https://doi.org/10.35336/VA-2023-2-12

FOCAL ACTIVITY IN ATRIAL FIBRILLATION: STATE OF THE ART

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Focal activity is one of the dominant triggers of atrial fibrillation. Its activity is revealed in paroxysmal as well as in persistent patterns of arrhythmia. Starting as a trigger of atrial fibrillation in pulmonary veins, over time with increasing of burden of atrial fibrillation, focal activity is more and more revealed out of pulmonary veins: anterior and posterior left atrial walls, interatrial septum, coronary sinus, ligament of Marshal and right atrium. Diagnostics of focal activity is a challenging clinical task despite implementation of mathematical algorithms of electrogram analysis because of its spatial instability and activation direction of the mapping electrode. All these items are discussed in the article.

Key words: atrial fibrillation; focal activity; mapping; catheter ablation; pulmonary vein; non-pulmonary vein triggers; dispersion

Conflict of interest: none.
Funding: none.
Received: 01.08.2022 **Revision received:** 23.10.2022 **Accepted:** 28.12.2022
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For citation: Aleksandrova IS, Chapurnykh AV. Focal activity in atrial fibrillation: state of the art. *Journal of Arrhythmology.* 2023;30(2): e12-e26. https://doi.org/10.35336/VA-2023-2-12.

THE ROLE OF FOCAL ACTIVITY IN THE GENESIS OF ATRIAL FIBRILLATION

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice worldwide and is a multifactorial disease with a complex pathogenesis. According to the Global Burden of Disease study, one in three members of the white race has a lifetime risk of AF, which reflects a trend toward an overall increased risk of AF over the past 10 years [1, 2].

The role of catheter ablation in rhythm control strategies today is impossible to overestimate. In comparison with paroxysmal AF, in which the rate of freedom from arrhythmia at 12-month follow-up after surgery is up to 90% according to some data [3], the outcomes of surgery in persistent AF are not so high, which naturally leads to the need for repeated procedures. Ongoing research aimed at studying the mechanisms underlying AF has revealed a variety of proarrhythmogenic substrates, the presence of which is not always correlated with the clinical course of the arrhythmia.

G.Moe was the first to demonstrate the multifactorial mechanism of AF. In his experiments [4] on isolated dog hearts, AF was induced by superfrequent stimulation from the right atrial appendage during vagus stimulation or aconitine injection. It was shown that isolation of the site of aconitine exposure resulted in cessation of arrhythmia. On the basis of this observation G.Moe has assumed the mechanism of development of AF, in which exactly the focal focus (FF) causes activation of atria with high frequency leading to heterogeneity of excitation of atria (fibrillatory conduction). At the same time, isolation of the stimulation site inducing AF during vagal stimulation did not lead to cardioversion, which further led researchers to the idea of the existence of true fibrillatory activity, in which the persistence of AF per se was independent of the presence of FF. This is the basis of the "multiple waves" theory, which was prevalent in the second half of the 20th century.

Despite the rapid development of various mapping techniques (endo-, epicardial, superficial), the question of what exact contribution each of these mechanisms makes to the development and persistence of arrhythmias is still open. This review discusses various methods for diagnosing focal activity (FA) in AF, their development based on an evolving understanding of arrhythmia mechanisms, and the effectiveness of FA ablation verified by various methods.

Focal activity of pulmonary veins

One of the most important in understanding the mechanisms of AF was the work of M. Haissaguerre (1998), who first demonstrated the important role of focal triggers located in the area of pulmonary vein (PV) ostium. Then it was shown that 94% of ectopic activity in paroxysmal AF is localized in the PV ostium. Electrophysiologically, PV activity was recorded as a "spike" on the mapping catheter, outpacing the P-wave of the ectopic complex on the electrocardiogram and recorded most early in the PV depth. Both a single pulse and a pack of consecutive pulses were sufficient to induce AF. FA PV was characterized by an irregular tachycardia cycle (from 110 to 270 ms) [5].

Initially, it was the ectopic PV activity that was given the dominant importance, which was confirmed by the

high frequency of arrhythmia cessation during focal ablation. However, it soon became evident that arrhythmia recurrences were associated with FA arising in other areas, different from the primary location of the focus, PV, so that focal ablation was superseded by PV isolation [6]. As often described in the literature, PV isolation is the "cornerstone" of treatment of AF and is recommended for all patients, as reflected, in the current recommendations of the European Society of Cardiology (Class I, level of evidence A) [7].

The main mechanisms of PV arrhythmogenicity include trigger activity and increase of automatism, formation of re-entry. A number of ontogenetic, morphological, and molecular features contribute to their formation. First, the myocardial fibers of the left atrium (LV) extend beyond it and "envelop" the pulmonary veins in their proximal part, forming "couplings". Secondly, the localization of the progenitor cells of the cardiac conduction system during embryonic development is determined by the process of folding of the embryo's primary heart tube. It is probably due to this process that electron microscopy data show P cells similar to cardiomyocytes of the sinoatrial node (NLPC, nodal-like P-cells) in PV, as well as cells similar to Purkinje fiber cells in patients with a history of AF [8]. There were also found Cajal cells (interstitial Cajal cells), which have the ability to spontaneous depolarization and behave as rhythm drivers [9]. Subsequently, Cajal cells were also found in the atrial myocardium [10], suggesting their involvement in arrhythmogenesis not only on the PV side.

The differences in electrophysiology between atrial cardiomyocytes and PV "couplings" are based on the ratio of ionic currents. According to the data obtained by the potential fixation method, PV cardiomyocytes exhibiting spontaneous electrical activity were characterized by a lower density of internal rectification potassium channels (IK1), transient potassium output channels (Ito) and L-type calcium channels (ICaL), whereas the current through delayed rectification channels (IKs and IKr) was greater [11, 12]. They also recorded a current resembling sodium current activated by hyperpolarization, or "funny"-current [11], which is the current of the phase of slow diastolic depolarization of the pacemaker cell in the atrial myocardium.

Spontaneous PV ectopic activity is also modulated by the intracellular concentration of calcium ions [13]. Moreover, the cardiomyocytes included in the PV couplings have characteristic features: shorter duration of action potential and lower rise rate of phase 0, which contribute to the formation of microreentry [12]. Such structural features of PV couplings as longitudinal dissociation and abrupt change of cardiomyocyte fiber orientation also contribute to this [14, 15]. Epicardial high-density mapping in PV couplings has demonstrated the presence of decremental conduction, functional blocks and rotational activation [16]. Probably, the predominance of one or another mechanism (abnormal automatism or re-entry) determines the clinical course of AF [17].

Since the description of PV focal activity and proposal of complete PV isolation as an effective method of treatment of AF, catheter ablation has undergone a way from an experimental procedure performed in rare cases to a widespread and high-tech interventional method of prevention of arrhythmia recurrence. However, the diagnosis of FA itself has remained the most debatable area of the study of the genesis and treatment of AF.

In contrast to paroxysmal AF, the results of ablation in persistent AF were not so encouraging [18]. The most probable explanation is considered to be the coexistence of local foci (focal or micro re-entry, which were traditionally separated in literature) in atrial myocardium, macro re-entry tachycardia and previously mentioned "multiple waves", contributing to persistence of AF [19-21]. Over the past two decades, many substrate modification strategies have been proposed for AF, from linear interventions to rotor ablation, complex fractionated atrial electrograms (CFAE), ganglionic plexus and ablation of low-voltage zones, with varying results.

Focal activity outside the pulmonary veins

FA outside PV refers to ectopic activity localized in atrial anatomical regions other than PV. FA outside the PV is most often found in the posterior wall (PW) of the LA, coronary sinus (CS), ligament of Marshall (LM), superior vena cava (SVC), border ridge (crista terminalis), interatrial septum, LA appendage (LAA). These anatomical structures contain cardiomyocytes, which retained the ability to spontaneous depolarization or were a substrate for the occurrence of microreentry, due to the increased conduction function [22, 23].

From the point of view of electrophysiology, the LAPW is the result of introduction of PV elements into the LA during embryogenesis and, accordingly, may contain areas of FA [24]. In addition to the electrophysiological properties described above, the heterogeneity of cardiomyocyte fiber orientation is characteristic for LAPW: along with the predominant orientation (back-to-front), the fiber course in the PV antrum has a circular course and a wave-like one in the junction with the PV [25]. Also, histologically high degree of fibrotic changes is characteristic for LAPW, which predisposes to formation of triggers due to molecular interactions of fibroblasts with cardiomycytes [26], as well as multiple areas of unidirectional conduction block.

In recent years, there have been several studies demonstrating that isolation of LAPW improves the outcome of radiofrequency ablation in patients with both persistent and paroxysmal AF [27-32]. Unfortunately, it is far from always possible to create continuous lines of transmural posterior wall damage - box lesion - which affects the number of recurrences after posterior wall isolation in the long term [33-35].

The LAA is a derivative of the primary LA of the embryo, which is formed from the primary PV and their branches. It is known that during embryogenesis, during the incorporation of PV smooth muscle cells into the LA myocardium, the contribution of the vascular component to the formation of the LAA increases, and the venous sinus component is limited to a small area surrounding the entrance to the LAA [36] The embryological origin of the LV appendage proves that the LAA can be as a potential trigger AF as the PV.

The LAA can be a source of localized re-entry, having centrifugal spread of the excitation front, especially

in patients with long-term persistent AF [37]. In a study by L.Di Biase et al. (2010), 27% of the triggering activity came from the LA appendage , and in 8.7%, this anatomical structure was the only trigger of AF. During the 1-year follow-up, there was no recurrence of FA in 68% of patients in the focal LAA ablation group and in 74% in the LAA isolation group, whereas in the group in which LAA foci were not ablated, SR persisted in only 25% ($p<0.001$) [38]. In the open randomized BELIEF trial, empirical electrical isolation of the LAA increased freedom from arrhythmia during long-term follow-up in patients with long-term persistent AF: recurrences were absent in 48 (56%) patients in the extended ablation and LAA isolation group and in 25 (28%) in the group without LAA isolation [39]. Electrical isolation of the LA appendage helps to reduce the recurrence rate in patients with nonparoxysmal AF, without increasing the risk of thromboembolic events [40].

A frequent localization of FA foci is the CS [41-43]. For the first time it was shown that in 66% of patients AF was no longer induced after electrical separation of CS and LA [41]. The coronary sinus is enveloped by muscle fibers of different thickness and orientation, connecting epicardially this structure with the right atrium (at the level of the CS ostium) and the left atrium (at the level of the middle portion of the CS). In addition to spontaneous electrical activity, the epicardial fibers of cardiomyocytes surrounding the CS have slow nondecremental conduction, which can potentially contribute to the formation of conduction block and re-entry [44]. Isolation of CS is the preferred strategy, as it promotes elimination not only of existing, but also of potential triggers of AF and is associated with the best results of ablation [45]. CS isolation is most effectively achieved by ablation of the endocardial (from the inferior-lateral part of the LA) and epicardial portions of the vessel until the potentials disappear, as it is associated with more favorable outcomes of surgery [46].

The Marshall's ligament is a rudimentary fold formed because of obliteration of the left anterior cardiac vein, through which, during intrauterine development, venous blood flows into the right atrium through the great cardiac vein and coronary sinus. In adults, the LM contains a portion of the Marshall vein, the myocardial bundle, myocardial fibers connecting it to the muscular elements of the CS, PV and atrial myocardium itself, as well as elements of the autonomic nervous system (sympathetic and parasympathetic ganglia) [47]. Thus, it is a linking element (a kind of shunt) with PV, which, as mentioned above, serve as FA sources. Marshall's ligament has been described as an independent source of trigger activity for arrhythmias with different mechanisms among patients with AF [48]. There is also data that LM is the cause of 30.2% of left atrial tachyarrhythmias after radiofrequency ablation of AF [49].

The right atrial myocardium extends to SVC similarly to the PV, "forming" couplings, in which cardiomyocytes also have abnormal automatism [50]. The predominant role of "couplings" in SVC arrhythmogenesis is confirmed by the data that SVC FA is manifested in patients with longer "couplings" (extending up to 30 mm from the vein ostium) and more amplitude electrograms recorded in this area (>1.0 mV) [51]. In a large study including 1,425 patients investigating the arrhythmogenicity of SVC, the vein was identified as the source of AF in 5.2% of patients and in 78.4% of them was a direct arrhythmia trigger. An unusual conclusion from the results was the fact that SVC can be both an initiator of arrhythmia (in AF itself a longer cycle length of tachycardia was recorded) and a structure supporting it (in 32.4% of cases conversion to atrial flutter, atrial tachycardia after SVC isolation) [52]. Isolation of SVC is a reasonable strategy in the verification of trigger activity in this area [53]-[58]. However, arrhythmogenicity of SVC is rarely confirmed in patients with long-term persistent AF [59].

The proportion of foci outside PV varies from study to study. Thus, in a study by Santageli et al. (2016), which included 2168 patients, FFs outside the PV provoked by the stimulation program or isoproterenol were detected in only 11%. An interesting fact is that no differences depending on the course of arrhythmia were found [60]. Thus, the results of the study support PV isolation as the main treatment strategy not only for paroxysmal but also for persistent AF.

In a study in which the detection of triggers was provoked by administration of high doses of isoproterenol (2 to 20 mg/min), it was shown that persistent AF was much more often associated with the presence of 2 or more FA foci than paroxysmal AF. Verification of multiple foci of focal activity in a patient was an independent factor contributing to the persistence of arrhythmia. Moreover, the group of patients with persistent AF lasting up to 12 months revealed a greater number of FFs than the group of patients with a duration of arrhythmia longer than a year [61]. Thus, multiple FA foci are most likely to contribute specifically to the development of persistent AF and have less influence on its maintenance.

At the same time, Y.Hung et al. (2017) revealed a greater number of foci outside PV in patients with long-term persistent AF. The greater volume of LA and detection of triggers outside PV were independent predictors of recurrence after radiofrequency ablation of the focus in long-term persistent AF [62]. As the disease progresses, the complexity of the organization of local AF drivers increases, manifested by an increase in the total number of FFs and microreentry foci and their stability over several cardiac cycles. The probability of sinus rhythm recovery during their ablation in this case progressively decreases in long-standing AF [63].

DIAGNOSTIC TECHNIQUES FOR FOCAL ACTIVITY

Verification of local drivers in FF is a nontrivial task in clinical practice due to the absence of signs of atrial electrograms, which are pathognomonic for FA, spatial and temporal instability of drivers, insufficient resolution of mapping techniques and tools. The task is even more complicated when mapping focal activity in persistent AF, requiring analysis of the type of activation and propagation of excitation, careful choice of reference electrode, long-term catheter placement on one point in intermittent AF activity, sometimes supplementing the study with entrainment mapping to verify the critical ismus of localized re-entry [64].

Analysis of the type of activation and propagation of excitation

In the study of Y. Takahashi et al. (2006), where a 20-pole diagnostic catheter with five beams for multielectrode mapping was used, the criterion for FA diagnosis was a centrifugal type of activation, in which early activation was recorded on the proximal electrodes, then excitation was spread to the distal electrodes simultaneously along all five beams. Thus, FA has been defined as a foci with centrifugal activation of myocardial area during three or more consecutive cardiac cycles [65]. The authors demonstrated that in the majority of patients with FA, restoration of sinus rhythm was obtained by ablation at sites other than the localization of FF. Nevertheless, in 2 of 12 patients, ablation at the site of verified FA was required in order to make arrhythmia re-induction impossible. The results of the study suggest that such FFs may be both secondary to the main arrhythmia drivers and may provoke arrhythmia in some cases.

It is worth noting that not all works support centrifugal pulse propagation as the main marker of FA. Thus, according to one noninvasive multielectrode mapping [66] performed in 103 patients, in which 4,720 local foci were detected, of which: 80.5% of micro-reentry foci and 19.5% of foci with centrifugal pulse propagation. Most of these foci were verified in LA. The microreentry foci were more stable (activation had a recurrent character) than foci with a true focal type of activation. The number of foci increased with increasing duration of persistent AF [66]. Thus, according to the results of the study, persistent AF in the early terms is maintained mainly by FFs, having in the basis the mechanism of micro re-entry.

An interesting finding of this study was the anatomical proximity of micro re-entry and foci with centrifugal type of activation, which suggests the commonality of tissue pathological processes provoking the appearance of local AF drivers or their functional connection: FA generates micro re-entry due to ultrastructural changes of atrial tissue, which, apparently, is not rare, given that most patients with AF suffer from structural heart disease and have atriopathy.

Analysis of monopolar endograms

Obviously, centrifugal activation is not the only manifestation of FA. In order to test the hypothesis whether persistent and long-onset AF is a consequence of activity of one or more foci, simultaneous high-density epicardial mapping of two atria was performed during open heart surgery in S.Lee et al. (2015) [64]. Atrial electrograms were collected and activation maps were constructed using 510-512 epicardial electrodes for 1-5 minutes. The focus of FA in the study was the site of the earliest activation, which corresponds to the QS wave on the monopolar electrogram and from which the excitation front propagates [67].

Multiple FA foci with different cycle lengths (175±18 ms), both stable and transient, were verified in 11 of 12 patients, with the latter variant being detected more frequently. Also, all patients were diagnosed with excitation breakthrough sites characterized by the presence of r or R waves on the monopolar electrogram, and they were not stable over time. Repetitive activation in the form of a QS wave in 5 of 12 patients generated a sequence of activation similar to re-entry (when the sequence of excitation acquired a twisting character as a result of encountering a functional block or line), while macro re-entry, i.e. excitation covering the entire heart chamber, was not registered in any patient [64]. Thus, high-density mapping made it possible to determine the assumed electrophysiological characteristics of FA: the presence of QS-wave and centrifugal type of activation.

The chaotic nature of activation in persistent AF has always been an obstacle to mapping FA foci using standard techniques (such as activation mapping). The analysis of a large data set associated with its verification can be a time-consuming and time-consuming task during surgery, and the results obtained can be subjective. That is why the use of computer algorithms in combination with endogram analysis in various studies recently can be considered a positive trend in this direction.

The algorithm of electrophysiological mapping of FA was proposed by S. Gizurarson et al. The first step was to identify recurrent activation variants using a computer-assisted periodic component analysis (PiCA). Then, the most frequent cycle length was determined and this cycle length was taken as the cycle length of the FA focus. The localization of recurrent activations with a dominant cycle length was visualized on the anatomical map of the PV Then we determined the morphology of bipolar and monopolar endograms corresponding to the selected areas. Thus, in this study the FA focus was defined as a periodic recurrent activation with a dominant cycle length, which corresponds predominantly to the QS-wave on the monopolar endogram (r-wave to S-wave ratio <0.1 in more than 90% of observations) [68].

Using the algorithm developed, the researchers were able to register FA in 63% of the patients enrolled in the study. Thirty-six percent of the foci were localized in PV, the remaining 64% were outside PV. Patients underwent PV isolation, and if tachycardia persisted, cardioversion was performed; ablation of FA foci was not performed. During a follow-up period of 14±9 months after PV isolation, 37% reported recurrent AF. Among patients with FA PV, only one patient had a relapse. The recurrence of AF was registered significantly more frequently in patients with FA outside PV [68], which is a logical consequence of this study, since no exposure to foci was performed, and may confirm the validity of this diagnostic method.

Fractionated activity as a marker of focal activity

Complex fractionated atrial electrograms (CFAE) and continuous electrical activity (CEA) repeatedly attracted close attention of electrophysiologists in the issue of FA diagnosis. Tissue anisotropy, collision of excitation fronts and delayed conduction at critical points with formation of re-entry were assumed to be the cause of CFAE formation as an electrophysiological phenomenon [69, 70]. It has been suggested that complex fractionated electrograms may be a manifestation of both excessive activity of the parasympathetic nervous system [71] and an electrophysiological marker of FA foci. Previously, the relationship between the localization of the dominant frequency and fractionated electrograms was revealed in experiments on sheep hearts, where AF was induced by acetylcholine [72]. FF in this model was supported by a rotor, at the outer boundary

of which the most fractionated signals were recorded. It has been hypothesized that CFAE is a consequence of the collision of excitation fronts due to the variability of the direction and speed of excitation propagation from cycle to cycle. The effectiveness of CFAE ablation in individual small studies, which was not confirmed in randomized studies [73], was explained by the creation of anatomical obstacles in the areas of fractionated signals, preventing the spread of excitation from the rotor foci.

Considering the spatial relationship of CFAE and FF not fully clarified, S. Kochhäuser et al. conducted a large analysis, considering already new data on the value of monopolar endograms [74]. Patients included in the SELECT AF study, which compared CFAE and CEA ablation in addition to PV isolation, were taken as the study group [75].

In this work, the criterion for FA diagnosis was periodic recurrent endograms corresponding to the QS wave on the monopolar endogram, as described earlier. The results of the analysis showed that FFs were more frequently (49% of cases) located in the CFAE boundary zone (within 5 mm of the signal with the highest fractionation). For the CEA border zone, similar calculations showed a FF location of only 7.8% (p=0.012). Thirty-eight percent of FFs were recorded outside the CFAE and CEA areas, and the number of foci located outside the CFAE areas was significantly lower than outside the CEA areas (38% and 91%, respectively; p=0.031). The number of FFs that did not undergo radiofrequency ablation was greater in the group of patients with recurrent FFs after surgery than in patients free of arrhythmia [74].

The authors of the study thus demonstrated that the number of unexposed FFs was associated with a greater number of recurrences, but in a multivariate analysis, only the use of CEA ablation as an approach was an independent predictor of FF recurrence, which is consistent with the results of the SELECT AF study.

A disadvantage of this study is the very definition of FF: the ratio of r-wave to S-wave <0.1, since the presence of the R wave may indicate either its epicardial location or the breakthrough of excitation from the epicardium, regardless of the presence of FA. Also, this work did not study such a characteristic of FFs as time instability, and the analysis of 2.5-second endogram recordings does not give a complete picture of their presence [76].

The use of CFAE as an FA marker is still an open question. For example, such a diagnostic criterion as the shortening of the local cycle length of the AF cycle, which precedes the maximum duration of the fractionated signal, may not be taken into account [70]. The results of several studies point to the increasing value of CFAE in the diagnosis of FA in multielectrode mapping [70, 77-79], as it allows to register endograms occurring not simultaneously, sequentially (temporal dispersion) and forming "clusters" (spatial dispersion).

Dispersion in the diagnosis of focal activity

J.Seitz et al. (2017) described endocardial electrograms with spatial and temporal dispersion, which can serve as markers of FA. "Areas of dispersion" were defined as clusters of electrograms, fractionated or unfractionated, that exhibited temporal and spatial dispersion on at least three adjacent bipoles, as well as spreading activation throughout the tachycardia cycle length. Ablation in the area of dispersions led to restoration of sinus rhythm or conversion to atrial flutter followed by mapping and its elimination in 95% of cases. After 18 months of follow-up, the recurrence of AF was 15% in the variance ablation group without PV isolation and 41% in the control group, in which PV isolation for paroxysmal AF and standard stepwise ablation for persistent AF were performed. Electrogram recordings and experimental results of optical mapping have shown that the simultaneous presence of spatial and temporal dispersion is present in places where the excitation front is strongly "twisted" [80]. Thus, the diagnostic value of CFAE, as a marker of the presence of a fibrillation driver, increases in the presence of variance.

Focal impulse and rotor modulation (FIRM)

In 2012 S.Narayan et al. demonstrated the ability of drivers with high activation frequency to maintain AF and manifest focal or rotary ("spiral") activation. They also developed a rotor and FF mapping and visualization system. Using a 64-electrode basket-catheter, we performed spatiotemporal analysis of electrograms and construction of isochronous maps during arrhythmia. It is worth noting that this mapping technique revealed rotor activity as a local focus much more frequently than focal activity [81].

The rotors rotate with high frequency, propagating a spiral-like wave front with a perpendicular direction of excitation propagation [82]. The points at which the depolarization and repolarization phases of action potentials meet are called phase singularity points - they are the core of the rotors [83]. Thus, rotors rotate around an area of unexcited but potentially excitable tissue, which conceptually distinguishes a rotor from a micro-re-entry.

Rotors, unlike re-entry, not only are not fixed around anatomical structures or foci of pathologically altered myocardium, but also can migrate with the change of rotation axis in certain regions along complex trajectories [84]. In addition to migrating around a relatively fixed core, rotors can move long distances. This migration may be related to the mutual effect of tissue properties and the presence of FFs near the rotor.

Although rotors and FFs are two different types of "drivers" in AF, these two models mutually coexist: so, rotors can arise due to an extraordinary discharge as a result of conduction block, and occurrence of focal activity in any part of myocardium can be a result of intramural location of a rotor.

Trigger activity provocation

For a number of patients, provocation of trigger activity is the main intraoperative diagnostic method. As a rule, it is used for verification of trigger activity outside PV. The method requires a sinus rhythm at the time of the provocation protocol in the operating room, so patients undergo cardioversion with repeated spontaneous recurrence of AF and trigger identification. If AF does not recur, isoproterinol infusion and stimulation tests are used [85].

Several catheters are used for sequence analysis, placed in the right and LA in the areas where trigger activity is most frequently recorded. The sequence of excitation at the occurrence of trigger activity triggering AF, when compared with the sequence of excitation at sinus rhythm, reveals the earliest activation, which allows to quickly

identify the localization of ectopy [86]. The method is still actively used due to the fact that it does not require sophisticated software and hardware. However, serious disadvantages are the necessity of several cardioversions in the presence of multiple triggers, the possibility of mechanical provocation of ectopy, the use of isoproterinol and its selective provocation of native arrhythmia foci.

Adenosine bolus application increases FF inducibility in paroxysmal arrhythmias, demasking latent conduction in PV after their antral isolation. Its use in persistent AF is based on the ability of the drug to stabilize localized re-entry within the fibrous tissue and to improve visualization of hidden drivers. During administration of adenosine, the refractory period of atrial tissue is shortened, which increases the activity of focal foci, shortens and stabilizes the re-entry cycle, making them temporarily more stable, reducing the spatial heterogeneity of activation wave propagation. In a number of cases, adenosine reveals the re-entry mechanism of the driver of AF, previously diagnosed as FA. Transient atrioventricular blockade induced by adenosine reduces the influence of the ventricular far-field signal on the electrogram. All this improves both FA mapping and efficiency of radiofrequency ablation of AF [87].

Analysis of low-voltage endograms

Several studies have reported that areas of reduced voltages detected by voltage mapping are involved in the pathogenesis of treatment-refractory AF. In this context, it is assumed that atrial remodeling contributes to the formation of FFs and microreentry foci that support arrhythmia [88, 89].

Because FFs can be localized in low-voltage areas, a study was carried out that examined the specific properties of endograms in areas of reduced voltages, ablation of which led to restoration of sinus rhythm or conversion of AF to atrial flutter [90].

Initially, areas of low-voltage (<0.5 mV) activity, characterized by at least one of the following endogram characteristics, were targeted for ablation 1) the presence of electrical activity constituting >70% of the tachycardia cycle length; 2) electrograms with discrete high-frequency activity (with a cycle length at least 15% shorter than its corresponding AF cycle measured at PV or CS appendage); 3) repeated sequential activation of the adjacent 8 circulating catheter electrodes (corresponding to rotational activity) constituting more than 70% of the tachycardia cycle length [89].

According to the results of the study, the AF cessation sites had more prolonged electrical activity, shorter local cycle length and higher stability of the activation type, while the amplitude of the endograms did not differ significantly compared to the ablation sites, where the rhythm did not recover. Also in 72% of ablation sites where sinus rhythm recovery was recorded, “atrial late potentials” - low-voltage (0.52±0.3 mV) fractionated electrograms (79±24 ms) with a delayed component in sinus rhythm were recorded [88-90]. These characteristics can become additional diagnostic criteria of AF FF when using low-voltage mapping.

The authors of these studies emphasize that the analysis of areas of reduced voltages, which are the localization sites of FFs, requires high-quality technical support, excluding the appearance of artifacts when recording endograms, the use of standard high and low frequency filters (0.05-250 Hz).

Unfortunately, voltage mapping is still not a perfect method in FF mapping, since the amplitude of bipolar endograms is affected by such factors as the orientation of the catheter with respect to the propagation of the excitation front, the angle between the catheter and the contact surface, the local conduction velocity, the distance between the two dipoles recording the signal [91].

In conclusion of this section, we would like to note that in clinical practice the diagnosis of FA is difficult due to the limited resolution of mapping systems (insufficient number of electrodes, insufficient computing power of mapping programs) and, therefore, inaccuracy of interpretation of local electrograms and excitation sequences. Plus, there are time constraints that do not allow intraoperative mapping for a long time.

INTRODUCTION OF FOCAL ACTIVITY DIAGNOSTICS IN NEPHLUOROSCOPIC ANATOMICAL MAPPING SYSTEMS AND RADIOFREQUENCY ABLATION

Currently proposed and used in the research methods of FA diagnosis directly affect the surgical outcomes. Y.Takahashi et al. (2018) showed that ablation of FA foci diagnosed on the basis of centrifugal activation type can improve surgical outcomes in patients with persistent AF. Sixty patients included in the study underwent PV isolation, ablation of FA foci. If after PV isolation and FA ablation the arrhythmia persisted, atrial defragmentation was performed. Patients who had previously undergone PV isolation and LA defragmentation were used as a control group. During the one-year follow-up period, 57% of patients in the study group and 38% of patients in the control group had no recurrence of the arrhythmia in the absence of antiarrhythmic drugs [92].

The strategy of CFAE ablation in addition to PV isolation in the STAR AF 2 study did not meet expectations: when comparing three techniques - PV isolation, PV isolation + CFAE, PV isolation + mitral isthmus/loop ablation - there were no differences in the outcomes of radiofrequency ablation and recurrence rate after different surgery options [73]. The lack of benefit in the CFAE ablation group was explained by the fact that CFAE as an electrophysiological phenomenon is not directly related to arrhythmia maintenance, although it may indirectly be a driver manifestation. On the other hand, local shortening of AF cycle length associated with maximal signal fractionation and conduction dispersion were not taken into account as additional diagnostic criteria. When comparing the effectiveness of CFAE and CEA ablation in the SELECT AF study, CEA ablation was associated with a significantly lower arrhythmia-free survival and a higher rate of repeat procedures [75].

The first study of FF and rotor ablation using FIRM (Focal Impulse and Rotor Modulation) showed a high percentage of patients with arrhythmia-free survival compared to the standard approach: 82.4% and 44.9%, respectively [93]. However, the results of further studies proved to be contradictory [94]. In a meta-analysis that included 6 studies (including REAFFIRM [95], OASIS [96], FIRMAP AF

[97], CONFIRM [93], and two retrospective studies [98, 99], rotor and FF ablation (with or without PV isolation) showed no reduction in arrhythmic recurrence rate compared to standard PV isolation. There was also a tendency for a higher recurrence rate in the group that used FIRM as a separate ablation strategy [100].

It is necessary to note the general technical shortcomings of carrying out above mentioned multicenter randomized researches investigating efficiency of ablation CFAE and rotors, namely, insufficient coverage of endocardial surface of atria by activation mapping (<50 %) when using basket catheters [101], circular catheters or at mapping point-by-point ablation catheter, dependence of a technique on experience of the electrophysiologist who carries out intervention, as well as absence of effect from radiofrequency ablation in case of use of the catheter without feedback [73, 102].

In any case, more randomized and experimental studies are needed to investigate and determine the definitive role of rotors and FFs using FIRM in AF ablation.

The first randomized controlled clinical trial evaluating the feasibility and efficacy of FA ablation based on monopolar signal analysis [103] was performed using the computer algorithm for FA mapping - FaST (Focal Source and Trigger). The study included patients with paroxysmal and persistent AF, who were divided into two groups: the first group underwent PV isolation, the second group - ablation of FA foci in addition to isolation (PV isolation + FaST ablation). FA foci mapping using FaST computer algorithm was performed intraoperatively in both groups. The mapping algorithm consisted in the sequential analysis of bipolar endograms using spectral analysis to determine their periodicity, determining the prevailing cycle length, and correlating them with monopolar QS morphology enodograms [104], as described earlier [68, 74].

All but one of the patients included in the study had FA foci, with more than half of them demonstrating temporal stability of more than 15 seconds. According to the results of the study, the group in which ablation of FA foci was performed demonstrated a tendency toward better survival free of arrhythmia without antiarrhythmic drugs; however, statistical significance was not achieved. The results confirm the role of the focal theory of AF development, especially since in all patients with PV reconnection detected at repeated procedures due to recurrence, in this study, FA PV was detected at the primary intervention. The authors of the study also note that recovery of sinus rhythm after PV isolation occurred in 25% and correlated with fewer foci outside the PV [103].

Later, the authors of the study performed offline analysis of periodic endograms of 80 patients included in the FaST study to characterize the activation types in AF and assess the relationship and prevalence of each of them [105]. Three activation options were identified. In addition to focal, a rotational type of activation, in which a set of bipolar electrograms with similar periodicity covered more than 80% of the cycle length during a 5-second recording, and a pseudorotational version covering less than 80% of the cycle length, have been identified [106]. The rotational and pseudorotational types of activation are characterized by a large atrial area with periodic activation and a shorter cycle length of periodicity [107]. According to the results of the study, the dominant type of activation was focal, detected in all patients. The rotational and pseudorotational variants were transient (recorded during 3-5 cycles) [105]. However, it is difficult to say whether this result is a real occurrence of the focal or rotational types of activation, or whether the rotational variant is less stable in time and space.

Today, the CARTOFINDER module (Biosense Webster, Irvine, California) is used in mapping systems to detect focal and rotational activity foci. The algorithm for finding FA foci is presented in S. Honakarbash et al. (2018) [101, 107]. Validation was performed in two stages: the first stage involved building a global dynamic activation map before and after PV isolation using wavelet analysis and determining the focal activation type [108]; the second stage involved offline map analysis and searching for "zones of interest", which had to have the following characteristics: 1) presence of a QS wave on the corresponding monopolar endogram, 2) advance at the place of QS wave registration relative to neighboring electrodes, 3) registration of the above features in at least two consecutive cardiocycles. In the offline map analysis, 86% of the FFs corresponded to "areas of interest" on maps collected with basket catheters and 73% with PentaRay catheters. After FF ablation for a follow-up period of 16.3±3.7 months, 70.6% of patients were free of arrhythmia recurrence [107].

The results of the study give hope for the possibility of using an algorithm to detect FFs or "areas of interest" using standard catheters (PentaRay). Obviously, this approach will reduce the cost and complexity of the procedure, but will not guarantee the verification of all possible foci. The appropriateness of their ablation and the effect on arrhythmia recurrence remains to be elucidated.

The automatic algorithm used in the module has been validated with acceptable sensitivity and specificity in small studies [107, 109]. The use of FA as a target for ablation has been associated with intraoperative restoration of sinus rhythm or prolongation of tachycardia cycle length [107, 110]. In the Find EU multicenter prospective study, which included 70 patients with persistent AF who underwent PV isolation and focal and rotational ablation under CARTOFINDER control using a basket catheter without using an automated algorithm, the preliminary results showed arrhythmia freedom of 66.7% at twelve months [111].

However, the study by M. Hemam et al. (2021) questioned the usefulness of focal and rotational detection algorithms. The work on canine hearts describes verification of FA using the two most commonly used systems in clinical practice CARTOFINDER and Topera (Abbott, Abbott Park, Illinois) with ultra-frequent stimulation from one and/or two localizations (coronary sinus, right upper PV), simulating focal activation trigger activity. The study used basket catheters and OctaRay multipole catheter and analyzed the maps constructed during stimulation without induction of AF (with registered fibrillatory conduction on diagnostic catheters) and with induction of AF. During mapping with the help of basket-catheters, variants of activation sequences were

recorded in which the interpretation of the presence of focal and rotational activity was not possible (when both mapping systems were used). Sequential mapping with OctaRay catheter revealed rotational activity in only 4.2% of charts with fibrillatory conduction and induced AF, localized in most cases in the right atrium. FA was verified on 60% of charts with fibrillatory conduction without induction of AF and on 72% of charts during induced AF. During stimulation from the right upper PV, FA was detected automatically in this anatomical region only in 36% of cases [112].

Thus, none of the systems reflected the real FF. A significant limitation of this study is that it was conducted on the hearts of healthy dogs, on which it is not possible to simulate the activation maps characteristic of electrophysiological and structural remodeling. It is also likely that stimulation artifacts affected the algorithm's ability to correctly recognize the location of focal and rotational activity.

CONCLUSION

Modern FA diagnostics have advanced considerably in technical equipment and computing power. However, their specificity and sensitivity to active AF drivers, ablation of which would unambiguously lead to restoration of sinus rhythm, is far from being perfect. Obviously, FA, due to the diversity of its manifestations, requires the complex use of several techniques and criteria. The ongoing randomized multicenter study STAR AF3 (STrategies for Satellite Ablation of PeRsistent Atrial Fibrillation) comparing three ablation strategies (PV isolation, PV isolation and ablation of AF drivers, PV isolation and posterior wall isolation) is intended to answer many questions faced by electrophysiologists.

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