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# THE USE OF DISTAL FEMORAL VENOUS ACCESS FOR PULMONARY VEIN CRYOBALLOON ABLATION AND LEFT ATRIAL APPENDAGE OCCLUDER IMPLANTATION: RANDOMIZED STUDY DESIGN AND PRELIMINARY RESULTS

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**Aim.** This study aims to compare the results of the distal femoral access with the classic approach in patients undergoing pulmonary vein cryoballoon ablation and left atrial appendage occluder implantation.

**Methods.** The primary results of the 1:1 randomized single-center study are presented. The study group recruited 47 patients who underwent the catheter-based procedure using ultrasound-assisted distal femoral access. 38 patients with traditional ultrasound-guided proximal femoral access were involved in the control group.

**Results.** Total 85 patients were included: 47 in the study group and 38 in the control group. The median age was 61 years, and pulmonary vein cryo-ablation was performed in 84%. 95% of patients were taking direct oral anticoagulants. In the study group, the most frequent topographic and anatomical variant was the location of the superficial femoral vein on the lateral side from the artery (81%), whereas in the control group it was on the medial side (81%). The median access time was 30 s in the study group for the right leg and 35 s for the left leg. In the control group, access time was 33 s and 39 s for the right and left leg respectively. Unintentional arterial puncture occurred more frequently in both groups when the vein was fully overlapped by the artery for both right and left legs, but the differences were statistical unsignificant ($p>0.05$ and $p=0.09$ in the main group, $p=0.24$ and $p=0.72$ in the control group). In a correlation analysis, neither body mass index ($p=0.19$) nor femoral circumference ($p=0.19$ for right and $p=0.06$ for left legs) influenced the access time and did not increase the number of unintended arterial punctures. Two patients in the control group required additional manual hemostasis. There was no postprocedural venous thrombosis in both groups. Back pain was observed only in patients in the control group.

**Conclusion.** The efficacy and safety of the distal femoral access approach are comparable to the traditional proximal approach. Earlier postprocedural activation of patients can help improve quality of life.

**Key words:** atrial fibrillation; quality of life; catheter ablation; radiofrequency ablation; cryoballon isolation of the pulmonary veins; percutaneous left atrial appendage occlusion; anticoagulant therapy; ultrasound procedure; vascular complications; vascular access

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Atrial fibrillation (AF) is the most frequent heart rhythm disorder, the prevalence of which increases with age [1, 2]. Arrhythmias lead to a significant decrease in patients' quality of life (QoL), increased hospitalizations, and worse prognosis, which is associated with a large burden on the healthcare system [3-6].

The dynamics of morbidity in the Russian Federation does not differ much from the global one. Thus, according to the data for 2010, the incidence of AF was 1766 per 100 thousand population, whereas for 2017 it was 2536 per 100 thousand population, indicating a 44% increase in the prevalence of arrhythmia [7].

Currently, catheter-based techniques, particularly pulmonary vein isolation procedures, have become a gold standard in rhythm control strategy and are significantly superior to drug therapy [8]. Also catheter-based interventions improve the prognosis even in patients with chronic heart failure with low reduced ejection fraction [9]. In terms of reducing the number of systemic emboli, in particular stroke, methods of endovascular occlusion of the left atrial appendage are not inferior to anticoagulant therapy and have economic advantages in the long-term perspective [10, 11]. Advances in catheter-based procedures for AF have led to their widespread use and thus an increase in the number of procedures performed annually.

Nevertheless, there are still concerns about potential complications of interventional procedures. These complications increase in-hospital time and lead to additional ex-

penses [12]. The necessity of vascular access leads to the prevalence of local vascular complications: hematomas, arteriovenous fistulas, pseudoaneurysms, venous thrombosis and infectious complications. Additional risk factors are usage of large diameter delivery systems and active intra- and postoperative anticoagulant therapy. The search for possible ways to reduce vascular complications in the electrophysiology laboratory has led to the widespread use of ultrasound-guided vascular access techniques to navigate the direction of the puncture needle. However standard femoral vein access wich is performed in the proximal segment of the femoral triangle under the inguinal ligament requires immobilization of patients for at least 8 hours after hemostasis. It often leads to the development of back pain, difficulty in urination, especially in men. Also the proximity of the access point to the inguinal region is fraught with the development of local infections and bleeding into the pelvic and retroperitoneal spaces. A possible way to resolve the problem is finding new areas of access, such as superficial femoral vein puncture in the mid-thigh segment. Such techniques have been used for the first time in the emergency department setting. The technique of distal femoral access for arrhythmological procedures was developed and patented by the author's team (Invention Patent No. 2748776).

The introduction of distal superficial femoral vein puncture into arrhythmological practice may lead to the possibility of early activation of patients and an in-hospital and cost of patient treatment time reduction.

The aim of the study is to compare distal femoral venous access which allows to activate patients in the early postoperative period with the standard one in terms of its efficacy and safety as well as patients' QoL.

## METHODS

Currently, a randomized single-center open trial with randomization of patients in the ratio of 1:1 into the group of standard and distal accesses is being conducted in FSBI «NMIC of therapy and preventive medicine» of the Ministry of Health of the Russian Federation. The study is performed in accordance with Good Clinical Practice standards and the principles of the Declaration of Helsinki. The study protocol was approved by the local ethical committee. Patients were informed and agreed to participate in study. The study design is shown in Fig. 1. The study tests the hypothesis that standard access and distal femoral venous puncture are comparable in terms of safety and efficacy with benefits in patients' quality of life.

The study included patients older than 18 years of age with AF hospitalized for primary catheter isolation of pulmonary vein by cryoballoon ablation or implantation of left atrial appendage occluding devices in accordance with current clinical guidelines. Inclusion in the study did not depend on sex, anthropometric characteristics, concomitant pathology of patients and data of instrumental methods of investigation. Cryoballoon isolation of pulmonary vein was performed in patients with both paroxysmal and persistent forms of AF when the arrhythmia affected the patient's quality of life (EHRA IIa and higher). Patients with thromboembolic risk according to the $CHA_2DS_2$-VASc scale of more than 2 and 3 points for males and females, respectively. Also patients with contraindications to oral anticoagulant therapy or bleeding history or patients refusing to take therapy were included for implantation of left atrial appendage occluders.

Patients who refused to participate in the study, who did not comply with the study design, as well as patients with anatomical features of the pulmonary veins and left atrial appendage that were not suitable for pulmonary vein isolation by cryoballoon ablation and percutaneous endovascular implantation of occluders of the left atrial auricle were excluded from the study. Patients with left atrial appendage thrombosis, previous pulmonary embolism, known procoagulant conditions, deep vein thrombosis and chronic dermatitis were not included in the study.

The choice of this category of patients is conditioned using larger diameter introducers for vascular access according to the protocol of these interventions and the necessity of antithrombotic therapy - anticoagulant therapy during pulmonary vein isolation procedures and combined therapy during implantation of occlusive devices.

The primary efficacy end point included procedural success, defined as achieving complete electrical isolation of the pulmonary vein in cryoballoon ablation procedures or complete occlusion of the left atrial appendage in occluding device implantation procedures according to PASS criteria, number of unintentional arterial punctures during access, success with puncture on the first attempt and time to access. The primary safety endpoint included the number of local complications (arteriovenous fistulas, pseudoaneurysms, BARC 1-5 bleeding), and the need for re-hemostasis in the early postoperative period. Secondary endpoints included patients' QoL, need for urinary catheter placement, and analgesic therapy.

It is the center's practice to temporarily interrupt all previous anticoagulant therapy prior the procedure for one half-life period for direct oral anticoagulants or to an INR level less than 2.0 for patients taking vitamin K antagonists. Prior surgery, a duplex study of the femoral vessels was performed to exclude existing anomalies of the structure and thrombosis of the deep veins of the lower extremities. A linear transducer with frequency from 7 to 8 MHz (Transducer 9L-RS (General Electric, Horten, Norway) connected to the Vivid device (General Electric, Horten, Norway) or a portable transducer Lumify L12-4 (Philips, Amsterdam, The Netherlands) is used to examine the vessels of the lower extremities. Point-of-care ultrasound 3-point protocol (Point-

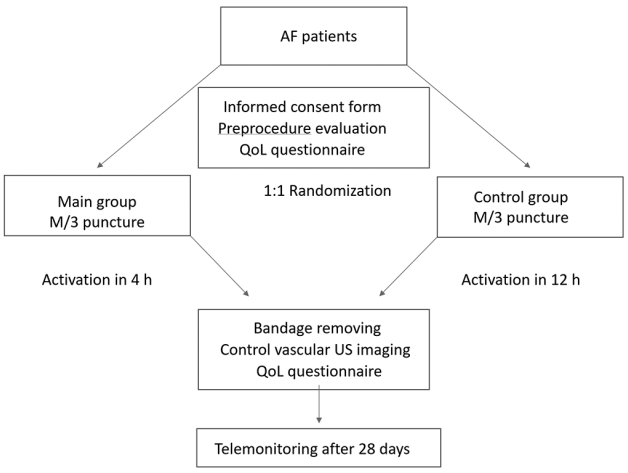


***Fig. 1. Study Design. Note: QoL - quality of life.***

of-care ultrasound 3-point protocol) was used. For segmentation, markings were made preoperatively with a marker on the anterior surface of the femur into three segments, proximal, distal, and medial (Fig. 2).

Preoperative (not more than 48 hours before the procedure) transesophageal echocardiography or multispiral computed tomography was used to exclude left atrial appendage thrombosis, to clarify its anatomy and the anatomy of the pulmonary vein inlet. During the procedure of implantation of the left atrial appendage occluder, the linear dimensions of the left atrial appendage, its shape, apex direction, number of lobes, anatomy of pulmonary vein appendages were also specified, the initial selection of the necessary occluding device was performed, the strategy of transseptal access was developed, and the projections of fluoroscopy convenient for the procedure were selected.

Femoral vein puncture was performed using the Seldinger technique under real-time ultrasound guidance. The linear transducer was placed in a sterile gel pouch for use in the operating field. The method of visualization of the puncture (longitudinal or transverse projection, in-plane, or out-of-plane) was not regulated and was performed at the operator's discretion.

In standard access, puncture of the common femoral vein was performed after combining the superficial and deep branches. When performing distal access, the superficial femoral vein was punctured below the line separating the middle and proximal segments at a distance of at least 10 cm from the inguinal ligament. Confirmation of needle location in the femoral vein lumen was performed by aspiration sampling, followed by placement of the introducer. Atrial septal puncture was performed under fluoroscopic and ultrasound guidance (intracardiac or transesophageal echocardiography), followed by intravenous heparin until a target ACT greater than 300 s was achieved and was maintained throughout the procedure. After the puncture, contrasting of the left atrial cavity was performed during frequent ventricular stimulation (250-300 ms) to clarify the anatomy of the pulmonary veins and to estimate their diameter. During implantation of left atrial appendage occluding device through the transseptal introducer, a diagnostic pigtail catheter was inserted into the appendage cavity, contrasting of the left atrial appendage was performed to clarify its anatomy and to choose a fluoroscopy projection convenient for implantation, after which the transseptal introducer was replaced by the delivery system of either occluding device or cryoballoon according to the surgical intervention plan.

After the procedure is completed, manual compression hemostasis was performed for 10 minutes, then pressure bandage were applied to the cannulation areas. Hemostatic devices and suture techniques were not used in both groups. Transthoracic echocardiography was performed postoperatively to exclude fluid accumulation in the pericardial cavity, after which direct oral anticoagulants were resumed in the cryoballoon ablation group and combination therapy in the left atrial appendage occluding device group. Intraoperatively, data on the topographic-anatomic relationship of vessels, namely arteries and veins in the selected area of cannulation, the time required for puncture, the number of unintentional arterial punctures, the diameter of the used intraducers and their number were recorded. In addition, the residual length of the working part of the used transseptal intraducers device necessary for predilatation of the puncture hole was recorded.

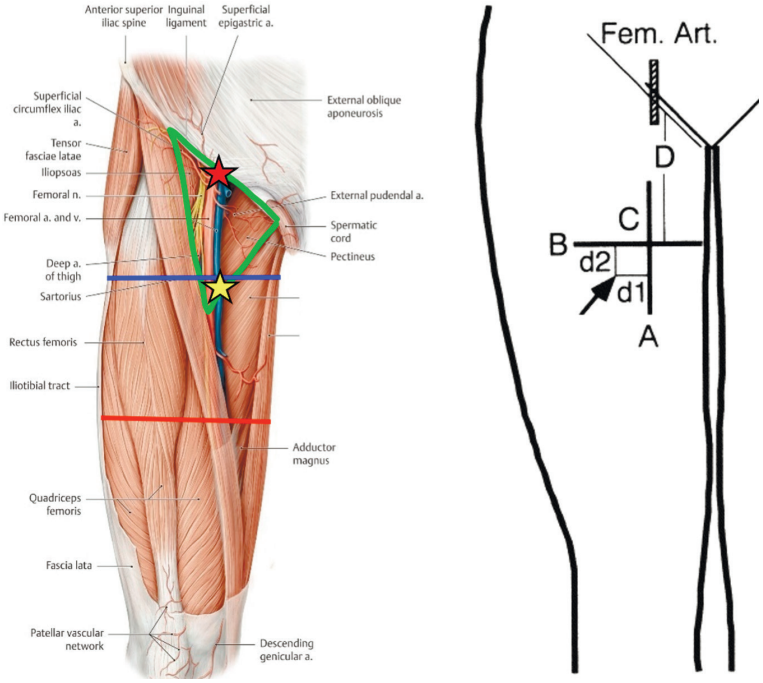


***Fig. 2. Femoral venous access technique: left - the femoral triangle (adapted from Atlas of Human Anatomy. Sinelnikov R.D., Sinelnikov Y.R., Sinelnikov A.Ya. 2009. Moscow); right - distal access technique (as described by Shigehito Sato et al., 1998). Note: The borders of the femoral triangle are highlighted in green. The blue line separates the proximal and middle segments of the femur, the red line separates the middle and distal segments. The red asterisk indicates the puncture area for classic access, yellow - for distal access, where A - long axis of the vessel, B - transverse line drawn at the level of the area with the most suitable topographic-anatomic relationships of vessels for puncture. Skin puncture is performed 2 cm lateral to line A (d1) and 2 cm below line B (d2).***

The Fast Cath Guiding Introducer SR0 and SL0 8/8.5F 63 cm (Abbott Medical, USA) and Transseptal Needle BRK-1 71 cm (Abbott Medical, USA), Medtronic Flex Cath Advance 15F cryoballoon delivery system (Medtronic Inc., Dublin, Ireland) (working length 65 cm) were considered standard length instruments. Longer length instruments include the Fast Cath Guiding Introducer SR0 and SL0 8F 81 cm (Abbott Medical, USA) and Transseptal Needle BRK-1 89 cm (Abbott Medical, USA), and the Boston Scientific DiRex 15.9F Delivery System (Boston Scientific Corporation, Marlborough, USA) (71 cm working length).

Patients in the standard puncture group maintained a horizontal body position for 12 hours after achieving hemostasis by manual compression; patients in the study group were active after no longer than 4 hours. Pressure bandages were removed after 12 hours in both

groups, then repeated duplex scanning of the lower limb vessels was performed to exclude deep vein thrombosis and postoperative complications.

In the pre- and postoperative periods, the patients' QoL and the intensity of back and leg pain syndrome were evaluated. The intensity of the pain syndrome was assessed by means of a visual analog scale (VAS), which is a straight-line segment 10 cm long with divisions from 0 to 10, where 0 is the absence of pain sensations, and 10 is unbearable pain. The intensity of pain syndrome according to the VAS is determined separately for the back and lower extremities.

The Russian-language version of the EQ-5D-5L questionnaire, consisting of two parts, was used to assess QoL. The form contains a health assessment in five areas (mobility, self-care, ability to perform activities of daily living, pain/discomfort, anxiety/depression) and allowed each section to be rated on a 5-point scale: 1 being taken as no problem, 5 being extreme severity. The second part was a VAS in the form of a 20-centimeter graduated line, on which the maximum bad health is taken as «0» and the maximum good health is taken as «100». The patients' quality of life was assessed preoperatively and after bandage removal in both groups.

The number of analgesics used, prescribed for pain syndrome in the back and cannulation area, as well as their effectiveness, the need for urine catheter placement associated with urinary retention, the number of infectious, hemorrhagic complications requiring hemotransfusion and repeated surgical interventions or interruption of antithrombotic therapy were recorded. Twenty-eight days after the intervention, the patients were interviewed by telephone: pain sensations in cannulation, possible delayed complications were clarified.

Statistical analysis was performed on a personal computer using Stata software (Version 15, StatSoft inc., USA). The Shapiro-Wilk test was used to test the normality of samples with quantitative variables. For quantitative measures, the mean and standard deviation or median with interquartile range were determined, and Student's t test or Mann-Whitney U-test were used for their comparison. Qualitative variables were described by absolute and relative frequencies (percentages). Pearson's criterion was used to compare qualitative indicators. Spearman's correlation coefficient (r) was calculated to determine the relationship between the parameters. Differences were considered statistically significant at a two-sided p value $< 0.05$.

The main aim of the study was to evaluate the effect of early activation of patients on quality of life compared to standard activation after 8-12 hours. In accordance with ultrasound usage for vascular puncture in both groups, no differences in the efficacy and safety of the different vascular access strategies were expected. It is known from the literature that up to 30-40% of patients experience pain in the back and access areas in the early postoperative period, with earlier activation within 4 hours reducing this percentage to 0-10%. An online calculator (clincalc.com/stats/samplesize.aspx) was used to calculate the sample size. Setting the confidence interval at 95% and the probability of first-order error equal to 0.05 required the recruit-

***Table 1.***

***Clinical and demographic characteristics of patients***

| | General group (n=85) | Distal puncture (n=47) | Standard puncture (n=38) | p |
|---|---|---|---|---|
| Age, years, M (min-max) | 61 (51-67) | 60 (50-67) | 63 (52-68) | 0.142 |
| Male gender, n (%) | 57 (67) | 27 (57) | 30 (79) | 0.03 |
| AF history, years M (min-max) | 3 (2-6) | 3 (1-5) | 4 (2-10) | 0.78 |
| $CHA_2DS_2$-VASc risk, points, M (min-max) | 2 (2-3) | 2 (2-4) | 2 (1-3) | 0.526 |
| HAS-BLED risk, scores, M (min-max) | 1 (0-1) | 1 (0-1) | 1 (0-1) | 0.09 |
| Height, cm, M (min-max) | 175 (169-180) | 173 (164-178) | 177 (172-180) | 0.37 |
| Weight, kg, M (min-max) | 89 (80-96) | 86 (79-95) | 90 (83-98) | 0.89 |
| BMI, $kg/m^2$, M (min-max) | 29 (27-31) | 29 (27-31) | 29 (27-31) | 0.47 |
| Right LE circumference, cm, M (min-max) | 56 ( 51-60) | 56 (52-60) | 56 (50-59) | 0.81 |
| Left LE circumference, cm, M (min-max) | 56 (51-59) | 56 (52-60) | 55 (50-59) | 0.97 |
| Hypertension, n (%) | 70 (82) | 39 (83) | 31 (82) | 0.9 |
| Coronary heart disease, n (%) | 9 (11) | 6 (13) | 3 (8) | 0.5 |
| Diabetes mellitus, n (%) | 10 (11) | 4 (11) | 6 (13) | 1.0 |
| Stroke, n (%) | 8 (9) | 6 (13) | 2 (5) | 0.3 |
| Additional therapy, n (%) | 13 (16) | 4 (9) | 9 (24) | 0.07 |
| LE varicose veins, n (%) | 16 (19) | 9 (19) | 7 (18) | 0.9 |
| Urinary system pathology, n (%) | 21 (25) | 11 (23) | 10 (26) | 0.8 |
| Musculoskeletal system pathology, n (%) | 45 (53) | 28 (60) | 17 (45) | 0.2 |
| Cryoballoon isolation of pulmonary vein orifices, n (%) | 71 (83) | 39 (83) | 32 (84) | 0.91 |
| Percutaneous occlusion of the left atrial appendage, n (%) | 14 (17) | 8 (17) | 6 (15) | 0.93 |

Note: AF - atrial fibrillation; BMI - body mass index; LE - lower extremity.

ment of 125 patients in each group to achieve statistically significant differences between groups.

## RESULTS

Eighty-five patients were included in the analysis, of whom 47 underwent distal puncture. The median age was 61 years (51.5-67.0 years). The paroxysmal form of AF was present in 73% of included patients, and the median duration of arrhythmia history was 3 years (2-6 years). Cryoballoon ablation procedure was performed in 84% of cases. Detailed information about the patients is presented in Table 1.

In the postoperative period, 95% of patients were on therapy with direct oral anticoagulants: 47% received apixaban (40% in the main group and 55% in the control group, p=0.2), 29% received rivaroxaban (36% in the main group and 21% in the control group, p=0.1), 18% received dabigatran etaxylate (21% in the main group and 16% in the control group, p=0.5); 6% of patients were on combination therapy (2% in the main group and 11% in the control group, p=0.1). No differences in antithrombotic therapy were noted between the groups.

In the distal puncture group, lateral location of the vein was observed in 81.6% of patients, whereas complete overlap was observed in 15.8% of observations. For the standard access group, the most frequent vessel relationship was the location of the vein on the medial side relative to the artery (81.2%), with complete overlap in 12.5% of observations (Table 2, Fig. 3). Complete arterial overlap of the vein on the right side was noted in 13 patients of the main group and 5 patients of the control group and did not differ significantly between the groups (p=0.1). On the left, complete overlap was observed in 7 patients in the main group and 6 in the control group and was also not significantly different (p=1). When comparing the groups, complete overlap was more frequently observed on the right side but did not reach statistical significance.

In both groups, all steps of the procedure were performed successfully. In the main group, unintentional arterial puncture was observed in 12% of cases, whereas in the control group it was observed in 9%. The differences did not reach a statistically significant difference. First attempt puncture was performed in 85% in the main group and 89% in the control group (p>0.05). The main reason for failure to provide access on the first attempt was arterial puncture.

The median time to distal puncture was 30 seconds (25-50 seconds) for the right limb and 35 seconds (21-70 seconds) for the left limb. In the standard puncture group, the median times were 33 (27-57 seconds) and 39 (30-60) for the right and left lower extremities, respectively. Time to access was not significantly different between groups for both limbs (p>0.05). Unintentional arterial puncture in both groups was more frequent when the vein was completely blocked by an artery for both the right and left lower limb, but the differences did not reach a statistically significant difference (p>0.05 and p=0.09 in the main group, p=0.24 and p=0.72 in the control group). Also, a slight increase in the time required for puncture was noted with this anatomy.

When correlation analysis was performed, neither body mass index (p=0.19) nor thigh volume (p=0.19 for the right and p=0.06 for the left lower extremity) affected puncture time or increased the number of unintended arterial punctures.

Stable hemostasis was achieved within 10 minutes of manual compression in both groups, and there was no need for heparin inactivation. All patients in the main group were activated up to 4 hours after the end of the procedure, whereas patients in the control group maintained a horizontal position for at least 12 hours. In 2 patients of the control group there was a need for repeated hemostasis due to bleeding from the puncture site within 4 hours from the end of the procedure, whereas in the main group no additional hemostasis was required.

According to duplex scanning of the lower limb vessels, no deep and superficial vein thrombosis after the procedure was detected in both groups. In one patient of the main group, the postoperative period was complicated by the development of a hematoma of the left lower limb, which was not accompanied by a decrease in hemoglobin level and did not require additional interventions. When intraoperative data were analyzed, complete arterial overlap of the vein was noted, which increased the time to access the vein to 80 seconds (with an average of 30 seconds in the distal access group). Also, in the distal puncture group, one patient developed hemopericardium in the early postoperative period, requiring drainage without conversion to open surgery.

The need to use transseptal introducer and longer delivery systems occurred only in the main group of patients and was not associated with height or distance from the inguinal ligament to the puncture site, nor did it lead to difficulties in performing the main stage of the procedure.

Analysis of back pain intensity revealed a statistically significant increase in VAS scores in the standard access group (0 points preoperatively vs. 2 points postoperatively, p<0.005). No such trend was observed in the main group (0 points preoperatively and 0 points postoperatively, p>0.05). In terms of pain in the puncture area, the preoperative VAS score in both groups was 0 points (p = 0.9). In the postoperative period, the pain score did not change in the main group, whereas in the control group the score increased to 2 (p=0.0024). The data on the visual analog scale of the EQ-5D-5L questionnaire

***Table 2.***

***Topographo-anatomic relationships of the vessels of the femoral triangle***

| | Medial vein location | | Lateral vein location | | Complete overlap | |
|---|---|---|---|---|---|---|
| | RL | LL | RL | LL | RL | LL |
| General group (n=85) | 29 | 28 | 43 | 25 | 13 | 18 |
| Distal puncture (n=47) | 1 | 1 | 39 | 25 | 7 | 13 |
| Standard puncture (n=38) | 28 | 27 | 4 | 0 | 6 | 5 |

Note: RL - right leg; LL - left leg.

are presented in Table 3. There were no significant differences in the components of the questionnaire between the groups.

Additional pain-related therapy was administered to 9 patients in the control group and 4 in the main group. In all cases, the drugs of choice were non-steroidal anti-inflammatory drugs. Pathology of the urogenital system was noted in 21 patients: 11 in the main group and 10 in the control group. Bladder catheterization for acute urinary retention was performed in 3 patients in the control group and 1 patient in the main group. No statistically significant difference was observed ($p>0.05$). No late complications or pain syndrome in the access areas were reported in both groups when patients were interviewed by telephone.

## DISCUSSION

According to the results, it can be concluded that the use of distal femoral venous access is not inferior in efficacy and safety to the standard femoral vein access but allows to improve QoL and reduce the frequency of additional therapy and urethral catheterizations.

The variability of the anatomic relationships of the femoral triangle vessels, namely the degree of arterial overlap with the vein and the location of the vein relative to the axis of the artery, often leads to difficulties in access, which is classically performed medial to the pulsation of the artery. The introduction of ultrasound-assisted access methods will reduce the number of complications to almost zero [13], as it allows a more detailed assessment of the topographic-anatomical relationships of the vein with adjacent arterial trunks and real-time tracking of the direction of the puncture needle.

According to the paper, the main factor associated with increased time to puncture was complete occlusion of the vein by the artery, which was also associated with an increased number of unintentional arterial punctures, potentially increasing local complications, and generally increasing local pain syndrome even without the development of complications. This relationship has been noted in earlier studies as well. The ULTRA-FAST study reported the development of arteriovenous fistula in a patient with complete arterial occlusion and an associated high number of inadvertent arterial punctures [14]. According to studies using multispiral computed tomography, the incidence of arterial vein occlusion can reach more than 60%; however, these data refer to the common femoral artery and vein located in the proximal femoral triangle [15]. In our study, the incidence of overlap in the proximal segment was 29%, with the vein passing distally to the lateral side from the artery, which facilitates puncture. Such an observation is consistent with data obtained in studies on the use of distal accesses in the ICU setting, especially pediatric ICUs.

The use of intraoperative ultrasound allows real-time diagnosis of complete overlap and selection of a more convenient area for puncture, which facilitates access and reduces local complications in the postoperative period.

Technically, performing distal access using ultrasound does not differ from standard access. The more frequent location of the vein on the lateral side of the artery dictates the need to enter the vessel with the needle directed from the lateral to the medial side, whereas with standard access, the needle is directed in the opposite direction. If the vein is completely occluded, it is more effective to perform the puncture with the needle directed from the lateral to the medial side.

In 2016, a group of authors led by Robert P. Richter published results on the use of distal femoral access in neonates with cardiovascular disease. Of the 31 patients, access was successfully performed in 92% of cases, and the mean number of attempts for access was 1. It should be noted that 11% of cases developed thrombotic complications, and 61% required systemic thrombolysis [16].

Distal femoral venous puncture was confirmed to be advantageous in a randomized trial that included neonates in the ICU with difficulty in placing peripheral venous lines. Patients were allocated in a 1:1 ratio to the axillary vein puncture group and the distal femoral venous access group performed under ultrasound guidance. A total of 60 neonates were included in the analysis. Successful puncture on the first attempt was significantly more common in the distal puncture group (77% vs. 37%, $p=0.001$). Also, distal puncture had advantages in terms of procedure time (309 vs. 523 seconds, $p<0.001$) and peri-procedural complications (4 vs. 12, $p=0.019$) [17].

A group of researchers from the Cancer Center of Wuhan University Hospital compared the placement of the central venous line by superficial femoral vein puncture in the middle third of the thigh with the use of superficial veins of the upper extremities in patients with superior vena cava syndrome. In both groups, access was performed using ultrasound-guided navigation. There were no significant differences in time and success on the first attempt ($p>0.05$). The number of infectious ($\chi^2 = 0.72$, $p>0.05$) and thrombotic complications ($\chi^2 = 0.28$, $p>0.05$) were not significantly different between groups [18, 19].

In our series, catheter steerability and procedural success did not differ between groups. However, when distal access was used in 17% of cases, a longer transseptal introducer length was necessary. No clear anthropometric predictors have been identified at this time. It should be noted that the average height of these patients was at least 179 cm, and the distance from the puncture hole to the inguinal fold was 13 cm. One patient in the control group also re-

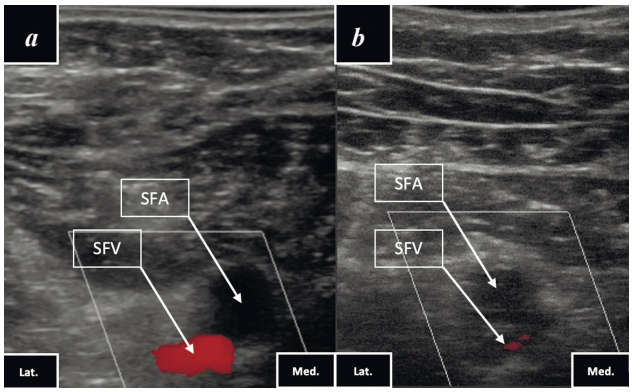


***Fig. 3. Topographic-anatomical relationships at distal access: a - location of the vein lateral to the artery, b - complete overlap of the superficial femoral vein with the artery. Note: Lat. - lateral femoral edge; Med. - medial femoral edge; SFA and SFV - superficial femoral artery and vein, respectively.***

quired the use of a long transseptal introducer; the patient's height was 182 cm.

The quality of life of patients in the postoperative period is considered in studies in isolation in terms of the impact of arrhythmic events on it. However, patients experience the most stress in the early postoperative period.

The topic of early activation looks quite relevant given the expanding indications for catheter procedures, including older patients with more comorbid pathology and, consequently, greater risks.

The peculiarities of management immediately after catheter procedures, namely the need to follow a special activity regime, are associated with the development of pain syndrome of various localizations, which causes emotional discomfort, has a negative immune effect, and can increase the length of stay of patients in hospital [20]. This issue has previously been insufficiently addressed in the studies conducted.

In this regard, adequate pain management is the cornerstone of postoperative management. Kerstin Bode first drew attention to the peculiarities of the course of the early postoperative period. In a prospective study performed, 61 of 102 included patients reported the development of pain syndrome, 44% of which was back pain; more than 90% required active therapy [21]. Nonsteroidal anti-inflammatory drugs are the drugs of choice for pain management; however, they increase the risks of acute kidney injury, gastropathies, and hemorrhagic events, which are more common in the older age group [22].

Considering the above, systems for vascular hemostasis of different designs were developed and tested: Angio-SealTM (Terumo Corporation, Tokyo, Japan), Perclose ProGlideTM (Abbott Laboratories, Abbott Park, IL, USA) ExoSeal1 (Cordis Corporation, Milpitas, CA, USA), VASCADE device (Cardiva medical inc., Santa Clara, USA). In a retrospective evaluation of VASCADE device use after cryoballoon ablations, where patient activation was performed within 2 hours, only 15 patients (4.9%) required bladder catheterization, whereas in the manual compression group, the procedure was performed in all patients. Subsequently, one patient with a diagnosed urethral injury required emergency surgical treatment. At follow-up, a higher incidence of infectious complications as well as urethral strictures was noted in the manual hemostasis group. Back pain syndrome and administration of analgesics were more frequently observed in the chiropractic hemostasis group [23].

However, hemostatic devices are not without disadvantages. This relates to their cost and concerns about the puncture technique and outcomes in patients requiring repeat procedures, which has not been tested in prospective studies. In our study, the distal access group recorded a significantly lower VAS score, which less often required additional analgesic therapy. In this regard, the use of distal femoral venous access appears to be a convenient and cost-effective alternative.

In addition, perioperative infusion support often leads to volume overload, requires the provision of comfortable conditions for urine evacuation, necessitating the need to perform bladder catheterization, which raises concerns in the focus of complications in the male group [24]. Minimizing the catheterizations performed can reduce the risks of genitourinary infection and traumatic urinary tract injury, and therefore reduce hematuria, dysuria, and the incidence of urethral strictures [25]. In numerous studies with both prospective and retrospective designs, catheterization avoidance significantly reduced the risks of problems such as urinary retention, need for repeat catheterization, hematuria, dysuria, urinary tract infection, and injury [26, 27]. The main risk factor for these complications is still age. Our center is committed to the tactics of maximal sharp catheterization, which in combination with a small sample does not currently provide definitive answers regarding the impact of access features.

When planning the study, there were concerns about the incidence of complications associated with lower extremity deep vein thrombosis due to direct damage to the vascular wall as well as venous stasis associated with intra-arterial placement.

The greater propensity for thrombosis, including venous thrombosis, in patients with AF and surgical stress must be considered [28]. Placing more introducers, especially large diameter ones, is a direct risk factor for thrombosis as reported by J.Y.Chen et al. (2004) in a prospective study of patients after catheter procedures, but did not increase the risk of thromboembolism [29]. The incidence of thrombosis in the routine use of duplex scanning after procedures ranges from 1 to 2% and varies depending on the type of procedure performed, as well as the duration of the procedure and the intra- and postoperative management of patients. According to the data of a systematic review, the detection of thrombosis after AF procedures is significantly lower despite the use of many vascular ports and, as a rule, a longer duration of surgery, which is associated with both intraoperative administration of heparin, especially against the background of continuous anticoagulation, and with the continuation of therapy in the postoperative period [30].

***Table 3.***

***Components of the EQ-5D-5L questionnaire***

| | Main group | | Control group | |
|---|---|---|---|---|
| | Before | After | Before | After |
| Mobility | 1 | 1 | 1 | 1 |
| Self-care | 1 | 1 | 1 | 1 |
| Habitual activities | 1 | 1 | 1 | 1 |
| Pain / Discomfort | 1 | 1 | 1 | 1.5 |
| Anxiety / Depression | 2 | 1 | 2 | 1 |

At present, there is no evidence that a revised strategy of antithrombotic therapy is needed in these patients and it usually resolves on its own at follow-up. A randomized study led by Dimitrios Karakitsos reported an increased incidence of deep vein thrombosis in emergency department patients with low femoral access, probably due to the smaller distal vein diameter [31]. However, according to our work using placement of larger diameter delivery

systems, no such complications were noted, which emphasizes the importance of anticoagulant therapy in the postoperative period. One of the leading risk factors is also prolonged immobilization of patients, aggravating the outflow of blood from the lower extremities, which also speaks in favor of early activation after catheter procedures.

The possibility of discharging patients after catheter-based treatment of AF on the day of the procedure is now widely discussed. Data from numerous studies indicate the safety and cost-effectiveness of early transfer of patients to outpatient follow-up [32-35]. The use of distal femoral access can further reduce economic costs as it does not require the use of additional consumables per se, without compromising patient safety. The main limitation of this work is the single-center nature of the study, and the inability to blind these patients due to different activation times.

## CONCLUSION

According to the preliminary data of the study, the use of distal femoral venous access in catheter-based treatment of AF is not inferior to standard access in terms of efficacy and safety. Distal access allows to activate patients in the earliest postoperative period, which has a positive effect on QoL without requiring additional treatment costs. However, final conclusions regarding the methodology can be made after the study is completed. Patient enrollment is currently ongoing.

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# RESYNCHRONIZATION THERAPY: RESULTS OF THE 2 YEAR FOLLOW-UP

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**Aim.** Cardiac contractility modulation (CCM) is a device therapy for patients with heart failure with reduced ejection fraction (HFrEF), most of the data on its programming are concerned patients with narrow QRS and of limited follow up. Our aim was to propose programming approach for Optimizer device in setting of wide QRS complex and fragmented ventricular local activation.

**Methods.** We enrolled 11 patients with HFrEF (median age, 8 males, median NYHA class 3) and LBBB-related wide QRS complex, who underwent Optimizer™ device implantation. Three patients got Optimizer™ IV system and eight patients were implanted Optimizer™ Smart. Ten patients were previously implanted with CRT-D due to HFrEF and LBBB; one patient received CRT-D after Optimizer™ implantation.

**Results.** During the implantation procedure ventricular local sense (LS) channel signal fragmentation was detected in all patients. In five patients signal detection was optimized by lead relocation. In six patients LS signal sensitivity limitations were resolved by programming. At two-year follow-up survival 4 patients died of noncardiac causes (1 intracranial hemorrhage, 1 gastrointestinal bleeding and 2 - terminal kidney failure). At 12-month follow-up we observed a non-significant improvement in 6-minute walking distance (300 vs 305, p=0.093), NYHA class (2.75 vs 2, p=0.085), MLHF score (53 vs 42, p=0.109) and left ventricular ejection fraction (LVEF) (30 vs 33.5, p=0.212).

**Conclusion.** CCM system implantation is feasible and safe in patients with HFrEF and LBBB-related wide QRS complex. Device programming maneuvers can resolve the challenges of ventricular local signal detection in these patients.

**Key words:** heart failure; cardiac contractility modulation; wide QRS; left bundle branch block; cardiac resynchronization therapy

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Cardiac contractility modulation (CCM) is a relatively new method (the Optimizer™ system by Impulse Dynamics, Orangeburg, NY, USA) used to treat patients with heart failure with reduced ejection fraction (HFrEF).

CCM is an invasive treatment that involves implantation of a pulse generator and two ventricular electrodes into the myocardium of the interventricular septum on the right ventricular side. Therapy consists of applying biphasic stimulation to the myocardium of the interventricular septum during the period of absolute refractoriness. High-amplitude pulses (7.5 V with a stimulus duration of 5.14 ms) are applied approximately 30 ms after the onset of the QRS complex and do not initiate a new ventricular contraction. The effect of CCM on cardiomyocytes normalizes cellular calcium metabolism without increasing myocardial oxygen demand, as has been shown in in vitro studies [1].

Data from clinical trials indicate a reduction in the severity of heart failure (HF) symptoms and a decrease in the number of hospitalizations due to decompensation in patients with New York Heart Association (NYHA) functional class (FC) II-IV and left ventricular ejection fraction (LVEF) <40% [2-5]. In the performed meta-analysis of these studies, improvements in exercise tolerance and quality of life were confirmed; however, no indication of a positive effect on patient prognosis and left ventricular remodeling was demonstrated [6, 7].

The relatively large studies performed to date have included only patients with a narrow QRS complex. Data on the use of in patients with a wide QRS complex are limited. H.Nagele et al (2008) [8] and J.Kuschyk et al (2019) [9], which included sixteen and seventeen patients respectively, showed the potential for implantation of CCM in

patients who have not responded to cardiac resynchronization therapy (CRT). All patients in these studies had sustained sinus (or artificially atrial) rhythm, and follow-up periods were predominantly limited to 6 months.

The aim of this work was to evaluate the use of CCM systems in patients with wide QRS complex, the clinical effect and the interaction between implanted CCM systems and CRT.

## METHODS

Eleven patients with HFrEF and persistent HF symptoms at NYHA II-IV FC and wide QRS complex on external ECG were implanted with CRT and CCM systems (Optimizer IV (n=2) and Optimizer Smart (n=9) (Impulse Dynamics, Orangeburg, NY, USA) from December 2016 to November 2019.

Inclusion criteria were age >18 years, HFrEF with NYHA ≥ II FC, presence of implanted CRT-D and no increase in LVEF (less than 5%), decrease in end-systolic volume (less than 15%), NYHA reduction of I or more, after CRT-D implantation, QRS complex width after CRT-D implantation ≥130 ms.

Exclusion criteria included waiting for heart transplantation, myocardial infarction, coronary artery bypass surgery or angioplasty with coronary artery stenting less than 3 months before inclusion, acute myocarditis, hypertrophic cardiomyopathy, reversible causes of heart failure, mechanical tricuspid valve, severe comorbid pathology.

Implantation and device programming

The devices were implanted under local anesthesia with lidocaine (10 mg/mL). The incision was performed in the subclavian region. Electrodes through the subclavian vein were guided to the heart. Optimizer IV devices were implanted - with three electrodes: one atrial (Boston Scientific 7741 Ingevity IS-1 52cm) and two ventricular (Boston Scientific 7742 Ingevity IS-1 59cm (Boston Scientific, Massachusetts, USA) or St Jude Tendril STS IS-1 59 cm (St. Jude Medical, Minnesota, USA)); and Optimizer Smart - with two ventricular electrodes (Boston Scientific 7742 Ingevity IS-1 59cm (Boston Scientific, Marlboro, Massachusetts, USA) or St Jude Tendril STS IS-1 59 cm (St. Jude Medical, Saint Paul, Minnesota, USA)). The atrial electrode was fixed in the region of the right atrial appendage, ventricular electrodes were fixed in the interventricular septum on the right ventricular side. The distance between ventricular electrode implantation sites was at least 2 cm. In the presence of implanted shock electrode CRT-D in the region of the right ventricular apex or interatrial septum, the distance between it and the nearest ventricular electrode of the modulator was also more than 2 cm. Parameters at the electrodes were tested using a Medtronic CareLink 2290 external analyzer (Medtronic, MN, USA) and after connection to an CCM pulse generator using an OMNI™ II Programmer (Impulse Dynamics, NY, USA).

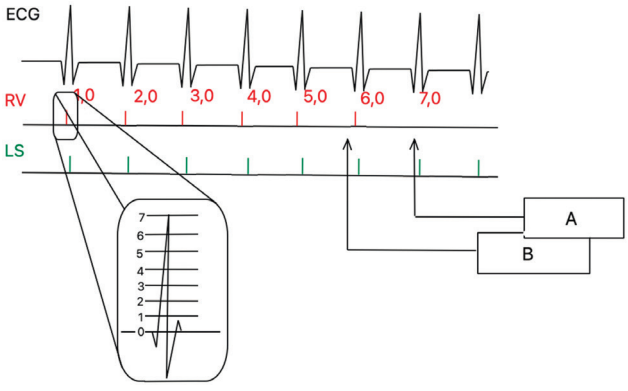


***Fig. 1. Determination of sensitivity on the RV channel. Note: during control by ECG on both electrodes events are recorded, which are recognized by the system, gradually increasing the sensitivity parameter on the RV-channel, the maximum amplitude of the local activation signal recognized by the system is determined. RV, LS - diagrams marking the recorded events on the corresponding ventricular electrodes, A - maximum sensitivity parameter, B - hyposensing on the RV-channel.***

When programming the devices, the main point was to adjust the sensitivity on the ventricular channels (hereinafter labeled as RV and LS channel) and the algorithm for discrimination of «normal» and abnormal contraction. Determination of the sensitivity amplitude was performed by gradually increasing the sensitivity value until the next ventricular channel event was no longer labeled by the system (Fig. 1). The sensitivity level and time intervals of the discrimination algorithm were set individually for each patient. The sensitivity on the LS channel varied from 5.4 to 24.5 mV. The peculiarity of sensitivity tuning on LS turned out to be a pronounced fragmentation of the local activation signal (Fig. 2).

When the system was turned on, the initial amplitude of the therapy delivery was 5 V, and when the therapy was satisfactorily tolerated, the amplitude was increased to 7.5 V. In case of poor tolerance to stimulation, the symptom-related electrode was repositioned. After the procedure, a «cross-talk» test was performed, for the interaction between the two devices (CRT and CCM).

The minimum follow-up period was 24 months with outpatient visits at 2, 6, 12, 18, and 24 months. Verification, and if necessary, adjustment of both devices (CCM and CRT-D), consultation with a heart failure specialist, echocardiography, and six-minute walk test were performed at all visits at 6 and 12 months. From 2020, the follow-up protocol was modified due to events resulting from the Covid-19 pandemic. 8 out of 11 patients received telephone counseling without outpatient visits at 18 and 24 months after implantation.

**Statistical analysis**

Statistical analysis was performed using the Stata program (v15.0 for Windows, StataCorp., USA). Median and interquantile spread were used to describe quantitative variables, while qualitative variables were described by absolute and relative frequencies (percentages). The Wilcoxon sign rank test was used to assess the significance of the indicators. Differences were considered statistically significant at two-sided p values <0.05.

## RESULTS

**Patient characteristics**

Eleven patients with HFrEF and wide QRS who were implanted with Optimizer IV (2 patients) and Optimizer Smart (9 patients) devices were included in the study. Device implantation was performed from December 2016

through November 2019. The median age of the patients was 61.5 years, 8 males. The median NYHA FC was 3 [2;3], median LVEF was 30.0% [24.0;32.75], median QRS complex width was 167 ms [158;180], and median 6-minute walk distance was 300 meters [180;310]. Ten patients had an implanted CRT-D at the time of inclusion. Almost all patients had >95% biventricular stimulation, patient #7 had a significant burden of polymorphic premature ventricular complexes (9 thousand per day). Iron deficiency anemia, suboptimal AV delay programming were excluded. One patient had a narrow QRS complex at the time of cardiac contractility modulator implantation. At 6 months after implantation, at the scheduled visit, the ECG showed a dynamic increase in QRS duration up to 150 ms with morphology of LBB blockade, and therefore the patient was implanted with CRT-D. Most patients had atrial fibrillation (AF) (9/11), two had persistent AF at the time of CCM implantation. All patients were receiving maximally tolerated heart failure therapy at the time of CMM system implantation, and left ventricular CRT electrodes were implanted in the lateral or posterior veins of the heart according to fluoroscopy. The baseline characteristics of the patients are presented in Table 1.

**Device implantation**

Successful implantation of the devices was performed in all patients. At intraoperative sensitivity tuning on the LS channel, pronounced fragmentation of local myocardial activity was registered in all patients (example - Fig. 1 B: 1 cardiac contraction corresponds to 3 separate events on the LS channel). Similar findings were revealed both against the background of their own rhythm in patients with preserved atrioventricular conduction and against the background of biventricular stimulation. In five patients, monolithic adhesions of local activation were achieved after repeated repositioning of the electrode. In six patients, electrode repositioning did not result in a significant change in the local activation pattern. The procedure time was 90 minutes [80;135].

**Follow-up**

Seven patients completed the two-year follow-up. Four patients (36.4%) died due to noncardiac causes: intracranial hemorrhage (11 months after implantation), gastrointestinal bleeding (2 months after implantation), two patients - terminal renal failure (at the 18th and 22nd month of follow-up), in patient #4 - renal failure was considered because of HF, in patient #5 - as an outcome of long-term chronic pyelonephritis.

**Device programming**

The median duration of therapy application in patients was 7.5 hours/day [7.0; 10.5]. The target volume of applied therapy (>90%) at interim visits was achieved in 8 patients (72.7%) and maintained for at least 12 months after implantation. A prerequisite for the application of CCM therapy is a sustained ventricular rhythm that the device would consider «normal». «Normality» of each heartbeat is determined by the interval between the local activation times at the RV and LS electrodes. The parameter that is responsible for discrimination is the Alert interval (referent is the time of local activation at the RV electrode, «alert start» is the time from the moment of activation at the RV to the beginning of the interval, «alert width» is the duration of the interval). If activity is logged on the RV, activity is expected to be logged on the LS channel in the «Alert» interval. A reduction is considered «normal» when the local activation on the LS channel falls within the «Alert» interval. Fragmentation of the signal on the LS-channel and, therefore, registration of more than one signal in the «alert» interval leads to the error «Double LS» (Fig. 3) - double signal perception. This circumstance required a tuning correction, for which the following tactic was used.

During sensitivity scanning on the LS channel (see Fig. 2), the morphology of the commissure of myocardial contraction was assessed by recording the number of isolated events on the LS channel during 1 cardiac contraction. The signal on the LS channel was defined as either monolithic (single) or fragmented (more than one isolated signal corresponds to a single reduction). The optimal level of sensitivity was determined by the maximum time interval between the end of the penultimate event and the beginning of the last event on the LS channel. Then, taking the event on the RV channel as a reference, we set the parameters of the «Alert» time interval as «Alert start» and «Alert width» so that the Alert interval starts no earlier than the middle of the interval between the last and previous event on the LS channel, defined as: X=B-A, where X is the in-

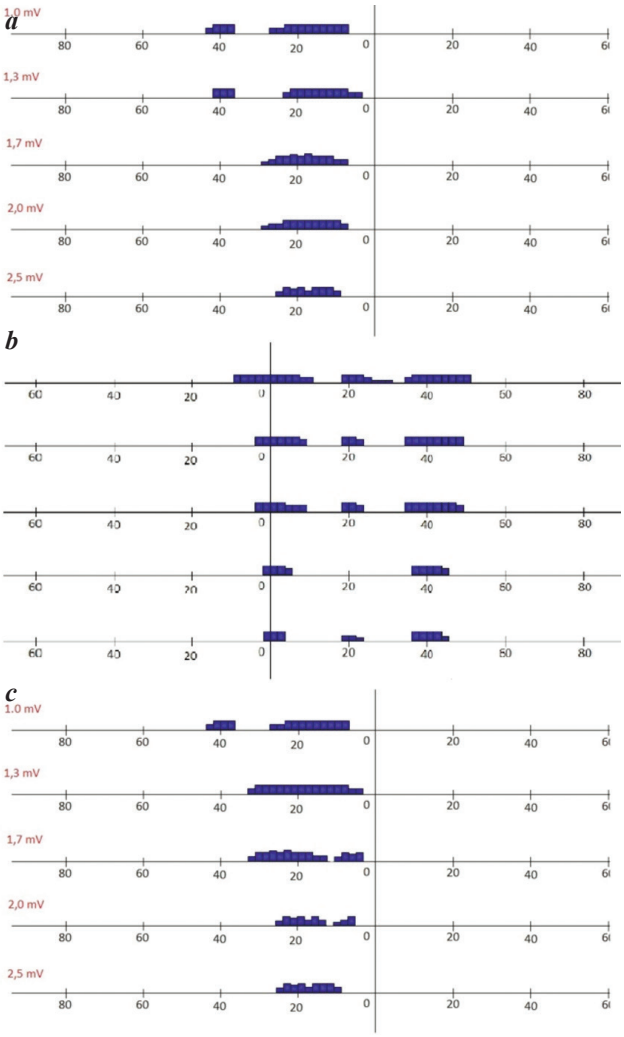


***Fig. 2. Sensitivity setting screen on LS-channel. Note: a - monolithic activation spike, b - pronounced fragmented activation spike - two/three separate events corresponding to one heartbeat, c - partial fragmentation of ventricular signal spike.***

terval between events on the LS channel, «A» and «B» are the end time of the penultimate event and the beginning of the last event on the LS channel, respectively (Fig. 4).

Patient #10 (Optimizer IV implanted) initially demonstrated close to 100% effective therapy delivery during device setup, against the background of which he noted an improvement in his well-being. The patient presented with a persistent AF for 6 months after device implantation. The development of AF stopped the application of therapy because a regular atrial rhythm was required for the Generation IV Optimizer to work. An attempt to restore rhythm by external cardioversion was ineffective. It was decided to refrain from performing catheter isolation of the pulmonary vein orifices due to the extremely high probability of surgical complications. The setting of the CRT-D and CCM was modified as follows. The sensitivity of the atrial electrode is maximized so that the CRT-D, ignoring the FA rhythm, applies sequential atrial-ventricular stimulation. The sensitivity of the atrial CCM channel was also increased to record only the artifact of atrial stimulation. Thus, an attempt was made to «mimic» a regular atrial rhythm to ensure stable Optimizer IV operation. Nevertheless, this adjustment resulted in a 44% CCM stimulation percentage.

Patient #6 died 2 two months after device implantation from gastrointestinal bleeding. Device verification and functional performance evaluation were not performed.

During the first outpatient checkup in patient #7 2 months after implantation, transient ventricular conduction disturbances were detected accompanied by fragmentation of the local activation signal recorded on the LS-channel. Attempts to program the device did not increase the percentage of CCM stimulation above 40%.

No episodes of CCM recording interpreted as ventricular rhythm disturbances were recorded during checks of implanted CRT-D.

In patient #9 (Boston Scientific 7742 Ingevity IS-1 59 cm and Optimizer Smart electrodes implanted), 1.5 and 2 years after implantation of the CCM system, bed stimulation was detected when delivering therapy from the RV and LS channels, respectively. The patient underwent revision of the modulator bed, and no mechanical defects of the electrodes were found on inspection. It was decided to form a separate bed for the electrodes and for the body of the device. No bed stimulation was noted after relocation of the electrode loops to a separate bed and inclusion of therapy. This patient continues to be followed up and at the time of publication 3 years after revision, no bed stimulation is noted.

**Echocardiography, quality of life, exercise tolerance**

During follow-up, there was no significant improvement in NYHA FC (3 [2;3] vs 2 [2;3] p=0.085), LVEF

***Table 1.***

***Initial characteristics of patients***

| | Patient (#) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
| Date of CCM implantation, m/y | 11/18 | 12/18 | 12/16 | 11/18 | 12/18 | 12/18 | 9/19 | 12/18 | 5/17 | 12/16 | 11/19 |
| Date of implantation of CRT-D, m/y | 6/19 | 6/16 | 6/16 | 2009 | 12/14 | 6/16 | 07/15 | 6/16 | 11/12 | 11/12 | 7/19 |
| Device type | smart | smart | IV | smart | smart | smart | smart | smart | smart | IV | smart |
| Age, years | 67 | 69 | 68 | 67 | 66 | 66 | 61 | 61 | 60 | 59 | 57 |
| Sex | m | f | m | m | m | m | f | m | m | m | f |
| QRS length, ms | 150 | 170 | 130 | 210 | 158 | 174 | 167 | 180 | 160 | 180 | 160 |
| CAD | yes | yes | yes | no | no | no | no | no | yes | yes | no |
| Hypertension | yes | yes | yes | no | no | no | no | yes | yes | yes | no |
| Atrial fibrillation | yes | yes | no | yes | yes | yes | yes | yes | no | yes | yes |
| NYHA | 4 | 4 | 3 | 3 | 2 | 4 | 3 | 2 | 2 | 2 | 3 |
| LVEF, % | 24 | 32 | 30 | 33 | 20 | 29 | 31 | 28 | 33 | 30 | 24 |
| 6-minute walk distance, meters | 200 | 315 | 180 | 300 | 400 | 340 | 200 | 390 | 300 | 310 | 100 |
| MLHF, points | 60 | 53 | 23 | 33 | 40 | 52 | 74 | 39 | 39 | 57 | 55 |
| Pharmacotherapy of heart failure | | | | | | | | | | | |
| ACEI/ARB/ARNI | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes |
| Beta-adrenoblocker | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes |
| Loop diuretics | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes |
| MRA | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes | yes |
| Digoxin | yes | yes | no | yes | no | no | no | no | no | no | yes |
| Amiodarone | no | no | no | yes | no | no | no | yes | no | yes | no |

Note: m/y, month, and year; CCM - cardiac contractility modulation; CRT-D - cardiac resynchronization therapy with defibrillator function; LVEF - left ventricular ejection fraction; MLHF - Minnesota Heart Failure Quality of Life Questionnaire; ARA - angiotensin-receptor antagonists; ARNI - angiotensin receptor angiotensin and neprilysin inhibitor; ACEI - angiotensin-converting enzyme inhibitors; MRA - mineralocorticoid receptor antagonists.

(30 [24.0;32.75] % vs 30.4 [25.25;35.75], p=0.212) and 6-minute walk distance (300 [180;310] vs 300 [270;320] p=0.095) 12 months after implantation. Regurgitations on mitral (2 [2;3] vs 2 [2;3] vs 2 [2;3] and tricuspid (2 [2;3]) vs 2 [1;3]) remained the same. There was also no significant improvement in NTproBNP (1319 [185;3760] vs 916[173;1165] p=0.225) and Minnesota Heart Failure Quality of Life Questionnaire (53 [36.0;58.5] vs 42 [30.0;53.5] p=0.109).

## DISCUSSION

Our study evaluated the feasibility and efficacy of CCM in patients with wide QRS complex with LBBB and persistent circulatory failure despite optimal drug therapy. Previously performed randomized controlled trials included only patients with narrow QRS [2-5]. The currently published observational studies of patients with an implanted CCM device and wide QRS included only patients with sinus rhythm or sustained atrial stimulation and were limited to a short follow-up period [8, 9]. In addition, these works did not describe the nature of the local activation signal changes or the results of CCM programming.

The proportion of patients not responding to CRT remains significant in both randomized and observational studies, and the cause may be atrial or ventricular rhythm disturbances, inadequate device settings, implantation of a left ventricular electrode in a non-target vein, and iron deficiency anemia [10]. In our study group, predictors for lack of response to resynchronization therapy were only in 3 patients (significant ventricular ectopy burden in patient #9, presence of persistent AF in patients #1 and #4). However, although the remaining patients had predictors of response to CRT (achieving biventricular stimulation >95%, ensuring sinus rhythm or adequate atrial stimulation, adequate device settings, titration of drugs to maximum tolerated dosages, and exclusion of iron deficiency), there was also no clinical benefit to CRT-D implantation. Patients had both ischemic and non-ischemic genesis of heart failure. Among the patients with CAD, only two suffered an anterior-posterior localization infarction. The lack of response may have been due to the terminal nature of heart failure and lack of contractile reserve.

In these clinical cases, we attempted to improve the condition of patients who did not respond to maximally tolerated pharmacologic and resynchronization therapy. When analyzing the literature, we were unable to find a description of the features of implantation of the CCM system in patients with CRT or their setting. The patients underwent surgery without any peculiarities. In addition, implantation of devices with two additional electrodes into the interventricular septum did not worsen regurgitation at the tricuspid valve.

The main feature we encountered during device implantation is fragmentation of the ventricular signal recorded by the device. Such signal fragmentation in patients with LBBB has been previously described in electrophysiologic mapping of interventricular septal myocardium in patients with LBBB [11]. The most likely cause of ventricular signal fragmentation may be myocardial fibrosis or LBBB-associated intraventricular conduction abnormalities. The same reason may be the presence of multipolar stimulation of the ventricular myocardium in patients with CRT-D. When analyzing the available literature, we did not find a description of the algorithm of CCM programming in this situation.

Ventricular signal fragmentation was noted in all patients, in five patients the situation resolved after repositioning of the electrode. In a proportion of patients, the change in sensitivity level was sufficient to achieve the target amount of applied therapy. However, in patients with pronounced signal fragmentation, changes in parameters of both the stimulation level and the parameters defining the Alert readiness window and refractoriness window for the LS channel were required.

The development of persistent AF in patient #10 with the Generation IV Optimizer prevented an assessment of the potential efficacy of therapy. Lack of stable rhythm in the atria led to inhibition of therapy, which was accompanied by worsening exercise tolerance. Similarly to the described method of S.Roger et al (2014) [12] we increased the sensitivity and amplitude of stimulation on the atrial channel of CRT-D. Although the described work indicates 60-95% successfully applied therapy, in our observation the percentage of effective stimulation was 44%. The latest generation of devices, the Optimizer Smart, does not require implantation of an atrial electrode, thus eliminating such complications in the future.

Electrode repositioning and/or correction of device parameters resulted in achieving the target stimulation

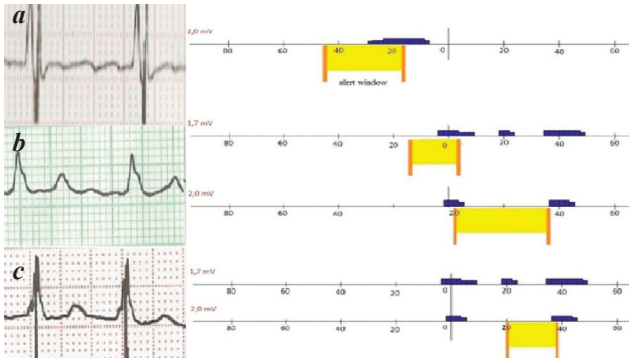


***Fig. 3. ECG and alert window positioning. Note: a - patient with monolithic signal of local activation on LS channel, b - patient with fragmented signal, «double LS» marker and inhibition of therapy, c - patient with fragmented signal and successful application of therapy.***

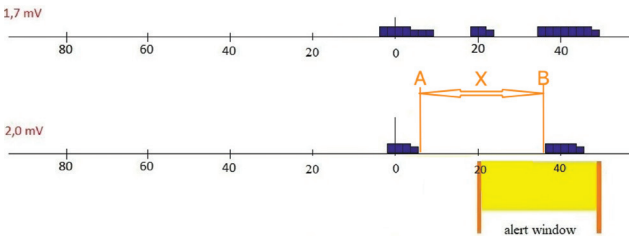


***Fig. 4. The scheme of setting the «Alert» window when there are two or more events on LS channel, where X is the time interval between events on LS channel, A is the time of the end of the penultimate event, B is the time of the beginning of the last event on LS channel, X=B-A, «Alert start» > X/2.***

percentage (>90%) in 73% of cases. Despite successful implantation and device customization, patients in our study did not demonstrate meaningful clinical or functional improvement. In view of the lack of proven effects on myocardial contractility of CCM therapy in randomized trials [2-5], and the absence of RCTs evaluating the combined use of CRT and CCM, routine implantation of these systems in patients who have not responded to optimal drug therapy and CRT may be considered as a desperation therapy.

Our findings and programming approach may be useful in exceptional cases - when CRT needs to be implanted in patients with implanted CCM to preserve the clinical effect of cardiac contractility modulation, or when CCM systems are implanted in patients with a wide QRS complex who do not meet the criteria for CRT implantation.

**Limitations of the study**

This paper is a retrospective analysis of data from a small number of patients; moreover, only patients with LBBB were included in this analysis. It should be noted that outpatient visits at month 18 and 24 in a portion of patients were replaced by a telephone call due to restrictions related to the Covid-19 pandemic.

## CONCLUSION

Implantation of CCM devices in patients with HFrEF, QRS complex dilation on the background of complete LBBB is possible and safe. The peculiarities of intraventricular conduction and the presence of CRT may require additional tuning of the CCM. The use of CCM in patients who did not respond to CRT did not lead to significant positive dynamics of echocardiographic parameters and quality of life.

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https://doi.org/10.35336/VA-1160

# THE EFFECTIVENESS OF THORACOSCOPIC TREATMENT OF NON-PAROXYSMAL ATRIAL FIBRILLATION

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**Aim.** To evaluate the efficacy of thoracoscopic ablation (TSA) of persistent and long-standing atrial fibrillation (AF) in the long-term follow-up period.

**Methods.** TSA of AF with unilateral left atrial appendage exclusion was performed in 50 patients with persistent (group I) and 50 patients with long-onset AF (group II). Efficacy was defined as the absence of any atrial tachyarrhythmia (atrial fibrillation, atrial flutter, or supraventricular tachycardia) lasting more than 30 seconds recorded on Holter ECG monitoring at study controls.

**Results.** TSA was 78% effective in group I and 63% effective in group II over the three-year follow-up period (p=0,037). Catheter ablations 3 months after TSA were required in 8 (16%) patients in group I and 9 (18%) in group II (p>0,05), of which two patients had typical atrial flutter on ECG, which required radiofrequency ablation of the cavotricuspid isthmus. The efficacy of staged treatment of AF at 3 months after additional catheter ablation was 100% and 88,2% after 6 months.

**Conclusion.** Video-assisted thoracoscopic ablation of atrial fibrillation should be considered a promising approach for the management of persistent and long-standing atrial fibrillation.

**Key words:** atrial fibrillation; toracoscopic ablation; persistent form; long-standing atrial fibrillation

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Atrial fibrillation (AF) is the most common tachyarrhythmia, its incidence in the general population is 1-2% among all cardiac arrhythmias [1-3]. An increase in AF patients is expected over the next few years, due to the rapid demographic aging of the population. AF is associated with a high risk of ischemic strokes, heart failure and is an independent predictor of mortality [1, 4, 5].

An urgent problem of modern arrhythmology is the search for highly effective, minimally invasive methods of treatment of isolated nonparoxysmal forms of AF, which account for up to 70% of all forms of AF [6].

For a long time, surgery was considered the only highly effective method for the treatment of AF. In modern arrhythmology, Cox-Maze IV surgery and its modifications are considered exclusively as an additional procedure in cardiac surgery [1, 7-9].

Thanks to the work of M.Haïssaguerre et al. (1998) [10], it was established that the main target of catheter ablation in AF should be considered pulmonary veins (PV), but the effectiveness of radiofrequency ablation in persistent forms of AF was extremely low [1]. Electroanatomical mapping data in patients with nonparoxysmal forms of AF usually demonstrate areas of marked low-amplitude activity in the left atrium (LA) [11]. In such cases, the long-term success rate of catheter ablations is 20-60%, decreasing with each subsequent procedure [12, 13]. Consequently, alternative surgical treatments have been developed that are closer in efficacy to the Cox-Maze procedure, but with a lower complication rate. Video-assisted thoracoscopic ablation (TA) of AF is an alternative surgical method for the treatment of isolated forms of AF in the working heart [1, 14]. Currently, thoracoscopic ablation of AF includes isolation of PV, fragmentation of the posterior wall of the LA (Box lesion technique) and amputation of the PV appendage [1, 15-18], but its efficacy varies considerably from 38 to 83% due to heterogeneity of patients, surgical technique, and follow-up period [17, 19, 20].

The aim of the present work was to evaluate the efficacy of thoracoscopic ablation of persistent and long-term persistent forms of atrial fibrillation in the long-term follow-up period.

## METHODS

Thoracoscopic ablation of AF with one-stage amputation of the LA appendage was performed in 100 patients

with persistent and long-term persistent form of AF included in the study. All patients were divided into two groups: group I included 50 patients with persistent form of AF, group II included 50 patients with long-term persistent form of AF.

All patients underwent complex examination before surgery, including: electrocardiogram (ECG), Holter monitoring (HM), transthoracic echocardiography (Echo), transesophageal Echo 24 hours before surgery and intraoperative control after LA appendage amputation, multispiral computed tomography with PV and LA contrast, coronary angiography.

Patient inclusion criteria: (1) symptomatic persistent (lasting more than 7 days to 1 year) and long-term persistent form of AF (lasting more than 1 year) [1, 2]; (2) EHRA symptom class III-IV.

Exclusion criteria: (1) paroxysmal form of AF; (2) symptomatic ischemic heart disease and hemodynamically significant coronary artery stenoses detected by coronarography; (3) acquired heart defects; (4) acute cerebral circulatory disorder of less than 6 months' duration; (5) left ventricular ejection fraction less than 40%; (6) chronic diseases in decompensation stage; (7) traumas and operations on chest organs.

The efficacy of the procedure (primary endpoints of the study) was determined every 3, 6, 12 months and annually thereafter by HM. The procedure was considered successful in the absence of any atrial tachyarrhythmia (atrial fibrillation, atrial flutter, or supraventricular tachycardia) lasting more than 30 seconds [1, 2, 16]. ECG recording was recommended for any symptomatic rapid non-rhythmic heartbeat. The "blind period" during the first 3 months after surgery was excluded from the study.

Secondary endpoints of the study were considered to be: major adverse cardiovascular events (MACE), operation time, ventilator time, hospitalization period (bed days), intra- and postoperative complications. The study design is shown in Fig. 1.

Before surgery, at least 5 days before surgery, all patients from new oral anticoagulants or warfarin were switched to low molecular weight heparins. Anticoagulant therapy with warfarin (target INR (2-3) or direct anticoagulants was started the day after surgery. No correction of antiarrhythmic therapy (AAT) was performed preoperatively. The preoperative Vaughan-Williams distribution of antiarrhythmic drugs is summarized in Table 1. In the absence of contraindications postoperatively, all patients received amiodarone. All medications were recommended to be continued for up to 3 months.

Prior to surgery, all patients were discussed in a consilium with a cardiologist, arrhythmologist, and cardiac surgeon. Participants gave informed consent to undergo video-assisted thoracoscopic ablation of AF. The study was approved by the local ethical committee.

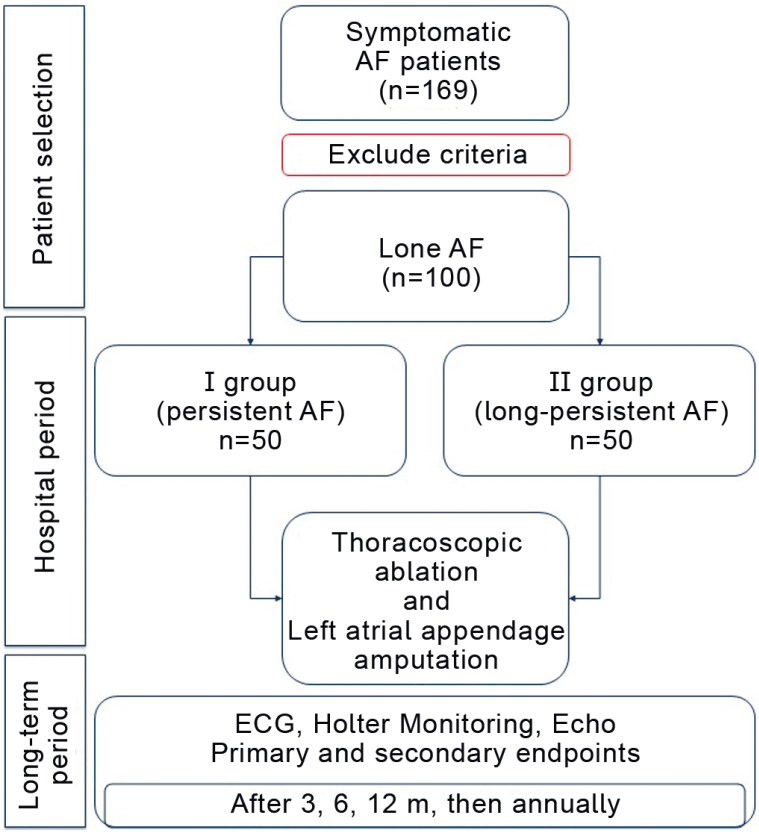


***Fig. 1. Study design. Note: AF - atrial fibrillation, ECG - electrocardiogram, m - month.***

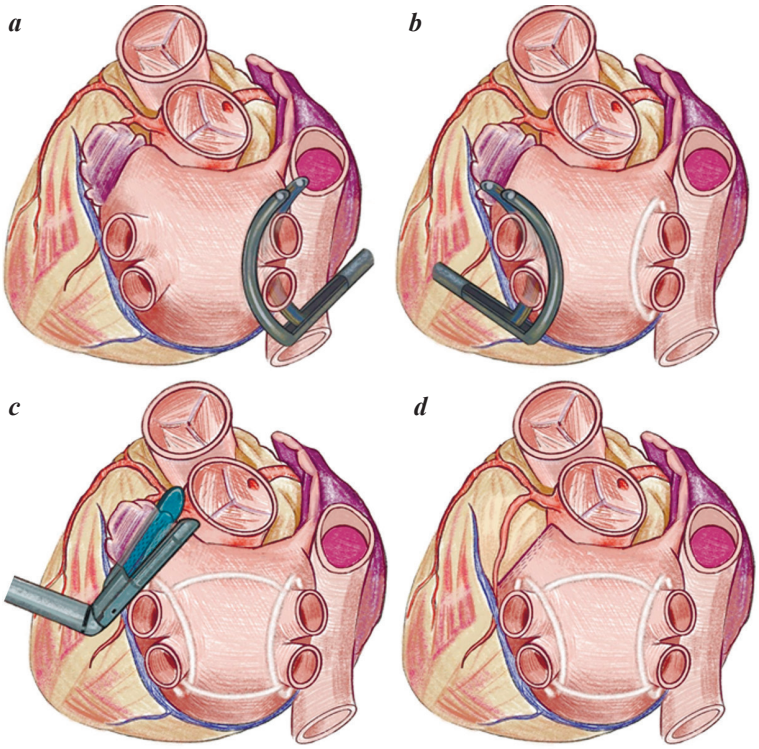


***Fig. 2. Stages of surgery. Note: a - radiofrequency ablation of the right pulmonary veins, b - radiofrequency ablation of the left pulmonary veins, c - fragmentation of the posterior wall of the left atrium according to the scheme «Box lesion», amputation of the left atrial appendage with the help of endostepler, d - final scheme of ablation lines.***

**Surgical technique**

All operations were performed in the cardiac surgical operating room by one surgical team, under general anesthesia with selective lung ventilation. The procedure was performed according to the Box lesion scheme (Fig. 2) [19]. PV isolation was performed using an ablation bipolar clamp (AtriCure, Inc., West Chester, Ohio, USA). Ablation was performed under impedance control. When the impedance decreased, the clamp was opened and repositioned to perform a subsequent series of applications to increase the ablation zone. The upper and lower Box lesion lines were formed, using a Cool Rail linear bipolar electrode (AtriCure, Inc., West Chester, Ohio, USA). LA appendage amputation was performed through one of the ports of left-sided access using EndoGIA cutting and cross-linking endostepper (Medtronic, Minneapolis, Minnesota, USA) under the control of transesophageal echocardiography. At all stages of surgery, transmurality and achievement of bidirectional conduction block through the performed ablation lines (exit and entrance block) were evaluated.

With the help of overdrive stimulation we provoked triggering of AF, its spontaneous suppression within 30 seconds was considered normal. In case of registration of sustained AF at the end of the procedure, cardioversion was performed. A detailed description and intraoperative photographs are presented in previously published papers [6, 21].

***Таблица 1.***

***Основные клинические характеристики пациентов и данные инструментальных методов исследования (n=100***

| Indicator | Group I (n=50) | Group II (n=50) | p |
|---|---|---|---|
| Sex (male), n (%) | 33.0 (75) | 34.0 (70.83) | 0.83 |
| Age, years (Me (IQR)) | 58 (51:63) | 56 (48:62.75) | 0.29 |
| BMI, kg/m2 (Me (IQR)) | 29 (27:31) | 30 (28:32.75) | 0.188 |
| History of AF, years (Me (IQR)) | 2.25 (0.77-5) | 5 (2-8) | 0.001 |
| DA, years (mean ± SD) | 0.53±0.27 | 4.4±3.2 | <0.0001 |
| EHRA III, n (%) | 38 (76) | 34 (68) | 0.46 |
| EHRA IV, n (%) | 12 (24) | 16 (32) | |
| Hypertension, n (%) | 38 (76) | 39 (78) | 0.99 |
| Diabetes mellitus, n (%) | 4 (8) | 9 (18) | 0.23 |
| CHF II FC NYHA, n (%) | 32 (64) | 40 (80) | 0.15 |
| CHF III FC NYHA, n (%) | 8 (16) | 6 (12) | |
| Prior RFA and CBA of PV, n (%) | 11 (22) | 12 (24) | 0.81 |
| Not receiving AAD | 2 (4) | 0 (0) | 0.24 |
| AAD class IC, n (%) | 5 (10) | 1 (2) | |
| AAD class II, n (%) | 26 (52) | 27 (54) | |
| AAD class III, n (%) | 12 (24) | 17 (34) | |
| AAD class IV, n (%) | 5 (10) | 5 (10) | |
| Not receiving ATT, n (%) | 7 (14) | 4 (8) | 0.06 |
| Apixaban, n (%) | 13 (26) | 15 (30) | |
| Rivaroxaban, n (%) | 24 (48) | 14 (28) | |
| Dabigatran, n (%) | 3 (6) | 7 (14) | |
| Warfarin, n (%) | 3 (6) | 10 (20) | |
| $CHA_2DS_2$-VASc, scores (Me (IQR)) | 2 (1-3) | 2 (1-2) | 0.698 |
| HAS-BLED, scores (Me (IQR)) | 1 (0-1) | 1 (0-1) | 0.232 |
| Simpson's LVEF, % (Me (IQR)) | 61.5 (59-68) | 61 (57-65.5) | 0.317 |
| LAVI, ml/m2 (Me (IQR)) | 35 (30.25-45.75) | 36 (31-47) | 0.836 |
| LA APD, mm (Me (IQR)) | 40.5 (39-43) | 42 (40-46) | 0.192 |
| No MR, n (%) | 28 (56) | 24 (48) | 0.50 |
| Minor MR, n (%) | 20 (40) | 25 (50) | |
| Moderate MR, n (%) | 2 (4) | 1 (2) | |

Note: BMI - body mass index; AF - atrial fibrillation; DA - duration of continuous arrhythmia; CHF - chronic heart failure; FC - functional class; RFA - radiofrequency ablation; CBA – cryoballoon ablation; PP - pulmonary vein; AAD - antiarrhythmic drugs; ATT - antithrombotic therapy; LVEF - left ventricular ejection fraction; LAVI - left atrial volume indexed to body surface area; LA APD, - left atrial anteroposterior dimension; MR - mitral regurgitation.

**Statistical analysis**

Statistical analysis and visualization of the obtained data were performed using JASP 2.3.18. statistical computing environment (Jamovi Software). Descriptive statistics are presented as number of observations (relative frequency) for qualitative variables and mean (standard deviation) and median (1st and 3rd quartiles) depending on normality of distribution - for quantitative variables. The Shapiro-Wilk test was used to test whether the sampling distribution conformed to the normal law. Kaplan-Meier method, log-rank test were used to evaluate the effectiveness of the procedure.

## RESULTS

The median age of patients was 58 (51-63) years and 56 (48-62.75) years, the two groups were male dominated 33 (75%) and 34 (70.83%) in group I and II, respectively. A statistically significant difference between groups preoperatively was obtained for total history of AF 2.25 (0.77-5) years in group I and 5 (2-8) years in group II (p=0.001). The mean duration of continuous arrhythmia in group I was 0.53±0.27 years and in group II 4.4±3.2 years (at p<0.0001). The complete clinical characteristics of patients and data of instrumental methods of investigation are presented in Table

1. All patients underwent radiofrequency ablation of the right and left PVs, upper and lower Box lesion line formation. The intraoperative features of the procedures are summarized in Table 2.

Postablation epicardial changes of PV aortic tissue were visualized in all 23 patients after prior CA. Moreover, right, and left PVs were isolated before TA in group I only in 8 (16%), in group II in 6 (12%) patients, p>0.05 (Table 2). Restoration of sinus rhythm at the time of ablation was in 3 (6%) and 5 (10%) patients in groups I and II, respectively. Restoration of sinus rhythm after LA appendage amputation was registered in 2 patients in group I and in one patient in group II (Table 2).

Sustained AF at the end of surgery was recorded in 89 (89%), which required cardioversion. Persistent sinus rhythm at the end of the procedure, after cardioversion, was registered in 100% and 96% of patients in groups I and II, respectively. Two patients were transferred to the intensive care unit with typical atrial flutter followed by successful cardioversion on amiodarone therapy. The mean operation time was 220 (188.5-260) min, the mean artificial ventilation (AVL) time was 9.4 (7.5-12) hours, and the mean duration of hospitalization was 6 (5-7) days.

**Efficacy of thoracoscopic ablation**

The mean follow-up period of the patients was 2.8±0.7 years. The efficacy of epicardial ablation of persistent AF was - 86.0% and 78.0%, and of long-term persistent AF - 77.1% and 68.8% after 6 and 12 months, respectively (p=0.037) (Fig. 3, Table 3) (Fig. 3, Table 3). In the remote follow-up period, the efficiency of TA in Group I was 78.0% and in Group II 63.0% (Fig. 3, Table 3). Catheter ablations for returning atrial tachyarrhythmias 3 months after TA were required in group I - 8 (16%) patients, in group II - 9 (18%), p>0.05. Two patients from group II had typical isthmus-dependent atrial flutter (AFt), 4 (4%) patients had recorded AF on ECG, and 11 (11%) patients were found to have atypical left atrial AFt.

Before the endocardial ablation procedure, all patients underwent high-density LA mapping with study of isolation zones and gaps zones. The PVs were isolated in all patients, confirming that transmurally was achieved with the use of the ablative bipolar clamp.

Residual fragmented commissural activity with absence of conduction in the LA during PV stimulation in 4 (4%) patients: right upper PV in 3 cases and left upper LV in 1 patient. In all cases, pointwise antral isolation of active PV segments was performed until the disappearance of potentials.

In 9 (9%) patients with atypical AFt, the area of failed thoracoscopic ablation was verified in the region of the upper «Box lesion» line of the LA roof. These patients underwent endocardial linear ablations between the upper PVs. The restoration of sinus rhythm or change of the activation front from left atrial to right atrial was noted. AFt with verification of a delayed conduction zone along the anterior wall of the LA was detected in 2 (2%) patients. We performed linear radiofrequency interventions from the roof of the LA to the mitral isthmus with restoration of sinus rhythm (Fig. 4).

In two patients with long-term persistent form of AF, typical AFt was registered at the onset of CA, in connection with which radiofrequency ablation of cavotricuspidal isthmus was performed, with successful restoration of sinus rhythm (Fig. 4). The efficacy of stage treatment of AF was 100% within 3 months after the second stage (CA). In the long-term follow-up period (24 months after additional CA) the efficacy of two-stage treatment of nonparoxysmal forms of AF was 86.9%.

**Complications**

Major complications were not reported in any patient. The incidence of minor complications in the two groups was 11% (Table 4). Bleeding was reported only in patients in group II (exclusively after prior CA) and accounted for 3% of the total complications. Conversion was not required in any patient, after surgical and medical hemostasis.

Pneumothorax that resolved on its own was reported in 4 (4%) patients in the two groups. Temporary diaphragmatic nerve palsy was reported in 4 (4%) patients that resolved within 12 months. MACE, thromboembolic complications including pulmonary embolism were not reported in any patient.

***Table 2.***

***Intraoperative features of the procedures (n=100)***

| Indicator | Group I (n=50) | Group II (n=50) | p |
|---|---|---|---|
| PV isolated, after previous CA n, (%) | | | |
| Right PVs | 8 (16) | 6 (12) | 0.49 |
| Left PVs | 8 (16) | 6 (12) | 0.99 |
| Rhythm recovery n, (%) | | | |
| At the time of right LV ablation | 0 (0) | 1 (2) | 0.99 |
| At the time of left PV ablation | 0 (0) | 1 (2) | 0.99 |
| At the time of upper line ablation | 0 (0) | 1 (2) | 0.99 |
| At the time of the lower line abla-tion. | 3 (6) | 2 (4) | 0.99 |
| At the time of the amputation of the LAA | 2 (4) | 1 (2) | 0.56 |
| ECV at the end of surgery | 45 (90) | 44 (88) | 0.61 |
| Rhythm at the end of the operation n, (%) | | | |
| Sinus rhythm | 50 (100) | 48 (96) | 0.11 |
| Typical atrial flutter. | 0 (0) | 2 (4) | |
| Operation time, min (Me (IQR)) | 221 (190-251.25) | 247.5 (197.5-305) | 0.077 |
| Ablation time, min (Me (IQR)) | 69.5 (58.75-84) | 73 (64-91) | 0.114 |
| Ventilation time, hour (Me (IQR)) | 9.125 (8-11.31) | 10 (6.55-15.525) | 0.759 |
| TSD, ml (Me (IQR)) | 200 (150-300) | 190 (100-200) | 0.050 |

Note: PV - pulmonary veins; CA - catheter ablations; LAA - left atrial appendage; ECV - electrical cardioversion; AVL - artificial ventilation; TSD - trace secretion by drains.

## DISCUSSION

The treatment of patients with persistent and long-standing persistent AF is challenging. The Cox-Maze procedure and its modifications are the gold standard for the treatment of stable forms of AF, but their widespread use in patients with isolated AF is limited due to their high traumatic nature and the need for artificial circulation [1, 7-9]. Radiofrequency ablation for persistent and long-term persistent forms of AF shows extremely low efficacy due to pronounced «electrophysiologic remodeling of atria» [6, 9, 22].

This led to the development of alternative surgical treatments that are closer in efficacy to the Cox-Maze procedure, but with a lower complication rate. For the first time, the method of video-assisted thoracoscopic ablation of PV and LA appendage amputation was proposed by R.Wolf et al. (2005) [14]. The authors presented the efficacy results of thoracoscopic ablation comparable to Maze III surgery [14]. Thus, epicardial ablation has become a new promising direction of treatment of isolated forms of AF. This technique may include PV isolation, fragmentation of the posterior wall of the LA, ablation of the ganglionic plexus, crossing of the ligament of Marshall, and removal of the appendage of the LA.

A multicenter study by E. Beyer et al. (2009) in a mixed patient population showed that the efficacy of TA for persistent AF was 96% and 71% for long-term persistent AF; after withdrawal of AAT, the overall efficacy of the procedure in all patients was 62%. Complications amounted to 13% and were represented by: pacemaker implantation, diaphragmatic nerve injury, postoperative hemothorax and transient ischemic attack [23].

The FAST and FAST II randomized clinical trials demonstrated high efficacy of TA 65.6% compared to catheter ablation 36.5% (p=0.002), but with a higher complication rate [20, 21]. According to the meta-analysis, freedom from AF after TA for patients with paroxysmal form was 72.7% (174/241), persistent 68.9% (111/161) and 54.2% (32/59) for long-standing persistent FP. The overall efficacy of the procedure with AAT was 68.8% (317/461) and without AAT was 63.3% at a mean follow-up period of 20±9 months [24].

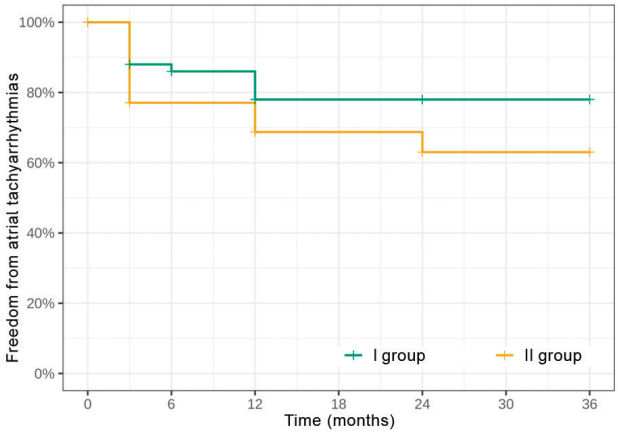


***Fig. 3. Kaplan-Meier survival curve of freedom from atrial tachyarrhythmias in the two study groups after thoracoscopic treatment (p=0.037).***

In the study by L.M.Vos et al (2020), freedom from AF was 60% (49/82) and 86% (42/49) after AAT withdrawal during a four-year follow-up period. The efficiency of TA for paroxysmal forms of AF was 71%, for non-paroxysmal forms of AF - 49% (p=0.07) [25]. The long-term results of our procedure are comparable with the data of M.S.Choi et al. (2020), which presented a comparison of the effectiveness of isolated TA and hybrid treatment of exclusively persistent forms of AF. The efficacy of TA and hybrid treatment for persistent AF at 1-year follow-up was 69.6% and 68.2% at p=0.920, respectively [26].

Similar results were obtained from isolated left-sided access. The efficacy of TA was 73% in nonparoxysmal forms of AF during 12 months of follow-up, without withdrawal of AAT [27]. Freedom from atrial tachyarrhythmias in the presented study in persistent form of AF was 78.0% and in long-term persistent AF - 63.0% (p<0.05).

In our study, additional CAs 3 months after TA were required in group I - 8 (16%) patients and in group II - 9 (18%) patients, p >0.05. Two patients from group II had typical isthmus-dependent AFt, 4 (4%) patients had AF recorded on ECG, and 11 (11%) patients showed atypical left AFt. Before the endocardial ablation procedure, all patients underwent high-density LA mapping with study of isolation zones and excitation breakthrough zones. The PVs were isolated in all patients, confirming that transmurality was achieved with the use of the ablative bipolar clamp.

Residual fragmented commissural activity with absence of conduction in the LA during PV stimulation in 4 (4%) patients: right upper PV in 3 cases and left upper LV in 1 patient. In all cases, pointwise antral isolation of active PV segments was performed until the disappearance of potentials. In 9 (9%) patients with atypical AFt, the area of failed thoracoscopic ablation was verified in the region of the upper «Box lesion» line of the LA roof. These patients underwent endocardial linear ablations between the upper PVs. Restoration of sinus rhythm or change of the activation front from left atrial to right atrial was noted. Perimitral AFt with verification of a delayed conduction zone along the anterior wall of the LA was detected in 2 (2%) patients. We performed linear radiofrequency interventions from the roof of the LA to the mitral isthmus with restoration of sinus rhythm (Fig. 3).

An important factor in failed epicardial ablations is most often epicardial fat along the posterior wall of the LA and in the region of the PV apertures. K.N.Hong et al

***Table 3.***

***Freedom from atrial tachyarrhythmias in the two study groups after thoracoscopic treatment***

| | 3 months | 6 months | 12 months | 24 months | 36 months |
|---|---|---|---|---|---|
| Group I, % | 88.0 [79.4; 97.5] | 86.0 [76.9; 96.2] | 78.0 [67.3; 90.4] | 78.0 [67.3; 90.4] | 78.0 [67.3; 90.4] |
| Group II, % | 77.1 [66.1; 89.9] | 77.1 [66.1; 89.9] | 68.8 [56.8; 83.2] | 63.0 [50.3; 79.0] | 63.0 [50.3; 79.0] |

Note: [Confidence interval, 95%].

(2007) in their study showed that epicardial transmural ablation lines can be performed only in patients with absence of epicardial fat, epicardial ablations are not effective in epicardial fat thickness more than 3 mm [28]. Another study showed that often, epicardial fat is more prevalent along the roof of the LA compared to the inferior portion, which may explain the efficient and reliable formation of the inferior Box lesion line in contrast to the superior line. The results of our study are in full agreement with the data of previously published works [29].

Two patients had typical atrial flutter at the onset of CA, and radiofrequency ablation of cavotricuspidal isthmus was performed, with successful restoration of sinus rhythm. Technically, from epicardial access, the cavotricuspidal isthmus lines and to the mitral isthmus are incomplete. Therefore, a staged treatment approach should be considered for some patients with persistent and long-standing persistent forms of AF [30].

In our study, AF after prior PV CA were isolated in 9 (9%) patients in two groups. In all 23 patients after previous CAs, intraoperatively there were marked fibrotic changes and adhesions in PV apertures, which technically complicated the operation. In this regard, three patients (3%) developed bleeding at the stage of PV isolation, which required surgical and medical hemostasis. However, a recent systematic review aimed at examining exclusively complications after thoracoscopic ablation showed that neither prior catheter ablation nor the form of AF was associated with the risk of intraoperative complications, with an overall complication rate for TA of 11.8% [31]. In our study, the incidence of all complications was 11%. The absence of major intraoperative complications and 30-day mortality were related to the experience of the surgical team.

An important advantage of TA is the ability to amputate the appendage of the LA. Today, there is no consensus on the optimal prophylaxis of thromboembolic events in patients with AF. However, it is proved that up to 90-95% of all thrombi in patients with non-valvular AF are formed in the appendage of the LA [4, 32, 33]. Therefore, occlusion or amputation of the appendage of the LA is of great clinical importance.

In our center, the endoscopic cutting and stapling device is preferred, which has proven itself in TA. LA appendage amputation was performed in 100%. All anastomoses in the LA appendage stump region were complete. After LA appendage amputation, restoration of sinus rhythm was registered in 2 (4%) patients with persistent AF and in 1 (2%) patient with long-term persistent form of AF, and sinus rhythm was registered in these patients in the long-term follow-up period. In the work of L. Di Biase et al (2016), it was shown that LA appendage isolation improves freedom from atrial tachyarrhythmias in patients with long-term persistent AF [34-36], which warrants further study.

TA combined with LA appendage amputation significantly reduces the risks of thromboembolic complications. This method has a simple and safe approach, and no MACE events were recorded in any of our patients in the long-term follow-up period. Anticoagulant therapy 6 months after TA was discontinued in 70 patients (group I - 40 patients, group II - 30 patients), after registration of stable sinus rhythm on 24-h HM ECG, results of $CHA_2DS_2$-VASc testing and exclusion of thrombus according to transesophageal Echo-CG and multispiral computed tomography with contrast.

## CONCLUSION

Video-assisted TA of AF should be considered an effective method of arrhythmia management for patients with persistent and long-term persistent AF. Freedom from atrial tachyarrhythmias was 78.0% for persistent AF and 63% for long-term persistent AF during the three-year follow-up period.

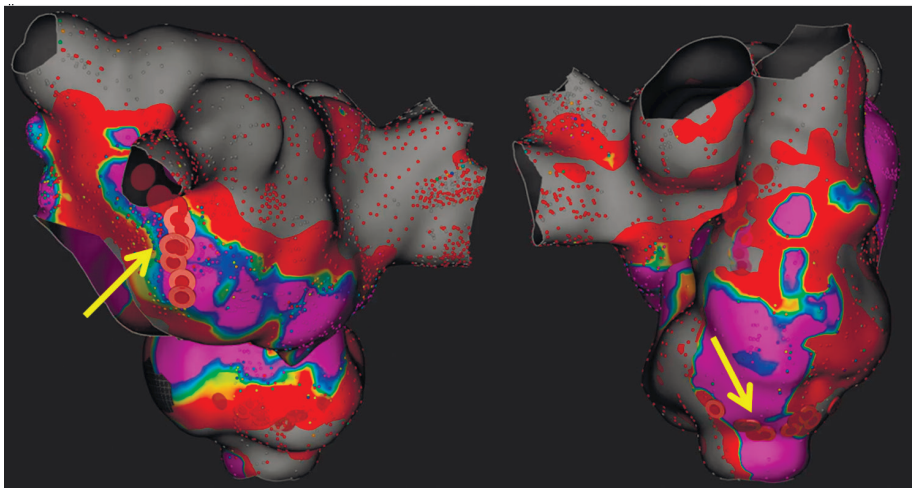

***Fig. 4. High-density mapping with additional endocardial ablations (yellow arrows) in the mitral isthmus and cavotricuspid isthmus regions.***

***Table 4.***

***Minor complications (n=100)***

| | All patients (n=100) | Group I (n=50) | Group II (n=50) | p |
|---|---|---|---|---|
| Bleeding, n (%) | 3 (3%) | 0 (0%) | 3 (6%) | 0.24 |
| Pneumonia, n (%) | 0 (0%) | 0 (0%) | 0 (0%) | - |
| Pneumothorax, n (%) | 4 (4%) | 3 (6%) | 1 (2%) | 0.49 |
| Hemothorax, n (%) | 1 (1%) | 0 (0%) | 1 (2%) | 0.99 |
| Hydrothorax, n (%) | 1 (1%) | 0 (0%) | 1 (2%) | 0.47 |
| TIA, n (%) | 0 (0%) | 0 (0%) | 0 (0%) | - |
| Temporary PDP, n (%) | 4 (4%) | 1 (2%) | 1 (2%) | 0.37 |
| Overall frequency, n (%) | 11 (11%) | 4 (8%) | 7 (14%) | 0.24 |

Note: TIA - transient ischemic attack; PDN – phrenic nerve palsy.

The efficacy of stage treatment of AF was 100% within 3 months after the second stage (radiofrequency catheter ablation). In the remote follow-up period (3 years after additional CA) the efficacy of two-stage treatment of nonparoxysmal forms of AF was 86.9% Stage treatment of nonparoxysmal forms of AF can increase the efficacy up to 86.9% in the remote follow-up period 24 months after the second stage (catheter ablation), which requires further study on a larger sample of patients. Thus, a staged approach should be considered as the method of choice for the treatment of persistent and long-term persistent forms of AF.

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# PREDICTION OF LOW-VOLTAGE AREAS IN THE LEFT ATRIUM IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION BY NON-INVASIVE MARKERS

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**Aim.** To develop a method for predicting the area of low-voltage area (LVA) in the left atrium (LA), associated with the minimum and maximum expected effectiveness of primary radiofrequency ablation (RFA) in patients with non-valvular atrial fibrillation (AF) using non-invasive predictors.

**Methods.** A longitudinal single-center study included 150 symptomatic non-valvular AF pts aged 20-72 years (median 59.0 [51.0; 64.0]), including 63 women (42%) hospitalized for primary RFA; 119 pts (79.3%) had paroxysmal and 31 (20.7%) - persistent AF. All pts initially underwent general clinical examination, transesophageal and advanced transthoracic echocardiography, estimation of NT-proBNP (pg/ml) and growth differentiation factor 15 (GDF-15, pg/ml) in the blood. Electroanatomical mapping was performed in sinus rhythm before RFA. The area of LVA (<0.5 mV) was calculated as percentage of total LA area. Left ventricular (LV) ejection fraction (LVEF) was >50% in all pts.

**Results.** LVA area varied from 0 to 95.3%, median was 13.7% [5.1; 30.9]. Depending on LVA area, pts were divided into 3 groups: 36 pts (<5%) in gr. 1; 74 pts (5-30%) in gr. 2; 40 pts (>30%) in gr. 3. Increase of LVA area was associated with age, presence, and severity of congestive heart failure (CHF), persistent AF, $CHA_2DS_2$-VASc score ≥3 points, increase of LA volume, LV hypertrophy and increase of NT-proBNP and GDF-15 levels. In univariate analysis, LVA area <5% was associated with NT-proBNP level <125 pg/ml, absence of obesity and CHF, lower LA volume index (<28 ml/m$^2$). Independent predictors of LVA <5% were: NT-proBNP <125 pg/ml, absence of obesity and LA volume index ≤28 ml/m$^2$. The model was of good quality, C-statistics was 0.775 (p<0.001). In univariate analysis, LVA area >30 % was associated with age >60 years, NT-proBNP >125 pg/ml, GDF-15 >840 pg/ml, persistent AF, presence of LV hypertrophy, LVEF ≤60%, LA volume index ≥ 32 ml/m$^2$. Independent predictors of LVA >30% were: LA volume index ≥32 ml/m$^2$, GDF-15 >840 pg/ml, and LVEF ≤60%. The model was of good quality, C-statistics was 0.752 (p<0.001).

**Conclusion.** Evaluation of noninvasive parameters, including clinical characteristics, echocardiographic parameters, and blood levels of NT-proBNP and GDF-15, allows prediction of electroanatomical substrate in left atrium in pts with non-valvular AF referred to primary RFA.

**Key words:** atrial fibrillation; electroanatomical mapping; low voltage areas; radiofrequency ablation; left atrial fibrosis

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Atrial fibrillation (AF) is the most common arrhythmia associated with a 5-fold increased risk of stroke and a 2-fold increased risk of death [1]. Catheter ablation (CA) is superior to drug therapy in terms of sinus rhythm restoration and improved quality of life when choosing a treatment strategy for AF and is reasonably safe in the hands of experienced operators [1]; however, the return of arrhythmias within the first year after CA after a three-month blind period is as high as 25-40% [2]. This necessitates the need to improve patient selection by identifying subgroups of patients with different expected CA performance [3].

Left atrial (LA) fibrosis is known to underlie the electroanatomical substrate of AF [1, 4]; while its size determines the stability of AF [5, 6] and the effectiveness of CA [6, 7]. Current methods used to assess fibrosis, including magnetic resonance imaging (MRI) with delayed contrast [8, 9] and endocardial bipolar electroanatomic mapping (EAM) with low-voltage areas (LVA) delineation [10, 11], correlate well with each other [12]. Studies using both methods have shown that the severity of LA fibrosis greater than 30% of the LA area may serve as an independent predictor of recurrent AF after CA [6, 13]. Nevertheless, the high economic and labor costs of MRI and the additional increase in the risk of complications associated with prolongation of CA time in case of EAM performance make it difficult to apply these methods in widespread clinical

practice. This explains the relevance of the problem of developing methods for predicting the severity of LVA using available noninvasive methods of investigation in patients with AF referred for CA.

The aim of the study was to develop a method to predict the area of LVA in the LA associated with the minimum and maximum expected efficacy of primary radiofrequency ablation (RFA) in patients with non-valvular AF using non-invasive markers.

## METHODS

A single-center study included 150 patients with symptomatic nonvalvular AF consecutively hospitalized at the Tyumen Cardiology Research Center for primary RFA, aged 20 to 72 years (median 59.0 [51.0; 64.0]), including 63 women (42%) and 87 men. Paroxysmal AF was present in 119 patients (79.3%) and persistent AF in 31 (20.7%).

Exclusion criteria were as follows: LA auricular thrombosis during transesophageal echocardiography (Echo), myocardial infarction or coronary artery interventions within the last 6 months, left ventricular ejection fraction (LVEF) below 50%, acute or chronic comorbidities in decompensation, chronic obstructive pulmonary disease, patient refusal to participate in the study, pregnancy.

All patients initially, before RFA, underwent general clinical examination, deployed transthoracic Echo, transesophageal Echo, endocardial bipolar EAC, and determination of blood levels of N-terminal brain natriuretic propeptide (NT-proBNP, pg/mL) and growth differentiation factor 15 (GDF-15, pg/mL).

Transthoracic Echo was performed in accordance with the current recommendations of the American Society of Echo and the European Association for Cardiovascular Imaging [14]; chamber sizes and volumes, left ventricular (LV) systolic and diastolic functions were evaluated. The studies were performed using a Vivid E9 ultrasound scanner (General Electric Medical Systems, USA). The presence of left ventricular hypertrophy (LVH) was considered as a criterion for the presence of LV myocardial mass index (LVMM index) exceeding the value of 95 g/m$^2$ for women and 115 g/m$^2$ for men. The types of LV geometry were determined based on LVMM index and relative LV wall thickness values [14].

Endocardial bipolar voltage LA mapping was performed in sinus rhythm as the first stage of primary RFA, and electrical cardioversion was performed beforehand in persistent AF. CARTO 3 3D navigation system (Biosense Webster), Thermocool Smart Touch ablation electrodes with 3.5 mm interelectrode spacing, and LASSO multipole circular mapping electrodes (Biosense Webster) with 2-5-2 mm interelectrode spacing were used to construct the electroanatomical map. When using the point-to-point method, at least 250 points taken at stable contact of the electrode with the endocardium of the LA were taken to construct the LA map. LA voltage analysis was performed by an experienced electrophysiologist in the postoperative period. LVAs were defined by the presence of 3 or more adjacent points with voltages <0.5 mV [13], and the total area of LVAs was calculated as % of the total area of the LA. The regions of the mitral valve and pulmonary vein apertures were excluded when calculating the total LA area.

Blood level of NT-proBNP (reference value below 125 pg/mL) was determined using an analyzer IMMULITE 2000 (Siemens Diagnostics, USA) by enzyme-linked immunosorbent assay. GDF-15 level (pg/mL) was determined on a Stat Fax 4200 microplate photometer (USA) by quantitative method (direct enzyme immunoassay) using the analytical kit «Human GDF-15/MIC-1 ELISA» (BioVender, Czech Republic) for research purposes (range of determinations from 35 to 2240 pg/mL). According to the instructions, medians in different age groups can be taken as reference levels: 378-648 pg/mL for men and 444-653 pg/mL for women.

The diagnoses of arterial hypertension, ischemic heart disease, and chronic heart failure (CHF) were established in accordance with the current recommendations of the Russian Society of Cardiology. Body mass index ≥30 kg/m$^2$ was adopted as the criterion for obesity.

Statistical processing of data was performed using IBM SPSS Statistics 21 and Statistica 12.0 programs. The distribution of quantitative variables was examined using the Shapiro-Wilk test. In normal distribution, data are presented as mean M and standard deviation (SD); in other distribution, data are presented as median (Me) and interquartile range [25%; 75%]. ANOVA analysis of variance and Kraskell-Wallis test were used for comparative analysis depending on the distribution of data. Qualitative data were compared by Pearson's $\chi^2$ test. Bonferroni correction was applied for multiple comparisons. Univariate and multivariate logistic regression were used to examine the association of variables and to find independent predictors of LVA area. Cutoff values of quantitative variables were searched for by ROC analysis. The quality of the models was assessed using C-statistics, sensitivity, and specificity. Results were evaluated at the $p < 0.05$ level as statistically significant and as tending to significant differences at the $p < 0.1$ level.

The study was conducted in accordance with the provisions of the Declaration of Helsinki, the study protocol was approved by the local ethics committee (protocol #176 dated November 23, 2021). Informed consent to participate in the study was obtained from all study subjects.

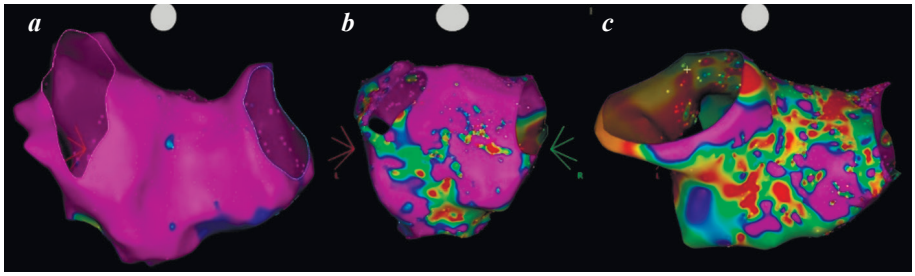


***Fig. 1. Results of voltaic electroanatomic mapping of the left atrium of patients with different area of low-voltage areas (indicated by color other than purple): a - area <5%, b - from 5 to 30%, c - >30%.***

## RESULTS

According to EAM data, the area of LVA ranged from 0 to 95.3%, with a median of 13.7% [5.1; 30.9]. According to the area of LVA, patients were divided

***Table 1.***

***Clinical and demographic characteristics and echocardiographic indices in groups with different low-voltage zone (LVA) areas***

| | | Group 1 (LVA <5%) (n=36) | Group 2 (LVA 5-30%) (n=74) | Group 3 (LVA >30%) (n=40) | Reliability of differences |
|---|---|---|---|---|---|
| Age, years | | 55.0 [47.5; 61.5] | 58.0 [52.0; 64.0] | 61.5 [53.5; 65.0] | P=0.017, $P_{1-2}$=0.289, $P_{1-3}$=0.013, $P_{2-3}$=0.321 |
| Female gender, n (%) | | 11 (30.6) | 31 (41.9) | 21 (52) | P=0.153, $P_{1-2}$=0.251, $P_{1-3}$=0.154, $P_{2-3}$=0.278 |
| Arterial hypertension, n (%) | Yes | 29 (80.6) | 61 (82.4) | 38 (95) | P=0.658, $P_{1-2}$=0.811, $P_{1-3}$=0.126, $P_{2-3}$=0.058 |
| | No | 7 (19.4) | 13 (17.6) | 2 (5) | |
| Coronary artery disease, n (%) | Yes | 12 (33.3) | 30 (40.5) | 19 (31.2) | P=0.954, $P_{1-2}$=0.465, $P_{1-3}$=0.455, $P_{2-3}$=0.474 |
| | No | 24 (66.7) | 44 (59.5) | 21 (68.8) | |
| Prior myocardial infarction, n (%) | Yes | 0 | 2 (2.7) | 1 (2.5) | P=0.914, $P_{1-2}$=0.319, $P_{1-3}$=0.615, $P_{2-3}$=0.949 |
| | No | 36 (100) | 72 (97.3) | 39 (97.5) | |
| Heart failure, n (%) | Yes | 29 (80.6) | 40 (54.1) | 15 (37.5)) | P=0.001, $P_{1-2}$=0.007, $P_{1-3}$=0.001, $P_{2-3}$=0.091 |
| | No | 7 (19.4) | 34 (45.9) | 25 (62.5) | |
| Paroxysmal AF, n (%) | | 33 (91.7) | 61 (82.4) | 25 (62.5) | P=0.005, $P_{1-2}$=0.197, $P_{1-3}$=0.005, $P_{2-3}$=0.018 |
| Persistent AF, n (%) | | 3 (8.3) | 13 (17.6) | 15 (37.5) | |
| Diabetes mellitus, n (%) | Yes | 4 (11.1) | 8 (10.8) | 5 (12.5) | P=0.999, $P_{1-2}$=0.962, $P_{1-3}$=0.963, $P_{2-3}$=0.786 |
| | No | 32 (88.9) | 66 (89.2) | 35 (87.5) | |
| Obesity, n (%) | Yes | 22 (61.1) | 28 (37.8) | 19 (47.5) | P=0.701, $P_{1-2}$=0.050. $P_{1-3}$=0.172, $P_{2-3}$=0.592 |
| | No | 14 (39.9) | 46 (62.2) | 21 (52.5) | |
| Smoking, n (%) | Yes | 31 (86.1) | 67 (90.5) | 38 (95) | P=0.412, $P_{1-2}$=0.484, $P_{1-3}$=0.412, $P_{2-3}$=0.400 |
| | No | 5 (13.9) | 7 (9.5) | 2 (5) | |
| $CHA_2DS_2$-VASc ≥3, n (%) | | 6 (16.7) | 20 (27.0) | 17 (43.6) | P=0.033, $P_{1-2}$=0.230. $P_{1-3}$=0.033, $P_{2-3}$=0.075 |
| GFR, ml/min/1.73 $m^2$ | | 82.5 [64.0; 94.5] | 83.0 [69.0; 96.0] | 87.0 [69.0; 94.0] | P=0.925, $P_{1-2}$=999, $P_{1-3}$=0.954, $P_{2-3}$=0.922 |
| NT-proBNP, pg/mL | | 64.6 [25.9; 107.0] | 93.0 [44.4; 194.0] | 132.5 [75.7; 361.0] | P=0.012, $P_{1-2}$=0.239, $P_{1-3}$=0.008, $P_{2-3}$=0.273 |
| GDF-15, pg/mL | | 694.0 [552.5; 1026] | 767.5 [622.5; 934.0] | 924.5 [758.5; 1162] | P=0.035, $P_{1-2}$=1.000. $P_{1-3}$=0.071, $P_{2-3}$=0.070 |
| LA volume index, ml/$m^2$ | | 27.2±7.0 | 31.3±8.5 | 35.1±9.9 | P=0.001, $P_{1-2}$=0.048, $P_{1-3}$=0.000. $P_{2-3}$=0.063 |
| LVMM index, g/$m^2$ | | 79.8 [72.3; 89.2] | 86.5 [76.1; 96.9] | 95.2 [83.9; 115.4] | P=0.006, $P_{1-2}$=0.497, $P_{1-3}$=0.005, $P_{2-3}$=0.072 |
| LESD index, mm/$m^2$ | | 14.5±1.9 | 15.2±2.1 | 16.5±3.2 | 0.003, $P_{1-2}$=0.370. $P_{1-3}$=0.002, $P_{2-3}$=0.029 |
| LV ejection fraction, % | | 64.0±5.6 | 64.5±7.3 | 61.4±6.9 | 0.075, $P_{1-2}$=0.942, $P_{1-3}$=0.229, $P_{2-3}$=0.063 |
| Normal LV geometry, n (%) | | 17 (47.2) | 44 (59.5) | 11 (27.5) | P=0.0024, $P_{1-2}$=0.377, $P_{1-3}$=0.002, $P_{2-3}$=0.001, |
| Concentric LV remodelling | | 13 (36.1) | 19 (25.7) | 10 (25.0) | |
| Concentric LVH, n (%) | | 4 (11.1) | 4 (5.4) | 10 (25.0) | |
| Eccentric LVH, n (%) | | 2 (5.6) | 7 (9.5) | 9 (22.5) | |
| LVH, n (%) | Yes | 6 (16.7) | 11 (14.9) | 19 (47.5) | P=0.0003, $P_{1-2}$=0.806, $P_{1-3}$=0.0002, $P_{2-3}$=0.0002 |
| | No | 30 (83.3) | 63 (85.1) | 21 (52.5) | |

Note: hereinafter, AF - atrial fibrillation; LV - left ventricle; GFR - glomerular filtration rate; LA - left atrium; LVMM - left ventricular myocardial mass; LVESD - LV end-systolic diameter; LVH - LV hypertrophy.

into 3 groups: group 1 (<5%) - 36 patients, group 2 (5-30%) - 74 patients, group 3 (>30%) - 40 patients. Figure 1 shows examples of electroanatomical charts of patients with different areas of LVA.

The clinical and demographic characteristics and Echo parameters of the patients in the different groups, as well as the results of multiple comparisons, are summarized in Table 1. Patients from different groups did not differ in the frequency of use and spectrum of antiarrhythmic drugs, oral anticoagulants, ACE inhibitors, and ARA.

In general, it should be noted that an increase in LVA was associated with increasing age, presence of CHF, an increase in the proportion of patients with persistent AF, presence of 3 or more $CHA_2DS_2$-VASc scores, an increase in LA diameter and volume indices, LVMM index and presence of LVH, and an increase in the levels of both biomarkers, NT-proBNP and GDF-15 (Table 1). In the group with minimal LVA area, there was a tendency to decrease the proportion of obese patients.

To find predictors of minimal (<5%) and pronounced (>30%) LVA area, variables that showed statistically significant differences or a trend toward them in the comparative between-group analysis were included in the single-factor logistic regression analysis. For quantitative variables, thresholds separating patients with LVA area <5% and >30% with optimal sensitivity-to-specificity ratios were additionally determined using ROC analysis. Final prediction models were searched for using multivariate logistic regression analysis, which included variables that had a significant association with minimum (<5%) or maximum (>30%) LVA area, as measured by single-factor regression analysis. In selecting the final model, optimal levels of C-statistics, sensitivity and specificity were chosen as criteria. The results are presented in Tables 2 and 3.

According to the results of multivariate regression analysis, the likelihood of having minimal (<5%) LVA area was 4.712-fold higher in patients with NT-proBNP levels less than 125 pg/mL and LA volume index ≤28 mL/m$^2$ 4.363-fold, and 78% lower in the presence of obesity. In assessing the quality of the model, the C-statistic of the model is 0.775 (p<0.001), with a sensitivity of 66.0% and specificity of 76%, which corresponds to good quality.

Thus, the likelihood of having a LVA area >30% is 3-fold higher in patients with GDF-15 levels >840 pg/mL and with an LVEF ≤60%, and 2.8-fold higher in the presence of an LA volume index ≥32 mL/m$^2$. The C-statistic was 0.752 (p <0.001), the sensitivity was 60%, and the specificity of the model was 79%, which corresponds to a good quality model.

## DISCUSSION

Predicting the area of LVA in the LA is important in a personalized approach to the choice of therapeutic tactics in patients with AF because it gives an idea of the severity of atrial cardiomyopathy [15] and the size of the electroanatomic substrate of AF before planned RFA [7, 13].

The results of the DECAAF study showed that the efficacy of RFA decreased with increasing severity of LA fibrosis assessed by MRI, and the recurrence rate of AF with an area of LA fibrosis >30% reached 69.4% at 15 months after RFA [6]. G.A.Begg et al. found that the area of LVA >30% can also be a predictor of AF recurrences during the first year after RFA [13], therefore we chose this index as a criterion corresponding to marked fibrosis.

Among clinical-instrumental parameters and biomarkers, we have identified factors associated with the increase of LVA area in LA: age, presence of CHD, persistent form of AF, presence of 3 or more points on the $CHA_2DS_2$-VASc scale, increased NT-proBNP and GDF-15, increased LA volume index, presence of LVH, decreased LV systolic function. Independent predictors of LVA area >30% associated with expected poor RFA performance [13] were: LA volume index ≥32 mL/m$^2$, LVEF ≤60%, GDF-15 >840 pg/mL.

Comparison of our results with the data of previous studies confirmed the significance of the index characterizing LA dilatation as the main predictor of LVA. The DR-FLASH scale developed by Kosiuk et al. (2015) [16] for predicting LVA and identifying patients for possible LA substrate modification includes LA diameter >45 mm. The similar APPLE scale proposed by J.Kornej et al. (2018) included a LA diameter ≥43 mm [17], which was replaced by an LA volume index ≥39 ml/m$^2$ in the modified APPLE scale [18]. Since the description of the LA size does not accurately reflect the anatomy of the LA and, consequent-

***Table 2.***

***Results of single-factor and multivariate analyses to find predictors of low-voltage zones <5%***

| Variables | Single-factor analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | B | p | OR [95% CI] | B | p | OR [95% CI] |
| Age >60 years | -0.811 | 0.130 | 0.444 [0.156; 1.268] | - | - | - |
| NT-proBNP <125 pg/mL | 1.394 | 0.020 | 4.032 [1.241; 13.101] | 1.550 | 0.019 | 4.712 [1.294; 17.158] |
| GDF-15 <745 pg/mL | 1.025 | 0.044 | 2.786 [1.028; 7.545] | - | - | - |
| Presence of obesity | -1.181 | 0.027 | 0.307 [0.107; 0.877] | -1.498 | 0.013 | 0.224 [0.069; 0.729] |
| Persistent AF | -0.693 | 0.306 | 0.500 [0.133; 1.887] | - | - | - |
| Presence of CHD | -1.580 | 0.017 | 0.206 [0.056; 0.758] | - | - | - |
| $CHA_2DS_2$-VASc ≥3 points | -0.829 | 0.219 | 0.437 [0.116; 1.637] | - | - | - |
| LVESD index (mm/m$^2$) | -0.156 | 0.177 | 0.856 [0.683; 1.073] | - | - | - |
| LA volume index ≤28 ml/m$^2$ | 1.122 | 0.027 | 3.072 [1.138; 8.295] | 1.473 | 0.010 | 4.363 [1.418; 13.423] |

Примечание: здесь и далее ОШ - отношение шансов; ДИ - доверительный интервал.

ly, the degree of LA dilatation, this was considered in the modified APPLE scale [18]. Our data suggest that LA volume index may be an independent predictor of both minimal and severe LVA area, but with different cutoff values of ≤28 mL/m$^2$ and ≥32 mL/m$^2$, respectively. The association of LA dilatation with the severity of LA fibrosis is well established and corresponds to the degree of progression of atrial cardiomyopathy in patients with AF [15].

According to the literature, the most frequent predictors of LVA are age [16-19], female gender [16, 17, 19, 20] and persistent form of AF [16-18, 20]. According to our results, age ≥60 years and persistent AF were associated with LVA area >30%, according to single-factor analysis, but were not included as independent predictors in the final model. Female gender in our study did not show itself as a predictor of fibrosis, which is probably due to the peculiarities of the study group.

The second independent predictor of severe (>30%) LVA area was LVEF ≤60%. In contrast to the study by J.Kornej et al. (2018) [17], according to the results of which LVEF <50% was included in the APPLE scale as an independent predictor of LVA, our study included only patients with LVEF ≥50%. Our data are consistent with the results of the study by G.J.Wehner et al. [21]. A study by these authors of the association of Echo study data with outcomes in a large population of cardiovascular patients showed that the lowest mortality (nadir of mortality) was associated with an LVEF in the range of 60-65% rather than a level of 50% [21]. This is also consistent with the current view that the cohort of patients with CHF with LVEF ≥50% is heterogeneous «in form and content» [22]. [22]. Our results, according to which the probability of a marked LVA area >30% (as a surrogate marker of LA fibrosis) increases at LVEF ≤60%, may also explain the decreased efficacy of antifibrotic drugs (valsartan+sacubitril or sodium-glucose cotransporter type 2 inhibitors) at LVEF >60% [22].

Biomarkers as potential predictors of LVA have been investigated in several studies. The study by V.A.Rossi et al. established the association of elevated NT-proBNP level with the presence of LVA in the LA [20]. In our study, normal NT-proBNP level was an independent predictor of minimal LVA area, and elevated NT-proBNP level was associated with severe (>30%) LVA area, according to single-factor analysis.

The association of GDF-15 level with the size of the LVA in the LA area was previously shown in a pilot study on 86 patients with non-valvular AF referred for primary RFA: GDF-15 level >767.5 pg/mL was a predictor of LVA area >20% [23]. In this study, on a larger group of patients, GDF-15 levels >840 pg/mL were associated with a larger area of LVA, >30%. This is consistent with the claim that GDF-15 expression and concentration in blood reflects an integral signal of cellular stress, organ dysfunction and biological aging of the cardiovascular and renal systems [24, 25]. GDF-15 is now a recognized biomarker of interstitial fibrosis: its level correlates with diffuse and focal myocardial fibrosis assessed by MRI [26].

According to our data, the ideal patient with AF referred for RFA should not be obese. Experimental studies have proven that in chronic obesity, the substrate for the development of AF may be fatty infiltration of the posterior wall of the LA by epicardial fat, which leads to decreased and inhomogeneous voltages [27]. This is consistent with the results of the study by V.A. Ionin et al.: there was a 4.5-fold increase in the relative risk of AF recurrence after RFA with an increase in epicardial fat thickness >6.4 mm in patients with AF and metabolic syndrome [28].

Thus, prediction of the area of LVA in patients with nonvalvular AF referred for primary RFA is an important component of a personalized approach to the choice of the optimal treatment strategy because it gives an idea of the severity of atrial cardiomyopathy [15] and the size of the electroanatomic substrate of AF before the planned RFA [7, 13].

## CONCLUSION

Evaluation of noninvasive parameters including clinical characteristics, echocardiographic parameters, and levels of circulating blood NT-proBNP and GDF-15 can predict the severity of electroanatomic substrate in the LA in patients with nonvalvular AF referred for primary RFA.

***Table 3.***

***Results of single-factor and multivariate analysis on finding predictors of low-voltage zones >30%***

| Variables | Single-factor analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | B | p | OR [95% CI] | B | p | OR [95% CI] |
| Age >60 years | 1.118 | 0.017 | 3.060 [1.218; 7.690] | - | - | - |
| NT-proBNP >125 pg/mL | 0.962 | 0.038 | 2.618 [1.054; 6.505] | - | - | - |
| GDF-15 >840 pg/mL | 1.118 | 0.017 | 3.060 [1.218; 7.690] | 1.108 | 0.029 | 3.030 [1.121; 8.189] |
| Persistent AF | 1.045 | 0.040 | 2.843 [1.048; 7.715] | - | - | - |
| Presence of CHD | 0.789 | 0.088 | 2.201 [0.890; 5.439] | - | - | - |
| $CHA_2DS_2$-VASc ≥3 points | 0.856 | 0.086 | 2.353 [0.886; 6.255] | - | - | - |
| LV ESD index ≥15.8 mm/m$^2$ | 0.993 | 0.049 | 2.700 [1.004; 7.262] | - | - | - |
| LV hypertrophy | 1.225 | 0.011 | 3.405 [1.321; 8.773] | - | - | - |
| Concentric LVH | 1.376 | 0.056 | 3.958 [0.966; 16.223] | - | - | - |
| Eccentric LVH | 1.440 | 0.021 | 4.222 [1.247; 14.301] | - | - | - |
| LVEF ≤60% | 1.460 | 0.003 | 4.308 [1.657; 11.199] | 1.107 | 0.036 | 3.024 [1.073; 8.522] |
| LA volume index ≥32 ml/m$^2$ | 1.219 | 0.011 | 3.385 [1.328; 8.626 ] | 1.029 | 0.049 | 2.799 [1.004; 7.799] |

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# EFFICACY OF DIFFERENT CRYOBALLOON ABLATION STRATEGIES IN PATIENTS WITH PERSISTENT ATRIAL FIBRILLATION

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**Aim.** To study the effectiveness of "extended" cryoballon ablation in patients with a persistent form of atrial fibrillation (AF) and to determine the risk factors for AF recurrence after cryoablation.

**Methods.** The study included 89 patients (62±10 years, 24 [27%] men) with a persistent form of AF. The patients were randomized into two groups: in the 1st, the pulmonary veins (PV) cryoablation was performed (n=48 [53.9%]); in the 2nd, the PV cryoablation was performed in combination with cryoablation of the posterior wall of the left atrium (n=41 [46.1%]). The number of patients at high risk of thromboembolic events predominated in Group 2 (p=0,03). There is a high frequency of taking antiarrhythmic drugs of class III in this group (p=0.018). The follow-up period was 12 months. Clinical efficacy was assessed during a survey and daily ECG monitoring at face-to-face visits after 3, 6 and 12 months.

**Results.** Antral isolation of PV was achieved in all 89 (100%) patients in both groups. In group 2, the average number of applications in the posterior wall of the PV was 10 [9; 13]. The effectiveness of cryoablation in group 1 by the end of the 12-month follow-up period was 54.2%, in group 2 - 56.1%. The complication rate (6.7%) in both groups did not differ statistically (p=0.683). The risk of arrhythmia recurrence didn't depend on the strategy of cryoablation in postablation period (p=0.834). When conducting a single-factor analysis, a statistically significant effect on the probability of AF recurrence in the period of 3-12 months in group 1 was caused by AF recurrence in the blind period (95% confidence interval (CI): 1.5-27.7, p=0.013), in group 2 belonging to the female sex (95% CI: 1.2-24.6, p=0.032) and AF relapse in the blind period (95% CI: 1.5-128.5, p=0.020). During multivariate analysis in group 2, a statistically significant influence on the risk of AF recurrence in the period of 3-12 months was exerted by belonging to the female sex (hazard ratio (HR) 7.84; 95% CI 1478-42,23; p=0.016) and the presence of early AF recurrence (HR 20.36; 95% CI 1.99-208.23; p=0.011).

**Conclusion.** Extended cryoablation in terms of efficiency and safety was comparable with the standard cryoablation. Early recurrence of AF (in the first 3 months after the intervention) turned out to be an independent risk factor for AF recurrence in the long-term period up to 12 months after cryoablation in both groups.

**Key words:** atrial fibrillation; cryoballon ablation; pulmonary veins; extended cryoaballon ablation; left atrium

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Catheter ablation (isolation) of pulmonary veins (PV) for persistent atrial fibrillation (AF) has a high level of recommendation in cases of symptomatic course of persistent AF, decreased quality of life, ineffectiveness of antiarrhythmic therapy and development of heart failure [1]. It is known that the efficacy of catheter ablation limited only to the PV area in persistent AF is significantly inferior to the same intervention in patients with paroxysmal form of this arrhythmia [2]. It has been shown that the evolution of AF from paroxysmal to persistent form may reflect the progression of electrical and structural remodeling of atrial myocardium as elements of atrial cardiomyopathy [3, 4]. These processes may contribute to the formation of an «arrhythmogenic» source of AF outside the PV. It is assumed that the emergence of technologies for verification of the triggering factors of AF lying outside the PV will improve

the effectiveness of endocardial interventions in persistent AF. Recently, there have been data on the prospects of using «extended» cryoballon ablation (CBA), which involves additional cryo-interventions in the region of the posterior wall of the left atrium (LA) in addition to isolation of the PV antral part [5].

The concept of extended cryoablation in LA assumes that the triggers of AF can be eliminated without their precise electro-anatomic identification. Therefore, the aim of our study was to comparatively investigate the efficacy of PV CBA and extended LA CBA in patients with persistent AF.

## METHODS

The prospective randomized study included patients with persistent AF who had indications for CBA according to current international and national guidelines. Patients were randomized into two groups using the closed envelope method. The first group included patients who were randomized to undergo endocardial PV CBA. The second group included patients who were supposed to undergo extended CBA of the LA, which involved PV antral isolation combined with cryoablation of the posterior wall of the LA (Fig. 1). Unequal randomization across the groups of included patients was due to their refusal of further follow-up and desire to withdraw from the study.

All patients underwent general clinical examination before the intervention: general and biochemical blood tests, control of thyroid hormones, 12 channel electrocardiogram (ECG), Holter ECG monitoring, transthoracic echocardiography, multispiral computed tomography of the heart with contrast to assess LA volume and PV anatomy. CBA was performed under endotracheal anesthesia. Intraoperatively, transesophageal echocardiography was performed to exclude atrial thrombosis, the effect of spontaneous echo contrast, and to control access to the left atrium during atrial septal puncture.

Antral PV isolation in both groups was performed according to the technique described previously [6]. The FlexCath Advance steerable intracardiac intra-arterial introdescer (Medtronic, Minneapolis, MN, USA) and the Arctic Front Advance 28 mm balloon catheter (Medtronic, Minneapolis, MN, USA) were inserted into the LA cavity via a guide catheter. PV mapping was performed using an Achieve Advance 20 mm circular diagnostic catheter (Medtronic, Minneapolis, MN, USA). Under fluoroscopic control, a multipolar guided diagnostic catheter (EP-XT, Boston Scientific, MN, USA) was placed in the coronary sinus area. Cryoablation was performed under the control of activated coagulation time of at least 350 seconds. In the antral part of each PV, ablation with a cryoballoon was performed once with a duration of exposure of 240 seconds each and reaching a temperature of -40 to -60 °C. The criterion of PV isolation was the presence of blockade of the input and output of electrical impulses 20 minutes after the completion of cryoablation. In case of absence of persistent PV isolation, repeated 180-second exposure was performed. During cryoablation of the right PV, high-amplitude stimulation of the right diaphragmatic nerve (10-25 mA; 1000-1200 ms) was performed using a diagnostic electrophysiologic catheter located in the superior vena cava. Exposure was terminated when there were signs of diaphragmatic nerve paresis (weakening or cessation of diaphragm movement in response to stimulation).

In group 2, in addition to PV CBA, a series of cryoballoon applications were performed in the region of the posterior wall of the LA. CBA of the posterior wall of the LA was performed according to the technique previously described by A.Aryana et al (2018) [5]. Isolation of the posterior LA wall was performed segmentally, with fixation of the circular catheter alternately in each PV (Fig. 1). From 9 to 13 cryoapplications were performed in the region of the posterior wall of the LA, with the duration of each exposure from 120 to 180 seconds. Intraoperatively, the effectiveness of LA posterior wall isolation using navigation mapping was not assessed. CBA in the region of the posterior wall of the LA was performed under control of the temperature sensor in the esophagus. When the temperature in the esophagus decreased below +15 °C, the exposure was stopped.

All patients were followed up for 1 year postoperatively. The criterion of efficacy was the absence of sustained (lasting more than 30 seconds) tachyarrhythmias (AF, atrial flutter, atrial tachycardia) registered according to ECG and ECG Holter monitoring, occurring after the end of the three-month «blanking» period, or subjective sensations of episodes of palpitations during the follow-up period. Early recurrences were episodes of AF recorded in the first 3 months after CBA. Holter ECG monitoring with heart rate assessment was performed on the 1st day after surgery, at 3, 6, and 12 months. After CBA, antiarrhythmic therapy with class IC or III drugs

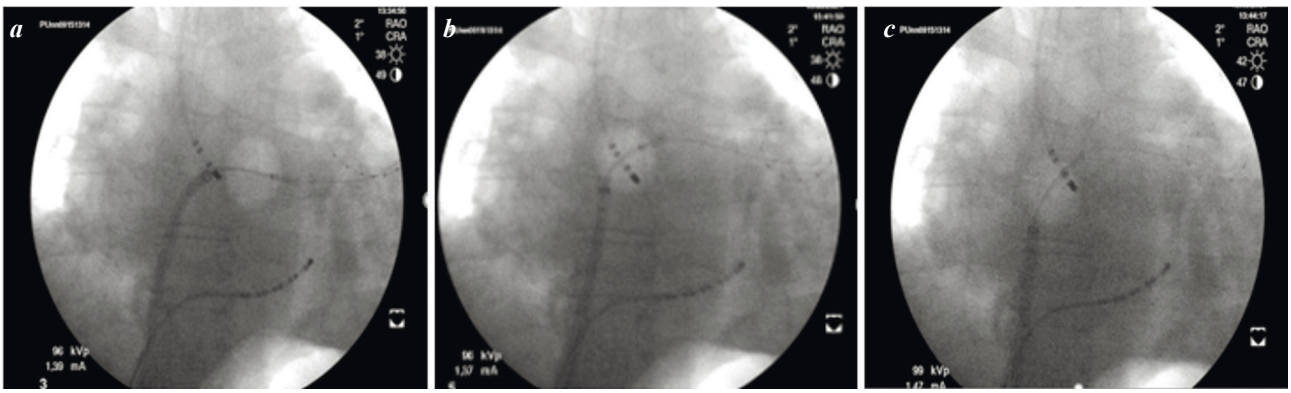


***Fig. 1. Different cryoballoon positioning (a, b, c) during posterior left atrial wall cryoablation where the temperature sensor-electrode is placed in the esophagus.***

(except amiodarone) or beta-blockers was resumed for up to three months (« blanking period») with further withdrawal. Anticoagulant therapy was resumed no later than 3 hours after completion of ablation. The period of anticoagulant therapy prescription was at least two months, with direct oral anticoagulants being preferred. At the end of this period, the decision to continue continuous anticoagulant therapy was based on the $CHA_2DS_2$-VASc thromboembolic risk score. Before the intervention and 12 months after the intervention, patients with recurrent

***Table 1.***

***Clinical and anamnestic characteristics of patients***

| Indicator | PV CBA (n=48) | PV CBA and LA posterior wall (n=41) | P | V | OR; 95% CI |
|---|---|---|---|---|---|
| Age, Me [IQR], years | 62.0 [57.5; 67.5] | 60.0 [54.0; 67.0] | 0.249 | - | - |
| Sex female, n (%) | 35 (72.9%) | 30 (73.2%) | 0.979 | 0.003 | 1.0; 0.4-2.5 |
| Sex male, n (%) | 13 (27.1%) | 11 (26.8%) | | | |
| BMI, M±SD (95% CI), kg/m$^2$ | 30.8±4.9 (29.4-32.3) | 30.0±4.3 (28.6-31.3) | 0.373 | - | - |
| $CHA_2DS_2$-VASc, n (%), points | | | | | |
| 0 | 7 (14.6%) | 1 (2.4%) | 0.03 | - | - |
| 1 | 7 (14.6%) | 16 (39.0%) | 0.06 | - | - |
| ≥2 | 34 (70.8%) | 24 (58.5%) | 0.2 | - | - |
| Arterial hypertension, n (%) | 34 (70.8%) | 35 (85.4%) | 0.129 | 0.174 | 2.4; 0.8-7.0 |
| Diabetes mellitus, n (%) | 7 (14.6%) | 5 (12.2%) | 1.0 | 0.035 | 0.8; 0.2-2.8 |
| Stroke/TIA, n (%) | 3 (6.3%) | 3 (7.3%) | 1.0 | 0.021 | 1.2; 0.2-6.2 |
| CHF, n (%) | 7 (14.6%) | 8 (19.5%) | 0.580 | 0.066 | 1.4; 0.5-4.3 |
| Coronary heart disease, n (%) | 12 (25.0%) | 7 (17.%) | 0.441 | 0.096 | 0.6; 0.2-1.8 |
| Myocardial infarction, n (%) | 3 (6.3%) | 4 (9.8%) | 0.699 | 0.065 | 1.6; 0.3-7.7 |
| TBA, n (%) | 10 (20.8%) | 4 (9.8%) | 0.243 | 0.152 | 0.4; 0.1-1.4 |
| Coronary bypass surgery, n (%) | 1 (2.1%) | 1 (2.4%) | 1.0 | 0.012 | 1.2; 0.1-19.4 |
| Chronic kidney disease, n (%) | 1 (2.1%) | 2 (4.9%) | 0.593 | 0.077 | 2.4; 0.2-27.6 |
| Maximum duration of the episode, n (%), months | | | | | |
| 0-3 | 15 (31.3%) | 9 (22.0%) | 0.148 | - | - |
| 3-6 | 13 (27.1%) | 21 (51.2%) | 0.8 | - | - |
| 6-12 | 19 (39.6%) | 10 (24.4%) | 0.2 | - | - |
| More than 12 | 1 (2.1%) | 1 (2.4%) | 0.3 | - | - |
| History of atrial fibrillation, n (%), years | | | | | |
| <1 | 3 (6.3%) | 1 (2.4%) | 0.59 | - | - |
| 1-2 | 9 (18.8%) | 8 (19.5%) | 0.76 | - | - |
| >2 | 36 (75.0%) | 32 (78.0%) | 0.5 | - | - |
| History of RFA CI, n (%) | 1 (2.1%) | 4 (9.8%) | 0.176 | 0.166 | 5.1; 0.5-47.4 |
| Antiarrhythmic therapy | | | | | |
| AAD class Ic, n (%) | 20 (41.7%) | 21 (51.2%) | 0.367 | 0.096 | 1.5; 0.6-3.4 |
| BB before intervention, n (%) | 42 (87.5%) | 35 (85.4%) | 1.0 | 0.031 | 0.8; 0.2-2.8 |
| AAD class III, n (%) | 22 (45.8%) | 29 (70.7%) | 0.018 | 0.251 | 2.9; 1.2-6.9 |
| AAD class IV, n (%) | 0 | 2 (4.9%) | 0.209 | 0.164 | - |
| Digoxin, n (%) | 2 (4.2%) | 4 (9.8%) | 0.408 | 0.111 | 2.5; 0.4-14.3 |
| LVEF, Me[IQR], % | 60.0 [55.0-60.0] | 55.0 [50.0-60.0] | 0.446 | - | - |
| LA APD, Me[IQR], cm | 4.4 [4.0-4.6] | 4.3 [4.1-4.6] | 0.849 | - | - |
| EchoCG LA volume, M±SD (95% CI), ml | 80.4±16.7 (75.6-85.3) | 81.0±15.4 (76.0-85.8) | 0.877 | - | - |
| LA CT volume, M±SD (95% CI), ml | 89.7±28.8 (80.6-98.8) | 96.9±8.4 (87.8-105.9) | 0.263 | - | - |

Note: hereinafter CBA - balloon cryoablation; PV - pulmonary veins; LA - left atrium; OR - odds ratio; CI - confidence interval; BMI - body mass index; TIA - transient ischemic attack; CHF - chronic heart failure; TBA - transluminal balloon angioplasty; RFA CI - radiofrequency ablation of cavotricuspidal isthmus; AAD - antiarrhythmic drugs; BB - beta-blockers; LVEF - left ventricular ejection fraction; APD - anteroposterior dimension; EchoCG - transthoracic echocardiography; MSCT - multispiral computed tomography.

AF/atrial flutter (AFt) were assessed for quality of life using the SF-36 questionnaire and evaluated for the severity of AF symptoms using the EHRA scale.

**Statistical analysis**

The SPSS Statistics software package version 26.0 (SPSS, Chicago, IL, USA) was used for statistical analysis of the obtained data. The normality of the distribution was checked using the Shapiro-Wilk criterion. The Mann-Whitney test was used to analyze quantitative data with a distribution other than normal in 2 independent samples; the Student's t-test was used to evaluate quantitative data with a normal distribution (if there was a statistically significant difference in variance, the Student's t-test modified by Welch was used). Pearson's chi-square or Fisher's exact test was applied to assess qualitative features in the 2 groups of patients, depending on the minimum expected number. For traits with statistically significant differences, odds estimate with 95% confidence interval (CI) were performed, and a measure of association between nominal traits was determined. Multifield contingency tables followed by post-hoc analysis were used to analyze nominal traits in the 3 groups. The McNemar test was used to assess nominal traits in linked populations at 2 stages of follow-up. A prognostic model was developed by binary logistic regression method to determine the risk of AF recurrence. Kaplan-Meier curves were constructed to graphically reflect the impact of various factors on CBA efficiency. Single- and multivariate analyses using Cox regression were performed to identify independent risk factors for recurrent AF after CBA. Only significant indicators were included in the multivariate analysis. Differences were considered statistically significant at $p<0.05$.

## RESULTS

A total of 89 patients with persistent form of AF were included in the study. 48 (53.9%) patients were randomized to group No.1, 41 (46.1%) patients were randomized to group No.2. According to the randomization conditions, all patients in group 1 underwent PV CBA, and patients in group 2 underwent PV CBA + posterior wall of the LA. Table 1 summarizes the comparative clinical and anamnestic characteristics of patients in both groups. The mean age of the patients was 62±10 years. Women 65 [73%] were predominant among those included in the study. The mean duration of history of AF was 3.0 [1.0; 6.0] years, and the mean duration of maximum AF episode was 5.15 months (95% CI: 4,20-6,10). The mean LA volume was 80.6±16.05 (95% CI: 77.28-84.05) mL. Computed tomography revealed a common PV vestibule in 30 (33.7%) patients. Statistically significant differences between both groups of patients were found when assessing the risk of thromboembolic complications using the $CHA_2DS_2$-VASc scale, as well as the frequency of taking class III antiarrhythmic drugs. Depending on the number of $CHA_2DS_2$-VASc scores, all patients were divided into 3 groups: group 1 included patients with 0 points, group 2 included patients with 1 point, and group 3 included patients with 2 points or more. When comparing patients in each group with different risk of thromboembolic complications, statistically significant differences were obtained with $CHA_2DS_2$-VASc scores of 0. Thus, when comparing the patients, 0 points were predominantly observed in the PV CBA group, which indicates that the patients who underwent PV CBA and LA posterior wall CBA had a higher risk of thromboembolic complications (p=0.03). Also, a higher frequency of class III antiarrhythmic drugs was found among these patients (n=29 [70.7%]). According to the other signs obtained because of clinical-instrumental examination and anamnesis collection, no statistically significant differences were found between patients of both groups.

Intraoperative parameters (Table 2) were not statistically significantly different between the groups. All patients underwent electrical and/or drug-induced cardioversion before the intervention. 43 (48.3%) of 89 patients underwent intervention against the background of sinus rhythm. The remaining 46 (51.7%) out of 89 patients subsequent-

***Table 2.***

***Intraoperative rates, complication rates and arrhythmia recurrence in the two treatment groups***

| | PV CBA (n=48) | PV CBA and LA AW (n=41) | P | V | OR; 95% CI |
|---|---|---|---|---|---|
| LV isolation, n (%) | 48 (100%) | 41 (100%) | - | - | - |
| Duration of operation, Me[IQR], min | 180 [80; 240] | 200 [160; 330] | 0.71 | - | - |
| Radiation dose, Me[IQR], mSv | 2.1 [1.8; 3.5] | 2 [1.6; 3] | 0.52 | - | - |
| Fluoroscopy time, Me[IQR], min | 7 [5; 11] | 7.2 [5.5; 12] | 0.92 | - | - |
| Number of impacts by ZS, Me[IQR], n | - | 10.0 [10.0; 11.0] | - | - | - |
| Thrombosis at the puncture site, n (%) | 4 (8.3%) | 2 (4.9%) | 0.683 | 0.069 | 0.6; 0.1-3.3 |
| RFA CI, n (%) | 6 (12.5%) | 7 (17.1%) | 0.563 | 0.065 | 1.4; 0.4-4.7 |
| Total LV vestibule, n (%) | 15 (31.3%) | 15 (36.6%) | 0.596 | 0.056 | 1.3; 0.5-3.1 |
| Early recurrences of AF/AFt in the blanking period, n (%) | 15 (31.3%) | 12 (29.3%) | 0.839 | 0.021 | 0.91; 0.37-2.26 |
| Long-term recurrences of AF/AFt (3-12 months), n (%) | 22 (45.8%) | 18 (43.9%) | 0.855 | 0.019 | 0.93; 0.4-2.14 |
| AFt, n (%) | 3 (3.35%) | 3 (3.35%) | 1.0 | 0.021 | 1.18; 0.23-6.21 |
| Paroxysmal AF after CBA, n (%) | 8 (9%) | 10 (11.2%) | 1.0 | 0.017 | 1.09; 0.41-2.89 |
| Persistent AF after CBA, n (%) | 9 (10.1%) | 7 (7.9%) | 0.79 | 0.048 | 0.78; 0.27-2.28 |

Note: Hereinafter, hereinafter RW stands for rear wall; AF - atrial fibrillation; AFt - atrial flutter.

ly developed a recurrence of AF and the intervention was performed against the background of arrhythmia recurrence. In 9 patients, restoration of sinus rhythm was noted during PV isolation, and 37 patients underwent electrical cardioversion intraoperatively after CBA. Antral electrical isolation of the PV was achieved in all 89 (100%) patients. The duration of surgery in both groups averaged 180 [157.5;240] min, fluoroscopy time 7.11 [5.41;11.7] min. In group 2, the mean number of applications in the posterior wall region of the LA was 10.0 [9.0; 13.0]. In 7 (7.8%) patients, a decrease in esophageal temperature below 20 °C was noted during CBA, and cryo-intervention was interrupted. In 7 (7.8%) patients there was a decrease in esophageal temperature during one of the exposures in the region of the posterior wall of the LA to +16-17 °C and was observed predominantly at 130-140 sec. Therefore, further cryablation was discontinued. Esophageal temperature recovered over 20°C within 1 minute. Radiofrequency ablation of the cavotricuspid isthmus due to concomitant typical atrial flutter was performed in 6 (12.5%) and 7 (17.1%) patients, respectively. The incidence of the only reported complication (venous thrombosis at the puncture site) was reported in 6 (6.7%) patients; the results in both groups were not statistically significantly different (p=0.683). No major complications (death, cardiac tamponade/hemopericardium, major bleeding, atrial-esophageal fistula, diaphragmatic nerve paresis) were reported during the follow-up period. The effectiveness of the intervention depending on the two CBA strategies, assessed using the log-rank (Mantel-Cox) criterion, was statistically insignificant (p=0.834) (Fig. 2). The mean time to recurrence of AF or atrial flutter (AFt) for patients who underwent PV CBA was 246.35±20.98 days (95% CI: 205.23-287.48), and for patients who underwent PV CBA and LA posterior wall CBA was 253.46±22.66 days (95% CI: 209.05-297.88).

CBA efficacy by the end of the 12-month follow-up period (excluding the blanking period of the first 3 months after CBA) was 54.2% in group 1 and 56.1% in group 2 (Fig. 2). Kaplan-Meier analysis showed that the mean time to occurrence of AF/AFt recurrence after performing CBA, regardless of intervention volume, was 249.63±15.4 days (95% CI: 219.44-279.82).

The study evaluated risk factors for recurrent AF/AFt (Table 3). In the present study, traditional risk factors such as total PV vestibule, LA volume, and duration of history of AF had no statistically significant effect on the risk of recurrent AF/AFt. In single-factor analysis, only recurrence of AF/AFt in the blanking period had a statistically significant effect (p=0.013) on the probability of recurrence of AF/AFt in group 1, which increased the probability of late arrhythmia recurrence 6.4-fold (95% CI: 1.5-27.7). For patients in group 2, in the single-factor analysis, a statistically significant influence on the probability of late recurrence of AF

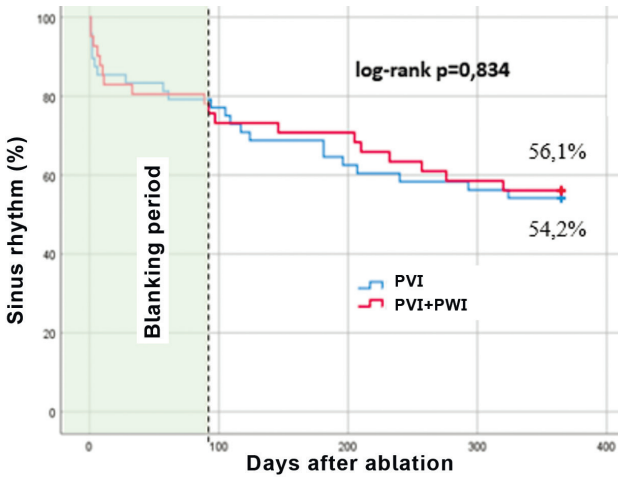


***Fig. 2. Frequency of preservation of sinus rhythm in groups of patients.***

***Table 3.***

***Single- and multivariate analysis of risk factors for atrial fibrillation recurrence after cryoballoon ablation***

| | PV CBA | | PV CBA and LA AW | |
|---|---|---|---|---|
| | HR (95% CI) | p | HR (95% CI) | p |
| Age, years | 1,0 (0,9-1,1) | 0,710 | 1,0 (0,98-1,12) | 0,218 |
| Gender, female | 2,4 (0,7-8,9) | 0,189 | 5,3 (1,2-24,6)* | 0,032 |
| BMI | 1,1 (0,97-1,26) | 0,126 | 0,95 (0,82-1,10) | 0,499 |
| $CHA_2DS_2$-VASc | 0,94 (0,44-2,04) | 0,882 | 1,4 (0,4-4,3) | 0,602 |
| Arterial hypertension | 1,2 (0,34-4,16) | 0,791 | 0,75 (0,13-4,3) | 0,745 |
| Diabetes mellitus | 3,6 (0,61-20,38) | 0,159 | 2,1 (0,3-14,2) | 0,446 |
| Stroke / TIA | 2,5 (0,21-29,6) | 0,467 | - | 0,999 |
| CHD | 1,7 (0,34-8,6) | 0,519 | 0,4 (0,1-2,0) | 0,242 |
| Ischemic heart disease | 0,3 (0,1-1,3) | 0,105 | 0,95 (0,2-4,9) | 0,951 |
| Myocardial infarction | 0,6 (0,04-6,8) | 0,657 | 4,4 (0,4-46,4) | 0,218 |
| AF MED | 1,1 (0,4-3,2) | 0,840 | 0,6 (0,2-2,2) | 0,435 |
| History of AF | 1,2 (0,5-3,4) | 0,665 | 1,2 (0,3-4,3) | 0,8 |
| LVEF | 1,0 (0,9-1,0) | 0,251 | 1,1 (0,96-1,15) | 0,270 |
| LA APD | 2,9 (0,7-12,6) | 0,161 | 0,31 (0,05-1,8) | 0,195 |
| LA volume Echocardiogram | 1,0 (0,97-1,05) | 0,521 | 0,97 (0,9-1,0) | 0,200 |
| Volume of LA CT | 1,0 (1,0 -1,05) | 0,053 | 1,0 (0,99-1,0) | 0,540 |
| Restore HR@ | 1,2 (0,4-3,9) | 0,715 | 0,8 (0,2-2,8) | 0,732 |
| Recurrence of AF and AFt& | 6,4 (1,5-27,7) | 0,013 | 14,0 (1,5-128,5)# | 0,20 |
| Total LV vestibule | 1,1 (0,3-3,6) | 0,938 | 1,8 (0,5-6,6) | 0,358 |
| PV insulation | 1,3 (0,3-4,7) | 0,738 | 0,5 (0,2-2,0) | 0,358 |

Note: HR - hazard ratio; MED - maximum episode duration; @ - during the intervention; & - during the blanking period; * - OR 7.87 (1.47-42.23), p=0.016; # - OR 20.36 (1.99-208.23), p=0.011.

was female sex, and, as in group 1, recurrence of AF/AFt in the first 3 months.

In multivariate analysis, the same factors had a statistically significant effect on the risk of recurrent AF. Considering the identified factors of AF recurrence, a prognostic model was developed to determine the risk of AAF recurrence in the postablation period by binary logistic regression. The regression model obtained is statistically significant (p=0.001). Based on the values of regression coefficients, paroxysm of AF/AFt in the blanking period and female gender have a direct association with the probability of late recurrence of AF and increases the probability of arrhythmia recurrence during the follow-up period by 20.36-fold (95% CI: 1.99-208.23) and 7.87-fold (95% CI: 1.47-42.23), respectively.

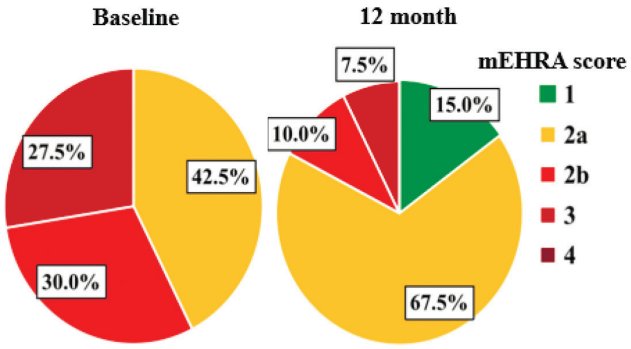


***Fig. 3. EHRA grade at baseline and 12 months after cryoballoon ablation in patients with recurrent atrial fibrillation after intervention.***

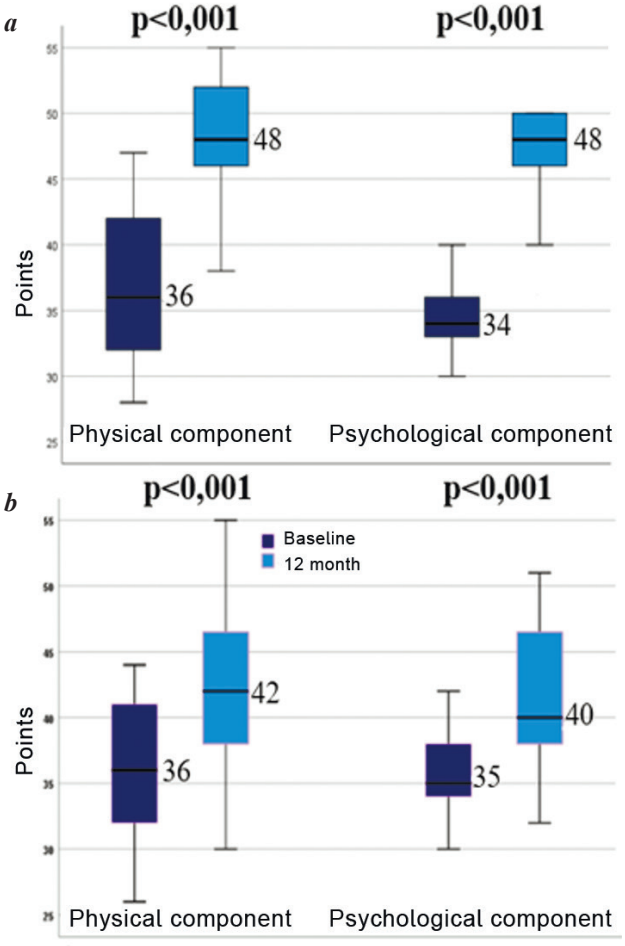


***Fig. 4. Dynamics of physical and psychological health component scores on the SF-36 scale at baseline and 12 months after cryoballoon ablation in patients without (a) and with (b) recurrences of atrial fibrillation after the intervention.***

The next section of our study was to evaluate arrhythmia-related symptoms and quality of life in patients before the intervention and 12 months after the intervention. In accordance with the obtained data, statistically significant dynamics was observed for all classes of the EHRA scale when comparing baseline values and after 12 months of follow-up: The number of patients with class 3 decreased from 11 (27.5%) patients to 3 (7.5%) (p=0.031), with class 2b from 12 (30.0%) to 4 (10.0%) (p=0.021), while the number of patients with class 2a increased from 17 (42.5%) to 27 (67.5%) (p=0.021). Initially, no patient was categorized as grade 1, and after 12 months, 6 patients had EHRA grade 1 (p=0.008). At both baseline and 12 months, no patients with grade 4 were noted (Fig. 3).

Consistent with these findings, there was a statistically significant increase in the psychological and physical component scores of the SF-36 scale (p<0.001) among patients who had a recurrence of AF after 12 months, regardless of the amount of intervention: from 36.0 points to 42.0 points on the physical component of the SF-36 scale and from 35.0 points to 40.0 points on the psychological component of the SF-36 scale in patients with recurrent AF, and from 36.0 points to 48.0 points on the physical component of the SF-36 scale and from 34.0 points to 48.0 points on the psychological component of the SF-36 scale in patients without recurrent AF. An increase in scores was observed in 82.5% of patients on the physical component of the SF-36 scale and in 80.0% of patients on the psychological component of the SF-36 scale (Fig. 4).

## DISCUSSION

In persistent AF, more pronounced electrical and structural remodeling of the LA is observed, especially in the region of the posterior LA wall [7, 8]. These pathologic processes contribute to the substrate that maintains AF and probably causes the insufficient effectiveness of PV isolation in persistent AF. Meta-analyses of several randomized and observational studies have shown some advantages of additional LA posterior wall ablation compared with PV isolation alone for this form of arrhythmia [9-11]. However, the role of additional influences outside of the PV is currently undefined [1].

It is anticipated that successful treatment of persistent AF will be determined by technologies that identify as accurately as possible the «arrhythmogenic substrate» - the non-PV trigger of AF. The concept of «extended» balloon cryoablation involving additional cryo-interventions in the region of the posterior wall of the LA was first proposed by A.Aryana et al. (2018) and is based on the assumption that the sources of AF can be eliminated without their precise electrophysiological and anatomical identification in the absence of technology for mapping of the said «sources» of AF to date [5]. In this study, higher intervention efficacy was observed in the group of patients who underwent cryoablation of the PV and LA posterior wall. In contrast to the work of A.Aryana et al. (2018), our study did not show significant benefits of «extended» LA cryoablation. First,

this may be due to the high-density voltage mapping of the LA performed by the foreign coauthors as part of the same extended cryoablation procedure and the application of additional radiofrequency ablation in the oposterior wall. Thus, according to the results of this work, more than 30% of patients had no electrical isolation in the region of the posterior wall of the LA, in connection with which radiofrequency ablation of this zone was performed to achieve isolation. Despite the lack of significant differences in the efficacy of the two approaches, our results indicate the safety of the extended cryoablation method. Compared to the work of A.Aryana et al (2018), no major complications were reported in both groups in our study.

According to the results of the performed study, the main predictor of AF recurrence in the interval of 3-12 months after CBA is the recurrence of AF/AFt in the blanking period. The obtained data are consistent with the results of earlier studies and meta-analyses indicating the appropriateness of individualized assessment of the risks of AF recurrence after cryoablation in patients with persistent AF [12, 13].

Another aspect of our study was to evaluate arrhythmia-related symptoms and quality of life in patients before and 12 months after intervention in patients with arrhythmia recurrence. After performing CBA, there is a significant improvement in quality of life in both patients without recurrent AF and patients with recurrent AF. In addition, the severity of arrhythmia-related symptoms is reduced in patients with recurrences after performing CBA.

At present, despite the use of modern ablation techniques, no benefit of additional off-PV interventions on improving the efficacy of the intervention has been demonstrated. Arguably, the strategy for the interventional treatment of persistent AF should include investigation of the LA substrate, which is known to be a major factor in the recurrence of AF after intervention. The study of structural changes in LA myocardium according to the data of cardiac magnetic resonance imaging with delayed contrast imaging will allow to improve the strategy of catheter ablation in persistent AF. Early recurrence of AF (in the first 3 months after the intervention) appeared to be an independent risk factor for recurrence of AF in the distant period after CBA in both groups. There was a significant reduction in symptom severity and improvement in quality of life after the intervention in patients with and without recurrent AF.

## CONCLUSION

Extended CBA combined with cryoablation of the LA posterior wall is comparable in efficacy to standard PV CBA. The indication for extended CBA should be determined considering potential clinical and instrumental predictors of intervention efficacy. A promising direction is the study of structural changes in LA myocardium according to the data of cardiac magnetic resonance imaging with delayed contrasting. Recurrence of AF/AFl in the blanking period is an independent risk factor for recurrence of AF in the distant periods after intervention. Improvement in quality of life and reduction in the severity of arrhythmia-related symptoms in patients with recurrences may indicate a partial effect of CBA.

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# MULTIFACTORIAL MODEL FOR PREDICTION OF THE DEVELOPMENT OF POLYMORPHIC VENTRICULAR TACHYCARDIA IN PATIENTS WITH DRUG-INDUCED QT INTERVAL PROLONGATION INDUCED BY CLASS III ANTIARRHYTHMIC DRUGS

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**Aim.** To develop a multifactorial model for predicting the development of polymorphic ventricular tachycardia (VT) in patients with drug-induced long QT syndrome (LQTS) induced by class III antiarrhythmic drugs (AADs) by identifying electrocardiographic, laboratory and molecular genetic predictors.

**Methods.** The study included 64 patients (37 (57.9%) women and 27 (42.1%) men, mean age 57.2±9.4 years) with ischemic heart disease and/or arterial hypertension. and cardiac arrhythmias, in which drug-induced prolongation of the QTc interval (Bazett) (over 450 ms in men and over 470 ms in women) was noted with the use of class III AADs (amiodarone or sotalol) in a cardiac hospital. Depending on the presence or absence of non-sustained polymorphic VT according to 24-hour ECG Holter monitoring, patients were further divided into two groups: 17 patients with episodes of non-sustained polymorphic VT and 47 patients without such episodes. All patients underwent clinical and laboratory, instrumental and molecular genetic studies, which included taking an anamnesis, recording ECG in 12 leads, biochemical blood test, determining the levels of neuronal NO-synthase (NOS1) and the adapter protein of neuronal NO-synthase (NOS1AP) in blood serum by enzyme immunoassay, determination of nitric oxide synthase gene polymorphisms by polymerase chain reaction. To assess the relationship of the studied parameters with the achievement of the end point, the method of logistic regression with a binary response and the logit function of the connection was used.

**Results.** To assess the risk of developing non-sustained polymorphic VT in patients with drug-induced LQTS while taking class III AADs, a complex binary logistic regression model was developed, including the following indicators: patient gender (p=0.019), relative variance of the QT interval (p=0.002), duration of the $T_{peak}$-$T_{end}$ interval, (p=0.034), serum magnesium (p=0.004) and NOS1 (p=0.004) levels, as well as the AA genotype of the G84A polymorphism of the NOS1 gene (p=0.049). With the calculated value of the threshold probability p≥0.48, the developed model makes it possible to identify patients at high risk of developing polymorphic VT in patients with drug-induced LQTS with a sensitivity of 94.12%, a specificity of 89.36%, and an area under the ROC curve of 0.977 (0.95-1.0, p<0.001).

**Conclusion.** The developed complex model will allow predicting the risk of proarrhythmic effects in patients with drug-induced LQTS, which will lead to a decrease in the number of cardiovascular events in this category of patients.

**Key words:** drug-induced long QT syndrome; ventricular tachycardia; antiarrhythmic drugs; magnesium; neuronal nitric oxide synthase; NOS1 gene G84A polymorphism

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Nowadays cardiovascular diseases are the main cause of death and disability in most countries of the world. The main causes of death from cardiovascular diseases are the progression of chronic heart failure (HF) (about half of all death cases) and sudden cardiac death (SCD) (the other half) [1]. In the majority of cases (85%), the mechanisms of SCD are ventricular tachyarrhythmias - ventricular tachycardia (VT) and ventricular fibrillation (VF) with subsequent development of asystole [2, 3].

QT interval prolongation is considered a generally accepted risk factor and an independent predictor of the development of life-threatening ventricular tachyarrhythmias and SCD in patients both with and without structural heart disease [2, 4, 5]. By creating a functional substrate for the transmural re-entry mechanism, QT interval prolongation can initiate the development of episodes of polymorphic VT, which transforms into VF in 20% of cases [5-7]. It leads to an ever-increasing interest in various aspects of the long QT syndrome (LQTS), methods of its diagnosis,

treatment and risk stratification in different categories of patients.

It is widely known that LQTS can be both congenital and acquired. Acquired form of LQTS occurs in clinical practice much more often and is associated mostly with the use of drugs that prolong the QT interval [6-9]. To date, more than two hundred drugs that have the ability to cause QT interval prolongation and ventricular arrhythmias have been described. The first place among them is held by class III antiarrhythmic drugs (AADs) - amiodarone and sotalol [7, 9, 10].

The frequency of AADs prescription worldwide is steadily increasing. The global AADs market volume in 2019 amounted to USD 796.8 million, and during 2020-2021, given the unprecedented impact of the Covid-19 pandemic, these figures increased by another 12.9% and are approaching USD 900 million. 32.3% of this volume falls on class III AADs, which rank second in terms of frequency of use among all antiarrhythmics and are second only to beta-blockers (34.6%) [11].

The number of detection and registration of cases of drug-induced LQTS also has a pronounced upward trend, largely due to an increase in the level of awareness of medical personnel and patient education, as well as an improvement in the quality of diagnosis [7, 10].

Risk stratification of drug-induced LQTS remains challenging. Traditionally used electrophysiological markers of drug-induced LQTS include corrected QT interval (QTc) duration, QT interval dispersion and microvolt T-wave alternation [12-16]. However, recently a number of questions have arisen regarding the methodology for determining the beginning and end of the QT interval, as well as finding the optimal QT correction formula, taking into account the individual form of the dependence of the QT interval duration on the heart rate (HR) for each patient [17]. Moreover, use of many of the promising research methods in patients with LQTS is difficult due to the presence of a persistent form of atrial fibrillation (AF), low-amplitude or negative T waves, widened QRS complexes and continuous ventricular pacing.

The role of the molecular genetic component in the mechanism of drug-induced LQTS is still insufficiently studied, and the literature data are largely contradictory in their estimates [18-21]. According to the «repolarization reserve» concept, in patients with drug-induced LQTS there is a genetically determined low repolarization reserve, that is, a set of mutations in the genes of ion transporters, which is not manifested clinically until contact with a trigger drug [22]. In recent years, a number of «latent» mutations in the genes of congenital LQTS have been identified and functional polymorphisms in the same or other genes associated with an increased risk of SCD have been found [18, 20, 23].

The results of diverse studies suggest that the nitric oxide (NO) synthesis system may be involved in the pathological process, one of the effects of which is participation in the regulation of ventricular repolarization [19, 24, 25].

To date, a number of scores and indices have been proposed that allow assessing the risk of developing drug-induced LQTS, the most common of which are the Tisdale, QT-DDI and RISQ-PATH scores [26, 27, 28]. However, none of the above mentioned scores makes it possible to predict the risk of developing drug-induced ventricular arrhythmias induced by QT interval prolongation.

Development of complex mathematical models which allow to assess the risk of drug-induced LQTS and associated polymorphic VT initiation will make it possible to implement the concept of a personalized approach to prescribing antiarrhythmic therapy, which will lead to a decrease in the number of side effects when taking class III AADs, a decrease in the number of cardiovascular complications and SCD cases in this category patients.

The aim of this study was to develop a comprehensive model for predicting the development of polymorphic VT in patients with drug-induced LQTS induced by class III AADs by identifying electrocardiographic, laboratory and molecular genetic predictors.

## METHODS

The study included 64 patients (37 (57.9%) women and 27 (42.1%) men, mean age 57.2±9.4 years) with coronary artery disease (CAD) and/or arterial hypertension and cardiac arrhythmias, in which drug-induced QTc interval prolongation (Bazett) (over 450 ms in men and over 470 ms in women) induced by class III AADs was noted in a cardiological hospital. Depending on the presence or absence of non-sustained polymorphic VT according to 24-hour Holter ECG monitoring (HM-ECG), the patients were divided into two groups: the «VT» group included 17 (26.6%) patients with episodes of non-sustained polymorphic VT and the «Without VT» group which consisted of 47 (73.4%) patients without episodes of non-sustained polymorphic VT. The average duration of an episode of polymorphic VT was 7353 [3250; 10861] ms, average HR in one episode - 245 [215; 268] beats per minute, the average number of episodes per day was 2.71 [1; 4].

In 7 patients (41.2%) the development of VT was accompanied by dizziness, in 3 (17.6%) - by presyncope,

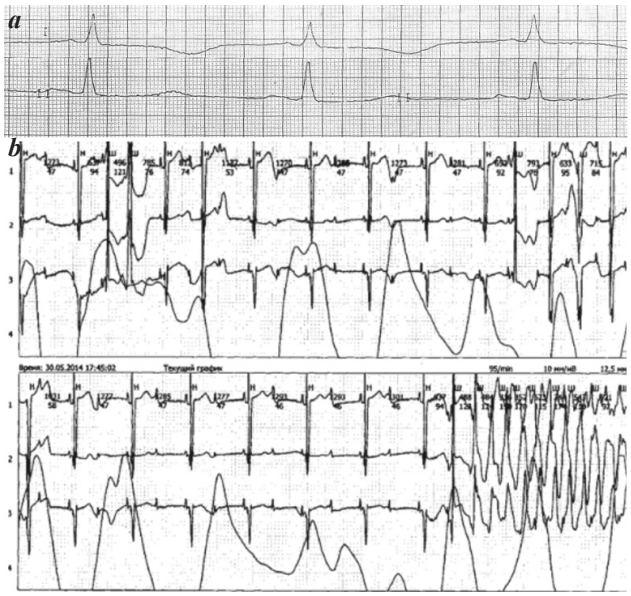


***Fig. 1. The results of the examination of a 51-year-old patient with drug-induced QT interval prolongation when using 400 mg of amiodarone per day: a - ECG fragment, b - HM-ECG fragment (an episode of non-sustained polymorphic VT).***

in 3 (17.6%) it manifested itself in the form of syncope, in 2 (11.8%) - in the form of chest pain, 6 (35.3%) were asymptomatic. Considering the absence of episodes of polymorphic VT in patients before the antiarrhythmic therapy initiation, all these episodes that occurred while taking drugs were classified as drug-induced. None of the patients included in the study experienced transformation of VT into VF or ventricular flutter.

Fig. 1 shows fragments of ECG (drug-induced prolongation of the QTc interval up to 527 ms) and HM-ECG (non-sustained polymorphic VT episode) of a 51-year-old patient taking 400 mg of amiodarone per day.

Patients with and without non-sustained polymorphic VT associated with drug-induced LQTS were comparable in age at the time of inclusion in the study. In the «VT» group, women predominated (77.5%), while in the «Without VT» group, female patients accounted for 51.1% (p=0.050). According to the clinical and nosological characteristics (presence and stage of hypertension, form of CAD, functional class of CHF according to NYHA classification), the groups of patients were comparable (Table 1).

It should be noted that before the antiarrhythmic therapy initiation in the «VT» group, episodes of non-sustained monomorphic VT were recorded in 7 (41.2%) patients, in the «Without VT» group - in 12 (25.5%) patients (p=0.331). There were no episodes of non-sustained polymorphic VT prior to antiarrhythmic therapy initiation in patients included in the study.

In the «VT» group amiodarone was prescribed to 10 (58.8%) patients and sotalol - to 7 (41.2%) patients, which did not significantly differ from the indices of the «Without VT» group, in which 32 patients (68.1%) received amiodarone and 15 (31.9%) received sotalol (p=0.563).

When assessing the total number of drugs that affect the QT interval duration, no significant differences between the groups were found (p=0.589). Thus, 5 (29.4%) patients in the «VT» group and 18 (38.2%) patients in the «Without VT» group took 2 drugs that affect the duration of the QT interval (class III AAD and diuretic). Meanwhile 12 (71.6%) patients in the «VT» group and 29 (61.2%) patients in the «Without VT» group were taking only one such drug (class III AAD).

***Table 1.***

***Clinical characteristics of the patient groups***

| | | Group | | p |
|---|---|---|---|---|
| | | «VT» (n=17) | «Without VT» (n=47) | |
| Female sex, n (%) | | 13 (77.5) | 24 (51.1) | 0.050 |
| Age, years (M±SD) | | 56.2±12.3 | 57.4±8.3 | 0.584 |
| BMI, kg/m$^2$ (M±SD) | | 28.3±5.1 | 30.2±4.3 | 0.145 |
| AH, n (%) | No AH | 3 (17.6) | 4 (8.5) | 0.322 |
| | Stage 1 | 4 (23.5) | 7 (14.9) | 0.431 |
| | Stage 2 | 10 (58.8) | 34 (72.3) | 0.310 |
| | Stage 3 | 0 (0) | 2 (4.3) | 0.960 |
| CAD, n (%) | No CAD | 4 (23.5) | 4 (8.5) | 0.129 |
| | CA | 1 (5.9) | 5 (10.6) | 0.547 |
| | VA | 2 (11.8) | 4 (8.5) | 0.700 |
| | CCS Grade I | 3 (17.6) | 11 (23.4) | 0.617 |
| | CCS Grade II | 6 (35.3) | 21 (44.7) | 0.502 |
| | CCS Grade III | 1 (5.9) | 2 (4.3) | 0.791 |
| | MI history | 3 (17.6) | 7 (14.9) | 0.789 |
| HF NYHA Class, n (%) | 0 | 1 (5.9) | 2 (4.3) | 0.791 |
| | I | 8 (47.1) | 27 (57.4) | 0.462 |
| | II | 6 (35.3) | 15 (31.9) | 0.801 |
| | III | 2 (11.8) | 3 (6.4) | 0.479 |
| Arrhythmias, n (%) | Paroxysmal AF | 3 (17.6) | 15 (31.9) | 0.382 |
| | Persistent AF | 4 (23.5) | 15 (31.9) | 0.610 |
| | Frequent PVCs | 7 (41.2) | 14 (29.8) | 0.478 |
| | NSMVT | 7 (41.2) | 12 (25.5) | 0.331 |
| | Frequent SVEs | 2 (11.8) | 3 (6.4) | 0.479 |

Note: here and further VT - ventricular tachycardia; BMI - body mass index; AH - arterial hypertension; CA - coronary atherosclerosis; VA - vasospastic angina; CAD - coronary artery disease; CCS - Canadian Cardiovascular Society; MI - myocardial infarction; HF - heart failure; NYHA - New York Heart Association; AF - atrial fibrillation; PVC - premature ventricular contraction; NSMVT - non-sustained monomorphic ventricular tachycardia; SVE - supraventricular extrasystole.

Exclusion criteria from the study were: QTc interval greater than 450 ms in men and 470 ms in women before class III AAD initiation; taking any drugs other than Class III AAD with a confirmed or probable risk of torsades de pointes, listed in the «CredibleMeds» database [29]; taking class III AAD at the outpatient stage (prior to admission to the hospital); genotyped congenital LQTS; recent acute myocardial infarction or coronary artery bypass grafting (less than 3 months before enrollment in the study); left ventricular hypertrophy (Sokolov-Lyon index >35mm); an increase in the duration of the QRS complex ≥100 ms; permanent and long-term persistent form of AF; 24 hours after restoration of sinus rhythm in patients with paroxysmal and persistent AF; disorders of atrioventricular conduction (2$^{nd}$ and 3$^{rd}$ degree AV-block); uncorrected pathology of the endocrine system; active inflammatory process of any localization of infectious, autoimmune or other etiology.

Drug-induced QTc interval prolongation was registered if QTc interval was greater than 450 ms in men and greater than 470 ms in women in accordance with the recommendations of the European Medicine Agency (European Medicine Agency CHMP/ICH/2/04. ICH Topic E 14 The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs) [30], as well as the 2009 AHA/ACCF/HRS Guidelines for Standardization and Interpretation of Electrocardiogram [31].

All patients underwent clinical, laboratory and instrumental studies, including history

taking, 12-lead ECG recording, 24-hour HM-ECG, biochemical blood test, determination of the levels of neuronal NO-synthase (NOS1) and the neuronal NO-synthase adapter protein (NOS1AP) in blood plasma by ELISA test, as well as the determination of polymorphism G84A of the NOS1 gene and C786T of the NOS3 gene using polymerase chain reaction.

An electrocardiographic study was performed in patients initially - before the antiarrhythmic therapy initiation, and then during the administration of antiarrhythmic therapy. Before the baseline ECG study all AADs, including beta-blockers, were canceled taking into account their elimination half-lives. ECG during antiarrhythmic therapy was recorded daily. We took into account the indicators recorded before the development of polymorphic VT («VT» group), or against the background of the first episode of drug-induced QT interval prolongation («Without VT»). HM-ECG was performed on the day when prolongation of the QT interval was recorded according to the standard ECG. When registering drug-induced VT, all class III AADs were canceled, and patients were transferred to beta-blockers.

Statistical analysis was performed using the STATISTICA 10.0 software package (developer - StatSoft. Inc), license number AXXAR207F394425FA-Q, and the RStudio 1.0.143 program (version of the «R» language - 3.4.1, package: «ROCR»).

Since most of the quantitative characteristics did not obey the normal distribution law, non-parametric methods were used for comparison. Comparison of numerical indicators between two independent groups was carried out using the non-parametric Mann-Whitney U-test. The statistical significance of differences between qualitative characteristics was assessed using the $\chi^2$-Pearson test. The threshold value of the level of statistical significance was taken equal to 0.05.

To assess the relationship of the studied parameters with the achievement of the end point, we used the method of logistic regression with binary response and the logit function of the connection. The method was chosen due to the fact that the dependent variable is dichotomous, and the independent variables characterize both categorical and quantitative features. To assess the diagnostic significance of the obtained regression model, the method of analyzing ROC curves was used. With its help, the optimal separating value of a quantitative trait was determined, which allowed to classify patients according to the degree of risk of outcome, with the best combination of sensitivity and specificity.

The study was performed in accordance with Good Clinical Practice standards and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion in the study.

## RESULTS

In patients with episodes of non-sustained polymorphic VT, there was a tendency to take class III AADs for a shorter period (2.88±1.22 days vs. 3.58±1.36 days in patients without polymorphic VT, p=0.053). The average daily dosages of AADs used in both groups were comparable: for amiodarone - 339±201 mg in the «VT» group vs. 311±143 mg in the «Without VT» group, p=0.711; for sotalol - 160±74 mg in the «VT» group vs. 160±38 mg in the «Without VT» group, p=0.920. Electrocardiographic parameters of patients while taking class III AADs are given in Table 2.

As follows from the table 2, patients with non-sustained polymorphic VT were characterized by a significantly longer QT interval duration (p=0.042), as well as QTc and JTc intervals duration (p=0.001), which characterize the total duration of myocardial repolarization. The QT and JT interval dispersion levels in both groups were comparable (p>0.05), however, at the same time, the relative QT interval dispersion was significantly higher in the «VT» group (5.55 [4.85; 6.11] vs. 4.40 [3.99; 4.72] in the «Without VT» group, p<0.001).

The tendency to larger values of the $T_{peak}$-$T_{end}$ interval duration (p=0.127) and dispersion (p=0.190) was observed, but did not reach the criteria of statistical significance. The values of indicators characterizing myocardial depolarization in the studied patients also did not have significant differences, with the exception of fQRS, which was significantly more common in patients with non-sustained polymorphic VT (29.4% vs. 6.4%, p=0.042). The values of the spatial QRS-T angle, on the contrary, showed

***Table 2.***

***Electrocardiographic parameters of patients while taking class III antiarrhythmic drugs***

| | Group | | p |
|---|---|---|---|
| | «VT» (n=17) | «Without VT» (n=47) | |
| Mean HR, b.p.m. | 65.1 [60; 70] | 64.2 [58; 69] | 0.789 |
| QT interval duration, ms | 492.1 [457; 537] | 461.9 [448; 483] | 0.042 |
| QTc interval duration (Bazett), ms | 509.7 [479; 542] | 474.4 [458; 488] | 0.002 |
| QT interval dispersion, ms | 83.6 [59; 98] | 69.7 [58; 82] | 0.419 |
| JTc interval duration (Bazett), ms | 427.9 [395; 462] | 388.1 [372; 398] | 0.001 |
| JT interval dispersion, ms | 77.2 [52; 90] | 65.3 [54; 75] | 0.435 |
| Tpeak-Tend interval duration, ms | 131.4 [113;147] | 123.1 [113; 135] | 0.187 |
| Tpeak-Tend interval dispersion, ms | 35.3 [30; 40] | 31.9 [20; 40] | 0.190 |
| Tpeak-Tend / QT ratio | 0.26 [0.25;0.29] | 0.27 [0.25; 0.29] | 0.665 |
| QRS complex duration, ms | 86.3 [80; 90] | 85.4 [80; 90] | 0.686 |
| fQRS, n (%) | 5 (29.4%) | 3 (6.4%) | 0.042 |
| Spatial QRS-T angle, degrees | 99.0 [74; 112] | 100.1 [71; 118] | 0.908 |
| Relative QT interval dispersion | 5.55 [4.85; 6.11] | 4.40 [3.99; 4.72] | <0.001 |

Note: here and further HR - heart rate; QTc - corrected QT interval; JTc - corrected JT interval; fQRS - QRS complex fragmentation.

no significant intergroup differences (median 99.0 vs. 100.1 degrees, p=0.908).

When studying the content of electrolyte balance indicators in groups of patients with and without non-sustained polymorphic VT, significant differences in the blood serum magnesium levels were revealed (0.76 [0.72; 0.82] vs. 0.89 [0.76; 0.90] mmol/l in the «VT» group compared with the «Without VT» group, p=0.042). The levels of other serum electrolytes in both groups were comparable (Table 3).

According to ELISA test results, in patients with episodes of non-sustained polymorphic VT, the level of neuronal nitric oxide synthase was significantly lower compared to patients without VT (1.44 [1.22; 1.67] μg/l and 1.88 [1.49; 2.06] μg/L, p=0.002). Similar differences were found for the level of neuronal nitric oxide synthase adapter protein (NOS1AP). In patients in the «VT» group, the level of NOS1AP was significantly lower compared to patients in the «Without VT» group (280 [218; 398] ng/l and 435 [277; 583] ng/L, p=0.02).

Results of a genetic study of polymorphic variants of nitric oxide synthase genes are presented in Table 4. Thus, in the «VT» group, there was a tendency towards a more frequent occurrence of the A allele (52.9%) of the G84A polymorphism of the NOS1 gene compared to patients in the «Without VT» group (33.0%, p=0.064). A similar trend was also registered for the AA genotype (29.4% in the «VT» group versus 10.6% in the «Without VT» group, p=0.068). There were no significant intergroup differences in the distribution of genotypes and alleles of the polymorphic variant C786T of the NOS3 gene.

In order to select the optimal statistical risk model for the development of non-sustained polymorphic VT in patients with drug-induced LQTS induced by class III AADs, we used the technology of stepwise direct selection of all possible models that can be built for a given set of variables on samples of limited volume.

As possible predictors, the analyzed models included clinical, electrocardiographic, laboratory and molecular genetic parameters. As a result, a logistic regression model with a binary response was selected, including the following predictors: patient's gender, relative QT interval dispersion, $T_{peak}$-$T_{end}$ interval duration, magnesium and NOS1 serum levels and AA genotype of the G84A polymorphism of the NOS1 gene. Estimates of the coefficients of the resulting model are presented in Table 5.

During the analysis, a logistic regression equation was calculated to assess the influence of a combination of factors on the likelihood of developing polymorphic VT:

$$p=1/(1+e^{-(18.9725+2.7637\cdot X1+0.0692\cdot X2+6.4356\cdot X3-15.529\cdot X4-7.2296\cdot X5+2.3781\cdot X6)}),$$

where X1 is the patient's gender (0 - male, 1 - female); X2 - $T_{peak}$-$T_{end}$ interval duration (ms); X3 - relative QT interval dispersion; X4 - magnesium serum level (mmol/l); X5 - NOS1 serum level (μg/l); X6 - AA genotype of the G84A polymorphism of the NOS1 gene (0 - absence, 1 - presence).

If a p value is ≥0.48, a decision is made to refer the patient to a group with a high risk of developing non-sustained polymorphic VT caused by drug-induced LQTS. If p<0.48, the patient is predicted to be at low risk of developing non-sustained polymorphic VT.

At the selected cut-off threshold, the sensitivity of the model was 94.12%, the specificity - 89.36% and the diagnostic accuracy - 90.62%. Cross-validation was performed using a cross-validation method with accuracy as a function of price: the average accuracy was 86.79%, the area under the

***Table 3.***

***Comparative characteristics of serum electrolytes levels in studied groups of patients***

| | Group | | p |
|---|---|---|---|
| | «VT» (n=17) | «Without VT» (n=47) | |
| Potassium, mmol/l | 4.15 [3.70; 4.50] | 4.34 [4.10; 4.50] | 0.261 |
| Sodium, mmol/l | 143.4 [142; 145] | 143.7 [142; 145] | 0.687 |
| Calcium, mmol/l | 2.23 [2.18; 2.31] | 2.27 [2.09; 2.46] | 0.855 |
| Magnesium, mmol/l | 0.76 [0.72; 0.82] | 0.89 [0.76; 0.90] | 0.042 |
| Chlorides, mmol/l | 105.6 [103; 108] | 104.9 [103; 107] | 0.433 |

***Table 4.***

***Distribution of frequencies of genotypes and alleles of polymorphisms of nitric oxide synthase genes among patients of the studied groups***

| | Group «VT» (n=17) | Group «Without VT» (n=47) | p |
|---|---|---|---|
| Genotype according to the G84A polymorphic variant of the NOS1 gene | | | |
| GG, n (%) | 4 (23.5) | 23 (48.9) | 0.121 |
| GA, n (%) | 8 (47.1) | 19 (40.4) | 0.636 |
| AA, n (%) | 5 (29.4) | 7 (10.6) | 0.068 |
| Allele of the G84A polymorphic variant of the NOS1 gene | | | |
| G, n (%) | 16 (47.1) | 63 (67.0) | 0.064 |
| A, n (%) | 18 (52.9) | 31 (33.0) | |
| Compliance with the Hardy-Weinberg equilibrium | $\chi^2$=0.05, p=0.97 | $\chi^2$=0.85, p=0.65 | - |
| Genotype according to the C786T polymorphic variant of the NOS3 gene | | | |
| CC, n (%) | 3 (17.6) | 12 (25.5) | 0.511 |
| CT, n (%) | 7 (41.2) | 19 (40.4) | 0.941 |
| TT, n (%) | 7 (41.2) | 16 (34.1) | 0.683 |
| Allele of the C786T polymorphic variant of the NOS3 gene | | | |
| C, n (%) | 13 (38.2) | 43 (45.8) | 0.450 |
| T, n (%) | 21 (61.8) | 51 (54.2) | |
| Compliance with the Hardy-Weinberg equilibrium | $\chi^2$=1.41, p=0.49 | $\chi^2$=0.73, p=0.69 | - |

Note: here and further NOS1 - neuronal NO-synthase; NOS3 - endothelial NO-synthase.

ROC curve - 0.977 (0.95-1.0, p<0.001), which indicated a high predictive ability of the obtained model (Fig. 2).

The possibility of calculating the threshold probability of developing non-sustained polymorphic VT is implemented in the form of an online calculator, the user interface of which for a personal computer is shown in fig. 3.

The value of each of the required indicators can be entered manually, and the gender and genotype of the patient should be chosen from provided variants. The program calculates the threshold probability and outputs a numerical value that is interpreted by the user according to the specified possible outcomes. A significant advantage of the developed online calculator is the simplification of the calculations, which allows it to be widely used in clinical practice.

## DISCUSSION

Nowadays there is no doubt that due to the frequent use of class III AADs and their combinations with other drugs, the risk of developing drug-induced QT interval prolongation and associated ventricular arrhythmias is increasing. A significant number of studies by domestic and foreign authors are devoted to identifying clinical, electrocardiographic, laboratory, and molecular genetic predictors of drug-induced QT interval prolongation and associated proarrhythmic effects [12, 15, 18, 19, 27, 28]. In real clinical practice, the use of only a small range of indicators widely described in the literature does not allow to assess the prognosis and predict the development of life-threatening ventricular arrhythmias in this category of patients. In this regard, the most reasonable and promising is an integrated approach that allows to use a combination of both electrocardiographic (primary and highly available) and laboratory and molecular genetic (more complex and specialized) methods, which determines the prospects and necessity of this study.

It should be noted that the developed multivariate model includes both widely studied markers (female gender, $T_{peak}$-$T_{end}$ interval duration, serum magnesium level) and new indicators not previously considered in this regard (relative QT interval dispersion, serum NOS1 level, AA genotype of the G84A polymorphism of the NOS1 gene).

Female gender is traditionally considered a risk factor for QT interval prolongation and the development of drug-induced ventricular arrhythmias [32]. According to various data, polymorphic VT is 2-3 times more often recorded in women, both with congenital and acquired LQTS [32, 33]. These differences are caused by a combination of anatomical, functional, hormonal, vegetative and genetic factors. In addition to a longer QT interval at rest, women's predisposition to drug-induced prolongation of the QT interval is explained by lower body weight compared to men and, consequently, increased plasma concentrations of drugs [34]. Moreover, female cardiomyocytes are smaller and contract more slowly, which causes an increase in the duration of the action potential [32]. In animal model studies, female cardiomyocytes showed a more pronounced drug-induced closure of fast potassium channels, which disrupted the outflow of potassium from the cell. These changes resulted in delayed repolarization, prolongation of the action potential, and subsequent early activation of sodium and L-type calcium channels, which, in turn, led to triggered early post-depolarizations, VT and SCD [35, 36].

QT interval dispersion is defined as the difference between the largest and smallest values of the QT interval measured in all ECG leads [15]. There is no clear definition of normal QT interval dispersion values. According to the literature data, the normal values of this indicator vary from 30 to 70 ms [13, 15]. Thus, according to the results of 51 studies conducted among more than 8 thousand healthy individuals of different ages, the average values of the dispersion of the QT interval were in the range from 10.5 ± 10 ms to 71 ± 7 ms, without significant difference depending on age and gender [13, 15, 37]. According to the Rotterdam study, which included more than 5,000 participants, in apparently healthy people over the age of 55, in a group with a QT interval dispersion of more than 60 ms, there was a two-fold increase in overall mortality compared with a group where the dispersion was less than 39 ms [37].

In patients with congenital LQTS, the diagnostic value of increased QT interval dispersion is also of great importance. S. Priori et al. showed that patients not responding to beta-blocker therapy have significantly higher QT interval dispersion than those responding well to this therapy (137±52 vs. 75±38 ms, p<0.05) [38]. In a recent study by A. Friedman et al. it was demonstrated that the QT interval dispersion when taking therapeutic doses of amiodarone was significantly higher than when taking sotalol and dofetilide (p=0.006), but it did not cause an increase in the risk of episodes of polymorphic VT [13]. Sotalol in patients with CAD did not cause an increase in QT interval dispersion, however, Dancey et al. described increased QT interval dispersion in 4 cases of torsades de pointes caused by sotalol in patients with chronic renal failure [39].

For a more accurate calculation, the indicator of relative QT interval dispersion was proposed: RQTD = (σ QT

***Table 5.***

***Estimates of the coefficients of the regression model***

| Coefficient | Estimate | Standard deviation | Z-score | p |
|---|---|---|---|---|
| (Intercept) | -18,972 | 8,416 | -2,254 | 0,024 |
| Patient's gender (0 - male, 1 - female) | 2,764 | 1,179 | 2,344 | 0,019 |
| $T_{peak}$-$T_{end}$ interval duration | 0,069 | 0,033 | 2,119 | 0,034 |
| Relative QT interval dispersion | 6,436 | 2,035 | 3,163 | 0,002 |
| Magnesium serum level | -15,529 | 5,421 | -2,864 | 0,004 |
| NOS1 serum level | -7,229 | 2,529 | -2,858 | 0,004 |
| AA polymorphism G84A of the NOS1 gene (0 - absence, 1 - presence) | 2,378 | 1,21 | 1,966 | 0,049 |

Note: Intercept - free coefficient

intervals / μ QT interval) * 100%, where RQTD is relative QT interval dispersion, σ QT intervals - the standard deviation of QT intervals in 12 ECG leads, μ QT interval - the average value of the QT interval in 12 ECG leads [38].

This marker was developed to overcome the limitations inherent in calculations based on two extreme values (minimum and maximum), and does not take into account the values of the QT interval in the remaining ECG leads. S.Priori et al. suggest that QT interval dispersion of ≥100 ms and RQTD of ≥6 predispose to the initiation of ventricular arrhythmias [38]. However, we did not find in the scientific literature studies on the association of RQTD with ventricular arrhythmias and drug-induced LQTS.

$T_{peak}$-$T_{end}$ interval duration and its dispersion are also considered as markers for predicting ventricular arrhythmias in patients with QT interval prolongation [12, 15]. This interval reflects the transmural dispersion of repolarization and is calculated from the perpendicular drawn through the top of the T wave to the end of the T wave [12]. Literature data on the prognostic significance of indicators of transmural dispersion of repolarization ($T_{peak}$-$T_{end}$ interval duration and its dispersion) are rather contradictory [12, 15, 40]. Thus, a meta-analysis of three studies that included 144 patients with drug-induced LQTS while taking class III AADs did not reveal statistically significant differences between the $T_{peak}$-$T_{end}$ interval duration in the groups of patients with and without non-sustained polymorphic VT (p=0.12) [12]. However, $T_{peak}$-$T_{end}$/QT interval ratio was higher in patients with polymorphic VT (p<0.001) [12]. In another study, which included 143 patients with drug-induced LQTS and AV conduction disorders, on the contrary, there were significant intergroup differences in the QTc interval (p=0.02) and the $T_{peak}$-$T_{end}$ interval duration (p<0.001), but no differences were found in the $T_{peak}$-$T_{end}$/QT interval ratio (p=0.27) [40].

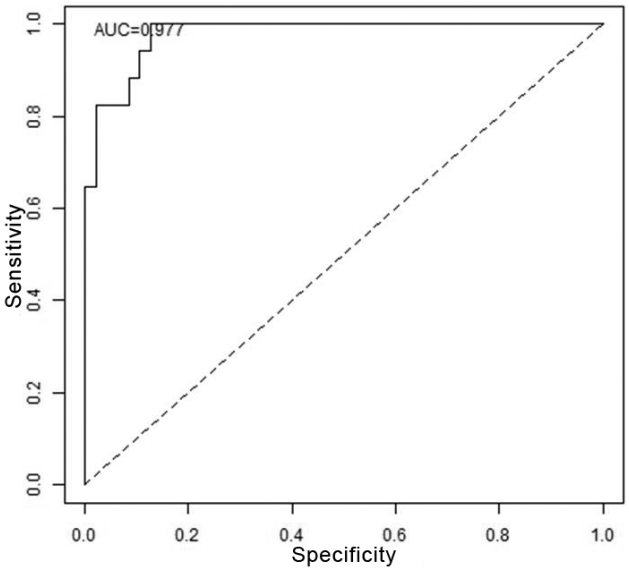


***Fig. 2 The ROC-curve of the model***

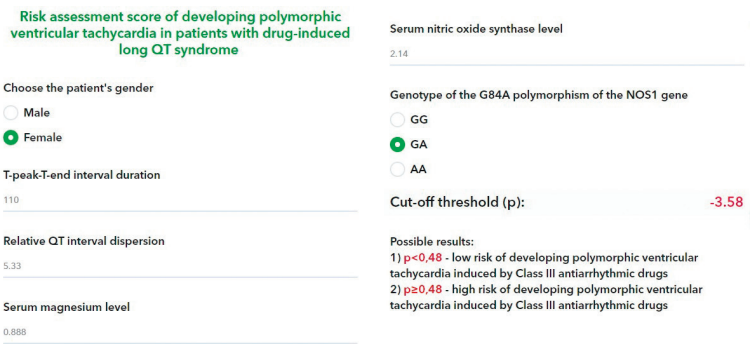


***Fig. 3. User interface of an online calculator for assessing the risk of developing non-sustained polymorphic ventricular tachycardia in patients with drug-induced QT interval prolongation caused by class III antiarrhythmic drugs.***

The effect of magnesium on the QT interval duration is mediated by complex molecular mechanisms involving potassium and calcium channels of cardiomyocytes, ryanodine receptors, and the calcium-binding protein calmodulin. As a natural calcium antagonist, magnesium is involved in the maintenance of intracellular calcium homeostasis and regulates the influx of calcium ions into cardiomyocytes by inhibiting L-type calcium channels [41]. With magnesium deficiency, there is a local increase in calcium in the cytoplasm, which can subsequently lead to its reuptake by the junctional sarcoplasmic reticulum and cause premature re-release of calcium through the ryanodine receptor in the form of spontaneous diastolic calcium waves, which create a potential substrate for the characteristic sinusoidal wave of polymorphic VT [41, 42].

A decrease in the serum magnesium level has been described in HF, CAD and hypertension, as well as in LQTS [42, 43]. Thus, K.Hoshino et al. found that more than half of patients with congenital LQTS are in a state of magnesium deficiency, which exacerbates QT interval prolongation and causes the VT initiation. When comparing the group of patients with congenital LQTS (n=22) and the control group (n=30), serum magnesium levels of less than 0.8 mmol/l were detected in 53% of patients in the main group and in 33% of participants in the control group (p<0.01) [43].

One of the promising laboratory predictors of QT interval prolongation and the polymorphic VT initiation is neuronal nitric oxide synthase (NOS1) and its adapter protein (NOS1AP) [24, 25]. In cardiomyocytes NOS1 is responsible for the process of S-nitrosylation of the calcium channel of the ryanodine receptor 2, and its deficiency leads to an increase in the calcium level and the appearance of diastolic calcium waves [25]. In turn, calcium waves are associated with the occurrence of early and delayed post-depolarizations, which appear on the ECG as QT interval prolongation and create a potential substrate for the development of polymorphic VT [25].

Although NOS1 is capable of direct S-nitrosylation of proteins without an adapter protein, in this case there are certain difficulties in implementing S-nitrosylation as a signaling mechanism for NO. Thus, the role of NOS1AP as an adapter protein for NOS1 is to direct it to other specific target proteins to perform the corresponding biological functions [24, 25].

The significance and functions of NOS1 have been shown in more detail in animal model studies. In the study by C. Ronchi et al. it has been shown that inhibition of NOS1 function

in guinea pig cardiomyocytes leads to the QT interval prolongation [24]. Pharmacological inhibition of NOS1 function led to an increase in the action potential, as well as an increase in the density of L-type calcium channels and an increased predisposition to the occurrence of post-depolarizations caused by sarcoplasmic reticulum instability [24].

NOS1 gene is located on the chromosome 12 long arm (12q24.22) and includes 33 exons [44]. To date, more than 100 polymorphisms of NOS1 gene are known; however, the polymorphism in exon 1c of the promoter of this gene, which is manifested by the replacement of guanine (G) with adenine (A) in the 84th position of the nucleotide sequence (rs41279104), has been most fully studied. In all likelihood, this substitution contributes to a decrease in the expression of the NOS1 gene: the -84AA genotype and the -84A allele are associated with a 30% decrease in vitro and a 50% in vivo expression of neuronal NO synthase, which may reduce the efficiency of implementation of its physiological effects in the myocardium [45]. At the same time, we did not find in the scientific literature any studies on the association of G84A polymorphism of NOS1 gene with ventricular arrhythmias and long QT interval syndrome, which add particular relevance to our study.

It should be noted that the score we have created is one of the first attempts to assess the risk of developing non-sustained polymorphic VT in patients with drug-induced LQTS treated with class III AADs (amiodarone or sotalol) in a cardiac hospital, which significantly limits the range of patients in whom it can be recommended for use. Tisdale, QT-DDI and RISQ-PATH scores described in the literature, on the contrary, are focused on a wide range of patients with various comorbidities (acute coronary syndrome, acute kidney injury, pneumonia, sepsis), including those being treated in intensive care units, which, with a sufficiently high sensitivity (74%, 83.9% and 87.4%, respectively), significantly limits their specificity (77%, 27.5% and 46.2%, respectively) and makes it difficult to assess the direct influence of drugs on the process of ventricular repolarization [26-28].

In addition, it would not be entirely correct to compare these scores with our model, since all of them are focused on assessing the risk of developing acquired QT interval prolongation without association with the development of VT, while our model is aimed at predicting the risk of proarrhythmogenic effects (in particular, polymorphic VT) in patients who already have drug-induced prolongation of the QT interval caused by class III AADs.

Our study had some limitations. Firstly, QRS complex, QT and $T_{peak}$-$T_{end}$ interval duration may change due to left ventricular remodeling in HF, arterial hypertension, and other comorbidities, which could limit the direct assessment of the effect of antiarrhythmic drugs. Secondly, we examined serum magnesium levels, which are less sensitive for assessing the total magnesium body content than the level of magnesium in erythrocytes and the level of magnesium in daily urine [42]. Thirdly, the sample size was limited, which could contribute to overestimation or underestimation of the magnitude of the associations found, as well as affect the lack of statistical significance of the obtained intergroup differences. In this regard, the results obtained require clarification and verification on a larger and more heterogeneous group of patients.

## CONCLUSION

To assess the risk of developing non-sustained polymorphic VT in patients with drug-induced LQTS while taking class III AADs, a multivariate binary logistic regression model was developed that includes the following parameters: patient's gender, relative QT interval dispersion, $T_{peak}$-$T_{end}$ interval duration, magnesium and NOS1 blood serum levels, AA genotype of the G84A polymorphism of the NOS1 gene. With a calculated threshold probability value of $\geq$0.48, the resulting model allows to identify patients at high risk of developing polymorphic VT caused by drug-induced LQTS with a sensitivity of 94.12% and a specificity of 89.36%. The ability to calculate the threshold probability is implemented in the form of an online calculator posted in the Internet public domain.

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# RELATIONSHIP BETWEEN LEFT VENTRICULAR MECHANICAL DYSSYNCHRONY WITH CARDIAC RESYNCHRONIZATION THERAPY RESPONSE IN CHRONIC HEART FAILURE PATIENTS WITH LEFT BUNDLE BRANCH BLOCK

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**Aim.** To investigate the relationship between left ventricular (LV) mechanical dyssynchrony with cardiac resynchronization therapy (CRT) response in chronic heart failure (CHF) pts with left bundle branch block.

**Methods.** Forty-nine pts (male - 34 [69.4%], average age 58.3±11.4 years) with sinus rhythm, permanent left bundle branch block with QRS duration ≥150 ms and New York Heart Association (NYHA) II-III functional class of CHF were included in the study. In addition to full examination, myocardial perfusion scintigraphy (MPS) and gated blood pool single-photon emission computed tomography (gBPS) were performed before and 6 months after CRT devices with cardioverter-defibrillator function implantation. Pts were considered as responders to CRT if they fulfilled after 6-month follow-up the following combined criteria: NYHA FC improvement ≥1 class + LV end systolic volume decrease >15% or NYHA FC improvement ≥1 class + LV ejection fraction improvement >5%.

**Results.** The 1st and 2nd groups included 35 (71.4%) and 14 (28.6%) pts with and without response to CRT respectively. Groups were comparable in terms of pre-CRT implantation clinical and instrumental parameters, except for MPS and gBPS parameters. The multivariate logistic regression had shown that only Δinterventricular dyssynchrony (adjusted odds ratio [OR] 1,0349; 95% confidence interval [CI] 1.0075-1,0631; p=0.01) and phase standard deviation of the anterior LV wall (OR 1.0669; 95% CI 1.0118-1.1251; p=0.01) were independently related with CRT response. An increase in the prognostic coefficient, calculated using the Δinterventricular dyssynchrony and phase standard deviation of the anterior LV wall, more than 0.67 was a predictor of CRT response (area under the curve 0.918; sensitivity 85.71; specificity 85.71; p <0.001).

**Conclusion.** The mechanical dyssynchrony assessed by MPS and gBPS is associated with CRT response. According to our predictive model, an increase in prognostic coefficient more than 0.67 is a predictor of CRT response.

**Key words:** left bundle branch block; chronic heart failure; cardiac resynchronization therapy; mechanical dyssynchrony of the left ventricle

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Nowadays heart failure (HF) is a serious public health problem due to the high risk of mortality and morbidity and the poor quality of life of patients [1]. Cardiac resynchronization therapy (CRT) is a recognized treatment option for patients with chronic HF, especially in patients with reduced left ventricular ejection fraction (LVEF) and left bundle branch block [2]. According to the recommendations on pacing and CRT, the main selection criteria for cardiac resynchronization therapy in symptomatic patients with HF are low LVEF and complete left bundle branch blockade (LBBB) with QRS complex duration more than 130 ms despite optimal drug therapy [3]. QRS prolongation (120 ms or more) is found in 14.0-47.0% of patients with CHF, and ventricular conduction disturbance, most commonly LBBB, is present in about one-third of patients with HF, leading to ventricular mechanical dyssynchrony

(MD) [4, 5]. In most patients, CRT restores impaired left ventricular (LV) contractile function. These patients are categorized as CRT responders. Nowadays the main predictors of a positive response to CRT are: nonischemic HF, female gender, QRS complex dilation ≥150 ms with LBBB morphology. Nevertheless, no improvement in cardiac contractile function and clinical status is observed in 30% of patients [6].

Several studies have shown that a method of assessing cardiac contractile function using transthoracic echocardiography, magnetic resonance, computed tomography, and single-photon emission computed tomography can play a key role in predicting response to CRT [7-10]. However, according to the multicenter PROSPECT study, the use of standard echocardiographic parameters of dyssynchrony was not a reliable predictor of response to CRT [11]. The use of magnetic resonance imaging, although highly accurate and informative, is limited by high cost, complexity of cardiac protocols, and the presence of operator-dependent techniques [12]. At the same time, myocardial perfusion scintigraphy (MPS) and radionuclide tomoventriculography (RTVG) are simple techniques that have higher reproducibility and can detect cardiac ventricular MD, blood flow abnormalities and myocardial scarring [13]. The prognostic value of MD assessed by MPS remains controversial. In several studies, MD correlates with a positive response to CRT in patients with CHF of ischemic and non-ischemic etiology [14, 15]. However, another work showed the lack of prognostic significance of MD in patients with ischemic cardiomyopathy [16, 17]. But there are few papers on the combined assessment of reverse remodeling-related factors that can be used to improve patient selection for CRT [18].

Therefore, the aim of our study was to identify the relationship between MD LV and response to CRT in patients with LBBB and CHF.

## METHODS

### Patient population and study design

This clinical, non-randomized, open-label, prospective study enrolled patients with indications for CRT according to ESC guidelines [3]. Inclusion and exclusion criteria were defined according to the research project «Single-photon Emission Computed Tomography for Prediction and Evaluation of Cardiac Resynchronization Therapy Efficacy in Chronic Heart Failure Patients,» ClinicalTrials.gov, NCT03667989). Patients included in the study met the following criteria: presence of HF (ischemic or nonischemic etiology), sinus rhythm, persistent LBBB with QRS complex duration ≥150 ms, New York Heart Association (NYHA) functional class (FC) of HF II-III, LVEF ≤35%, and optimal drug therapy for at least 3 months. Patients with NYHA HF I, IV FC, decompensated HF, recent myocardial infarction (less than 3 months), right bundle branch block, previously implanted pacemaker or cardioverter-defibrillator, severe comorbidities, cognitive impairment, indications for revascularization and heart transplantation, and patients younger than 18 years of age were excluded from the study. The etiology of HF was considered ischemic in the presence of significant coronary artery disease (≥50% stenosis of one or more major coronary arteries) and/or a history of myocardial infarction or previous revascularization.

All patients underwent complete physical examination (6-minute walk test, electrocardiography, transthoracic echocardiography (TTE), 24-hour electrocardiogram (ECG) monitoring, coronary angiography, and blood tests), MPS with $^{99}$mTc-MIBI, and RTVG before and 6 months after device implantation. In all cases, cardiac resynchronization therapy devices with cardioverter-defibrillator (CRT-D) function were implanted according to ESC guidelines [3]. All patients received baseline therapy in accordance with current recommendations. Follow-up was performed 6 months after implantation of CRT-D.

### Agreement form

The study was conducted in accordance with the principles of the Declaration of Helsinki and standards of good clinical practice. The study was approved by the local ethical committee and was performed at a research institute. All participants obtained written informed consent prior to inclusion in the study.

### The 6-minute walk test

The severity of HF was assessed using NYHA criteria, with the 6-minute walk test. Walking distance in meters and the NYHA FC to which it corresponded were used for analysis:

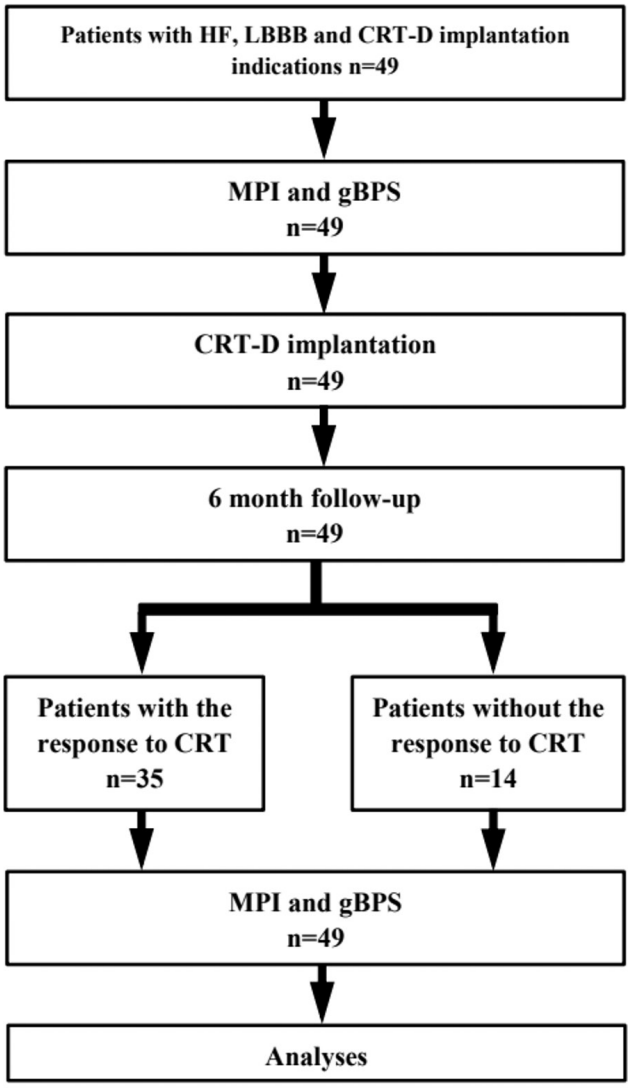


*Fig. 1. Study flow chart.*

- more than 551 m - the patient has no signs of HF;
- 426-550 m - belong to I FC;
- 301-425 m - belong to II FC;
- 151-300 m - belong to III FC;
- less than 150 m - belong to IV FC.

**Transthoracic echo**

Transthoracic echo with evaluation of intracardiac hemodynamic parameters was performed on a Philips HD15 PureWave ultrasonic diagnostic device (Netherlands) before and 6 months after implantation of CRT-D. The study was performed from standard Echo positions with determination of left atrium, right ventricle (RV) size, interventricular septum (IVS) thickness, LV posterior wall, LV end-systolic dimension (LVESD), LV end-diastolic dimension, LV end-systolic volume (LVESV), LV end-diastolic volume, myocardial mass index, LVEF, LV systolic pressure, stroke volume, end-systolic index, end-diastolic index, left atrial index, and right atrial index. Mitral, tricuspid, and aortic valve function, as well as LV and LV contractility were assessed.

**Radionuclide imaging**

Radionuclide studies were performed on a Discovery NM/CT 570c single-photon emission computed tomography scanner (GE Healthcare, Haifa, Israel) equipped with a gamma camera with semiconductor cadmium-zinc-tellurium detectors. Images were acquired in tomographic mode using a low-energy multi-pinhole collimator in 19 projections in a 32×32 pixel matrix. The center of the energy window was

***Table 1.***

***Clinical and demographic characteristics of patients by groups***

| | Total (n=49) | Group 1 respondents (n=35) | Group 2 nonresponders (n=14) | $P_{2-3}$ |
|---|---|---|---|---|
| | 1 | 2 | 3 | |
| Age, years, M±SD | 58.3±11.4 | 57.9±10.2 | 59.1±14.5 | 0.911 |
| Male gender, n (%) | 34 (69.4) | 24 (68.5) | 10 (71.4) | 0.885 |
| Ischemic cardiomyopathy, n (%) | 16 (32.6) | 10 (28.5) | 6 (42.8) | 0.445 |
| Non-ischemic cardiomyopathy, n (%) | 33 (67.4) | 25 (71.5) | 8 (57.2) | 0.445 |
| 6-minute walk test, m, M±SD | 294.9±67.6 | 289.4±65.3 | 308.5±73.5 | 0.382 |
| NYHA functional class of heart failure: | | | | |
| II, n (%) | 23 (46.9) | 14 (40.0) | 9 (64.3) | 0.191 |
| III, n (%) | 26 (53.1) | 21 (60.0) | 5 (35.7) | 0.191 |
| Arrhythmias prior to implantation of a cardiac resynchronization therapy device with defibrillation function | | | | |
| Persistent VT, n (%) | 4 (8.1) | 2 (5.7) | 2 (14.3) | 0.650 |
| Unstable VT, n (%) | 16 (32.6) | 12 (34.3) | 4 (28.6) | 0.765 |
| Atrial fibrillation, n (%) | 14 (28.5) | 9 (25.7) | 5 (35.7) | 0.595 |
| Associated pathology | | | | |
| Arterial hypertension, n (%) | 16 (32.6) | 11 (31.5) | 5 (35.7) | 0.623 |
| LV myocardial hypertrophy, n (%) | 40 (81.6) | 27 (77.1) | 13 (92.8) | 0.400 |
| Diabetes mellitus, n (%) | 8 (16.3) | 7 (20.0) | 1 (7.1) | 0.492 |
| Body mass index, kg/m$^2$, M±SD | 28.8±4.9 | 29.4±5.3 | 27.4±3.4 | 0.298 |
| Dyslipidemia, n (%) | 23 (46.9) | 17 (48.5) | 6 (42.8) | 0.765 |
| eGFR, ml/min/1.73 m$^2$, M±SD | 74.3±19.8 | 77.5±19.3 | 66.0±19.1 | 0.101 |
| Drug therapy | | | | |
| Beta-adrenoblockers, n (%) | 48 (97.9) | 34 (97.1) | 14 (100.0) | 0.885 |
| Loop diuretics, n (%) | 31 (63.2) | 18 (51.4) | 13 (92.8) | 0.025 |
| Aldosterone antagonists, n (%) | 35 (71.4) | 28 (80.0) | 7 (50.0) | 0.106 |
| ACEI, n (%) | 22 (44.9) | 14 (40.0) | 8 (57.2) | 0.353 |
| Antiplatelets, n (%) | 30 (61.2) | 20 (57.1) | 10 (71.4) | 0.445 |
| Statins, n (%) | 35 (71.4) | 28 (80.0) | 7 (50.0) | 0.106 |
| Amiodarone, n (%) | 17 (34.7) | 11 (31.5) | 6 (42.8) | 0.542 |
| Angiotensin receptor antagonists, n (%) | 24 (48.9) | 20 (57.1) | 4 (28.6) | 0.124 |
| SGLT2 inhibitors, n (%) | 8 (16.3) | 7 (20.0) | 1 (7.1) | 0.492 |

Note: hereafter, M±SD values for quantitative variables and n (%) values for categorical variables; NYHA - New York Heart Association; VT - ventricular tachycardia; LV, left ventricle; eGFR estimated glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitors; SGLT2, sodium-glucose cotransporter type 2.

set to a $^{99m}$Tc photopeak of 140 keV; the width of the energy window was symmetric and 20%. The obtained data were processed on a specialized workstation (Xeleris II; GE Healthcare, Haifa, Israel). MPS and RTVG were performed before and 6 months after implantation of CRT-D.

MPS was performed in the patient in the state of functional rest, 90 minutes after the injection of 370-450 MBq with $^{99m}$Tc-MIBI. The study was performed in tomographic mode with ECG synchronization (16 frames per cardiac cycle). The duration of the recording was 6 minutes. Image reconstruction was performed along the short and long (horizontal and vertical) axes of the heart, as well as using a normalized 17-segment LV polar map. Semi-quantitative calculation of local LV perfusion abnormalities was performed as a percentage. Perfusion disturbance was calculated in points in each of 17 LV segments according to 5-point scale, where 0 - normal accumulation of radiopharmaceutical in myocardium, and 4 points - sharply expressed defects of indicator accumulation. The total percentage of perfusion impairment was defined as the ratio of the sum of scores in all 17 segments to the maximum possible perfusion impairment value of 68.

To perform RTVG, the patient was injected intravenously with 2 mL of Pirfotech solution. Then, intravenous injection of 555-720 MBq of $^{99m}$Tc-pertechnetate was performed 10 minutes later. After 10 minutes, data were recorded on a gamma camera. The patient was positioned so that the center of the left ventricle of the heart was in the center of the detector field of view. Recordings were performed in ECG-synchronized mode, recording duration - 10 minutes. Postprocessing of the results included separation of the cavities of both ventricles of the heart with subsequent determination of their contours. Parameters characterizing the ventricular function of the heart were calculated from the dynamics of the count rate per cardiac cycle in the corresponding zone of interest. Phase characteristics were calculated from phase histograms obtained using the Fourier transform. Quantitative indices (phase standard deviation, phase histogram width and entropy) of global dyssynchrony were calculated and separately for each zone of interest: anterior, lateral posterior LV wall, IVS, and LV free wall.

**Implantation and programming of CRT-D**

Implantation of atrial and defibrillating electrodes with active fixation and left ventricular electrode (LVE) with passive fixation was performed under fluoroscopic control through transvenous access. The defibrillating electrode was implanted in the apex of the LV or IVS. Electrode positioning was performed under fluoroscopy in the anteroposterior and left lateral projections. Stimulation threshold, intracardiac signal amplitude and electrode impedance were measured using a cardiac stimulation system analyzer (Medtronic, USA) with sterile cables with clamps.

LVE implantation was performed by cannulation of one of the veins of the coronary sinus using a delivery system. Venogram was performed in anteroposterior and left lateral projections. Access to the target vein in the coronary sinus and subsequent advancement of the LVE was performed using a guidewire. A subselector was used if there was difficulty in catheterizing the target vein. LVE positioning in the target vein was performed after testing electrode thresholds and verifying diaphragmatic nerve stimulation.

Programming of CRT-D was carried out in accordance with international standards [19]. All patients were programmed for biventricular stimulation with optimal atrioventricular and interventricular (LV was stimulated before RV by 0-40 ms) delay. In each CRT-D, a monitoring zone was programmed with a heart rate of 140-170 beats

***Table 2.***

***Postoperative parameters in groups of patients***

| | Total (n=49) | Group 1 respondents (n=35) | Group 2 nonresponders (n=14) | $P_{2-3}$ |
|---|---|---|---|---|
| | 1 | 2 | 3 | |
| Position of the left ventricular electrode in the target vein | | | | |
| Collateral vein, n (%) | 20 (40.8) | 17 (48.5) | 3 (21.4) | 0.144 |
| Posterolateral vein, n (%) | 15 (30.6) | 9 (25.7) | 6 (42.8) | 0.358 |
| Anterolateral vein, n (%) | 9 (18.4) | 8 (17.1) | 3 (21.4) | 0.824 |
| Posterior vein, n (%) | 5 (10.2) | 3 (8.5) | 2 (14.3) | 0.765 |
| Quadripolar left ventricular electrode, n (%) | 28 (57.2) | 24 (68.5) | 4 (28.6) | 0.030 |
| Bipolar left ventricular electrode, n (%) | 21 (42.8) | 11 (31.5) | 10 (71.4) | 0.030 |
| QRS complex duration | | | | |
| Native QRS, ms, M±SD | 171.0±15.6 | 172.3±15.7 | 168.0±15.5 | 0.394 |
| Stimulated QRS, ms, M±SD | 135.9±13.0 | 135.4±13.5 | 137.1±12.0 | 0.603 |
| ΔQRS, ms, M±SD | 35.1±14.2 | 36.8±12.9 | 30.8±16.9 | 0.180 |
| Programmed delaysи | | | | |
| Paced AV delay, ms, M±SD | 153.8±15.6 | 154.0±15.0 | 153.5±17.8 | 0.773 |
| Sensed AV delay, ms, M±SD | 119.1±18.0 | 120.5±17.9 | 115.3±18.4 | 0.587 |
| Interventricular delay, ms, Me [Q1, Q3] | 30.0 [20.0; 40.0] | 30.0 [20.0; 40.0] | 20.0 [10.0; 40.0] | 0.610 |

Note: hereafter AV is atrioventricular.

per minute (bpm) with more than 50 consecutive cycles without antitachycardia stimulation and shock discharge. Ventricular tachycardia (VT) zone was programmed at 170-200 beats/min with 30 cycles and with antitachycardia stimulation (≥1 «burst» stimulation and ≥1 «ramp» stimulation) and shock discharge (first discharge with submaximal magnitude). Ventricular fibrillation zone was programmed at 201-240 beats/min with 12 cycles and with antitachycardia stimulation during CRT-D shock charge recruitment and maximal shock discharge.

**Follow-up**

Information on arrhythmic events was determined by interview and CRT-D programming. Arrhythmic events (VT, ventricular fibrillation, atrial fibrillation, adequate and inadequate CRT-D therapy), percentage of biventricular stimulation, as well as indices (stimulation threshold, intracardiac signal amplitude and impedance) of CRT-D electrodes were evaluated. The block diagram of the study is presented in Fig. 1. The criteria for positive response after 6 months of follow-up were as follows: improvement in NYHA FC ≥1 class + decrease in LVESV >15% or improvement in NYHA FC ≥1 class + improvement in LVEF >5% [17].

**Statistical analysis**

Statistical analysis was performed using Statistica 10.0 program package, StatSoft (USA). The Shapiro-Wilk test was used to assess the normality of the trait distribution. The mean (M) and standard deviation (SD) were calculated for variables with normal distribution, and the median (Me) with interquartile range [Q1, Q3] was calculated for the others. Nonparametric Mann-Whitney test for independent samples and Wilcoxon test for dependent samples were used. Spearman's nonparametric analysis was used to assess correlations and collinearity between pairs of quantitative traits. Efficiency analysis was performed using logistic regression analysis. Stepwise logistic regression analysis was used to assess independent predictors of response to CRT. ROC analysis was used to determine the diagnostic efficiency of the method using the MedCalc statistical software package. At the significance level p less than 0.05, it was considered that the studied indicator in the compared groups had statistically significant differences.

## RESULTS

**Patient characteristics**

A total of 49 (100.0%) patients who underwent MPS and RTVG before and 6 months after implantation of CRT-D were included in the study. The first group consisted of 35 (71.4%) patients with a positive response to CRT (responders), and the second group consisted of 14 (28.6%) patients without a positive response to CRT (nonresponders). Baseline demographic and clinical characteristics of the included patients are presented in Table 1. The mean age of the patients was 58.3±11.4 years, 34 (69.4%) were male. Baseline 6-minute walk test, NYHA CHF, QRS complex duration, arrhythmias recorded before CRT-D implantation, LVE position, CHF etiology, concomitant pathology, and drug treatment of patients in the groups are also shown in the Table 1. The groups did not differ sig-

***Table 3.***

***Main indices of intracardiac hemodynamics according to echocardiography results***

| | Group 1 respondents (n=35) | | | Group 2 nonresponders (n=14) | | | $P_{1-4}$ | $P_{2-5}$ |
|---|---|---|---|---|---|---|---|---|
| | Initially | After 6 months | P | Initially | After 6 months | P | | |
| | 1 | 2 | 3 | 4 | 5 | 6 | | |
| LVESV, ml | 162.0 [130.0; 200.0] | 112.0 [93.0; 142.0] | <0.001 | 197.5 [151.0; 263.0] | 195.0 [132.0; 265.0] | 0.694 | 0.106 | <0.001 |
| LVEF, % | 30.0 [25.0; 33.0] | 38.0 [35.0; 44.0] | <0.001 | 27.0 [22.0; 31.0] | 28.5 [25.0; 30.0] | 0.059 | 0.358 | <0.001 |
| MMI, g/m$^2$ | 135.0 [118.0; 150.0] | 112.0 [99.0; 136.0] | 0.004 | 150.5 [130.0; 166.0] | 144.0 [125.0; 194.0] | 0.463 | 0.116 | 0.002 |
| LVEF, ml | 234.0 [198.0; 263.0] | 188.0 [148.0; 220.0] | <0.001 | 266.0 [216.0; 341.0] | 266.0 [200.0; 351.0] | 0.916 | 0.207 | 0.003 |
| LAI, ml/m$^2$ | 53.3 [45.0; 65.2] | 46.2 [35.2; 53.0] | <0.001 | 60.9 [48.5; 72.1] | 67.4 [44.7; 76.5] | 0.386 | 0.199 | 0.009 |
| RAI, ml/m$^2$ | 32.7 [27.7; 48.4] | 32.2 [28.1; 42.6] | 0.075 | 44.5 [31.3; 56.4] | 46.4 [34.7; 62.0] | 0.332 | 0.240 | 0.014 |
| EDI, ml/m$^2$ | 118.6 [99.8; 141.1] | 95.4 [74.4; 116.2] | <0.001 | 127.9 [117.4; 152.9] | 132.4 [106.7; 177.1] | 0.593 | 0.126 | <0.001 |
| ESI, ml/m$^2$ | 85.0 [68.6; 97.7] | 56.0 [47.6; 76.7] | <0.001 | 92.6 [82.6; 122.4] | 98.2 [70.4; 132.7] | 0.396 | 0.090 | <0.001 |
| RVSP, mm Hg | 30.0 [25.0; 41.0] | 29.0 [26.0; 35.0] | 0.154 | 33.5 [25.0; 46.0] | 37.5 [27.0; 47.0] | 0.123 | 0.406 | 0.050 |
| LVSI | 0.66 [0.60; 0.72] | 0.61 [0.57; 0.65] | <0.001 | 0.69 [0.67; 0.72] | 0.68 [0.63; 0.71] | 0.875 | 0.268 | 0.001 |

Note: LVESV - end-systolic volume, LVEF - LV ejection fraction, MMI - myocardial mass index, LVEDV - left ventricular end-diastolic volume, LAI - left atrial index, RAI - right atrial index, EDI - end-diastolic index, ESI - end-systolic index, RVSP - right ventricular systolic pressure, LVSI - left ventricular sphericity index.

nificantly in baseline clinical and demographic variables, except for loop diuretics administration. There were significantly more patients taking loop diuretics in the second group than in the first group (p=0.025).

All patients were implanted with CRT-D. Postoperative parameters are presented in Table 2. The groups did not differ significantly in terms of postoperative parameters except for the following: implanted quadripolar and bipolar LVEs. There were significantly more patients in the second group of patients who were implanted with bipolar LVE than in the first group (p=0.03, respectively). In the first group, the number of patients who were implanted with quadripolar LVEs was significantly higher than in the second group (p=0.03). Given that multipole stimulation was not used in this study and that there were no differences between the groups in stimulated QRS complex duration, atrioventricular and interventricular delay, such heterogeneity in the number of implanted quadripolar LVEs did not significantly affect the positive response to CRT.

Echo was performed in all patients before and 6 months after implantation of CRT-D. The main parameters of echocardiography with assessment of intracardiac hemodynamics are presented in Table 3. The groups were comparable in terms of the main indices of intracardiac hemodynamics assessed by transthoracic echo before CRT-D implantation. At 6 months after implantation of CRT-D in the group of responders there was a significant improvement of all parameters, except for the right atrial index and right ventricular systolic pressure. No improvement was found in the non-responders group 6 months after CRT-D implantation.

In addition to basic diagnostic methods, all patients underwent resting MPS and RTVG. The main indicators of radionuclide diagnostics are presented in Table 4. The groups were comparable in terms of baseline resting

***Table 4.***

***Main indices of myocardial perfusion scintigraphy and radionuclide tomoventriculography***

| | Group 1 respondents (n=35) | | | Group 2 nonresponders (n=14) | | | $P_{1-4}$ | $P_{2-5}$ |
|---|---|---|---|---|---|---|---|---|
| | Initially | After 6 months | P | Initially | After 6 months | P | | |
| | 1 | 2 | 3 | 4 | 5 | 6 | | |
| InterVD, ms | 93.0 [48.0;123.0] | 53.0 [37.0;72.0] | 0.004 | 31.4 [20.0;42.3] | 60.8 [20.0;42.3] | 0.050 | <0.001 | 0.748 |
| IntraVD LV, ms | 137.0 [105.0;181.0] | 91.0 [56.0;123.0] | <0.001 | 132.4 [96.7;153.0] | 105.3 [90.7;119.4] | 0.020 | 0.499 | 0.313 |
| IntraVD RV, ms | 104.0 [66.6;149.1] | 90.0 [56.4;115.0] | 0.019 | 89.9 [54.7;132.0] | 82.6 [45.0;161.0] | 0.952 | 0.465 | 0.947 |
| LV wall entropy: | | | | | | | | |
| LV, % | 72.0 [66.0;82.0] | 70.0 [62.0;76.0] | 0.186 | 66.0 [52.0;72.0] | 71.0 [63.0;81.0] | 0.278 | 0.032 | 0.790 |
| SW, % | 68.0 [57.0;79.0] | 53.0 [42.0;65.0] | <0.001 | 56.0 [50.0;65.0] | 57.0 [44.0;70.0] | 0.484 | 0.184 | 0.438 |
| AW, % | 52.0 [45.0;62.0] | 49.0 [39.0;55.0] | 0.016 | 37.5 [30.0;50.0] | 48.5 [39.0;57.0] | 0.109 | <0.001 | 0.991 |
| LW, %. | 37.0 [31.0;49.0] | 46.0 [35.0;54.0] | 0.092 | 36.0 [30.0;50.0] | 49.5 [32.0;58.0] | 0.015 | 0.506 | 0.690 |
| IW, % | 58.0 [49.0;63.0] | 52.0 [42.0;65.0] | 0.467 | 59.5 [58.0;64.0] | 62.5 [54.0;72.0] | 0.552 | 0.207 | 0.031 |
| PSD LV wall: | | | | | | | | |
| SW, ° | 40.0 [27.0;60.0] | 24.0 [14.0;30.0] | <0.001 | 23.0 [15.0;35.0] | 23.5 [16.0;37.0] | 0.593 | 0.024 | 0.412 |
| AW, ° | 25.0 [17.0;34.0] | 18.0 [11.0;24.0] | 0.008 | 10.0 [9.0;24.0] | 21.5 [15.0;32.0] | 0.008 | <0.001 | 0.259 |
| LW, ° | 12.0 [8.0;25.0] | 14.0 [9.0;21.0] | 0.411 | 12.0 [7.0;20.0] | 27.5 [8.0;47.0] | 0.034 | 0.690 | 0.173 |
| IW, ° | 26.0 [17.0;39.0] | 19.0 [11.0;30.0] | 0.317 | 28.0 [25.0;43.0] | 35.5 [24.0;50.0] | 0.888 | 0.156 | 0.004 |
| SRS, % | 5.0 [3.0;11.0] | 5.0 [3.0;8.0] | 0.308 | 8.5 [4.0;13.0] | 12.0 [4.0;13.0] | 0.132 | 0.513 | 0.004 |
| HBW LV, ° | 212.0 [175.0;234.0] | 195.2 [175.0;241.0] | 0.805 | 199.0 [192.0;211.0] | 201.0 [208.3;213.1] | 0.278 | 0.535 | 0.090 |

Note: LVHBW - left ventricular histogram bandwidth, PSD - standard deviation of phase histogram, SRS - resting radiopharmaceutical filling defect, LW - lateral wall, IntraVD - intraventricular dyssynchrony, LV - left ventricle, InterVD - interventricular dyssynchrony, IW - inferior wall, RV - right ventricle, SW - septal wall, AW - anterior wall.

MPS and RTVG before CRT-D implantation, except for interventricular dyssynchrony (InterVD) (p<0.001), LV entropy (p=0.032), LV anterior wall entropy (p<0.001) and LV septal phase histogram standard deviation (PSD) (p<0.001). 6 months after implantation of CRT-D in the group of responders there was a significant improvement in the following indices of LV mechanical dyssynchrony: InterVD, intraventricular LV and LV dyssynchrony, entropy and PSD of the septum and LV anterior wall (Table 4). In the nonresponders group, there was a significant improvement in LV intraventricular dyssynchrony, worsening of entropy and PSD of the LV lateral wall, and PSD of the LV anterior wall (AWLV).

**Arrhythmic events according to CRT-D data**

During 6 months of follow-up, episodes of VT as measured by the CRT-D questionnaire were reported in 9 (18.3%) patients in both groups. In the group of responders, VT was registered in 5 (14.3%) patients: 4 patients had unstable VT (self-corrected) and 1 patient had stable VT, treated with CRT-D shock. In the group of nonresponders, VT was registered in 4 (28.5%) patients (p=0.445). In this group, all 4 patients had an unstable VT. Shock triggers in the nonresponders group have not been documented. No dysfunction of the CRT-D-electrode system, electrode dislocations, or unwarranted CRT-D therapy was observed in either group. The percentage of biventricular stimulation 6 months after CRT-D implantation was 97.8±2.6% in the responder group and 98.4±0.9% in the nonresponder group. During 6 months of follow-up, paroxysms of atrial fibrillation were recorded by CRT-D in 2 patients from both groups, 1 in the responder group and 1 in the nonresponder group (p=0.706). Atrial fibrillation in these patients resolved on its own.

**Predictors of CRT responsiveness**

Logistic regression analysis as a method of mathematical modeling allows not only to identify predictors of events, but also to build a predictive model that considers several parameters. Considering the impossibility of including in one prognostic model the factors between which there is a statistical relationship, before creating a mathematical model including more than one predictor, we tested the prognostic factors for collinearity - we identified correlations and associations between the factors. According to the results of correlation analysis, the following parameters were excluded from the prognostic model: ΔQRS (correlates with QRS [r=0.611; p<0.001]), Δ6-minute walk test (correlates with ΔInterVD [r=-0.449; p=0.001]), Δ LVESV (correlates with PSD [r=0.437; p=0.001]) and entropy [r=0.419; p=0.001] of AWLV), ΔLVEF (correlates with Δ6-minute walk test [r=0.662; p<0.001], ΔLVESV [r=-0.674; p<0.001] and standard deviation of left ventricular anterior wall phase histogram (PSD of AWLV) [r=-0.511; p<0.001]), InterVD (correlates with ΔInterVD [r=0.718; p<0.001]), LV entropy (correlates with entropy [r=0.617; p<0.001] and PSD [r=0.500; p<0.001] of AWLV), PSD of LV septum (correlates with PSD of AWLV [r=0.558; p<0.001]), ΔPSD of AWLV (correlates with PSD of LV PSD [r=0.668; p<0.001]) and entropy of AWLV (correlates with PSD of AWLV [r=0.854; p<0.001]).

According to the collinearity results, commonly known predictors of positive response to CRT (QRS complex duration, female sex, and non-ischemic cardiomyopathy) and indices with significant differences between groups (ΔInterVD, ΔPSD of LV septum and anterior wall, and Δentropy of AWLV) were included in multivariate logistic regression analysis. This analysis showed that only ΔInterVD (odds ratio [OR] 1.0349; 95% confidence interval [CI] 1.0075-1.0631; p=0.01) and PSD of AWLV (OR 1.1693; 95% CI 1.0502-1.3020; p=0.004) were independently associated with a positive response to CRT. An increase in the prognostic coefficient calculated using ΔInterVD and PSD of the LV anterior wall greater than 0.67 was a predictor of a positive response to CRT (area under the curve 0.918; sensitivity 85.71; specificity 85.71; p<0.001) (Figure 2). Pairwise comparison of the ROC curve of PC of positive response to CRT with ΔInterVD and PSD of AWLV showed significant differences with ΔInterVD (p=0.009) (Figure 3).

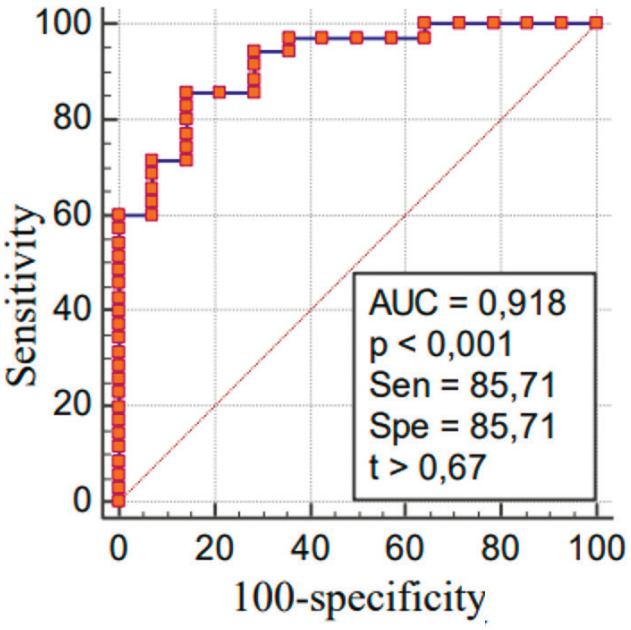


***Fig. 2. CRT response probability indicator, calculated according to the predictive model. Notes: AUC - area under curve, Sen - sensitivity, Spe - specificity, t - threshold value.***

## DISCUSSION

The present study shows that mechanical dyssynchrony (standard deviation of left ventricular anterior wall phase histogram and Δ interventricular dyssynchrony), as measured by MPS and RTVG in patients with CHF and LBBB, may have prognostic value. Thus, PSD of AWLV and ΔInterVD are prognostic indicators of a positive response to CRT. This may be due to marked interventricular delay and involvement of the LV anterior wall in mechanical dyssynchrony.

It has been previously reported that nonischemic cardiomyopathy is a predictor of reverse LV myocardial remodeling in patients with CHF. According to C.Ypenburg et al (2009) CRT responders and super responders were more likely to have a non-ischemic etiology of CHF [20]. In a study by D.Verhaert et al (2010), female gender and non-ischemic cardiomyopathy were shown to be associat-

ed with a positive response to CRT in the early period after CRT device implantation [21]. Another study by F.Said et al (2021) showed that female subjects were more likely to have a greater positive echocardiographic response to CRT after 6 months of follow-up [22]. However, after adjusting for body surface area and ischemic etiology, no differences in LV function and survival were found, suggesting that the non-ischemic etiology of CHF is responsible for the higher rates of positive response in women receiving CRT [22]. In our study, the number of patients with ischemic and non-ischemic cardiomyopathies in the groups with and without a positive response to CRT was not significantly different (p=0.445). Among others, multivariate logistic regression showed that nonischemic cardiomyopathy was not a predictor of positive response to CRT. This is probably due to the small sample size, which may affect the results.

The prognostic value of LV mechanical dyssynchrony assessed by MPS and RTVG for patient selection for CRT has been extensively studied. In a study involving 142 patients with CRT, MD LV parameters such as phase histogram width during systole (95% CI 0.98-1.00, p=0.041) and diastole (95% CI 0.98-1.00, p=0.028), phase deviation of histogram during diastole (95% CI 0.94-1.00, p=0.041) were significant independent predictors of CRT response only in patients with non-ischemic cardiomyopathy [16]. For individuals with ischemic cardiomyopathy, all parameters of LV mechanical dyssynchrony were not significant [16]. In a study by M.Henneman et al (2007) ROC analysis showed that the optimal threshold value of PSD and phase histogram width were 43° (sensitivity and specificity 74%) and 135° (sensitivity and specificity 70%), respectively [23]. In a study involving 324 patients with non-ischemic cardiomyopathy and an CRT device, it was shown that PSD adjusted for age, hypertension, diabetes, aspirin intake, beta-blocker, diuretic, QRS duration and LVEF was an independent predictor of all-cause mortality (OR 1.97, 95% CI 1.06-3.66, p=0.033) [24].

In our study, responders and nonresponders did not differ in measures of global LV mechanical dyssynchrony such as phase histogram width, and this index had no prognostic value, but PSD and InterVD were higher in the responders' sample. However, the novelty of our study was the use of RTVG to assess regional mechanical dyssynchrony separately for the septum, anterior, posterior, and lateral LV walls. These parameters were statistically significant predictors of response to CRT. Multivariate logistic regression showed that ΔInterVD (OR 1.0349; 95% CI 1.0075-1.0631; p=0.01) and PSD of AWLV (OR 1.1693; 95% CI 1.0502-1.3020; p=0.004) were independently associated with a positive response to CRT. This may suggest that assessment of regional myocardial dyssynchrony may provide additional information for successful resynchronization therapy. But disagreements with previous studies emphasize the importance of these results and the need for future large-scale studies.

Few publications on the combined assessment of factors associated with reverse myocardial remodeling that can be used to improve patient selection for CRT are found in the available literature. The value of assessing response to CRT was shown in the large randomized MADIT-CRT trial [18]. According to this study, a multivariate analysis including seven factors associated with echocardiographic response to CRT-D (female sex, nonischemic cardiomyopathy, LBBB, QRS complex duration ≥150 ms, prior hospitalization for CHF, LV end-diastolic volume index ≥125 ml/m$^2$ and left atrial volume index <40 ml/m$^2$) showed a significant reduction in the risk of CHF or death in subgroups of up to 69% (p<0.001).

In our study, multivariate logistic regression, which included such commonly occurring factors as QRS complex duration, female sex, non-ischemic cardiomyopathy, and indices of mechanical dyssynchrony with significant differences between groups (ΔInterVD, ΔPSD of LV septum and anterior wall, Δentropy of LV AV) showed that ΔInterVD (OR 1.0349; 95% CI 1.0075-1.0631; p=0.01) and PSD of AWLV (OR 1.1693; 95% CI 1.0502-1.3020; p=0.004) were independent predictors of positive response to CRT. An increase in the prognostic coefficient calculated using ΔInterVD and PSD of the LV anterior wall greater than 0.67 was a predictor of a positive response to CRT (area under the curve 0.918; sensitivity 85.71; specificity 85.71; p<0.001).

Thus, the prognostic model with the combination of PSD of AWLV and ΔInterVD has a high prognostic value and can be used as an additional predictor of positive response of CRT in patients with CHF.

**Limitations of the study**

Limitations of the study include the relatively small sample size, short follow-up period, and the fact that it was non-randomized and single-center, which could ultimately affect the final results.

## CONCLUSION

Mechanical dyssynchrony assessed by MPS and RTVG is associated with a positive response to CRT in patients with CHF and LBBB. According to our prognostic model, a combined score of factors associated with reverse myocardial remodeling (PSD of AWLV and ΔInterVD) and an increase in PC greater than 0.67 is a predictor of a positive response to CRT.

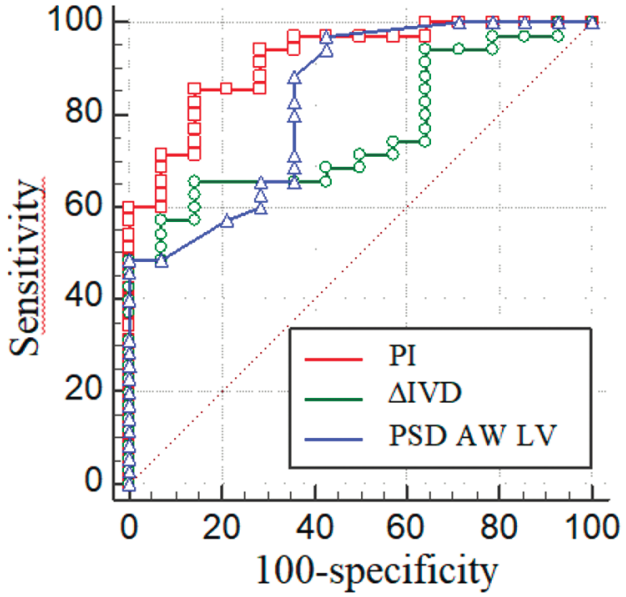


***Fig. 3. Comparison of ROC curves of PI with the response to CRT. Notes: PI - probability indicator; ΔIVD - interventricular dyssynchrony; PSD AW LV - phase standard deviation anterior wall left ventricle.***

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# FAMILIAL ATRIAL FIBRILLATION AS A POLYGENIC DISEASE WITH STRUCTURAL CARDIAC ABNORMALITIES: ASSESSMENT OF GENETIC RISK AND POSSIBILITIES FOR GENE THERAPY

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*The prevalence of familial atrial fibrillation (AF) in the general population and in the structure of AF is considered, and genetic predictors of AF and pathogenetic mechanisms of atrial remodeling are analyzed. The assessment of the genetic risk of AF occurrence, the prediction of its outcomes and the effectiveness of AF therapy, as well as the prospects for AF gene therapy are discussed.*

**Key words:** antiarrhythmic therapy; genetic testing; catheter ablation; atrial cardiomyopathy; atrial fibrillation

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Atrial fibrillation (AF) is the most common arrhythmia affecting up to 1% of the population worldwide [1, 2]. The prevalence of AF increases exponentially with age and can reach the mark of 8% in the elderly population [3]. Epidemiologic studies have confirmed the essential importance of the genetic aspect in the pathophysiology of AF [4]. Currently, more than 160 genes have been found to be associated with AF [5]. Some have been identified using classical linkage studies, but most rely on functional or genome-wide association studies [6]. Genome-wide association studies (GWAS) in individuals with documented familial AF have identified common single nucleotide polymorphisms associated with AF [7, 8].

Depending on the underlying cause of AF, there are differentiated: AF caused by external risk factors, the so-called acquired AF; congenital AF and genetic (familial) AF [2]. Acquired AF is associated with the effects of aging as well as risk factors such as arterial hypertension, diabetes mellitus, obesity, coronary heart disease, and chronic kidney disease. Approximately 5% of patients with congenital heart disease develop AF due to a combination of embryogenesis and peri- and postoperative factors related to the correction of the heart defect [9, 10]. Congenital AF is characterized by the onset of AF at a younger age and a relatively rapid transformation of paroxysmal AF into persistent AF [3, 11]. In about 15% of patients with congenital AF, it is familial, suggesting a genetic predisposition [12]. The interaction between genetic predictors and acquired risk factors for AF is also important [13].

## EPIDEMIOLOGY OF FAMILY FORM OF AF

The inheritability of AF has been extensively investigated since the first report of family form of AF in 1936 [11]. This is due to the high prevalence of isolated AF and differences in its incidence according to gender and ethnic groups [1, 7]. The frequency of familial form of AF is unknown, but recent studies suggest that up to 30% of patients with isolated AF (i.e., without known cardiac pathology or risk factors) have a history of the disease in their family [6, 11]. L.C.Weng, et al. [8], based on the study of common genetic variants of AF, showed that the inheritance of AF in people of European descent is about 22% of all cases of AF. In the Framingham Heart Study, having a family history of AF was associated with a 40% increased risk of AF [2]. In the Mayo Clinic AF registry, 5% of all patients and 15% of patients with isolated AF had a family history of AF [14].

A population-based cohort study of patients with AF demonstrated significant familial incidence of AF and a high probability of heritability among patients with AF. According to Christopherson et al. [5], among 5000 Icelanders, first-degree relatives of patients with AF were 1.8 times more susceptible to the development of AF than in the general population, and in patients younger than 60 years of age, the relative risk of AF reached 4.67. In a study of Danish twins, the risk of developing AF was 12% for monozygotic twins and 22% for dizygotic twins [5]. It is found that more than 60% of the variance in AF is explained by genetic effects. The remaining heritability of AF can be explained by promoter variants, epigenetics, structural variants, and undiscovered genetic mechanisms [11]. Recommendations for the clinical use of genetic testing for familial AF are described in the Genetics Home Reference at https://medlineplus.gov/genetics/condition/familial-atrial-fibrillation [16].

L.Staerk et al. [1] showed that the incidence rate of familial AF was 3.48 in patients in whom first-degree rel-

atives were affected and 1.64 in those in whom second-degree relatives were affected. An increased risk has been identified, especially if there are multiple affected relatives and relatives with onset of AF at a young age. The ORBIT-AF registry showed that patients with familial AF had more symptoms than other variants of AF [15]. However, there were no differences between the two groups in terms of AF recurrence, hospitalization rates, complications, and overall mortality.

GWAS have identified more than 100 genetic loci associated with AF [17]. Most of them point to ion channels, transcription factors, and regulatory genes involved in the mechanisms leading to the development of AF (Table 1). The GWAS consensus implies that AF is both polygenic and pleiotropic in nature [6]. With the advent of whole genome and whole exome sequencing, both common and rare genetic variants of AF have been identified and linked to the pathogenetic basis of the familial form of AF [4].

Among the genes involved in the realization of various pathogenetic mechanisms of AF occurrence there are genes affecting potassium channels (*KCNA5, KCND3, KCNE1, KCNE2, KCNE3, KCNE4, KCNE5, KCNH2, KCNJ2, KCNJ5, KCNJ8, KCNN3, KCNQ1, ABCC9*), on sodium/potassium channels (*HCN4*), and on sodium channels (*SCN1B-4B, SCN5A, SCN10A*); genes involved in cellular calcium homeostasis (*RyR2, CACNB2, CACNA2D4*); genes involved in the development of fibrosis and remodeling of the extracellular matrix (*NPPA. MMP3, COMP, COL12A1, COL23A1, COL21A1, ANGPTL2, COLQ*); genes involved in cardiac morphogenesis (*GATA4, GATA5, GATA6, GREM2, NKX2-6*); genes involved in intercellular communication (*GJA1, GJA5*) and genes involved in nuclear structure (*LMNA, NUP155*).

## COMMON GENETIC VARIANTS OF AF

Familial AF is very heterogeneous and may have autosomal dominant or recessive inheritance [4, 14]. A GWAS meta-analysis of more than 50 studies involving more than 65,000 patients with AF found a more than 3-fold increase in the number of loci associated with AF [17]. An association between earlier onset of AF and high genetic risk of AF variants has also been found [18].

It was shown that the most significantly associated with familial AF single-nucleotide polymorphism is in the noncoding region of chromosome 4q25 of the *PITX2* gene (paired homeodomain-2 gene) [19]. In addition, *PITX2* expression is significantly reduced in patients with AF, suggesting a link between loss of function in *PITX2* and AF [14]. In experiment, loss of *PITX2* function was found to be associated with sarcomere disruption, increased fibrosis, and a more than 4-fold increase in *HCN* passthrough gene expression [6, 19].

Another significant single nucleotide polymorphism identified using GWAS is the rs2106261 locus located on chromosome 16q22, intronic to the *ZFHX3* transcription factor gene [4]. The *ZFHX3* gene is expressed in the heart and is associated with myogenic and neuronal differentiation [8]. The association of AF with the *KCNN3* gene (locus located on chromosome 1q21), which encodes the calcium-activated potassium channel SK3 and is involved in atrial repolarization, has also been revealed [17]. Blocking these channels leads to antiarrhythmic effects by selectively prolonging the action potential (AP) in the atria [18].

In addition, two identified loci were located near genes that are targets for antiarrhythmic drugs, *SCN5A* and *KCNH2* [20]. The *SCN5A* gene, encoding Nav1.5 channel, is a target for sodium channel blockers, and the *KCNH2* gene, encoding Kv11.1 channel, is a target for drugs that inhibit potassium channels [13]. *KCNH2* gene variants associated with both loss-of-function and gain-of-function Kv11.1 channels are associated with frequent paroxysms of AF.

AF has also been reported to be associated with two common variants in the *RPL3L* gene on chromosome 16 and one variant in the *MYZAP* gene on chromosome 15 [21]. Another locus associated with AF was found on chromosome 10q22 and is located near the *SYNPO2L* and *MYOZ1* genes. The structural proteins encoded by these genes are expressed in both skeletal muscle and heart and are closely associated with the phenotype of atrial cardiomyopathy (ACM) [8]. I.E.Christophersen, et al. [5] identified 12 new loci of AF using GWAS involved in genes involved in structural remodeling of the heart. The most significant association was observed at locus 2q31, carrying seven highly correlated missense variants of the *TTN* (connectin, encodes the protein titin) gene, which is a strong candidate gene for AF that is involved in myocardial structural integrity and elasticity [22].

Transcription factors have been shown to play an important role in predisposition to familial AF [23]. They bind to specific DNA sequences in the promoter regions of genes and regulate their expression. Cardiac-specific transcription factors are involved in the regulation of gene expression (e.g., *GATA4, GATA6, MYH6, NKX2-5, PITX2*) involved in the formation of cardiac structures and the conduction system and are also associated with the risk of developing AF [17].

Given the complex polygenic origin of familial AF, which is important for disease outcomes and choice of therapy, 4 phenotypes of familial AF have been conventionally identified: Phenotype A (genes encoding various peptides and enzymes, e.g., *NPPA, PRKAG2*, angiotensin-converting enzyme - ACE); Phenotype B (various transcription factors; e.g., *PITX2, TBX5, ZHX3*); phenotype C (genes involved in the formation of structural components of the heart; e.g., *MYL4, TTN*) and phenotype D (genes encoding ion channel functions; e.g., *KCNQ1, SCN5A*).

## RARE GENETIC VARIANTS OF AF

The first association between rare variants in the *KCNQ1* gene encoding the α-subunit of slow potassium current $I_{Ks}$ and familial AF was found in 2003 [24]. β-subunits of potential-dependent potassium channels are encoded by *KCNE1-KCNE5* genes and carry rare variants associated with isolated and familial AF [12]. The functional effects of these variants are associated with an increase in current $I_{Ks}$ and potential effects on transient sodium current ($I_{to}$) and fast potassium current ($I_{Kr}$).

A rare variant of the *KCNH2* gene, which encodes the α-subunit of the fast potassium current channel $I_{Kr}$, has been identified in a family with AF and shortened QT

interval syndrome, suggesting overlapping phenotypes [24]. The Kir2.1 inward rectifier channel mediates the abnormal $I_{K1}$ potassium current involved in repolarization and is encoded by the *KCNJ2* gene. Functional analysis demonstrated enhanced channel function, suggesting a role for this gene in the initiation and/or maintenance of AF [12]. In a cohort of patients with AF, rare variants were also found in the *KCNJ8* gene encoding the Kir6.1 channel and in the *KCNJ2* gene encoding the α-subunit of the Kir3.4 channel [25].

Of particular interest is the *KCNA5* gene, which encodes an atrial-specific Kv1.5 channel involved in cardiac repolarization. I.E.Christophersen, et al. [5] identified various rare variants in the *KCNA5* gene in patients with early onset of isolated AF, both with loss of function and with gain of function of the Kv1.5 channel, which provides ultrafast potassium current ($I_{Kur}$), which increases susceptibility to AF.

AF has also been found to be associated with genes encoding potential-dependent sodium channels. For example, about 10 rare variants of the *SCN5A* gene have been identified in patients with early-onset AF, and most of them were previously diagnosed with prolonged QT interval syndrome [26]. Functional studies revealed abnormalities in both transient sodium current ($I_{to}$) and an increase in steady-state sodium current.

In addition, variants in four β-subunit sodium channels encoded by the *SCN1B-SCN4B* genes have been identified in patients with familial AF. Variants in these genes cause changes in the gating properties of sodium channels and attenuation of sodium current [25]. Ten rare missense variants of the *SCN10A* gene encoding the Nav1.8 sodium channel have also been found in patients with isolated AF. Functional studies revealed both gain and loss of Nav1.8 channel function, suggesting the involvement of *SCN10A* in the development of familial AF.

It should be noted that enhanced diastolic release of calcium ions ($Ca^{2+}$) from the sarcoplasmic reticulum into the cytoplasm via ryanodine receptor type 2 (RyR2) is one of the mechanisms of AF development [27]. Increased expression of *RYR2* gene in atria has been found in patients with paroxysmal AF [17]. It has been shown that microRNA (miRNA)-mediated posttranscriptional regulation of *RYR2* may be the main mechanism of AF development [23]. A full-exome study in families with early-onset AF revealed rare variants in the *CACNB2* and *CACNA2D4* genes, which encode L-type calcium channels with overlapping effects on Cav1.2, emphasizing the important role of these genes in predisposition to AF [28].

Recently, there is increasing evidence that structural genes are involved in the development of familial AF [13, 17, 21, 29]. An increased role of fibrosis and atrial ACM in the pathogenesis of AF has also been reported [4, 29]. These findings challenge the traditional view of AF as an electrical disease and allow for improved diagnosis and treatment of AF in the future [2, 4, 6, 10].

A homozygous variant, c.1172G> A in the *NUP155* gene was found to be segregated in family members with AF [17]. The *NUP155* gene encodes nucleoporin, which is a major component of nuclear pores involved in cytoplasmic transport. A variant of the *NPPA* gene has been identified in a family with autosomal dominant inheritance of AF [20]. *NPPA* encodes an atrial natriuretic peptide involved in the regulation of blood pressure. Rare variants in *MYH7, MYBPC3, MYL4* and *TTN* genes have been found to be associated with atrial ACM [30], which is characterized by altered sarcomeric architecture that contributes to re-entry and AF [22].

Intercellular gap junctions have been found to play an important role in the arrhythmogenesis of AF. For example, connexin-43 and connexin-40, encoded by the *GJA1* and *GJA5* genes, respectively, are gap junction proteins in the atrial myocardium [31]. An increased risk of AF with polymorphisms in the renin-angiotensin-aldosterone system (RAAS) genes encoding ACE inhibitor and angiotensinogen have also been reported [7, 32].

AF as a polygenic disease with a structural component is associated with different variants of genes encoding cytoskeletal proteins [4]. Thus, the most common variants of *MYH7* and *MYBPC3* genes are associated with hypertrophic ACM [33]. Arrhythmogenic right ventricular ACM has also been shown to be associated with variants in intercalated disc genes, and patients with this condition have an increased risk of AF and ventricular arrhythmias [6].

O.B.Vad et al. [34] identified rare loss-of-function variants in three different genes of dilated BMP (*DMD, PDLIM3, FKTN*) associated with early onset of AF, which is probably due to the development of atrial ACM. In addition, atrial ACM has been found to be associated with the *MYL4* gene (myosin-4 light chain gene), which is responsible for the electrical, contractile, and structural integrity of the atria [34]. A *MYL4* variant associated with a high risk of stroke has been identified in a patient with atrial ACM and recessive form of AF [22]. H.Cochet et al. [35] found a high degree of re-entry activity in the atrial fibrosis zone in patients with persistent AF. Drug blockade of RAAS has been found to reduce atrial fibrosis and duration of AF.

GWAS studies have identified genes associated with AF that are involved in various inherited arrhythmias, conduction diseases and cardiomyopathies [4]. This emphasizes the pleiotropy of these genes as well as the polygenic nature of AF. Overlap syndromes of AF with other hereditary arrhythmia phenotypes such as Brugada syndrome, prolonged and shortened QT interval syndromes have been identified [6]. Patients with congenital long QT syndrome have been shown to have a higher risk of early onset of AF than in the general population [26]. In patients with Brugada syndrome, the incidence of isolated AF ranges from 11% to 39%, being an indicator of poor prognosis [36].

Increased expression of *MYH6* and *MYH7* genes in atria was also found. The *MYH6* gene encoding the α-subunit of myosin heavy chain (α-MyHC) has been shown to be associated with AF and sinus node dysfunction, and the *MYH7* gene encoding the β-subunit of myosin (β-MyHC) has been shown to be associated with chronic AF [33]. β-MyHC is activated in heart failure and other cardiac diseases, whereas α-MyHC is suppressed, which confirms the role of MyHC isoforms in determining cardiac contractility. Another study identified a variant in the *PLEC* gene, which encodes structur-

al components of the cardiomyocyte, and was associated with a 55% increased risk of AF and 64% increased risk of sinus node dysfunction [21].

## ELECTRICAL AND STRUCTURAL REMODELING OF ATRIA - THE PATHOGENETIC BASIS OF AF

The pathogenesis of AF is poorly understood, which to some extent complicates the development of effective treatment methods. Variants in genes encoding ion channels, signaling molecules, additional subunits, and gap junctions associated with AF have been shown to lead to the development of AF by different pathways [7, 30].

Atrial remodeling likely begins with electrical remodeling characterized by a reduction in atrial refractoriness, an increase in repolarization dispersion, and a slowing of conduction [30]. These changes occur because of abnormalities in AP currents caused by excessive $Ca2^{+}$ influx into cardiomyocytes and impairment of its subsequent homeostasis. Further, alterations in the $Ca2^{+}$ exchange cycle contribute to ectopic activity and diastolic $Ca2^{+}$ leakage from the sarcoplasmic reticulum via RyR2 receptors [27]. As a result, atrial re-entry circulation is stabilized and atrial vulnerability to AF is increased [13].

Due to atrial structural changes caused by variants in genes encoding myocardial cytoskeletal proteins, fibrosis and atrial ACM develop, which contribute to increased myocardial collagen volume and decreased intercellular gap junctions [29, 31]. The result is a slowing of conduction and an increase in repolarization dispersion in the atria, which constitute the structural and/or electrical substrate for the onset and/or maintenance of AF [30].

It should be noted that atrial remodeling refers to any persistent changes in atrial structure and/or function [13, 37]. Atrial structural remodeling includes inflammation, cell hypertrophy, atrial dilatation, apoptosis, and fibrosis, which together contribute to abnormal formation and conduction of electrical impulses as an arrhythmogenic substrate [3, 35]. It is also known that hemodynamic atrial overload in AF causes RAAS activation, which is associated with endothelial damage and recruitment of cytokine-secreting inflammatory cells [11].

Atrial fibrosis is thought to alter both the overall expression of gap junction proteins and their distribution along the cell membrane, causing a decrease in intercellular communication [4]. In addition, acquired risk factors for AF, especially cardiovascular disease, also influence atrial electrical and/or structural remodeling, which accounts for approximately 50% [13]. Finally, atrial remodeling can be caused by AF itself, leading to electrophysiological, contractile, and structural changes [10, 30].

In recent years, familial and population genetic studies of AF have led to the discovery of transcription factors as potentially important factors involved in atrial remodeling that contributes to arrhythmia susceptibility. Transcription factors can create a proarrhythmogenic substrate in pulmonary veins and atria. However, further studies are needed to fully characterize the links between these proteins and the pathogenesis of AF, which could potentially lead to the development of new treatments for arrhythmias.

## GENETIC RISK ASSESSMENT OF AF

Genetic testing is useful to confirm the diagnosis as well as for differential diagnosis, recurrence risk calculation and prenatal diagnosis in families with known genetic variants of AF [5, 7]. The differential diagnosis should consider the presence of reversible causes of AF in the patient, especially metabolic disorders, and cardiovascular disease [13]. According to the recent Expert Consensus of the European Heart Rhythm Association / Heart Rhythm Society / Asia-Pacific Heart Rhythm Society / Latin American Heart Rhythm Society [38], the clinical value and applicability of genetic testing in AF is primarily considered from a prognostic standpoint and should be aimed at early identification of high-risk patients, which may contribute to the reduction of cardiovascular complications and mortality with adequate therapeutic options. The eligibility criteria for genetic testing for suspected familial form of AF are [2, 38]: 1) the presence of ECG-documented signs of AF; 2) a clinical picture of AF as the main clinical manifestation (phenotype) with early onset (before 60 years of age); 3) identification of a family history of at least one sick family member of the first or second degree of consanguinity. Genetic testing of *SCN5A, KCNQ1, MYL4,* and *TTN* truncating variants can be performed in all patients younger than 60 years of age with an established diagnosis of familial AF based on a review of the patient's medical history, family history, and ECG characterization [38].

GWAS studies have identified common variants in more than 100 genetic loci responsible for the development of AF. Several studies have attempted to incorporate genotype into de novo AF prediction models [18]. In this regard, the AF-PRS (atrial fibrillation polygenic risk score) was developed in 2013 to identify individuals at high risk of AF, its clinical outcomes, and to predict rhythm control therapy [17, 39].

This assessment consisted of 12 risk alleles at nine loci associated with isolated AF. Although the AF-PRS score is calculated based on multiple variants to identify a population at high risk of developing AF, a few prerequisites must be met [5]. First, the GWAS must be large enough to identify all common variants associated with AF. Second, there must be sufficient power to reproduce the AF-PRS in the validation dataset. AF-PRS score has been shown to predict the occurrence of AF than the association of clinical risk factors [8, 13] more clearly.

It has been shown that when the AF-PRS score was added to the basic model for predicting the development of AF in 20,000 women without cardiovascular disease, the area under the predictive value curve increased to 0.74 [13]. A PRS analysis of AF with 6.6 million variants in more than 500,000 patients found that 6.1% of the general population had a 3-fold higher risk of developing AF [40]. Identification of individuals with a 3-fold increased risk of developing AF is potentially «actionable» and may lead to increased screening and earlier therapeutic intervention and prevention of progression to persistent or permanent forms of AF [8].

It has been shown that multiple single nucleotide polymorphisms can improve the prediction of the devel-

opment of AF, including asymptomatic AF, and ischemic stroke [8]. AF-PRS assessment also has potential value as an indicator of anticoagulant therapy [40]. In addition, AF-PRS was as powerful as arterial hypertension in assessing clinical outcomes of AF [41]. No intergenic interaction regarding susceptibility to AF was detected.

The value of AF-PRS in predicting the recurrence of AF after treatment of AF was also evaluated. The presence of either of two single nucleotide polymorphisms, rs2200733 and rs10033464, on chromosome 4q25 has been shown to be an independent predictor of AF recurrence in patients undergoing electrical cardioversion [20]. Similarly, in patients with AF who underwent catheter ablation (CA), the presence of either of the same two single nucleotide polymorphisms increased the risk of early recurrence of AF (after ≤7 days) by 2-fold and late recurrence of AF (after 3-6 months) by 4-fold [24].

In addition, AF-PRS calculation based on analysis of 127 genetic variants, identified patients with a 2-fold increased likelihood of cardioembolic stroke [41]. In another study, calculation of AF-PRS with 32 variants in more than 50,000 patients with cardiovascular disease showed a 4-fold increase in stroke incidence in patients with high genetic risk, compared with a relatively «low risk» $CHA_2DS_2$-VASc score of 2.57 [41].

It should be noted that prediction models for the development of AF based on genetic information are not yet judged to be sufficiently convincing to distinguish between people at low and high risk of AF because of testing of a small number of variants, pleiotropy of AF genes, and the interaction of these genes with external risk factors.

## TREATMENT OF FAMILIAL AF

Current therapies for rhythm control in AF include drug therapy and CA [35]. This paper reviews the genetic approach to therapy in familial AF and the prospects for gene therapy for AF.

### General principles of gene therapy for AF

Among the potential cardiac arrhythmias that can be treated with gene therapy, AF is the most intensively studied [2, 42]. Advantages of gene therapy for AF include tissue specificity with fewer side effects, and possibly increased therapeutic efficacy [42]. For clinical practice, the safety of using gene therapy, the optimal way to deliver genetic material into the heart, and the establishment of long-term gene expression for myocardial modification are of great importance [43, 44]. Therefore, effective, and prolonged gene therapy for AF requires the development of innovative approaches to expand the therapeutic options.

Gene delivery can be accomplished using viral or non-viral vectors with varying degrees of gene inclusion and expression [20, 44]. Adenovirus and adeno-associated viruses are currently the most used viral vectors for cardiac gene therapy [45]. Viral vectors are live viruses, and their advantages include incorporation of genetic material into the genome of the target tissue as well as minimally invasive delivery through the bloodstream. A basic non-viral vector directly injected into the myocardium consists of a DNA plasmid containing the gene of interest, with or without other coating agents to improve DNA uptake by cells [44]. The advantages of plasmid DNA administration include a limited cellular and antibody-mediated immune response, allowing for repeated treatment.

There are several methods of gene delivery to the left atrium: epicardial injection of a plasmid carrying the gene of interest combined with electroporation; epicardial viral gene delivery and epicardial gene staining [6]. The gene staining technique is the optimal method for delivering target genes to the pulmonary veins and left atrium. The successful solution of endocardial gene staining technique may be the most appropriate way for electrophysiologists to perform gene therapy [44]. Using this technique, almost 100% of cells examined transmurally had evidence of gene transfer [42].

Although there is no «perfect» vector or delivery method that can target, integrate, and safely express genes in the myocardium in a «seamless» manner, the development of both viral and non-viral vectors and the creation of safer and more effective gene therapies for AF continues.

### Genotypic approach to AF therapy

Variability in response to pharmacologic and non-pharmacologic therapy has been established in patients with AF [20, 32]. For example, some patients are free of AF for long periods of time with antiarrhythmic therapy, while others require repeated AF ablation within a few weeks [3]. The limited success of rhythm control therapy in AF is partly due to an incomplete understanding of the pathophysiologic mechanisms [10].

Recognizing that common genetic variants increase susceptibility to AF reinforces the possibility that they may also modulate response to rhythm control therapy. One of the first pharmacogenetic studies investigated whether there was a response to antiarrhythmic therapy (AAT) in symptomatic AF modified by the ACE I/D polymorphism [20]. This polymorphism, associated with increased ACE activity and cardiac fibrosis, was a significant predictor of AAT ineffectiveness in patients with early-onset AF. Patients with ACE genotype I/I showed a pronounced reduction of symptoms on the background of therapy, while in patients with genotype D/D the response to AAT was weak. In addition, we found that the single nucleotide polymorphism rs10033464 on chromosome 4q25 was an independent predictor of successful rhythm control in patients carrying the ancestral allele, having a fourfold increased chance of maintaining sinus rhythm. It has also been shown that the activity of flecainide is increased in patients with AF and β1AR Arg389Arg genotype, while heart rate control is achieved at lower doses of this drug [43].

F.Syeda et al. [19] showed that variable expression of PITX2 not only modulates atrial resting membrane potential, but also confirms the clinical observation that flecainide is more effective in suppressing AF than sotalol. In addition, patients carrying the variant allele rs10033464 responded better to treatment with class I versus class III antiarrhythmic drugs.

Overall, studies investigating the role of AF-PRS genetic risk for predicting the efficacy of AAT in AF are scarce. This is partly due to the growing importance of catheter ablation of AF and the lack of need to assess the response to AAT using AF-PRS [2, 20]. At the same time, with the expected increase in the need for rhythm control therapy for stroke prevention, there is great potential in the

application of AF genetic risk assessment for the management of AAT in the general population [10]. It is important to emphasize that almost all pharmacogenetic studies evaluating the response to AAT in AF have not been replicated and their effects are modest, reinforcing the need for randomized clinical trials before such approaches can be implemented in clinical practice.

Predicting the recurrence of AF after CA based on genetic testing may help identify patients who are indicated for regular clinical and electrocardiographic follow-up. For example, it has been shown that like the risk of first-onset AF, PITX2 was a major factor in the recurrence of AF after CA [32]. While clinical and echocardiographic variables could not predict recurrence, any variant alleles were associated with early and late recurrence of atrial arrhythmias after CA [46]. Another study confirmed the predictive value of ACE I/D polymorphism in the occurrence of early recurrence of AF after CA [32]. DD genotype and left atrial enlargement were found to be significantly associated with recurrence of AF. These studies have shown that genes involved in the pathogenesis of AF may not only predict risk of AF but also response to therapy.

The rs751141 variant in the *EPHX2* gene (encodes epoxyeicosatrienoic acids, which are involved in the modulation of cardiac ion channels) has also been shown to be associated with an increased risk of AF recurrence after CA [25]. Since nitric oxide has been implicated in modulation of cardiac vagus nerve activity and cardiac remodeling, the rs1799983 polymorphism in the *NOS3* gene has also been shown to be associated with early recurrence of AF after CA [24].

However, the value of screening for incident rare variants as predictors of recurrent AF after CA remains questionable. For example, rare variants in cardiac sodium channel genes, *SCN5A* and *SCN1B-4B*, were not significantly associated with CA outcome [25]. Despite some controversial points, AF-PRS assessment is a promising approach for predicting the efficacy of AF treatment in clinical practice.

**Therapeutic targets of gene therapy for AF**

Given the multifactorial origin of AF, different therapeutic targets for gene therapy of AF have been identified depending on their contribution to the re-entry mechanism [43]: shortened AP (ion channels, autonomic modulation) or slowed conduction (gap junctions, structural remodeling).

It should be noted that gene therapy aimed at modifying the electrical substrate of AF by reducing the expression of the fast potassium current $I_{Kr}$ by inhibiting the *KCNH2* gene promotes atrial AP prolongation, increases their refractoriness and prevents AF [43]. It has also been shown that gene therapy leading to increased expression of L-type calcium channels either through up-regulation or by adding a highly expressed copy of the gene may be effective in preventing the occurrence of AF. In this case, T-type calcium channel blockers are the most effective compared to sodium, potassium and L-type calcium channel blockers.

Kv1.5 potassium channels are another potential target for gene therapy of AF [42-44], which regulate $I_{Kur}$ current and lead to selective prolongation of atrial AP. It has been shown that Kv1.5 channel knockdown or knockout can have therapeutic effects without the need for repeated antiarrhythmic treatment. Some drugs that act at the atrial level, such as AVE 0118, have been shown to affect $I_{Kur}$ current in the atrial auricles, shortening the duration of AP in chronic AF. In addition, inhibition of the potassium channel Task-1, which is an atrial-selective regulator of AP duration, is an attractive target for antiarrhythmic therapy in AF, especially in patients with heart failure [47]. Thus, therapeutic agents targeting ion channels may be useful in an early cardioversion strategy.

It has been demonstrated experimentally that restoring the structure/function of connexins may be useful in the treatment of AF [31, 44]. Connexin-40 and connexin-43 gene transfer using the epicardial staining method has been shown to significantly improve protein expression and localization, increase the concentration of gap junctions, and thereby cause improved conduction and reduced risk of AF [28, 29].

One effective treatment strategy for familial AF is to attenuate parasympathetic impulses (signaling). The left atrium, especially its posterior wall, is known to have a denser parasympathetic innervation compared to other atrial regions [48]. It has been demonstrated experimentally that stimulation of the cervical portion of the left vagus nerve causes shortening of the atrial refractory period and increased vulnerability to AF, whereas local pharmacologic blockade is protective [31]. It has also been found that gene therapy of AF by inhibiting the primary effector molecules of the Gαi/Gαo system attenuates the vagus nerve-induced shortening of the atrial refractory period and thus reduces the inducibility of AF [43].

Gene-based strategies to modify the structural substrate of AF involve suppression of inflammation and oxidative stress in the atria and consequently cellular fibrosis and apoptosis [43]. The main sign of age-related fibrosis is the activation of beta-transforming growth factor TGF-β [47]. A.Kunamalla et al. [49], in an experimental model of AF tried to modulate atrial fibrosis by delivery of dominant-negative TGF-β type II receptor to the posterior part of the left atrium. Therapy targeting TGF-β resulted in decreased fibrosis and reduced AF inducibility compared with the control group.

It has also been shown that transduction of lentivirus against miRNA206 into the superior left ganglionic plexus caused suppression of apoptosis, prolongation of AP and decreased AF inducibility [44]. Gene therapy for AF targeting cellular apoptosis involves suppression of caspase-3 activity, which can be inhibited by small or short interfering RNA (siRNA). In an experiment, treatment with an adenovirus vector containing siRNA resulted in suppression of apoptotic activity in the atrium and delayed the onset of persistent AF [42].

Active oxygen species (AOS) generated by oxidative stress have multiple interactions with several known triggers of AF, modulation of which has high therapeutic potential [37]. It has been shown that patients with AF have lower nitric oxide bioavailability than those without AP [43]. In addition, high levels of AOS are associated with enhanced TGF-β signaling, and the presence of atrial fibrosis [37]. AOS can damage mitochondrial DNA, caus-

ing myocyte calcium overload and electrical remodeling, leading to AF. Finally, high levels of AOS correlate with increased oxidation of calmodulin-dependent kinase II, which is associated with altered calcium cycling (turnover) and hence atrial electrical remodeling. Thus, oxidative stress-induced AOS are a compelling and multilevel target of AF therapy.

## CONCLUSION

Given the relatively high prevalence of familial AF in the population, it is relevant to assess the potential risk of AF among relatives of a patient with isolated AF, and if genetic predisposition is suspected, it is advisable to perform genetic testing. Therefore, further studies are needed, primarily to test the clinical utility of information on family history of AF in addition to established risk factors for the development of AF. It also seems important to conduct genotype-phenotype association studies irrespective of allele frequency.

The response to antiarrhythmic therapy and CA of AF is known to be partially modulated by shared genetic variability; therefore, the development of a comprehensive clinical and genetic risk scale will allow the use of genetic data for the management of patients with FP. It should be noted that one of the most challenging aspects of AF treatment is the heterogeneity of genetic, structural, and electrical abnormalities that lead to the development of AF. Therefore, the use of targeted genetic alterations for personalized drug therapy of AF is a relevant problem. Currently, intensive experimental studies of suitable therapeutic targets for gene therapy of AF and the implementation of their results into clinical practice in patients with familial AF, as well as the development of effective and safe methods of gene therapy are ongoing. Given the economic impact of the AF epidemic, even small changes in therapeutic efficacy can result in substantial improvements for patients and the health care system.

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# EVALUATION OF OPPORTUNITY FOR AIR TRAVELING OF PATIENTS WITH CARDIAC ARRHYTHMIAS

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*The increasing use of air transport by people with cardiovascular diseases, prone to problems associated with air travel, and require more attention during the entire journey. Considerations for preventing the worsening of the condition of patients during air travel based on the available data are summarised, algorithms for preliminary risk assessment and preparation of patients with cardiac arrhythmias are given.*

**Key words:** aviation environment; air travel; arrhythmias; tachyarrhythmias; bradyarrhythmias; cardiac implantable electronic devices

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Nowadays, more and more people suffering from cardiovascular diseases use air travel. This is partly due to the greater availability of air travel, and partly to advances in cardiology and medicine in general. Progress in the diagnosis and treatment of cardiac arrhythmias is evident, and, accordingly, a significant proportion of patients with cardiac arrhythmias can be found among the passengers of modern commercial airlines. These patients tend to have problems with air travel and may need more attention during travel. Nevertheless, there are few studies that can provide recommendations for patients with cardiac arrhythmias who wish to travel on commercial airlines. In this review, we have attempted to summarise considerations for preventing deterioration in quality of life during air travel based on the available evidence and to provide (as far as possible) reasonable algorithms for the pretesting and preparation of patients with cardiac arrhythmias.

## FACTORS AFFECTING THE PATIENT WITH ARRHYTHMIA DURING AIR TRAVEL

Even for a large proportion of modern people, flying aboard an airplane is not part of the routine of life, and some people even tend to perceive it as something extreme, because the conditions to which a person is exposed during an air journey are different from the conditions in which he lives on a daily basis and for the life he is designed to lead. When considering the effects of the flight environment on the cardiovascular system, the changes in the atmosphere during the flight (physiological factors) are of course primarily taken into account, but one must not ignore the influences that occur before take-off and after landing. These include, for example, the change of time zones or the experience of waiting for a flight or being delayed, i.e. psychological and physical stress factors [1, 2], as well as failures to take medication [3].

### Effect of cabin atmosphere

There are few direct clinical studies on the pathophysiological effects of flight conditions on patients with pre-existing cardiovascular disease. Concerns about possible adverse effects are based on extrapolating what is known about the physics of gases at different altitudes, cardiovascular physiology and studies that attempt to simulate flight conditions, either by studying patients adapting to life on land at high altitude or by studying the effects of hypoxia in artificially created conditions [4-6].

First and foremost among the findings from the physics of gases is Dalton's law, or rather one of the two Dalton's laws that interest us, namely the «law of the total pressure of a gas mixture», which is formulated as follows: The pressure of a mixture of chemically non-interacting ideal gases is equal to the sum of their partial pressures. Accordingly, as altitude increases and atmospheric pressure drops, the partial pressure of oxygen drops simultaneously. Hypobaric hypoxia, which is associated with a drop in partial pressure of oxygen, can be a definite health risk in patients with cardiovascular disease [7]. Although pressurisation of aircraft cabins results in the barometric altitude in the cabin being much lower than the altitude at which normal commercial flights take place (between 6000 and 13500 m), there is still a drop in the partial pressure of oxygen, but not beyond the «barometric altitude limit». Aviation regulations dictate that cabin pressure must not exceed 2438 m (8000 ft) at the aircraft's maximum operating altitude [8], which most aircraft have been shown to be able to maintain at all times [9]. This barometric altitude limit, depends on the type of aircraft. For example, for the Airbus A320 family it is 2438 meters and for the A340-200/300 it is 2240 meters. According to the standard oxy-

gen dissociation curve of a healthy person, at a barometric altitude of 2438 m in the cabin, if the partial pressure of oxygen in the cabin is 118 mmHg, oxygen saturation is maintained at 90-93%. [10].

To be fair, it should be noted that hypoxia under flight conditions does not cause extreme changes in resting circulatory parameters [4-8], and circulatory changes are limited to a slight (probably transient) increase in heart rate, a slight decrease in total peripheral resistance, which may lead to an increase in minute volume and some increase in coronary blood flow. That said, an oxygen saturation of 80% at barometric altitudes of 2438 m is unlikely in commercial aircraft. Nevertheless, a number of aspects of hypobaric hypoxia that cause the development of cardiovascular changes are still not fully understood, including ischaemia [11], heart failure [12] and thrombosis [13].

There are very few well-designed studies assessing arrhythmia risks in humans in hypobaric environments, and most of the studies suggesting an increased arrhythmia risk at high altitudes have generally been conducted at much higher barometric altitudes (e.g. extreme mountaineering) than in commercial aircraft cabins or in animals, making extrapolation of their results to passengers somewhat difficult [14]. Cardiac arrhythmias are thought to be caused by activation of the sympathetic nervous system in susceptible passengers, especially those with underlying heart disease, and there are many factors (hypoxia, tachycardia, hyperventilation, psychological stress, omitted medication, etc.) for this activation during air travel [15].

Most interesting are studies in which healthy volunteers, while continuously recording ECGs, ascended (and then descended) by cable car to the second highest peak of the High Tatras, Lomnický Štítit, in Slovakia. The altitude to which the volunteers climbed was 2632 m; there was also a transfer point along the way with an altitude of 1764 m [16, 17]. The researchers noted a linear correlation between the increase in height and the frequency of extrasystoles, both ventricular and supraventricular. These results did not extend to sustained or hemodynamically significant ventricular arrhythmias.

It can therefore be assumed that passengers with cardiomyopathies, especially those over 50 years of age, are more susceptible to cardiac arrhythmias during air travel, even though the absolute increase in risk is probably only small.

**Electric and magnetic fields**

One of the factors one is exposed to when travelling by air, both in the cockpit and at airports, is exposure to electric and magnetic fields. Of interest are the effects on the cardiovascular system in patients with cardiac implantable electronic devices (CIEDs), including pacemakers, defibrillators and ECG loop recorders. Large-scale studies on the interaction of the CIED with the environment in the aircraft cabin are currently few. It seems likely that such studies will be done in the future, as the number of people with CIEDs is progressively increasing year by year.

Concerns that draw attention to the issue of operating CIEDs under flight conditions relate to the operation of electronic equipment on board (such as radars, rangefinders, etc.) that generate electromagnetic radiation in the cockpit of a passenger aircraft that is higher and/or of a different nature than in everyday life. Non-cardiac signals, either from the body or from external electrical devices, can potentially mimic arrhythmias that may result in inappropriate cardiac pacing or unwarranted defibrillator activation.

The above concerns stem from two studies that examined the effects of being surrounded by a single-engine aircraft. The choice of such an aircraft is due to the fact that its passenger seats are closer to the on-board radio electronics than in a large multi-engine commercial aircraft. To assess the electromagnetic interference of pacemakers [18] or cardioverter defibrillators [19], the performance of these devices placed in an artificial chest was evaluated before, during and after the test flight. The devices were working normally. Although the study tested only a few devices and only on one aircraft, it is assumed that the results are transferable to other types of CIEDs as well as to other aircraft.

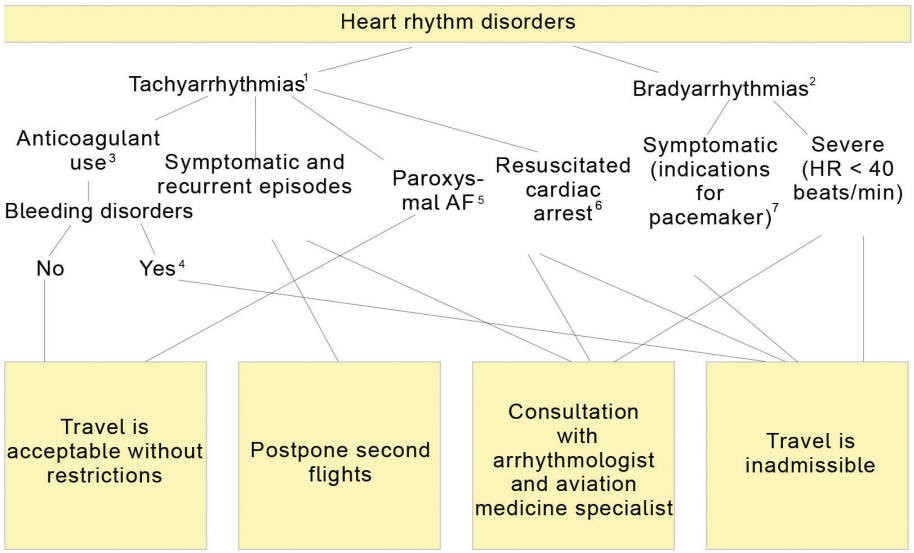


***Fig. 1. Algorithm for evaluation of the patient with arrhythmia on air travel, where [1] - atrial fibrillation with rapid ventricular rhythm, atrial tachycardia, supraventricular tachycardia; [2] - sick sinus syndrome, high degree atrioventricular block; [3] - both direct-acting oral anticoagulants and vitamin K antagonists; in the latter case, check the international normalized ratio (INR) 24-48 hours before the flight, also consider skipping the next 1-2 doses and rechecking the INR upon arrival at the destination; [4] - INR >4; [5] - medication must be carried in a pocket on board and within easy reach; [6] - due to arrhythmic syncope (ventricular tachycardia / ventricular fibrillation / torsades de pointes) without implanted cardioverter-defibrillator and with left ventricular ejection fraction < 35% or without reversible / correctable cause; [7] - travel inadmissible before pacemaker implantation.***

More important are the issues of CIED's interaction with security systems that work with electromagnetic fields and are widely used at airports. Walk-through or hand-held metal detectors are used for safety purposes to detect disturbances in electromagnetic fields. Curved metal detectors operate in continuous wave (5-10 kHz) or pulse mode (200-400 Hz) and provide a much higher magnetic field strength compared to portable metal detectors which operate in a much stronger continuous wave mode (80-130 kHz).

The effects of curved (stationary) metal detectors at airports on implanted pacemakers have been studied for almost two decades. In the observed patients, as expected, the metal detection signal was always activated when they passed without interruption through such metal detectors set to maximum sensitivity, but the behaviour of the pacemaker system was not affected in any of the patients. In particular, none of the devices were set to «noise reversal mode» or asynchronous (fixed speed) operation. However, the devices could be inhibited by 1 heartbeat [20]. Distance from the device and duration of exposure are important risk factors when assessing the interaction between CIEDs and safety systems [21]. For example, wearable metal detectors with magnets have a greater potential to interact with the implanted device.

Therefore, the effects of such electromagnetic interference on CIEDs are usually short-lived and passengers with such devices should be warned to inform security personnel about their implants to avoid prolonged contact with security devices and to avoid unnecessary stress from inadvertently triggering alarms when such devices are detected [6].

## CONTRAINDICATIONS TO AIR TRAVEL FOR PEOPLE WITH HEART RHYTHM DISORDERS

Russian legislation is quite complicated when it comes to the exclusion from air travel of people who show signs of decompensation of a disease, including cardiovascular disease. Moreover, according to cl. 108 of the Order of the Ministry of Transport No. 82 «On Approval of Federal Aviation Rules «General Rules for Air Transportation of Passengers, Baggage, Cargo and Requirements for Servicing Passengers, Shippers, Consignees» of June 28, 2007, «a passenger is obliged to independently determine the possibility of using air transportation, based on the state of his/her health», which is problematic even for a medical worker, let alone a person who does not have such com-

***Table 1.***

***General considerations for evaluating and preparing for air travel in the patient with arrhythmias***

| | |
|---|---|
| Aeromedical assessment | Determining suitability for traveling alone, accompanied or medically accompanied.<br>Determining the need for consultation with an attending cardiologist and/or aviation medicine specialist in special and complex cases. |
| Clinical assessment | Anamnesis.<br>Pulse oximeter measurement of baseline SpO2 at rest and, in some cases, in a stress test.<br>Standard ECG in 12 leads.<br>Chest radiography (after implantation of CIED).<br>INR while taking warfarin (no earlier than 24-48 hours before departure).<br>Prior consultation with a cardiologist about the interaction of cardiovascular drugs with prophylactic drugs against infectious diseases, if such drugs are required at the destination (e.g. antimalarials, etc.), is necessary. |
| Patient education | Prepare and carry the appropriate documents for relocation and admission through airport security control.<br>Ensure that a device or equipment card is on hand.<br>Carry a copy or printout of the most recent device test report and copies of a 12-lead ECG with and without a pacemaker.<br>Provide advance communication with a qualified clinic and, in some cases, a manufacturer's representative at the destination.<br>Advise security personnel not to place movable detectors over the device.<br>Minimise the time spent near metal detectors. Provide assistance in advance (usually 3 days in advance) at the airport and during the flight with luggage, especially stowing and unloading.. |
| In-flight measures (patient education) | Inform the flight attendant of your condition.<br>Have your most recent doctor's orders (with information on drug allergies) on hand (in your hand luggage).<br>Carry in your hand luggage an adequate supply of medication for the duration of the flight plus 3-5 days thereafter (in case of traveling to destinations with poor medical care, lost luggage, etc.).<br>Carry emergency medications (e.g., antiarrhythmic drugs for paroxysmal atrial fibrillation) in your carry-on baggage.<br>In neurocardiogenic syncope: inform flight attendant, rest in seat (recline if possible), cross legs, drink.<br>For paroxysmal supraventricular tachycardia: inform flight attendant, Valsalva maneuver. |

Notes: $SpO_2$ - oxygen saturation, ECG - electrocardiography, CIED - cardiac implantable electronic devices, INR - international normalized ratio.

petencies. In a number of cases, the medical staff of the health centre and the crew members of an aircraft are confronted by some passengers with a blatant disregard for the seriousness of their own condition. In such situations, one should be guided by Article 107 of Federal Law No. 60- FZ «Air Transport Code of the Russian Federation» of March 05, 1997 (with amendments and modifications), which states that «the air carrier may unilaterally terminate the contract for carriage of a passenger <...> if a passenger's state of health requires special conditions of air carriage or endangers the safety of the passenger or other persons, as confirmed by medical documents, as well as causes disorder and irreparable inconvenience to other passengers and the passenger's health and safety.

In many respects, the above position is in line with the International Air Transport Association, which establishes the following general criteria [22] for airlines to ensure that a passenger receives the necessary medical clearance for the flight if he/she:

1. suffers from any disease that is considered contagious and infectious;
2. may pose a danger or cause discomfort to other passengers due to a physical or behavioral condition;
3. is a potential risk to the safety or punctuality of the flight, including the possibility of diversion or unscheduled landing;
4. can't take care of himself/herself and requires special assistance;
5. has a medical condition that may be adversely affected by flight conditions.

In general, passengers with cardiac rhythm disorders, acute or chronic, fall into the categories described in paragraphs 4 and 5 above, and grounds for refusal to fly on board a civil aircraft may include:

- shock states (if cardiogenic shock is included);
- acute heart rhythm disturbance;
- cardiovascular diseases in decompensation stage (stage 3).

This list can be expanded and the wording replaced with more up-to-date formulations by selecting absolute cardiovascular contraindications for patients with cardiac rhythm disorders from various international guidelines and consensus documents [4-6, 8, 23, 24]. They are as follows:

- Uncontrolled ventricular or supraventricular arrhythmias;
- Resuscitated cardiac arrest caused by arrhythmic collapse, without an implantable cardioverter-defibrillator and with a left ventricular ejection fraction <35% or no reversible/correctable cause within 6 months.

The above documents usually add that this list is not exhaustive and physicians, in determining fitness to fly, must assess passengers on an individual basis. If a passenger is diagnosed with any of the above contraindications, air travel should initially be postponed and the existing clinical condition should be treated in a timely manner.

## ASSESSMENT OF FITNESS FOR AIR TRAVEL IN TACHY A ND BRADYARRHYTHMIAS

As a rule, recommendations for active arrhythmias include brief notes on flight tolerance if they are «stable» or «uncomplicated» This is currently insufficient as a wide range of clinical scenarios and severities may occur in different patients. Therefore, a more comprehensive algorithm is needed to help the treating physician make a more appropriate decision during counselling.

One aspect of determining in-flight risks is related to the propensity for increased thrombogenicity [8, 13, 25, 26], but the number of passengers taking anticoagulants, particularly vitamin K antagonists, to prevent thromboembolism in atrial fibrillation or flutter has increased quite substantially recently. As a result, bleeding rather than thrombogenicity has become an urgent concern, and there is little research on the safety of air travel in relation to the risk of bleeding when taking anticoagulants. Consequently, for the time being, all recommendations for the acceptability of air travel must be derived from ground-based studies on this risk.

There are several publications suggesting that it is probably possible to set a safety limit for taking vitamin K antagonists at an International Normalized Ratio of 4 [6, 23, 27]. In this case, assessing the presence or absence of ongoing bleeding is of paramount importance when examining a patient, especially in patients taking oral direct-act-

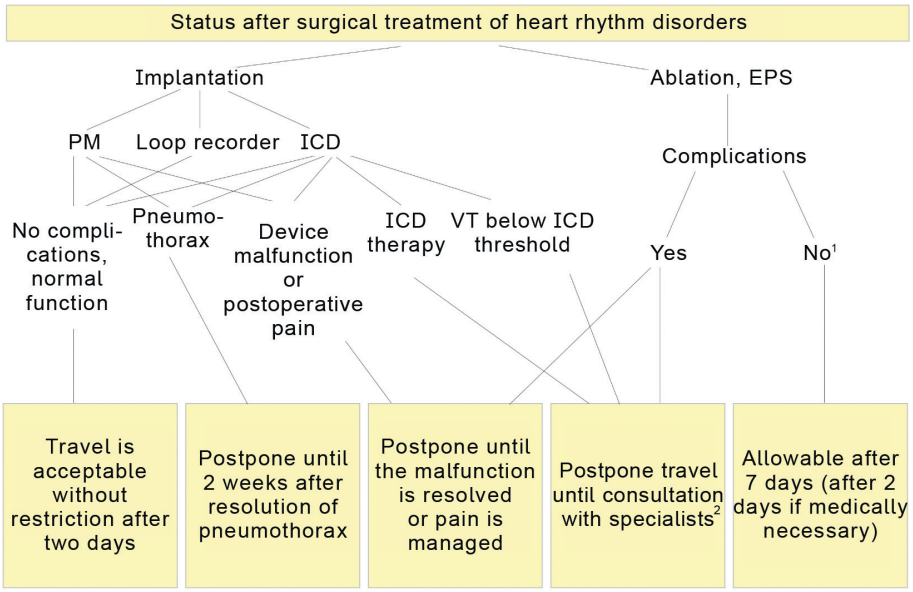


***Fig. 2. Algorithm for evaluating a patient after surgical treatment of arrhythmias for airway, where [1] - no access site bleeding or hematoma, pericardial effusion, stroke, thromboembolism, valve or myocardial damage, etc. to minimize the risk of thromboembolism, antithrombotic agents are needed for left-sided ablation; [2] - consult a cardiac surgeon-arrhythmologist and aviation medicine specialist; ICD - implantable cardioverter-defibrillator, PM – pacemaker, EPS - electrophysiological study, VT - ventricular tachycardia.***

ing anticoagulants (dabigatran, rivaroxaban, apixaban, etc.) whose activity is more difficult to monitor [28].

Fig. 1 shows the algorithm we have developed for the assessment of patients with arrhythmias based on the summary of expert opinions [6, 8, 9, 22, 23, 27, 28], which also refer to aspects other than bleeding. Table 1 is supplementing the figure.

## ASSESSMENT AFTER SURGICAL TREATMENT OF ARRHYTHMIAS

Implantation of pacemakers and cardioverter defibrillators requires access to the central veins, and pneumothorax is a common complication of their puncture. The incidence of ipsilateral pneumothorax due to needle injury to the pleura while searching the subclavian vein averages 2%. Risk factors for pneumothorax are: female gender, body mass index < 20, age > 80 years, chronic obstructive pulmonary disease, bullous emphysema, corticosteroid treatment, anticoagulant therapy, antiplatelet therapy, emergency surgery, anxious and uncooperative patient and inexperience of the surgeon. In addition, the risk is increased in patients with congenital venous or thoracic anomalies, previous procedures, surgery, trauma or radiotherapy to the affected area, a history of clavicle deformities and fractures, the use of an oversized catheter or two electrodes, more than two puncture attempts / long duration of the procedure and revision of the electrode [29].

In some cases pneumothorax may be asymptomatic, in others it may cause pain, dyspnoea, tachypnoea and tachycardia. More severe symptoms such as hypoxia (oxygen saturation < 90%), arterial hypotension, swollen neck veins, tracheal shift and decreased or absent breath sounds clearly indicate a tension pneumothorax and can be life-threatening. Whenever a patient presents with classic signs and symptoms associated with pneumothorax within a few hours of CIED implantation, it should be assumed that the patient develops a pneumothorax until proven otherwise. The usual routine examination after CIED implantation is a review chest radiograph, and specialists evaluating this examination should be alert for pneumothorax, even a small one.

The more severe manifestation of pneumothorax is due to the inherent property of gas expansion at altitude according to the Boyle-Marriott law, which can impair respiratory function or, in rare cases, even lead to tension pneumothorax. Any pneumothorax is a contraindication for air travel. However, there is consensus among guidelines and professional organizations that passenger air travel is safe 2 weeks after resolution of pneumothorax [4, 6, 8, 30].

Other aspects of surgery for cardiac arrhythmias include invasive electrophysiological investigations and/or ablation. In a typical procedure, 4-5 introducers are placed in the femoral veins through which catheters are inserted into the heart. If necessary, the left ventricles are accessed by septal puncture or by retrograde access to the left ventricle via the femoral artery. The period of immobility during and after the procedure is usually up to six hours and represents an additional thrombotic risk factor. The incidence of asymptomatic deep vein thrombosis in these conditions ranges from 5 to 18%; the clinical incidence is much lower (0.4-2%) [31].

In particular, patients undergoing left-sided procedures are a higher risk group, as any potential thrombi that form either from catheters or from endocardial lesions after ablation can cause systemic embolism [32], with the first week after the procedure being the most dangerous window for thrombus formation. Therefore, patients should be advised to postpone non-urgent air travel during this period [6, 8].

Fig. 2 shows our algorithm for assessing patients who wish to travel by air after surgical treatment for cardiac arrhythmias, based on the general opinion of experts and international recommendations [4, 6, 8, 27, 29-33]. See also Table 1.

## CONCLUSION

Thus, after reviewing the current literature covering various aspects related to air travel of passengers with cardiac arrhythmias, one can conclude that such patients should be appropriately assessed and prepared based on their travel intentions. Both the attending physician and the flight medics should know both the contraindications for flight and the correct procedure (algorithms) for a preliminary risk assessment in these individuals.

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