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CLINICAL SIGNIFICANCE OF PREMATURE ATRIAL CONTRACTIONS AND APPROACHES TO ITS TREATMENT

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Supraventricular premature beats (PACs) are common in the general population. Previously considered a benign ECG finding with little clinical significance. However, increasing evidence now suggests a positive correlation between the frequency of PACs and the risk of developing atrial fibrillation, ischemic stroke, transient ischemic attack, and all-cause mortality. This has highlighted the importance of determining the clinical significance of PACs and the management strategies for affected patients.

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Premature atrial contractions (PACs) are premature electrical activations of the heart (relative to the sinus rhythm), caused by impulses originating in the atria, pulmonary veins, or the atrioventricular junction. PACs can be single or paired, as well as exhibit an allorhythmia pattern (bi-, tri-, quadrigeminy).

PACs are one of the most common arrhythmias in clinical practice and can be found in individuals of all ages. According to D. Conen et al. (2012), among patients over 50 years of age, the detection rate of PACs during 24-hour Holter monitoring reached 99% [1]. According to domestic researchers, the prevalence of PACs in men and women over the age of 20 was 92.1% and 90.8%, respectively, reaching 100% in men and 94% in women in the group over 60 years of age [2]. In a study by V.M. Tikhonenko et al. (2018), heart rhythm and conduction disorders were recorded in most healthy individuals (97%), with ventricular arrhythmias in 59% and supraventricular arrhythmias in the majority (92.5%) [3].

The development of PACs is associated with various risk factors, such as age [1], ischemic heart disease [4], obstructive sleep apnea syndrome [5], heart failure, structural heart diseases, physical activity, dyslipidemia, and chronic obstructive pulmonary disease [6].

Previously, PACs were considered a benign ECG finding with little clinical significance. However, increasing data point to a positive relationship between the frequency of PACs and the risk of atrial fibrillation (AF), ischemic stroke, transient ischemic attacks, and overall mortality [7-9].

Several explanations have been proposed for the relationship between PACs, AF, and adverse outcomes, primarily with stroke. The presence of frequent PACs identifies patients at high risk of developing AF in the future, which leads to an increased risk of stroke and death. Another explanation suggests that frequent PACs are a marker of subclinical atrial cardiomyopathy, which may contribute to both the development of AF and the increased risk of stroke [7, 9-12]. Convincing evidence for this hypothesis has been provided by genetic studies demonstrating a connection between mutations in specific genes and the development of AF [13, 14].

According to the EHRA/HRS/APHRS/SOLAECE consensus, atrial cardiomyopathy is defined as any combination of structural, contractile, or electrophysiological changes affecting the atria and potentially causing clinically significant manifestations [10].

Among the structural changes, authors note hypertrophy of cardiomyocytes, atrial fibrosis (interstitial, perivascular), and infiltration by adipose tissue or amyloid deposits. These changes can be caused by long-term pressure or volume overload, such as in hypertension, heart failure, or valvular disease. It is important to note that the atria are more sensitive to pathological changes than the ventricles, and these processes often begin earlier and manifest more strongly.

Architectural changes involve alterations in the cellular structure of the atria. These include disruptions in the arrangement of muscle fibers and the formation of ab-

normal intercellular connections, leading to asynchronous contractions and impaired electrical conductivity. For example, the redistribution of myofibrils and damage to intercellular connections create conditions for the development of micro re-entry, contributing to AF.

Contractile changes include a reduction in the ability of the atria to contract effectively. This occurs due to the loss of normal architectural structure and the accumulation of fibrous tissue, which reduces myocardial contractility.

Electrophysiological changes include slowed conduction, decreased refractoriness, and heterogeneity in the electrical activity of the atria. These occur due to alterations in ion balance, dysfunction of sodium, potassium, and calcium channels, as well as increased oxidative stress and inflammation.

The key primary factors for changes in the atria are chronic increases in filling pressures, aging, obesity, and comorbidities such as hypertension, ischemic heart disease, and diabetes. These factors trigger a chain of pathological processes, starting from increased stress on the atria and culminating in remodeling and the development of arrhythmias.

Currently, there are no clinical guidelines on the management of patients with PACs, either domestic or international. Unresolved questions include: what is considered "frequent" or clinically significant PACs, how to assess the risk of developing AF, stroke, and mortality in patients with PACs, what are the indications for prescribing anticoagulants, antiarrhythmic drugs, and/or interventional treatments, how benign is the asymptomatic course of PACs, and does the treatment of patients with high PAC burden with antiarrhythmic drugs or catheter ablation reduce the risk of developing AF, stroke, and mortality?

METHODS

In the PubMed database, 51 publications were selected using a search strategy based on the following keywords: supraventricular premature beats, atrial fibrillation, stroke, transient ischemic attack. An additional manual search was also conducted using references from articles identified as relevant. No date restrictions were applied. Articles not available in English and Russian were excluded. Furthermore, reference lists were manually checked for other suitable studies.

RESULTS

What Defines Frequent PACs? Risks Associated with PACs

Currently, there is no established threshold for the frequency of premature atrial beats (PACs) that determines an increased risk of AF and other cardiovascular outcomes. Additionally, a precise definition of excessive supraventricular ectopic activity (ESVEA) is lacking. In most studies on PACs/ESVEA and their cardiovascular outcomes, the most common screening method is 24- or 48-hour Holter monitoring (Holter monitoring). Although routine 12-lead ECGs, 15-second ECGs, 2-minute ECGs, and loop recorders are also used, Holter monitoring is considered the most reliable method for determining the burden of PACs and predicting cardiovascular outcomes.

The definition of frequent PACs varies among different authors and is not solely based on the frequency of PACs but also on their clinical significance, i.e., the association with patient prognosis. K. Sasaki et al. (2021) defined frequent PACs as >0.4% of heartbeats per day, which was independently associated with the development of AF (odds ratio (OR) = 5.28; 95% confidence interval (CI): 1.28-26.11; p = 0.023).

N. Prasitlumkum et al. (2018) proposed a cut-off of 100 PACs per day for patients with symptoms (palpitations, syncope, dizziness). This criterion was based on the results of a study by T. Acharya et al. (2015), where a value of >100 beats/day had a sensitivity of 77.8% and specificity of 75.8% for predicting the development of AF in this patient group.

B. Chong et al. (2012), in a study of 428 patients with complaints of palpitations, dizziness, and syncope, showed that a threshold of >100 PACs per day was an independent predictor of the development of AF, ischemic stroke, congestive heart failure, and death during 6.1 years of follow-up.

According to S. Suzuki et al. (2013), in patients with frequent PACs, the development of AF was associated with the presence of additional negative factors: the risk of its occurrence was approximately 10 times higher in patients with >102 PACs per day and at least 2 points on the $CHADS_2$ score compared to those with <102 PACs per day and less than 2 points on the $CHADS_2$ score. Additionally, patients with high-frequency PACs (>102 per day) had a significantly higher prevalence of hypertension (39.9% vs. 25.4%, $p < 0.001$) and chronic kidney disease (17.3% vs. 8.5%, $p < 0.001$) compared to the low-frequency group. Furthermore, patients with frequent PACs had more pronounced structural heart changes, such as increased left atrial size (mean diameter 35.4±6.7 mm vs. 33.4±5.7 mm in the low-frequency group, $p < 0.001$). However, the left ventricular ejection fraction (LVEF) was similar in both groups: 66.5±9.7% vs. 65.8±9.1%, respectively. 15.6% of patients with frequent PACs had ≥2 points on the $CHADS_2$ score, whereas only 6.6% of patients in the low-frequency PAC group had this ($p < 0.001$).

Other authors have defined frequent ectopic beats as >30 PACs per hour, which is equivalent to >720 PACs per day. The presence of more than 30 PACs per hour in apparently healthy individuals was associated with the development of AF. Given this, it becomes relevant to determine the threshold value for the number of PACs to assess the risk of AF development and prognosis in different patient groups.

In the study by V.M. Tikhonenko et al., it was concluded that for healthy individuals, single, paired, and group PACs up to 50 per day (up to 2 per hour) can be considered «normal.» However, five or more consecutive PACs or a frequency of 500 or more PACs per day (20 or more per hour) are considered «abnormal» and not «normal» for healthy individuals [3].

In the consensus document by D. Arnar et al. (2019) [11], a high burden of PACs was defined as more than 500 PACs per day. This choice was based on the EMBRACE study, which included 287 patients aged over 55 years with a history of cryptogenic stroke or TIA and without AF. The

average age of the patients was 72.2±8.6 years, 46% of whom were women, and 71% had hypertension, with 16% having experienced a prior stroke. The mean $CHADS_2$ score was 3 (range 3-4). According to this study, the predicted probability of AF was 7-9% in patients with <100 PACs per 24 hours, 9-24% in those with 100-499 PACs, 25-37% in those with 500-999 PACs, 37-40% in those with 1000-1499 PACs, and plateaued at approximately 40% in those with ≥1500 PACs per day [22].

Based on the results of the EMBRACE study and possible mechanisms linking PACs with AF, stroke, and mortality, D. Arnar et al. (2019) proposed the following:
1. Patients with a high burden of PACs (>500 PACs per 24 hours as determined by Holter monitoring) should be considered at increased risk for developing AF. These patients should be informed about the symptoms of AF and referred for further investigation, including more detailed or extended rhythm monitoring. In some cases, structural heart disease should be evaluated, such as with transthoracic echocardiography or magnetic resonance imaging.
2. Patients with a high burden of PACs should undergo comprehensive modification of cardiovascular risk factors.
3. Short episodes of AF and a higher burden of PACs (>500 PACs per 24 hours or any episode of >20 PACs) can influence the decision to start anticoagulation therapy.
4. Low and moderate PAC burdens without documented AF do not indicate the need for oral anticoagulants.

It is important to note that the EMBRACE study investigated the role of frequent PACs in predicting AF in patients with cryptogenic stroke, which could have been caused by subclinical episodes of AF. Therefore, the prognostic role of the threshold of >500 PACs per day has been proven only for patients who have had cryptogenic stroke. It is unclear whether this threshold is applicable to patients with PACs who do not have a history of stroke, AF, or other known risk factors for cerebrovascular events, where the increased risk of stroke may be directly related to atrial cardiomyopathy.

In the study by Z. Binici et al. (2010), the association between PACs and various outcomes, such as the development of AF, stroke, and death, was investigated using data from the Copenhagen Holter Study. The study included 678 participants aged 55-75 years without a history of cardiovascular disease, stroke, or AF. According to the results of 48-hour Holter monitoring monitoring, patients were divided into two groups: 99 patients (14.6%) with excessive supraventricular ectopic activity (ESVEA ≥30 PACs per hour or episodes with ≥20 PACs) and 579 patients (85.4%) without ESVEA. It should be noted that, at baseline, the groups were comparable in terms of gender, body mass index, alcohol consumption, smoking frequency, low physical activity, and the prevalence of diabetes. However, patients with ESVEA had significantly higher age (67.6 vs. 63.9 years, p<0.0001), systolic (162 vs. 155 mmHg, p=0.009) and diastolic (92 vs. 91 mmHg, p=0.016) blood pressure, and NT-proBNP levels (12.4 (5.5-25.7) vs. 6.3 (3.3-12.3) pmol/L).

Over 6.3 years of follow-up, 27 strokes were recorded, with 10 cases (18.8%) occurring in the ESVEA group and 17 cases (4.9%) in the non-ESVEA group (OR 3.88, 95% CI 1.78-8.48, p=0.0007; after adjusting for sex and age, OR 2.79, 95% CI 1.23-6.30, p=0.014; after adjusting for other risk factors—smoking, diabetes, systolic blood pressure, and body mass index, OR 2.37, 95% CI 1.02-5.50, p=0.044).

AF was statistically significantly more common in the ESVEA group (OR 3.19, 95% CI 1.30-7.86, p=0.011; after adjusting for sex and age, OR 2.73, 95% CI 1.07-6.96, p=0.035; adjusting for other risk factors did not change the result). Moreover, frequent PACs were associated with higher overall mortality (OR 2.12, 95% CI 1.30-3.47, p=0.003); however, after adjusting for other risk factors, this relationship lost statistical significance. Thus, in patients without diagnosed cardiovascular pathology, a connection was observed between frequent PACs and an increased risk of stroke and the development of AF [23].

A longer follow-up (15 years) of patients from the Copenhagen Holter Study confirmed the clinical significance of PACs. Frequent ectopic activity was associated with a twofold increase in stroke risk. However, less than 15% of patients with frequent PACs and a subsequent stroke had previously been diagnosed with AF. Moreover, the annual stroke risk in patients with excessive atrial ectopic activity combined with a CHA_2DS_2-VASc score >2 was 2.4% per year, which is within the same range as patients with AF and a CHA_2DS_2-VASc >2. This supports the view that PACs may be a potential surrogate marker for AF [24].

Currently, there are four meta-analyses dedicated to frequent PACs and their association with adverse outcomes such as AF, stroke, and all-cause mortality. In the meta-analysis conducted by L. Meng et al. (2020), frequent PACs were defined as >30 PACs per hour and/or any tachycardia with ≥20 PACs per day. The combined analysis showed that frequent PACs doubled the risk of AF (OR 2.19, 95% CI 1.70-2.82) and stroke (OR 2.23, 95% CI 1.24-4.02). Frequent PACs were also associated with higher all-cause mortality (OR 1.61, 95% CI 1.25-2.07) [9].

Another systematic review conducted by J. Himmelreich et al. (2019) did not identify a threshold value for defining frequent PACs due to the high heterogeneity of the included studies. However, it showed that frequent PACs doubled the risk of AF (OR 2.96, 95% CI 2.33-3.76), stroke (OR 2.54, 95% CI 1.68-3.83), and all-cause mortality (OR 2.14, 95% CI 1.94-2.37) [8].

In the meta-analysis by B. Huang et al. (2017), frequent PACs were shown to be associated with an increased risk of stroke (unadjusted OR 2.20, 95% CI: 1.79-2.70; adjusted OR 1.41, 95% CI: 1.25-1.60) and all-cause mortality (unadjusted OR 2.17, 95% CI: 1.80-2.63; adjusted OR 1.26, 95% CI: 1.13-1.41) [7].

M. Yang et al. (2022) demonstrated that frequent PACs are associated with an increased risk of developing AF (OR 2.57, 95% CI 2.16-3.05), a higher risk of developing AF in patients with ischemic stroke (OR 2.91, 95% CI 1.80-4.69), and all-cause mortality (OR 1.41, 95% CI 1.24-1.59) [25].

Thus, the presence of frequent PACs identifies patients prone to developing AF, which increases the risk of stroke and mortality. Another important result of these observations is that frequent PACs may be an independent marker of subclinical atrial cardiomyopathy, which contributes to both the development of AF and the increased

risk of stroke [23, 24]. This «atrial cardiomyopathy» hypothesis suggests that the development of AF and PACs is an epiphenomenon, unrelated causally to the cardiomyopathy and stroke [11].

In patients with cryptogenic stroke without AF, PACs are considered a possible cause of cardioembolism. K. Todo et al. (2009) retrospectively studied patients with ischemic stroke, including 163 with non-cardioembolic stroke (group A), 24 patients with stroke of unknown etiology (group B), and 37 patients with cardioembolic stroke and previously diagnosed paroxysmal AF but in sinus rhythm (group C). The frequency of PACs was significantly higher in groups B and C compared to group A. Moreover, more than half of the patients with cryptogenic stroke had frequent PACs (≥200 per day). The authors suggest that frequent PACs should be considered as a masked form of paroxysmal AF and should be included among the causes of cardioembolic stroke [26].

In the study by Y. Shimada et al. (2024), the relationship between PAC frequency and the detection of AF in patients with cryptogenic stroke was examined. Among 381 patients with cryptogenic stroke who had a loop recorder implanted, 227 patients (59.6%) had hypertension, and 82 patients (21.5%) had diabetes. The patients were divided into three groups based on the number of PACs on 24-hour Holter monitoring: ≤200 (group L), 200-500 (group M), and >500 (group H). The frequency of hypertension and diabetes in the groups was 56.7% and 22.0% in group L, 61.9% and 26.2% in group M, and 70.1% and 16.1% in group H. The frequency of new AF cases was higher in the groups with more frequent PACs (15.5% per year in group L (n=277) vs. 44.0% per year in group M (n=42) vs. 71.4% per year in group H (n=62)). Compared with group L, the adjusted ORs for detecting AF in groups M and H were 2.11 (95% CI, 1.24-3.58) and 3.23 (95% CI, 2.07-5.04), respectively, and the adjusted odds ratios for high AF burden in groups M and H were 2.57 (95% CI, 1.14-5.74) and 4.25 (95% CI, 2.14-8.47), respectively. This study demonstrated a dose-dependent relationship between PAC frequency and AF detection in patients with cryptogenic stroke [16].

here are publications reporting the development of heart chamber dilation and heart failure in patients with PACs. It is well known that tachyinduced cardiomyopathy occurs in cases of persistent atrial arrhythmias (such as AF) and frequent ventricular premature contractions (VPCs). However, impaired systolic function of the left ventricle (LV) secondary to frequent PACs is rarely described.

A case was reported of a 44-year-old man who had a reduction in LV ejection fraction (EF) to 40% due to frequent PACs (19% per day on 24-hour Holter monitoring). After catheter ablation of the ectopic focus located in the area of the tricuspid valve ring, the LV EF increased from 40% to 56% over 8 weeks, as assessed by echocardiography [27].

C. Hasdemir et al. (2013) described a patient with frequent PACs (20.9% per day) and an LV EF of 48%. Ten months after successful ablation of PACs from the junction of the superior vena cava and the right atrium, his LV EF normalized [28].

A similar case was described by P. Vervueren et al. (2012). They reported a 40-year-old man who was hospitalized with severe heart failure, the cause of which remained undetermined after magnetic resonance imaging and coronary angiography. A 24-hour Holter monitoring showed 40,000 PACs, which were resistant to treatment with beta-blockers and amiodarone. Radiofrequency ablation of the arrhythmic substrate on the posterior wall of the left atrium was performed. Seven months later, the patient had no complaints, the size of the left atrium decreased from 32 to 12 cm², the left ventricular end-diastolic dimension decreased from 71 to 58 mm, and the LV EF increased from 28% to 50% [29].

All these cases demonstrate the reversible nature of PAC-induced cardiomyopathy after successful interventional treatment.

Medical treatment

In domestic clinical guidelines, drug therapy for asymptomatic and mildly symptomatic PACs is not recommended (III C). In cases where PACs are accompanied by significant subjective discomfort, beta-blockers (bisoprolol, nebivolol, metoprolol) or verapamil are recommended as symptomatic therapy (IIa C). If PACs are a factor in the development of symptomatic supraventricular tachycardia, atrial flutter, or AF, the guidelines suggest following the recommendations for treating these arrhythmias (IIa C). For patients with a high burden of PACs, comprehensive modification of cardiovascular risk factors (treatment of hypertension, weight reduction, identification and correction of obstructive sleep apnea) is recommended to reduce the risk of supraventricular tachycardia [30].

The EHRA and ESC consensus document on the use of antiarrhythmic drugs (2018) [31] recommends the following:

1. For symptomatic patients with frequent PACs and unstable paroxysms of atrial tachycardia without structural heart disease, beta-blockers, sotalol, flecainide, or propafenone are recommended.
2. For patients with structural heart disease, experiencing symptoms and/or a high burden of PACs and/or short paroxysms of atrial tachycardia, beta-blockers or amiodarone are recommended. Additionally, optimization of drug therapy for the underlying disease may reduce arrhythmia burden and prevent the development of arrhythmic cardiomyopathy.

Magnesium sulfate (MS) has been considered for treating PACs in several studies, based on the hypothesis that low intracellular magnesium may contribute to arrhythmia [32-34]. For example, in the study by C. Falco et al. (2012), patients with symptomatic PACs and VPCs (>240 PACs or VPCs per day) were randomized into two groups: one received placebo, and the other received MS orally at a dose of 3.0 g/day for 30 days. The outcome was measured using questionnaires. Clinical success was considered as a reduction of premature beats by more than 70% from baseline. In the MS group, 76.6% had a reduction of >70%, 10% had a reduction of >50%, and 13.4% had a reduction of <50%. In the placebo group, 40% had a slight improvement, with a reduction of <30%. A decrease in symptom severity was achieved in 93.3% of the MS group compared to 16.7% in the placebo group ($p<0.001$) [35]. However, after 15 months of observation, it was found that 37.8% of patients in the MS group ex-

perienced a recurrence of ectopy. In these patients, MS treatment was repeated, and a statistically significant reduction in the burden of premature beats was observed, with 78.5% showing clinical improvement. Patients who had initially received placebo and continued to experience symptoms were switched to MS, and their PAC and VPC burden significantly decreased, with 71.4% showing improvement in symptoms. The results of the study indicate that while MS has an antiarrhythmic effect, it does not persist after discontinuation. A limitation of this study is that it evaluated PACs combined with VPCs, considering the total number of premature beats per day. Notably, the treatment mostly reduced the number of VPCs rather than PACs [36].

In another small pilot double-blind randomized study by P. Lutsey et al. (2018), magnesium 400 mg daily for 12 weeks did not reduce the frequency of PACs. The authors attributed this to the small sample size (n=59), which did not allow detection of clinically significant differences [37].

D. Reĭngardene et al. (2004) evaluated the antiarrhythmic effectiveness of amiodarone for treating refractory PACs. The antiarrhythmic effect of amiodarone was studied in 70 patients with an average age of 49.6 ± 1.7 years and an arrhythmia burden of 4.9 ± 1.5 years. The dose was 600-1200 mg over 10 days, followed by a maintenance dose of 1656.25 mg per week. The treatment duration was 27.5 ± 3.2 months. According to the study, amiodarone had a therapeutic effect in 78.5% of patients during the loading phase and 65.7% during the maintenance phase. A partial antiarrhythmic effect was observed in 8.57% and 16.41% of patients, respectively [38].

In the study by T. Huang et al. (2022), the role of beta-blockers in reducing mortality in patients with frequent PACs was examined. Patients were divided into subgroups with high PAC frequency (>100 PACs per 24 hours) and low PAC frequency (<100 PACs per 24 hours). In each subgroup, patients who regularly received beta-blockers for ≥80% of the entire observation period were designated as the treatment group, while patients who never or rarely (<20% of the observation period) used beta-blockers were designated as the non-treatment group. The results showed that beta-blockers reduced all-cause mortality both in the high PAC frequency group (OR = 0.521, 95% CI = 0.294-0.923, p = 0.025) and in the low PAC frequency group (OR = 0.601, 95% CI = 0.396-0.913, p = 0.017). However, no differences were found in the incidence of new stroke or AF between the groups receiving and not receiving treatment [39].

An open question remains regarding the need for anticoagulant therapy in patients with frequent PACs to prevent ischemic stroke. Despite studies showing an increased risk of AF and stroke, current clinical guidelines indicate that anticoagulants and antiplatelets are not necessary for patients with frequent PACs. Two studies failed to prove the effectiveness of direct oral anticoagulants in patients with cryptogenic strokes in the absence of AF compared to antiplatelet therapy [40, 41]. The ARCADIA study showed that in patients with cryptogenic stroke and atrial cardiomyopathy, apixaban did not reduce the risk of recurrent stroke compared to low-dose aspirin [42].

Eleclazine (Eleclazine GS-6615) is an experimental selective sodium channel inhibitor that predominantly suppresses late sodium currents. In the study by H. Fuller et al. (2016), a good treatment effect was demonstrated in pigs: the number of ectopic beats caused by adrenaline decreased more than threefold after the infusion of eleclazine (0.9 mg/kg). The combined administration of adrenaline and acetylcholine stimulated the development of PACs, leading to AF in all tested animals. When eleclazine was administered beforehand, the development of AF was suppressed in all animals (p = 0.04). Moreover, the drug did not produce a negative inotropic effect or proarrhythmic action, which distinguishes it from current antiarrhythmic drugs [43].

Interventional treatment

It is known that PACs originating from the pulmonary vein ostia (PVs) act as triggers for AF, and such sources can be eliminated through pulmonary vein isolation via catheter ablation [44]. There is a limited number of reports in the available literature on ablation of arrhythmic substrates from other locations [28, 45-49].

Currently, there are no specific guidelines or expert consensus regarding radiofrequency catheter ablation for treating PACs, however, increasing data suggests the feasibility and effectiveness of catheter ablation for eliminating PACs.

The efficacy of interventional treatment for PACs was evaluated in the study by X. Huang et al. (2018), which included 81 patients with symptomatic, frequent (13,199 ± 5744 PACs per day), and drug-resistant PACs. All patients underwent electrophysiological study of the heart, and based on the source of ectopic activity, three groups were formed: Group A - PACs originating from PVs, Group B - PACs from other sources, Group C - PACs from both PVs and other sources. The most common ectopic localizations were: PVs, coronary sinus, upper and lower caval vein ostia, mitral and tricuspid valve annuli, non-coronary aortic valve cusp, ridge crest, and left and right atrial appendages. Paroxysmal AF was present in the medical history of 44.4% of patients in Group A and 50.0% in Group C, while it was observed in only 12.5% in Group B (p < 0.05). The authors confirmed the hypothesis that frequent PACs originating from PVs are linked to an increased incidence of AF compared to ectopy from other locations. Depending on the source of the ectopy, all patients underwent PV isolation, focal ablation, or superior vena cava isolation. After a postoperative follow-up of 21.3 ± 14.3 months, atrial arrhythmias did not recur in 40 (88.9%) patients from Group A, 21 (87.5%) from Group B, and 10 (83.3%) from Group C. On average, the frequency of PACs decreased from 13,199 ± 5744 to 439.3 ± 146.1 beats per day [50].

In a similar study by X. Wang et al. (2017), 70 patients with PACs (mean frequency 25,567 ± 12,508 PACs per day) were divided into two equal groups: Group A - PACs without AF, and Group B - AF induced by PACs. The study compared coupling intervals from ECG data. It was found that PACs that triggered AF had shorter coupling intervals compared to Group A, regardless of their source (PVs or other foci) (362.8 ± 23.0 ms vs. 470.6 ± 60.1 ms and 515.6 ± 77.2 ms, p < 0.001). Electrophysiological study identified 35 different ectopic focus loca-

tions in Group A. Most of them were located in the PVs, the ridge crest, and the proximal part of the His bundle. In Group B, ectopic foci were located in the left PVs in 21 patients, right PVs in 13 patients, and in the upper caval vein in 1 patient. Focal ablation of the superior vena cava or PV isolation was performed based on the clinical situation. Immediately after the procedure, PACs were not recorded in 32 (91.4%) patients in Group A and in all patients in Group B. After 12 months, PACs did not recur in 29 (82.8%) patients in Group A and 28 (80%) patients in Group B after discontinuation of antiarrhythmic therapy. Six patients with recurrent PACs were referred for repeat ablation, which was successful in 1 patient in Group A and 3 patients in Group B [44].

PACs are the most common type of cardiac arrhythmia. Frequent PACs may serve as a marker for atrial cardiomyopathy and an increased risk of AF, which in turn raises the risk of stroke and mortality. This makes PACs an important indicator for patient prognosis.

Currently, there are no clear clinical guidelines for managing patients with frequent PACs. Issues regarding threshold values for PAC frequency and indications for treatment remain unresolved. However, by consensus among experts, a high burden of PACs is considered to be more than 500 PACs per 24 hours according to Holter monitoring data. Despite limited evidence, radiofrequency catheter ablation may be an effective treatment option for patients with frequent and symptomatic PACs resistant to pharmacological therapy. The results of pharmacological treatment are conflicting, and more research is required to optimize it. Furthermore, there is currently no data indicating whether treatment of patients with a high burden of PACs using antiarrhythmic therapy or catheter ablation reduces the risk of developing AF, stroke, or mortality [51].

In 2023, the American College of Cardiology introduced a new 4-stage classification for AF, which for the first time introduces the concept of «pre-AF» – structural and electrical changes in the heart that predispose the patient to develop AF, such as atrial enlargement and frequent supraventricular ectopic activity [52]. The inclusion of the «pre-AF» stage emphasizes the importance of early detection and monitoring of PACs as a potential precursor to more serious arrhythmias.

Additional research aimed at developing modern guidelines for the treatment of PACs and choosing the optimal management strategy for patients is needed to improve outcomes and reduce the risk of cardiovascular complications.

CONCLUSION

Thus, PACs, which were once not considered a serious condition, now require more careful attention and close monitoring, as they are a predictor of the risk of developing atrial fibrillation and stroke.

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