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Предикторы возникновения послеоперационной фибрилляции предсердий

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Цель обзора: изучить предикторы возникновения послеоперационной фибрилляции предсердий (ПОФП), эффективные способы прогнозирования и лечения по данным анализа мировых литературных данных.

В настоящее время ПОФП считается одним из наиболее частых среди всех сердечно-сосудистых осложнений и развивается в 30–65% случаев у пациентов после операций на сердце. В последние десятилетия частота ПОФП постоянно увеличивалась, несмотря на достижения хирургии и анестезиологии. ПОФП является значимым осложнением, влияющим на течение послеоперационного периода и требующим особого внимания, так как приводит к более длительному пребыванию в стационаре, увеличивает затраты, необходимые для лечения пациентов данной категории, а также может привести к смерти. Учитывая последствия ПОФП, было проведено много исследований для выявления факторов, связанных с патофизиологией фибрилляции предсердий и позволяющих разрабатывать профилактические меры, направленные на лечение пациентов с повышенным риском, минимизировать побочные эффекты антиаритмических препаратов. Представлен обзор и анализ мировой литературы, посвященный причинам, профилактике и лечению ПОФП.

Ключевые слова: кардиохирургия, послеоперационная фибрилляция предсердий, патофизиология, предикторы, объем левого предсердия, профилактика, лечение

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Predictors of postoperative atrial fibrillation

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Review purpose: to study the occurrence predictors of postoperative atrial fibrillation (PAF), effective predicting and treating methods according to global literature.

Currently, PAF is considered one of the most frequent events among all cardiovascular complications as it develops in 30–65% of cases in patients after heart surgery. In recent decades, the PAF incidence has steadily increased despite advances in surgery and anesthesiology. PAF is a significant complication that affects the course of the postoperative period and requires special attention, since it leads to a longer hospital stay, increased treatment costs and can also lead to lethal outcomes in patients in this category. Considering PAF consequences, many studies have been performed to identify factors associated with the atrial fibrillation pathophysiology, to develop preventive measures aimed at treating high risk patients and minimize the side effects of antiarrhythmic drugs. The review and analysis of the global literature on the PAF causes, prevention and treatment are presented.

Keywords: cardiac surgery, postoperative atrial fibrillation, pathophysiology, predictors, left atrial volume, prevention, treatment

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Every year, postoperative atrial fibrillation (PAF) after cardiac surgery is becoming an increasingly urgent issue. The PAF frequency back in the 1970s was about 10%, and by 2019 this figure reached 65% of the operated patients [1–4].

PAF rate varies in different types of surgery, indicating surgical interventions as triggers of the formation of increased predisposition of the atrial myocardium to develop atrial fibrillation (AF) [5].

The literature demonstrates that in cardiac surgery, PAF rate is 30% after coronary artery bypass graft surgery (CABG) and 40% after correction of heart valves, while the risk of PAF increases to 50% with combined interventions (CABG, valve repair and replacement), [6, 7]. To compare, in thoracic surgery, at lung operations, PAF rate is 12.5 to 33% [8], and in patients undergoing noncardiothoracic surgery, it varies from 0.4 to 12% [9].

In some cases, atrial fibrillation is accompanied by life-threatening disorders of central and systemic hemodynamics, increases the risk of cerebrovascular accidents and thromboembolic complications, thus worsening the surgery outcomes [10]. The rate of atrial fibrillation in the early postoperative period has a significant share in higher mortality rate of cardiac surgery patients. Thus, the risk of mortality increases by 9.7% [11]. The problems associated with the onset of atrial fibrillation in the first few days after cardiac surgery prompt many researchers to seek predictors of its development and ways of timely and effective prevention of this complication [10]. The issue of determining prognostic parameters that would allow a high probability prediction of defining the patients with high PAF development risk becomes especially urgent [12, 13].

Early and late postoperative atrial fibrillations are classified. Early PAF occurs within the first 5 days after cardiac surgery, mostly on day 2 after the operation, and 70% of cases occur within days 1–4 [10, 14]. Late PAF occurs between days 6 to 30 after the operation [15].

Various publications show that the following factors make a large contribution to PAF development: age, race (higher risk in Caucasians, compared to African Americans), atria dilatation, underlying structural heart damage, hypertension and other morbid conditions [16, 17]. Among cases with AF developed after surgery, elderly patients and those with major surgeries predominate [3].

The causes contributing to PAF development may also include electrolytes imbalance, excessive secretion of the own or external catecholamines, changes in sympathetic and parasympathetic tone, higher or lower circulating blood volume, neurohumoral activation and systemic inflammation, adding to the direct triggering of arrhythmias, increase in C-reactive protein [18, 19]. The inflammatory response after coronary artery bypass grafting is one of the important mechanisms of PAF development [18].

AF promotes such local and systemic disorders as myocardial ischemia, impaired cardiopulmonary hemodynamics, and thromboembolic complications [10, 14]. PAF patients have a higher risk of cardiovascular mortality, stroke, and other arrhythmias compared with patients without PAF [5].

PAF is a serious clinical problem due to the significant increase in costs of the postoperative treatment of this complication. PAF can worsen the condition due to readmission, as well as thromboembolism and death. Despite a large number of studies, there is still no clear understanding of PAF pathophysiology after cardiac surgery; nevertheless, it is no doubt its inner mechanics is multifactorial in nature [4, 14, 20, 21].

In H. Jawad et al., 13% of PAF patients developed thromboembolic syndrome. The overall AF readmission rate was 48.2% [20].

In M. Lin et al., 160 stroke cases were found in 8,588 PAF patients (1.9%), while 240 stroke cases – in 24,731 patients without PAF (1.0%). Moreover, 1,269 deaths were seen in 30,361 PAF patients (4.2%), while 7,942 deaths were seen in 428,823 patients without PAF (1.9%). Pooled random effects showed PAF was associated with an increased risk of early stroke and early mortality. At the same time, with PAF prevention performed early, the stroke rate decreased [22].

In addition, 5 studies were reported where PAF led to deaths: the total of 1,437 deaths were recorded, 8,693 of which in PAF patients (16.5%), while of 26,438 deaths 2,672 were seen in patients without PAF (10.1%). Pooled data also showed high PAF risk for long-term mortality (OR, 1.43; 95% CI, 1.21–1.70; $P < 0.0001$) [22–27].

Also, 5,912 deaths were registered in 18,080 PAF patients (32.7%), while 15,720 deaths were seen in 70,217 patients without PAF (22.4%). Pooled

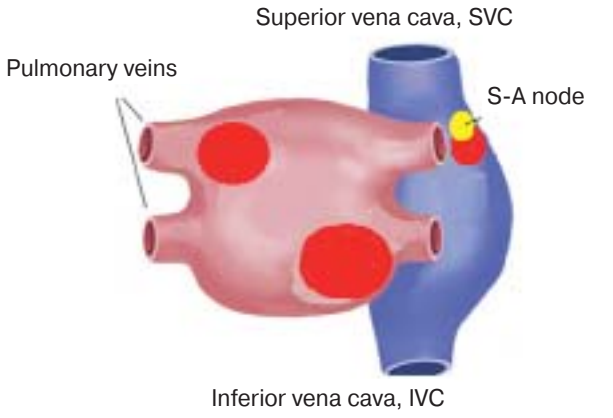

Fig. 1. Areas of the heart arrhythmogenic activity (red).

Рис. 1. Зоны аритмогенной активности сердца (выделены красным).

random effects showed that PAF was associated with an increased risk of long-term stroke and long-term mortality [22].

Nonvalvular atrial fibrillation increases the risk of ischemic stroke by 4–5 times. Patients with established chronic atrial fibrillation are at high stroke risk and as a consequence, have increased hospital stay, higher risk of mortality and lower functional levels compared to peers without atrial fibrillation [22, 28].

PAF development areas

The arrhythmogenic activity most often develops in the areas of the so-called "sheaths" of left atrias (LAs) located in the pulmonary vein ostia (Fig. 1). Due to some histological, anatomical and electrophysiological properties of the pulmonary veins, the arrhythmogenic activity is much higher here compared to other parts of the myocardium.

Other "nonpulmonary" foci are known accountable for AF triggering. They include coronary sinus, fold of left vena cava, LA posterior wall, atrial septum, superior vena cava, and LA appendage [8].

Main PAF risk factors

It should be noted that the basis for PAF development is a combination of several predisposing factors. It is generally accepted that in each individual case, PAF can caused by various factors leading to structural and electrophysiological changes, thus creating conditions favorable for the initiation and preservation of atrial fibrillation (Table 1).

Table 1. Risk factors for new postoperative atrial fibrillation [4, 12, 13, 19, 29–35]

Таблица 1. Факторы риска впервые возникшей послеоперационной фибрилляции предсердий [4, 12, 13, 19, 29–35]

Risk factors / Факторы риска		
Preoperative Предоперационные	**Intraoperative Интраоперационные**	**Postoperative Послеоперационные**
• elderly age / пожилой возраст • history of atrial fibrillation / фибрилляция предсердий в анамнезе • essential hypertension / гипертоническая болезнь • increased LA / увеличение ЛП • COPD / ХОБЛ • LV reduced EF / сниженная фракция выброса ЛЖ • cardiac impairment / сердечная недостаточность • IHD / ишемическая болезнь сердца • cardiomyopathy / кардиомиопатии • valvular pathology / клапанная патология • diabetes mellitus / сахарный диабет • obesity / ожирение • smoking / курение • alcohol addiction / алкоголизм • hyperthyroidism / гипертиреоидизм • genetic disposition / генетическая предрасположенность	• heart valve surgery / операции на клапанах сердца • use of artificial circulation / использование искусственного кровообращения • venous cannulation / венозная канюляция • pericardium and atria damage / повреждение перикарда и предсердий	• hypervolemia / гиперволемия • hypovolemia / гиповолемия • high afterload / увеличенная постнагрузка • hypotonia / гипотония • p-blockers withdrawal / отмена р-блокаторов • ACE inhibitors withdrawal / отмена ингибиторов АПФ • low Ca and Mg in serum / снижение уровня калия и магния в сыворотке крови • high C-reactive protein / повышение С-реактивного белка

PAF development mechanisms

The mechanism of PAF development is believed to have much in common with that of other AF forms. Until recently, the pathogenesis of atrial fibrillation has been explained by multifocal excitation waves and focal activity. It is assumed that here, as with other ectopic tachycardias, two main mechanisms are important:

1) local changes in conductivity due to the presence of cells with different refractory periods in the cardiac conducting system, which makes it possible to re-conduct excitation (micro- and macro-reentries).

2) high automatism of the cells of the cardiac conducting system, which causes the formation of one or more ectopic foci that generate high frequency excitation waves.

The mechanism of macro-re-entry explains the occurrence of circular motion of the excitation wave, and increased automatism or the mechanism of micro-re-entry leads to the emergence of one or many high-frequency impulse foci. These mechanisms are present in both classical theories of the pathogenesis of atrial fibrillation [36].

Recently, PAF development has been strongly associated with the activation of proinflammatory mediators and oxidative stress (Fig. 2). The severity of inflammation and oxidative stress in the postoperative period is believed to be the result of both preoperative status and surgery-associated factors [3, 37].

In CAD patients undergoing HB, cardiopulmonary bypass surgery was credibly associated with higher PAF rate [38].

In S.Yu. Ivanov et al., the study of 134 patients of different sex and age, all patients had CAD in history, 60% – myocardial infarction, 47% – concomitant arterial hypertension, 33% – atrial fibrillation in history. All 134 patients were operated for CABG; a 6-day postoperative electrocardiographic (ECG) follow-up, AF paroxysms were recorded in 60 patients (45% of cases). Of these, 31 patients had AF for the first time (in 23% of cases). On average, the onset of the first paroxysm after surgery was on day 2 (30.2 hours) after operation [39].

O.A. Rubanenko et al. found that among 469 patients of different sex and age operated for CABG, in the early postoperative period AF occurred in 17.7% of patients with the standard approach surgery: median sternotomy with cardia bypass (CB) and in 7.5% of patients operated off-pump without CB. In the former case, AF prevalence was higher than in the latter [26]. The univariate analysis (S. Davoodil et al.) also proved that in the CB group, a higher PAF incidence was noted compared to the group without CB [40].

Early PAF is an independent predictor of late PAF. M. Rowlens et al. proved that of 60% of patients with early PAF after cardiac surgery also developed late PAF with the mean time of onset 8.3 ± 4.2 years. The highest risk of late PAF was observed during the first year after cardiac surgery – 18%, gradually decreasing to about 7.2% per year for five years and to 5.5% per year for ten years [41].

G. Filardo et al. conducted their large volume study in three academic centers in the United States and

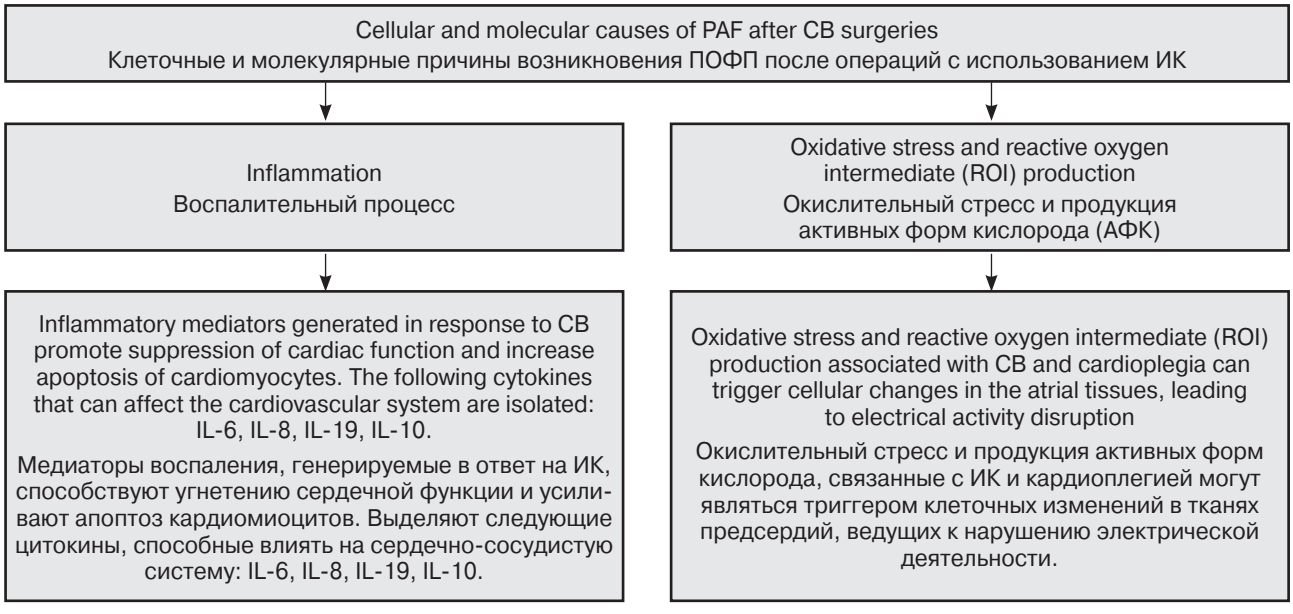

Fig. 2. PAF pathogenesis

Рис. 2. Патогенез возникновения ПОФП

one large specialized cardiological hospital; such factor as the patient's gender was proved to play an important role in PAF incidence. PAF rate after predisposition-adjusted coronary bypass surgery was 32.8% in men and 27.4% in women. During the 9-year study period, women had a significantly lower risk of developing PAF after coronary artery bypass grafting and shorter PAF episodes when compared with men [42].

The release of tumor necrosis factor – α, interleukins and C-reactive protein after cardiopulmonary bypass plays an important role in PAF occurrence by changing electrical activity. An increase in C-reactive protein values leads to impaired release of nitric oxide [43–45]. In the Ucar HI clinical study, an increase in preoperative interleukin-6 and C-reactive protein parameters were predictors of PAF occurrence after surgery [46]. This indicates that surgical intervention in some patients will inevitably lead to PAF [46–48].

Oxidative stress increase in open heart surgery is mediated by ischemia / reperfusion, at which reactive oxygen intermediate (ROI) production occurs, leading to tissue damage [4]. An increased level of ROI in myocytes may contribute to the development of arrhythmias along the main pathways: altered sodium channels, abnormal Ca2+ processing, mitochondrial dysfunction, and remodeling of intercellular connections [49].

Besides, atrial nicotinamide adenine dinucleotide phosphate (NADP) oxidase activity is increased in AF patients compared to those without AF. Y.M. Kim et al. found that NADP-stimulated ROI release significantly increases PAF incidence in patients, suggesting a role for oxidative stress in AF pathogenesis [50]. NADP acts as the main source of oxidation in AF development. Perioperative blood transfusion increases oxidative stress. In addition, diabetes mellitus and atherosclerosis in history are also tied to increase in oxidative stress [51].

F. Mikael et al. revealed the conformity between the time after surgery and the survival rate of patients with and without PAF. Of the patients without PAF, 96.3% were alive one year after surgery, compared with 90.1% of patients with PAF. 10-year difference in survival after surgery was 70.2% of patients without PAF in history vs. 55.2% of patients with PAF in history. Thus, it can be concluded that the difference in survival obviously increased over time (6% after 1 year and 15%after 10 years) [52].

E.M. Mahoney et al. developed a predictive model for atrial fibrillation after valve surgery, including age, ejection fraction, time of aortic clamping and ischemia [53].

M. Osranek et al. proposed a different prognostic model that included age and LA volume over 32 ml/m^2. LA volume was significantly greater in patients who developed AF. Patients with an LA volume of >32 ml/m^2 had an almost five-fold increased risk of PAF, regardless of age and clinical risk factors [54].

Finally, G. Mariscalco et al. analyzed data of over 17,000 patients who underwent coronary artery bypass grafting and / or valve replacement and developed a risk prognosis score that included age, COPD, glomerular filtration rate, preoperative use of an intra-aortic balloon pump, left ventricular (LV) ejection fraction <30% and any valve operation as independent predictors of postoperative atrial fibrillation [32].

Thus, it can be concluded that significant indicators determining the occurrence of arrhythmia were the patient's age and sex, LA volume, LV ejection fraction, time of aortic clamping and ischemia [38, 42].

PAF diagnosis

The patients should be identified at high PAF risk, given the relatively high rate of the complication (Tabl. 2). Data on the timing of PAF occurrence are presented in Table 3. The main issue is to understand the cause of early AF relapses, since a relapse can be paroxysmal and/or asymptomatic.

The following PAF diagnostic methods are distinguished:

1) collection of complaints and anamnesis;
2) instrumental examination [15, 33, 55–57];
   – ECG registration to verify AF diagnosis;
   – Holter ECG monitoring;
   – to assess the state of the heart and determine the treatment tactics, transthoracic echocardiography is recommended (for patients with AF paroxysm for more than 48 hours, it is recommended to perform a transesophageal EchoCG to verify LA and LA thrombosis before the planned cardioversion);
   – MRI.
3) laboratory diagnostics (to evaluate K, glucose, thyroid hormones, Ca and Mg) [15, 33,58].

Various studies noted that of all the methods for PAF diagnosing, such echocardiographic parameters as the degree of impairment of LV diastolic function and LA volume are the most important criteria in the study in the postoperative period [54, 59].

L.M. Burgos et al. conducted a single-center cohort study by performing a retrospective analysis of prospectively collected data. The study included consecutive patients from January 2010 to December 2016, who underwent cardiac surgery. No history of atrial fibrillation. A total of 3113 patients underwent heart surgery during the study: CABG surgery (45%), valve replacement (24%), combined procedure (revascularization, valve surgery) (15%) and other pro-

Table 2. PAF incidence rate after cardiac surgery according to the literature

Таблица 2. Частота возникновения ПОФП после кардиохирургических операций на сердце по данным литературы

Source Источник	Surgery Операция	PAF incidence, % % возникновения ПОФП
Bockeria L.A. et al. [3] Ivanov S.Yu. et al. [39] Lee S.H. et al. [52] Steinberg B.A. et al. [84] Ismail M.F. et al. [85] Maimari M. et al. [86]	HB (with and without CB) КШ (с и без ИК)	18.5–45
Bockeria L.A. et al. [3] Blessberger H. et al. [31] Mariscalco G. et al. [32] Maimari M. et al. [86]	Concurrent procedures (HB, valve repair and replacement) Сочетанные операции (КШ, пластика и протезирование клапанов)	36.6–50
Rubenko O.A. et al. [38]	HB (off-pump) КШ (на работающем сердце)	7.5
Mariscalco G. et al. [32] Rubenko O.A. et al. [38]	HB (with CB) КШ (с ИК)	17.7–23
Bockeria L.A. et al. [3] Mariscalco G. et al. [32] Maimari M. et al. [86]	Valve correction Коррекция клапанов	31–40
Carter-Storch R. et al. [19]	Aortic valve replacement Протезирование аортального клапана	53

Table 3. PAF timing after cardiac surgery according to the literature

Таблица 3. Сроки возникновения ПОФП после кардиохирургических операций на сердце по данным литературы

Reference Источник	PAF incidence rate, % Частота возникновения ПОФП в %	Days Сутки
Bockeria L.A. et al. [3]	до 60	1 to 4 с 1 по 4-е сутки
Lomivorotov V. V. et al. [8]	30–50	1 to 5 с 1 по 5-е сутки
Chelazzi C. et al. [9]	16–46	2 to 5 от 2 до 5-е суток
Centurión O.A. et al. [15]	до 45	from 5 с 5-х суток
Lancaster T.S. et al. [33]	17,8	1 to 3 с 1 по 3-и сутки
Dobrev D. et al. [37]	20–40	2 to 4 со 2 по 4-е сутки
Ivanov S.Yu. et al. [39]	45	first 5 первые 5-е суток
Kato M. et al. [81]	22	2 to 4 со 2 по 4-е сутки
Chaudhary R. et al. [82]	25–40	from 2 со 2-х суток
Kron J. et al. [83]	50	1 to 7 с 1 по 7-е сутки

Table 4. Sampling characteristics and univariate analysis [21]
Таблица 4. Характеристики выборки и одномерный анализ [21]

Variable Переменная		All patients Все пациенты (n = 1054)	PAF ПОФП (n = 272)	Without PAF Без ПОФП (n = 782)	RR	95% CI	p
Age ⩾ 70 Возраст ⩾ 70 лет		281 (26.8%)	141 (41.9%)	167 (21.2%)	2.67	1.99–3.59	<0.0001
Mean age ± Средний возраст ±		60.1 ± 12.1					
Male Мужчина		690 (65.2%)	182 (66.9%)	508 (64.6%)	1.1	0.82–1.48	0.507
Surgery Тип хирургического вмешательства	Revascularization Реваскуляризация	675 (63.8%)	141 (51.8%)	534 (67.9%)	1		
	Valve surgery Клапанная хирургия	306 (28.9%)	105 (38.6%)	201 (25.6%)	1.98	1.45–2.70	<0.001
	Combined surgery Комбинированная хирургия	77 (7.3%)	26 (9.6%)	51 (6.5%)	1.93	1.11–3.28	0.14
	Mitral valve diseases Заболевания митрального клапана	109 (10.3%)	46 (16.9%)	63 (8%)	2.33	1.55–3.51	<0.001
	No beta blocker Отсутствие бета-блокатора	454 (42.9%)	197 (72.4%)	257 (32.7%)	5.40	3.98–7.33	<0.001
	Water balance >1,500 ml Водный баланс > 1,500 мл	685 (64.7%)	203 (74.6%)	482 (61.3%)	1.85	1.36–2.52	<0.001

*p-values: exact chi-squared test; POAF – postoperative atrial fibrillation; CI – confidence interval.
*p-значения: точный тест Фишера; POAF – послеоперационная фибрилляция предсердий; CI – доверительный интервал.

cedures (16%). Postoperative atrial fibrillation had 21% of patients. The median scores in patients with postoperative atrial fibrillation were significantly higher (P < 0.001). CHAD2DS2-VASc score showed greater discriminatory ability to predict an event (0.77; 95% confidence interval [CI], 0.75–0.79) compared to POAF score and HATCH score (0.71; 95% CI, 0,69–0.73 and 0.70; 95% CI, 0.67–0.72, respectively). All 3 assessments presented good calibration according to H. Lemeshow test, univariate and multivariate analysis showed that the independent predictors of postoperative atrial fibrillation were: CHA2DS2-VASc odds ratio 1.87 (95% CI, 1.64–2.13), POAF odds the ratio is 1.18 (95% CI, 1.01–1.36), and the HATCH odds ratio is 1.62 (95% CI, 1.37–1.92) [60, 61].

According to R.M. Ronsoni et al., of the total sample (n = 1.054), 272 patients had PAF (25.7%). When considering operations for myocardial revascularization (63.8%), the PAF rate was 20.3%. With valve interventions (23.9%), the incidence of PAF was 34.3%, and with combined interventions (7.3%), the highest prevalence was observed – 36.6%. The average age of patients was 60.1 ± 12.1 years, and 26.6% of patients were over 70 years old. Most of the patients (65.2%) were men (Table 4). PAF is associated with longer hospital stays compared to patients with this complication (median 10 days vs. 7 days, respectively, P < 0.05) and increased in-hospital mortality (5.5% vs. 1.0%, respectively; P < 0.001). In addition, with a median follow-up of five years, there was a higher late mortality rate for patients with PAF compared with patients without PAF (6.5% vs. 1.4%, respectively, P = 0.002). Multivariate analysis of predictors in the derivational cohort (n = 448) is described in Table 5. Based on their statistical significance, the predictors selected for the assessment included age (⩾70 years), mitral valve disease, non-use or discontinuation of beta-blocker therapy, and positive water balance over 1500 ml [21].

LA volume can be taken as a direct predictor of PAF occurrence. It also serves as an indicator of the process duration and reflects not only the severity of diastolic dysfunction, but also the degree of changes in the atrium, which is a substrate that predisposes to electrophysiological disturbances and arrhythmia development [62–66]. The LA volume is assessed using the apical 4- and 2-chamber position, measured at the end of systole before mitral valve opening. Reconstruction of 2D and 3D images is required for reliable estimation of LA volume. Although 3D echocardiography is now becoming more widely available, 2D echocardiographic techniques are still easier to implement and more commonly used. However, LA may increase asymmetrically due to surrounding

Table 5. Logit regression and multivariate risk estimate [21]
Таблица 5. Логистическая регрессия и многомерная оценка риска [21]

Variable Переменная	B	p	RR	95% CI	Points Точки
Age ⩾ 70 Возраст ⩾ 70 лет	0.96	<0.001	2.67	1.59–4.48	2
Mitral valve diseases Заболевания митрального клапана	0.77	0.03	2.18	1.08–4.35	1
No beta blocker Отсутствие бета-блокатора	0.91	<0.001	2.49	1.53–4.03	1.5
Water balance >1,500 ml Водный баланс> 1,500 мл	0.5	0.06	1.65	0.96–2.83	0.5
Constant Постоянный	–2.471	<0.001		0.08	

Table 6. Multivariate logit regression model for PAF prediction [67]
Таблица 6. Многомерная логистическая регрессионная модель для прогнозирования ПОФП [67]

Parameter / Показатели	Odd ratio (95% confidence interval) Нечетное соотношение (95% интервал достоверности)	p
LA volume index (increase by 1 ml / m^2) / Индекс объема ЛП (увеличение на 1 мл/$м^2$)	1.046 (1.007–1.087)	0.0198
Age / Возраст	1.032 (0.985–1.081)	0.1866
Male / Мужчины	1.254 (0.482–3.258)	0.6426
Diastolic dysfunction / Диастолическая дисфункция	1.14 (0.367–3.542)	0.8213
Cerebrovascular disease (accident) / Цереброваскулярные заболеваний (несчастный случай)	1.219 (0.308–4.828)	0.7778
CCF / Застойная сердечная недостаточность	3.612 (0.589–22.152)	0.1652
AMI / Инфаркт миокарда	1.372 (0.331–5.686)	0.6629
Arterial hypertension / Артериальная гипертония	0.591 (0.237–1.473)	0.2588
Obesity / Ожирение	1.821 (0.737–4.501)	0.194
Nonvalvular cardiac surgery / Неклапанная кардиохирургия	5.995 (1.164–30.875)	0.0371
Valvular cardiac surgery / Клапанная кардиохирургия	10.145 (1.709–60.231)	–
Diabetes mellitus / Сахарный диабет	1.381 (0.507–3.76)	0.5272

structures such as the aorta, chest wall, and eccentrically directed stream of mitral regurgitation, which leads to incorrect size estimation [19, 54].

E. Mahmood et al. conducted a prospective cohort study identifying PAF-significant predictors: age increase, increase in LA volume indexed by body surface area, and diastolic dysfunction (p = 0.02, 0.0001, and 0.001, respectively). Multivariate spline regressions demonstrated a non-linear correlation between the increase in LA volume and the risk of PAF. Before surgery, you can efficiently estimate the LA volume and predict the PAF. The study also demonstrated that LA volume provides a simple measure for identifying patients in need of targeted PAF prophylaxis (Table 6) [67].

Speckle tracking echocardiography is a promising current technique for assessing structural and functional changes in the myocardium. It allows to assess the global longitudinal deformation of the myocardium. To assess LA deformity, the endocardial contour is traced in the apical 4-chamber position after contraction, when LA has a minimum volume. Then the epicardial contour is isolated, the difference in bending indicates dysfunction of the subepicardial fibers. Early dysfunction of subepicardial fibers is associated with a higher risk of PAF due to increased electrical atrial vulnerability and neurohumoral activation. Disruption of LV systolic function causes electrical remodeling and also results in PAF. LA systolic deformity and LV deformity were significant predictors of PAF according to various authors. Such echocardiographic parameters will help identify patients at increased risk of developing PAF [59, 64–66, 68–75].

In addition, preoperative LA function can be assessed with speckle tracking echocardiography based on velocity vector imaging (VVI). Positive systolic peak, early and late diastolic strain rates are measured with VVI [63].

D.P. Leong et al. performed the study to assess the relationship between new two-dimensional transthoracic measures of LA mechanical function (speckle tracking and tissue Doppler parameters), conventional measures (peak A-wave velocity) and transesophageal echocardiographic parameters (LA appendage ejection rate and spontaneous echo contrast) and to assess the clinical feasibility of measuring speckle tracking indicators. Assessment of LA mechanical function with speckle tracking echocardiography is a valid approach compared to transesophageal echocardiography (TEE). The main results of this study showed that in a population of patients with a wide range of indications and LA function, both speckle tracking and tissue Doppler deformity of the reservoir, and the rate of contraction of the contractile atrium showed a moderately strong correlation with the rate of LA appendage ejection; however, the parameters obtained from the tracking were more predictable for moderate to severe spontaneous echo contrast, measured technically faster and easier. Determination of LA mechanical function with speckle-tracking echocardiography is a valid approach compared to TEE and potentially promising for clinical use [76].

G. Pessoa-Amorim et al. give evidence that structural and functional LA remodeling may increase atrial arrhythmias risk, both before and after surgery. With speckle tracking echocardiography (STE) to analyze LA from the apical position, two-dimensional, gray scale 4-camera views were obtained at a frame rate of 50–100 frames / sec. The LA endocardial border was manually traced, analysis was performed using velocity vector imaging software (Syngo VVI 2.0, Siemens Medical Solutions USA Inc), the software divides the LA into 6 segments, and image quality was visually checked in all segments. The maximum LA volume, the minimum LA volume, and the pre-A wave were measured. The LA reserve function is measured using the emptying fraction LP ([maximum LA volume – minimum LA volume] / maximum LA volume × 100), and the expansion index LA ([maximum LA volume – minimum LA volume] / minimum LA volume ×100). The LA conduit function was also determined using the passive evacuation volume LA (maximum LA volume – pre-A volume LA), passive emptying fraction LA ([maximum volume LA – pre-A volume LA] / maximum volume LA), and also the volume LA (stroke volume LV – [maximum volume LA – minimum volume]) (Table 7) [74, 77].

LA deformity consists of a positive wave with the peaks at the end of ventricular systole, followed by a decrease after mitral valve opening. From the mean of the strain curves from all segments, the peak LA load at the end of the ventricular systole (PALS) was estimated, which is a measure of LA reservoir function, peaks of atrial contraction stress (PACS) which can be considered a marker of LA pumping function. LA was then calculated using the passive ejection tension (PALS-PACS), which is a measure of the LA conductance function and active LA emptying tension (PACS-minimum voltage) as a measure of LA tension in a patient with severe aortic stenosis [74].

Main conclusions:

1) impaired reservoir and pumping function were associated with LV hypertrophy, high LV pressure and LA dilatation;

2) AF after aortic valve replacement can be independently predicted using LA stretch and volumes assessed by speckle tracking echocardiography;

3) LA distension can predict AF onset;

4) LA deformity disorder predicts the risk of developing AF in patients without LA dilatation [65, 75].

In aortic stenosis, increased afterload causes a number of changes in LV structure and diastolic function leading to an increase in LV filling pressure and, therefore, to an increase in LA pressure and dilatation. This study showed that impairment of LA reservoir and pumping function, represented by decreased PALS and PACS, respectively, and correlated with increased LA volume index and LV size. This correlation was observed regardless of age, aortic valve area index, comorbidities (such as diabetes mellitus or arterial hypertension), and the use of beta-blockers or statins [74, 78–80]. The predictors of AF recurrence are shown in Figure 3.

Also, a useful diagnostic criterion is P wave duration and variance (PWD), which is considered a non-invasive ECG marker for atrial remodeling and a predictor for AF. PWD reflects abnormalities of intra-atrial and interatrial conduction and is defined as the difference between the length of the longitudinal dental wave, which is wider and narrower, recorded from 12 ECG leads at a paper speed of 50 mm/s. It has been shown that an increase in the duration of the P wave and PWD reflects an increase in the time of intra-atrial and interatrial conduction and non-uniform propagation of sinus impulses in the atrium. An extensive clinical assessment of P wave dispersion was carried out in assessing the risk of atrial fibrillation in patients without organic heart disease, in patients with arterial hypertension, in patients with coronary artery disease, in patients undergoing coronary artery bypass grafting, in patients with congenital heart defects. as well as in other groups of patients suffering from various

Table 7. Regression analysis of LA dimension and function with AF incidence after aortic valve replacement [74]

Таблица 7. Регрессионный анализ размеров и функции ЛП с частотой возникновения ФП после замены аортального клапана [74]

Parameters / Показатели	1D / Одномерный				Model 1 / Модель 1			
	HR	Under 95%CI Ниже 95%CI	Over 95%CI Выше 95%CI	P	HR	Under 95%CI Ниже 95%CI	Over 95%CI Выше 95%CI	P
LA structure / Структура ЛП								
LA dia Диаметр ЛП	1.055	1.004	1.111	0.035	1.075	1.021	1.132	0.006
LA volume index (BP) Индекс объема ЛП (BP)	1.014	0.993	1.035	0.203	1.021	0.996	1.046	0.099
Max LA volume* Максимальный объем ЛП*	1.008	1.001	1.016	0.031	1.010	1.002	1.019	0.017
Min LA volume* Минимальный объем ЛП*	1.010	1.001	1.020	0.036	1.016	1.004	1.027	0.009
Pre-A LA volume Пре-А объем ЛП	1.008	1.001	1.017	0.048	1.012	1.001	1.022	0.025
LA reservoir function / Функция резервуара ЛП								
PALS	0.968	0.938	0.998	0.042	0.946	0.910	0.983	0.005
LA ejection fraction Фракция опорожнения ЛП	0.976	0.953	0.999	0.045	0.015	0.001	0.275	0.005
LA dilatation index Индекс расширения ЛП	0.493	0.252	0.967	0.04	0.341	0.151	0.767	0.009
LA conductance function / Кондуитная функция ЛП								
Passive ejection volume Пассивный объем опорожнения	1.019	0.991	1.048	0.174	1.019	0.989	1.050	0.206
Passive ejection fraction Пассивная фракция опорожнения	0.984	0.953	1.015	0.315	0.116	0.004	3.101	0.2
Conductance volume Кондуитный объем	0.948	0.984	1.013	0.802	1.000	0.984	1.016	0.965
PALS–PACS	0.963	0.913	1.014	0.154	0.953	0.900	1.008	0.096
LA pump function / Насосная функция ЛП								
PACS	0.962	0.919	1.007	0.098	0.932	0.883	0.984	0.011
LA passive ejection fraction Активная фракция опорожнения ЛП	0.973	0.948	0.998	0.037	0.010	0.004	0.222	0.003
LA active ejection fraction Активный объем опорожнения ЛП	1.006	0.971	1.041	0.749	0.995	0.958	1.033	0.816
PACS min.def. PACS минимальная деформация	0.949	0.904	0.998	0.041	0.934	0.991	0.978	0.004

95% CI, 95% confidence interval; BP – biplanar; HR – hazard ratio; LA – left atrial; PACS - peak atrial contraction stress; PALS – peak atrial lateral stress; STE – speckle tracking echocardiography. Model 1 includes preoperative treatment with beta-blockers or statins, type of procedure (only CABG or CABG combined with coronary artery bypass grafting).

* By Speckle tracking echocardiography

95% CI, 95% доверительный интервал; BP – бипланарный; HR – отношение рисков; ЛП – левое предсердие; PACS – пиковое напряжение сокращения предсердий; PALS – пиковое продольное напряжение предсердий; STE – спекл-трекинг эхокардиография. Модель 1 включает в себя предоперационное лечение бета-адреноблокаторами или статинами, тип процедуры (только АКШ или АКШ в сочетании с аортокоронарным шунтированием).

* Оценивается по спекл-трекинг эхокардиографии.

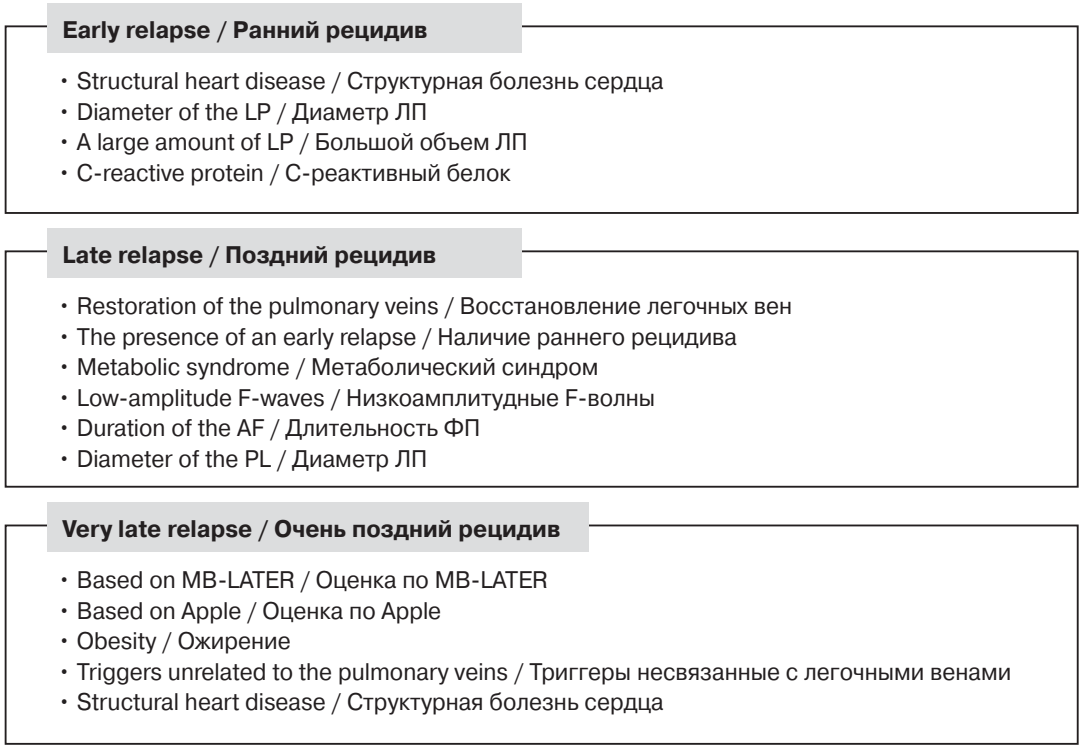

Fig. 3. AF relapse predictors (APPLE evaluation – one point per age > 65, constant AF, constant rate of glomerular filtration ("60 m / min / 1.73 m), LA diameter over 43 mm, ejection fraction <50%; MB-LATER evaluation – male, His bundle branch block, LA, AF type (paroxysmal, persistent or long-term) and early recurrent AF).

Рис. 3. Предикторы рецидивов ФП (APPLE оценка - по одному баллу за возраст> 65 лет, наличие постоянной ФП, постоянная скорость клубочковой фильтрации ("60 м / мин / 1,73 м), Диаметр ЛП более 43 мм, фракция выброса <50%; MB-LATER оценка – мужчины, блокада ножек пучка Гисса, ЛП, тип ФП (пароксизмальная, постоянная или длительно стойкая) и ранняя рецидивирующая ФП).

heart or non-cardiac diseases. Hence, PWD may be useful in identifying patients who are prone to developing paroxysmal PAF [15].

Prevention and treatment

The clinical relevance of PAF depends on the duration of paroxysmal events, ventricular rate, response to treatment, and comorbidities. In most cases, postoperative atrial fibrillation is self-limited. It is statistically shown that the cessation of arrhythmia can occur within 2 hours in 30% of patients, within 24 hours with the use of antiarrhythmic drugs or without drug therapy – in 70%. Modern prevention of atrial fibrillation after surgery includes medication (Tabl. 8) and non-medication approaches, as well as their various combinations [3, 87].

1. Beta-blockers. This group of drugs is most effective when used both before and after cardiac surgery, compared to using only before or only after surgery. At least 1 week before the intervention, treatment with a beta1-blocker, which does not have intrinsic sympathomimetic activity, should be started [3, 6, 8, 82, 85].

2. Amiodarone. The drug is the most widely studied antiarrhythmic drug used for the relief of supraventricular and ventricular arrhythmias. Prophylactic use of Amiodarone reduced the incidence of postoperative AF (OR 0.50; 95% CI 0.42–0.59), significantly reduced the length of hospital stay, decreased the incidence of strokes and postoperative ventricular tachyarrhythmias, but did not affect postoperative mortality. The frequency of AF in the amiodarone group was lower than in the placebo group (OR 0.52; 95% CI 0.34–0.69), including in patients <65 years of age and ⩾65 years of age, patients undergoing coronary artery bypass grafting or heart valve surgery with or without coronary artery bypass grafting, as well as in patients who received and did not receive beta-blockers before surgery [3, 4, 6, 8, 82, 85].

3. Sotalol. With this drug, the incidence of postoperative AF was reduced by 64% compared with placebo, but it did not affect length of hospital stay, risk of stroke or mortality [3, 8, 82].

4. Magnesium. Due to its low cost and relative safety of use, magnesium is often used in the pre- and postoperative period. In a meta-analysis of 20 rand-

Table 8. Drugs and dosage for PAF treatment and prevention

Таблица 8. Препараты и их дозы для лечения и профилактики ПОФП [8]

Drugs Препараты	Indications Показания	Dosage Дозы	Side effects Побочные эффекты
β-blockers	Prevention of AF, myocardial ischemia	Metoprolol 150 mg / day per os for 14 days after admission to ICU. Carvedilol 40–50 mg / day per os 10 days before surgery	Bradycardia, hypotension, bronchospasm, heart failure
В-блокаторы	Профилактика ФП, ишемия миокрада	Метопролол 150 мг/сут per os в течение 14 дней после поступления пациента в ОРИТ. Карведилол 40–50 мг/сут per os за 10 дней до операции	Брадикардия,гипотония, бронхоспазм, сердечная недостаточность
Sotalol	AF prevention	160–240 mg per os daily up to 6 days after surgery, starting in the morning of the first DAS	Bradycardia, prolongation of the QT interval, fatigue, dizziness, headache, heart palpitations
Соталол	Профилактика ФП	160–240 мг per os в сутки до 6 дней после операции начиная с утра первого ПОД	Брадикардия, удлинение интервала QT, усталость, головокружение, головная боль, учащенное сердцебиение
Amiodarone	AF prevention	5–15 mg / kg per day per os 1–6 days before surgery or iv (1 g / day for 2 days) immediately after surgery	Bradycardia, prolongation of the QT interval, gastrointestinal disorders, constipation
Амиодарон	Профилактика ФП	5–15 мг/кг в сутки per os за 1–6 дней перед операцией или в/в (1 г/сут в течение 2 дней) сразу после операции	Брадикардия, удлинение интервала QT, ЖКТ расстройства, запор
Omega-30-PFA	AF prevention	2 g / day per os, 5–7 days before surgery until discharge	Increased risk of bleeding
Омега-30 ПЖК	Профилактика ФП	2 г/сут per os за 5–7 дней перед операцией до выписки	Повышенный риск кровотечения
Statins	Stabilization of atherosclerotic plaques, prevention of AF	Atorvastatin 40 mg / day per os, 7 days before surgery	Rhabdomyolysis, increased liver enzymes, diabetes risk
Сатины	Стабилизация атеросклеротических бляшек, профилактика ФП	Аторвастатин 40 мг/сут per os за 7 дней до операции	Рабдомиолиз, повышение уровня печеночных ферментов, риск развития диабета
Corticosteroids	Decrease of inflammatory response	Dexamethasone 0.6–1 mg/kg iv after anesthesia induction or 100 mg hydrocortisone: first dose the evening before surgery, then every 8 hours for 3 days	Hyperglycemia, osteoporosis, ulceration, hypertension, retinopathy
Кортикостероиды	Снижение воспалительного ответа	Дексаметазон, 0,6–1 мг/кг в/в после индукции анестезии или 100 мг гидрокортизона: первая доза вечером накануне операции, затем каждые 8 ч в течение 3 дней	Гипергликемия, остеопороз, язвообразование, гипертония, ретинопатия
Mg	AF prevention	10 mmol of magnesium sulfate iv for 3 days after surgery or 6 mmol preoperative	Hypotension, bradycardia, nausea, vomiting, diarrhea and postoperative
Магний	Профилактика ФП	10 ммоль сульфата магния в/в в течение 3 дней после операции или 6 ммоль предоперационно	Гипотония, брадикардия, тошнота, рвота, диарея и послеоперационно

Drugs Препараты	Indications Показания	Dosage Дозы	Side effects Побочные эффекты
Colchicine	Prevention of post-pericardiotomy syndrome and AF	1.0 mg twice a day per os from the 3rd DAS with a maintenance dose of 0.5 mg twice a day for 1 month	GIT disorders, neuropathy, anemia, hair loss
Колхицин	Профилактика постперикардиотомного синдрома и ФП	1,0 мг дважды в день per os начиная с 3-го ПОД с поддерживающей дозой 0,5 мг дважды в день в течение 1 мес.	ЖКТ расстройства, нейропатия, анемия, выпадение волос
NSAIDs	Decrease of inflammatory response	Ketolorac 30 mg iv every 6 hours before per os possible, then ibuprofen 600 mg orally 3 times a day (up to 7 days)	Renal dysfunction, dyspepsia, ulceration, diarrhea
НПВС	Снижение воспалительного ответа	Кетолорак 30 мг в/в каждые 6 ч до возможности приема per os, затем ибупрофен 600 мг per os 3 раза в сутки (до 7 дней)	Почечная дисфункция, диспепсия, язвообразование, диарея

Abbreviations: AF – atrial fibrillation, ICU – resuscitation and intensive care unit, iv – intravenously, DAS – day after surgery, GIT – gastrointestinal tract, omega-3-PFA – omega-3- polyunsaturated fatty acids, NSAIDs – non-steroidal anti-inflammatory drugs.

Сокращения: ФП – фибрилляция предсердий, ОРИТ – отделение интенсивной терапии, в/в – внутривенный путь введения, ПОД – послеоперационный день, ЖКТ – желудочно-кишечный тракт, омега-3-ПЖК – омега-3-полиненасыщенные жирные кислоты, НПВС – нестероидные противовоспалительные препараты.

omized trials, including 2490 patients in total, it was shown that prophylactic intravenous magnesium administration reduces the likelihood of postoperative AF (OR 0.54; 95% CI 0.38–0.75) (by A.Sh. Revishvili. [58] and Ho K.M. [88]).

However, the large randomized double-blind study by R.Y. Klinger et al. showed that large doses of magnesium did not reduce the risk of PAF after cardiac surgery [89].

5. Statins. Given the important role of the inflammatory process in the formation of a substrate for arrhythmia, statins have been shown to be effective in the prevention of PAF. Taking statins reduces the risk of PAF by 22–34% [3, 58].

6. Corticosteroids. According to a meta-analysis, treatment with corticosteroids was associated with a 26–45% decrease in the incidence of postoperative AF and a decrease in the length of hospital stay [58].

7. Vitamins are widely used for the prevention of PAF after cardiac surgery [38]. A meta-analysis by H. Hemila and T. Suonsyrja showed that perioperative vitamin C intake was associated with a significant decrease in POAF and a decrease in the length of hospital stay [90]. In addition, the use of vitamin C, vitamin E and N-3 polyunsaturated fatty acids was associated with a significant decrease in PAF (9.7% PAF in the vitamin C group, 32% in the placebo group) [91].

8. Atria stimulation. In a meta-analysis of 8 studies, prophylactic atrial pacing was shown to reduce the incidence of postoperative AF regardless of the location or algorithm of pacing (OR 0.57; 95% CI 0.38-0.84), but other studies have not confirmed the effectiveness of this method (cited after Ucar HI [46], Steinberg BA [85], Burgess DC [92].

Current guidelines for cardiothoracic surgery recommend anticoagulant therapy for 12-48 hours after the onset of postoperative AF, balancing the risk of bleeding after cardiac surgery. Most cardiac surgeons usually discontinue anticoagulant therapy as soon as sinus rhythm is restored to avoid late bleeding complications [93].

Preventive measures including such pharmacological strategies as early resumption of beta-blockers and early correction of electrolyte imbalances, in particular those targeted at high-risk patients, can reduce cost and, more importantly, postoperative morbidity and mortality [65, 89].

Concomitant AF ablation in patients after CABG and heart valve surgery in combination with other cardiac surgery is currently a Class I recommendation. Numerous studies have shown that concomitant AF ablation can be performed safely and effectively during CABG and valve replacement, which leads to a return to sinus rhythm after surgery and improved long-term results. However, it is performed less frequently than it should be [67].

Also, it is worth noting that existing preventive and therapeutic strategies may be useful only in a certain category of patients after heart surgery. Currently, none of the proposed preventive therapy regimens

guarantees 100% protection of the patient from the development of PAF and associated complications [8].

Thus, postoperative atrial fibrillation is a common complication after cardiac surgery, which directly lengthens the period of early rehabilitation in patients undergoing cardiac surgery. The increased LA volume, as a marker of chronically increased LA pressure, is closely associated with the occurrence of PAF. The atrium dilatation can be an indicator of the process duration and directly reflect remodeling, being a quantitatively replaceable arrhythmogenic substrate [54, 81, 94].

In patients with coronary artery disease undergoing HB, cardiopulmonary bypass surgery was reliably associated with a more frequent occurrence of PAF [38, 40].

A systematic review and meta-analysis were performed to assess the risk of stroke after PAF in non-cardiac surgery. Articles published prior to April 2020 were searched through MEDLINE, Cochrane, and EMBASE for studies of patients undergoing cardiac surgery who reported the incidence of new PAF cases. We have not contacted the authors for additional information. More details have been obtained through a manual link search from recent reviews and corresponding published original studies.

The results of numerous clinical and experimental studies have demonstrated the prognostic significance of neurohumoral markers, markers of inflammation, fibrosis, and myocardial damage in relation to the development of arrhythmia and its complications [95].

Significant indicators determining the occurrence of arrhythmia in patients after cardiac surgery are the patient's age and sex, LA volume, LV ejection fraction, time of aortic clamping and ischemia [38, 42].

STE is an important technique in predicting the development of postoperative AF after cardiac surgery. LA dysfunction is an important prognostic predictor for assessing the risk of developing PAF. Studies have shown that LA deformity was one of the most important predictors of PAF development and is also a significant indicator in predicting cardiovascular events such as stroke, AF and myocardial infarction [34, 63, 75].

POAF, CHA2DS2-VASc and HATCH screening systems have shown good discrimination and calibration for predicting postoperative atrial fibrillation in patients undergoing cardiac surgery. Among these, the CHA2DS2-Vasc score presented the best discriminating ability of postoperative atrial fibrillation and has the advantage of simplicity of calculation [60].

It is necessary to focus on identifying patients at risk of developing PAF, since this complication leads to hemodynamic instability, thromboembolic events, longer hospital stay and increases treatment costs [68, 69].

Acute atrial fibrillation increases the risk of thrombus formation in the LA appendage, which leads to an increased risk of systemic embolization and stroke. PAF after heart surgery significantly increases the risk of early stroke and mortality. Most PAF occurred within 2–4 days after surgery, with a peak incidence on day 2 after surgery [22].

Conclusion

Currently, PAF is an extremely urgent problem. According to the world literature data, the incidence of PAF in the period from 1970 to 2019. increased from 10 to 65% of the total number of operated patients. The main causes of postoperative atrial fibrillation are not fully understood. This complication is a significant problem requiring an even more detailed analysis of the molecular and pathogenetic mechanisms of its occurrence and progression. A complete understanding of the pathogenetic mechanisms of the development of arrhythmias will help reduce the cost of hospitalization of patients, reduce postoperative complications caused by this arrhythmia, and also increase the life expectancy of this category of patients. Evaluation of echocardiographic parameters is required to identify patients requiring PAF prophylaxis. The main task of the researcher at present is to draw up a unified algorithm for predicting and preventing episodes of postoperative atrial fibrillation.

Authors' participation

Kadyrova M. – conducting research, text preparation and editing.

Stepanova Yu.A. – statistical analysis, responsibility for the integrity of all parts of the article.

Grinberg M.S. – collection and analysis of data, analysis and interpretation of the obtained data.

Raguzina V.Y. – collection and analysis of data,writing text.

Malyshenko E.S. – conducting research, participation in scientific design.

Popov V.A. – participation in scientific design, responsibility for the integrity of all parts of the article.

Revishvili A.Sh. – concept and design of the study.

Участие авторов

Кадырова Мадина – проведение исследования, подготовка и редактирование текста.

Степанова Юлия Александровна – статистическая обработка данных, ответственность за целостность всех частей статьи.

Гринберг Мария Сергеевна – сбор и обработка данных, анализ и интерпретация полученных данных.

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Ревишвили Амиран Шотаевич – концепция и дизайн исследования.

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