



Epicardial Application of Hydrogel with Amiodarone for Prevention of Postoperative Atrial Fibrillation in Patients After Coronary Artery Bypass Grafting

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Abstract

The objective of this study was to assess the safety and efficacy of local epicardial application of amiodarone-releasing hydrogel for prevention of postoperative atrial fibrillation (POAF) in patients after coronary artery bypass grafting. Patients were randomized into two groups: with the application of amiodarone-releasing hydrogel and the control group. It included 60 patients (47 males, 13 females) (mean age of 62 ± 8.5). POAF incidence differences were statistically significant between two groups: in the study group, the POAF incidence was 3.3%, while in the control group, the POAF incidence was 37% ($p < 0.001$). Statistically significant differences were revealed in the PQ interval duration. The risk of POAF incidence was calculated using the Cox regression model: the age and the application of amiodarone-releasing hydrogel application were statistically significant. Hospital length of stay in two groups was also different ($p < 0.001$). The age and the application of amiodarone-releasing hydrogel were statistically significant for POAF incidence.

Keywords Amiodarone-releasing hydrogel · Coronary artery bypass surgery · Postoperative atrial fibrillation · Prevention · Clinical study

Introduction

Postoperative atrial fibrillation (POAF) is the most frequent complication following an open heart surgery [1, 2]. The incidence rate depends on the type of the surgical intervention and falls within the range of 10–60%. Some studies have demonstrated that POAF raises the risk of ventricular arrhythmias, acute cardiac failure, and thromboembolic complications and also increases the hospital length of stay and economic costs of the patient treatment [3–5].

Amiodarone is the most effective antiarrhythmic drug known for POAF correction [6]. However, the use of amiodarone in clinical practice is often limited as it is associated with a high incidence of extracardiac adverse effects. As a rule, amiodarone-related effects are caused by the systemic drug saturation effects [7]. The most frequent of them are presented in Table 1 [8]. Because of its ability to accumulate, some of its side effects may occur after a long time after discontinuation of the drug [9]. The meta-analysis of ATMAI analyzed the main side effects of amiodarone which were reported in 6 double-blind placebo-controlled trials. After 2 years, more patients in the amiodarone group refused treatment than in the placebo group, mainly due to side effects [10].

Currently, the local application of drugs is gaining popularity, and specifically there are several studies on local application of amiodarone (such as epicardial application of amiodarone-releasing adhesive hydrogel in situ, intrapericardial infusion of amiodarone solutions, and two-layer strips or disks with amiodarone, attached to the epicardium) [11–13].

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Table 1 Side effects of amiodarone by Naccarelli et al. [8]

Organ/system	Side effect (%)
Cardiovascular system	Bradycardia (6%), A-V blockades, proarrhythmogenic action (1%)
Lungs	Interstitial pneumonitis (3–7%)
Liver	Increased level of liver enzymes (up to 50%)
Thyroid	Hypothyroidism (1–2%) Hyperthyroidism (up to 25%) Thyrotoxicosis (1–12%)
Eyes	Microdeposition in the cornea (1%) Photophobia (1–2%)
Nervous system	Neuropathy (1–5%)

The work of W. Wang et al. was the first publication in which the use of hydrogel with amiodarone in the clinic in humans was studied [12]. Later, the authors continued to study the idea of using hydrogel as an adhesive material for a longer retention of the drug reagent. In [14], the authors showed the safety of hydrogel in humans, its good biodegradability and neutrality to atrial tissues.

In our previous experimental animal study of the local epicardial amiodarone use, the technical ability and safety of the proposed method was demonstrated [15]. The application of amiodarone-releasing hydrogel took only a few minutes to complete. It means that this procedure would not significantly increase the duration of the main stage of surgery, when used in addition to a heart surgery in the clinic. This method of drug delivery minimizes its systemic side effects against a proper efficacy profile. It is concluded that the hydrogel does not act as an aggressive infectious agent, though it is directly applied to the epicardium: the histologic study did not reveal any myocardial inflammatory structural changes.

The transfer of the results obtained in the study of clinical practice was agreed on the Ethics Committee at Bakoulev National Medical Research Center for Cardiovascular Surgery of Ministry of Health of the Russian Federation. Phase I clinical study protocol no. 2 of March 29, 2018, was approved.

Thus, *the objective of this study* was to assess the safety and efficacy of local epicardial application of amiodarone-releasing hydrogel for the POAF prevention in patients after coronary artery bypass grafting (CABG).

Material and Methods

The study design was an open-label randomized prospective clinical study. It was performed at the department of surgical treatment of interactive pathology at Bakoulev National Medical Research Center for Cardiovascular Surgery of Ministry of Health of the Russian Federation.

Patients were randomized into two groups: the study group (with the application of amiodarone-releasing hydrogel) and the control group. The method of randomization used was restricted using sealed envelopes. The total number of enrolled patients planned was 60 patients. The dose of amiodarone in hydrogel material was calculated as ≈ 1 mg/kg body weight that was determined in the experimental study [15].

Scheduled isolated CABG was used as the inclusion criterion in the study.

Withdrawal criteria include the following:

- Interventions combined with CABG (CABG combined with mitral valve correction; CABG combined with correction of myocardial structural defects (left ventricular aneurysm, ventricular septal defect, etc.);
- Prior atrial fibrillation (AF) history (history of AF episodes documented by ECG results, results of the Holter monitor, medical discharge, etc.);
- Malignant neoplasms;
- Severe renal failure (creatinine clearance according to Cockcroft-Gault formula < 50 ml/min);
- Severe chronic heart failure (left ventricular ejection fraction $< 35\%$);
- Organic lesions of the central nervous system;
- Any mental illness;
- Any endocrine disorders;
- Hyper- or hypothyroidism;
- Patients undergoing immunosuppressive and anti-inflammatory therapy for comorbidity.

All patients underwent both standard diagnostic evaluation (laboratory and instrumental testing), as well as more in-depth analysis of some parameters (for example, an assessment of the duration of ECG interval dynamics and expanded blood profile test).

For Holter ECG monitoring, portable 3-channel Holter-DMS systems were used. According to the study protocol, Holter ECG monitoring was carried out continuously during the first 72 h after surgery. After 72 h, the heart rhythm was

evaluated using standard ECG monitoring in the event of complains of abnormal heart rhythm and as part of the regular check twice daily. On day 5, after the surgery, all the patients underwent additional daily (24 h) Holter ECG monitoring. POAF onset was documented as an AF episode lasting more than 5 min.

Based on the study protocol, the complete blood count including measurement of formed elements of blood and WBC differential was carried out before surgery and on day 1 and day 5 after surgery. The toxic effect and the risk of infection of the hydrogel were evaluated by assessing the inflammatory reaction based on WBC count and differential parameters.

Clinical Protocol for Surgical Intervention

Median sternotomy was performed to access to the surgical site. The longitudinal T-shaped incision was applied to open the pericardium. Standard cannulation of the aorta, separate cannulation of the superior vena cava and inferior vena cava. Extracorporeal circulation was performed under normothermia. The main stage of CABG was subsequently carried out. When the main stage of surgery was completed, temporary epicardial electrodes were placed on the right ventricle and right atrium in all patients. On termination of extracorporeal

circulation, decannulation from the vena cava and aorta was carried out. The next step was biatrial epicardial application of amiodarone-releasing hydrogel. The hydrogel was applied with a sprayer (Fig. 1) on the surface of both atria (Fig. 2) in the amount of 5–8 ml (at a concentration calculated as 1 mg/kg body weight). Layered wound closure. The end of the operation.

It was planned to use temporary epicardial electrodes in the event of severe sinus bradycardia or significant atrioventricular conduction disturbances. However, looking ahead, we can say that there was no need for atrial pacing; no episodes of intracardiac conduction disturbances were reported.

Postoperative Stage

In the early postoperative period, all patients received the optimal drug therapy according to accepted international guidelines. No preventive antiarrhythmic drug therapy was prescribed postoperatively.

Statistical Analysis

Statistical analysis was conducted using the STATISTICA 10.0 (StatSoft) program. Initially, all data were tested for



Fig. 1 Sprayer of the drug

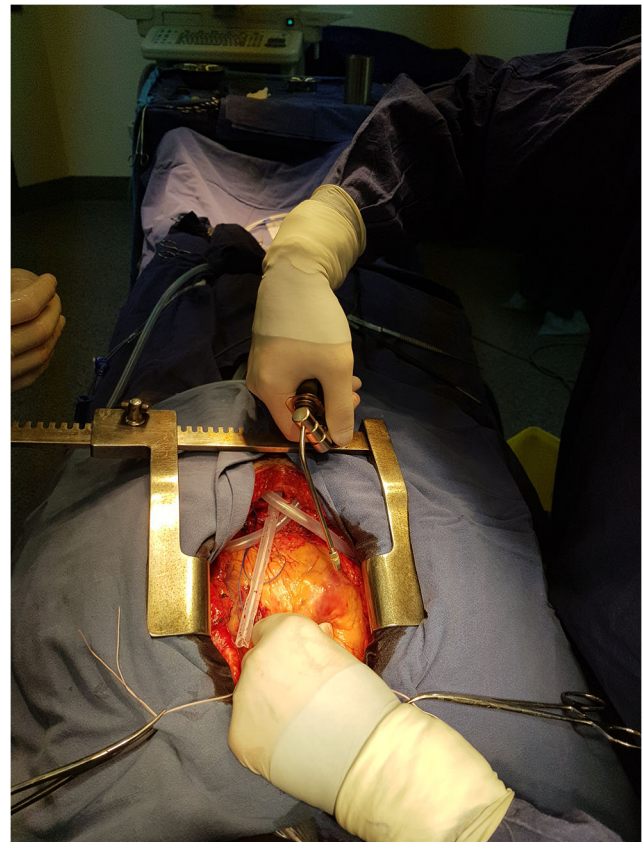


Fig. 2 Operating stage: application of the hydrogel with amiodarone

normal distribution (the Shapiro-Wilk test). In a normal distribution, data are shown as mean and standard deviation ($M \pm SD$). In a distribution different from normal, they are presented as median and interquartile range ($Me (Q1; Q3)$). We used either parametric or non-parametric statistical methods corresponding to each distribution.

The parametric Student's *t* test or the non-parametric Mann-Whitney *U* test was used to compare two independent samples. The Cox regression model was applied to assess the risk of POAF incidence.

Results

The study was completed according to the protocol. It included 60 patients (47 males, 13 females) (mean age of 62 ± 8.5).

Baseline clinical, laboratory, and instrumental parameters in groups did not have nearly any statistically significant differences. Only one parameter (left atrial volume) was significantly different. However, the difference had upward bias in the study group (left atrial volume tended to be greater in the group with the application of amiodarone-releasing hydrogel) rather than in the control group. Therefore, we were confident that this would not affect the study results and supposed that the groups were relatively homogeneous and their further comparison was eligible (Table 2).

No statistically significant differences in the intraoperative data were reported either.

POAF incidence was statistically significant between two groups: in the study group, POAF was diagnosed in 1 patient, which was 3.3%, while in the control group, the POAF incidence was 37% ($p < 0.001$).

WBC count on day 1 after surgery was comparable between groups and did not significantly differ: $12 (10; 14) \times 10^9/\text{ml}$ in the study group and $13 (9; 17) \times 10^9/\text{ml}$ in the control group ($p = 0.34$). On day 5, there were also no statistically significant differences among all the laboratory parameters: WBC count and glucose, lactate, and creatinine levels (Table 3).

ECG on day 5 revealed statistically significant differences in the PQ interval duration: the PQ interval was 0.14 (0.12; 0.16) in the study group compared with 0.12 (0.12; 0.14) ($p = 0.002$) in the control group. Significant changes in QRS and QT intervals were not detected.

According to the Holter ECG monitoring, the average heart rate on day 5 in the study group was 59 (52; 60) beats per minute versus 69 (65; 75) beats per minute in the control group, which was statistically significant ($p < 0.001$). Minimum heart rate per day was also significantly different: in the study group, minimum heart rate was 50 (49; 55) beats per minute versus 55 (50; 58) beats per minute in the control group ($p = 0.008$).

The dynamics of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels initially and after using hydrogel with amiodarone were as follows: AST—31 (16; 34) versus 30 (17; 33), $p = 0.416$; ALT—26 (22; 31) versus 27 (23; 33), $p = 0.521$.

Hospital length of stay in two groups was also different: 6 (6; 7) bed-days in the study group versus 8 (8; 9) bed-days in the control group ($p < 0.001$).

The risk of POAF incidence was calculated using the Cox regression model. The parameters with high intercorrelation ($r > 0.7$) were excluded: for example, such parameters as EDV, EDD, and ESV showed intercorrelation $r > 0.7$, which was why only EDV parameter was chosen.

Among all clinical, laboratory, and instrumental parameters, the age ($p = 0.009$) and the procedure of amiodarone-releasing hydrogel application ($p = 0.011$) were statistically significant. At that risk, score in the Cox model of hydrogel application comprised 18.9, while regression coefficient was $\beta (-2.9)$. It means that the use of hydrogel with amiodarone reduces POAF incidence by almost 19 times (Table 4).

Discussions

Numerous studies undertaken on POAF incidence after cardiac surgeries do not provide a definite answer to the question about the causes of its occurrence. There is no doubt that there are multiple predisposing factors for AF development following an open heart surgery. They are both baseline clinical and operational factors, such as age, hypertension, diabetes, obesity, left atrial enlargement, cardioplegia, cardiac trauma after surgery, electrolyte derangements in the postoperative period, and inflammation [16].

In this study, we obtained a statistically significant difference in POAF development with local application of amiodarone in CABG surgery. POAF was diagnosed in one patient in the amiodarone-based group only (in 3.3% of cases). POAF incidence in the control group was 37%.

In general, POFP incidence discussed in this study is consistent with the data of the global literature [2, 16, 17], although in our previous study [18], the parameter values were slightly lower. Perhaps, that was due to the retrospective nature of the study and associated with the occurrence of asymptomatic paroxysmal AF episodes.

The mechanisms of action of amiodarone as an antiarrhythmic agent are absolutely the same as with the systemic one: it prolongs phase III of the cardiac action potential and the effective refractory period and reduces the myocardial excitability (Fig. 3). The penetration of amiodarone from a hydrogel into the cell is associated with diffusion mechanisms [19]. The hydrogel itself has no pro- or anti-inflammatory effect on the myocardium. This is confirmed by the absence of any laboratory shifts in WBC count (the parameters was comparable in both

Table 2 Clinical and instrumental parameters of the groups

Parameters	Study group (n = 30)	Control group (n = 30)	p
Clinical data			
Age, years	61 ± 8.2	63 ± 8.8	0.264
Male, %	90	77	0.375
BMI	27.6 ± 3.5	29 ± 4.1	0.139
Prior MI, %	53	56	0.824
Remoteness of prior MI, month	7 (4; 18)	12 (7; 36)	0.117
Angina, CCS class	3 (3; 3)	3 (3; 3)	0.505
Stroke %	0	6	0.657
Arterial hypertension, %	93	93	0.999
Smoking, %	27	20	0.657
Diabetes, %	30	10	0.183
COPD, %	23	13	0.505
Drug therapy			
ACEi	97	100	0.824
ASA	100	100	0.999
Statins	100	100	0.999
β-Blockers	100	100	0.997
CCB	20	26	0.657
Instrumental data			
EDV, ml	111 (102; 129)	118 (107; 126)	0.584
ESV, ml	48 (41; 58)	47 (37; 58)	0.468
EDD, sm	5 (4.8; 5.2)	5 (4.9; 5.4)	0.217
LV EF, %	57 (56; 58)	58 (56; 59)	0.355
Left atrium volume, ml	79 (77; 80)	77 (69; 79)	0.039
Average heart rate (Holter ECG), n/min	68 (64; 70)	61 (59; 68)	0.060
PQ, ms	0.12 (0.12; 0.14)	0.12 (0.12; 0.14)	0.554
QT, ms	0.34 (0.32; 0.38)	0.34 (0.32; 0.36)	0.888
Laboratory data			
Creatinine, μmol/l	74 (70; 90)	84 (73; 102)	0.103
Glucose, mmol/l	5 (4.6; 6)	5 (4.5; 6)	0.778
WBC, $n \times 10^9/\text{ml}$	7 (6.3; 8.4)	7.6 (6; 8.3)	0.841
Fibrinogen, g/l	3 (2; 3)	3 (2; 3)	0.180

BMI body mass index, MI myocardial infarction, CCS class of angina Canadian Cardiovascular Society angina class, COPD chronic obstructive pulmonary disease, ACEi angiotensin-converting enzyme inhibitor, ASA acetylsalicylic acid, CCB calcium channel blockers, LA left atrium, EDV end-diastolic volume, ESV end-systolic volume, EDD end-diastolic dimension, LV EF left ventricular ejection fraction, WBC white blood cells

Note: italics shows statistically significant differences in groups

groups) at all control points of the study. The mechanism of elimination of the hydrogel substance from the pericardial cavity is associated with the processes of lymphatic drainage [12].

Multivariate regression analysis demonstrated that among all clinical, laboratory, and instrumental parameters, the age ($p = 0.009$) and the procedure of amiodarone-releasing hydrogel application ($p = 0.011$) were statistically significant. This proves the multifactorial nature of POAF incidence. In many studies, the age factor is undoubtedly associated with AF.

There are studies in the literature reporting that WBC and neutrophil count are independent predictors of POAF [13].

These studies demonstrated the inflammatory character of POAF incidence, and in particular, they considered the use of the anti-inflammatory action of statins in the prevention of POAF [20]. In our study, the drug therapy at baseline was absolutely the same, which might probably be attributable to the absence of any significant effect of the therapy received on the results of the study.

ECG revealed that on day 5, the PQ interval duration was significantly different compared with the control group. We also associate the increased duration of the PQ interval with the effect of amiodarone on the atrial myocardium. No

Table 3 Intraoperative and postoperative parameters of the groups

Parameters	Study group (<i>n</i> = 30)	Control group (<i>n</i> = 30)	<i>p</i>
Intraoperative parameters			
Operation time, hour	3.9 ± 0.99	3.5 ± 0.85	0.379
Time of CPB, min	84 (65; 105)	75 (60; 97)	0.437
The number of grafts, <i>n</i>	2 (2; 3)	2 (2; 3)	0.657
Lactate (the end of the operation)	1.4 (1.2; 1.9)	1.5 (1.3; 2)	0.689
Glucose (the end of the operation)	7.3 (6.9; 9.4)	7 (6; 9.6)	0.610
Postoperative parameters			
Time of artificial lung ventilation, hour	14 (12; 16)	16 (14; 16)	0.255
WBC, day 1	112 (10; 14)	13 (9; 13)	0.344
AF after surgery, %	3.3	37	< 0.001
Lactate, day 5	0.6 (0; 1)	0.5 (0; 1)	0.898
WBC, day 5	11 (8.8; 12)	11 (9; 13)	0.270
Glucose, day 5	5 (4.9; 6)	5 (4.7; 5.7)	0.614
Creatinine, day 5	78 (70; 89)	79 (72; 110)	0.128
QT, day 5, ms	0.34 (0.32; 0.36)	0.34 (0.32; 0.36)	0.851
PQ, day 5, ms	0.14 (0.12; 0.16)	0.12 (0.12; 0.14)	0.002
Average heart rate (Holter ECG), day 5, <i>n</i> /min	59 (52; 60)	69 (65; 75)	< 0.001
Minimum heart rate (Holter ECG), day 5, <i>n</i> /min	50 (49; 55)	55 (50; 58)	0.008
Number of bed-days	6 (6; 7)	8 (8; 9)	< 0.001

CPB cardiopulmonary bypass, WBC white blood cells

Note: italics shows statistically significant differences in groups

changes in the QRS and QT intervals between groups were detected, which may prove that the study material does not affect the ventricular myocardium.

The effects of amiodarone explain the differences in the average heart rate and minimum heart rate in the study and control groups on day 5 after the surgery. Despite the decrease in heart rate detected in the study group, we did not record any episodes of interatrial and intraventricular conduction abnormalities. These results are probably correlated to the results of our previous study where we properly determined a safe and effective dosage of the active substance (amiodarone) in a hydrogel [15].

Some of the possible manifestations of extracardiac side effects associated with amiodarone were assessed. The most frequent of them, as we have already mentioned in Table 1, are the increased level of liver enzymes, thyroid dysfunction, and interstitial pneumonitis. Moreover, due to the cumulative properties of amiodarone, most manifestations of side extracardiac effects occur, as a rule, after a long time of amiodarone use [9].

In this research, we studied one of the possible “fast” side effects—the dynamics of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels initially and after using hydrogel with amiodarone.

Table 4 Cox regression model for assessing the risk of development of POAF in patients after CABG ($\chi^2 = 23.4$; $p = 0.0014$)

Parameter	Regression coefficient β	Standard error	The exponent beta (risk index exp. <i>B</i>)	Wald criterion	<i>p</i>
Age, years	0.164	0.063	1.178	6.716	0.009
Application of amiodarone-releasing hydrogel	− 2.939	1.168	18.914	6.329	0.011
Time of CPB, min	0.021	0.011	1.020	2.995	0.835
LV EF, %	− 0.111	0.075	0.894	2.178	0.139
The number of grafts, <i>n</i>	− 1.307	0.926	0.270	1.989	0.158
EDV, ml	− 0.009	0.014	0.991	0.348	0.554
Male	− 0.481	0.818	0.618	0.345	0.557

CPB cardiopulmonary bypass, LV EF left ventricular ejection fraction, EDV end-diastolic volume

Note: the statistically significant parameters in The Cox regression model are shown in italics

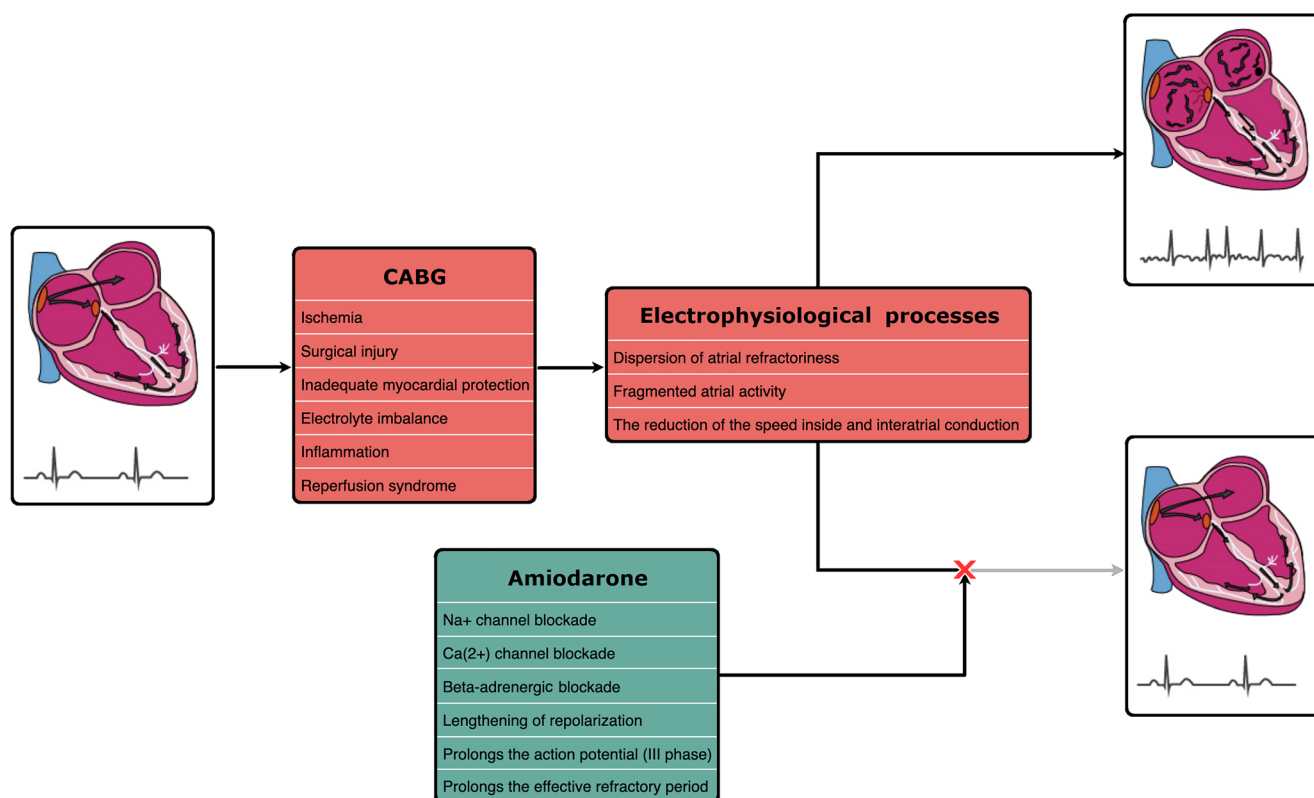


Fig. 3 Scheme of the amiodarone influence on some pathogenic mechanisms of AF after CABG

Lung damage was assessed by x-ray examination in the postoperative hospital period. There were no cases of pneumonitis in the study group.

In general, there were no manifestations of extracardiac side effects, which is logically combined with the general idea of this study.

Another significant result of the study was the application of amiodarone-releasing hydrogel as a preventative therapy for paroxysmal AF that led to a decrease in hospital length of stay. It seems logical since the time taken to restore the rhythm increases the total hospital length of stay. In this study, POAF lasted 6 h on average and 14 h as maximum.

During postoperative parameter analysis (temperature monitoring, blood test, and instrumental examination results), no cases of infection processes were registered. Considering the changes, we can declare the local epicardial amiodarone delivery using hydrogel material to be a safe method.

Conclusions

The local epicardial amiodarone delivery using hydrogel material is a safe method. No cases of infection processes were registered.

Amiodarone-releasing hydrogel at a dose of 1 mg/kg body weight is an effective treatment in the prevention of POAF in patients after coronary artery bypass graft surgery (CABG) compared with the control group ($p < 0.001$). The dose can

also be considered safe, as we did not record any episodes of interatrial and intraventricular conduction abnormalities.

In the regression model, a statistically significant association with POAF was determined with two parameters: the age of the patient, with the increase of which, the probability of POAF also increased, and the epicardial use of hydrogel with amiodarone, with the application of which, the probability of developing POAF decreased.

Limitations

Certainly, the limitation of this work is a small number of patients. However, this number of observations was initially planned as the part of phase 1 of the clinical study, which is characterized by a small sample of patients. In the next stage, we plan to conduct phase 2 with a larger sample of patients (about 400 patients) and to use the placebo control.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Statement The study was approved by the Ethics Committee at Bakoulev National Medical Research Center for Cardiovascular Surgery of Ministry of Health of the Russian Federation (protocol no. 2 of March 29, 2018).

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