHg% (log-rank $p = 0.024$) and septal WW ≤181 mmHg% (log-rank $p = 0.001$). Both CW ≤878 mmHg% (HR 2.01; 95% CI: 1.07–3.79, $p = 0.031$) and septal WW ≤181 mmHg% (HR 2.60; 95% CI: 1.38–4.90; $p = 0.003$) were significant predictors of combined all-cause death and hospitalization due to HF at two-year follow-up. Figure 5 displays the Kaplan–Meier curves stratified by the combined LW CW and septal WW parameters. Patients categorized in the "both" group, characterized by both LW CW >878 mmHg% and septal WW >181 mmHg%, demonstrated the most favorable



Variables	Baseline model	Baseline model + lateral wall CW >878 mmHg%	Baseline model + lateral wall CW >878 mmHg% + septal WW >181 mmHg%
Nonischemic etiology	5.76 (2.52–13.15), *p* <0.001	5.25 (2.18–12.61), *p* <0.001	5.52 (2.12–14.39), *p* <0.001
LVEDV, per 10 mL increase	0.92 (0.86–0.98), *p* = 0.008	0.97 (0.90–1.04), *p* = 0.368	0.96 (0.89–1.04), *p* = 0.309
Lateral wall CW >878 mmHg%		5.70 (2.18–14.90), *p* <0.001	4.09 (1.44–11.62), *p* = 0.008
Septal WW >181 mmHg%			7.37 (2.64–20.63), *p* <0.001

FIGURE 3
Predicting reverse remodeling after CRT. Model χ^2 values are presented for a series of nested models. The baseline model included non-ischemic etiology and left ventricular end-diastolic volume (LVEDV).

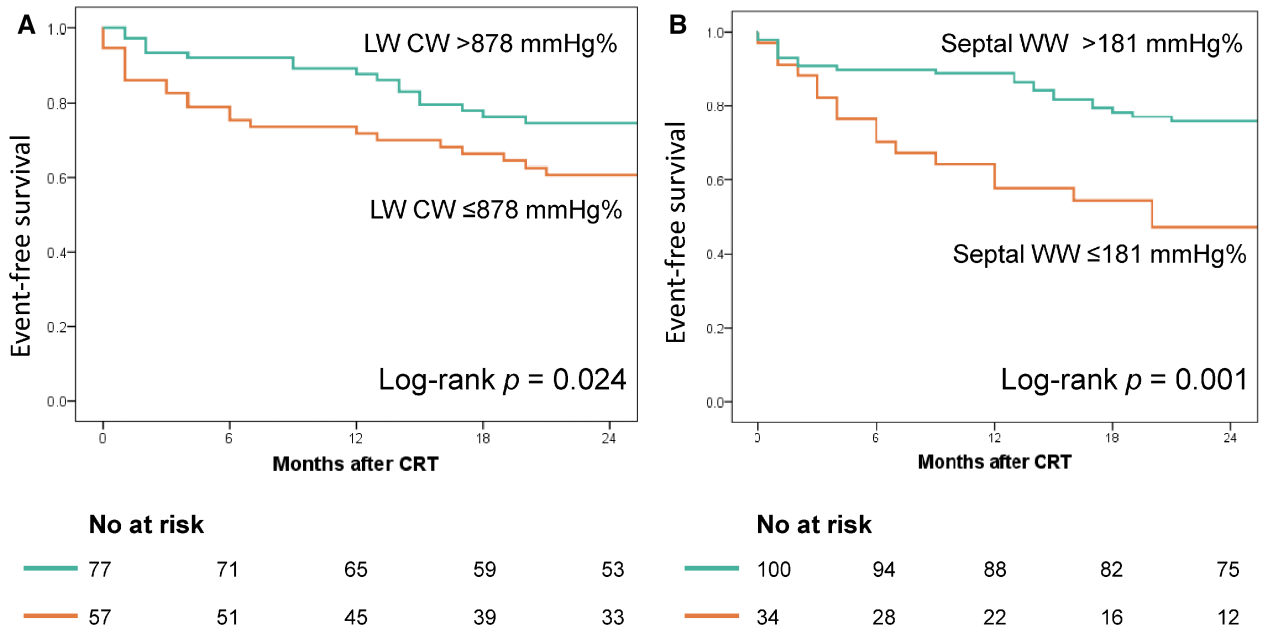


FIGURE 4
Association of lateral wall (LW) CW and septal WW with event-free survival. The Kaplan–Meier curves were stratified based on the cut-off values for LW CW (878 mmHg%, Panel **A**) and septal WW (181 mmHg%, Panel **B**).

outcomes in terms of combined all-cause death and HF hospitalization. Conversely, individuals in the "neither" group, characterized by neither LW CW >878 mmHg% nor septal WW >181 mmHg %, exhibited the worst outcomes. Patients in the "either" group, with only one parameter meeting the criteria, were positioned between the "both" and "neither" groups in terms of their outcomes.

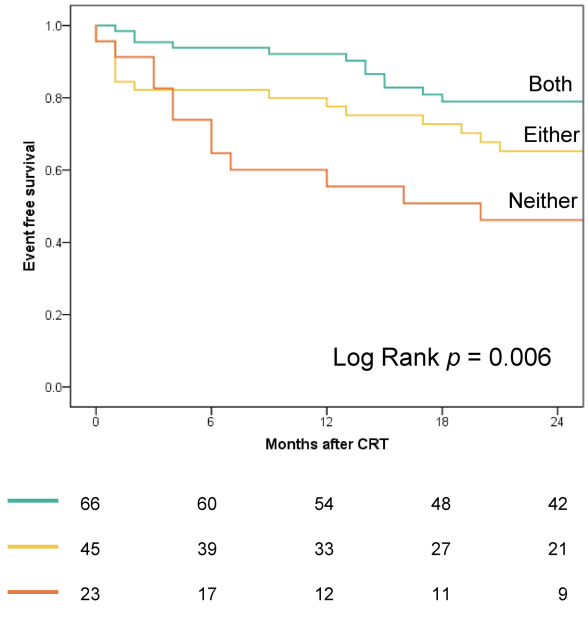


FIGURE 5
Kaplan–Meier curves, stratified by combined LW CW and septal WW parameters, depict outcomes for combined all-cause death and heart failure hospitalization. "Both" group: LW CW >878 mmHg% and septal WW >181 mmHg; "Either" group: LW CW >878 mmHg% or septal WW >181 mmHg (but not both); "Neither" group: Neither CW >878 mmHg% nor septal WW >181 mmHg.

Alternative approaches

Septal flash, apical rocking, and LBBB strain pattern predicted reverse remodeling with AUC values of 0.729 (95% CI: 0.632–0.826), 0.732 (95% CI: 0.633–0.832), and 0.753 (95% CI: 0.659–0.847), respectively (Table 4). There were no significant differences when comparing the AUC for work difference (0.780; 95% CI: 0.698–0.863) with septal flash ($p = 0.291$) or apical rocking ($p = 0.386$). In contrast, the combination of LW CW and septal WW (AUC: 0.832; 95% CI: 0.755–0.908) was superior to septal flash ($p = 0.029$) and apical rocking ($p = 0.035$) in predicting reverse remodeling. Furthermore, in multivariate logistic regression analysis, combining LW CW and septal WW (odds ratio 1.23; 95% CI: 1.02–1.49) but not work difference (odds ratio 0.90; 95% CI: 0.72–1.13) was an independent factor associated with reverse remodeling (Table 5).

Signs of mechanical dyssynchrony and LW CW & septal WW

Patients with septal flash exhibited significantly elevated LW CW values (1,113 ± 459 mmHg% vs. 848 ± 517 mmHg%, $p < 0.001$) and septal WW values (486 ± 271 mmHg% vs. 245 ± 225 mmHg%, $p = 0.003$) compared to those without this characteristic. Similarly, patients with apical rocking displayed notably higher LW CW

TABLE 4 Comparison of the area under the curves for predicting reverse remodeling after CRT.

		Compared with work difference		Compared with lateral CW + 1.5 × septal WW	
	AUC (95% CI)	Difference in AUC (95% CI)	*p*-value	Difference in AUC (95% CI)	*p*-value
Septal flash	0.729 (0.632–0.826)	0.051 (−0.044 to 0.146)	0.291	0.102 (0.011 to 0.194)	0.029
Apical rocking	0.732 (0.633–0.832)	0.048 (−0.060 to 0.156)	0.386	0.099 (0.007 to 0.191)	0.035
LBBB strain pattern	0.753 (0.659–0.847)	0.027 (−0.060 to 0.115)	0.541	0.079 (−0.008 to 0.165)	0.075
Work difference	0.780 (0.698–0.863)	—		0.051 (−0.006 to 0.108)	0.077
LW CW + 1.5 × septal WW	0.832 (0.755–0.908)	—		—	

LW, lateral wall; CW, constructive work; WW, wasted work.

TABLE 5 Multivariate logistic regressiona analysis with LV reverse remodeling as dependent variable.

Regression variable	OR	95% CI	*p*-value
LV end-diastolic volume per 10-ml increase	0.93	0.86–1.01	0.067
Non-ischemic etiology	3.88	1.30–11.59	0.015
Septal flash	1.76	0.56–5.55	0.337
Apical rocking	2.42	0.70–8.35	0.161
LBBB strain pattern	3.66	1.05–12.79	0.042
Work difference, per 100-mmHg% increase	0.90	0.72–1.13	0.364
LW CW + 1.5 × septal WW, per 100-mmHg% increase	1.23	1.02–1.49	0.033

CI, confidence interval; CW, constructive work; LW, lateral wall; OR, odds ratio; WW, wasted work.
$N = 134$, Cox and Snell $R^2 = 0.415$.

values (1,095 ± 459 mmHg% vs. 846 ± 537 mmHg%, $p < 0.001$) and septal WW values (488 ± 275 mmHg% vs. 193 ± 149 mmHg%, $p = 0.008$) than those without.

Non-ischemic and ischemic patient subgroups

There were no significant differences in LW CW (1,057 ± 471 mmHg% vs. 975 ± 527 mmHg%; $p = 0.353$) and septal WW (438 ± 278 mmHg% vs. 355 ± 280 mmHg%; $p = 0.098$) between non-ischemic and ischemic patients. In patients with non-ischemic etiology, LW CW and septal WW were correlated with the reductions in LV ESV and had high AUC values (LW CW: 0.827, 95% CI: 0.693–0.961; septal WW: 0.761, 95% CI: 0.627–0.896; Supplementary Table S3). Including both LW CW and septal WW in the model increased the AUC to 0.875 (95% CI: 0.753–0.998). In patients with ischemic etiology, LW CW rather than septal WW was correlated with reductions in LV ESV. LW CW (AUC: 0.749; 95% CI: 0.617–0.892) and septal WW (AUC: 0.704; 95% CI: 0.559–0.848) varied between responders and non-responders. Including both LW CW and septal WW in the model increased the AUC to 0.771 (95% CI: 0.642–0.901).

Inter- and intra-observer variability and reproducibility

Calculations of LW CW and septal WW in 20 patients by two independent observers differed on average by 109 mmHg% and 74 mmHg%, respectively. Repeat calculations these measures by the same observer differed on average by 95 mmHg% and 57 mmHg%, respectively. The intraclass correlation coefficient between the two observers was 0.96 (95% CI: 0.89–0.98) and 0.97 (95% CI: 0.92–0.99) for LW CW and septal WW, respectively. The intra-observer intraclass correlation coefficient was 0.98 (95% CI: 0.95–0.99) and 0.97 (95% CI: 0.94–0.99) for LW CW and septal WW, indicating good reproducibility.

Discussion

This study extends prior researches on myocardial work and presents the novel finding that the assessment of regional CW and WW via non-invasive pressure–strain loops can offer valuable prognostic insights for individuals who were being considered for CRT. Prior to CRT, LW CW and septal WW were significantly correlated with the reductions in LV ESV after CRT and independently predicted reverse remodeling and clinical outcomes after CRT. Global CW and WW were similarly correlated with the extent of reverse remodeling; however, they did not independently predict reverse remodeling when LW CW and septal WW were taken into account. The latter two measures were useful for predicting CRT response among both ischemic and non-ischemic patients.

The rationale for using LW CW and septal WW to predict CRT outcomes is that electrical conduction delay in the failing heart provokes discoordinate contraction between the early-activated septum and the late-activated LW. In patients with HF and LBBB, the ventricular septum contracts early during the isovolumic contraction phase, and during ejection, the out-of-phase septal relaxation counteracts LV free wall contraction. Regional CW quantifies the work performed during systolic shortening and negative work while lengthening during isovolumic relaxation, and reflects the contractile reserve. Regional WW computes the amount of negative work performed while lengthening during systole and work performed while shortening during isovolumic relaxation, and reflects energy waste caused by mechanical dyssynchrony. CRT can recruit myocardial work that is internally wasted by discoordinate contraction, and assessing the LW CW and septal WW facilitates identification of the contractile reserve and recruitable substrate that are amenable to CRT.

Previous studies have shown the prognostic value of global CW and WW in CRT candidates (12–15). In a study of 97 patients undergoing CRT, global CW was associated with CRT response and was significantly correlated with the reductions in LV ESV after CRT (12). Despite higher values of LW CW and septal

WW in responders, neither measure was independently associated with CRT response after adjusting for global CW and septal flash (12). Two studies have shown the ability of global WW to predict response to CRT (14, 15). One study found that combining global CW greater than 1,057 mmHg% and global WW greater than 364 mmHg% had a high specificity but low sensitivity for predicting CRT response (14). Another study involving 249 patients with HF found that a pre-CRT GWW of less than 200 mmHg% was associated with a high risk of all-cause mortality and CRT non-response (15). In our study, higher values of global CW and WW before CRT were associated with CRT response. Of the regional CW and WW values, LW CW and septal WW best distinguished CRT responders from non-responders. LW CW and septal WW performed better than global CW and global WW, respectively, with respect to reverse remodeling. This finding differs from the aforementioned study by Galli et al. (12). One possible reason for this discrepancy is that global measures of CW and WW, derived from the average of all segments, may lose significant information that is embedded in the nonhomogeneous distribution of regional CW and WW in CRT candidates. Our results agree with the results of two other studies that separately showed the prognostic value of LW CW or septal WW in patients undergoing CRT (16, 19). In a brief report on 168 CRT candidates, LW CW rather than septal WW was independently associated with CRT response, and a LW CW >881 mmHg% was associated with a 2.2-fold increase in CRT response odds (16). In a small study of 21 patients receiving CRT, septal WW rather than global WW was the only myocardial work factor that predicted LV ESV reductions after CRT (19). However, the definition of septal WW, negative work in percentage of positive work, differs from ours (19).

In the present study, we found that septal WW was less related to reverse remodeling after CRT in patients with ischemic cardiomyopathy. Distinguishing between systolic lengthening of the septum due to transmural scar and septal systolic stretching resulting from LBBB, presents a challenge. Consequently, the similarity in septal WW between patients with myocardial scar and patients with electrical conduction delay may account for the weaker association of septal WW with reverse remodeling after CRT in patients with ischemic cardiomyopathy. The considerable variability in the extent of septal WW among patients with LBBB likely reflects, at least in part, this mixed etiology of systolic lengthening.

The use in clinical practice of myocardial work assessment derived from non-invasive pressure–strain loops for prognostic and clinical decision-making purposes is increasing (17, 20–26). The reliability of non-invasive measures of myocardial work in comparison to invasive measures has been validated in experimental evaluations and computer simulations (18, 27). In the present study, the combined approach of LW CW and septal WW offers a clinically feasible and relatively simple method for identifying CRT responders. Both parameters were measured from the basal- and mid-segments of the LW and septum in the apical four-chamber view, which can be obtained for all patients. Evaluating LW CW and septal WW incorporates the assessment of contractile reserve and energy waste, which are key factors determining the response to CRT.

Limitations

This study has some limitations. Firstly, it is a single-center study, which may limit the generalization of its findings to clinical practice. Secondly, the lack of a validation cohort to examine the results further limits its generalizability. Thirdly, to assess myocardial work, a vendor-specific module (EchoPAC, GE) that combines LV strain data with a non-invasive LV pressure curve is required. Lastly, the study did not evaluate septal viability, and it is unclear whether it provides additional valve over septal WW and LW CW. Further study may be needed to address this issue.

Conclusion

This study revealed that LW CW and septal WW before CRT, assessed based on pressure–strain loops, predicted reverse remodeling and clinical outcomes after CRT. These two measurements reliably identified potential CRT responders in both ischemic and non-ischemic patients, and may better identifying CRT responders than the work difference between septum and LW.

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 Chang Gung Medical Foundation Institutional Review Board. 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

CL-W: Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal Analysis, Conceptualization. L-SW: Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. C-TW: Writing – review & editing, Methodology, Data curation. Y-HY: Writing – review & editing, Methodology, Data curation. Y-WC: Writing – review & editing, Methodology, Data curation. K-CY: Writing – review & editing, Methodology, Data curation. Y-HC: Writing – review & editing. CC: Writing – review & editing. C-TK: Writing – review & editing. P-HC: 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2024.1301140/full#supplementary-material

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Case Report: Pulsed field ablation for epicardial right-sided accessory pathway

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We present a case of a 32-year-old male with a history of palpitations and preexcitation on ECG who underwent altogether four failed catheter ablations using different approaches in the two other electrophysiology centers within two years. ECG showed overt preexcitation with a positive delta wave in lead I and negative in leads V1–V3, suggesting a right free wall accessory pathway. During the electrophysiological study, the accessory pathway was localized on the free lateral wall. However, the electrograms and mapping during atrial and ventricular pacing suggested the presence of true epicardial accessory pathway. Repeated radiofrequency energy delivery with the support of the steerable sheath and excellent contact (as assessed by intracardiac echocardiography) at the earliest ventricular activation was not successful. Therefore, the Farawave catheter (Boston Scientific, Inc) was used, and a flower configuration with the intention to cover the entire atrial attachment of the pathway during ventricular pacing was selected. Application of pulsed field resulted in interruption of accessory pathway conduction. An electrophysiological study one year later confirmed the persistent effect of ablation. This case illustrates the potential utility of pulsed field energy for the ablation of atrial insertion of the accessory pathway with an epicardial course. Such an approach can avoid epicardial mapping and access and may improve the safety of the procedure.

KEYWORDS

accessory pathway, radiofrequency ablation, pulsed field ablation, intracardiac echocardiography, electroanatomical mapping

Introduction

Accessory pathway ablation is highly successful in experienced centers, making it the therapy of choice for patients with Wolff-Parkinson-White syndrome (1). Some rare failures are attributed to anatomically unusual pathways or their epicardial locations (2–6). Epicardial accessory pathways are often located in the posterior septal space, connecting via muscular bands around the coronary sinus or its tributaries. Rarely, the pathway connects the right atrial appendage with the right ventricle or is located lower on the tricuspid annulus lateral side (7–11). Catheter ablation of these pathways may be challenging.

Case description

A 32-year-old male with a history of palpitations and preexcitation on ECG underwent altogether four failed catheter ablations in the two other electrophysiology centers between

2020 and 2022. Different strategies were used, including access to the right atrium via jugular vein. The patient was implanted with an implantable loop recorder (Biomonitor, Biotronik), which showed multiple episodes of orthodromic AV re-entrant tachycardia. Over time, arrhythmias became more frequent, and the patient was referred for a re-ablation to our center.

His physical examination was normal. ECG showed overt preexcitation with a positive delta wave in lead I and negative in leads V1–V3, suggesting a right free wall accessory pathway (Figure 1A). Echocardiography revealed a non-dilated left ventricle with a normal ejection fraction and borderline thickness of the interventricular septum (11 mm). Besides a trivial tricuspid regurgitation, no valvular heart disease was observed, and no signs of pulmonary hypertension were present.

Diagnostic assessment and therapeutic intervention

An electrophysiology study was performed under conscious sedation. Both femoral veins were used to introduce diagnostic catheters into the coronary sinus, the His bundle region, and the right ventricle or atrium. Finally, an intracardiac echocardiography probe (Acuson AcuNav 10F, Siemens Medical Solutions) was introduced to the right atrium to monitor the ablation catheter location and tissue contact. The electroanatomical mapping system (CARTO 3, Biosense Webster, Inc) was employed to support the procedure. Point-by-point mapping with 4 mm tip was used (Thermocool catheter, Biosense Webster).

During sinus rhythm, the PQ interval was 108 ms, AH interval 76 ms, and HV interval 22 ms; the antegrade and retrograde refractory periods of the accessory pathway were 375 ms and 344 ms, respectively. An orthodromic AV reentry with cycle length of (CL) 400 ms could be readily induced. The procedure was complicated by episodes of atrial fibrillation that were easily inducible by catheter manipulation and that required electrical cardioversion. Rapid mapping around the tricuspid annulus confirmed the lateral location of the pathway. However, in the position of the earliest ventricular activation (−29 ms) during atrial pacing, the AV interval was not very short, and no electrograms of interest could be recorded (Figure 2A). Mapping below the tricuspid valve revealed a relatively large area of early activation. Ablation at the site the earliest ventricular activation (35 W/30 ml/min, 60 s) had no effect. During ventricular pacing, the earliest atrial activation was localized remotely from the tricuspid annulus (15 mm), suggesting true epicardial accessory pathway (Figure 2B). Repeated radiofrequency energy delivery with the support of the steerable sheath and excellent contact (as assessed by intracardiac echocardiography) at this spot was not successful (30–35 W/15 ml/min, up to 90 s). Therefore, the decision to change ablation strategy was made. The Farawave catheter (Boston Scientific, Inc) was used, and a flower configuration with the intention to cover the entire atrial attachment of the pathway was selected (Figures 3A,B). Application of pulsed field resulted in immediate interruption of accessory pathway conduction (Figure 1B). However, the conduction recurred repeatedly within minutes. After 14 deliveries, the effect persisted for thirty minutes. Subsequent electrophysiology study showed 1:1 conduction through the AV node up to 150 beats per minute (400 ms). Adenosine administration resulted in a transient AV block without accessory pathway conduction. No ST segment elevations or other complications were noted.

The next day, the preexcitation pattern transiently reappeared on ECG. However, during subsequent follow-up, the patient had normal ECG without preexcitation and no arrhythmic events. The effect persists for more than one year. In December 2023, the patient underwent repeated EP study for short episodes of palpitations and documented short runs of supraventricular tachycardia on the implantable monitor. No preexcitation was documented as well as no retrograde conduction. Adenosine administration resulted in a transient complete AV block. No arrhythmia was inducible by programmed atrial or ventricular stimulation, including isoprenaline administration.

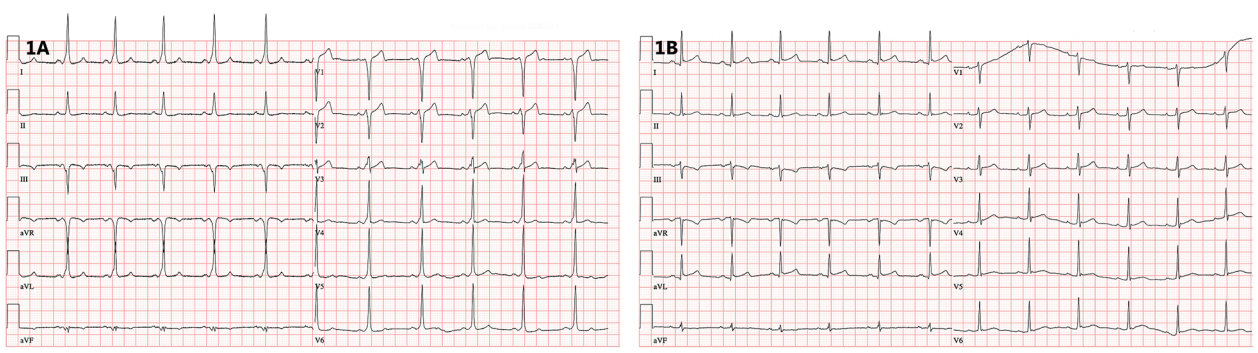

FIGURE 1
(A) 12-lead ECG showing ventricular preexcitation with a negative delta wave in the right precordial leads. (B) 12-lead ECG after successful catheter ablation documenting loss of preexcitation (recorded at 25 mm/s).

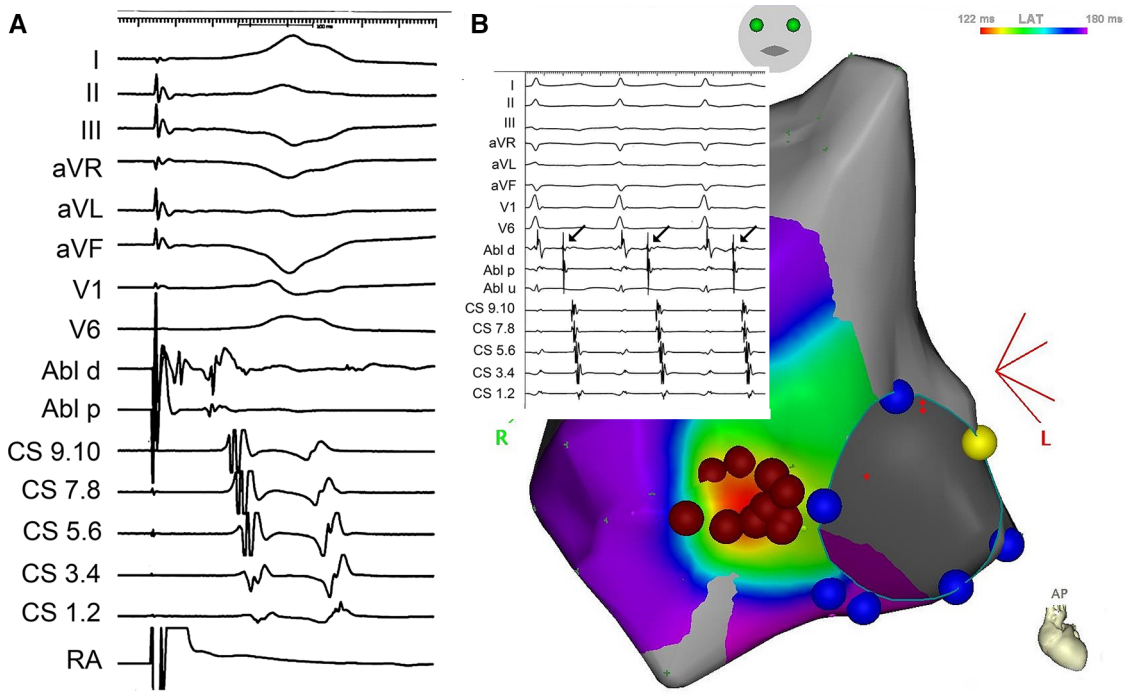

FIGURE 2
(A) Local signals from the ablation catheter (ABLd and ABLp) at the site of the earliest ventricular activation during pacing in the right atrium (RA). Upper part shows surface ECG leads, lower part signals from the coronary sinus). (B) Electroanatomical activation map of the right atrium during right ventricular pacing, documenting the earliest activation remotely from the tricuspid annulus (red dots mark radiofrequency ablation cloud with the central tag removed to depict early activation). Inset depicts local electrogram at the tricuspid annulus during orthodromic AV reentry.

Discussion

Our case illustrates that pulsed field ablation could be used even in rare cases of epicardially located accessory pathways. To the best of our knowledge, this is the first documented case of epicardial accessory pathway ablation using pulsed field energy. After ineffective radiofrequency ablation at the area of atrial insertion of the pathway, the Farawave catheter was used in the flower configuration, placed across this region, and repeated pulsed field energy delivery interrupted accessory pathway conduction.

Right-sided accessory pathways with epicardial course are considered resistant to conventional ablation (6–9). Some groups described the value of electroanatomic mapping to accurately localize the atrial insertion sites of these accessory pathways and facilitate catheter ablation (9, 10). Chen et al, reported on a series of eleven patients mapped with electroanatomic mapping system and successfully ablated after previously failed one or more procedures. Atrial insertion was separated from the tricuspid annulus by an average of 14.3 ± 3.9 mm, and the local activation time was 27.8 ± 17.0 ms earlier than that of the corresponding annular point. Radiofrequency ablation at the site of the earliest atrial activation was successful. Another strategy of electroanatomic mapping was described by Fishberger et al. (11), in which a microcatheter was placed in the right coronary artery as a roadmap to facilitate the quick and accurate location of the accessory pathway.

Regarding the strategy of catheter ablation, one option could be cryoablation, which also solves the problem of catheter instability because of catheter adherence (12). Bipolar radiofrequency ablation may be effective and safe in cases of posteroseptal accessory pathways potentially of epicardial location, which are resistant to conventional unipolar radiofrequency ablation from endo- and epicardium (13). Other groups suggested percutaneous epicardial mapping and ablation (14, 15). Alternative approaches, such as a superior venous access/approach and/or reverse loop within the right ventricular inflow, were already used in previous ablation attempts. We discussed with the patient the possibility of epicardial mapping and ablation against the attempt with pulsed field energy. The patient preferred the latter solution. Regarding the selection of a pulsed field delivery tool, we believed that the use of a large footprint catheter to ablate the entire area of atrial insertion of the pathway would be preferable to the use of a solid tip catheter. These were the only available options available to us at that time. Having a fair experience with the Farapulse system both for ablation of atrial fibrillation and typical atrial flutter (several hundred cases at the time of this procedure) with an excellent safety profile, we considered this approach as reasonable option. Especially, taking into account four previous failed ablation procedures. The choice likely worked, blocking area of atrial tissue that serves as an entrance to the accessory pathway rather than hitting epicardial fibers itself. In our previous experience with a few similar cases, we achieved exclusion of the atrial insertion area by circumferential radiofrequency ablation around the earliest atrial activation during ventricular pacing. Interestingly, it appears that pulsed

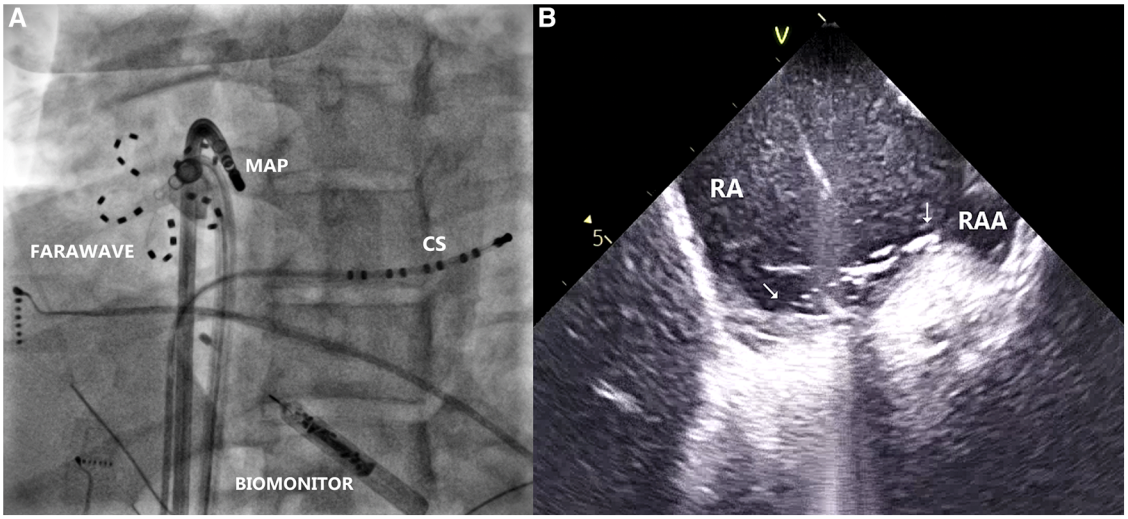

FIGURE 3
(A) Radiogram in left anterior oblique projection, showing farawave catheter at the site of the earliest atrial activation during ventricular pacing, parallel to mapping catheter (MAP). Decapolar catheter is introduced in the coronary sinus (CS). Biomonitor is visible in lower part of the image. (B) Intracardiac echocardiogram depicting location of the Farawave catheter and its contact with the tissue at the ablation site (arrows). RA, right atrium; RAA, right atrial appendage.

field energy may need some time to achieve lesion maturation since the conduction through the pathway transiently reappeared the next day after ablation.

In conclusion, this case illustrates the potential utility of pulsed field energy for the ablation of atrial insertion of the accessory pathway with an epicardial course. This approach can avoid epicardial mapping and access and may improve the safety of the procedure.

Patient perspective

From a patient's point of view, the described solution was accepted against the alternative of epicardial mapping and ablation. More than one year after the procedure, the patient has no complaints, and his ECG remains without preexcitation.

Data availability statement

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

Ethics statement

Ethical approval was not required for the studies involving humans because this is a case report. The patient provided an informed consent for the procedure to the hospital and also for a publication of this case. 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. 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

JH: Writing – original draft, Investigation. PP: Writing – review & editing, Investigation, Visualization. EB: Writing – review & editing, Investigation. JK: Writing – review & editing, Conceptualization, Investigation, Visualization.

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Conflict of interest

JK reports personal fees from Biosense Webster, Boston Scientific, GE Healthcare, Medtronic, and St. Jude Medical (Abbott) for participation in scientific advisory boards, and has received speaker honoraria from Biosense Webster, Biotronik, Boston Scientific, Medtronic, St. Jude Medical (Abbott). PP has

received speaker honoraria from St Jude Medical (Abbott) and has served as a consultant for Biotronik and Boston Scientific.

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.2024.1392264/full#supplementary-material

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Case Report: Lacosamide unmasking *SCN5A*-associated Brugada syndrome in a young female with epilepsy

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Background: Lacosamide is frequently used as a mono- or adjunctive therapy for the treatment of adults with epilepsy. Although lacosamide is known to act on both neuronal and cardiac sodium channels, potentially leading to cardiac arrhythmias, including Brugada syndrome (BrS), its adverse effects in individuals with genetic susceptibility are less understood.
Case: We report a 33-year-old female with underlying epilepsy who presented to the emergency department with a four-day history of seizure clusters, and was initially treated with lacosamide therapy. During the intravenous lacosamide infusion, the patient developed sudden cardiac arrest caused by ventricular arrhythmias necessitating resuscitation. Of note, the patient had a family history of sudden cardiac death. Workup including routine laboratory results, 12-lead electrocardiogram (ECG), echocardiogram, and coronary angiogram was non-specific. However, a characteristic type 1 Brugada ECG pattern was identified by ajmaline provocation testing; thus, confirming the diagnosis of BrS. Subsequently, the genotypic diagnosis was confirmed by Sanger sequencing, which revealed a heterozygous mutation (c.2893C>T, p.Arg965Cys) in the *SCN5A* gene. Eventually, the patient underwent implantable cardioverter-defibrillator implantation and was discharged with full neurological recovery.
Conclusion: This case highlights a rare but lethal adverse event associated with lacosamide treatment in patients with genetic susceptibility. Further research is warranted to investigate the interactions between lacosamide and *SCN5A* variants.

KEYWORDS

arrhythmia, Brugada syndrome, epilepsy, lacosamide, *SCN5A*, seizure

1 Introduction

Lacosamide is a third-generation anti-seizure medication (ASM) characterized by enhancing slow-inactivated state of neuronal voltage-gated sodium channels (1). It is commonly used in adult patients for the treatment of seizure emergencies, such as status epilepticus or seizure clusters, because of its favorable safety profile, tolerability,

Abbreviations
ASM, anti-seizure medication; BrS, Brugada syndrome; ECG, electrocardiogram; ED, emergency department; EEG, electroencephalogram; ICU, intensive care unit; IV, intravenous; V-A ECMO, venoarterial extracorporeal membrane oxygenation; VF, ventricular fibrillation; VT, ventricular tachycardia.

and feasibility with intravenous (IV) administration (2, 3). Lacosamide also acts on cardiac sodium channels, which can potentially trigger cardiac arrhythmias, especially in patients who already have a predisposition, whether it be genetic, such as patients with Brugada syndrome (BrS), or of another type (4).

BrS is an inherited cardiac channelopathy associated with malignant arrhythmias and sudden cardiac death in young adults with structurally normal hearts, and is particularly prevalent in Asian populations (5). Notably, BrS is more commonly diagnosed in middle-aged males, typically at around 40 years of age. The incidence of BrS varies among different populations, showing marked genetic heterogeneity and geographical differences (6–8). Prior studies have estimated the prevalence of BrS at 12/10,000 in Southeast Asia, with a much lower rate of ~5/10,000 in Western countries (9–10). The diagnostic hallmark of BrS is the presence of a type 1 Brugada electrocardiogram (ECG) pattern, which exhibits coved ST-segment elevation, followed by a negative T wave in the right precordial leads V1–V3. This specific ECG finding can occur spontaneously or be provoked by a drug provocation test using sodium channel blockers, such as ajmaline (5). Although BrS can be inherited in an autosomal dominant pattern, patients may present with diverse phenotypes owing to incomplete penetrance and variable expression, leading to diagnostic challenges (5).

Here, we report a unique case of a young lady with epilepsy who was resuscitated from sudden cardiac arrest during lacosamide therapy due to refractory ventricular arrhythmias, and was subsequently diagnosed as *SCN5A*-associated BrS.

2 Case presentation

A 33-year-old Indonesian woman, who worked as a live-in caretaker in Taiwan, initially presented to the neurological outpatient department with recurrent episodes of syncope with an upward eye deviation, which had been noticed over a period of two years. The routine awake electroencephalogram (EEG) revealed focal epileptiform discharges over the left temporal region (Supplementary Figure S1), suggesting epileptic seizure. No intracranial abnormalities were detected on the brain magnetic resonance imaging, and there were no abnormal laboratory findings. Initially, she was prescribed levetiracetam at a dose of 500 mg twice daily, but later switched to oxcarbazepine 300 mg twice daily due to intolerable dizziness. After ASM adjustment, she remained seizure-free for the following one year. However, she reported poor adherence to oxcarbazepine over the past one month due to financial issues. Three days before admission, she presented to another hospital with a head injury attributed to an unwitnessed fall at home. She was initially found unconscious on the ground by her employer, but regained consciousness upon arrival at the hospital. A head computed tomography scan revealed no abnormalities, and she was discharged. However, in the following hours, she experienced frequent episodes of sudden loss of consciousness, followed by bilateral hand twitching lasting for a few minutes, occasionally witnessed by her employer. Although she regained consciousness within five minutes, she had difficulty recalling the details of these events. Due to an increase in the frequency of episodic unconsciousness to six times a day, she was brought to our emergency department (ED) for medical attention.

Upon arrival at the ED, the patient was observed to have clonic movements in both hands, accompanied by upward gazing and impaired consciousness, lasting approximately two minutes. However, before receiving an IV push of lorazepam (2 mg) as prescribed by the ED physician, she gradually regained consciousness, albeit experiencing mild dizziness. In response to the suspicion of convulsive status epilepticus, IV treatment of ASM was initiated. A single IV loading dose of lacosamide (200 mg) was administered in 100 ml of normal saline, infused at a rate of 200 ml/h over 30 min. The ECG recorded on ED admission before lacosamide treatment was unremarkable. However, during the IV infusion of half the loading dose of lacosamide, the patient was found to be cyanotic and pulseless. As such, lacosamide was immediately discontinued due to concerns about its adverse cardiovascular effects. Cardiopulmonary resuscitation was initiated, with initial rhythm exhibiting ventricular fibrillation (VF) (Figure 1A). After two rounds of cardiac defibrillations, a transient return of spontaneous circulation was achieved. However, the cardiac rhythm of the patient degenerated into polymorphic ventricular tachycardia (VT) (Figure 1B), requiring further cardiac defibrillations. Venoarterial extracorporeal membrane oxygenation (V-A ECMO) was established as hemodynamic support. Concurrently, myoclonic jerks involving the left limbs with the head turning to the right were noted. Therefore, IV levetiracetam was administered for suspected focal motor seizures. Anti-arrhythmic drugs such as amiodarone, lidocaine and esmolol, in addition to deep sedation and magnesium sulfate were subsequently administered. Emergent coronary angiography revealed patent coronary arteries. Nevertheless, during the procedure, VT/VF persisted, despite repeated defibrillations. Therefore, a temporary transvenous pacemaker was placed for overdrive pacing.

After transfer to the intensive care unit (ICU), the ventricular arrhythmias disappeared, and her hemodynamic parameters gradually stabilized. A comprehensive workup, including electrolytes, thyroid function, drug screening of blood and urine, as well as transthoracic echocardiography, was unremarkable. The testing of lacosamide plasma concentrations was not available at our hospital. Continuous EEG monitoring in the ICU after discontinuing sedative agents revealed focal interictal epileptiform discharges in the left frontal region, leading to the diagnosis of focal impaired awareness motor seizure. Afterwards, the patient regained consciousness at baseline level, and was weaned off the V-A ECMO on the fourth day of admission. Notably, although there was no positive family history of epilepsy, the patient reported that three relatives had experienced sudden cardiac death before the age of 40 years; hence, BrS was suspected. After tapering the overdrive pacing, repeat ECGs showed saddleback ST segment elevation in precordial leads V1–V3, suggestive a Brugada type 2 pattern (Figure 2A). Following this finding, an ajmaline drug provocation test was performed in the ICU. Serial ECGs showed a typical Brugada type 1 ECG

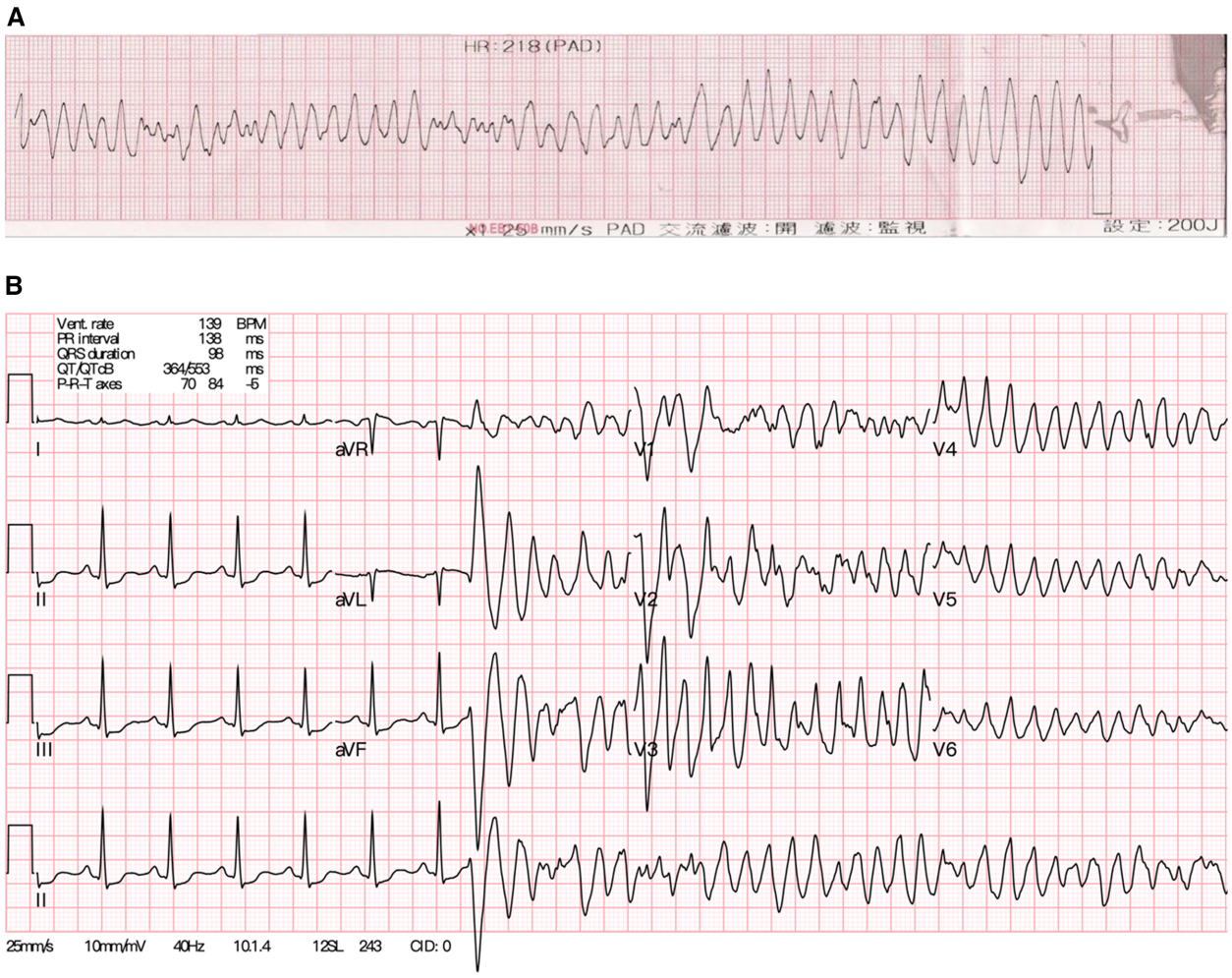

FIGURE 1
(A) The electrocardiogram of the young female patient showing ventricular fibrillation during resuscitation initially. (B) After achieving recovery of spontaneous circulation, the sinus rhythm soon degenerated into polymorphic ventricular tachycardia again.

pattern in the pericardial standard and high intercostal leads (Figure 2B), thus confirming the diagnosis of BrS in this young female patient. Subsequently, the patient underwent implantable cardioverter-defibrillator implantation and was discharged with full neurological recovery. Since the patient was a migrant worker, she was referred back to Indonesia for further medical care.

3 Analysis of genetic variants

Because of the significant family history of sudden death in this young adult and refractory ventricular arrhythmias following the use of sodium blocker, genetic variants in *SCN5A*, the most common gene associated with BrS, were screened by Sanger sequencing. Eventually, a heterozygous missense variant NM_198056.3: c.2893C>T (p. R965C) in exon 17 of *SCN5A* gene was identified (Supplementary Figure S2). The detected variant was previously described in ClinVar (variation ID: 67763). While *SCN5A* p.R965C variant is rare (minor allele frequency = 0.00001) in the general population database (gnomAD-ALL), its frequency is relatively higher in Asian populations, particularly enriched in the Thai population (0.00188), possibly as a result of the funder effect (11, 12). Its deleterious effect as predicted by silico predictions, conservation analysis and published functional studies (13). This variant was thus classified as likely pathogenic, according to the following American College of Medical Genetics and Genomics (ACMG) criteria (14): PS3, PP2, PP3, and BS1. Consequently, the patient was diagnosed with *SCN5A* mutation associated with BrS and epilepsy.

4 Discussion

We report a unique case of lacosamide unmasking *SCN5A*-associated BrS in a young Indonesian female with epilepsy. Mutations in *SCN5A*, which encodes for the alpha subunit of the cardiac voltage-gated sodium channel (Nav1.5), are the predominant genotype in BrS, accounting for 80% of all

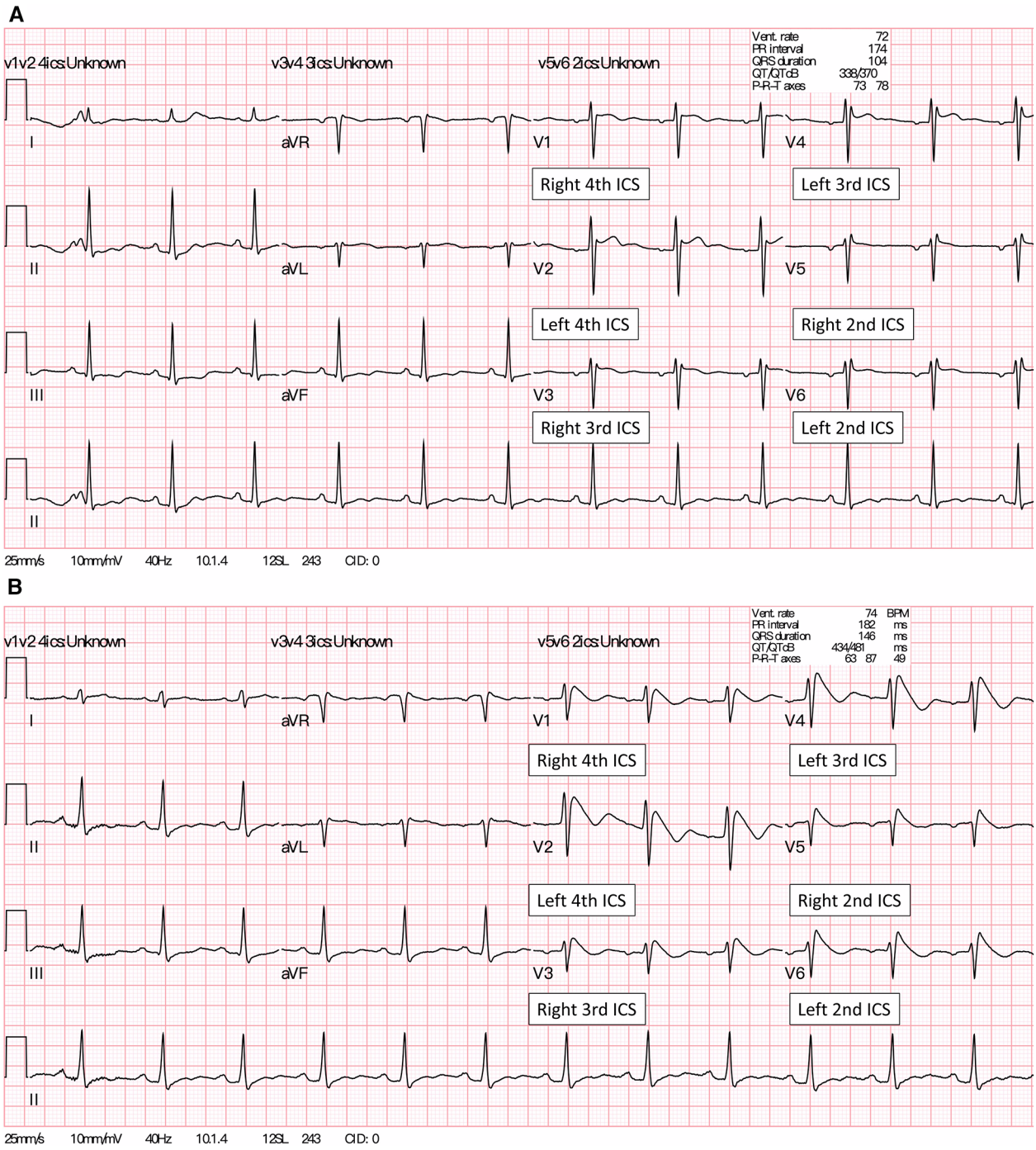

FIGURE 2
(A) A baseline 12-lead ECG of the patient showed a Brugada type 2 pattern (saddleback ST-segment elevation) in the precordial leads V1 placed at 4th ICS and lead V2 placed at 4th ICS. (B) About four minutes after the IV ajmaline injection, a Brugada type 1 pattern (coved-type ST-segment elevation) appeared in all precordial and high intercostal leads (V3-V6). Of note, lead V3 at the right 3rd ICS and lead V4 were placed at the left 3rd ICS, whereas lead V5 at right 2nd ICS and lead V6 were placed at the left 2nd ICS, respectively. ICS, intercostal space.

genotype-positive patients (15). In addition to the cardiac sodium channel, *SCN5A* is expressed on neuronal sodium channels in mouse and human brains (16). The dysfunction of *SCN5A* has been associated with epileptic seizure and increased risk of sudden unexpected death in epilepsy (17). Although several studies have identified the *SCN5A* mutation in patients with epilepsy co-existing with cardiac arrhythmias (18, 19), the c.2893C>T (p. R965C) mutation in *SCN5A* has not been reported in patients with seizure disorders.

In our case, it can be challenging to differentiate between seizure-like syncope and convulsive syncope secondary to inherited cardiac arrhythmias at the beginning of diagnosis,

particularly if in the absence of EEG recording. Nevertheless, the diagnosis of focal impaired awareness seizure before the occurrence of lacosamide-related arrhythmia was confirmed in our patient based on the focal interictal epileptiform discharges recorded on the initial EEG, as well as a good response to ASM. Furthermore, the presence of focal epileptogenicity was also noticed on the continuous EEG monitoring after the patient experienced refractory ventricular tachyarrhythmias triggered by lacosamide. Therefore, the diagnosis of epileptic seizure in our patient could be ascertained. However, we did not perform continuous EEG monitoring concurrently with the ajmaline drug provocation test that triggered the Brugada type 1 pattern, so the direct impact of this variant on epilepsy phenotype was uncertain. More studies are required to analyze the genotype and phenotype of epilepsy caused by R965C mutation in *SCN5A*.

Hsueh et al. conducted an electrophysiological study of *SCN5A* p.R965C in a Taiwanese patient with BrS, demonstrating that this variant caused a loss of function in the cardiac sodium channel. This loss of function was attributed to a left shift of steady-state inactivation curve and slower recovery from inactivation of the sodium channel, resulting in a decrease in sodium current (13). When taking this study into account, *SCN5A* p.R965C variant would have been considered a deleterious mutation associated with BrS due to its alterations to channel functions. Prior studies have revealed ancestral differences in *SCN5A* p. R965C variants (11, 20). Compared to non-Asian ancestries, the allele frequency of the *SCN5A* p. R965C variant is higher in East Asian (0.00038, gnomAD) and South Asian (0.00006, gnomAD) (12, 20). Walsh et al. reported this variant as a rare non-coding enhancer variant in *SCN5A* in Thai patients with BrS (12). Although data for Indonesia populations remains uncertain, it is noteworthy that the highest frequency of this variant is observed in individuals of Thai and Malay ancestry, suggesting a significant enrichment in Southeast Asian populations (12). Taken together, our case supported the previous report and implied that the *SCN5A* p. R965C variant is not just a likely pathogenic variant but also a risk factor specifically for Asian patients with BrS (11, 12).

While the arrhythmogenic potential of lacosamide has previously been published (21), Goodnough et al. reported one case of lacosamide-induced Brugada ECG pattern. The patient was an 83-year-old man with septicemia who had previously received a six-month lacosamide treatment for a seizure disorder (4). In contrast, our young female patient presented with refractory VT/VF triggered by a single lacosamide infusion, without other concurrent triggering factors such as fever or infection. This difference may imply varying etiologies of lacosamide-induced BrS. The previous case may be attributed to acquired causes, while our patient's condition was related to inherited channelopathy. Furthermore, we had performed target genetic testing using Sanger sequencing, which increased diagnostic accuracy of inherited BrS.

Lacosamide is characterized by its stronger and faster binding to the slow-inactivated state compared to the fast-inactivated state, which may contribute to infrahisian conduction delay and QRS prolongation (1). In patients with *SCN5A* mutations, the use of lacosamide may cause the augmentation of slow inactivation of cardiac sodium channels, potentially leading to re-entrant arrhythmias and early afterdepolarizations in ventricular cardiac tissue (1, 21), which greatly increases the risk of refractory ventricular tachyarrhythmias and sudden cardiac arrest. In vitro, lacosamide has been shown to exert a concentration-dependent inhibitory effect on the peak amplitude of sodium currents in human embryonic kidney (HEK293T) cells expressing *SCN5A* (22). Nevertheless, further functional studies are warranted to explore the impact of lacosamide on *SCN5A* p.R965C variants. Interestingly, our patient receiving long-term treatment with oxcarbazepine, another sodium channel blocker, without triggering symptomatic cardiac conduction disorders, probably due to the lower serum plasma drug levels achieved by parenteral administration. However, considering the concentration-dependent inhibitory effect of lacosamide on sodium currents, a single IV loading of lacosamide may rapidly increase he serum concentration, potentially increasing the risk of VT/VF.

In conclusion, this case highlights that lacosamide can cause fatal ventricular tachyarrhythmias in patients with *SCN5A* mutation. Clinicians should be aware of these rare adverse effects when treating epileptic patients with lacosamide, particularly in Asia populations. Further research is warranted to investigate the interaction between lacosamide and *SCN5A* variants.

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

Y-CS: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. J-CW: Writing – review & editing. T-TL: Formal Analysis, Writing – review & editing. K-CC: Writing – review & editing. J-JS: Supervision, Writing – review & editing. J-MJ: Funding acquisition, Resources, 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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Tachyarrhythmias in congenital heart disease

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The prevalence of congenital heart disease (CHD) in adult patients has risen with advances in diagnostic and surgical techniques. Surgical modifications and hemodynamic changes increase the susceptibility to arrhythmias, impacting morbidity and mortality rates, with arrhythmias being the leading cause of hospitalizations and sudden deaths. Patients with CHD commonly experience both supraventricular and ventricular arrhythmias, with each CHD type associated with different arrhythmia patterns. Macroreentrant atrial tachycardias, particularly cavotricuspid isthmus-dependent flutter, are frequently reported. Ventricular arrhythmias, including monomorphic ventricular tachycardia, are prevalent, especially in patients with surgical scars. Pharmacological therapy involves antiarrhythmic and anticoagulant drugs, though data are limited with potential adverse effects. Catheter ablation is preferred, demanding meticulous procedural planning due to anatomical complexity and vascular access challenges. Combining imaging techniques with electroanatomic navigation enhances outcomes. However, risk stratification for sudden death remains challenging due to anatomical variability. This article practically reviews the most common tachyarrhythmias, treatment options, and clinical management strategies for these patients.

KEYWORDS
congenital heart disease, arrhythmias, rhythm disorders, tachycardia, sudden cardiac death

Introduction

The number of adult patients with congenital heart disease (CHD) has significantly increased in recent years, primarily due to technological advances in diagnostic and surgical techniques (1). A considerable proportion of these patients are prone to developing arrhythmias because of surgical modifications, such as suture lines and prosthetic materials like patches, as well as hemodynamic alterations arising from long-term pressure or volume overload, atrial and ventricular remodeling, and, in some cases, cyanosis. Up to 50% of patients with CHD may experience supraventricular arrhythmias (SVAs), and in certain CHDs, such as Tetralogy of Fallot (ToF), ventricular arrhythmias may occur in up to 14%, carrying a non-negligible risk of SD (2).

Arrhythmias in patients with CHD have been associated with increased morbidity and mortality, exerting a negative impact on quality of life (3). Additionally, according to the Dutch Concor registry, arrhythmias constitute the most frequent cause of hospital admission in patients with CHD, accounting for up to 31% of cases (4). For instance, in a Canadian study involving over 38,000 patients with CHD, the presence of atrial arrhythmias was associated with a 50% increased risk of mortality and a 50% increase in

morbidity in the form of stroke or heart failure (5). This worse prognosis may be more pronounced when considering populations with more complex cardiac conditions. For example, in palliative transposition of the great arteries (TGA) with atrial switch surgery, atrial arrhythmias increase the risk of mortality fivefold. Similarly, in patients undergoing Fontan surgeries, the risk increases sixfold (6). In all CHDs, the most common cause of sudden death (SD) is arrhythmic (7). Arrhythmias represent an increase of up to more than three times the risk of SD in the general population with CHD (8), with two potential mechanisms: complete atrioventricular block and ventricular arrhythmias.

In this article, the most common tachyarrhythmias, treatment options, and clinical management strategies for these patients are discussed. The information provided is mostly based on a narrative review of the literature, incorporating the authors' own experience in the subject as well.

Arrhythmia substrates in congenital heart disease

Patients with CHD can be affected by various types of arrhythmias, including intranodal reentry tachycardias, accessory pathway tachycardias, focal atrial tachycardia, macroreentrant atrial tachycardias (MRAT), atrial fibrillation (AF), ventricular tachycardia (VT), and ventricular fibrillation. MRAT are the most common arrhythmias in patients with CHD. Cavotricuspid isthmus-dependent flutter (CTI), similar to the general population, remains the most frequently reported, accounting for up to 40%–60% of these arrhythmias (2, 9).

The occurrence of each type of arrhythmia is determined by the timing and type of repair, the scars generated, and the subsequent remodeling. Therefore, each form of CHD is associated with different types of arrhythmia (1, 10) (Table 1). The Fontan procedure and physiological correction of TGA (Senning and Mustard), which involve creating suture lines and altering hemodynamics, render these patients the most predisposed to developing SVAs. This risk can reach up to 50% for patients with the classic Fontan procedure at 10 years post-surgery (11). Furthermore, these patients often have poorer hemodynamic tolerance due to limited distensibility of neo-atria, dysfunction of the single ventricle or systemic ventricle, and volume or pressure overload resulting from valve abnormalities or residual shunts.

In other CHD, pre-existing arrhythmias may be observed prior to surgical intervention. This is evident in cases such as atrioventricular connections in patients with Ebstein's anomaly and congenitally corrected transposition of the great arteries (ccTGA).

Management of arrhythmias in congenital heart disease

Arrhythmias diagnosis

The diagnosis of symptomatic arrhythmias in patients with CHD is conducted similarly to the general population. Diagnostic tools such as cumulative Holter monitoring, 2-week continuous monitors, single-lead ECG devices integrated into smartwatches and smartphones, and implantable loop recorders (ILRs) are available (12–20).

In patients presenting with syncope, the ILR and electrophysiological study play an important role. In patients with a high clinical risk profile, especially those with myocardial scar or conduction disturbances, EPS not only yields a substantial number of diagnoses but also identifies patients at lower risk of arrhythmic syncope (21–29). However, its negative predictive value has been considered to be suboptimal (around 70%) (24, 30), and in such cases, further work up might be needed. The implantation of an ILR enables prolonged cardiac monitoring, offering the possibility to correlate arrhythmic events with symptoms (17, 21, 22, 31–33). This allows for additional diagnostic yield and is considered safe (17, 21, 22, 31–33).

Screening asymptomatic patients with periodic assessments beyond 12-lead ECGs or periodic Holter monitoring is of uncertain value, as a high prevalence of asymptomatic findings has been reported that seldom impact management (12, 34). Further studies are necessary to determine whether early event detection and intervention can reduce morbidity and mortality in this patient cohort.

TABLE 1 Risk of arrhythmias according to congenital heart disease type.

CHD type	Atrial tachycardia	Atrial fibrillation	Ventricular tachycardia	Accessory pathways
ASD	↑↑	↑↑↑		
VSD	↑		↑	
CoA		↑	↑↑	
AV canal	↑			
Ebstein's anomaly	↑↑		↑	↑↑↑
ToF	↑↑		↑↑	
TGA (atrial switch)	↑↑↑	↑↑	↑↑	
ccTGA	↑	↑	↑	↑
LVOT obstruction			↑↑	
Classic Fontan	↑↑↑	↑		
Lateral tunnel Fontan	↑			

Summary of the risk of specific types of arrhythmias according to the type of congenital heart disease (1).
CHD, congenital heart disease; ASD, atrial septal defect; VSD, ventricular septal defect; CoA, aortic coarctation; ToF, tetralogy of Fallot; TGA, transposition of the great arteries; ccTGA, congenitally corrected transposition of the great arteries; LVOT, left ventricular outflow tract.

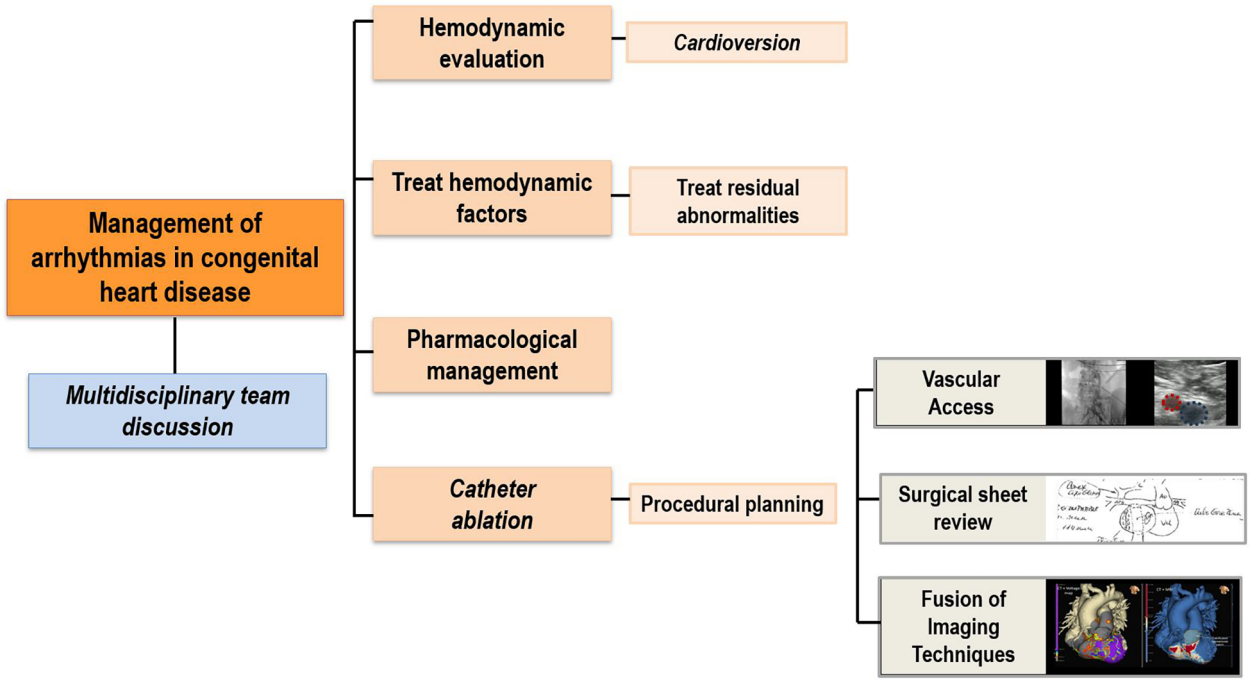

FIGURE 1
General arrhythmia workflow. Diagram outlining the description of the main steps in the evaluation and treatment of arrhythmias in patients with congenital heart diseases.

Hemodynamic assessment and treatment

Similarly to the general population, the initial step in the treatment of arrhythmias depends on their hemodynamic tolerance. SVAs may be poorly tolerated and can manifest as heart failure, shock, syncope or even electromechanical dissociation in extreme cases (2, 5, 21, 35–36). In the case of MRAT, the presence of patches and surgical scars leads to a slowing of conduction velocity, resulting in slower atrial cycles during tachycardia. This favors faster atrioventricular conduction, leading to hemodynamic compromise and even myocardial stunning. Patients with highly complex CHDs, such as TGA, those with dysfunction of the systemic ventricle, or severe dilation of the venous atrium, are at a higher risk of experiencing severe clinical manifestations during tachycardia episodes (37). If the patient exhibits hemodynamic compromise, urgent cardioversion should be considered. Anteroposterior pad placement is usually suitable for most patients and provides the highest rate of success (2). It should be adapted to the cardiac position (e.g., in patients with dextrocardia). In the case of SVAs, some patients, such as those with TGA, may experience sinus arrest or severe bradycardia after cardioversion, often requiring the administration of atropine/isoproterenol or external cardiac stimulation.

If patients with ASDs demonstrate good tolerance and a duration >48 h, the presence of cardiac thrombus should be ruled out through transesophageal echocardiography or appropriate anticoagulation (for more than 3 weeks), and medications for heart rate control (beta-blocker or calcium antagonist, depending on the characteristics of the heart disease) should be considered before cardioversion (1). In the case of ventricular tachycardias with good hemodynamic tolerance, the administration of intravenous drugs (amiodarone or procainamide) may be considered before considering electrical cardioversion (ECV).

In addition, reversible causes such as hyperthyroidism, an inflammatory process, or anemia need to be ruled out. In patients with CHD, the presence of hemodynamic alterations should be assessed, as they may influence the onset of arrhythmias and warrant consideration of targeted treatment. For example, in patients having undergone classic Fontan surgery, associated with a high prevalence of MRAT; in some cases, a conversion to Fontan surgeries with intra or extracardiac tunnel may be considered. Other examples include possible intracardiac shunts, progressive valvular abnormalities, etc.

For a comprehensive assessment of all these factors, it is essential to promptly refer the patient to a specialized center with a multidisciplinary team experienced in the treatment of arrhythmias in patients with CHD (Figure 1).

Pharmacological management

Anticoagulant therapy

Regarding anticoagulant drugs, there is no clear consensus on indications, and specific risk stratification is needed. Thromboembolic cerebrovascular complications are a fundamental cause of morbidity in the CHD population. According to the TACTIC study, thromboembolic events are

more associated with the complexity of the heart disease than with risk scales used in the general population. However, the CHA2DS2-VASc score may be applicable in simple CHD (38). Anatomical groups with a higher known embolic risk include uncorrected cyanotic heart diseases, Eisenmenger physiology, uncorrected atrial septal defects, and Fontan circulation (2).

Antiarrhythmic therapy

There is a lack of data due to the heterogeneity and limited number of patients with CHD included in the studies. Rhythm control is the preferred approach in this population, as the loss of sinus rhythm is frequently poorly tolerated, especially in patients with complex cardiac conditions. Similarly to the general population, antiarrhythmic drugs have low efficacy and significant adverse effects, both extracardiac and cardiac, due to negative inotropic and/or dromotropic effects.

In the acute treatment of arrhythmias, adenosine is the drug of choice for tachycardias involving the AV node and serves as a differential diagnostic method. Special care must be taken in patients with a low ejection fraction whose cardiac output depends on heart rate. It is noteworthy that in patients with Fontan physiology, adenosine may be ineffective due to its rapid metabolism through enzymatic degradation in blood and peripheral tissues, without manifesting its cardiac effects (2).

In terms of chronic treatment, class I antiarrhythmic drugs are recommended for patients without significant ventricular dysfunction, hypertrophy, or atrial scars. However, they are not recommended for treating MRAT, as their effect on slowing intra-atrial conduction may facilitate faster ventricular responses.

Class III antiarrhythmic drugs, specifically amiodarone, are the most commonly used in these patients, particularly in those with moderate and severe CHD. Amiodarone is highly effective for maintaining sinus rhythm and treating chronic ventricular arrhythmias; however, it is associated with many long-term side effects. Up to 56% of significant side effects were reported in a cohort of patients with moderate and complex CHD during a median follow-up of 2.7 years, with 30% experiencing amiodarone-induced thyrotoxicosis, more frequently observed in Fontan physiology patients. These adverse effects led to discontinuation of the drug in 42% of cases, despite its effectiveness in those who tolerated it, with an overall or partial efficacy rate of 98% (39). Caution is advised in cyanotic patients or those with pre-existing thyroid, pulmonary, or hepatic dysfunction.

Sotalol is preferred in young patients due to its fewer side effects. As has been reported in a case series with moderate and complex CHD, sotalol has proven to be reasonably well-tolerated (only 18% discontinued treatment primarily due to fatigue or dyspnea) and safe (no arrhythmias or sudden deaths were documented, and only 13% of patients experienced significant bradycardia, mainly those with Fontan surgery). Sotalol was completely or partially effective in 94% of patients (40).

There is limited experience with dronedarone in this population, but it may be another therapeutic option that has the advantage of avoiding the thyroid effects associated with amiodarone. Liver function should also be monitored, and its use is contraindicated in heart failure (41).

Finally, beta-blockers are recommended for both heart rate control in SVAs and non-sustained ventricular arrhythmias. In acute management, they should be administered carefully to patients with ventricular dysfunction due to their negative inotropic effect. Calcium channel blockers and digoxin may also be useful for rate control.

Catheter ablation

Due to the limitations of antiarrhythmic drugs, catheter ablation (CA) has become the first-line treatment for arrhythmias in CHD (2, 5, 42–46). This procedure represents a challenge, given the anatomical complexity and the frequent difficulty in vascular access. Meticulous procedure planning is crucial, considering the patient's anatomical characteristics and surgical techniques (2, 24, 45). Correct identification of the specific conduction system in relation to individual anatomy is essential in these patients. This is particularly important in the ablation of some arrhythmias, such as intranodal reentrant tachycardias, or in VT in patients with rToF with surgical closure of VSD, in whom the ablation site may be more challenging to locate due to variability in reference structures, increasing the risk of complete atrioventricular (AV) block.

For all these reasons, patients should be referred to centers with experience in arrhythmia ablation in CHD, especially in the case of complex CHD (47). Careful pre-procedure planning is always important.

Vascular access

In the planning of ablation procedures for patients with CHD, it is necessary to anticipate potential challenges with conventional femoral accesses. It is not uncommon for these patients to experience femoral vein occlusion, inferior vena cava atresia, or surgical obstacles such as prostheses or patches (Figure 2). To overcome these challenges, alternative vascular access, including internal jugular vein, subclavian vein, transapical, or transhepatic access may be necessary (48). In certain cases, a transesophageal catheter is employed, particularly in pediatric cases with difficulties in vascular access, to obtain intracardiac electrograms (49). Performing complex accesses, such as transeptal or transpatch procedures, requires significant electrophysiology expertise, especially in patients with corrected TGA using Senning or Mustard surgery or those with Fontan physiology involving an intracardiac tube. Utilizing intraprocedural imaging techniques like intravascular ultrasound or the fusion of previous imaging tests and electroanatomic mapping (EAM) enhances procedural guidance (50). Pre-procedural imaging tests, such as computed tomography (CT), play a crucial role in assessing vascular accesses beforehand and serving as an intraprocedural reference.

Anatomical knowledge

Accurate knowledge of the patient's anatomy is crucial, requiring a comprehensive examination of surgical records for those who have undergone cardiac repair. Evaluation of ventricular function and identification of residual hemodynamic

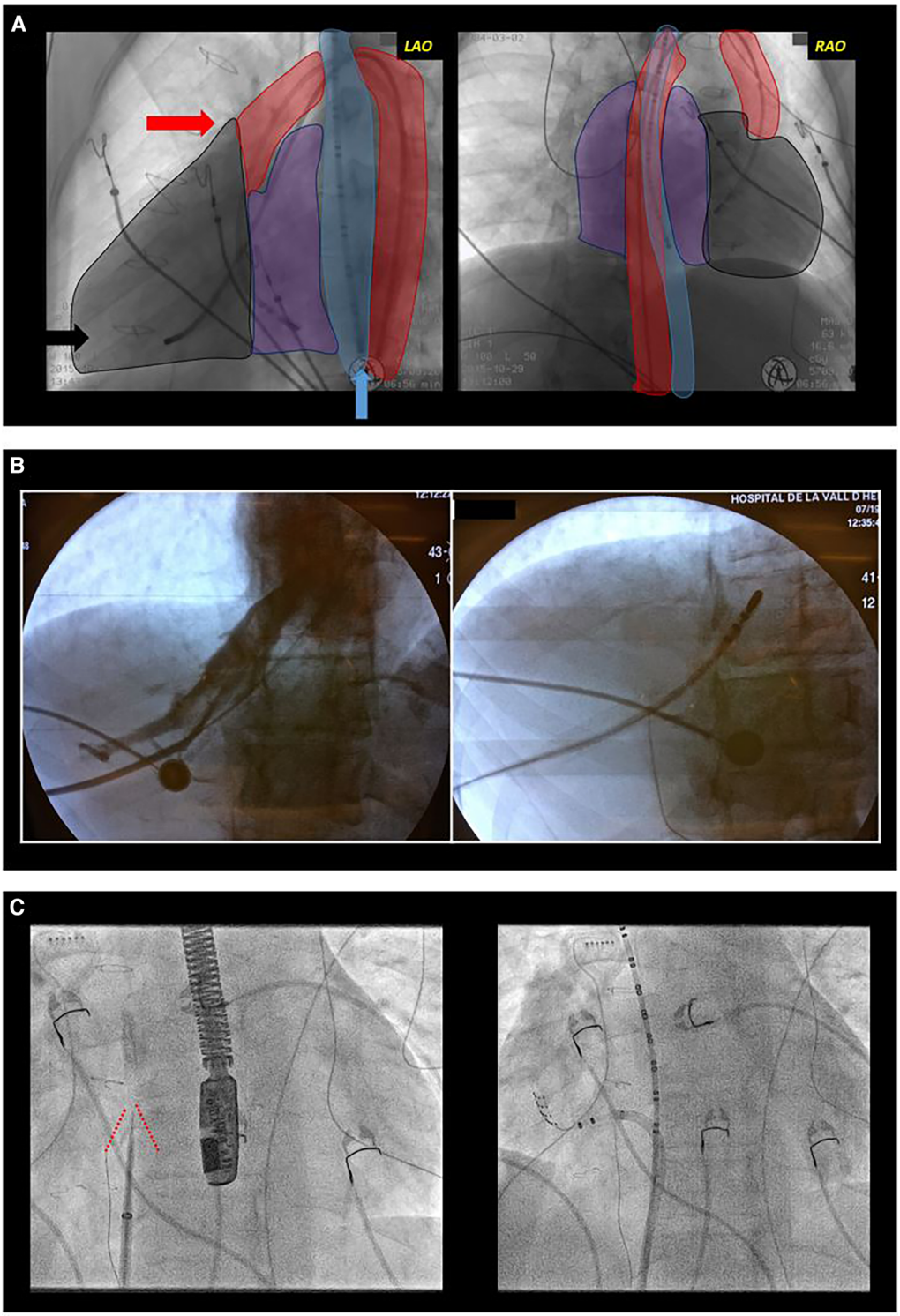

FIGURE 2
Difficult access. (**A**) Complex congenital heart disease with a single ventricle type, mesocardia, and dextroapex, initially repaired with classic Fontan surgery which was later converted to Fontan with intracardiac tube. Electrophysiological study was performed due to syncopal supraventricular tachycardia. Conventional radiological projections are shown: left anterior oblique (LAO, left image) and right anterior oblique (RAO, right image). The outlines of the esophagus (blue), aorta (red), ventricle (black), and atria (purple) are shaded. Due to the absence of femoral venous access, a transesophageal diagnostic catheter (blue arrow) was introduced for atrial sensing, and through the femoral artery, a tetrapolar catheter to the ventricle (black arrow) for rescue ventricular stimulation and a mapping-ablation catheter for treatment (red arrow) were progressed. (**B**) Transhepatic access guided by fluoroscopy. In the first fluoroscopy image, contrast injection into the hepatic venous system can be observed. In the second image, the catheter is progressed through this venous system. (**C**) Transeptal access in a patient with transposition of the great arteries corrected with atrial switch surgery (Senning). Both fluoroscopy images show an left anterior oblique projection. In the left image, a transeptal puncture needle oriented anteriorly and towards the right shoulder. Tenting of the interatrial baffle is observed (red lines). In the right image, a mapping-ablation catheter has been advanced through a long sheath to the neo-pulmonary venous atria.

anomalies, such as leaks or valve issues, is essential. These findings have implications for arrhythmias and may influence the planning of ablation procedures. The presence of significant hemodynamic abnormalities can significantly influence the occurrence of arrhythmias, prompting consideration for repair if necessary. Some of these alterations may impact ablation procedures, either by facilitating access to cardiac chambers (for example, in cases of residual communications between neo-atria in patients having undergone Senning or Mustard surgeries) or by acting as an anatomical barrier to accessing specific regions (for example, in cases of percutaneous pulmonary valve prostheses in ToF or mechanical prostheses in any location) (Figure 3).

Conventional imaging methods such as echocardiograms may be insufficient, requiring right and left heart catheterization and cardiac magnetic resonance imaging (MRI) for detailed assessments, especially in complex cases like univentricular hearts or tetralogy of Fallot. The increasing use of three-dimensional models in CHD patients enhances understanding and aids in planning interventions and educating medical professionals, patients, and families (51).

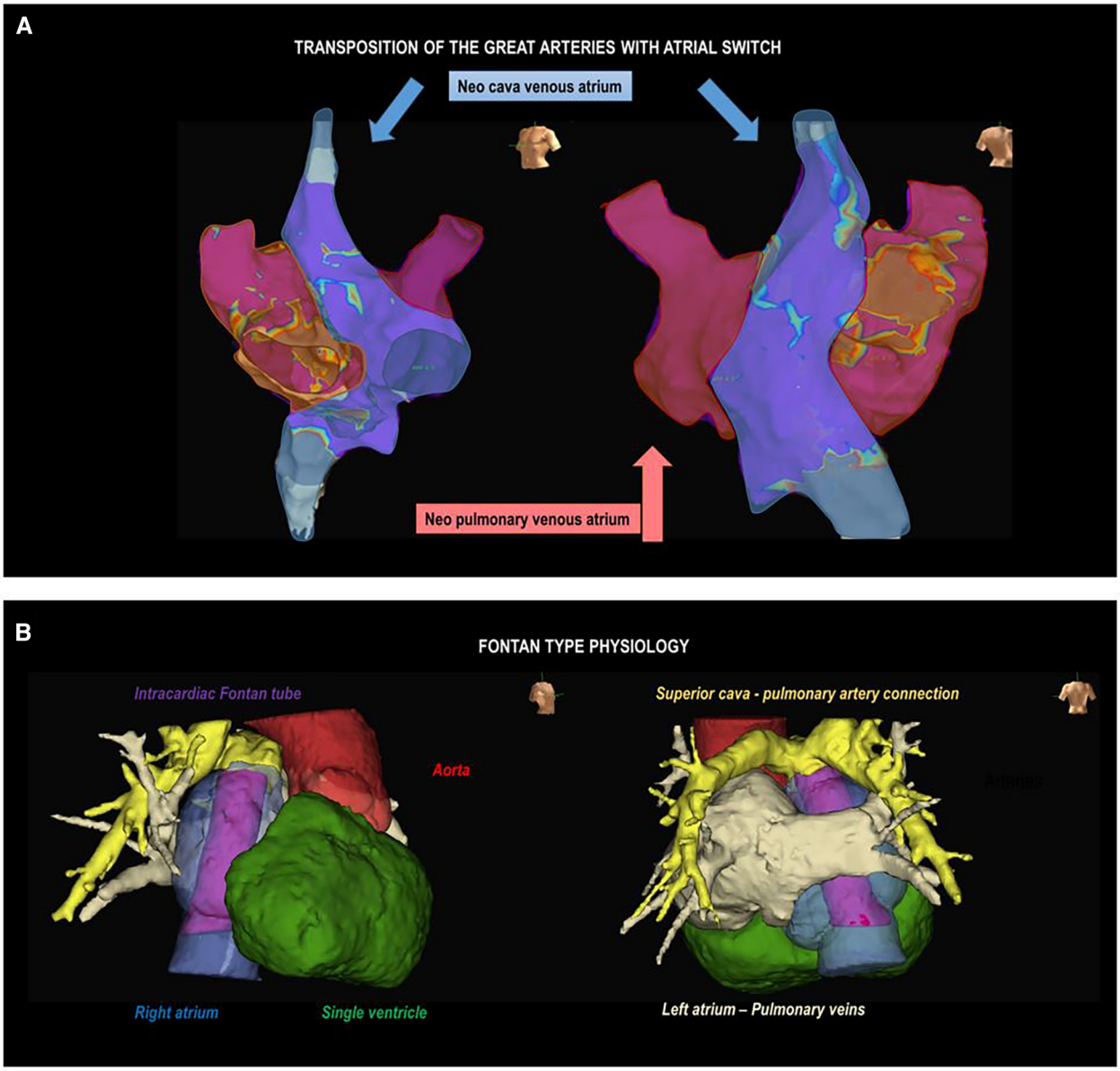

FIGURE 3
Complex anatomies. (**A**) Electroanatomic voltage map of the atrium in a patient with a transposition of the great arteries corrected with atrial switch surgery (Senning). Left oblique (left) and right posterolateral (right) projections are observed. The shaded areas represent the neopulmonary vein atrium (red) and the neocaval vein atrium (blue). (**B**) Anatomical reconstruction using image post-processing software in a patient with Fontan surgery, mesocardia, and dextroapex. A right lateral projection (on the left) shows the intracardiac tube (purple), right atrium (blue), aorta (red), and single ventricle (green); and a posteroanterior projection shows the superior vena cava-pulmonary artery connection (yellow) and left atrium-pulmonary veins (beige).

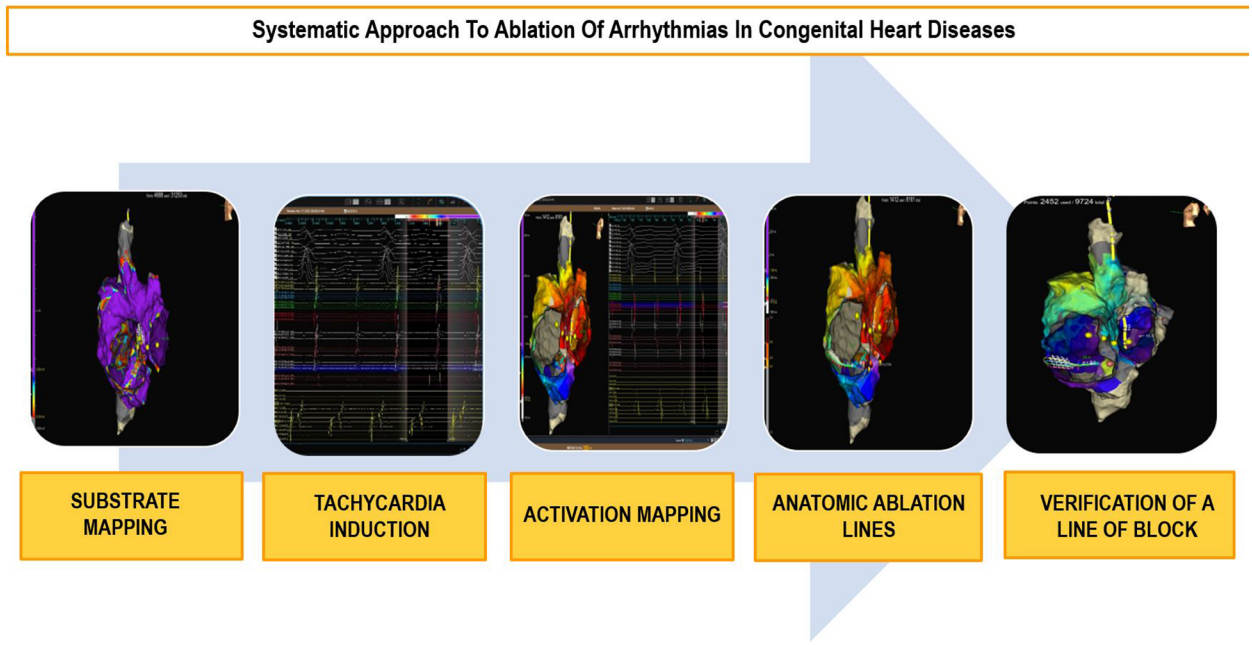

FIGURE 4
Ablation workflow in congenital heart diseases. Diagram outlining the systematic approach to ablation in congenital heart diseases in five steps.

Fusion of imaging techniques

Multimodality imaging techniques, particularly cardiac MRI and CT, are increasingly crucial for diagnosing and monitoring CHD patients. These techniques not only aid in pre-ablation planning but also serve as intraprocedural guidance by fusing with EAM. Fusion has proven beneficial in complex heart conditions, such as VT and left-sided flutter ablation, enhancing outcomes (52–54). In patients with ToF, the correlation of cardiac MRI findings with EAM has also been demonstrated (55). Substrate characterization often involves image post-processing software (e.g., ADAS Galgo Medical), enhancing integration for comprehensive planning and guidance during procedures.

Ablation techniques

Because of the anatomical difficulties and the high prevalence of complex arrhythmias in CHD patients, systematic planning of these procedures using electroanatomic navigation systems is recommended (2, 42, 44, 56). Continuous technological advancements in navigation systems allow for better anatomical and substrate characterization, such as identifying surgical scars and areas of fibrosis. This aids in the identification of reentries and the planning of ablation lines (Figure 4). High-density mapping catheters provide precise mapping, even in challenging accesses like transhepatic or trans-baffle, contributing to the prediction of ablation success (57, 58).

Electroanatomic navigation systems offer the advantage of reducing radiation exposure. Fusion systems, combining fluoroscopy with EAM (Carto, Univu, Biosense Webster), intravascular echocardiography with EAM (Cartosound, Biosense Webster), and transesophageal echocardiography with fluoroscopy, reduce radiation exposure and enhance mapping efficiency (59). These advances are also very useful in those patients that require a transseptal or trans-baffle approach. Image techniques are often necessary to ensure the correct localization of the needle tip before puncture and to avoid potential complications, especially in those patients with more distorted anatomies. In addition to puncture, trans-baffle access can be challenging due to tissue rigidity, which may sometimes require the use of steerable sheaths or ones with a smoother profile, or even dilation of the same.

Beyond access difficulties, the anomalous location of the specific conduction system poses a challenge in CHD patients. Cryoablation is frequently used in the ablation of arrhythmias near the AV node, offering reversible lesions and greater stability due to catheter adhesion to the endocardial surface. Its safety and moderate effectiveness were demonstrated in a series of complex CHD cases (60). For ablations in other locations, irrigated-tip catheters with steerable sheaths that facilitate the introduction of catheters into areas with complex access are recommended. Intracardiac echocardiography is acquiring an increasing role in this type of ablations. Among other benefits, it allows live visualization of the real anatomy, planning of ablation lines, and also ensures optimal tissue contact.

Remote magnetic navigation is a technological solution adaptable to CHD patients, enabling access to unconventional areas and reducing the risk of perforation. Its main limitations are its cost and availability. Its utility has been demonstrated, for example, for retroaortic access to the atrium of the pulmonary veins in cases of TGA with Senning or Mustard surgery. Remote magnetic navigation has proven to be effective and safe in this context (61).

Specific arrhythmia types

Atrial tachycardia

Atrial tachycardia (AT), predominantly MRAT, is the most frequently documented arrhythmia in patients with CHD. For example, in recent studies (2, 42, 62), incidences of 30% have been described in patients with Ebstein's anomaly and TGA treated with atrial switch, 20% in patients with atrial septal defects and in patients with repaired TOF, or even up to half of patients undergoing Fontan surgeries.

The natural history of AT varies significantly depending on the type of CHD. In patients with complex heart diseases, AT tends to occur at an earlier age and with a higher arrhythmic burden (62). Thus, in patients with univentricular physiology and in TGA, the onset of arrhythmias usually occurs around the second decade of life, whereas in patients with atrial septal defects, it is delayed until the fifth decade (62).

The presence of surgical scars, prosthetic material, anatomic obstacles, and other areas of fibrosis demarcates tissue with slowed conduction, a crucial factor for the onset of MRAT. In these areas of anomalous tissue, there is the possibility of unidirectional block, serving as the necessary substrate for the occurrence of macroreentrant arrhythmias. Due to slowed intra-atrial conduction, MRAT involving the CTI is much more frequent than in the general population and, in fact, constitutes the most frequently encountered macroreentrant circuit in this population (2, 63, 64). However, other circuits that do not involve the CTI are also common, representing, according to some case series, more than 50% or even 70% of cases in certain substrates (65). Likewise, it is not uncommon for the same patient to have both types of tachycardia (CTI-dependent and non-CTI-dependent). In a study of 94 patients, 51% presented CTI-dependent MRAT, 21% CTI-independent MRAT, and 28% both mechanisms (63). The complexity of CHD was a strong predictor of CTI-independent MRAT. The electrocardiogram (ECG) and cardiac monitoring registers in patients with complex CHD can be challenging to interpret (2, 14, 66). On the one hand, about a third of ECGs with patterns not suggestive of CTI-dependent flutter may, in fact, be CTI-dependent (63). On the other, some patients may have very low-amplitude atrial waves due to extensive atrial fibrosis, which can even make the arrhythmia go unnoticed (67, 68) (Figure 5).

Less frequently, ATs may also manifest a focal pattern (5%–10% of cases) (2, 68, 69). Electrocardiographically, they are often indistinguishable from MRAT and the diagnosis is typically established during mapping in the electrophysiology study (EPS).

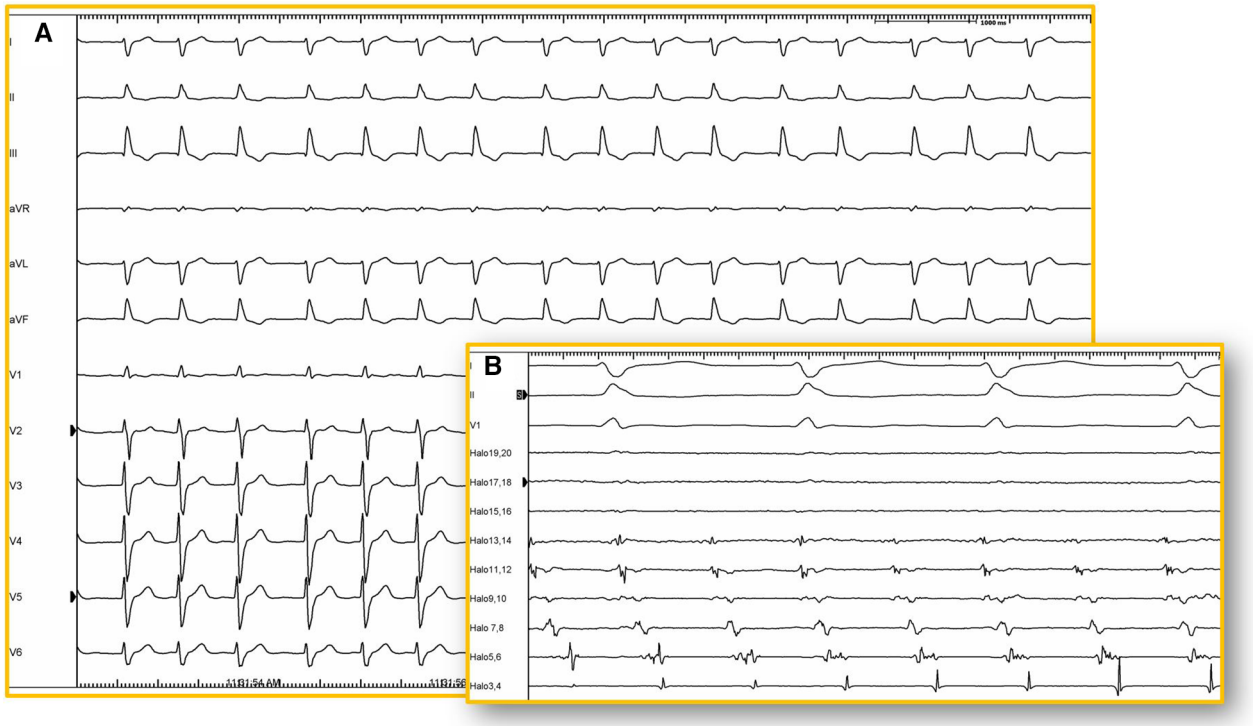

FIGURE 5
12-lead ECG. (A) Twelve-lead electrocardiogram (25 mm/s) of a patient with corrected d-TGA using the Senning technique. Atrial activity is very difficult to visualize due to its low amplitude and may be interpreted as atrial fibrillation. However, in the intracavitary recording (B) of the same patient, atrial activity is shown recorded by a duodecapolar catheter positioned between the superior and inferior vena cava (100 mm/s), revealing organized and regular activity. Electroanatomical mapping confirmed the presence of typical atrial flutter with a circuit around the tricuspid annulus (isthmus-dependent).

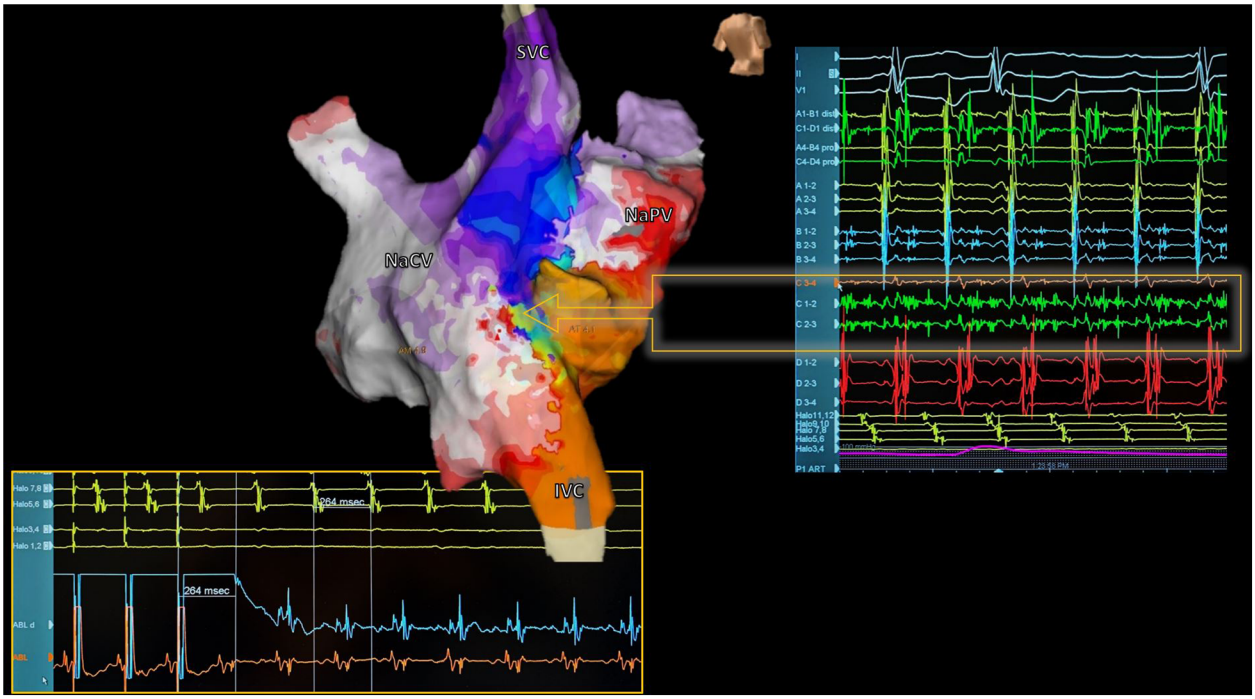

FIGURE 6
Reentrant atrial tachycardia electroanatomical mapping. Electroanatomic activation map of both neoatria during atrial tachycardia in a patient with corrected d-TGA using the Senning technique (Posterior view). Septal activation shows reentry-compatible activation (Arrow): Careful analysis of electrograms during mapping with a multipolar catheter identified a zone with fragmented and pandiastolic electrograms highly suggestive of the protected isthmus of the tachycardia (Right). At the bottom of the image, the catheter ablation maneuver positioned in this zone is shown, confirming the diagnosis. The tachycardia resolved during the first radiofrequency application. SVC, superior vena cava; IVC, inferior vena cava; NaVC, neocaval atrium; NaPV, neopulmonary vein atrium.

Antiarrhythmic therapy

There are currently no randomized clinical trials available, nor are any expected, to assess the efficacy of antiarrhythmic treatments in this population. Therefore, the evidence on pharmacological management is based on a few case series and expert opinions. Both antiarrhythmic drugs and rate-controlling agents may play a role; however, rhythm control is the preferred approach.

Amiodarone is likely the most commonly used antiarrhythmic drug, both acutely to restore sinus rhythm and chronically in this context. Ibutilide, dofetilide and sotalol may also be useful for restoring sinus rhythm. To achieve rate control, beta-blockers, calcium channel blockers, and digoxin may be useful with some considerations. Digoxin is often less effective for heart rate control during exercise in young patients, especially in cases of MRAT.

Catheter ablation

Catheter ablation is the first-line treatment for MRAT. While acute efficacy is high at around 80%, short-term recurrence is significant (30%–50%), due to the substantial atrial myopathy present in these patients (2, 46, 64). In a series of 130 patients with CHD treated at our center, with a high percentage of complex heart disease, during a mean follow-up of 4 years, 23% experienced a recurrence of the same arrhythmia, 14% developed another left MRAT, and 8% developed AF. The efficacy of a second procedure was high, with 78% maintaining long-term sinus rhythm (46). The presence of non-ICT-dependent MRAT and the induction or prior history of AF was associated with a higher risk of recurrences.

Meticulous procedure planning is essential, considering patient anatomical characteristics and surgical techniques. During the ablation, special attention must be paid to the location of the phrenic nerve and the conduction tissue, which may be anatomically displaced. It is highly useful to have a multipolar catheter around the AV ring in the venous atrium (e.g., a duodecapolar catheter) and in the coronary sinus. Not only does this allow for the evaluation of activation patterns, but it also aids in diagnosing changes in MRAT (Figure 6).

Electroanatomical navigation systems are very useful when dealing with scar-related flutter, figure-eight patterns, and multiple circuits, which are more common in patients with CHD. These advanced systems enable precise and efficient characterization of chamber anatomy, identifying blocking zones and fibrosis areas essential for planning the ablation line. Despite the increasing accuracy of automatic annotation systems, traditional electrophysiology remains valuable. Operators analyzing electrograms ensure proper annotation, particularly in areas with double potentials, delayed potentials, or absence of capture, contributing to precise anatomical substrate characterization. Accurate identification of blocking zones and

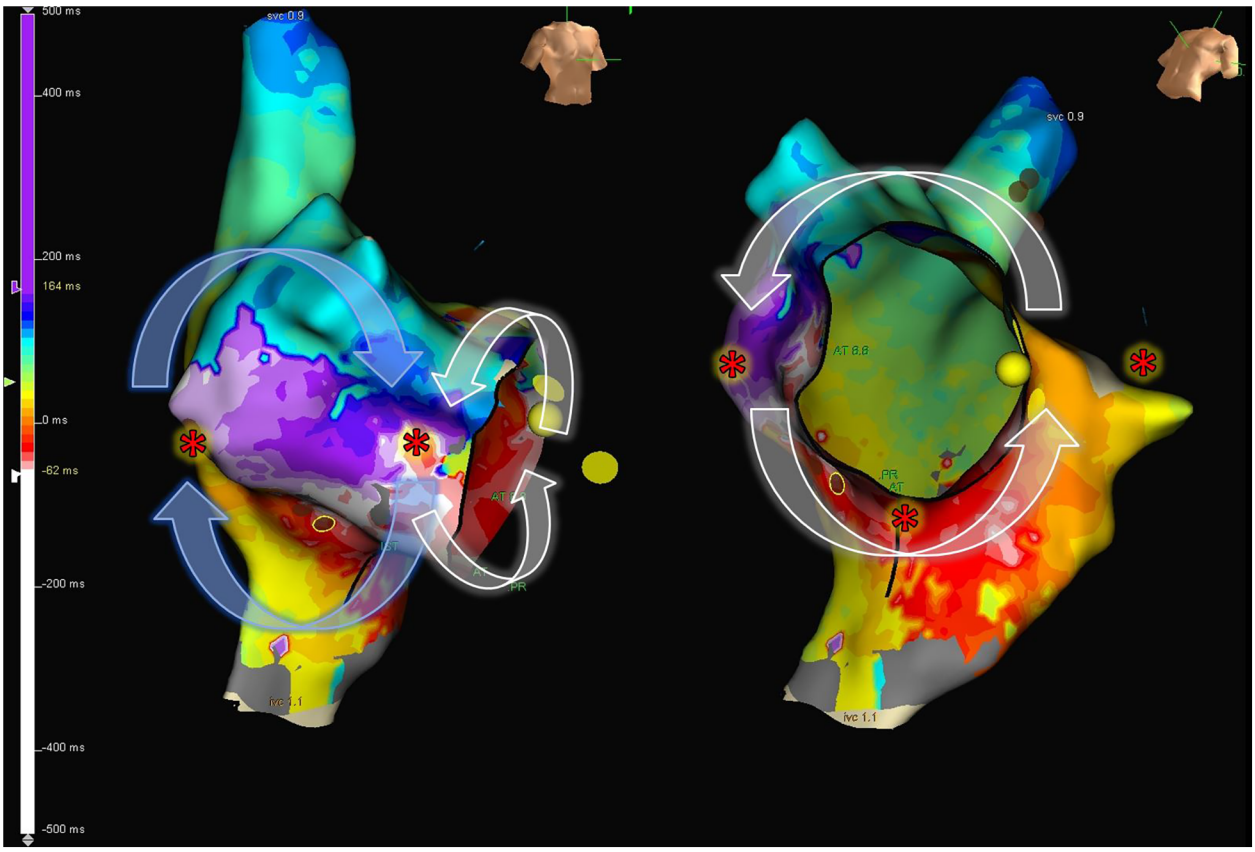

FIGURE 7
8-shape figure atrial flutter. Electroanatomic map of the right atrium, showing activation during tachycardia in a patient with repaired Tetralogy of Fallot. An 8-shaped figure with counterclockwise rotation around the cavotricuspid isthmus and clockwise rotation in the lateral wall is observed. The "*" indicates sites frequently used to perform entrainment maneuvers to determine the active circuit of the tachycardia.

dense scar, and also additional diagnostic maneuvers, such as entrainment, are useful when planning the ablation line. For instance, in patients with atriotomy scars (such as those performed in the majority of repaired ToF cases), a possible figure-eight pattern may be identified after EAM, with a counterclockwise circuit in the CTI and a clockwise circuit in the lateral wall, peri-scar (63). While only a small proportion genuinely exhibit a figure-eight flutter, ablation in the CTI is often sufficient to eliminate the tachycardia. Entrainments are also important for diagnosis. A long return cycle from the posterolateral aspect of the right atrium (posterior to the atriotomy scar) will suggest a passive rotation (Figure 7).

The main objective of ablation is the termination and non-reinduction of clinical arrhythmia (2, 45, 66, 70–71). However, it is not uncommon for the patient to present in sinus rhythm, or for more than one arrhythmia to be induced. In the first scenario, it is important to conduct an atrial induction protocol (since in most cases, at least one AT can be induced) and map it. In situations where mapping and determining the critical isthmus of the tachycardia cannot be achieved, either due to a lack of inducibility or the presence of unstable arrhythmias, empirical ablation of the CTI or its equivalent would be appropriate, given that it is the most frequently involved anatomical substrate. If other arrhythmias that can be mapped are induced after the ablation of the clinical arrhythmia, these can also be ablated. Recent research indicates a lower recurrence of arrhythmias in patients who underwent ablation for all induced ATs compared to those where only the clinical arrhythmia was addressed (45). There remains some debate surrounding the need to empirically address possible anatomical isthmuses that have not been confirmed to be involved in the genesis of a clinically or induced AT.

An ablation line must be created between two anatomical obstacles or scars to interrupt the circuit, preferably addressing the protected isthmus. It is essential to emphasize the importance of verifying bidirectional block of the ablation line to prevent future recurrences. Although it may be more challenging in complex anatomies, maneuvers such as differential pacing, preferably associated with new EAM, generally allow for confirmation of the blockade of the line or for the identification of possible gaps in the event of persistent conduction.

Atrial fibrillation

Atrial fibrillation was previously considered much less frequent than MRAT. Nevertheless, its prevalence has significantly increased

TABLE 2 Predictors of ventricular arrhythmias and sudden death in repaired tetralogy.

Group	Risk factor	Author/year
Demographic	Age	Katz. 1982
MR late enhancement	Myocardial fibrosis	Babu-Narayan. 2006
Surgical	Age at corrective surgery	Gatzoulis. 2000
	Palliative surgery	Khairy. 2008
	Ventriculotomy	Khairy. 2008
Electrocardiographic and Holter	High-grade ventricular premature beat	Harrison. 1997
	Non-sustained VT	Harrison. 1997, Khairy. 2008
	Sustained atrial arrhythmias	Valente. 2014
	QRS >180ms	Gatzoulis. 1995
	QT dispersion >70%	Gatzoulis. 1997
	QRS fragmentation	Bokma. 2016
Hemodynamic	Moderate-severe RV systolic dysfunction	Knauth. 2006, Valente. 2014
	Severe RV dilation	Knauth. 2006
	Disproportionate RV hypertrophy	Valente. 2014
	Moderate-severe LV systolic dysfunction	Ghai. 2022, Knauth. 2006, Valente. 2014
	Severe pulmonary regurgitation	Ghai. 2022
	Elevated LV telediastolic pressure	Khairy. 2008
Electrophysiological study/EAM	Induction of sustained VT	Khairy. 2004
	Isthmus of slow conduction	Kapel. 2016
	Prolonged RV activation time	Rivas-Gándara. 2021
	HV interval >55 ms	Rivas-Gándara. 2021

EAM, electroanatomic mapping; MR, magnetic resonance; VT, tachycardia ventricular; RV, right ventricle; LV, left ventricle.

in current cohorts due to improved survival of patients with complex cardiopathies (2, 62). AF often appears in patients with a history of prior MRAT, indicating a more advanced stage of atrial cardiomyopathy. A rhythm control strategy is usually preferred, as the loss of atrial contraction can be poorly tolerated. However, treatment effectiveness is suboptimal, and despite therapeutic efforts, patients may experience recurrences and a tendency toward chronicity. The results of AF ablation in patients with complex CHD have been disappointing thus far, likely because the automatic activity of the pulmonary veins (typically addressed in conventional AF ablation) represents only a small part of its pathophysiology (44). AF appears in more advanced stages of the disease, with highly fibrotic and diseased atria. Therefore, treating MRAT, which often precedes AF, in its early stages is crucial to attempting to prevent the progression of atrial cardiomyopathy secondary to the tachyarrhythmia. In this context, it is also important to assess and treat potential reversible causes, such as residual communications or obstructions, in order to reduce recurrence. Another important aspect to consider is the embolic risk and the need for anticoagulation. Commonly used scales (such as CHA2DS2-VASc) have not been validated in this population, so the decision for long-term anticoagulation should be made on an individualized basis. In patients with complex CHD with persistent or recurrent AF, long-term anticoagulation is likely indicated regardless of other thrombotic risk factors (2).

Other supraventricular arrhythmias

Supraventricular arrhythmias, such as atrioventricular nodal reentrant tachycardia and accessory pathway-mediated tachycardia, can also occur in patients with CHD. Accessory pathways may be present in up to 20% of patients with Ebstein's anomaly. "Atypical" pathways, such as atriofascicular (Mahaim) pathways or the presence of multiple pathways, are also more prevalent in these patients (2). A nearly specific type of SVA in cases of right isomerism syndrome and congenitally corrected TGA is twin atrioventricular nodal reentrant tachycardia. This rare type of reentry occurs in patients who have two AV nodes, resulting in an atrioventricular reentry circuit between them.

Similar to the general population, CA is usually the treatment of choice, although the procedure is often more complex due to anatomical peculiarities. Nevertheless, experienced centers achieve high success rates and safety in CA. Knowledge of anatomy is crucial when planning the ablation. Special attention should be given to the location of the conduction system, as some substrates such as TGA, heterotaxy syndromes, or patients with septal defects may be displaced, increasing the risk of AV block during the procedure.

Ventricular arrhythmias

Ventricular arrhythmias in this population include monomorphic VT, polymorphic VT, and ventricular fibrillation. Monomorphic VT is more prevalent in patients with incisions or patches in the ventricular myocardium. In patients with CHD, monomorphic VTs can be very fast and hemodynamically poorly tolerated, potentially leading to SD, even in patients with preserved ventricular function. In fact, in patients with repaired ToF and TGA who have implantable cardioverter-defibrillators (ICD), most appropriate therapies correspond to episodes of high-frequency monomorphic VT (72, 73).

Risk stratification

The identification of patients at a higher risk of ventricular arrhythmias would allow for the implementation of primary prevention measures and the minimization of complications from unnecessary therapies. However, the stratification of arrhythmic risk in the CHD population is complex due to the significant anatomical variability and variations in surgical repairs, the low SD rate, and the need for prolonged follow-up, making randomized clinical trials challenging. Although moderate-to-severe ventricular dysfunction, especially of the systemic ventricle, is a risk factor associated with SD, patients with preserved or only slightly impaired ventricular function may experience fatal arrhythmic events. Repaired ToF (rToF) is the best-studied cardiac condition, with multiple risk factors

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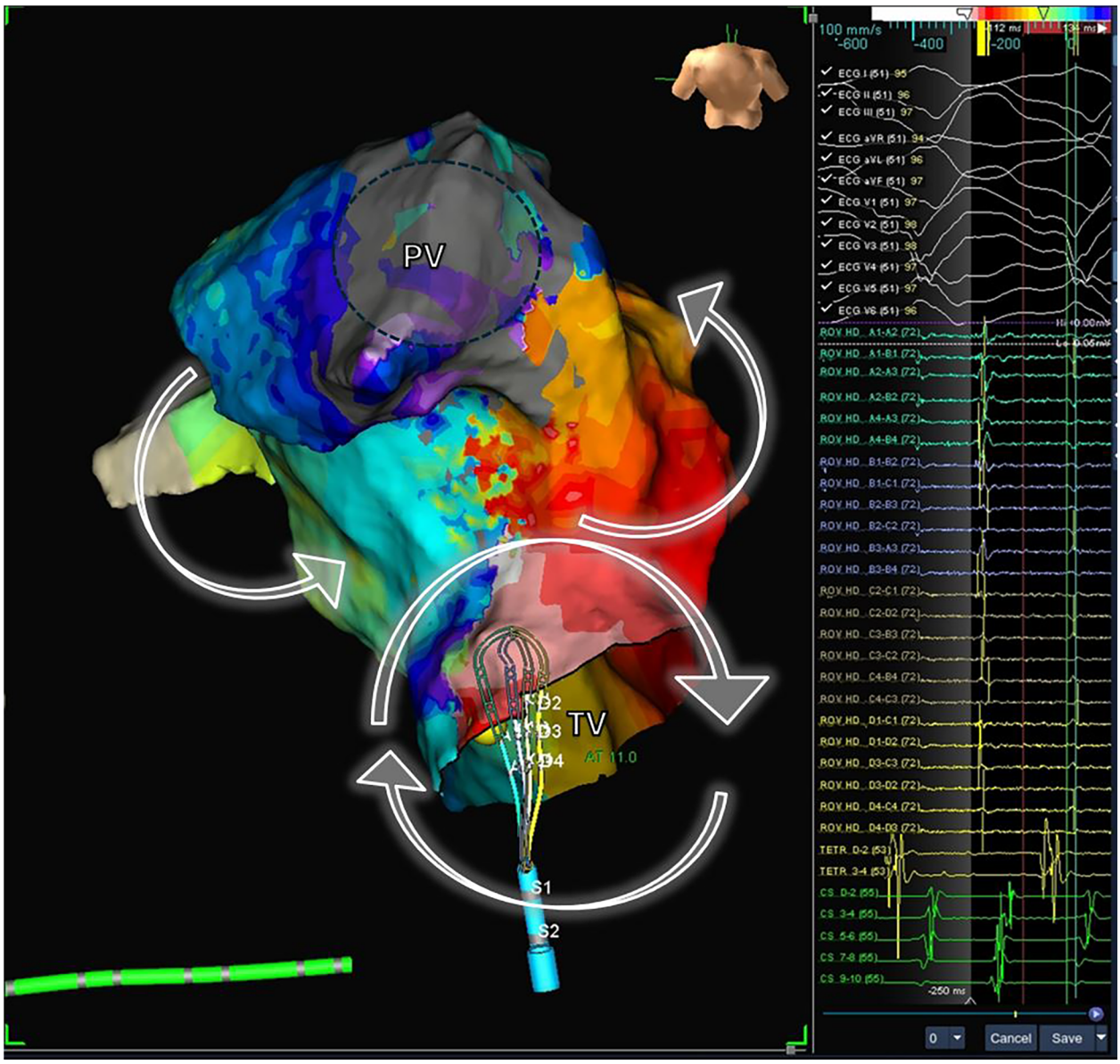

FIGURE 8
Electrophysiological study and electroanatomic mapping of ventricular tachycardia. The electroanatomic activation map of a ventricular tachycardia in a patient with repaired Tetralogy of Fallot is shown. The mechanism of VT is a macro-reentrant circuit with clockwise activation around the tricuspid valve (VP) and counterclock activation around the pulmonary valve (PV). The mapping catheter is located in the critical isthmus, showing mid-diastolic potentials (right panel). PV, pulmonary valve; TV, tricuspid valve.

associated with ventricular arrhythmias and/or SD having been described (Table 2) (74–77).

In patients with rToF, the occurrence of non-sustained ventricular tachycardia identifies a specific subset of patients who require careful monitoring. Some accessible non-invasive markers, such as filtered QRS duration, low amplitude signal duration in the terminal portion of the filtered QRS complex and the ratio of the maximum short-axis diameters of the right and left ventricles have been associated with potentially malignant ventricular arrhythmias (78, 79).

However, when considered individually, the predictive value of these risk factors is limited. Therefore, the indication for implantation of an ICD in primary prevention in patients with repaired ToF, aside from severe dysfunction of the systemic ventricle (left ventricular ejection fraction <35%) in patients in NYHA functional class II-III (class IIa), is based on the combination of several risk factors (class IIa), including systolic or diastolic dysfunction of the left ventricle, documentation of non-sustained VT, QRS duration ≥180 ms, inducibility of sustained VT in EPS, and the presence of extensive fibrosis in the right ventricle analyzed by cardiac magnetic resonance imaging (1, 55, 80).

In recent years, new tools for stratifying the risk of SCD in patients with CHD have emerged, such as the PREVENTION-

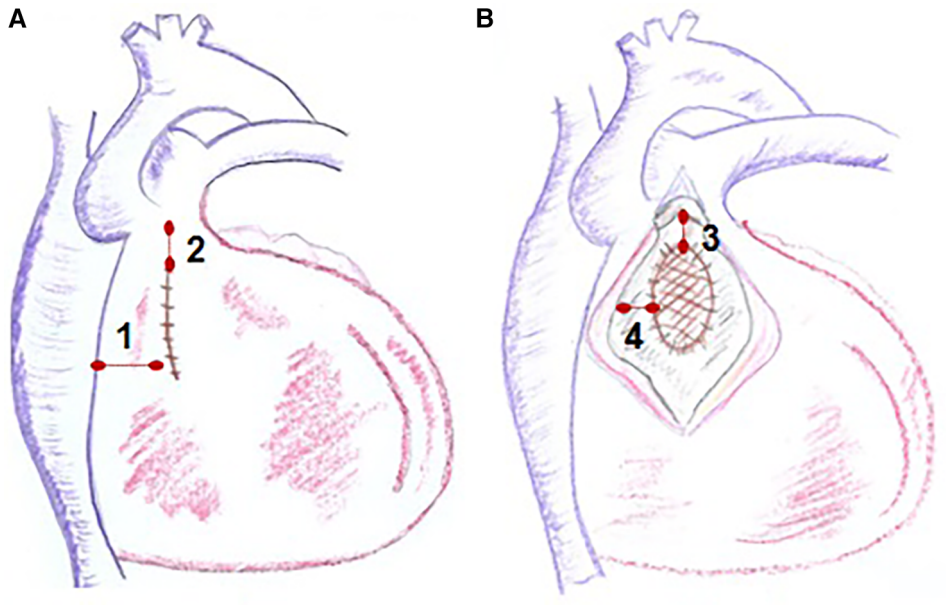

FIGURE 9
Anatomical isthmuses in repaired tetralogy of fallot. Diagram of the anatomical isthmuses responsible for ventricular tachycardia (VT) in repaired ToF, as defined by Zeppenfeld et al. (A) Between ventriculotomy or transannular patch and tricuspid annulus (isthmus 1), between ventriculotomy and pulmonary annulus (isthmus 2). (B) Between VSD patch and pulmonary annulus (isthmus 3) and between VSD and tricuspid annulus (isthmus 4). VSD, ventricular septal defect.

ACHD risk score model (81). This model incorporates common clinical variables like coronary artery disease, NYHA class II/III, supraventricular tachycardia, systemic ejection fraction <40%, subpulmonary ejection fraction <40%, and QRS duration. Its accuracy exceeds current guideline indications, potentially aiding in the selection of CHD patients who may benefit from preventive implantable ICD implantation (81).

Mechanism and anatomic substrate of ventricular tachycardia

Patients with CHD exhibit a substrate that predisposes them to ventricular arrhythmias, due to a combination of surgical scars, anatomical barriers, and myocardial tissue injury. Repaired ToF is the most emblematic example of CHD repair with this substrate. Studies have demonstrated that the most common ventricular arrhythmia in patients with repaired ToF is monomorphic ventricular tachycardia (82), and the underlying mechanism is macro-reentry (83). These macro-reentrant circuits are typically situated in the right ventricular outflow tract (RVOT) and are associated with the repair surgery (83, 84). Previously, ToF repair surgery involved a ventricular approach, aiming for extensive release of the RVOT, working from the assumption that residual pulmonary insufficiency had no long-term repercussions. Consequently, in addition to the patch for closing the VSD, most patients have a ventriculotomy scar, and in many cases, a transannular patch for RVOT enlargement (Figure 8). The substrate formed by surgical repair and myocardial changes due to hemodynamic overload from residual lesions, with residual pulmonary insufficiency being the most common, is responsible for the development of ventricular arrhythmias in adulthood among these patients.

Electroanatomic mapping

Electroanatomic mapping techniques, combined with electrophysiological entrainment maneuvers, enable precise identification of the macro-reentrant electrical circuit in these arrhythmias and establish the critical isthmus maintaining the arrhythmia (Figure 8). In repaired Tetralogy of Fallot (rToF), the critical anatomical isthmuses sustaining these macro-reentrant circuits are delineated by the non-excitable tissue of the valvular rings, prosthetic patches, and surgical scars. Electro-anatomic mapping of right ventricular voltage in sinus rhythm (considering electrograms >1.5 mV as high voltage and electrically non-excitable tissue as electrograms with voltage <0.5 mV and without ventricular capture with 10 mA stimulation and 2 ms) has identified four anatomical isthmuses that may be present in these patients (85). These four isthmuses are defined between the following structures: isthmus 1 between the transannular patch/ventriculotomy and the tricuspid ring, isthmus 2 between ventriculotomy and the pulmonary ring, isthmus 3 between VSD patch and the pulmonary ring, and isthmus 4 between the VSD patch and the tricuspid ring (Figure 9) (85). It is noteworthy that although the majority of rToF patients have at least one of these anatomical isthmuses, not all can propagate sustained monomorphic VT. In this regard, it has been observed that arrhythmogenic isthmuses are longer, narrower, and have a slower conduction velocity, which can help define the anatomical location of the ablation (86).

In other anatomical substrates, scientific evidence regarding the mechanism of VT and the arrhythmic substrate is limited, and additional anatomical isthmuses have been described in patients with TGA, VSD, or repaired pulmonary stenosis (87).

Ablation

Radiofrequency ablation of VT in patients with repaired CHD is feasible, with reported acute efficacy ranging from 50% to 100% and variable recurrence rates (85, 88). Comparing published studies is complex due to small sample sizes, the use of diverse mapping and ablation technologies, and different efficacy criteria. Kapel et al. reported an acute efficacy of 74% with no recurrences in a mean follow-up of 46 months, utilizing EAM systems and irrigated ablation catheters. The procedure was considered effective when achieving conduction block at the critical anatomical isthmus level and demonstrating absence of inducibility. Therefore, considering the macro-reentrant mechanism of these arrhythmias, it seems reasonable to aim for bidirectional block of the critical isthmus and absence of inducibility in ablation procedures.

In those patients in whom sustained monomorphic VT is induced with good hemodynamic tolerance, the identification of arrhythmogenic isthmuses for ablation can be based on electro-anatomic mapping during tachycardia and entrainment maneuvers. However, complete mapping during VT is often not possible due to lack of inducibility or poor hemodynamic tolerance (72, 73). In the case of patients with rToF, considering the association between the substrate identified in sinus rhythm and the induced VTs, substrate ablation can be considered with the goal of blocking conduction through the arrhythmogenic isthmuses considered (86).

The efficacy of ablation may be limited due to dilation of the cavities, hypertrophy of the myocardial tissue, or the presence of prosthetic material [e.g., after pulmonary valve replacement (PVR)]. In patients with rToF where blockade of septal isthmuses cannot be achieved, either due to hypertrophy or the presence of a pulmonary valve prosthesis, it may be useful to complement the ablation line contralaterally using a left-sided approach.

The role of empirical ablation at the time of PVR in patients with rToF and severe residual pulmonary insufficiency is a subject of controversy. Since residual hemodynamic defects are associated with a higher risk of VT and SD, addressing their treatment is important. However, there is doubt as to whether PVR reduces the long-term arrhythmic risk and whether it should be associated with ablation of anatomical isthmuses (89, 90). Sometimes, the arrhythmogenic substrate does not completely revert after PVR, even with overall remodeling of the right ventricle (reduction in volumes and improvement in systolic function). Additionally, access to isthmus 3 (between the pulmonary ring and VSD) may be limited after PVR due to the interposition of the prosthesis in the pulmonary position. Therefore, it seems reasonable to consider associating ablation of arrhythmogenic isthmuses before or during PVR with the aim of preventing monomorphic VTs during follow-up. Although cryoablation during PVR surgery has not been reported to be proarrhythmic and could have a protective role in the long term (59), long-term studies are needed to clarify this point.

Assessment of arrhythmic substrate using imaging techniques

Late gadolinium enhancement study in cardiac MRI allows the extent and distribution of fibrotic tissue to be determined. In fact, the 3D reconstruction of images obtained with late gadolinium enhancement MRI has proven to be useful for characterizing the arrhythmic substrate of the left ventricle in patients with ischemic heart disease. A good correlation has been documented in the identification of fibrosis and conduction channels between EAM and late gadolinium enhancement MRI, with the latter providing appropriate guidance for planning and guiding the ablation procedure (52, 91). However, the analysis of the right ventricle, which is often involved in VTs in patients with CHD, is more complex due to its thinner wall and the proximity of epicardial fat. There appears to be an association between the extent of fibrosis in late gadolinium enhancement MRI and the history of arrhythmias in patients with repaired Tetralogy of Fallot (92). Additionally, the 3D reconstruction of late gadolinium enhancement MRI of the right ventricle has demonstrated correlation with the substrate identified by voltage mapping, both in the extent and location of fibrosis (55, 93), as well as in the identification of anatomical isthmuses (55), making it potentially useful for guiding the ablation procedure.

Future perspectives

The shift in the surgical approach during corrective procedures, avoiding ventriculotomy through transatrial and transpulmonary methods, and the minimization of residual hemodynamic lesions, will modify the arrhythmic substrate of the ventricular myocardium in patients with repaired CHD. This change has the potential to influence the risk of arrhythmias and the treatment approach through ablation. The characterization of the arrhythmogenic substrate and anatomical isthmuses, achieved via 3D reconstruction of late gadolinium-enhanced MRI, EPS and EAM in sinus rhythm, could emerge as a valuable tool for risk stratification concerning VT and SD in individuals with repaired CHD (23, 55, 94, 95). Further studies are necessary to elucidate the role of empirical ablation during pulmonary valve replacement in patients with repaired Tetralogy of Fallot (96, 97).

Author contributions

JF-P: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. NM: Writing – original draft. AS-O: Writing – review & editing. NR-G: Conceptualization, Project administration, Writing – review & editing.

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Conflict of interest

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Cardioneuroablation: the known and the unknown

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Cardioneuroablation (CNA) is a novel interventional procedure for the treatment of recurrent vasovagal syncope (VVS) and advanced atrioventricular block secondary to hyperactivation of vagal tone in young patients. By damaging the cardiac parasympathetic ganglia, CNA seems to be able to mitigate and/or abolish the excessive vagal activity and improve patients' outcome. This review is intended to give a detailed and comprehensive overview of the current evidences regarding (1) the clinical applications of CNA (2) the identification of ablation targets and procedural endpoints (3) the medium-long term effect of the procedure and its future perspectives. However, clinical data are still limited, and expert consensus or recommendations in the guidelines regarding this technique are still lacking.

KEYWORDS

cardioneuroablation (CNA), vasovagal syncope, atrioventricular block, high-frequency stimulation (HFS), fractionated electrograms, cardioinhibitory syncope

Introduction

Vasovagal syncope (VVS) is the prevailing cause of syncope and it is due to an imbalance between the sympathetic and parasympathetic components of the autonomous nervous system (ANS). An excessive parasympathetic response to a trigger may provoke a syncope as the result of bradycardia and hypotension leading to cerebral hypoperfusion. According to the VASIS classification, VVS is generally divided into 3 types, based on the underlying mechanism: mixed (I), cardioinhibitory (IIa-b), and vasodepressive (III) (1).

These syncopal episodes are generally benign and usually occur in healthy persons, but if recurrent they can significantly worsen the patients' quality of life, especially if unresponsive to conservative measures, such as patient education to execution of hand-gripping and leg crossing maneuvers at the onset of symptoms.

According to the latest guidelines, in case of recurrent cardioinhibitory syncope pacing is indicated only in patients aged >40 years, thus CNA could be a favorable therapeutic option in younger patients (1, 2).

Cardioneuroablation (CNA), consisting of vagal denervation in correspondence of AF nest at the pulmonary veins antral regions, was originally evaluated as a potential integration to atrial fibrillation (AF) ablation (3). Pachon et al. were the first to propose the CNA as a therapeutic strategy for the management of syncope or bradyarrhythmias associated with the hyperactivity of the vagal tone (4), by ablating the cardiac ganglionated plexuses and mitigating the underlying parasympathetic overdrive (5). Furthermore, some evidences suggest a role for CNA also for the treatment of

functional atrio-ventricular block (AVB) and sinus node dysfunction (SND) (6, 7). As recent studies show convincing results, the number of electrophysiologists performing this type of procedure and thus the number of patients undergoing this treatment are increasing and in parallel also the number of publication on this topic has seen an exponential growth in the last decade (Figure 1).

However, despite the great interest for this novel technique, there aren't at the moment recommendations in guidelines nor Expert Consensus about CNA. Remarkably, there is still high variability either in patients' selection as well as in procedures performance and outcomes evaluation. There is moreover a lack of large RCTs demonstrating the superiority of this kind of therapy on the conventional pharmacological and non pharmacological therapy.

This review aims at elucidating (1) the rationale and the clinical applications of CNA (2) the identification of ablation targets and procedural endpoints (3) the medium-long term effect of the procedure and its future perspectives.

Anatomy and functioning of the autonomic nervous system

The autonomic cardiac nervous system is composed by the central nuclei in the brainstem, and 2 peripheral main cells, the preganglionic and the postganglionic neurons. Furthermore, the efferent ANS is divided in two components, parasympathetic and sympathetic, having opposite functions and a different structural organization. While the sympathetic postganglionic neurons with their long axonal endings are mainly located in the paravertebral sympathetic chain, on the other hand the parasympathetic postganglionic neurons with very short axonal endings are organized in ganglionated plexuses (GPs), that are situated in the atrial wall. Therefore, the parasympathetic ganglia can be more easily destroyed from the endocardium with radiofrequency ablation, and when the re-innervation occurs, this is a slow process as it requires the differentiation of interneurons. Some sympathetic fibers are also localized in the fat pad surrounding the heart and thus these can be damaged during ablation, however the sympathetic re-innervation is easier as it derives from the regeneration of the same neurons (8–10).

Noteworthy, myocardial activity is not dependent on the autonomic innervation: thus, where the skeletal muscle atrophies after denervation, the cardiac muscle preserves its activity and function regardless of the denervation.

The anatomical localization of GPs has been studied and described by different Authors.

Cardiac parasympathetic ganglia are usually localized as follows (Figure 2, courtesy of Aksu T. et al). The right superior ganglionated plexus (RSGP) is in between the superior vena cava and the right superior pulmonary vein. From this ganglion, most of the efferent parasympathetic fibers travel into the atria through the medial part of superior vena cava and the aortic root (11). The right inferior ganglionated plexus (RIGP) is positioned between the right pulmonary veins and the right atrium (12). The posteromedial left ganglionated plexus (PMLGP) is located in the posterior portion of the interatrial septum, between the wall of the left atrium, the inferior vena cava, and coronary sinus ostium, even if a part of the fibers related to this GP may extend to the left atrial side. These three ganglia are sometimes named as ganglion A, B and C

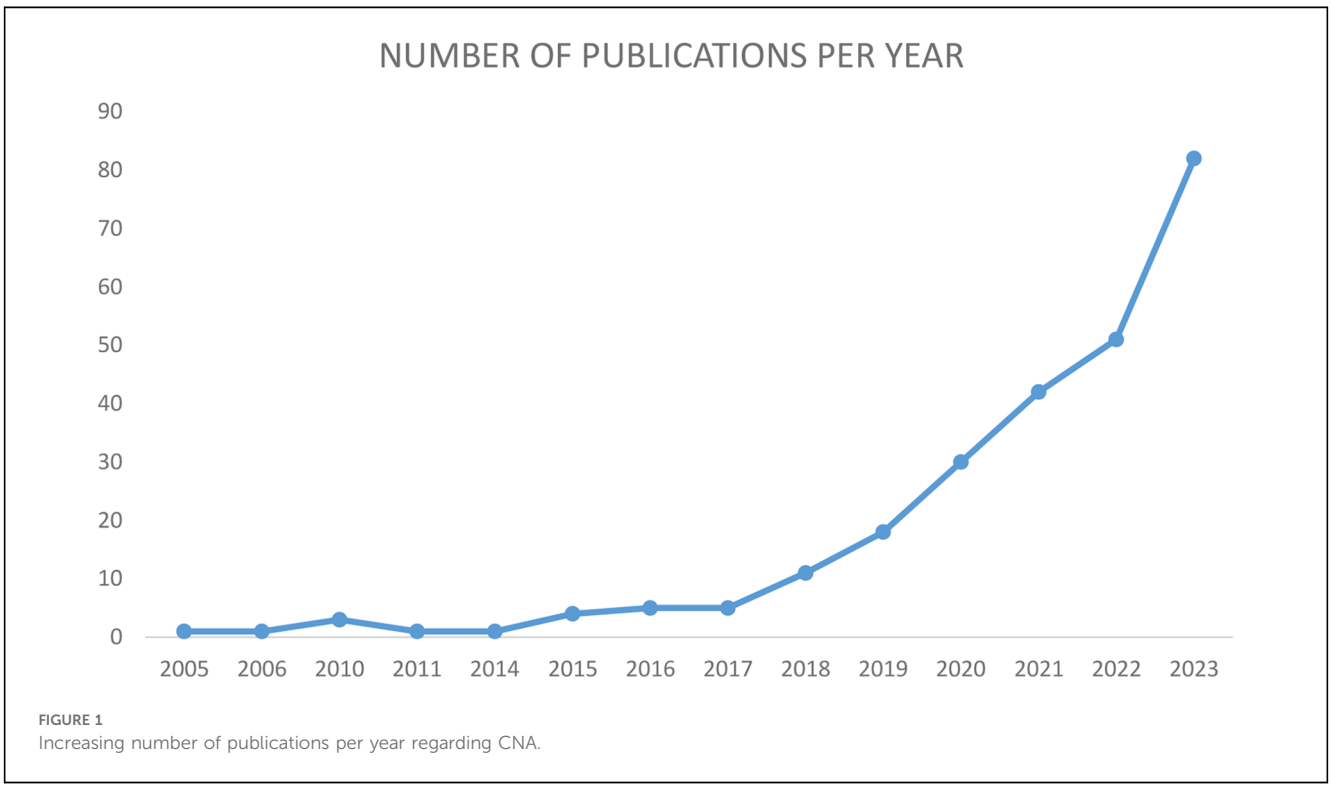

FIGURE 1
Increasing number of publications per year regarding CNA.

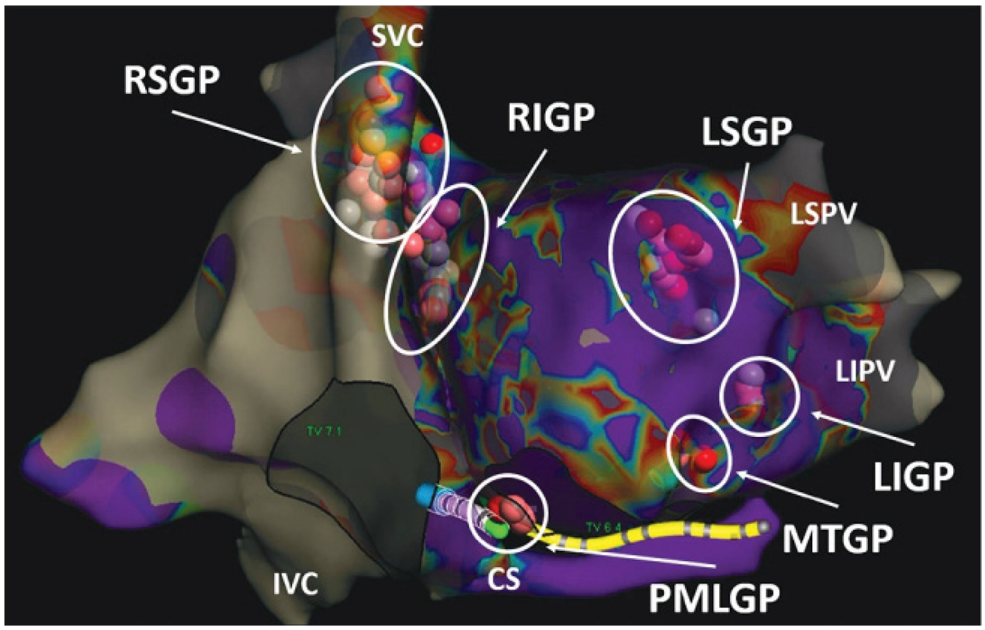

FIGURE 2
Localization of right and left ganglia. Courtesy of Aksu et al. (doi: 10.15420/aer.2022.37).

respectively (13). The left superior ganglionated plexus (LSGP) is situated between the left atrial appendage and the left superior pulmonary vein. The left inferior ganglionated plexus (LIGP) is located inside the fat pad anterior to the left inferior pulmonary vein (14, 15). Lastly, the Marshall ligament is currently considered as part of the cardiac ANS as contains cholinergic vagal fibers and is named Marshall tract ganglionated plexus (MTGP) (16).

However, the specific GPs locations vary significantly from individual to individual, thus their described anatomical locations are not always accurate, although the localization of the right ganglia is quite constant (17).

Several studies indicate that the sinus atrial node (SAN) and the atrio-ventricular node (AVN) are respectively innervated by the RSGP, mainly composed by the right vagus nerve fibers, and by the RIGP/PMLGP, as the final pathway of left vagus nerve to AVN, thus allowing a selective destruction of these ganglia in case of bradyarrhythmias related to atrio-ventricular block or sinus node dysfunction, and thus sparing the remaining autonomous system (18–22).

Clinical applications of the CNA: patients selection

Even if there are not universally accepted criteria for patients' selection, CNA could be proposed in case of recurrent syncopal episodes per year and failure of conservative strategies, for patients in whom, due to age <40 years, pacing would not be desirable. Anyway the definition of the underlying mechanisms of syncope is essential: in fact, in case of vasodepressive syncope, CNA is unable to effectively prevent the recurrence of syncopal episodes, whereas CNA by avoiding excessive vagal influence on sinoatrial node or atrio-ventricular node (23), may counteract the cardioinhibitory syncope and partially also the mixed forms.

The head-up tilt test (HUTT) is the most useful test to identify patients with an autonomic substrate for VVS. According to the VASIS classification, the HUTT response are the following: type 1, mixed response, for a reduction in both blood pressure and heart rate (>40 bpm or <40 bpm but for <10 s); type 2A, cardioinhibitory for heart rate reduction <40 bpm for >10 s, but without asystole; type 2B, cardioinhibitory with asystole >3 s; and type 3 (vasodepressor response) (24). Patients affected by cardioinhibitory syncope, especially those with asystole, but also those with type 2A, may be good candidates to CNA. While there is still no clear indication of CNA for type 3, due to its vasodepressive nature, the CNA may be beneficial in some patients with type 1 (19, 25, 26).

The HUTT is a widely adopted diagnostic test to induce syncope, however the results are poorly reproducible and this may significantly limit its value. Furthermore, even when the HUTT result suggests a vasodepressive nature of the syncopal episode, in some patients also implanted with a loop recorder (ILR), a cardioinhibitory episode can be recorded, leading to a change in therapeutic approach. Thus, an accurate selection of patients undergoing to CNA is crucial (27, 28). The demonstration of asystole during a spontaneous syncope, documented by ILR, and the exclusion of susceptibility to hypotension via 24-hours blood pressure Holter monitoring may help to identify those patients who may benefit the most from a CNA.

Atropine test is frequently used for the selection of patient candidate to CNA. Atropine blocks cardiac muscarinic receptors

and thus vagal activity, therefore during the infusion of this agent normally there is an increase in HR. Particularly, an acceleration of HR over 90 bpm or an increase over 25% than baseline after intravenous atropine bolus (Dose: 0,04 mg/Kg, Maximum dose 3 mg) suggest a prevalence of the parasympathetic system (25, 29). In case of a negative response to atropine test, the CNA should be discouraged and the implant of a pacemaker should be preferred, as it indicates a poor effect of vagal tone on heart rhythm (30).

Furthermore, heart rate variability (HRV) and deceleration capacity (DC) are two non-invasive parameters that can be derived by the ECG monitoring through specific algorithms. The first, derives from the RR interval variability on ECG, which is often reduced in patients with VVS story; the second, derives from HRV analysis, and values >7.5 ms, suggest an increased parasympathetic overactivity (28–30).

Procedural aspects of the CNA

Epicardial ganglia localization during the ablation procedure

Different methods have been used for ganglionic plexuses localization: fractionated EGM evaluation, high frequencies stimulation (HFS), anatomic approach and recently the computed-tomography and the Iodine 123 metaiodobenzylguanidine (MIBG) SPECT.

In 2004 Pachon et al. proposed a new method for endocardial potentials study during AF ablation, applying the Fast-Fourier transformation (FFT), a mathematical algorithm that enables the visualization of any wave as the sum of several sinus waves which create a frequency spectrum. In this way, they found that the myocardial organized conduction has a narrow frequency spectrum of signal, and described two different types of atrial myocardium (Figure 3): the compact one, presenting a homogeneous range with one dominant frequency around 40 Hz and with uniform conduction, and the fibrillar one, presenting a heterogeneous range with several fraction having frequencies >100 Hz (31, 32). They found that in the absence of cardiopathy, fibrillar spectrum can be localized not only in correspondence of fibers of cardiac conduction system, but also in many other localizations, mostly near cardiac para-ganglia (33).

Therefore, through a specific software that automatically identifies these fractionated electrograms (EGM) and tag them (Ensite Precision system©), it is possible to localize the parasympathetic ganglia during electroanatomic mapping of the left (LA) and right atrium (RA) (34, 35). The AF nests are atrial sites with high frequencies components, where it is possible to localize ganglia sites by setting the filters between 200 Hz and 500 Hz, respectively, and by recognizing the fragmented EGM with ≥4 deflections (36).

During routine atrial mapping, usually performed through a decapolar catheter for right atrium and a steerable quadripolar catheter for left atrium, EGMs are classified into 3 groups according to their amplitude and number of deflections: (1) normal atrial EGM, with a deflection number <4; (2) low-amplitude fractionated EGM (LAFE), with ≥4 deflections and amplitude <0.7 mV; and (3) high-amplitude fractionated EGM (HAFE), with ≥4 deflections and an amplitude ≥0.7 mV (37). The presence of HAFE or LAFE pattern, at a sweep speed of 400 mm/s, recorded in a region near to probable localization of GPs are tagged as ablation targets.

CNA may be performed solely by anatomic landmarks, delivering radiofrequency energy (RF) in presumed locations of atrial epicardial fat pad, however this approach can easily be inaccurate, especially for the left GPs, due to interpatient variability. On the other hand, more recently enhanced anatomical approaches

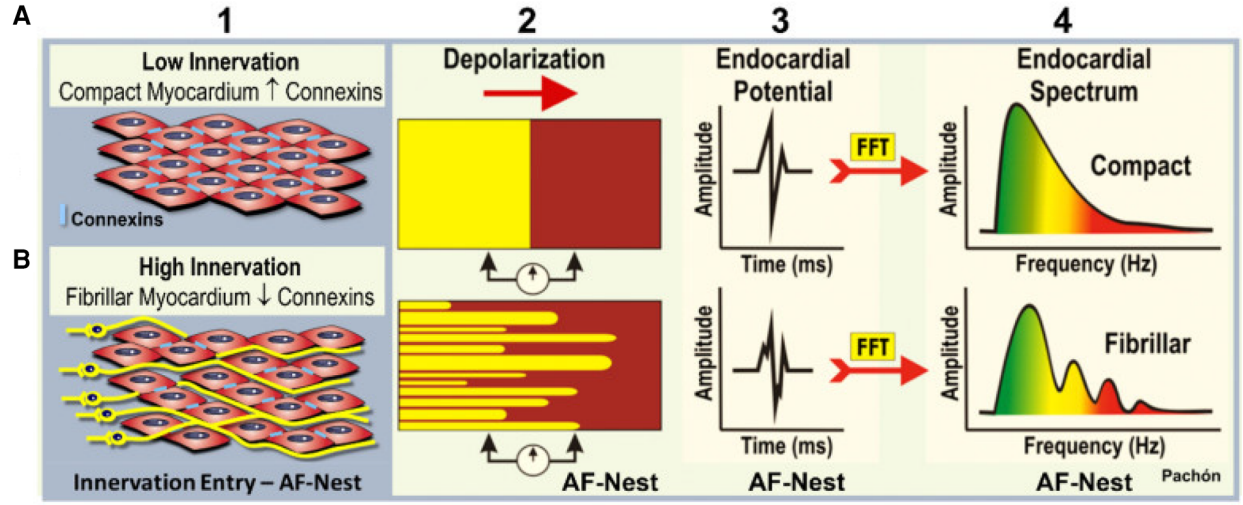

FIGURE 3
Mapping of endocardial potentials to find ganglia through the fast Fourier transformation. (A) Compact myocardium has a poor innervation, and the electrical conduction is homogeneous and paracellular due to the presence of connexins. That result in a clear and delineated endocardial potential. (B) Fibrillar myocardium: at the level of the neuro-myocardial interface, as in correspondence of the cardiac ganglia, the neural fibers determine a spectrum of highly fragmented endocardial potentials. *Courtesy by Pachon et al.* (32).

have been proposed and these include a CT-based identification of ganglia to improve the precision of RF delivery during CNA (38, 39), and the use of D- SPECT [123I]I-metaiodobenzylguanidine cardiac SPECT to provide anatomical quantification of autonomic nervous system structures (40).

Also high frequency stimulation (HFS) has been described for parasympathetic ganglia localization. Usually, HFS is delivered to GPs sites with these parameters: voltage of 10–20 V, amplitude of 30 mA, frequency of 20 Hz, and pulse duration of 5s (41). This stimulation may determine two types of atrial response: a prolongation of the PR or RR intervals by 50%, a transient ventricular asystole, or an AV block, which is defined as vagal response (VR), or the absence of changes in the PR or RR intervals, which is defined as a normal response (42, 43). The first response is typical of the GP sites whereas the second one reflects a normal atrial myocardium. The major limitations of HFS are the following: atrial fibrillation induction, need of general anesthesia, and inadvertent excitation of atrial wall nociceptors that leads to negative dromotropic or chronotropic effects. Additionally, because a significant portion of autonomic nerve fibers are located distant from the major GPs, the stimulation of these fibers, such those close to the pulmonary vein antrum, may lead to a false positive response.

Beyond the described methods, the best marker of the accurate location of the GPs is the immediate response to RF application, with asystole or a significant increase of the RR intervals occurring within a few seconds of application.

How to perform the ablation

The procedure is generally performed under general anesthesia to guarantee a high vagal tone during the procedure and to increase patients' tolerance, however the use of halogenated gas should be preferred, as with these drugs there is no risk of blunting the response to CNA. The use of conscious or deep sedation (midazolam and midazolam + propofol, respectively) is associated with a reduction of vagal response during ablation of right and left GPs (44).

The transseptal puncture is necessary in case the ablation is performed also in the left atrium.

The mapping is generally performed using 3D navigation systems. Once the 3D atrial map is reconstructed, the radiofrequency energy is delivered with irrigated catheters with a power commonly limited to 40 W (45) in cycle of 30 s or more. The ablation is commonly performed until the HAFE pattern is significantly reduced (a peak to peak distance <0.05 mV in bipolar electrogram) and vagal response to HFS disappears (32, 46–48).

Right or left atrium: where to start?

Chiou et al. demonstrated that several vagal fibers directed to the atrionodal sinus and the atrioventricular node travel across a fat pad close to the RSGP, in close proximity with superior vena cava (SVC), right pulmonary artery and aortic root (Ao). This so called "SVC-Ao fat pad" could be considered as a connection zone of all vagal fibers (11).

The ablation of the RSGP first was associated to significant modifications of vagal responses during the procedure, in term of changes in HR and blood pressure (49, 19).

Therefore, ablating the RSGP first, makes difficult the evaluation of subsequent ganglia denervation (37, 44). Aksu et al. therefore recommend a precise sequence of ablation, which implies the right-sided ganglia last: (1) LSGP, (2) LIGP and MTGP, (3) RSGP, (4) and RIGP (30). Anyway, there is still not a clearly approved order for ganglia denervation.

Brignole et al. proposed the execution of CNA via the right atrial approach alone, through the ablation of the sole RSGP in patients with recurrent cardioinhibitory syncope, and the ablation of the LIGP in case of functional AVB, exclusively or in addition to RSGP, considering these ganglia as the anatomical common pathway of cardiac parasympathetic fibers (50). Both ganglia are in the close proximity of the interatrial septum, and may be reached by ablation from right atria, avoiding a biatrial approach, which needs the transseptal puncture, thus reducing the duration of the procedure and the related risks, as embolization or pericardial effusion (12, 51, 52). Nevertheless, the right atrial ablation may be effective for the denervation of sinus node GPs, but may be not enough for the AV node GPs. Even if the ablation solely from the right atrium may be effective for cardiac nerve modulation and to prevent syncope recurrences, the ablation from both atria seems able to reach a more extensive denervation when it is quantitatively evaluated by extracardiac vagal stimulations (53–55).

Furthermore, the recent ROMAN2 study compared the acute effectiveness of the ablation from right vs. left atrium: when the ablation was performed in the right atrium, it was associated to a lower rate of complete vagal denervation, needing the cross-over to the other atrium to achieve an effective denervation (65% vs. 20%) (56).

However, there are yet no studies of head-to-head comparison of long-term results between right-sided, left-sided and biatrial approach for CNA, necessary to confirm the reproducibility of the right-sided alone ablation (48).

Ablation endpoint

The CNA appears to be more effective when associated with an extensive vagal denervation, as the probability of re-innervation is lower, however there is still not a clear strategy to evaluate that, thus it would be more appropriate to name it cardioneuromodulation rather than cardioneuroablation. Furthermore, a complete vagal denervation is also not desirable for the potential harmful effects, as discussed later in the text.

The HFS, repeated at each ablation site, is used to assess the elimination of a positive VR. The latter may be considered a suitable ablation endpoint, indeed further ablation is needed when VR remains positive. However, HFS is neither sensitive nor specific and, cannot predict the long-term effect of the ablation.

The absence of HR changes during atropine infusion is also considered a proof of satisfying vagal denervation. However, atropine should be given only at the end of the procedure, due to its long-lasting effect. Pachon et al, proposed a novel approach to evaluate the efficacy of vagal denervation during CNA, by

performing an extracardiac vagal stimulation (ECVS), during general anesthesia, via the internal jugular vein, taking advantage of the great proximity of the vagus to that vein (34). By advancing a quadripolar irrigated ablation catheter to jugular foramens bilaterally, the stimulation with an amplitude of 1 V/kg, maximum 70 V, with a width of 50 ms, and a frequency of 50 Hz for 5 s may elicit the VR (33). When the response is still positive after ablation this suggests an incomplete vagal denervation. The ECVS can be performed during CNA or at the end of the procedure. Ultrasound can be used to easily localize the vagus nerve, which appears thin and hyporeflective along the venous wall: some evidences showed that ultrasound-guided ECVS more frequently than fluoroscopy-guided ECVS enables to reach vagal positive response (57, 58).

It has recently been confirmed the superiority of an ECVS-guided approach in comparison to a CNA relying on anatomical landmarks and fractionated potentials mapping: indeed, performing ECVS before ablation to evaluate basal responses, during the procedure and after every cycle of radiofrequency to confirm the success of denervation, was associated to a lower rate of syncope recurrence compared to CNA performed without ECVS guidance (59).

Anyway, ECVS may have different effects depending from which side the stimulation is performed: usually, the right vagus nerve is more commonly stimulated because of the easiness of access of right jugular vein, but the AVN is mainly controlled by the left vagus nerve, thus the absence of VR to right ECVS doesn't guarantee always an effective denervation (60). Thus, bilateral vagal nerve stimulation should be performed to ensure the clinical efficacy of CNA, especially in patients with a relevant AVN disfunction.

Therefore, ECVS is an interesting method to evaluate vagal denervation, but it lacks of a long-term follow-up in order to make any comparison with the other methods.

Ablation outcomes and safety

CNA appears to be able to significantly reduce the recurrence of cardioinhibitory syncope (Table 1). A recent meta-analysis proves a freedom from syncope recurrence of 92% (57). A RCT published by Piotrowski et al. in 2022 compared syncope recurrence after CNA vs. non-pharmacological optimal therapy in 48 patients: they reported 8% recurrence in CNA patient group vs. 54% recurrence in controls group, during a 2-years follow-up (69). In a case report, the recurrence of syncope after CNA was associated to a vasodepressor response at HUTT, thus confirming the success of cardiac denervation, although the persistence of symptoms (70).

Overall, CNA can be considered a safe procedure (71). However, also for CNA the typical complications of invasive procedure are reported, such as pericardial effusion, thrombotic events, vascular complications (AV fistula, pseudoaneurysm); Also induction of Postural Orthostatic Tachycardia Syndrome (POTS) and isolated cases of acute occlusion of the sinus node artery are reported (72), to avoid which reducing the contact force may improve the safety of the procedure. Moreover, targeting the posterior aspect of the SVC could lead to phrenic nerve injury.

However biological long-term effects of CNA are still not well defined. An extensive parasympathetic denervation could determine a durable imbalance in autonomic cardiac regulation, and the sympathetic predominance associated to a higher heart rate may have long-term deleterious effects (73). The loss of sympatho-vagal balance may determine also endothelial (74) and cardiac metabolic dysfunction (71). Furthermore, in a canine model cardiac autonomic denervation determined a reduction of atrial effective refractory period, promoting arrhythmia inducibility (75, 76).

Reinnervation is a theoretical limitation to the efficacy of CNA, because it could be associated to a recovery of the vagal hyperactivity. This is a natural process that physiologically occurs in the first year, considering the massive distribution of nerve endings and the possible overlap of fibers from different GPs, or from the numerous surrounding micro-GP (77). However, a rate of reinnervation up to 30%–50% seems not able to reduce the long-term efficacy of CNA (78). On the other hand, reinnervation may be partially desirable, allowing the repair of the damage on axonal ends of sympathetic and parasympathetic fibers, and avoiding an excessive imbalance in autonomic cardiac regulation (67).

TABLE 1 Freedom from syncope recurrence after CNA, as reported by the current literature.

Authors	Year of publication	Number of patients	Type of approach	Follow-up (Months)	% of Success at follow-up	Approach for Ganglia localitation
Pachon et al. (32)	2005	21	Both atria	9.2 ± 4.1	100%	Spectral mapping
Pachon et al. (25)	2011	43	Both atria	45.1 ± 22	93%	Spectral mapping
Yao et al. (61)	2012	10	Left atria	30 ± 16	100%	HFS
Sun et al. (62)	2016	57	Left atria	36.4 ± 22.2	91%	HFS/Anatomic
Rivarola et al. (63)	2017	14	Both atria	22.5 ± 11.3	71.4%	EAM
Aksu et al. (37)	2019	20	Both atria	12	90%	EAM/HFS + Spectral analysis
Hu et al. (19)	2019	115	Left atria	21.4 ± 13.1	92%	HFS and or Anatomic
Calo et al. (48)	2020	18	Right atria	34.1 ± 6.1	83%	Anatomic
Aksu et al. (64)	2020	51	Both atria	11	94%	HFS + Spectral analysis
Pachon et al. (65)	2020	83	Both atria	40	80%	Anatomic + FEGM
Huang et al. (66)	2020	49	Left atria	17.8 ± 10.5	92%	EAM
Debruyne et al. (26)	2021	51	Right atria	12	95%	CT-guided
Piotrowski et al. (67)	2021	20	Both atria	12	100%	Anatomic + FEGM
Joza et al. (68)	2024	6	Both atria	13.4	67%	FEGM + HFS

HFS, high-frequency stimulation; EAM, electroanatomic mapping; FEGM, fractionated electrograms.

Other applications of CNA

The CNA may be performed as an alternative to cardiac pacing in patients with atrio-ventricular block (AVB) or sinus bradycardia due to parasympathetic hyperactivity (13, 79, 80).

These functional disorders are often paroxysmal, as symptoms usually occur at rest and during sleep and reduce with the exercise. Otherwise, in case of persistent advanced degree AVB, complete resolution of atrio-ventricular block during atropine administration or exercise test can be considered for differential diagnosis of functional AVB.

Several cases of CNA for treatment of I-II degree functional AV block and sinus bradycardia are reported in literature, especially in young and pediatric patients, avoiding an inappropriate pacemaker implantation (6, 81).

In these patients, considering the previously mentioned specific innervation of SAN and AVN, selective denervation of only the necessary ganglia, respectively RSGP and LIGP, could be a good strategy to make the procedure simpler and more precise. Indeed, selective denervation of RSGP for SAN dysfunction showed satisfactory results at 1 year follow-up (82), and most importantly ageing doesn't seem to affect the acute procedural success of CNA (83).

As for the AV node dysfunction, the selective denervation of PMLGP around the perimitral region of the inferior left atrium seems to reach good results (84). Nevertheless, the AV node may receive innervation from many other ganglionic plexuses, thus a bi-atrial approach seems to be more effective, as demonstrated by the multicentric international registry, PIRECNA study, where 90% of patients received biatrial ablation and 96% of procedural success was reached (80).

Pediatric population

The CNA seems to be safe also for pediatric patients, as reported by some case reports in the last years, and has been used not only for the treatment of cardioinhibitory syncope, but also for pathological symptomatic bradycardia (85), functional sinus node dysfunction and paroxysmal atrioventricular block (86).

Gaps in evidence and future perspectives

The CNA may be a valid option for patients aged <40 years with recurrent cardioinhibitory syncope, as a PMK implantation is not recommended in this age group, although there are not yet data from any controlled clinical trials that strongly confirm its effectiveness compared to that of pacing in young individuals.

Eventually, an individualized approach may be dedicated to patients aged between 40 and 60 years. Of note, the age does not impact the outcomes of CNA, if a careful selection of patients is performed (83). Furthermore, CNA could be considered as an alternative to cardiac pacing in case of functional AV block and of recurrent swallowing syncope or carotid sinus syndrome, in absence of intrinsic sinoatrial or AVN dysfunction, in elderly healthy patients aged >60 years (30, 87, 88).

However, the emerging evidence of CNA effectiveness is mainly based on case reports or observational studies. Further investigations and the results of large multicentric prospective registries as the CAN_FWRD registry (45), are highly awaited to evaluate the long-term efficacy and the safety of this procedure.

Author contributions

AM: Writing – review & editing, Writing – original draft. RP: Writing – review & editing, Writing – original draft. EP: Writing – original draft. DF: Writing – original draft. AS: Writing – original draft. GC: Writing – review & editing. VP: Writing – review & editing. GA: Writing – review & editing, Writing – original draft. LA: Writing – review & editing. CF: Writing – review & editing. LC: Writing – review & editing. AV: Writing – review & editing. PV: Writing – review & editing. AR: Writing – review & editing, Writing – original draft. TS: Writing – review & editing, Writing – original draft.

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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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Dietary interventions in the management of atrial fibrillation

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Atrial fibrillation (AF) represents the most common cardiac arrhythmia with significant morbidity and mortality implications. It is a common cause of hospital admissions, significantly impacts quality of life, increases morbidity and decreases life expectancy. Despite advancements in treatment options, prevalence of AF remains exceptionally high. AF is a challenging disease to manage, not just clinically but also financially. Evidence suggests lifestyle modification, including dietary changes, plays a significant role in the treatment of AF. This review aims to analyze the existing literature on the effects of dietary modifications on the incidence, progression, and outcomes of atrial fibrillation. It examines various dietary components, including alcohol, caffeine, omega-3 polyunsaturated fatty acids and minerals, and their impact on AF incidence, progression, and outcomes. The evidence surrounding the effects of dietary patterns, such as the Mediterranean and low carbohydrate diets, on AF is also evaluated. Overall, this review underscores the importance of dietary interventions as part of a comprehensive approach to AF management and highlights the need for further research in this emerging field.

KEYWORDS

atrial fibrillation, diet, nutrients, alcohol, caffeine, prevention

Introduction

Atrial fibrillation is the most common cardiac arrhythmia characterized by irregular and often rapid heartbeat (1). It is a common cause of hospital admissions with high readmission rates and significantly impacts quality of life (2). Patients with atrial fibrillation have an average reduction in their life expectancy and significant morbidity (3). Despite advancements in pharmacological therapy and catheter-based procedures, the prevalence of AF remains exceptionally high. There are many factors associated with AF, and the chance of spontaneous conversion back to sinus rhythm is lower with the existence of one or more of these risk factors, which include, but are not limited to, heart failure, left atrial size, and duration of the patient in AF (4, 5) As these risk factors are commonly present in the patients of modern times, the prevalence of AF remains high. It is a challenging disease to manage, not just clinically but also financially, as it places a tremendous burden on healthcare globally (2). Previous studies and emerging evidence suggest lifestyle changes, including dietary changes, play a significant role in preventing and managing AF (6) Its recurrent nature, associated symptoms, increased risk of stroke, heart failure, and overall cardiovascular morbidity and mortality demands significant attention and development of more effective management strategies. The current

therapeutic approach primarily focuses on symptom and heart rate management via rate and/or rhythm control, in addition to stroke prevention with the implementation of anticoagulation or mechanical exclusion of the left atrial appendage. A growing body of evidence supports restoration and maintenance of sinus rhythm as the preferred management strategy (7). Limited success maintaining sinus rhythm long term, toxicity of the antiarrhythmic drugs, progressive nature of associated co-morbidities and limited understanding of the atrial pathophysiology involved in the natural history of AF, has made it difficult to halt or slow its progression. However, the association of alcohol intake, obesity, diabetes, and autonomic imbalance with the incidence, recurrence and progression of AF has been well-recognized for quite some time (6). More recently, there has been a growing body of research supporting the adoption of risk factor modification as the fourth pillar in the management of AF, as proposed in the latest revision of the clinical practice guidelines published by the American College of Cardiology and American Heart Association Joint Committee (8). Lifestyle modifications have demonstrated a significant impact on the prevention and recurrence of AF. Dietary changes are a significant part of these lifestyle modifications. This review aims to provide a thorough overview of the evidence supporting specific dietary modifications in managing AF.

Methods

Databases and search strategy

A comprehensive and systematic literature search was conducted in two major electronic databases: PubMed and the Cochrane Library. These databases were selected due to their extensive collections of medical and clinical research articles. The aim was to identify studies published up to 2024 that examined the relationship between dietary factors and atrial fibrillation.

Keywords and search terms

The search strategy utilized a combination of keywords to ensure a broad and thorough search. Key terms included “Atrial fibrillation”, “Diet”, “Nutrition”, “Dietary interventions”. These terms were chosen to capture a wide range of studies that could provide insights into how diet and nutrition impact AF.

Inclusion criteria

To ensure relevance and quality, studies had to meet the following inclusion criteria:

Population: Studies involved human participants diagnosed with AF or those at risk of developing the condition.

Publication: Only studies published in peer-reviewed journals were considered.

Screening and selection process

The selection process involved several steps to ensure rigorous filtering and inclusion of relevant studies:

Initial Screening: Three independent reviewers screened the titles and abstracts of all identified articles. This initial step was crucial for excluding studies that were clearly irrelevant based on the title and abstract alone.

Full-Text Assessment: Articles that passed the initial screening were then subjected to a full-text assessment and the content of each of these studies was further investigated.

Discrepancy Resolution: Any discrepancies or disagreements among the reviewers were resolved through discussion and consensus, ensuring that the selection process was both thorough and unbiased.

Data extraction and synthesis

Given the anticipated diversity in study designs, populations, dietary interventions, and outcomes, a narrative synthesis approach was adopted. This method involves summarizing and interpreting the findings of the included studies in a descriptive manner rather than relying solely on statistical analysis. The narrative synthesis allowed for identification of common themes and highlighting consistent findings across different studies, contextual analysis which helped in understanding how different dietary factors may influence AF in various contexts and integration of diverse evidence by combining results from studies with varying methodologies to provide a comprehensive overview.

Summary of findings

The narrative synthesis aimed to collate and summarize the evidence regarding the impact of dietary interventions on atrial fibrillation. Key aspects included:

Types of dietary interventions: Examination of specific diets (e.g., Mediterranean diet), individual nutrients (e.g., omega-3 fatty acids), and other dietary components.

Outcomes: Analysis of outcomes such as AF incidence, symptom severity, and recurrence rates.

Population characteristics: Consideration of how different populations (e.g., age groups, comorbid conditions) respond to dietary changes.

By employing this systematic and structured approach, the review aimed to provide a detailed and comprehensive understanding of the current evidence on dietary interventions and their effects on atrial fibrillation.

Diets, nutrients and atrial fibrillation

Omega-3 fatty acids

The potential role of omega-3 fatty acids, primarily derived from fish consumption or supplementation, in influencing AF incidence has been extensively studied. Several lines of evidence from observational studies and randomized trials shed light on the complex relationship between omega-3 fatty acids and AF risk. Observational studies initially suggested a preventive effect of fish consumption against new-onset AF, particularly among elderly adults (9). Specifically, greater intake of broiled/baked fish, notably tuna, has been associated with a lower risk of AF. The protective effect is attributed to the beneficial impact of long-chain omega-3 fatty acids in fatty fish. However, fried fish or fish sandwiches did not confer the same protective effect, underscoring the importance of preparation methods (9). In contrast, randomized trials exploring marine omega-3 fatty acid supplementation for primary AF prevention have yielded discouraging results (10). A trial over 5.3 years found no significant effect in AF incidence compared to placebo, challenging the efficacy of omega-3 fatty acid supplements (10). In the other hand, a large cohort study involving over 54,000 participants over 13 years found that *in vivo* levels of omega-3 fatty acids had no association to the risk of incident AF, supporting their safety to regards to AF risk (11). A recent meta-analysis of prospective studies involving more than 200,000 participants and up to 12,000 cases of AF found no significant association between higher fish consumption or intake of omega-3 polyunsaturated fatty acids (PUFAs) and the development of AF (12). While fish and omega-3 PUFAs have been inversely associated with various cardiovascular diseases, including stroke and coronary heart disease, no significant inverse association was found with AF in this meta-analysis. The conflicting outcomes of clinical trials and observational studies may be attributed to various factors, including the heterogeneity of patient populations, differences in fish preparation methods, and the complex interplay between dietary components and cardiovascular health. Furthermore, the electrophysiological effects of omega-3 PUFAs, particularly EPA and DHA found in fish oil, on cardiac ion channels and membrane properties add another layer of complexity to the understanding of their potential role in arrhythmia prevention (13, 14). It is hypothesized that fatty acids may influence parameters crucial for generating and maintaining arrhythmias, but their impact on AF recurrence or postoperative AF, remains unclear. While omega-3 fatty acids derived from fish consumption or supplementation have been associated with various cardiovascular benefits, including potential anti-arrhythmic effects, currently they have no role in AF prevention or management. Further research and a higher level of evidence is necessary to better understand the association between omega-3 fatty acids, their modality of consumption, and cardiovascular health before their inclusion in strategies to treat or prevent AF.

Mediterranean diet

The Mediterranean Diet (Med-Diet) characterized by a high consumption of fruits, vegetables, whole grains, legumes, nuts, seeds, olive oil, a modest intake of fish and poultry, and a low consumption of red meat and sweets (15) has emerged as a robust preventative strategy against the development of AF. Numerous studies have demonstrated that adherence to the Mediterranean diet reduces the risk of AF and other manifestations of cardiovascular disease (16). Paradoxically and despite the lack of definitive evidence in support of omega 3 fatty acids supplements, it has been postulated that the Mediterranean diet's emphasis on foods rich in omega-3 fatty acids may contribute to decrease inflammation and improve cardiac function, lowering the risk of AF. Another proposed mechanism is the Mediterranean diet's high intake of fruits, vegetables, and olive oil which provide ample antioxidants and polyphenols, which have anti-inflammatory and cardioprotective effects (16). Hence the benefit could be attributable to the latter or their combination. The PREDIMAR study investigated the efficacy of a remotely delivered Med-Diet-based nutritional intervention in preventing atrial tachyarrhythmia recurrence post-catheter ablation in AF patients (17). The intervention, utilizing phone contacts, web-based tools, and resource access, enhanced adherence to the Med-Diet, notably resulting in positive dietary habit changes but failed to demonstrate an effect on AF recurrence post ablation. By recognizing diet as a crucial element of lifestyle modification, tools to optimize adherence could play a pivotal role in reducing AF risk. The study underlines the benefits of the predominantly plant-based traditional Mediterranean diet, focusing on fish, olive oil, nuts, fruits, and vegetables. Intriguingly in this study, the fish component of the Med-diet, rich in n-3 fatty acids, exhibits a "U" shaped curve, highlighting the delicate balance for optimal AF protection. A secondary analysis of the PREDIMED trial reveals significant AF protection with a Med-Diet supplemented with extra virgin olive oil (EVOO), emphasizing its anti-inflammatory and antioxidant properties (18). Other studies have evaluated the Med-Diet's intersection with metabolites in the tryptophan-kynurenine pathway, which are associated with heart failure and AF risk (19) The Med-Diet, especially when supplemented with EVOO, demonstrates potential counteraction against these metabolites, emphasizing its role in regulating inflammation (18). The comprehensive PREDIMED study showed a 30% reduction in cardiovascular events, improved blood pressure, insulin resistance, and lipid profiles, emphasizing its multifaceted impact (20). Additionally, Med-Diet has a positive impact in weight loss, triglycerides, blood pressure, and diabetes mellitus, presenting a holistic approach to cardiovascular health and hence offering a dietary formula to decreasing the various risk factors involved in the development of AF. A complementary study from 2014 further supports the cardiovascular benefits of the Med-Diet, highlighting its association with reduced platelet activation and thromboxane A2 production in AF patients (21). This study, focusing on elderly AF patients at high risk of atherosclerosis and thromboembolism, establishes a link between higher Med-Diet adherence and diminished platelet activation, supported by a reduction on

thromboxane B2 biosynthesis (22). Notably, wine and olive oil consumption, integral to the Med-Diet by some definitions, were independently associated with lower platelet activation levels, suggesting a beneficial effect. While the study's observational nature and limited sample size pose constraints, it introduces a novel biological explanation for the cardiovascular advantages of Med-Diet, particularly when enriched with extra virgin olive oil. Alcohol consumption, nevertheless, has been associated with higher incidence of AF as discussed later in this review and should probably be excluded for now from the Med-Diet recommendations for patients with AF. In summary, the Mediterranean Diet has been described as a nutritional powerhouse, rich in antioxidants and displaying favorable metabolic effects. Its protective role in preventing AF still needs to be further evaluated but evidence supports that the diet addresses risk factors associated with metabolic syndrome which underscores the overall value of dietary interventions in promoting cardiovascular health. The nuanced relationships between specific dietary components, remote nutritional interventions, and metabolites further emphasize the need for additional research, including larger and better controlled interventional studies, to explore the clinical impact of the Med-Diet in AF patients and its potential role in reducing cardiovascular events and disease progression. Funding and scale for such studies remains a challenge. Currently, its potential benefits and lack of evidence for harm supports a cautious recommendation in favor of the Mediterranean Diet, excluding regular alcohol intake, as a healthy alternative for patients at risk or with AF. Future research may help optimize the elements of the diet, confirm, reject or identify specific populations more likely to benefit from this recommendation.

DASH diet

Another dietary intervention that has shown positive effect on the management of hypertension and statistical association with improved survival is the DASH diet but an effect on incidence, recurrence or progression of AF has not been demonstrated. In the Dietary Approaches to Stop Hypertension (DASH) study (23), a diet rich in fruits and vegetables combined with low-fat dairy foods in addition to reduced total and saturated fat resulted in significant blood pressure lowering effect and good adherence. Subsequent large population studies have shown an association between DASH and similar diets with improved cardiovascular outcomes and decreased mortality (24) but once corrected for other lifestyle factors have not shown a definitive effect on AF (25). Considering the effects on blood pressure, cardiovascular health, mortality and weight, it is reasonable to consider DASH as a healthy dietary alternative to recommend for patients with AF particularly those with associated hypertension and diabetes.

Low-carbohydrate diet

Diabetes mellitus, a complex metabolic disorder, constitutes a significant contributor to the heightened risk of AF, with studies indicating a 40% increase in AF risk associated with diabetes (26). The risk escalates with higher hemoglobin A1c levels and prolonged diabetes duration, establishing a direct correlation between diabetes severity and AF susceptibility. The intricate pathophysiologic mechanisms associated to diabetes exert their effect not only directly but also indirectly, intertwining with other AF comorbidities like obesity and dietary habits. Aggressive diabetes control is recommended as part of the comprehensive lifestyle modification intervention that proved successful in the management of AF in the ARREST AF trial (27). Surprisingly and complicating our understanding, a large prospective cohort study (ARIC study) spanning over two decades unravels a novel association between dietary choices and AF incidence (28). The research identifies a higher risk of incident AF linked to a low-carbohydrate intake as a percentage of energy. This marks a departure from traditional dietary assessments primarily focused on factors like omega-3 fatty acids. The study's robust design, involving a large community-based cohort with extensive follow-up and thorough statistical adjustments, underscores the reliability of its findings. The inverse relationship between carbohydrate intake and incident AF prompts considerations about the potential mechanisms at play. The study posits that low-carbohydrate diets lead to reduced intake of anti-inflammatory foods, trigger oxidative stress, and potentially elevate the risk of other cardiovascular diseases, all of which are established risk factors for AF. However, the study also acknowledges limitations inherent in its observational nature, including potential measurement errors in dietary assessments and challenges in accurately classifying AF types. Despite these caveats, the findings highlight the cautious evaluation of low-carbohydrate diets and their implications on arrhythmia. The call for additional research, including randomized controlled trials, echoes the need to delve deeper into the intricate relationship between dietary choices, metabolic conditions like diabetes, and the multifaceted landscape of AF risk factors. Further exploration is essential to guide recommendations and interventions for primary AF prevention in the complex interplay between metabolic health and dietary patterns.

Alcohol

Despite moderate alcohol intake being considered in the past an element of the Mediterranean Diet and a potential protective intervention against coronary artery disease, a meta-analysis conducted in 2010 consistently showed a clear association between alcohol consumption and the risk of AF onset across different settings, with varying strengths of association (29). A dose-response relationship between daily alcohol intake and AF risk was observed, suggesting a potential threshold under which the increased risk of AF may not be significant. Temporal analyses and interventions indicate the reversibility of AF following changes in alcohol consumption. The proposed mechanism is the effect of alcohol on the atrial tissue and its electrical properties, leading to abnormalities such as decreased conduction velocity and shortened refractory periods, promoting the development of atrial re-entry and the various

pathophysiologic mechanism underlying AF (30). Another proposed pathophysiology mechanism involves affecting histamine levels and cytosolic sulfotransferases. Additionally, alcohol-related hypertension may contribute to atrial remodeling, further increasing the risk of AF onset (31). Both clinical and pathophysiological evidence strongly suggest that regular alcohol consumption may cause AF. A multicenter randomized controlled trial aimed to investigate the impact of reducing alcohol consumption on AF recurrence among regular drinkers with symptomatic AF found that substantial reduction in alcohol intake was associated with a decrease in AF recurrence and a reduced proportion of time spent in AF (32). Previous studies have shown a dose-related increased risk of incident AF with alcohol consumption, even with low levels of intake. However, limitations include relying on patient-reported alcohol quantities subject to recall bias, potential confounding factors, and challenges assessing secondary outcomes such as cardiovascular events. Gender variations are evident regarding the link between moderate alcohol intake and AF, with males showing a more pronounced increase in risk (33). A Danish study found that increasing alcohol intake over five years correlated with higher AF risk, but reducing intake did not significantly reduce risk (29). Overall, it has been recognized that regular alcohol consumption is a modifiable risk factor for AF and reducing alcohol intake might lead to a reduction in AF burden and recurrence. Prospective data on alcohol changes and AF risk is sparse. Limitations include self-reported alcohol intake, possible selection bias, and lack of consideration for binge drinking and sleep apnea. Observational data cannot establish causality, and AF assessment has frequently relied on diagnosis codes, possibly underestimating incidence. Based on current evidence alcohol abstinence is recommended to prevent AF and AF recurrences.

Gluten

Celiac disease (CD) is a chronic gastrointestinal inflammatory disorder characterized by malabsorption in individuals sensitive to gluten-containing grains. While its global prevalence in the general population is around 1%, it is notably higher in patients with autoimmune disorders, reaching 8%–20% (34). CD has been linked to a significantly higher risk of major adverse cardiovascular events, including cardiac arrhythmias (35). Cardiovascular disease is the most common cause of death among these patients (36). Theoretically, inflammation and fibrosis play a significant role in developing AF (37). Studies have shown a slightly elevated risk of AF in patients with CD, both before and after the diagnosis; however, the risk was higher around the time of the diagnosis, suggesting a role of increased amount of inflammation aggravating both CD as well as AF (38). Studies have found a link to various inflammatory markers like high-sensitivity C-reactive protein, sICAM-1, and fibrinogen (38, 39). Furthermore, cases of ventricular arrhythmia in CD patients with autoimmune myocarditis improved with a gluten-free diet, indicating a potential link between CD and arrhythmias in general (40). Our group has reported a small case series of patients with gluten sensitive arrhythmias including AF and idiopathic premature ventricular contractions with near resolution of symptoms after adopting a gluten free diet (41). In summary, there is a link between autoimmune diseases and the risk of development of AF, particularly in patients with CD; however, once the confounding factors are adjusted, the risk remains only small at around 30% (38). An evaluation to rule out sub-clinical or undiagnosed CD as well as an empiric trial of gluten avoidance in patients with idiopathic or "lone" AF may be reasonable based on its simplicity and lack of harm.

Caffeine

Contrary to common believe and the sporadic anecdotal association of caffeine intake to cardiac arrhythmias, a 2016 cohort study found that coffee ingestion and total caffeine intake were associated with a reduced risk of developing AF across various risk groups (42). While caffeine has been extensively studied, coffee contains numerous compounds besides caffeine that may contribute to health effects (43). Some studies suggest that compounds in coffee may counterbalance adverse effects of caffeine, with potential benefits for cardiovascular health. However, the specific compounds responsible for these benefits remain unidentified (43, 44). In a meta-analysis, participants consuming higher levels of coffee showed a lower risk of AF, consistent with prior findings (44). However, the study had limitations, such as potential residual confounding and the inability to distinguish between caffeinated and decaffeinated coffee intake. Despite these limitations, the study's strengths included a large sample size, detailed data collection, and almost complete adherence to follow-up. A 2018 meta-analysis concluded again that caffeine does not increase the risk of AF (45). It demonstrated an association between higher caffeine intake and a lower incidence of AF. A Potential mechanism for caffeine's protective effect against AF includes its lack of acute arrhythmogenicity in healthy individuals (44). Other studies have also found favorable outcomes associated with caffeine intake or coffee consumption, including reduced risk of death from various causes and no relationship between chronic caffeine consumption and ventricular ectopy (46). In another prospective study involving healthy middle-aged women, caffeine use was not associated with an increased risk of AF (47). Women in the highest quintile of caffeine intake had a similar AF risk to those in the lowest quintile, with minimal changes after multivariable adjustment. Interestingly, women in the third quintile of caffeine consumption were found to have lower risk of AF, suggesting the potential benefits of moderate caffeine intake. These findings, as mentioned earlier, suggest that increased caffeine consumption does not contribute to the increasing burden of AF in the general population, and moderate caffeine intake may even have a protective effect. Further studies are needed to elucidate coffee's cardioprotective effects beyond caffeine and determine potential differences in sensitivity between coffee and pure caffeine intake. The current body of evidence supports the conclusion that caffeine consumption does not increase AF incidence and could even reduce it, particularly with moderate coffee consumption. Nevertheless, most of this favorable data derive from

large population studies. It remains unclear if a sub-group of individuals could be particularly sensitive to caffeine, subjects among whom caffeine intake could lead to AF or AF recurrences, acting perhaps as a trigger. In clinical practice, few patients report this clinical association and among them it remains reasonable to recommend avoidance of caffeine once identified as their reproducible trigger, regardless of the mechanism involved.

Chocolate

Chocolate consumption in its association with AF has yielded inconsistent findings across various studies (48). A Danish population-based cohort study involving 55,502 participants over an average of 13.5 years revealed a significant association between chocolate intake and reduced AF risk (49). However, two prior studies, the Women's Health Study and a cohort study of US male physicians, found no statistically significant associations between chocolate consumption and AF risk (50, 51). The Women's Health Study, with more than 33,000 female participants followed for over 14 years, showed non-significant hazard ratios across quintiles of chocolate consumption, except for the third quintile (50). Similarly, the Physicians' Health Study, following 18,819 US male physicians for approximately nine years, revealed non-significant hazard ratios for various levels of chocolate consumption (51). Data from two cohort studies and a meta-analysis, including 180,454 participants, also found no evidence of an association between chocolate consumption and AF risk (50). In an analysis of two prospective multicenter Swiss AF cohort studies (Swiss-AF) and (BEAT-AF), chocolate consumption was found to have no association with major adverse cardiac events such as ischemic stroke, myocardial infarction or cardiovascular death in a patient population with AF (52). While some studies have shown a beneficial link between moderate chocolate consumption and other cardiovascular diseases like ischemic heart disease, heart failure, and stroke, the impact on AF appears to be neutral (53). This discrepancy could be due to the cardiovascular effects of cocoa products, such as improved endothelial function and modest reductions in blood pressure and insulin resistance, which may have less influence on AF than atherosclerosis-related cardiovascular diseases (54). Strengths of the Swedish cohort studies included their large sample sizes, adjustment for major potential confounders, and reliance on objective data from the Swedish Patient Register. However, limitations such as inevitable misclassification of chocolate consumption, lack of information on milk chocolate vs. dark chocolate consumption, and the observational design should be noted. Despite the large sample size in the meta-analysis, no association between chocolate consumption and AF risk was observed. No definitive recommendation can be made regarding chocolate consumption in relationship to AF.

Salt

In a large-scale prospective observational study involving 473,080 adults, the relationship between estimated daily salt intake and the risk of new-onset AF was investigated (55). The study utilized urinary sodium excretion as a proxy for dietary salt intake, revealing a U-shaped association between sodium intake and AF risk among men; very low and high estimated daily sodium intakes were associated with elevated AF risk. Among women, while there was initially a tendency for a J-shaped association between sodium excretion and AF risk, this trend vanished after adjusting for established cardiovascular risk factors. A Finnish study, albeit smaller in scale, supported the association between high salt intake and increased AF risk but did not report the association between low sodium intake and AF risk among men (56). Other investigations have provided additional insights into the complex interplay between sodium intake and cardiovascular health, including its potential role on the pathophysiology of atrial tachycardia and atrial fibrillation, not solely from hypertension but also by elevating intracellular calcium levels within cardiac tissue via the sodium/calcium exchange mechanism. This elevation subsequently influences intracellular calcium release from the sarcoplasmic reticulum, consequently contributing to arrhythmias. Moreover, sodium can alter the mechano-electrical dynamics of the myocardium, potentially precipitating arrhythmias due to modifications in cell length or tension (57, 58). On the contrary, a meta-analysis of more than 1.4 million participants in 2021 indicated that salt intake does not correlate with a heightened risk of developing new-onset AF and that factors beyond salt intake itself may exert a more significant influence on the occurrence of new-onset AF (59). However, this study had some significant limitations. It combined studies with different designs, such as Mendelian randomization and cohort studies, which could lead to methodological heterogeneity. Additionally, observational studies, including Mendelian randomization studies, may suffer from selection bias as they typically recruit survivors, potentially missing individuals who have died due to cardiovascular disease related to salt intake. This could lead to a false null association between salt intake and AF risk due to competing risks rather than indicating no relationship between salt intake and AF risk. To summarize, most studies have found a strong link between salt intake and AF risk; low sodium intake is also associated with better blood pressure control and better cardiovascular outcomes which in turn may result in lower risk of AF. However, further research is warranted to elucidate causality and better understand sodium intake's role in AF development, prevention and management.

Antioxidants and micronutrients

Carotenoids

Low plasma concentrations of lutein and zeaxanthin are associated with a nearly twofold increased risk of AF (60). However, carotenoids such as b-cryptoxanthin, lycopene, a-carotene, b-carotene, and total carotenoid deficiency did not significantly correlate with AF risk. Recurrent AF was used in the risk analysis, with a high incidence observed despite antiarrhythmic therapy. It emphasizes the role of inflammation and oxidative stress in AF development and suggests that

carotenoids, known for their antioxidant properties, may mitigate these factors. The anti-inflammatory and antioxidant effects of carotenoids may contribute to the remodeling of atrial myocytes, reducing the risk of AF. Carotenoids, in combination with different antioxidants found in fruits and vegetables, may have synergistic effects, providing more significant health benefits than individual antioxidants. With their reported interactions in the human body by scavenging free radicals, carotenoids may independently contribute to a decreased risk of AF. In conclusion, the low plasma levels of lutein and zeaxanthin are associated with an elevated risk of AF in the elderly. It supports the idea that consuming foods rich in carotenoids like fruits and vegetables as emphasized in the Mediterranean and DASH diets may be protective against AF.

Flavonoids

The postulated potential benefits of flavonoids in reducing AF risk remain inconsistent. In a large Danish cohort study spanning 23 years, higher habitual intake of total flavonoids was not significantly associated with lower incident AF risk overall. However, intriguingly, flavonoid intake showed a protective effect in smokers and heavy alcohol consumers (61). Flavonoids have been implicated in mitigating cardiovascular disease markers through anti-inflammatory and anti-thrombogenic pathways, but their role in AF prevention remains uncertain (61). Notably, the observed association between flavonoid intake and reduced AF risk in specific subgroups suggests potential protective effects mediated through inflammatory and oxidative stress pathways rather than direct antiarrhythmic properties (62). While studies have provided valuable insights, limitations inherent to observational research, such as unmeasured confounders and potential changes in dietary habits over time, warrant cautious interpretation of the results. Further research is needed to authenticate these findings and explore the potential benefits of flavonoid-rich foods, particularly in high-risk populations such as smokers and heavy alcohol consumers, for AF prevention.

Magnesium

A study involving 3,530 participants from the Framingham Offspring Study investigated the association between serum magnesium levels at baseline and the risk of atrial fibrillation in individuals free of cardiovascular disease (63). Using Cox proportional hazard regression analysis and adjusting for various factors, including conventional AF risk factors, the researchers found that lower serum magnesium levels were moderately associated with a higher risk of developing AF over a follow-up of up to 20 years. Individuals in the lower quartile of serum magnesium were approximately 50% more likely to develop AF than those in the upper quartiles. The results remained consistent even after excluding individuals on diuretics from the analysis. Given the common occurrence of hypomagnesemia in the general population, this research has potential clinical implications. Additionally, in critically ill patients, where post-operative AF is common, magnesium supplementation has shown promise in preventing AF development, likely through its anti-inflammatory and anti-arrhythmic effects (64). However, limitations such as small sample sizes, high risk of bias in some studies, and heterogeneity in outcomes should be considered when interpreting the findings. Further research is needed to validate these results, especially in critically ill populations, to improve patient outcomes and reduce healthcare utilization costs associated with AF.

Potassium

Hypokalemia has been associated with higher risk of AF (65, 66), cardiovascular events, stroke and mortality in the general population (67, 68) and among patients with hypertension (69). It is a recognized risk factor for AF after cardiac surgery (70). Low potassium has been shown to reduce sinoatrial node activity and increase pulmonary vein firing in animal models (71). Potassium-rich foods seem to counteract the negative effect of sodium by promoting diuresis and reducing aldosterone secretion (72). Surprisingly, potassium supplementation has failed to demonstrate a reduction in the incidence of AF after cardiac surgery (73). On the other hand, the use of potassium chloride supplementation and combination of sodium and potassium chloride as dietary substitutes for sodium has been shown to have a positive effect on hypertension, cardiovascular events and death (74–77). Direct evidence on the effects of potassium supplementation in AF is still lacking. Extrapolating from its beneficial effects on hypertension and cardiovascular outcomes and evidence in favor of the Mediterranean and DASH diet, it is reasonable to consider the recommendation of potassium-based salt substitutes for patients with or at risk of AF. Caution and close monitoring must be considered amongst patients with renal function impairment and at risk for hyperkalemia.

Miscellaneous micronutrients

Deficiencies and levels of certain other micronutrients, such as selenium (Se) and iron (Fe), have been linked to new-onset atrial fibrillation in a large community-based cohort. After adjusting for potential confounders, Se deficiency, similar to Mg deficiency, was associated with an increased risk of new-onset AF, particularly in non-smoking participants (78). Se deficiency also showed a significant association with non-smoking participants experiencing over a 65% increased risk. Mechanistically, it may contribute to mitochondrial dysfunction and oxidative stress, two factors involved in the pathogenesis of AF and heart failure. However, Fe deficiency did not show a significant association with new-onset AF, although it was observed that older men had a slightly higher risk (78). Histamine, derived from histidine, plays a role in immune responses and cardiovascular regulation. Elevated levels are associated with arrhythmogenic potential, stimulating H2 receptors to accelerate heart rate and trigger diastolic depolarization, potentially leading to atrial tachycardia (79). Histamine-induced depolarization of Purkinje fibers may promote ventricular tachycardia (79). Rare cases link hyper-histaminemia to cardiac arrests and AF (80). Due to its wide range of pro-arrhythmic

properties, a pilot study suggested elevated levels in 21.2% of AF patients, possibly due to histamine-containing foods, allergies, infections, or immune disorders (81). However, prospective data on histamine's role in AF are limited. These findings suggest that nutritional imbalances may represent modifiable risk factors for AF, independent of heart failure development, highlighting potential avenues and research for AF prevention.

Obesity and atrial fibrillation

Obesity is prevalent in the US, where both obesity and AF burdens are high. The Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY) study, focusing on 355 overweight AF patients, demonstrated the remarkable impact of modest weight loss (82). During the waiting period for their AF ablation procedure, 38% successfully lost around 36 pounds, resulting in significant AF reduction. Nearly half of the patients achieved complete remission solely through weight loss, eliminating the need for antiarrhythmics or ablation. Moreover, improvements were observed in systolic blood pressure, C-reactive protein, diabetes remission, LDL levels, triglycerides, echocardiographic abnormalities, and overall sense of well-being. Obesity's intricate relationship with AF involves complex mechanisms, including inflammation and oxidative stress, with weight loss showing promise in reducing AF development and recurrence (83). Similar reductions in AF have been reported among patients undergoing bariatric surgery (84). Challenges remain in understanding variations in AF risk associated with different fat types and the impact of obesity on permanent AF. Despite the mainstream belief in weight loss benefits, a post hoc analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study demonstrated an "obesity paradox" with better clinical outcomes amongst obese patients with AF (85). On the other hand, early-life obesity has been recognized as a predictor of AF risk. Epicardial fat, a key player in left atrial remodeling, poses imaging challenges when quantifying it to establish its relationship with AF severity. Based on the overall benefits of weight reduction in cardiovascular health, blood pressure and the results of the LEGACY (82) and similar clinical studies, weight reduction is recommended for reduction in the burden of AF and as co-adjuvant to antiarrhythmic drug therapy and catheter-based ablation.

Bacteriome, diet and atrial fibrillation

Multiple studies have demonstrated a strong association between alterations in the gut microbiota and the risk of cardiovascular disease and AF. It is described that patients with AF develop dysbiotic gut microbiota with higher microbial diversity and specific composition patterns. It is recognized that diet and drugs could be important determinants in the composition of the gut bacteriome (22). Bacteria metabolites like gut-derived lipopolysaccharide, Trimethylamine N-Oxide, secondary bile acids (86–89) are found elevated in patients with AF and linked to atrial inflammation and adverse electrical remodeling. Meanwhile the gut microbiota changes accompanying AF are also associated with disrupted production of the rather protective short chain fatty acids (90). Fecal transplantion studies in animals has demonstrated that transplanting dysbiotic microbiota or microbiota from aged animals to healthy subjects results in higher susceptibility to AF, increased levels of circulating lipopolysaccharide and evidence of inflammation and fibrosis in the atrium (91, 92). Despite the current body of evidence supporting an association between AF, the gut microbiota and its derived metabolites, it is not clear if they have causal or modulation effect. Even less understood is the potential opportunity to intervene via diet, pharmacotherapy or fecal transplantation in the prevention or treatment of AF (93).

Proposed mechanisms

AF is a complex arrhythmia with multiple underlying mechanisms. Several dietary factors and micronutrients studied for their potential role in the pathophysiology of AF affect various of these mechanisms, as described in this article. There is an overlap between the different mechanisms outlined here, but it is important to recognize the contrast between these separate processes and their respective significance in the complex pathophysiology of this arrythmia. Following is a brief overview of the various proposed mechanisms of action mediating the interactions between diet and the pathophysiology, clinical manifestation and progression of AF.

Inflammation and oxidative stress

Oxidative stress, caused by an imbalance between reactive oxygen species (ROS) production and the body's antioxidant defenses, is significantly implicated in AF development and remodeling (94). Studies have demonstrated that increased oxidative stress in atrial tissue leads to protein modifications and calcium accumulation, contributing to AF by reducing antioxidant levels like vitamin C and glutathione (95). Key sources of ROS in AF include NADPH oxidase, xanthine oxidase, nitric oxide synthase uncoupling, myeloperoxidase, and monoamine oxidase. These enzymes, particularly NADPH oxidase, are activated by conditions such as hypertension and hyperglycemia, leading to fibrosis and atrial remodeling. Experimental evidence also points to mitochondrial dysfunction and ROS production causing calcium leaks that trigger AF. Myeloperoxidase and monoamine oxidase further contribute to atrial fibrosis and oxidative damage, exacerbating AF risk. Ultimately, excessive ROS alter ionic currents and cellular signaling, prolonging action potentials, reducing cardiac conduction, and promoting re-entry and focal activity, which are central to AF pathogenesis. Diets rich in antioxidants, like fruits, vegetables, and whole grains, may help mitigate inflammation and oxidative stress. Micronutrients like vitamins C and E and

polyphenols found in foods like berries and green tea have antioxidant properties and may reduce AF risk by combating oxidative damage (62). As previously mentioned in this review, the Mediterranean diet and a diet rich in carotenoids may mitigate the development and progression of AF through their antioxidant properties. Coffee has also been linked to decrease inflammation as it contains high levels of antioxidants such as cafestol, polyphenol, trigonelline, chlorogenic acid, and quinine. Moderate coffee consumption, through the aforementioned mechanism, has been linked to decrease incidence and risk of developing atrial fibrillation (44).

Electrical and structural remodeling

AF is associated with electrical as well as structural remodeling of the atria, characterized by alteration in ion channel function and atrial conduction. Omega-3 fatty acids found in fatty fish, like salmon and mackerel, have been shown to modulate ion channel function and stabilize atrial electrical activity, potentially reducing susceptibility to AF (96). This mechanism may be shared with other nutrients that prevent atrial inflammation, mechanical stress and cellular uncoupling. Structural changes in the atria, such as fibrosis and hypertrophy, contribute to AF substrate formation. Diets low in sodium help mitigate atrial fibrosis by reducing inflammation, hypertension and oxidative stress (97). Hyperglycemia and foods rich in sodium have been linked to atrial fibrosis, left atrial enlargement, and cause electrical and autonomic remodeling which can lead to inter and intra-atrial conduction delays. Potassium-rich foods like bananas, potatoes, and avocados may counteract the pro-fibrotic effects of sodium by promoting diuresis and reducing aldosterone secretion (72).

Autonomic nervous system dysfunction

Imbalances in the autonomic nervous system, both sympathetic and parasympathetic overactivity, can promote AF initiation and maintenance (98). In patients with established AF or structural heart abnormalities, sympathetic stimulation may be the driving factor in AF initiation (99). Vagal stimuli such as eating, sleeping, relaxation, and alcohol consumption have been identified as triggers for AF, particularly in younger individuals or those with a family history of AF (100, 101). Alcohol has been linked to shortened effective refractory period and low alcohol consumption may help reduce sympathetic tone and lower AF risk (33). Also, alcohol consumption has been linked to increased vagal stimulation and increasing the incidence of AF (101). This was more commonly reported in younger individuals and with beer and red wine consumption. Additionally, magnesium, present in foods like nuts, seeds, and leafy greens, plays a role in regulating autonomic function and may have antiarrhythmic effects with low magnesium levels been linked to increased automaticity (63). There have been multiple reports of vagal AF induced by ingestion of cold beverages as well (102). Vagal triggers for AF, such as eating or occurrences solely at night without adrenergic triggers, have been reported by a significant proportion of patients with paroxysmal AF (103).

Cell membrane stability

Deficiencies in certain micronutrients, such as magnesium and potassium, have been implicated in AF pathogenesis. By its effect on the slow-activating delayed rectifier K channel (IKs) and calcium channels (L-type) in the atria, Magnesium can stabilize the cardiac cell membrane and play a protective role against AF (104). PUFAs stabilize cardiomyocyte membranes and their integration into the cell membrane's phospholipids alters ionic currents, such as the sodium and calcium channels, leading to antiarrhythmic effects (105). Chronic administration of PUFAs results in membrane incorporation that modifies ion channel behaviors and reduces arrhythmogenic activity. By inhibiting atrial-specific potassium currents and decreasing Na+ -Ca2+ exchange current, it reduces delayed after depolarizations and arrhythmia risk. Balanced diets containing adequate amounts of these nutrients, along with supplementation, when necessary, may help maintain cardiac electrical stability and reduce AF susceptibility (64).

In summary, various dietary factors and micronutrients can influence multiple mechanisms involved in AF pathogenesis, including inflammation, oxidative stress, electrical and structural remodeling, autonomic dysfunction, and metabolic abnormalities (Figure 1). Adopting a balanced and nutrient-rich diet may reduce AF risk and improve outcomes. However, individual dietary strategies should be tailored based on specific patient characteristics and influenced by potentially identifiable individual underlying mechanisms contributing to AF.

Highlighted studies

Table 1.

Future directions and clinical implications

Future directions and clinical implications of exploring diets and micronutrients in their relationship with AF encompass several key areas, focusing on both preventive strategies and therapeutic interventions. Here are some potential future directions and their clinical implications:

Precision nutrition approaches

Future research may delve into personalized nutrition strategies tailored to individuals based on their genetic predispositions, comorbidities, and lifestyle factors. Precision nutrition aims to optimize dietary interventions for AF prevention and management by considering individual variations in metabolism,

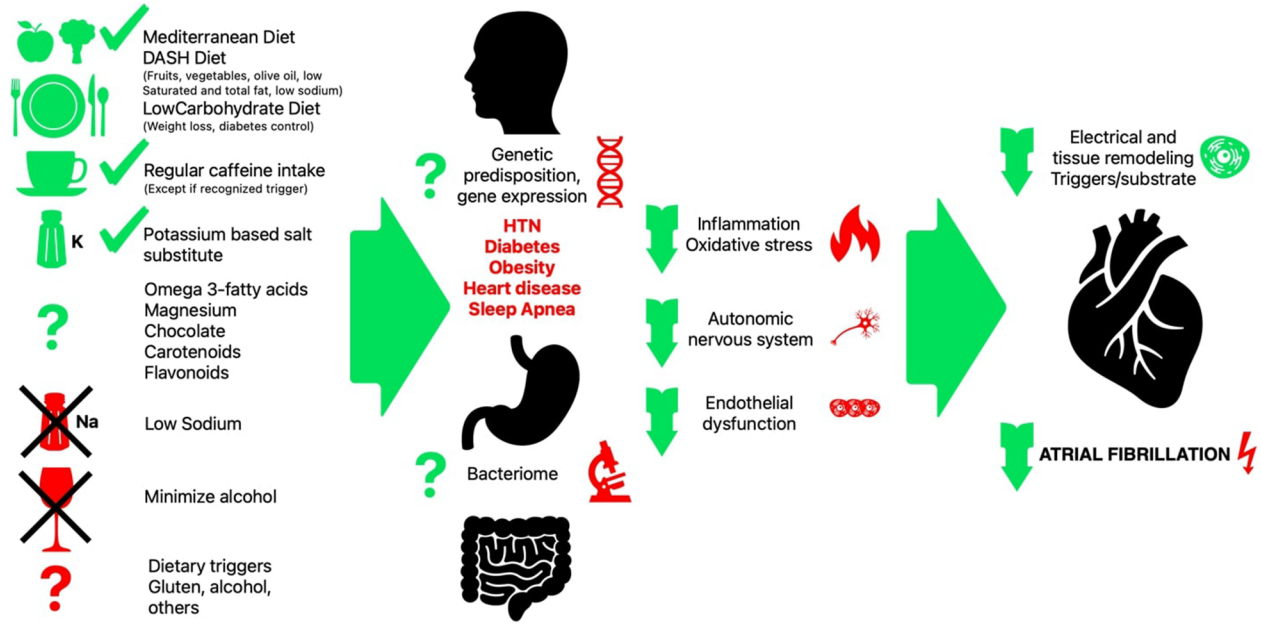

FIGURE 1
Graphic representation of recognized positive and negative dietary risk factors and their interaction with individual non dietary risk factors. The poorly understood contribution of some dietary components, triggers, genetic predisposition and gut bacteriome is represented with question marks.

gut microbiota composition, and dietary preferences. Clinical implementation of precision nutrition in AF management could involve comprehensive dietary assessments, genetic testing, and targeted nutritional interventions tailored to each patient's specific needs.

Clinical trials of dietary interventions

Large-scale randomized controlled trials investigating the efficacy of specific dietary interventions in preventing or managing AF are needed. These trials should evaluate various dietary patterns (e.g., Mediterranean diet, DASH diet), individual nutrients (e.g., omega-3 fatty acids, magnesium), and dietary supplements (e.g., antioxidants, vitamin D) in diverse patient populations with AF. Clinical trials should assess the effects of dietary interventions on AF recurrence and their impact on clinical outcomes, such as AF burden, progression, stroke risk, hospitalizations, heart failure and mortality.

Longitudinal cohort studies

Prospective longitudinal cohort studies with extended follow-up duration are essential for elucidating the long-term effects of dietary habits and nutrient intake on AF incidence and progression. To accurately capture dietary exposures, these studies should incorporate comprehensive dietary assessments, including food frequency questionnaires, 24-h dietary recalls, and biomarker measurements. Longitudinal cohorts can provide valuable insights into the temporal relationship between dietary factors and AF risk, identify potential dietary biomarkers of AF susceptibility, and elucidate the mechanisms underlying diet-AF associations. Modern tools like artificial intelligence and personal digital devices will facilitate collection, management and analysis of more detailed and accurate data points amongst larger populations.

Mechanistic studies

Further mechanistic studies are warranted to better understand the precise pathways through which specific diets and micronutrients influence AF pathogenesis. Mechanistic investigations should explore the effects of dietary components on inflammation, oxidative stress, ion channel function, autonomic tone, cardiac remodeling and other vital mechanisms underlying AF initiation and maintenance. Advanced experimental techniques, such as cellular electrophysiology, tissue engineering, and omics approaches, can help unravel the molecular mechanisms mediating the effects of diet on cardiac electrophysiology and structure.

Integration of nutritional counseling into AF management

Incorporating nutritional counseling and lifestyle modifications into routine AF management can optimize patient care and

TABLE 1 Overview of some of the important and highlighted articles.

Title	No. of patients	Result	Author name, publication year	PMID/ reference no.
Fish intake and risk of incident atrial fibrillation	4,815	Consuming tuna or other broiled or baked fish was linked to a lower risk of AF, likely due to long-chain n-3 fatty acids' beneficial effects on cardiovascular health. However, no similar benefit was observed with fried fish or fish sandwiches, possibly due to differences in nutrient composition.	Mozaffarian, 2004	15262826
Effect of Marine Omega-3 Fatty Acid and Vitamin D Supplementation on Incident Atrial Fibrillation: A Randomized Clinical Trial	24,127	Supplementation with marine omega-3 fatty acids and/or vitamin D3 did not significantly affect the incidence of AF over a median of 5.3 years. The results indicate no benefit or major risk associated with these supplements for AF prevention, suggesting that neither omega-3 fatty acids nor vitamin D3 should be used for the primary prevention of AF.	Albert, 2021	33724323
Omega-3 Fatty Acid Biomarkers and Incident Atrial Fibrillation	7,720	Higher levels of circulating and tissue omega-3 fatty acid biomarkers were not linked to an increased incidence of AF, suggesting that findings from high-dose omega-3 supplementation trials in cardiovascular disease populations may not apply to lower habitual dietary intakes.	Qian, 2023	37468189
Dietary Fish and Long-Chain n-3 Polyunsaturated Fatty Acids Intake and Risk of Atrial Fibrillation: A Meta-Analysis	12,913	This meta-analysis found no overall association between higher fish consumption or intake of n-PUFAs and AF development. However, a cautious interpretation is advised regarding very high PUFA intake showing a potential increased risk of AF, which was sensitive to individual studies. Despite the known cardiovascular benefits of n-3 PUFAs, this meta-analysis suggests that dietary guidelines recommending fish consumption for general cardiovascular health should continue, though their impact on AF prevention remains uncertain.	Li, 2017	28850090
Prevention of recurrent arrhythmias with Mediterranean diet (PREDIMAR) study in patients with atrial fibrillation: Rationale, design and methods	720	The PREDIMED trial provides strong evidence for the Mediterranean diet enriched with extra EVOO as an effective strategy for primary AF prevention, likely due to its anti-inflammatory and antioxidant properties. Managing cardiovascular risk factors through diet and lifestyle modifications can reduce the burden and severity of AF, lowering the incidence and recurrence post-ablation.	Barrio-Lopez, 2020	31809992
Extravirgin olive oil consumption reduces risk of atrial fibrillation: the PREDIMED trial	6,705	In this secondary analysis of the PREDIMED trial, a Mediterranean diet enriched with EVOO was found to significantly reduce the relative risk of AF by 38%. The strong anti-inflammatory and antioxidant properties of EVOO, attributed to its phenolic compounds, likely explain its protective effect against AF, highlighting the potential of the MeDiet with EVOO for primary AF prevention.	Barrio-Lopez, 2020	24787471
A Remote Nutritional Intervention to Change the Dietary Habits of Patients Undergoing Ablation of Atrial Fibrillation: Randomized Controlled Trial	720	A remote nutritional intervention inspired by the PREDIMAR trial effectively enhanced participants' knowledge, skills, and adherence to a Mediterranean diet. Additionally, the study suggests that such remote health promotion interventions could be a cost-effective strategy for mitigating the growing health burden.	Goni, 2020	33284131
A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group	459	This trial showed that a diet rich in fruits, vegetables, and low-fat dairy products, with reduced saturated and total fat, significantly lowered blood pressure in adults, demonstrating an effective non-pharmacological approach for preventing and treating hypertension, with implications for reducing cardiovascular disease risk across the population.	Appel, 1997	9099655
Mediterranean, DASH, and Alternate Healthy Eating Index Dietary Patterns and Risk of Death in the Physicians' Health Study	15,768	In this study of US male physicians, higher MED, DASH, and AHEI diet scores were inversely associated with total mortality. The benefits of these dietary patterns on mortality may be due to the cohort's high education level and adherence to optimal medical treatments and dietary recommendations, as well as potential biological mechanisms such as improved inflammation, vascular function, and glucose-insulin homeostasis.	Patel, 2021	34072912
Associations of dietary patterns, ultra-processed food and nutrient intake with incident atrial fibrillation	121,300	This observational study found that higher consumption of ultra-processed foods increased the risk of incident AF. While adherence to Mediterranean-style and DASH diets initially appeared to reduce AF risk, these associations lost significance after adjusting for BMI and lifestyle factors, suggesting that focusing on modifiable risk factors like weight may be more crucial than specific dietary patterns for preventing AF.	Tu, 2023	37460193
Low-Carbohydrate Diets and Risk of Incident Atrial Fibrillation: A Prospective Cohort Study	13,385	In this study, low-carbohydrate intake was associated with a higher risk of incident AF, independent of other risk factors. This adverse association was consistently observed in multiple sensitivity analyses, suggesting that the increased risk may be due to reduced intake of anti-inflammatory foods and increased oxidative stress. This study is the first to explore the relationship between carbohydrate intake and AF risk, highlighting the potential long-term cardiovascular risks of low-carbohydrate diets.	Zhang, 2019	31020911

(*Continued*)

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TABLE 1 Continued

Title	No. of patients	Result	Author name, publication year	PMID/ reference no.
Five-year changes in alcohol intake and risk of atrial fibrillation: a Danish cohort study	43,758	This study found that increasing high alcohol intake over five years was linked to a higher risk of AF compared to maintaining a low or moderate alcohol intake. On the other hand, reducing alcohol intake did not significantly alter the risk of AF compared to stable consumption levels. These findings indicate that to prevent AF, it is advisable to avoid increasing alcohol consumption.	Frederiksen, 2023	36508613
Alcohol Abstinence in Drinkers with Atrial Fibrillation	140	AF is common, and alcohol consumption can influence its occurrence. This study showed that significantly reducing alcohol intake in regular drinkers with symptomatic AF led to fewer AF recurrences and less time spent in AF. Regular alcohol consumption is a modifiable risk factor for AF and reducing intake from an average of 17 drinks per week to 2 drinks per week can decrease AF burden and recurrence risk.	Voskoboinik, 2020	31893513
Alcohol and incident atrial fibrillation - A systematic review and meta-analysis	n/a	Low alcohol intake does not contribute to the development of AF. However, gender differences are observed with moderate alcohol intake: men show a higher increase in AF risk than women. High alcohol intake significantly increases the risk of AF in both genders.	Gallagher, 2017	28867013
Risk of idiopathic dilated cardiomyopathy in 29 000 patients with celiac disease	144,429	This study is the first to confirm dilated cardiomyopathy (DCM) diagnosis with patient charts and echocardiography in celiac disease (CD) patients, finding a 73% increased DCM risk, especially in the first year after CD diagnosis. The study identified 17 patients with both CD and idiopathic DCM, supporting previous reports of increased DCM prevalence in CD patients. Despite some limitations, the findings suggest a possible link between CD and DCM through shared inflammation and autoimmune mechanisms.	Emilsson, 2012	23130142
Small-Intestinal Histopathology and Mortality Risk in Celiac Disease	46,121	This study examined mortality risk in CD relative to small-intestinal histopathology, finding a small but significant excess mortality risk, particularly in the first year post-diagnosis. Over 3,000 deaths were recorded among 29,000 CD patients, with an overall mortality hazard ratio (HR) of 1.39, lower than many previous studies. The study uniquely explored mortality in patients with inflammation without villous atrophy and latent CD, indicating the highest mortality risk in those with inflammation.	Ludvigsson, 2009	19755695
Risk of atrial fibrillation associated with coffee intake: Findings from the Danish Diet, Cancer, and Health study	57,053	This study found that both coffee consumption and total caffeine intake are associated with a reduced rate of incident AF, consistent across various subgroups. Coffee's health impacts may stem from its complex mixture of bioactive compounds, beyond just caffeine. Despite some limitations, the study's strengths include a large sample size and comprehensive data, supporting the potential cardiovascular benefits of coffee.	Mostofsky, 2016	26701875
Association of Coffee Consumption with Atrial Fibrillation Risk: An Updated Dose-Response Meta-Analysis of Prospective Studies	723,825	This meta-analysis found no increased risk of AF with high or moderate coffee consumption, and suggested a potential decrease in AF risk with higher coffee intake. Unlike previous analyses mixing caffeine and coffee, this study focused on pure coffee and found a possible protective effect. Despite limitations, the study's large sample size and high-quality prospective design provide robust evidence that moderate to high coffee consumption does not increase AF incidence and may even have protective benefits.	Cao, 2022	35872898
Does Caffeine Consumption Increase the Risk of New-Onset Atrial Fibrillation	176,675	Coffee consumption does not increase the incidence of AF. In fact, our findings indicate a lower incidence of AF when caffeine consumption exceeds 436 mg/day. Consequently, based on the available evidence, there is no link between caffeine intake and an increased risk of AF.	Abdelfattah, 2018	29966128
Chocolate intake and risk of clinically apparent atrial fibrillation: the Danish Diet, Cancer, and Health Study	55,502	Study found that higher chocolate intake was associated with a lower rate of clinically apparent AF among both men and women, even after adjusting for total caloric intake. This supports results from previous studies, though findings varied based on sex and methodology. The study suggests that chocolate's antioxidant, anti-inflammatory, and magnesium content may contribute to cardiovascular benefits, despite potential limitations such as unmeasured confounding factors and reliance on self-reported data.	Mostofsky, 2017	28536115
Chocolate consumption and risk of atrial fibrillation: Two cohort studies and a meta-analysis	40,009	In this study, chocolate consumption showed no association with the risk of AF after adjusting for other risk factors, a finding confirmed by a complementary meta-analysis. These results contrast with earlier observations of inverse associations between moderate chocolate consumption and the risk of ischemic heart disease, heart failure, and stroke, both in the Swedish cohorts and in meta-analyses of all available cohort data.	Larsson, 2018	29224650
Estimated salt intake and risk of atrial fibrillation in a prospective community-based cohort	473,080	This study revealed a U-shaped relationship between estimated daily salt intake and the risk of AF among men. While a potential J-shaped association in women was not statistically significant, the analyses may have lacked sufficient statistical power. These findings indicate that beyond a certain physiological minimum level, higher salt intake correlates with an increased risk of AF.	Wuopio, 2021	33210391

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TABLE 1 Continued

Title	No. of patients	Result	Author name, publication year	PMID/ reference no.
Salt as a Trigger for Atrial Tachycardia/Fibrillation	473,080	Excessive sodium intake, contributing to fluid retention and hypertension, is a recognized risk factor for AF. Beyond hypertension, sodium may trigger arrhythmias like AF by influencing intracellular calcium levels and altering the mechano-electrical environment of the heart through stretch-induced mechanisms. Controlled studies involving larger patient populations are crucial to fully understand salt's role as a trigger for paroxysmal atrial fibrillation.	Goddard, 2022	35891840
Urinary Sodium Excretion, Blood Pressure, and Risk of Future Cardiovascular Disease and Mortality in Subjects Without Prior Cardiovascular Disease	457,484	This study demonstrated a consistent relationship between estimated urinary sodium excretion (a marker of sodium intake) and elevated blood pressure, even when restricted to subjects without baseline comorbidities. Despite clear evidence linking sodium intake to increased blood pressure, no straightforward linear relationship between high sodium intake and increased risk of mortality or cardiovascular disease was found. These findings support public health policies advocating sodium reduction to lower blood pressure, though the long-term benefits on cardiovascular events require further investigation.	Welsh, 2019	31067194
Salt intake and new-onset of atrial fibrillation: A meta-analysis of over 1.4 million participants	1,421,826	This study demonstrated a significant correlation between genetically determined high dietary salt intake and an increased risk of AF. Future research is needed to further elucidate this relationship and confirm the generalizability of our findings across more socioeconomically and ethnically diverse populations.	Bhagavathula, 2021	33933725
Low levels of plasma carotenoids are associated with an increased risk of atrial fibrillation	1,847	This prospective cohort study found that low plasma concentrations of lutein and zeaxanthin are associated with nearly a twofold increased risk of AF, while other carotenoids were not linked to AF risk. Hypertension and oxidative stress are key factors in AF development, with carotenoids potentially reducing AF risk through their antioxidant and anti-inflammatory properties. The study suggests that a diet rich in carotenoids from fruits and vegetables may help protect against AF, especially in the elderly.	Karppi, 2013	23238698
Intake of dietary flavonoids and incidence of ischemic heart disease	54,496	In this study, no clear associations were found between total flavonoid intake and ischemic heart disease (IHD) risk. However, higher intakes of flavonols and flavanol oligo + polymers were linked to lower IHD risk among ever-smokers, but not never-smokers. These findings suggest flavonoids may offer modest protection against IHD, particularly for smokers, though further research is needed.	Parmenter, 2023	36284213
Low serum magnesium and the development of atrial fibrillation in the community: the Framingham Heart Study	3,530	In this longitudinal, community-based cohort, low serum magnesium was linked to the development of AF. This study extends the known association between low magnesium and AF risk beyond the context of cardiac surgery. The findings suggest potential public health implications, warranting further research to confirm if magnesium supplementation could reduce AF risk in other populations.	Khan, 2013	23172839
Effects of magnesium on atrial fibrillation after cardiac surgery: a meta-analysis	2,490	Magnesium administration effectively reduces postoperative AF, with an impact comparable to proposed antiarrhythmic drugs. However, it did not significantly decrease hospital length of stay or mortality. Further research is needed to determine the optimal administration regimen and its efficacy when combined with other medications.	Miller, 2005	15831645
Serum potassium levels and the risk of atrial fibrillation: the Rotterdam Study	4,059	This study demonstrated that low serum potassium levels are linked to an increased risk of AF in the general population, independent of various potential confounders. Although the proportion of cases attributable to low serum potassium may be small, this finding is significant at a population level due to the routine measurement of serum potassium and the common and serious consequences of atrial fibrillation, such as stroke. Further research with repeated measurements of serum potassium and its association with atrial fibrillation risk would be valuable.	Krijthe, 2013	24012173
Serum electrolyte concentrations and risk of atrial fibrillation: an observational and mendelian randomization study	15,792	An observational study indicated that hypokalemia, hypomagnesemia, and hyperphosphatemia are associated with the onset of AF. However, MR analysis did not confirm a causal role for serum electrolytes in the development of AF. Consequently, therapies targeting electrolyte disorders like hypokalemia, hypomagnesemia, and hyperphosphatemia to prevent AF may offer limited clinical benefit.	Wu, 2024	38493091

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improve clinical outcomes. Healthcare providers should assess patients' dietary habits, provide personalized recommendations based on evidence-based guidelines, and support behavior change. Multidisciplinary care teams, including dietitians, nurses, and pharmacists, can collaborate to deliver comprehensive nutritional interventions tailored to each patient's unique needs and preferences. Adequate monitoring and ongoing reinforcement are also recommended.

Telehealth and digital health solutions

Leveraging telehealth and digital health platforms can facilitate not only research but the delivery of dietary counseling and monitoring for patients with AF, especially in remote or underserved areas. Telehealth platforms can enable real-time dietary tracking, remote consultations with healthcare providers, virtual support groups, and nutrition and AF management educational resources. Integrating digital health solutions into routine clinical practice can enhance patient engagement, adherence to dietary recommendations, and self-management of AF.

Future directions in exploring dietary interventions and micronutrients in AF development encompass a multifaceted approach involving precision nutrition, clinical trials, longitudinal cohort studies, mechanistic research, nutritional counseling, and digital health solutions. By advancing our understanding of the role of diet in AF pathophysiology and implementing evidence-based nutritional interventions, healthcare providers can empower patients to adopt healthy dietary habits and reduce their risk of AF-related complications.

The HEAD-2-TOES scheme

The HEAD-2-TOES scheme was recently proposed as a comprehensive method to assist clinicians in managing and controlling specific risk factors associated with the development of atrial fibrillation (106). Controlling these modifiable risk factors is particularly crucial in the context of primary prevention. This scheme identifies and addresses various determinants, detailed in the table below, and provides an overview of both primary and secondary prevention targets. Additionally, it discusses the impact of various diets on these risk factors, highlighting how dietary choices can influence the effectiveness of prevention strategies (Table 2).

TABLE 2 HEAD-2-TOES table of various diets and their effect on atrial fibrillation.

Acronym	Risk factor	Primary prevention targets	Secondary prevention targets	Effect of various diets
H	Heart failure with reduced ejection fraction	ACE inhibitor or ARB, β-blocker, MRA, SGLT2 inhibitor	ACE inhibitor or ARB, MRA	Mediterranean diet has been shown to reduce inflammation and lower the risk of hospitalization and mortality in HFrEF patients. DASH diet can help lower blood pressure and improve heart health in HFrEF patients.
E	Exercise (physical inactivity)	≥150 min per week MVPA	≥200 min/per week MVPA	Mediterranean, DASH and high-fiber diets can reduce inflammation, lower blood pressure and decrease fluid retention, lessening the workload on the heart and help increase exercise tolerance and physical capacity of these patients.
A	Arterial hypertension	BP <130/80 mmHg	BP <130/80 mmHg (rest) and <200/100 mmHg (exercise)	Mediterranean, DASH and diets rich in Omega-3 fatty acids can reduce inflammation, decrease salt retention and decrease the strain on the heart, hence, help treat and reduce the incidence of essential hypertension and mitigates risk of AF.
D2	Diabetes mellitus type 2	HbA1c <6.5%	Dietary changes and HbA1c <6.5%	Low carbohydrate diet as well as Mediterranean, DASH and high-fiber diets can improve insulin sensitivity and reduce blood sugar levels which reduces the risk of AFib complications in people with diabetes.
T	Tobacco smoking	Complete cessation	Complete cessation	Various diets, including diets rich in antioxidants can help protect against oxidative stress caused by smoking, reducing damage to the heart and blood vessels, which can benefit those with AFib. This includes Mediterranean, DASH, Omega-3 fatty acids and diets rich in fruits and vegetables.
O	Obesity	BMI ≤25 kg/m^2	10% weight reduction; BMI ≤27 kg/m^2	Mediterranean, low-carbohydrate, DASH, Omega-3 fatty acids diets stabilize blood sugar levels, promote weight loss, lower blood pressure, and enhances heart health, making it beneficial for obese patients with AFib.
E	Ethanol consumption	≤1 standard drink per day	≤3 standard drinks per week	Some of the same diets as above can help provide antioxidants that help mitigate some of the negative effects of alcohol on the heart, benefiting AFib patients.
S	Sleep apnea	AHI <15	AHI <15 without CPAP; CPAP for AHI ≥30 or AHI ≥20 with hypertension	Mediterranean diet can improve cardiovascular health, reduce inflammation, and aid in weight management, which can alleviate symptoms of OSA and benefit AFib patients. SImilarly, DASH and low-carbohydrate diets can lower blood pressure, improve heart health, and promote weight loss, which can help manage both OSA and AFib.

Conclusions

In conclusion, dietary interventions represent a promising avenue in managing AF. This review highlights the growing body of evidence supporting the role of diet in modulating AF risk and progression. A comprehensive analysis of existing literature has elucidated the potential mechanisms by which various dietary patterns, nutrients, and supplements may influence AF pathophysiology. From adopting heart-healthy dietary patterns such as the Mediterranean diet and DASH diet to incorporating specific nutrients like omega-3 fatty acids, magnesium, and antioxidants, dietary interventions offer a holistic approach to AF management. Moreover, emerging research underscores the importance of personalized nutrition strategies tailored to individual patient profiles, genetic predispositions, and lifestyle factors. Large clinical trials, longitudinal cohort studies, and mechanistic research are needed to elucidate further dietary interventions' efficacy, safety, and mechanisms in AF prevention and treatment. By integrating nutritional counseling, lifestyle modifications, and digital health solutions into routine clinical practice, healthcare providers could empower patients to optimize their dietary habits and improve their AF outcomes. Overall, dietary interventions hold promise as adjunctive therapies in the comprehensive management of AF and warrant further exploration in future research endeavors

Important take-home points

- Dietary interventions offer a promising approach for managing atrial fibrillation, with potential in modulating AF risk and progression.
- Adopting heart-healthy dietary patterns such as the Mediterranean diet and DASH diet is particularly beneficial for AF management.
- Incorporating specific nutrients like omega-3 fatty acids, magnesium, and antioxidants can positively impact AF management.
- Emerging research underscores the importance of personalized nutrition strategies tailored to individual patient profiles, genetic predispositions, and lifestyle factors.
- Large clinical trials, longitudinal cohort studies, and mechanistic research are needed to further elucidate the efficacy, safety, and mechanisms of dietary interventions in AF prevention and treatment.
- Integrating nutritional counseling, lifestyle modifications, and digital health solutions into routine clinical practice can empower patients to optimize their dietary habits and improve their AF outcomes.

Data availability statement

Requests to access the datasets should be directed to muhammad.nabil@bswhealth.org.

Author contributions

MN: Data curation, Investigation, Writing – original draft, Writing – review & editing. LR: Data curation, Investigation, Writing – original draft. AN: Data curation, Investigation, Writing – original draft. PC: Conceptualization, Investigation, Supervision, Writing – review & editing. GO: Conceptualization, Writing – review & editing. JM: Conceptualization, Writing – review & editing. AT: Conceptualization, Writing – review & editing. S-SH: Data curation, Investigation, Writing – original draft. JB: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

PC and AT have ownership interest in AlfredAI Inc.

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.

Publisher's note

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Maintenance of sinus rhythm after electrical cardioversion to identify patients with persistent atrial fibrillation who respond favorably to pulmonary vein isolation: the pre-pacific study

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Background: Pulmonary vein isolation (PVI) is successful in approximately 50% of patients with persistent atrial fibrillation (PsAF) at one year. Identifying pre-procedurally the patients who respond favorably to a PVI alone strategy could improve their management. The present study aims to assess the predictive value of clinical response to pre-ablation electrical cardioversion (ECV) to identify the responders to PVI.
Methods: Consecutive patients undergoing catheter ablation for PsAF were retrospectively classified, as "ECV successful" vs. "ECV failure", according to the rhythm of presentation after an ECV performed ≥4 weeks. Clinical and procedural data were analyzed in both groups according to the ablation strategy applied (PVI vs. PVI + substrate modification).
Results: In total, 58 patients (39.4%) had successful ECVs and 89 (60.6%) had failed ECV. Preprocedural characteristics were similar in both groups. Compared to the ECV failure group, patients with successful ECV presented less frequently (34% vs. 60%; $P = 0.004$) and less extended ($21.3 \pm 22.2\%$ vs. $38.9 \pm 27.4\%$ of LA surface, $P = 0.008$) low-voltage areas. Over 55 ± 19 weeks of follow-up, AF-free survival was similar in both groups (72.7% vs. 67.8%, $p = 0.39$). PVI alone resulted in 83% AF-free survival among patients in the ECV successful group at 13 months.
Conclusion: In approximately 40% of patients with PsAF, sinus rhythm can be restored by ECV and maintained for at least 1 month prior to catheter ablation. This clinical response is associated with less abnormal substrate as identified by left atrial voltage mapping and a procedural success rate of >80% with PVI alone.

KEYWORDS

persistent atrial fibrillation, electrical cardioversion, sinus rhythm, atrial remodeling, pulmonary vein isolation

Introduction

In unselected patients with persistent atrial fibrillation (PsAF) pulmonary vein isolation (PVI) results in maintenance of sinus rhythm (SR) at one year in approximately 50% of cases (1–3). Currently, there is no established means of predicting in whom PVI alone will be successful and in whom additional ablation strategies may be required. Accurately discriminating between these two populations pre-procedurally would be of considerable value given that PVI is a relatively straightforward and safe procedure whereas ablation strategies beyond PVI can entail more complex approaches and increased risks.

Restoring and maintaining SR with electrical cardioversion (ECV) (4) or antiarrhythmic drugs (AADs) (5–8) prior to catheter ablation has been linked to a favorable response to PVI in patients with PsAF. If true, whether sustained SR prior to catheter ablation mediates or simply acts as a marker for PVI success is unknown, but this association may identify patients in whom PVI alone is effective. We sought to test this hypothesis by retrospectively examining whether restoring SR for at least four weeks prior to catheter ablation predicted ablation procedural success with PVI alone among patients with PsAF.

Matherials and methods

Study population

Consecutive patients with PsAF admitted to the Service de Cardiologie, Hôpital Privé Les Franciscaines, Nîmes, France for catheter ablation between January 2021 and April 2022 were retrospectively analyzed.

Exclusion criteria included an age <18 or >85 years, active malignancy, active hyperthyroidism, hypertrophic cardiomyopathy, left ventricular ejection fraction <40%, the presence of a mechanical or bioprosthetic valve, presence of a left atrium (LA) thrombus, a contraindication to anticoagulation, transient ischemic attack or stroke within the preceding 6 months, active cardiac ischemia, ECV performed <4 weeks before catheter ablation, and an inability to restore SR after 3 ECV attempts. The use of AADs was at the discretion of treating physicians. AADs were not discontinued before catheter ablation.

The study was approved by the local ethics committee and all patients provided informed and signed consent.

Design of the study

All patients had symptomatic PsAF and underwent pre-ablation elective ECV for symptom management as per protocol at our center. All patients who arrived at the EP laboratory for catheter ablation in SR were included in the group "ECV effective" whereas those in AF formed the group "ECV failure" (Figure 1).

Procedural aspects

Ablation procedures were carried out under general anesthesia and on uninterrupted direct oral anticoagulant or vitamin K antagonist (international normalized ratio 2.0–3.0). Transesophageal

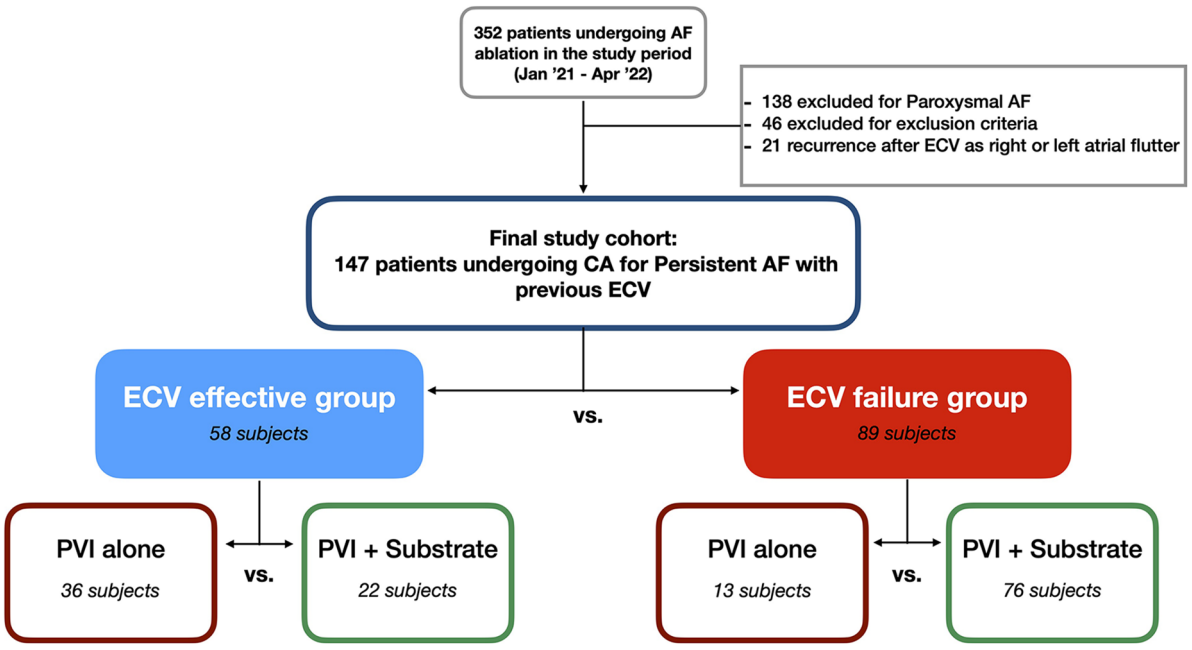

FIGURE 1
Consort flow diagram showing the enrollment of subjects in the present analysis.

echocardiography was systematically performed to exclude the presence of intracardiac thrombi and to guide transseptal puncture. Before LA access was obtained, intravenous heparin was administered to achieve an activated clotting time >350 s throughout the entire procedure.

Ablation procedures were conducted under electronatomical navigation system guidance (CARTO 3, Biosense Webster, Diamond Bar, CA) using a multipolar diagnostic catheter (Pentaray, Biosense Webster) and an open irrigated contact force-sensing ablation catheter (SmartTouch SF, Biosense Webster). Before reconstruction of LA anatomy, ECV was performed to obtain analysis of endocardial voltage during SR in all patients. A second ECV was performed after PVI in the case SR was not restored or AF was triggered again during mapping.

Low voltage areas (LVAs) were defined as regions of the LA with endocardial bipolar voltage <0.5 mV. In patients with previous AF ablation, PVs antra were not included in the amount of LVA.

The total surface of the LVA was indexed to the total surface of the LA and classified into 4 stages of atrial myopathy as reported in the DECAAF study (Figure 2) (9, 10).

Radiofrequency lesions (RF) were delivered as previously reported (11–13). The energy power used was 50W except in the great cardiac vein (GCV) where it was 25W. The ablation indices targeted were 250 inside the GCV, 350 on the posterior aspects of the LA, and ≥450 elsewhere. All procedures were performed by two experienced operators (GL, AB) and the ablation strategies used (PVI alone, Marshal-PLAN, or PVI + LVA isolation) was determined by operator preference (14, 15).

Mitral line block was obtained using the following steps in all the patients, as previously described (14). After CS cannulation using a steerable sheath, iodine contrast was injected in the proximity of the Vieussens valve through a left internal mammary artery catheter to localize the VOM. An angioplasty guidewire and subsequently a preloaded angioplasty balloon (length 6–8 mm, nominal diameter 2–3.5 mm) was dilatated at 3–5 atm in the proximal VOM to occlude its lumen. A contrast injection in the balloon lumen was performed to visualize VOM tributary branches before the injection of 8–10 ml of 96% ethanol (3 separate 1 min injections 3 ml). Ethanol infusion was considered successful if repeat angiograms between the 3 injections demonstrated (1) stability of the angioplasty balloon; (2) visualization of the distal VOM arborization; (3) absence of contrast leakage back in the CS; (4) absence or limited dissection of the VOM; and (5) progressive appearance of tissue contrast staining. In all the patients after VOM alcoholization, a new endocardial electroanatomic map of the mitral isthmus region was acquired to visualize the effect of VOM alcoholization and RF ablation was performed (of the "saddle" area between the high ridge, left atrial appendage, left superior pulmonary vein) targeting endocardial insertion site of Marshall bundles and completing an endocardial mitral line from left inferior PV to mitral annulus. RF ablation was also performed in the CS targeting epicardial muscular bundles identified by sharp near-field signals, in correspondence with endocardial scar resulting from VOM alcoholization and avoiding RF delivery in the proximal CS. Mitral isthmus block will be validated in SR by pacing maneuvers.

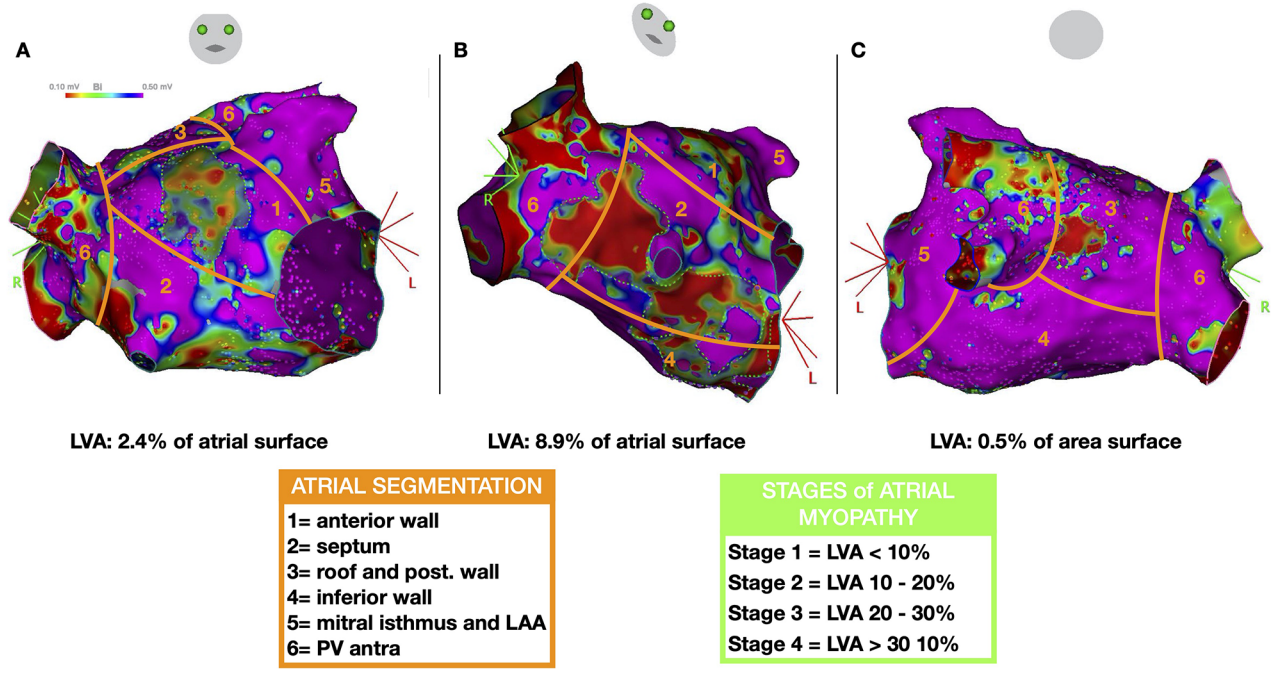

FIGURE 2
Left atrial segmentation to characterize the distribution of low voltage areas (LVA) and stages of atrial myopathy. Representative case of a patient with LVAs: cranial right anterior oblique [RAO, **(A)**], RAO **(B)** and caudal postero-anterior views **(C)** demonstrating three LVAs on the anterior, septal, and posterior walls (delineated by green dotted lines) encompassing 11.5% of the left atrial surface area (classified as stage 2 atrial myopathy).

Follow-up

Follow-up visits were performed in an outpatient clinic at 3, 6, and 12 months after the index ablation procedure. When treating physicians prescribed AADs at hospital discharge, they were maintained for 4 weeks after the procedure.

Subsequently, follow-up visits occurred once yearly. Clinical examination, an ECG, and a 48 h Holter were performed at each visit in addition to any investigations initiated in response to patient symptoms suggestive of AF recurrence. AF recurrence was defined as any documented episode of AF lasting longer than 30 s after a 90-day blanking period post-procedure.

Statistical analysis

Continuous variables are expressed as mean value ± standard deviation or median value with interquartile range, as appropriate. Categorical variables are presented as number and percentages, and their proportions were compared using a Chi-square analysis or Fisher's exact tests, as appropriate. Continuous variables were compared using Student *t*-tests for independent samples or Mann–Whitney *U* tests, depending on data normality.

Clinical variables associated with ECV group as well as LVAs were identified using logistic regression and are presented as odds ratio point estimates with 95% confidence intervals. Univariate and multivariate analyses were performed with the Cox proportional hazard regression model to identify variables associated to AF recurrences. Variables identified as significant based on $p < 0.1$ in univariable analyses were included in a multivariable model. Kaplan–Meier curve and log-rank test were used to assess AF-free survival during the whole follow-up. Data were analyzed with SPSS software version 26.0 (SPSS Inc., Chicago, Illinois).

Results

Patient characteristics

In total, 147 consecutive patients were included (Table 1). Their mean age was 70.1 ± 9.4 years and 98 (66.7%) were male. PVI alone was performed in 49 patients (33.3%), 8 of whom had LVAs identified on the day of the procedure (16.3%). Additional substrate ablation was performed in the remaining 98 patients (66.7%), 63 of whom had LVAs (64.3%).

Nine minor complications (6.1%) occurred (4 groin hematomas, 1 arteriovenous fistula and 4 pericarditis). There were no cases of cardiac tamponade, stroke-transient ischemic attack, atrioesophageal fistula, or death.

ECV was performed a mean of 10.4 ± 7.4 weeks before ablation procedures. On the day of the ablation procedure, 58 patients (39.4%) were in SR (*ECV effective*) whereas 89 patients (60.6%) were in AF (*ECV failure*). CHA_2DS_2-VASc scores were higher

TABLE 1 Baseline patient characteristics.

	Overall *N* = 147	ECV effective *N* = 58 (39.5%)	ECV failure *N* = 89 (60.5%)	*P*
Male sex	98 (66.7)	39 (67.2)	59 (66.3)	0.1
Age (years)	70.1 ± 9.4	71 ± 9.1	69 ± 9.7	0.08
LVEF (%)	52.3 ± 9.9	50.7 ± 9.5	53.3 ± 10.5	0.13
LA volume (ml)	143.2 ± 34.6	136 ± 37.5	147 ± 32.2	0.14
LAVI (ml/m^2)	71.1 ± 23.3	65.5 ± 25.9	74.7 ± 20.8	0.02
Duration of AF history (months)	49.7 ± 54.4	49.2 ± 51.3	49.9 ± 56.5	0.9
Time from ECV to catheter ablation (weeks)	10.4 ± 7.5	9.2 ± 6.1	11.2 ± 8.3	0.11
Comorbidities				
Hypertension	111 (75.5)	45 (77.6)	66 (74.2)	0.69
Dyslipidemia	42 (28.6)	19 (32.8)	23 (25.8)	0.45
Diabetes mellitus	32 (21.8)	15 (5.9)	17 (19.1)	0.41
Tobacco use	30 (20.4)	12 (20.7)	18 (20.2)	1.0
History of stroke	14 (9.5)	7 (12.1)	7 (7.9)	0.41
History of coronary artery disease	41 (27.9)	18 (31.0)	23 (25.8)	0.57
Obstructive sleep apnea	30 (20.4)	15 (25.9)	15 (16.9)	0.21
Peripheral vascular disease	14 (9.5)	3 (5.6)	11 (12.4)	0.24
History of Tachycardia-induced cardiomyopathy	44 (29.9)	22 (37.9)	22 (24.7)	0.1
Overweight	34 (23.1)	13 (22.4)	21 (23.6)	1.0
Body mass index (kg/m^2)	29.2 ± 4.9	29.5 ± 4.7	28.9 ± 5.1	0.41
CHA_2DS_2-VASc score	3.0 ± 1.5	3.1 ± 1.5	2.8 ± 1.4	0.02
Moderate valvular disease	22 (15.0)	9 (15.5)	13 (14)	1.0
Previous AF ablation	42 (28.6)	17 (29.3)	25 (28.1)	1.0
Reconnected PV[a]	15 (35.7)	7 (41.2)	6 (24.0)	0.1
Previous CTI ablation	8 (5.4)	3 (5.2)	5 (5.6)	1.0
Procedural characteristics				
Presence of LVA	72 (49.7)	18 (31.0)	54 (60.7)	0.0001
LVA area (%)	34.7 ± 26.9	21.3 ± 22.1	38.9 ± 27.4	0.008
Atrial myopathy stage				
1	84 (57.1)	43 (74.1)	41 (46.1)	0.001
2	18 (12.2)	7 (12.1)	11 (12.4)	
3	11 (7.5)	4 (6.9)	7 (7.9)	
4	34 (23.1)	4 (6.9)	30 (33.7)	
Localization of LVA				
Roof-posterior	46 (63.8)	8 (44.4)	38 (70.4)	0.08
Anterior	48 (66.6)	12 (66.7)	26 (48.1)	0.28
Inferior	18 (25.0)	1 (5.5)	17 (31.4)	0.03
Lateral	7 (16.7)	3 (16.7)	4 (7.4)	0.35
Septum	17 (23.1)	1 (5.5)	16 (29.6)	0.05
Atrial tachycardia during the procedure	8 (5.4)	3 (5.2)	5 (5.6)	0.61
PVI alone	49 (33.3)	36 (62.1)	13 (14.6)	0.0001
Anti-arrhythmic medications before the procedure				
Beta-blockers	40 (27.2)	18 (31.0)	22 (24.7)	0.45
Class 1C-3	48 (32.6)	20 (34.5)	28 (31.5)	0.72
Anti-arrhythmic medications during follow-up				
Class 1C-3	35 (30.6)	13 (22.4)	32 (36.0)	0.1

Data are presented as *N*.(%) or mean ± SD.

AF, atrial fibrillation; ECV, electrical cardioversion; CTI, cavo-tricuspid isthmus; LA, Left atrium; LAVI, left atrium volum indexed for body surface area; LVA, low-voltage areas LVEF, left ventricular ejection fraction; PVI, pulmonary vein isolation.

[a]Percentage calculated on the number of REDO patients.

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but LAVI values were lower in the ECV effective than in the ECV failure group (3.1 ± 1.5 vs. 2.8 ± 1.4, $P = 0.02$; and 65.5 ± 25.9 vs. 74.7 ± 20.8 ml/m^2, $P = 0.02$; respectively). In the multivariable regression model, CHA_2DS_2-VASc scores (OR 1.39, 1.08–1.79) and presence of low-voltage areas (0.29, 0.14-0.62) predicted the ECV Efficacy group (Supplementary Table S1).

A previous AF ablation was reported in 42 subjects (28.6%) with a rate of reconnected pulmonary veins of 41.2% in the ECV effective and 24.0% in the ECV failure groups ($p = 0.1$).

LVAs were more frequently found in the ECV failure group (34% vs. 60% of patients; $P = 0.004$) and, when present, they were more extensive when indexed to the total LA surface (21.3 ± 22.2% vs. 38.9 ± 27.4%, $P = 0.008$). Overall, fewer patients in the ECV effective group were classified as having advanced (stage 3 or 4) atrial myopathy (14% vs. 42%, $P < 0.001$). In the multivariable regression model, ECV failure was the only independent predictor of LVA at electroanatomic mapping (OR 3.2, 1.5–6.9; $P = 0.002$) (Supplementary Table S2).

Ablation strategies

Among the 58 patients in the ECV effective group, 36 underwent PVI alone (62%) and 22 underwent PVI + substrate ablation (38%). Among the remaining 89 patients, 13 (15%) underwent PVI alone and 76 (85%) underwent PVI + substrate ablation (Table 2). Marshall-PLAN approach was more frequently executed in patients in the ECV failure group. As reported in Table 3, substrate ablation strategies included Marshall-PLAN approach (which included a posterior box in all the patients) in 4 (18.2%) and 45 (59.2%), respectively. A posterior box and an anterior line targeting LVAs were respectively executed in 10 and 9 patients in the ECV effective group and in 19 and 10 patients in the ECV failure groups.

TABLE 2 Set of procedural lesions performed in the substrate groups among ECV effective and ECV failure groups.

	ECV effective (*N.* 22)	ECV failure (*N.* 76)	*P*-value
Posterior box	14 (63.6)	64 (84.2)	0.06
Mitral isthmus block	4 (18.2)	45 (59.2)	0.001
Success rate of VOM[a]	3 (75.0)	36 (80.0)	1.000
Anterior line	9 (40.9)	10 (13.1)	0.01
CTI	6 (27.7)	6 (7.8)	0.02

VOM, vein of marshal ethanol infusion; CTI, cavo-tricuspid isthmus ablation.
[a]Calculated on the total of attempted VOM alcoholizations.

TABLE 3 Characteristics of the population according to group and procedures.

	ECV effective			ECV failure		
	PVI alone	Substrate	*P*	PVI alone	Substrate	*P*
No (%)	36 (62.1)	22 (37.1)		13 (14.6)	76 (85.4)	
Male sex	24 (66.7)	15 (68.1)	1.0	7 (53.8)	52 (68.4)	0.35
Age	71.3 ± 10.5	72.4 ± 8.5	0.68	69.4 ± 9.0	68.9 ± 9.3	0.89
LVEF	50.4 ± 11.5	51.1 ± 9.1	0.83	54.8 ± 6.5	53.1 ± 9.9	0.58
LA volume (ml)	141.6 ± 40.4	128.8 ± 31.4	0.22	126.5 ± 31.0	150.8 ± 31.2	0.1
LAVI (ml/m^2)	69.0 ± 26.6	59.9 ± 24.3	0.19	61.6 ± 24.0	77.0 ± 19.5	0.04
LAVI > 70 ml/m^2	13 (36.1)	9 (40.9)	0.78	3 (23.1)	46 (60.5)	0.01
BMI (kg/m^2)	28.6 ± 4.3	31.2 ± 5.1	0.06	30.6 ± 5.7	28.6 ± 5.0	0.25
Time between ECV and ablation	67.5 ± 14.9	84.1 ± 35.4	0.52	84.7 ± 80.0	77.5 ± 53.8	0.67
AF duration (months)	29.7 ± 29.6	80.8 ± 63.1	0.0001	35.4 ± 38.9	52.5 ± 58.9	0.31
Prior AF ablation (%)	5 (13.9)	12 (54.5)	0.002	0 (0)	25 (32.9)	0.02
History of CAD	23 (25.8)	18 (31.0)	1.0	3 (23.1)	20 (26.3)	1.0
LVA	6 (17.1)	12 (57.1)	0.003	2 (15.4)	51 (67.1)	0.001
– *LVA not targeted*	5 (83.3)	1 (8.3)		2 (100)	10 (19.6)	
– *LVA completely targeted*	0	6 (50.0)	0.0001	0	12 (23.5)	0.002
– *LVA partially targeted*	1 (16.7)	5 (41.7)		0	29 (56.9)	
LA-indexed LVA area (%)	20.0 ± 18.9	21.9 ± 24.2	0.86	40.0 ± 42.4	38.8 ± 27.3	0.95
Atrial myopathy (stage)						
1	32 (88.9)	11 (50.0)	0.007	11 (84.6)	30 (39.5)	0.004
2	1 (2.8)	6 (27.3)		1 (7.7)	10 (13.2)	
3	2 (5.6)	2 (9.1)		0	7 (9.2)	
4	1 (2.8)	3 (13.6)		1 (7.7)	29 (38.2)	
Atrial tachycardia	0	3 (13.6)	0.05	0	5 (6.6)	0.44
Procedural duration	71.3 ± 13.0	100.6 ± 28.5	0.02	71.3 ± 13.0	100.6 ± 28.5	0.0001
RF ablation duration	899.3 ± 298.8	713.7 ± 434.8	0.07	862.3 ± 205.0	1,052.1 ± 424.4	0.02
Complications	1 (2.8)	4 (18.2)	0.06	1 (7.7)	3 (3.9)	0.47

Data are presented as *N.* (%) or mean ± SD.
AF, atrial fibrillation; ECV, electrical cardioversion; CTI, cavo-tricuspid isthmus; LA, Left atrium; LAVI, left atrium volum indexed for body surface area; LVA, low-voltage areas; LVEF, left ventricular ejection fraction; PVI, pulmonary vein isolation.

Among patients in the ECV effective group, substrate modification beyond PVI was more often performed in patients with longer AF durations (80.8 ± 63.1 vs. 29.7 ± 29.7 months, $P = 0.002$), with LVAs (57% vs. 17%, $P = 0.003$), and previous AF ablation (55% vs. 14%, $P = 0.002$). Among patients in the ECV failure group, substrate modification was more often performed in patients with larger LAVIs (77.1 vs. 61.6 ml/m^2, $P = 0.04$), with LVAs (67% vs. 15%, $P = 0.001$), and previous AF ablation (33% vs. 0%, $P = 0.02$).

Clinical outcomes

Patients were followed for 55 ± 19 weeks following ablation procedures. Eight patients (5.4%) had incomplete follow-up. Forty-two patients (30%) had recurrent AF. AF-free survival was similar in ECV effective and in the ECV failure groups (73% vs. 68%, $P = 0.39$) at 58.8 ± 18.3 and 52.4 ± 18.6 weeks, respectively (Figure 3). In the ECV effective group, patients treated with PVI alone had greater AF-free survival than those who underwent additional substrate ablation (83% vs. 59%; $P = 0.02$). In the ECV failure group, AF-free survival was similar among patients treated with PVI and with additional substrate ablation (64% vs. 70%, $P = 0.75$).

Patients undergoing their first procedure presented better AF-free survival compared to subjects undergoing a REDO (Supplementary Figure S1). At multivariate analysis (Table 4), LVA not targeted by ablation was the strongest predictor of AF recurrences (HR 1.39, 95CI: 0.97–1.98; $p = 0.07$).

Discussion

Main findings

The present study sought to assess the response to ECV as a potential tool to identify patients with PsAF who might respond favorably to PVI alone. The principal findings of this study are as follows: (1) In an unselected cohort of patients with PsAF, SR could be restored and maintained in 40% for ≥4 weeks prior to catheter ablation. (2) The predictive ability of the clinical variables tested in this study for ECV success was poor. (3) Patients in whom ECV resulted in sustained SR were less likely to have LVA detected on endocardial mapping and, when LVAs were present, were less extensive than in patients in whom AF recurred. (4) PVI alone resulted in SR maintenance of 83% at 1 year in the ECV effective group and 64% in the ECV failure group.

Response to ECV to stratify patients with psAF

Patients with PsAF are characterized by considerable variability in their degree of atrial remodeling (10, 16). The presence of LVAs has been proposed as a marker of more advanced atrial remodeling and has been linked to poor results from PVI alone (15, 17–19).

In our study, the presence and extent of LVAs were almost twice as great in patients in whom SR could not be maintained prior to catheter ablation than in those in whom SR was maintained and ECV failure was the only independent predictor of LVAs in our analysis.

Of importance, in the cohort here analyzed patients belonging to the ECV effective group could not be identified based on pre-procedural available parameters.

If maintenance of sustained SR prior to catheter ablation is associated with less extensive substrate abnormalities in patients with PsAF, it may serve pre-procedurally to identify individuals in whom PVI alone is sufficient.

This is supported by previously published data. In a large retrospective analysis, Eberly et al. found that PVI led to excellent long-term outcomes in patients with PsAF in whom SR was stably restored prior to catheter ablation (8). In a study of catheter ablation for PsAF targeting LVAs, PVI alone led to AF-free survival of 84% at 13 months in the subgroup of patients without LVAs and in whom SR was stably restored after ECV (4). Similarly, in two prospective single-center studies, the clinical response to AADs identified patients with PsAF who were more likely to respond to PVI (5, 7). Notably, however, not all studies examining the clinical response to ECV or AAD have found it to be predictive of PVI success (20).

Whether maintenance of SR mediates or is simply a marker of PVI effectiveness in patients with PsAF is unknown. However, there are data to suggest that it may not simply reflect less extensive extrapulmonary vein abnormalities. Benák et al. observed that patients experiencing a "step-back" to a paroxysmal AF phenotype with amiodarone had satisfactory long-term success from PVI alone (6). Rivard et al. reported that SR restoration by ECV before PsAF catheter ablation was associated with less extensive ablation required to restore SR when ablating during spontaneous or induced AF with similar long-term clinical success rates. On these bases the authors postulated that SR maintenance prior to catheter ablation may reverse adverse atrial remodeling (21).

For instance, the adoption in our study of a minimum of time of 4 weeks between ECV and catheter ablation is explained by the fact that reverse electrical remodeling in clinical and experimental models of chronic AF requires at least 4 weeks to take place (21–24).

PVI alone for patients with persistent AF

The 1-year success rate of PVI alone in unselected patients with PsAF is approximately 50%–60% (16). Accordingly, ablation strategies beyond PVI have been developed, many of which incorporate targeting presumably abnormal substrate and have been reported to yield favorable results (14, 15, 25). These approaches included the Marshall-PLAN and PVI + LVAs ablations which aims at making fibrillatory conduction less probable through transecting conduction through atrial *isthmi* or eliminating conduction throughout diseased areas (14, 15, 25). These approaches have been adopted in the present series

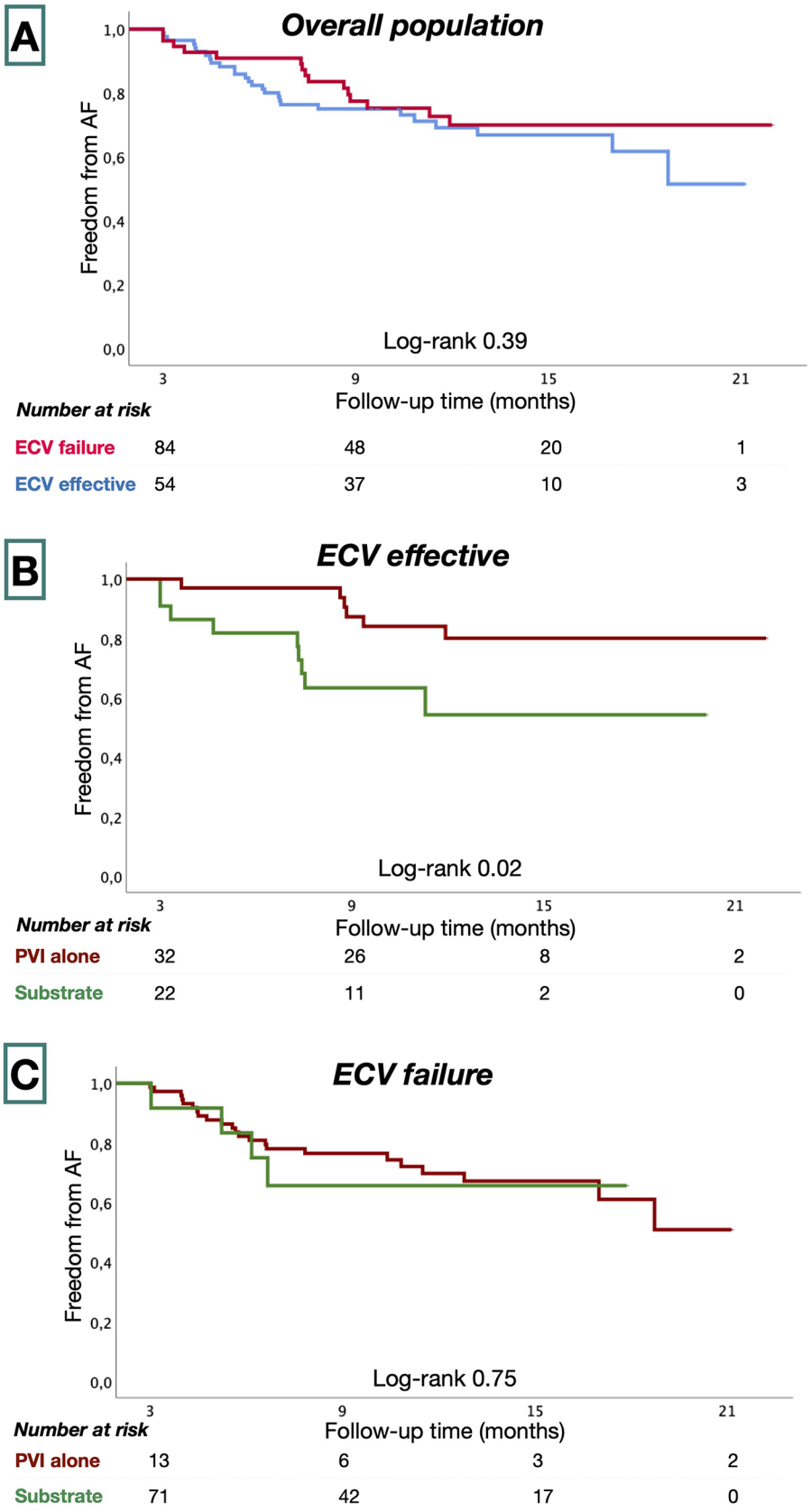

FIGURE 3
Kaplan–Meier survival estimates from AF recurrence in the overall study population (**A**), ECV effective (**B**), and ECV failure groups (**C**).

TABLE 4 Univariate and multivariate predictors of AF recurrences.

	Univariate				Multivariate			
			95 CI				95 CI	
	P value	HR	lower	upper	*P* value	HR	lower	upper
ECV working	0.39	1.31	0.70	2.47				
LAVI	0.73	1.00	0,99	1,02				
LA dimensions <70 ml/m^2	0.12	1.64	0.87	3.08				
LVEF	0.60	1.01	0.98	1.04				
Age	0.36	1.01	0.98	1.05				
Female sex	0.16	156	0.83	2.93				
DM	0.21	1.56	0.78	3.13				
LVA	0.09	1.73	0.91	3.29	0.57	1.15	0.69	1.93
LVA not targeted	0.02	2.04	1.11	3.76	0.07	1.39	0.97	1.98
Atrial myopathy stage	0.11	1.21	0.96	1.52				
CAD	0.02	2.77	1.18	6.58	0.09	1.39	0.94	2.04
CHADS-VASc score	0.79	1.02	0.83	1,26				
OSAS	0.18	0.53	0.21	1.35				
HF	0. 78	0.89	0.39	2.01				
AF duration <24 months	0.13	0.60	0.31	1.17				
Previous AF ablation	0.003	2.55	1.37	4.74	0.50	1.15	0.78	1.68

ECV, electrical cardioversion; AF, atrial fibrillation; LAVI, left atrium volum indexed for body surface area; LVEF, left ventricular ejection fraction; LVA, low-voltage areas; CAD, coronary artery disease; OSAS, obstructive sleep apnea syndrome; HF, heart failure.

according to operator choice. However, whether all patients with PsAF benefit from these more extensive ablation approaches is less clear, but it is conceivable that PVI alone may be sufficient for a sizeable proportion of patients with "earlier" stages of atrial remodeling. Our data suggest this to be the case, as patients with a favorable response to pre-ablation ECV exhibited AF-free survival of 83% with PVI alone at 13 months. These patients, although meeting criteria for PsAF, had shorter AF durations and were less likely to have LVAs (and when LVAs were present they were less extensive) when compared to their counterparts in whom AF recurred following ECV.

Since this is true also when comparing patients in the ECV effective group undergoing PVI alone or substrate modulations procedures. It is thus presumable that other parameters too, like substrate evaluation which can be in turn related to history of AF duration or previous catheter ablations, could play a role in selecting ablation strategy. However, taken altogether, our results suggest that assessing the results of ECV after an adequate period (i.e., 4–6 weeks) (22, 23) in a population with PsAF may represent a valuable pre-procedure tool to identify the healthiest patients of persistent AF spectrum with less diseased atria who may benefit from a PVI only ablation strategy. This information could be of pivotal importance for procedural planning considering the recent emerging of new technologies and energies for PVI among patients with PsAF (26, 27).

Limitations

The retrospective, single-center, and non-randomized nature of the study is an important limitation of this analysis. The risk of selection bias exists whereby "healthier" patients were treated with PVI alone, which is supported by the difference in the proportion of patients who underwent PVI in the ECV success and ECV failure groups (62% vs. 15%). However, this does not negate the conclusion that a subset of patients with PsAF can be effectively treated with PVI alone nor that the clinical response to ECV prior to ablation can help identify such "healthier" patients. The limited dimensions of the present study do not permit to make firm conclusions on populations subgroups, like patients undergoing a REDO procedure.

This study is not aimed at evaluating specific substrate ablation strategies beyond PVI and therefore this objective is beyond the aims of the present study. LVA-based ablation strategies have been more robustly evaluated by others still yielding conflicting results to date (3, 15, 18, 28–32). Since data of PsAF recurrence after ECV was collected as a dichotomic variable at admission, we can not provide information regarding timing of recurrence.

Finally, our results may not be generalizable to the full spectrum of patients with PsAF given that our exclusion criteria included potentially important variables such as a low left ventricular ejection fraction and the presence of a prosthetic valve. Given these limitations, our study should be considered hypothesis-generating. Our hypothesis is currently being evaluated in the *Pulmonary vein isolation Alone or in Combination wIth substrate modulation aFter electrIcal Cardioversion failure in patients with persistent atrial fibrillation* (PACIFIC) *study*. This multicenter, prospective, randomized study will use patients' clinical response to ECV to guide adjunctive ablation strategies beyond PVI (24).

Conclusions

In our study, in approximately 40% of patients with PsAF SR was stably restored by ECV for at least 1 month prior to catheter

ablation. This subgroup of patients tended to have evidence of less extensive atrial remodeling as defined by voltage mapping and exhibited AF-free survival exceeding 80% at 13 months with PVI alone. We could not identify strong clinical predictors of ECV success. Among patients with PsAF planned to undergo catheter ablation, the response to ECV may be a simple method to identify those in whom PVI alone is sufficient.

Data availability statement

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

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 the 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

LL: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. GL: Conceptualization, Investigation, Writing – original draft. FR: Writing – review & editing. J-PA: Conceptualization, Investigation, Supervision, Validation, Writing – review & editing. SC: Conceptualization, Writing – review & editing. PL: Conceptualization, Writing – review & editing. ZK: Conceptualization, Supervision, Writing – review & editing. AB: Conceptualization, Supervision, 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.2024.1416975/full#supplementary-material

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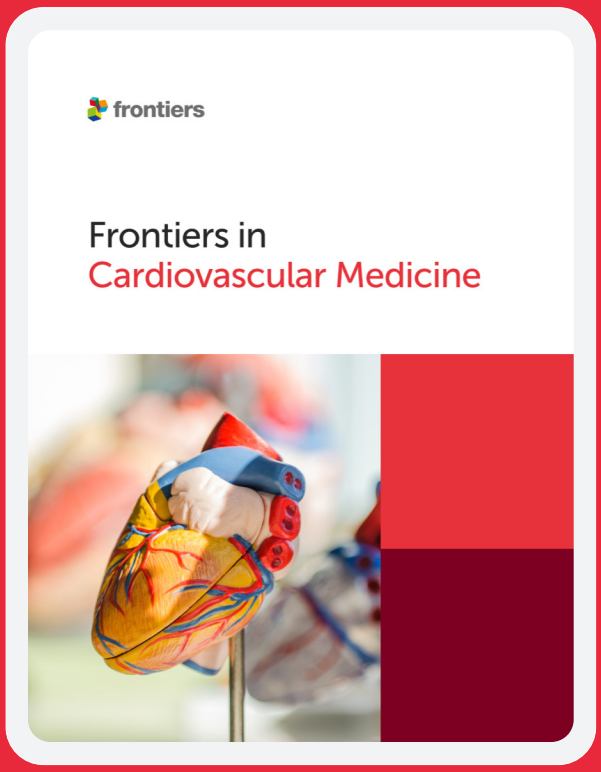

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