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CORRELATION BETWEEN PULMONARY VEIN ISOLATION EFFICACY AND MYOCARDIAL MORPHOLOGICAL CHANGES

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Aim. To investigate the correlation between the efficacy of pulmonary vein ostial isolation and morphological changes in the myocardium.

Methods. The study included 118 patients with paroxysmal or persistent atrial fibrillation (AF) and no significant structural heart disease. All patients underwent primary cryoballoon isolation of the pulmonary vein ostia with simultaneous implantation of a loop ECG recorder (Medtronic Reveal XT) and myocardial biopsy of the interatrial septum (IAS) and the interventricular septum (IVS). Tissue samples were obtained before cryoballoon ablation (CBA). Patients were followed for one year with regular visits at 3, 6, and 12 months. If AF recurred, patients underwent a repeat electrophysiological study to assess the durability of pulmonary vein isolation. In cases of recovered pulmonary vein conduction, reisolation was performed, followed by another year of followup using the same visit schedule. Consequently, two patient groups were formed: those without AF recurrence (after one or two procedures) and those with recurrence (after two catheter isolation attempts).

Results. Owing to an insufficient number of representative IAS biopsy samples (the biopsy material mainly consisted of the fibrous portion of the IAS), the analysis of the relationship between IAS morphological changes and nonpulmonaryveindependent AF recurrence could not be performed. In IVS biopsy samples, the most common morphological findings were myocardial hypertrophy, loss of myocardial crossstriation, endocardial thickening and lipomatosis, and cardiomyocyte dystrophy.

Conclusion. In all AF patients without severe organic heart disease, various morphological changes of the IVS myocardium were identified, including fibrosis, lipomatosis, and dystrophy. Histological changes in myocardial biopsies from AF patients, such as cardiomyocyte degeneration and endocardial thickening, are important components of atrial remodelling that contribute to arrhythmia initiation, maintenance, and progression - consistent with the concept of atrial cardiomyopathy (atrial myopathy) regardless of its origin. A deeper understanding of these cellular and molecular changes may inform the development of novel targeted strategies for AF prevention and treatment. No clear predictors of a specific electrophysiological type of AF recurrence (pulmonaryveindependent vs. nonpulmonaryveindependent) after radiofrequency ablation were identified, which may reflect common underlying mechanisms and warrants further investigation.

Key words: interatrial septum biopsy; atrial fibrillation; myocardial biopsy; loop ECG recorder; pulmonary vein isolation

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Atrial fibrillation (AF) has long remained the most common cardiac arrhythmia [1]. In most cases, the pathogenesis of AF is related to the electrical activity of the pulmonary vein (PV) sleeves; however, in many patients, recurrent AF episodes may be associated with the presence or emergence of ectopic foci outside the PVs [2]. Currently, there are no clear predictors of nonPVrelated AF, and therefore it cannot be predicted, prevented, or adequately managed with appropriate therapy for the respective patients.

The search for and development of new theories of arrhythmogenesis continues. One of the actively discussed theories is the role of the inflammatory process as a trigger and substrate for AF maintenance. One of the earliest works linking inflammatory myocardial changes and AF was published in 1991. In 14 patients with no thyroid dys-

function, an anteroposterior left atrium (LA) dimension <40 mm, no coronary pathology, and no other chronic diseases, with AF refractory to antiarrhythmic therapy, myocardial biopsy was performed. In more than half of the patients, ventricular myocardial fibrosis and/or cardiomyocyte necrosis was found, active myocarditis in three, and changes consistent with cardiomyopathy in three [3].

This line of research was continued, and in 2010, the results of a study of biopsy material from the interatrial septum (IAS) in patients with idiopathic AF refractory to antiarrhythmic therapy were published. Myocardial changes were detected in 100% of patients, including signs of active myocarditis in 66%. Moreover, in patients with successful immunosuppressive therapy for myocarditis, sustained remission of AF was achieved, suggesting a crucial role of the inflammatory process in the genesis of atrial tachyarrhythmias, particularly AF [4]. It is also important to compare the criteria for active myocarditis in biopsies from the IAS and the interventricular septum (IVS): their concordance has been proven, allowing reliance on IVS biopsy data, which is more commonly performed in clinical practice.

Confirmation of the impact of myocardial inflammation on arrhythmias was also obtained by our compatriots in 2015. An association between heart rate variability in rats with autoimmune myocarditis was demonstrated, with a decrease in parasympathetic and an increase in sympathetic influence during a cold stress test [5].

Since 2012, catheter treatment has been the mainstay of therapy for AF refractory to pharmacological management (class IA recommendation), and pulmonary vein isolation is the primary method to achieve efficacy [6, 7].

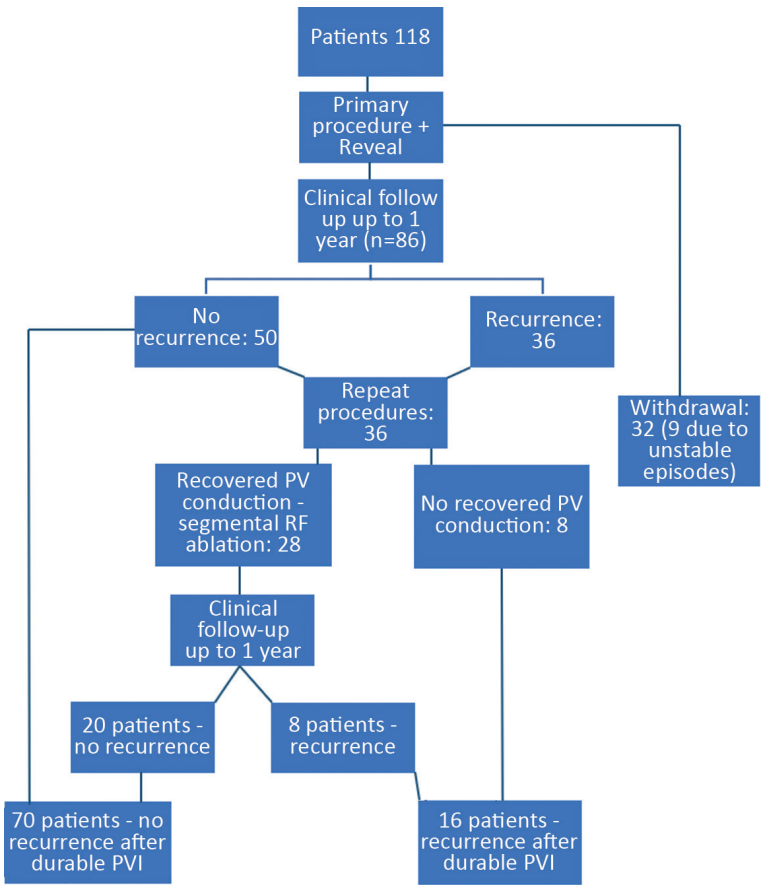

Fig. 1. Graphical representation of the study design.

However, according to a 2009 systematic metaanalysis including 31 studies, the success rate of the initial radiofrequency ablation (RFA) procedure is 57%, and the success rate of repeat procedures is 71% in patients without any antiarrhythmic therapy (AAT) [8].

In our study, we divide AF variants into two categories: (1) AF predominantly arising from the PV ostia ("PVdependent" AF) and (2) AF predominantly developing from sources outside the PVs ("nonPVdependent" AF). Hypothetically, achieving durable electrical isolation of the PVs by catheter ablation (in our study, cryoballoon ablation) in patients with the first category should result in complete freedom from arrhythmia. In contrast, patients in the second category would experience recurrences. This division is logically applicable but somewhat arbitrary, as AF may be triggered by several sources simultaneously, and PV isolation may have a partial effect (e.g., recurrence of episodes with reduced frequency and duration). Within this framework, we make another assumption: after repeat PV isolation, the likelihood of AF recurrence associated with PV activity is negligible. This distinction has practical value - dividing patients into those who can be treated with PV isolation and those who require extended ablation, since PV isolation is currently the goldstandard, universally accepted treatment for nonvalvular AF.

The aim of this study is to investigate the correlation between the efficacy of isolated PV ostial isolation and morphological changes in the myocardium.

MATERIAL AND METHODS

This is a prospective, singlecentre study. Patient enrolment was performed consecutively from 2017 to 2021, with a total of 118 patients included. All patients signed written informed consent before enrolment. The protocol was approved by the local ethics committee and complied with the Helsinki Declaration. The main objective of the study was to identify "PVdependent" and "nonPVdependent" AF groups and compare the results of endomyocardial biopsy (EMB). Any morphological changes in either the IAS or the IVS were considered equally relevant. The primary efficacy endpoint was AF recurrence within one year after one or two catheter procedures (outside the "blanking period", which lasts 3 months after the intervention). To achieve this goal, the following study design was planned.

Study design

The study included patients >18 years of age with paroxysmal or persistent AF, EHRA symptom class 2b4, who signed informed consent and underwent cryoballoon ablation of the pulmonary vein ostia (CBA PVI) with simultaneous implantation of a loop ECG recorder and EMB. Exclusion criteria included: decompensated comorbidities (hypertension, diabetes mellitus, unstable coronary artery disease, etc.), significant structural heart disease on echocardiography (LA >50 mm, intracardiac thrombosis, mitral regurgitation grade ≥3,

LVEF <40%, myocardial hypertrophy >14 mm), and withdrawal from the study at any stage.

Primary CBA PVI with simultaneous implantation of a loop ECG recorder (Medtronic Reveal XT) and biopsy of endocardium and myocardium from the IAS and IVS (tissue sampling was performed before CBA) was performed in 118 patients. However, 23 patients withdrew from the study voluntarily before the first followup visit, and 9 patients also withdrew because of unstable paroxysms lasting <30 seconds at the 6month followup visit. Consequently, the statistical analysis was performed on a cohort of 86 patients (53 men and 33 women) with paroxysmal (n=63) and persistent (n=23) AF, with a mean age of 56±9.9 years (Fig. 1). Detailed clinical characteristics are presented in Table 1.

Prospective followup

The first followup period lasted 12 months with regular visits at 3, 6, and 12 months. When sustained AF recurrences (symptomatic or asymptomatic after the blanking period - >3 months after the intervention) were detected by ECG, Holter monitoring, or the loop recorder, patients were referred for a repeat PV isolation procedure with assessment of PV activity and subsequent catheter treatment. In patients in whom the repeat electrophysiological study revealed nondurable PVI, segmental RFA of the PVs alone (reisolation) was performed; these patients then continued followup on the same visit schedule for an additional 12 months. If the repeat procedure showed no electrical activity in any PV, the patient was considered to have reached the endpoint, assigned to the "nonPVdependent" AF group, and could receive additional ablation outside the PVs as part of standard clinical practice. Based on the followup results, two groups were formed: patients with sustained remission after one or two procedures and patients with AF recurrence despite durable PVI or after repeat PVonly isolation.

The study was considered complete after 12 months of followup after the last catheter procedure, or upon AF recurrence with verification of PVI durability during a repeat procedure, or upon AF recurrence (after the blanking period) after the second intervention.

Study methods

Intraoperatively, patients underwent CBA of the PVs using a cryoconsole and Arctic Front Advance cryoballoon (Medtronic, USA), and implantation of a Reveal XT loop ECG recorder (Medtronic Reveal XT, USA). Postoperatively, no routine antiarrhythmic therapy was prescribed; betablockers were given to a few patients with symptomatic postoperative sinus tachycardia. Recurrence was defined as detected AF episodes lasting >2 minutes on the loop recorder, or >30 seconds on a 12lead ECG or Holter monitoring.

Table 1.

Clinical and demographic characteristics of the overall patient group

Parameter	Overall group (n=86)	PV dependent AF (n=70)	Non PV dependent AF (n=16)	p
Age, years	56 [48;62]	56 [47.75;62]	57 [51;67]	0.365
Age at arrhythmia onset, years	50 [42.5;59]	50 [43.75;59]	51 [40;58]	0.904
AF history duration, years	3 [1.5;6]	3 [1;5]	6 [3;9]	0.027
Body mass index, kg/m^2	30.1 [26.75;32.9]	29.8 [26.8;32.9]	30.7 [26.3;32.9]	0.894
Left atrial volume, mL	42 [39;46]	42 [39;45]	43 [41;49]	0.215
Left ventricular ejection fraction, %	62 [60;66]	62.5 [60;66]	61 [58;65]	0.146
Left ventricular end diastolic dimension, mm	51 [48;54]	51 [47;54.2]	51 [49;54]	1.000
CHA_2DS_2 VASc score	2 [1;3]	1.5 [1;3]	2 [2;2]	0.439
HAS BLED score	0 [0;2]	1 [0;2]	0 [0;1]	0.302
High sensitivity CRP	1.83 [0.95;4.00]	2.04 [1.01;4.24]	1.60 [0.785;3.140]	0.402
NT proBNP	272 [90.9;697.0]	191 [72.9;573]	719 [225;1235]	0.014
Hypertrophy (>14 mm), n (%)	9 (10.6)	4 (5.8%)	5 (31.3%)	0.010
Male sex, n (%)	53 (61.6)	46 (65.7%)	7 (43.8)	0.103
Persistent AF, n (%)	63 (73.3)	52 (74.3)	11 (68.8%)	0.652
Hypertension, n (%)	54 (62.8)	43 (61.4)	11 (68.8%)	0.585
Systemic diseases, n (%)	5 (5.8)	4 (5.7%)	1 (6.3%)	1.000
Obesity, n (%)	41 (47.7)	33 (47.1%)	8 (50%)	0.880
Coronary artery disease, n (%)	4 (4.7)	4 (5.7%)	0 (0)	1.000
Stroke, n (%)	4 (4.7)	3 (4.3%)	1 (6.3%)	0.568
Transient ischaemic attack, n (%)	3 (3.5)	2 (2.9%)	1 (6.3%)	0.465
Diabetes mellitus, n (%)	9 (10.5)	7 (10%)	2 (12.5%)	0.672
Impaired glucose tolerance, n (%)	4 (4.7)	4 (5.7%)	0 (0)	1.000

Note: PV - pulmonary veins; AF - atrial fibrillation; CRP - C reactive protein; NT proBNP - N terminal pro B type natriuretic peptide; p - significance of differences between PV dependent and non PV dependent AF groups.

EMB was performed in the catheterisation laboratory via femoral vein puncture using Cordis Biopsy Forceps 7F 104 cm. Under intracardiac echocardiography and fluoroscopic guidance (RAO 30°, LAO 40°), biopsy samples were obtained from the IAS (one site, aiming for the muscular portion of the septum) and the lower third of the IVS (two sites). Tissue was placed in buffered formalin, stained with haematoxylineosin and Van Gieson, and subjected to morphological examination. Biopsy data analysis included a description of individual morphological changes. Changes in the IAS and IVS were considered of equal value in this study.

The aim of this study was not to detect myocarditis or its activity, but merely to attempt to find a correlation between morphological changes and the arrhythmia focus localisation; therefore, immunohistochemical examination was not performed (to avoid unjustified cost increase).

Statistical analysis

Statistical analysis was performed using R v. 3.6.1. The ShapiroWilk test was used to check normality. Quantitative variables were expressed as mean ± standard deviation or median with interquartile range, and compared using Student's ttest or the MannWhitney Utest. Categorical variables were expressed as absolute and relative frequencies (percentages), and compared using Pearson's χ^2 test or Fisher's exact test. Univariate and multivariate regression analyses were used to identify predictors of AF recurrence in patients with durable PVI (i.e., predictors of "nonPVdependent" AF). Differences were considered significant at twosided $p<0.05$.

RESULTS

The study included 118 patients; however, after followup, 86 patients were included in the analysis for morphological predictors, of whom 70 had "PVdependent" AF and 16 had "nonPVdependent" AF. The remaining patients were excluded from the analysis due to incomplete followup (mostly due to refusal of a repeat procedure in the presence of clinically insignificant recurrences and, consequently, inability to assess PVI status). Differences in clinical parameters between the two groups are presented in Table 1. The AF recurrence rate, considering asymptomatic recurrences detected by the implantable subcutaneous loop recorder, was 58.1% after primary CBA PVI, and 71.4% after repeat PV isolation without additional ablation.

Table 2.

Frequency of individual morphological changes in interventricular septum biopsy samples

Parameter	PV dependent AF (n=70)	Non PV dependent AF (n=16)	p
Endocardial blood clots, n (%)	2 (2.86)	0 (0)	0.494
Endocardial thickening, n (%)	13 (18.6)	7 (43.75)	0.031
Endocardial sclerosis, n (%)	28 (40)	8 (50)	0.464
Lymphocytic infiltration of endocardium, n (%)	4 (5.7)	2 (12.5)	0.309
Eosinophils in endocardium, n (%)	2 (2.86)	0 (0)	1.000
Endocardial lipomatosis, n (%)	15 (21.4)	7 (43.75)	0.108
Endocardial hyalinosis, n (%)	0 (0)	1 (6.25)	0.186
Endocardial fibrosis, n (%)	0 (0)	0 (0)	-
Myocardial hypertrophy, n (%)	64 (91.4)	15 (93.75)	1.000
Loss of myocardial cross striation, n (%)	39 (55.7)	10 (62.5)	0.621
Contraction bands in myocardium, n (%)	28 (40)	4 (25)	0.263
Cardiomyocyte dystrophy, n (%)	45 (64.3)	3 (37.5)	<0.001
Necrosis / myolysis / apoptosis of cardiomyocytes, n (%)	12 (17.1)	1 (6.25)	0.446
Lipofuscin in cardiomyocytes, n (%)	20 (28.6)	7 (43.75)	0.238
Loss / lysis of cardiomyocyte nuclei, n (%)	21 (30)	5 (31.25)	1.000
Perinuclear cytolysis of cardiomyocytes, n (%)	12 (17.1)	0 (0)	0.111
Fatty degeneration of cardiomyocytes, n (%)	9 (12.9)	1 (6.25)	0.680
Karyopyknosis / karyorrhexis of cardiomyocytes, n (%)	1 (1.4)	0 (0)	1.000
Interstitial expansion, n (%)	6 (8.6)	2 (12.5)	0.639
Interstitial oedema, n (%)	7 (10)	1 (6.25)	1.000
Perimuscular interstitial sclerosis, n (%)	28 (40)	6 (37.5)	0.854
Perivascular interstitial sclerosis, n (%)	31 (44.3)	6 (37.5)	0.621
Focal interstitial sclerosis, n (%)	3 (4.3)	0 (0)	1.000
Interstitial infiltration with 10-13 cells, n (%)	3 (4.3)	1 (6.25)	0.568
Interstitial infiltration with >14 cells, n (%)	52 (74.3)	12 (75%)	1.000
Eosinophils in interstitium, n (%)	0 (0)	0 (0)	-

According to the study results, analysis of the relationship between IAS morphological changes and "nonPVdependent" AF recurrence was not performed because of an insufficient number of representative IAS biopsy samples (the biopsy material mainly consisted of the membranous portion of the IAS). In IVS biopsy samples, the most common morphological findings were myocardial hypertrophy, loss of myocardial crossstriation, endocardial thickening and lipomatosis, and cardiomyocyte dystrophy. Detailed frequencies of morphological criteria are presented in Table 2. Among the analyzed parameters, predictors of "nonPVdependent" AF were endocardial thickening (p=0.031) and cardiomyocyte dystrophy (p<0.001). Other morphological parameters did not demonstrate significant predictive value for AF recurrence in patients with durable PVI.

DISCUSSION

To increase the efficacy of catheter interventions based on previously obtained data on the relationship between myocardial changes and AF, a study of 54 patients with AF refractory to AAT who underwent CBA PVI was conducted at the National Medical Research Center for Therapy and Preventive Medicine. The results suggested that inflammation is one of the significant and potentially treatable causes of insufficient CBA efficacy in AF patients [9]. The present study is a continuation of that work [9]. Both studies (the initial and the current, with an expanded cohort) aimed to identify among morphological changes predictors of "PVdependent" AF. The previous analysis, including 54 patients, demonstrated a predictor role of interstitial oedema for "nonPVdependent" AF. After expanding the sample and reanalysis, the predictive value of interstitial oedema was not confirmed, while two other parameters showed prognostic significance - endocardial thickening (p=0.031) and cardiomyocyte dystrophy (p=0.001). Cardiomyocyte dystrophy itself is a nonspecific myocardial change encompassing many subtypes; it can develop through various mechanisms, reflecting cell and structural damage resulting from different factors, one of which is inflammation, leading to subsequent fibrosis and myocardial remodelling.

A comparison of catheter ablation outcomes for AF and EMB data was recently performed by our compatriots: only 13.4% of 67 patients with "idiopathic" AF had no histological changes; fibrosis was found in 38.8%, and Dallas criteria for myocarditis in 47.8% [10]. Followup of 9.3±3.7 months after ablation showed that the procedure's success directly depended on the myocardial changes - it was 88.9% in patients with intact myocardium (no early recurrences), 46.2% in patients with various degrees of fibrosis, and only 34.4% in patients with myocarditis. Previously, we also established a high (up to 75%) incidence of immuneinflammatory diseases (myocarditis, vasculitis) on right ventricular EMB in patients with "idiopathic" AF, increased efficacy of medical and interventional treatment as a result of immunosuppressive therapy for detected myocarditis, and partial loss of the effect over the longterm (up to 10 years or more) due to gradual therapy withdrawal and, probably, the development of irreversible atrial changes [11]. These data once again confirm that the goal of complete AF elimination is often unattainable because of the multicomponent pathogenesis and the dependence on the overall condition of the atria and their individual zones.

The morphological results obtained in this study primarily indicate that all AF patients without socalled severe organic heart disease have pronounced and diverse changes in ventricular myocardium. The mere presence of these changes (which can reasonably be assumed to also occur in the atria) is a factor that predisposes to AF recurrences after catheter ablation. To our knowledge, no study has attempted to correlate the type of morphological changes with a specific AF recurrence mechanism ("PVdependent" vs. "nonPVdependent"). This study also did not yield definitive results, possibly due to the low informative value of IAS biopsy samples. Most likely, the morphological changes leading to both pathological activation of the PV ostia and atrial myocardial substrate are not substantially different; the crucial factor is their presence and progression (the "extent" of involvement) - and the specific mechanism in an individual patient may be less important for understanding the nature of the process (though it remains important for choosing repeat intervention).

In addition to histological studies, recent electrophysiological evidence of the involvement of fibrosis and cardiomyocyte changes in AF substrate formation has emerged. In one recent study of 230 patients, EMB results (from the IAS under intracardiac echocardiography and fluoroscopy) were compared with electroanatomical multipolar mapping of the atria in AF patients. Histological factors associated with electroanatomical characteristics were fibrosis, stromal expansion (intercellular space), and loss of myofibrils and cardiomyocyte nuclear density (which are particular manifestations of cardiomyocyte dystrophy). The degree of fibrosis in biopsy samples significantly correlated with altered global LA voltage during mapping, and stromal changes were associated with the proportion of fractionated activity. Moreover, all these histological findings were related to the detection of areas with slow conduction [12]. Another study of EMB in patients with "lone" AF demonstrated significant histological changes in the atria, including vacuolar dystrophy, also a subtype of dystrophy [13].

Thus, cardiomyocyte dystrophy appears to be a common finding in patients with AF refractory to catheter treatment. This finding supports the hypothesis that the more extensive the myocardial damage outside the PVs, the less likely a therapeutic effect from PV ostial isolation. Detected endocardial thickening may also be viewed as a result of fibrosis due to an inflammatory process, analogous to the beststudied rheumatic endocarditis. Direct studies addressing the role of endocardial thickening in AF are lacking. However, endocardial thickening is often mentioned as a component of general "atrial remodelling" in AF and it is found in patients with the most treatmentresistant "idiopathic" AF [11].

In our study, the AF recurrence rate, accounting for asymptomatic episodes, was considerably higher than in previous reports: 58.1% after primary CBA PVI and 71.4% after repeat PV isolation. This is obviously due to the use of the implantable subcutaneous loop recorder, which allows detection of significantly more arrhythmia episodes compared with standard monitoring methods.

Study limitations

The main limitations include the small sample size and the lack of immunohistochemical analysis. On the other hand, this study was not designed to diagnose myocarditis, as many similar projects by colleagues have failed. The goal was to move one step closer to understanding the pathogenesis of AF sources outside the PVs. It should also be noted that the concept of AF sources outside the PV ostia is somewhat conditional, based on the absence of arrhythmia recurrences after one or two stages of PVonly isolation.

CONCLUSION

In all AF patients without severe organic heart disease, various morphological changes of the IVS myocardium were identified, including fibrosis, lipomatosis, and dystrophy. Histological changes in EMB from AF patients, such as cardiomyocyte degeneration and endocardial thickening, are important components of atrial remodelling that may be associated with arrhythmia initiation, maintenance, and progression - consistent with the theory of atrial cardiomyopathy (atrial myopathy) regardless of its origin. A deeper understanding of these cellular and molecular changes may inform the development of novel targeted strategies for AF prevention and treatment. No clear morphological predictors of a specific electrophysiological focus of arrhythmia in or outside the PVs were identified, likely due to the common mechanisms of atrial myopathy regardless of its location.

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