Association of atrial fibrillation and atrial flutter with sick sinus syndrome: a review of the issue based on examples of clinical observations


Aim. To review current therapies for AF and sick sinus syndrome (SSS) and analyze peculiarities of the SSS development after RFA for AF.

Materials and methods. The analysis of the world literature data was carried out along with the analysis of our own clinical observations of patients with AF who underwent RFA.

Results. As a result of the data analysis, it was proposed to identify three possible groups of causes why AF patients may develop SSS after RFA: 1) organic (associated with degenerative fibrosis of the sinus node tissue that occurs during aging, or with other underlying organic changes in the sinus node), 2) functional (associated with the remodeling of the sinus node tissue and the surrounding tissue of the atrial myocardium caused by prolonged AF persistence), 3) iatrogenic (associated with the effects of antiarrhythmic drugs on the sinus node or caused by the RFA itself). Each group of causes identified was illustrated by a clinical case with the following analysis of long-term results of RFA.

Conclusions. It was proposed to develop a scale for SSS prediction in patients after RFA for AF evaluating a patient's medical history, resting electrocardiography, 24-hour electrocardiographic monitoring, and, in some cases, coronary angiography to assess the peculiarities of the sinus node blood supply. The use of the above predictors could reduce the percentage of possible complications such as development of SSS in patients after RFA and also help to identify patients who may need a pacemaker implantation in the future.

Keywords: atrial fibrillation, atrial flutter, sick sinus syndrome, radiofrequency ablation.
Atrial fibrillation (AF) and atrial flutter (AFI) are the most common persistent cardiac arrhythmias that are seen in clinical practice in patients of various age groups. According to numerous generally accepted data, AF occurs more often than AFI; however, the exact reasons for this difference have not been established. Advances in the research of the leading electrophysiological mechanisms responsible for AF and AFI have contributed to the development of therapeutic tactics based on conception of the cardiac anatomy and the mechanisms of heart rhythm disturbance [15].

Treatment of these two conditions is a challenge for physicians. Heart rate control along with rhythm control and anticoagulant therapy constitutes the first-line treatment for symptomatic AF, AFI with rapid ventricular rate. However, in some cases, control of rhythm with antiarrhythmic drugs is ineffective, and cardioversion and/or catheter ablation are indicated for heart rhythm restoration [16,17]. Radiofrequency catheter ablation (RFA) is an effective treatment option for patients with AF and AFI who are resistant to drug therapy [16]. Catheter ablation has proven to be an effective, reliable, and safe method for the treatment of arrhythmias. In certain instances, RFA becomes a preferred approach over life-long drug therapy, especially for AF treatment [17].

Aim

To review current therapies for AF and sick sinus syndrome (SSS) and analyze peculiarities of the SSS development after RFA for AF.

Materials and methods

Despite the significant progress in the management of patients with cardiac arrhythmias, AF remains one of the leading causes of serious cardiovascular events such as stroke, myocardial infarction, heart failure, sudden death, and the number of patients with AF increases dramatically every year worldwide [1]. According to the European Society of Cardiology, more than 8 million cases of AF were recorded among the elderly over 65 years old in Europe in 2020, and this number is projected to increase by 2030, reaching 10 million cases. According to the cumulative AF incidence curve, males over the age of 50 lead by the number. At the age of 55, the incidence of AF reaches 37 % in one of three Europeans. A history of risk factors for AF increases the lifetime risk of AF from 23.4 % to 38.4 % [1].

According to some estimates, AF accounts for approximately 0.5 % of the adult population younger than 40 years old and more than 5 % of the population over 65. High prevalence is observed among the elderly and patients with arterial hypertension, chronic heart failure, coronary heart disease, heart defects, obesity, type 2 diabetes mellitus, or chronic kidney disease [2,3]. Modifiable risk factors such as a sedentary lifestyle, smoking, obstructive sleep apnea, and high blood pressure predispose to AF, as each factor induces structural and electrical remodeling of the atria [3]. Detection of people at increased risk of developing AF and screening for early diagnosis of arrhythmias may facilitate preventive measures choice, for example, in high-risk subgroups such as patients after stroke [1].

AF can be classified based on etiology, depending on whether it occurs with unspecified etiology in patients with a structurally normal heart or is a complication of hypertension, valve disease, or other structural heart disease [4]. Any condition that leads to inflammation, stress, injury, or ischemia of the myocardium can lead to the development of AF. The classification recommended previously was based on the time of arrhythmia occurrence. Patients seeking medical treatment may be newly diagnosed with an episode of AF or, if previous episodes have been documented, recurrent arrhythmia [5].

AF is considered recurrent when a patient has two or more episodes. If recurrent AF spontaneously terminates, this form is called paroxysmal AF, when episodes stop spontaneously within 7 days. In persistent AF, episodes last more than 7 days, and if associated with a rapid and uncontrollable ventricular rhythm, this can lead to electrical remodeling of cardiac myocytes, causing dilated cardiomyopathy. This type of AF can occur as the first episode or as a result of recurrent episodes of paroxysmal AF. Long-lasting persistent AF present for more than 12 months requires electrical or pharmacological cardioversion to stop the arrhythmia and restore sinus rhythm. AF that can not be successfully cured by cardioversion and prolonged AF for more than 1 year, when cardioversion is not indicated or has not been undertaken, is called persistent [5,6]. AF that is asymptomatic, is called “silent AF” [9,10].

The onset of AF may not be accompanied by symptoms. Most AF patients report symptoms associated with this disease at a certain time, during arrhythmia paroxysms, but a significant number of patients (12.0–42.5 %) remain completely asymptomatic during each manifestation of AF [8]. The most common symptoms associated with AF include fatigue, shortness of breath, palpitations, chest pain and discomfort, dizziness. The first two symptoms are the most frequent. AF-related symptoms are often interfered with daily activity due to exercise intolerance and arrhythmia-induced stress condition, which, as a result, affect adversely the quality of life. For decades, there has been a prevailing belief that AF manifestation starts with paroxysmal episodes which increase in frequency and duration causing progression to more persistent AF subtypes. This so-called “AF generates AF” postulate was based on early experimental evidence that tachycardia induces electrophysiological atrial remodeling leading to AF persistence [3]. In the Canadian Registry of Atrial Fibrillation, the progression of paroxysmal AF to persistent AF was 8.6 % after 1 year and 24.7 % after 5 years [11]. According to the Euro Heart Survey of the European Society of Cardiology, a one-year follow-up of 5 333 patients with AF showed that in 80 % of patients with paroxysmal AF the latter did not progress to another form of AF, while in 30 % of patients with persistent AF it progressed to permanent AF [12]. Significant predictors of AF progression from paroxysmal to persistent or persistent to permanent AF, according to the American Heart Association, are increased body mass index, increased heart rate, age, increased systolic blood pressure as well as a history of hyperthyroidism, stroke, or heart failure [13].

Over the past three decades, there has been a significant increase in knowledge and advances in clinical management of AF [3]. Investigation of the pathophysiological mechanisms of the onset and progression of arrhythmia, the relationship between comorbidity and risk factors for
the arrhythmia development provide a fundamental understanding of the mechanisms underlying AF, which allows to discover new, rational therapeutic approaches, research of which continues to the present.

AF is characterized by high-frequency excitation of the atria, which leads to both asynchronous atrial contraction, and irregular excitation of the ventricles. While AF can occur in the absence of known structural or electrophysiological abnormalities, epidemiological studies are increasingly eliciting comorbidities, many of which have been shown to cause structural and histopathological changes that form a unique substrate for AF or atrial cardiomyopathy [3].

The mechanism of AF is based on re-entry and/or rapid local ectopic excitation of the atrial myocardium. Irregular atrial contractions, typical for AF, may result from an irregular atrial response to ectopic stimulation or re-entry of the excitation wave [14].

In their study, Haïssaguerre et al. were the first to identify focal ectopic excitation arising in pulmonary vein myocytes in patients with paroxysmal AF. Elimination of these ectopic foci reduced the burden of AF demonstrating their role in the genesis of AF. Pulmonary veins are now known to have unique electrical properties and complex fiber structure that promote re-entry and ectopic activity to initiate AF [3].

Specification of the optimal treatment approach for AF is still a challenge for clinicians, since the onset and maintenance of AF occurs as a result of complex interaction between arrhythmia triggers, changes in the atrial substrate and changes in the autonomic nervous system [18]. Pulmonary vein isolation is recommended for the treatment of drug-refractory symptomatic AF in patients who can not tolerate or do not want to take antiarrhythmic drug therapy. In patients with paroxysmal AF, ablation successfully affects target triggers that are predominantly located in the pulmonary veins, with a clinical success rate of 60–80 %. However, a significant proportion of patients with persistent or permanent AF often do not respond to catheter ablation or require multiple repeated procedures [18].

Recently, more and more attention has been drawn to the progression of paroxysmal AF to a persistent or permanent type. A growing number of data indicates significant morbidity and mortality associated with the transition from one condition to the other [7]. In a systematic review by the American Society of Cardiology in 2015, the articles collected were divided into 2 groups: 1) general population studies (mainly with drug therapy) and 2) studies considering the progression of AF after ablation. The first group included 21 studies, the second – 8. In the first group, the percentage of AF progression ranged from 10 % to 20 % after 1 year. Studies that included longer follow-up found a higher percentage of progression (50 % to 77 % after 12 years). Among patients who underwent catheter ablation, the percentage of progression was significantly lower (from 2.4 % to 2.7 % after a 5-year follow-up). The percentage of progression after catheter ablation did not change with the duration of follow-up. Thus, ablation of AF is associated with a significant reduction in progression to permanent AF compared with studies in the general population. Prevention of long-term progression of AF can be clinically significant after AF ablation [7].

Atrial flutter is the second most common cardiac arrhythmia after AF that relates to persistent supraventricular tachycardias. [3] The term “supraventricular tachycardia” (SVT) literally means tachycardia with an atrial rate greater than 100 beats per minute at rest and has traditionally been used to describe all types of tachycardias except ventricular and atrial fibrillation. In the general population, the prevalence of SVT is 2.25 per 1000 people while the risk of developing SVT in women is twice as high as in men, and in people over 65 years old, the risk of developing SVT is more than 5 times higher than in young people. Atrioventricular nodal reciprocating tachycardia (AVNRT) is the most commonly treated substrate after AF followed by AF and AVNRT in patients undergoing catheter ablation. It is also reliably known that AF and AF can coexist [19].

AFI is common in patients with underlying medical conditions such as chronic obstructive pulmonary disease, pulmonary hypertension, and heart failure. Isolated AFI in the absence of structural heart disease is rare. AFI is more than 2.5 times more common in men than in women and increases exponentially with age. Associated risk factors include hypertension, diabetes mellitus, and a history of alcohol abuse [7,19].

AFI relates to a macro re-entry tachycardia which can be typical or atypical, depending on the occurrence site. Electrocardiographic signs of AFI are flutter waves without an isoelectric line between QRS complexes. The most common type of AFI is a typical, or cavotricuspid isthmus (CTI)-dependent, that occurs in the right atrium at the level of the tricuspid annulus. Atypical AFI is independent of CTI, and the cause of the arrhythmia may be in the right or left atrium [7].

Electrophysiological studies and intracardiac mapping are the only methods to determine the exact mechanism or area causing AFI. Unlike typical AFI, the development of the atypical form is associated with a structural heart disease such as previous cardiac surgery or ablation procedures [7].

Control of the rhythm and its frequency, as well as anticoagulant therapy to prevent thrombotic complications can be used both in patients with AF and AFI. In the case of drug-refractory AF or AFI, ablation of the arrhythmia substrate is indicated. RFA of CTI is a standard treatment for typical AFI with a 95 % success rate and few post-procedure complications [7].

RFA has now become an effective treatment for drug-refractory AF and AFI. In general, the incidence of complications associated with RFA is estimated to be in the range of 3.5–5.0 % [20,41]. Over the past decade, among the complications of RFA due to AF, the leading ones are cardiac tamponade detected in 0.5–2.4 % of cases after AF ablation, peripheral vascular complications (hematomas, pseudoaneurysms, arteriovenous fistulas) recorded in 1–2 % of cases, and thromboembolism including stroke and transient ischemic attack in 0.20 % and 0.94 % of cases, respectively [20].

Complications of AF ablation depend on the side of origin of AF. Right-sided AFI is associated with fewer complications than ablation of left-sided AFI since it is associated with the need for a transseptal access during the procedure to ablate foci of the left atrial arrhythmia. Transseptal puncture provides a temporary connection between left and right chambers of the heart; however, during puncture, the risk of embolic strokes is also increased with ablation of left-sided AFI compared with ablation of AFI of the right atrium [7].
Catheter ablation is also used in patients with tachy-brady syndrome. Recent studies have shown that ablation, compared to pacemaker implantation, reduces the number of hospitalizations associated with tachy-brady syndrome and is effective in controlling AF with long pauses. Nevertheless, long-terming follow-up data are necessary, as some patients may require pacemaker implantation after AF substrate ablation due to progressive sinus node (SN) dysfunction. Thus, the question of whether catheter ablation should be considered as first-line therapy for tachy-brady syndrome in AF remains open [21,52].

Sick sinus syndrome (SSS) is a group of arrhythmias caused by impaired formation and conduction of impulses in the SN [24,26]. The pathophysiological mechanisms of SSS are multiple and include both electrophysiologically and structural changes [23,24,39].

SSS can manifest at any age, however, there is a certain dependence on age and sex [23,25,31,32]. In patients over 45 years old, the incidence of SSS is 1 in 1000 patients, and in people over 65, it reaches a ratio of 1 in 600. Many authors have reported that women, especially during menopause, are more likely to suffer from SSS compared to men [44].

The course of SSS is characterized by the progressive development of various rhythm disturbances, more often of bradyarrhythmias. The time “progression” from bradycardia to different types of sinoatrial blockade or sinus arrest can be prolonged and unpredictable — according to some data, on average, up to 13 years (from 7 to 29 years) [38,47]. Also, one of the typical features of the progressive course of SSS is the manifestation of supraventricular arrhythmias among which AF is the most common one [38]. SSS can be associated with both organic damage of the SN tissue (endogenous causes — such as degenerative or inflammatory lesions of the SN), and with exogenous causes that suppress its function (electrolyte disturbances, some drugs, some endocrine disorders, connective tissue diseases) [25,40].

Diagnostics is usually performed according to the data of an electrocardiogram (ECG) or daily ECG monitoring. Signs of SSS on ECG can be inadequate sinus bradycardia or chronotropic insufficiency, pauses against a background of sinus arrest or sinoatrial blockade as well as tachy-brady syndrome [24,25,33]. Typical clinical symptoms include fainting, dizziness, palpitations, shortness of breath on exertion, and fatigue. It should be noted that the course of SSS in early stages may be asymptomatic [25,26]. The main method of treatment for manifest SSS (on condition that all possible causes suppressing its function are excluded) is implantation of a pacemaker.

There is a great amount of evidence that SSS often coexists with AF and/or AF [23,27,29,30]. The first works reporting frequent combination of these rhythm disturbances evolved in the 1960s and belong to Irene Ferrer [44]. Lamas G. A. et al. studied a group of more than 2000 patients who had an artificial pacemaker (AP) implanted because of diagnosed SSS. It was found that 53 % of the group had various supraventricular arrhythmias, including AF, before the pacemaker implantation [46]. Hung-Yu Chang et al. in their work demonstrated that in patients with paroxysmal AF, regional atrial remodeling near the SN of the right atrium was associated with SSS [51]. At the same time, other authors considered both possible options of the development: they described the mechanisms when AF was a predictor of SSS as well as observations demonstrating that AF progressed in patients secondary to the initial SSS [33,34].

Results

Based on the studied data, we can distinguish causes of SSS developed in AF patients after RFA in 3 groups: organic, iatrogenic and functional.

1. Organic (associated with degenerative fibrosis of the SN tissue, occurring during aging, or with other pre-existing organic changes in the SN)

Clinical electrophysiological studies have shown that with age, there was a slowdown in the SN recovery time, conduction processes and impairment of refactoriness processes in atrial tissue, as well as an increase in the number of elastic fibers along with fatty infiltration and uneven distribution and size of muscle fibers [31,38,39].

The abovementioned structural and electrophysiological changes occurring with age in the atriums and SN were described in detail by Peter M. Kistler et al. on the example of a group of 13 patients over 60 years old (in comparison with a control group of 13 patients aged 31–59 and 15 patients under 30) [38]. Among the study group patients, deviations in the electrophysiological processes of the atrial tissue were recorded constituting 9 cases of elongated atrial refractory period and decreased voltage (during electroanatomical mapping, etc.), which were more significant, comparing to the control group.

Some concomitant diseases (heart failure, atherosclerosis, as well as some diseases of connective tissue) also lead to changes in the SN [30,40,41]. For instance, myocardial ischemia can result in a decrease in perfusion or damage of the SN tissue [40]. In a study, among 46 patients who had experienced inferior myocardial infarction, stenosis of the artery supplying the SN was found in 76 % [40].

Connective tissue diseases can also manifest with SN dysfunction. For example, scientists from one of the Turkish universities reported a case of exacerbation of systemic lupus erythematosus manifested by severe sinus bradycardia [41].

Also, in recent years, more and more attention has been paid to the role of genes and gene mutations which may be associated with idiopathic cases of both SSS and AF [48–50]. Taisuke Ishikawa et al. also found association of SSS with AF in most patients with mutations in the HCN4 gene [47,48]. Rosa B. Thorolfsdottir et al. in a large genetic study have found six loci in the genome associated with SSS, some of which were also associated with other arrhythmias. However, p.Gly62Cys in the KRT8 gene was not associated with any other cardiovascular traits and indicated a mechanism only specific for the development of SSS [50].

2. Iatrogenic (associated with the impact of antiarrhythmic drugs on the SN or caused by ablation procedure)

Pharmacological agents that usually lead to dysfunction of the SN are antiarrhythmics of the I–III classes, beta-blockers, nondenhydropridine calcium channel blockers, digoxin, lithium, sympatholytics [26,27]. In the work, T. Nakamura described that SN dysfunction (SND) was induced
by cardiovascular drugs in 42 out of 77 patients admitted to the department with signs of SSS [42].

The second considered iatrogenic factor, as mentioned above, is the ablation procedure [27–29]. Clinically evident damage of coronary arteries during RFA for AF is rare and, according to a number of authors, is only about 0.09 % [53,54]. However, it can be associated with the development of acute SND, requiring pacemaker implantation.

According to a number of authors, such injuries to the SN artery (SNA) were associated with its abnormal origin; coronary angiography revealed that in some patients, the SNA did not origin from the right coronary artery, but from the proximal region of the left circumflex artery, which corresponded to the site of RFA.

3. Functional (associated with remodeling of the SN tissue and the surrounding tissue of atrial myocardium caused by persistence of AF [23,27,28])

According to some authors, within 1 week after RFA for AF, 3.2 % [28] – 9.1 % of observed patients needed pacemaker implantation [21].

Structural remodeling of the SN in recurrent paroxysms of AF or long-term persistent AF usually includes changes at the cellular and molecular levels: apoptosis of cardiomyocytes, progressive fibrosis, electrical disorganization [39,40]. Some studies have described stenosis of the artery supplying the SN in patients with long-term persistent AF [32].

Many studies have shown that AF can cause transient myocardial ischemia [32,33]. There are studies demonstrating that paroxysmal AF can lead to inhibition of SN function which leads to prolonged sinus pauses after the end of AF paroxysm [38]. Many authors consider prolonged sinus pauses on termination AF as predictors to pacemaker implantation in AF patients after RFA [21,35,37,45]. There were only divergences in the length of the pauses. Thus, Dong-Hyeok Kim et al. classified pauses of more than 6.3 seconds as predictors [21,36], while Binquan You et al. paid attention to pauses of more than 2.6 seconds [35].

Besides, old age, female sex, significant enlargement of the left atrium, and decreased left ventricular ejection fraction are predictors of pacemaker implantation in patients with AF after RFA [22,34,44]. Morishima I. et al. define the age over 75 as a predictor [34]. Ursula Doris et al. associate higher incidence of SSS in women with significant differences in the expression of Cav1.3, Kir3.1, and Nnx2-5 at mRNA and/or protein levels in men and women. Cav1.3 plays an important role in the pacemaker function of the SN [43].

In accordance with the groups that we classified, there are 3 clinical cases below that illustrate various etiological mechanisms of the SSS development in AF patients.

Case 1 illustrates the organic causes of SSS secondary to AF

A 79-year-old patient Z. complained of sudden-onset palpitations, interruptions in the heart beats that were accompanied by shortness of breath, weakness and stopped with taking some drugs. Anamnesis: January 2018 – non-Q-wave anterior septal left ventricular (LV) myocardial infarction; coronarography – intact coronary arteries. The patient had a 11-year history of irregular heartbeat sensations with much more increased frequency and duration over the last six months and no alleviating factors other than drug intake resulting in marked bradycardia. Echocardiography: end-diastolic dimension – 4.5 cm, end-systolic dimension – 2.7 cm, ejection fraction – 60 %, atrial septum – 1.3 cm, LV posterior wall – 1.3 cm, left atrium – 3.6 × 3.9 cm (V – 44 ml), right atrium – 4.5 cm.

Radiofrequency ablation of pulmonary veins was performed (Fig. 1).

Since increased SN recovery time (SNRT), increased corrected SNRT, as well as prolongation of the H-V interval (82 ms) were registered with the existing left bundle branch block, the patient underwent elective endocardial implantation of the pacemaker Kora 100DR (Sorin–Microport) in AAIR-DDDR mode, because of symptomatic sinus bradycardia and the risk of developing complete atrioventricular block (Fig. 2).

In this case, SSS could be associated with the remodeling of the SN following long-term AF and age-related changes. The planned pacemaker implantation significantly improved the patient’s prognosis and the quality of life.

**Case 2 illustrates the iatrogenic cause of SSS (SN injury during RFA)**

A 51-year-old patient Z. complained of daily episodes of sudden-onset palpitations for 5 years which were accompanied by severe weakness, dizziness, shortness of breath at rest and light-intensity physical activity. The patient had a past medical history of diffuse goiter with thyrotoxicosis which was diagnosed 2 years ago and had undergone a thyroidectomy. On admission, the patient was taking hormone replacement therapy (levothyroxine 100 mg). Echocardiography: end-diastolic dimension – 4.4 cm, end-systolic dimension – 2.7 cm, ejection fraction – 57 %, left atrium – 3.5 × 3.8 cm (V – 29.7 ml).

In accordance to ambulatory ECG monitoring and echocardiography findings, the diagnosis was established: Paroxysmal atrial fibrillation. CHA₂DS₂-VASc – 1 point, HAS-BLED – 0 points, EHRA III.

Pulmonary vein isolation was performed. However, in 3 months after RFA, the patient developed complaints on dizziness. During 24-hour ECG monitoring, pauses of 6 sec leading to short episodes of AF were recorded. SSS was diagnosed. Following the diagnosis, a pacemaker device was implanted (Fig. 3).

After a pacemaker implantation the patient did not present complaints associated with bradycardia and atrial fibrillation. There was absolute absence of atrial fibrillation according to the pacemaker diagnostics data.

**Case 3 illustrates the functional causes of the SSS development against a background of atrial fibrillation**

A 68-year-old woman was admitted with complaints of light-headedness, dizziness, weakness and palpitations. Her past medical history included hypertension diagnosed more than 10 years ago. She noticed feeling of palpitations for 6 years.

The ECG showed a paroxysmal form of AF with pauses and recovery time up to 6.0 seconds (Fig. 4).

According to echocardiography (the examination was performed during tachysystolic AF with 150 beats per minute), signs of moderate LV hypertrophy and dilation of both atriums were detected (end-diastolic dimension – 4.0 cm, end-systolic dimension – 2.2 cm, ventricular septum – 1.5 cm, LV posterior wall – 1.3 cm, ejection fraction – 62 %, left atrium – 4.0 × 5.0 cm, right atrium – 3.9 cm)

RFA was performed resulting in successful treatment of AF in accordance with the data of clinical, ECG and 24-hour ECG monitoring (Fig. 6).

The patient became free of any clinical and objective signs of significant bradycardia at follow-up.

**Conclusions**

1. At present, RFA is still the most effective method for treatment of AF and AFI refractory to drugs. Patients with bradycardia and pauses present no signs of SN dysfunction after sinus rhythm restoration following RFA in most cases and do not need post-procedural pacemaker implantation. However, in a number of patients, AF and/or AFI may be accompanied by SSS which may require a pacemaker device implantation.

2. The development of a scale with prognostic parameters (predictors) for the SSS in AF/AFI patients after RFA such as a patient’s medical history, resting and ambulatory ECG monitoring findings, and, in some cases, coronary angiography to assess the SN blood supply can help minimize possible complications and contribute to early identification of patients requiring post-procedural pacemaker implantation.

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