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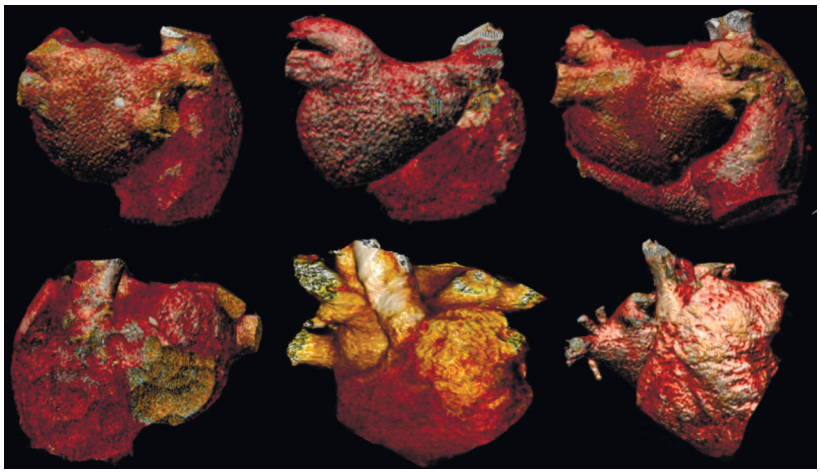

Figure from the article by N.Yu.Kashtanova, E.V.Kondratyev, G.G.Karmazanovsky et al.

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CONTENT

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FACTORS ASSOCIATED WITH THE EFFICACY OF ATRIAL FIBRILLATION RADIOFREQUENCY CATHETER ABLATION: OPINION OF THE SPECIALISTS WHO USE THE "ABLATION INDEX" MODULE

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This document provides an overview of current problems and trends in the catheter ablation of atrial fibrillation, summarizes the opinions of specialists, obtained during a web-based electronic survey, on aspects and parameters of radiofrequency ablation. The approaches on improving the efficacy and safety of radiofrequency catheter ablation of atrial fibrillation are provided.

Key words: atrial fibrillation; radiofrequency ablation; ablation parameters; ablation index; expert consensus

Conflict of Interests: E.N.Mikhaylov reports receiving speaker and consultation honoraria from Biosense Webster, Boehringer Ingelheim, Boston Scientific, Pfizer; N.Z.Gasimova receiving speaker and consultation honoraria from Biosense Webster; E.A.Artyukhina reports receiving speaker honoraria from or participation in clinical trials sponsored by Biosense Webster, Boston Scientific, Boehringer Ingelheim, Biotronik, Medtronic, Abbott; G.A.Gromyko reports receiving speaker and consultation honoraria from Biosense Webster, Bayer, Boehringer Ingelheim; D.S.Lebedev reports receiving speaker and consultation honoraria from Biosense Webster, Boston Scientific, Medtronic, Biotronik; other authors declare no conflict of interests.

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In the Russian population, atrial fibrillation (AF) occurs in 6.7% of people over 55 years old and is associated with increased cardiovascular and all-cause mortality [1]. The clinical and social significance of AF is determined by a 5-fold increased risk of heart failure (HF), a 5-7-fold increased risk of stroke, and a 2-fold increased cardiovascular mortality [2].

The following main directions in AF treatment are distinguished: better symptom control, stroke prevention, heart failure prevention, and improving the quality of life. To achieve these goals, the following approaches are used: rhythm and rate control strategies, anticoagulation, management of the underlying and concomitant diseases.

Antiarrhythmic drug (AAD) therapy for rhythm control strategy and AF recurrences prevention is often limited, associated with side effects, and ineffective. But AF catheter ablation (CA) is associated with long-term maintenance of sinus rhythm, improvement of quality of life, as well as fewer hospitalization and mortality rate due to HF according to randomized and non-randomized multicenter studies [3-6].

In the Russian Federation, about 8.000-10.000 AF CA are performed per year, which makes a significant contribution to European statistics. However, these figures are still far from the true need for AF catheter treatment [7]. Although, 10-20% of CA are redo procedures due to AF recurrent [6, 8].

Several modifiable clinical factors affect the efficacy of AF CA: obesity, obstructive sleep apnea syndrome (OSA), hypertension, alcohol intake. Successful prevention of AF recurrent lies not only in the elimination of the trigger in the pulmonary veins (PV) and/or modification of the arrhythmogenic substrate in the left atrium (LA) but also in the risk factors modification.

There are several official documents of the professional community summarizing recommendations in the field of AF CA, constantly updated scientific data and the rapid progress of AF ablation technologies stimulate the coverage of some aspects of AF treatment in the expert consensus statement. It also seems impossible to conduct randomized controlled trials on absolutely all aspects of the interventional treatment of AF, which indicates the relevance of providing expert opinion on certain issues.

This project aims to study the opinion of specialists in the atrial fibrillation radiofrequency (RF) catheter ablation about factors contributing to the improvement of the efficacy of AF interventional treatment. This document is a summary of the opinions of specialists in RF CA in Russia. The project was planned during the face-to-face meeting of the authors of the document on September 16, 2019. The work on this project consisted of two steps.

Step 1. Discussion and formation of the clinical aspects, RF parameters, and patient management strategies, potentially influencing the results of AF CA (group of specialists - the authors of this publication). Based on the results of published works and their own clinical experience, the authors agreed on the following main groups of factors that clearly or potentially affect the estimated efficacy of AF CA:

- patients' clinical characteristics undergoing AF ablation (AF type, duration, structural heart disease, HF, comorbidity, etc.);
- the preparation for catheter ablation, including antiarrhythmic therapy before, during and after ablation;
- operators' experience;
- AF ablation technology;
- additional parameters used during catheter ablation (type of catheter, program settings, automatic modules);
- additional linear lesions in the left and right atriums;
- AF recurrence criteria.

Step 2. Interactive voluntary correspondence survey of specialists according to the list of prepared questions. The second step involved specialists who independently perform AF RF CA using the Ablation Index technology (Biosense Webster, USA). The Internet survey was formulated based on the Survey Monkey resource and consisted of 40 questions. After the respondent provided answers to all questions, the Internet survey was blocked to re-fill the questionnaire by IP address. A complete list of questions included in the online questionnaire is presented in the Appendix.

Respondents' characteristics

Invitations to participate in the survey were sent to 73 specialists working in the Russian Federation (10 subjects) and Belarus (Minsk). Answers were received from 37 (51%) specialists. The mean age of the respondents was 41.4±7.6 years (from 27 to 59 years). The mean experience with AF catheter ablation was 9.0±4.1 years. The number of procedures per year of self-performed AF CA by operators varies, with most operators performing a significant amount of ablation (Fig. 1). In addition to the operators' experience, the experience of the clinical department in performing complex catheter ablation is of great importance, since this is associated with the effectiveness of treatment

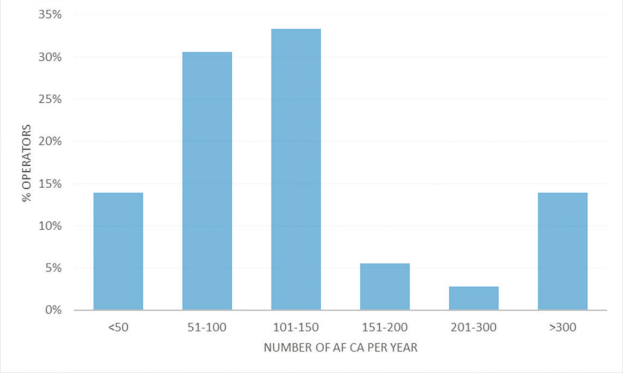

Fig. 1. The number of atrial fibrillation (AF) catheter ablation (CA) performed by a specialist per year.

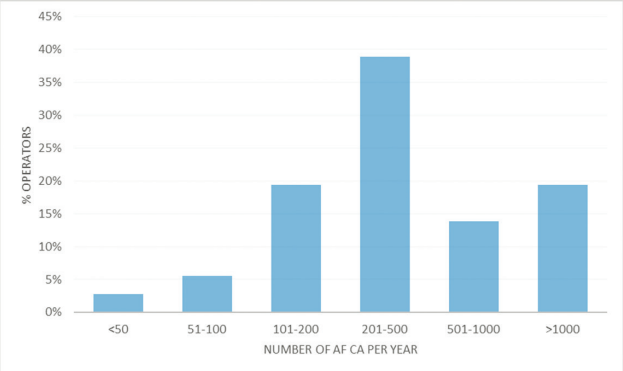

Fig. 2. The number of atrial fibrillation (AF) catheter ablation (CA) performed in the specialists' department per year.

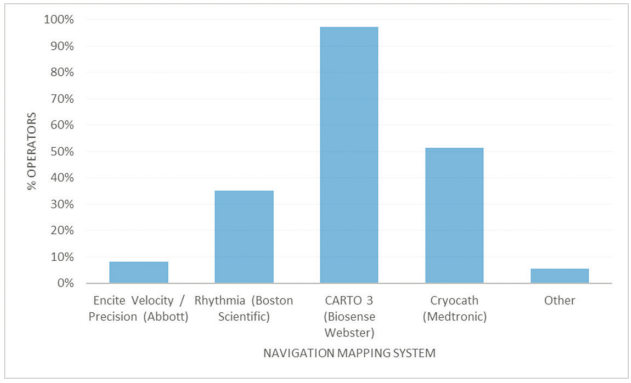

Fig. 3. Navigational mapping systems and ablation technology used by specialists in daily practice.

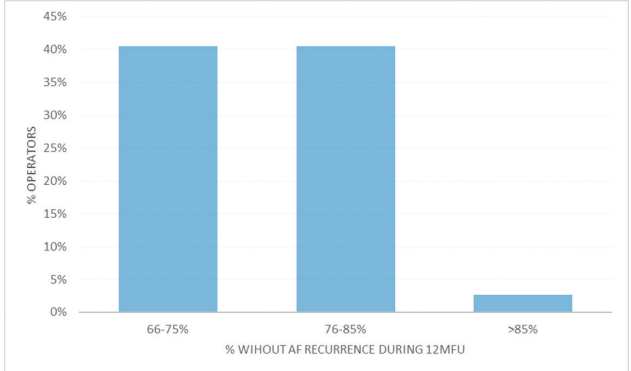

Fig. 4. Efficacy of paroxysmal atrial fibrillation (AF) ablation according to respondents (12 months follow-up (12MFU), without antiarrhythmic therapy).

and the risk of complications [9]. The respondents to this survey in most cases work in clinics with a higher volume of AF CA per year (Fig. 2). It should be noted that most respondents in their daily practice use the CARTO electroanatomical mapping system (Biosense Webster, USA) (Fig. 3).

Patients' characteristics undergoing AF ablation

In 84% of cases, respondents agreed that patient selection is an extremely important step in determining the outcome of catheter ablation. The decision to refer a patient for AF catheter ablation should be made collectively, considering the patient's preferences, after informing him of the risk of arrhythmia recurrence and the risk of adverse events associated with catheter ablation.

Large randomized and observational studies have shown that the following characteristics are associated with a more favorable long-term effect: a short history of AF, a paroxysmal AF, small LA size, no structural heart disease, non-inducible arrhythmia, no recurrence in the blanking period [10, 11]. While the following clinical signs and ablation rates are associated with a higher incidence of arrhythmia recurrence: older age, hypertension, obesity, OSA, non-paroxysmal AF (in particular, long-standing), LA dilation, LA fibrosis, confirmed by magnetic resonance imaging, phased RF ablation of AF (not used in Russia), LA additional linear lesions, antiarrhythmic drug therapy [12-18]. To predict the risk of arrhythmia recurrence, such scores as CAAP-AF, APPLE, SUCCESS have been developed and tested [19-21].

According to the authors of this document, despite the broad indications of AF CA in official documents (the presence of symptomatic AF refractory to antiarrhythmic therapy with 1 AAD, or even in the absence of a history of antiarrhythmic drug therapy in some patient groups) [22, 23], nevertheless the risk of arrhythmia recurrence should be considered when referring patients.

Obese patients (BMI> 30 kg/m^2) should be advised to reduce body weight before AF ablation since high BMI values are associated with a greater risk of arrhythmia recurrence after ablation [24]. The effect of obesity was also studied in the ARREST-AF study, where the strategy of aggressive weight loss led to a 5-fold increase in the likelihood of maintaining sinus rhythm after AF ablation compared with the control group [13]. It is well-known that the AF prevalence and progression are closely related to OSA, mainly due to atrial remodeling [14]. Although the OSA in patients with AF increases the risk of arrhythmia recurrence after AF CA, CPAP therapy increases the frequency of maintaining sinus rhythm to a level comparable to the patient population without OSA [15]. Hypertension is a well-known and independent predictor of both the risk of development and the risk of AF recurrence after ablation [16]. Patients with medically controlled hypertension have the same risk profile for AF recurrence as patients without hypertension. Although studies show a decrease in the recurrences in patients with controlled hypertension, the effect of aggressive blood pressure lowering, including with interventional treatment methods (renal denervation, baroreceptor stimulation), on AF recurrence after ablation has not been fully understood. However, blood pressure control significantly reduces the risk of major cardiovascular events that occur in both hypertensive and AF patients [10]. The relationship between alcohol consumption and the development of AF after ablation is known [17], while changes in the atria caused by the toxic effect of alcohol are associated with the presence of AF triggers outside the PV. The ARREST-AF study also demonstrated that modification of risk factors for cardiovascular complications, including a decrease in alcohol consumption of less than 30 g per week, is associated with a decrease of AF recurrence [13].

Respondents' perception of the current AF ablation effectiveness

The effectiveness of a first AF ablation according to Russian data was 66% when followed for one year after the intervention [12], which is comparable with global data [25]. However, due to the improvement of ablation technologies and the increase in the experience of the intervention, the efficacy of ablation continues to grow [26, 27]. One of the tasks of the survey was to assess the expected effectiveness of AF ablation by operators themselves. Thus, the distribution of the expected effectiveness of catheter ablation of paroxysmal and persistent AF is shown in Fig. 4 and 5, respectively. In this aspect, the results of a survey of experts on the alleged absence of arrhythmia recurrence are presented when observed within 12 months after ablation without antiarrhythmic therapy. At the same time, the proportion of patients with persistent AF is on average 30-50% (Fig. 6).

We consider it necessary to comment on these results. In the European registry AF CA, which collected Russian data, the efficacy of AF ablation, taking into account both

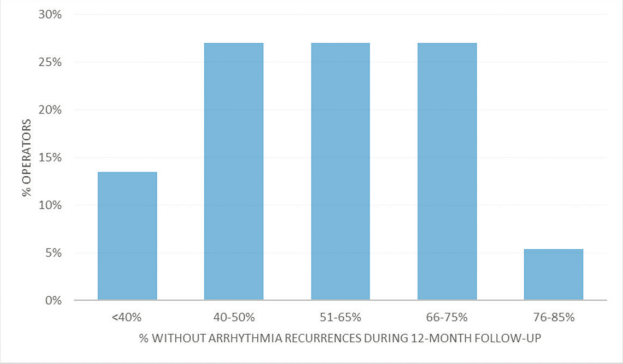

Fig. 5. Efficacy of persistent atrial fibrillation catheter ablation according to respondents' opinion (12 months follow-up, without antiarrhythmic therapy).

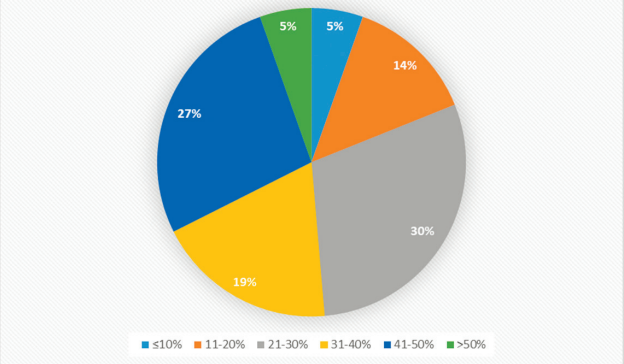

Fig. 6. Percentage of patients with non-paroxysmal atrial fibrillation undergoing ablation in respondents' practice.

paroxysmal and non-paroxysmal AF, was 66% [12], which is comparable to the efficacy with other technologies [28]. In this survey, the effectiveness of paroxysmal AF ablation is 76-85% according to 40% of respondents. These values may reflect both the real frequency of the absence of arrhythmia recurrences with the use of modern technologies (introduced into practice after 2016), and the theoretical assumption of operators, to a lesser extent based on careful registration of all arrhythmia recurrences.

Regarding the need for redo ablation to maintain sinus rhythm, according to most responders, one in five patients with paroxysmal AF requires a redo ablation (Fig. 7). In the case of redo CA of persistent AF, the distribution of responses turned out to be more diverse: from 20 to 50% of patients in the practice of responders may require repeated ablation (Fig. 8). Thus, the need for AF CA in Russia is comparable to world data [6], with a greater need for patients with persistent AF.

Patient management after AF ablation

Conventionally in the early period after catheter ablation (the first 3 months, blanking period) recurrences of arrhythmias occur quite often (up to 30-40% of cases), but in most cases, such recurrences are self-administered and are not observed further [29, 30]. This statement is currently disputed by some authors since the risk of late recurrences in patients with early arrhythmia recurrence is quite high and increases with prolonged follow-up [31-33]. It is believed that early recurrences can be caused by transient changes in the atrial myocardium after ablation, as well as by the "electrophysiological memory" of the atria due to a long arrhythmic history [10, 34]. To suppress early and late arrhythmia recurrences, protective antiarrhythmic therapy is prescribed in most cases, which is consistent with international and national clinical guidelines [35]. It has been shown that the use of antiarrhythmic drugs in the period up to three months after CA significantly reduces recurrences, however, this strategy does not seem so convincing in the long-term 6-12 months follow-up [36, 37]. At the same time, newer studies demonstrate that if patients do not develop arrhythmia recurrence by the end of the first three months, then the use of a previously ineffective antiarrhythmic drug is associated with a decrease in the incidence of atrial tachyarrhythmias during long-term follow-up [38]. Thus, the benefits of prescribing or discontinuing AAD after the "blanking period" on long-term results of AF CA are unknown and require further research.

At the same time, interest in increasing the long-term efficacy of AF ablation does not stop only with the study of antiarrhythmic drug therapy. It is known that when RF energy is applied to the atrial myocardium, acute inflammatory changes occur. Recently, the use of anti-inflammatory drugs in the perioperative period has been of great interest. Short-term use of corticosteroid therapy in the perioperative period is associated with a decrease in early recurrences of arrhythmia (3 months after ablation) but is not effective in preventing late recurrences when followed up to 24 months [39]. Colchicine is another drug used to suppress the inflammatory response and reduce the risk of early AF recurrence after surgical ablation [40-42].

In addition to antiarrhythmic drug therapy, it is necessary to continue therapy for cardiovascular diseases by the relevant recommendations. The use of beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, mineralocorticoid receptor blockers is associated with reverse cardiac remodeling and a lower risk of arrhythmia recurrence [10, 21, 43]. Patient compliance with diet, lifestyle (performing regular aerobic physical activity) modification, limiting alcohol consumption is associated with a decrease in cardiovascular risks and a decrease in AF recurrence [13]. Most respondents (97%) indicated the need to monitor adherence to recommendations for antiarrhythmic therapy and therapy of concomitant cardiovascular diseases, lifestyle modifications in patients after AF ablation since this significantly affects the risk of arrhythmia recurrence.

Methodology of RF pulmonary veins isolation (PVI) for AF treatment

Several recent studies have shown that in CA for PV isolation, adherence to the following principles is associated with the highest treatment efficacy in patients by increasing the transmurality and continuity of the created ablation lines around the PV [44, 45]. During the face-to-face meeting of experts, all participants agreed with these positions:

- maintenance the catheter position stability during RF application;
- maintenance of a sufficient RF application time;
- maintenance adequate contact force;
- interlesion distance between application points should be the minimum to prevent the gaps formation;
- RF application with sufficient power.

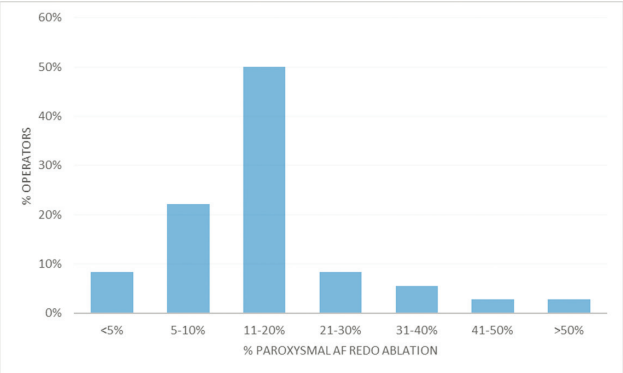

Fig. 7. Frequency of redo ablation in patients with paroxysmal atrial fibrillation (AF).

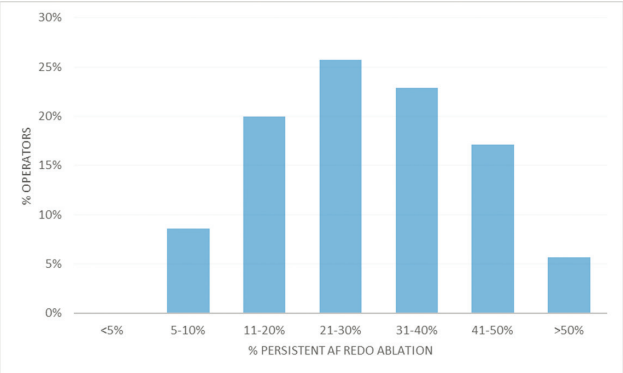

Fig. 8. Frequency of redo catheter ablation in patients with persistent atrial fibrillation (AF).

At the same time, the minimum threshold values for these parameters may vary depending on the technology used, patients' characteristics, and among different operators. The combination of parameters with different values can lead to the formation of lines of necrosis of different widths, depths, and continuity. The following differences were found when interviewing experts: RF power (Fig. 9), duration of each RF application (Fig. 10), the maximum distance between ablation points around the PV (Fig. 11), the width of the isolation zone around the PV - is the distance from the ostium to the ablation points (Fig. 12).

Ablation aspects: contact force monitoring

Before the Contact Force (CF) was implemented in daily practice, operators were guided by the X-ray and/or relied on their tactile sensations during ablation. However, CF-sensing catheters were introduced operators can measure their own «tactile sensation». With unchanged values of RF power and application time, the size of the damage increases with increasing contact force, excessive CF values are associated with the development of the "steam-pop" effect and thrombosis in the LA, and with simultaneous control of the CF, power, and RF application time, it is possible to predict lesion size [10]. The use of CF in real-time has demonstrated a high acute and long-term effectiveness, and a decrease in the procedure time [46-48]. In the studies EFFICAS I and EFFICAS II, the practical role of CF was studied: it became known that at its minimum value, the risk of a breakthrough in conduction in the PV increases. The target values of the CF and the associated Force-Time Integral (FTI) were determined [49, 50]. Nevertheless, although the CF is an important physical unit, its use does not provide any information about the amount of energy delivered directly to the myocardium. It has also been shown in some studies that the use of catheters with CF control did not lead to an improvement in the results of ablation and may also be associated with a higher incidence of esophagus injury [51]. In a meta-analysis of 5 studies, it was shown that the use of the ablation index compared with the CF is associated with a reduced risk of PV reconnections during the acute period AF ablation and a low incidence of atrial arrhythmias during a one-year follow-up [52]. Most experts noted that the introduction of CF-sensing catheters into practice significantly improved the results of ablation in comparison with standard catheters (Table 1). One answer "the use of the CF has harmed" was left without comment, and we cannot give a reason for such a response.

Ablation aspects: Ablation Index

The RF ablation technique using the Ablation Index (AI, Biosense Webster, USA) was developed to predict the size of myocardial injury during RF application and to standardize the AF ablation procedure for each operator. The ablation index is an integral product of power, time, and contact force, and has a linear relationship with the size of RF damage in a certain range. Although catheter stability values are not included in the formula, only applications with stable values (range in mm, time in seconds) are assigned a specific AI value. AI is widely used in clinical practice, and its higher values are associated with a higher frequency of maintaining sinus rhythm [53-55]. The target values of the AI are determined for each operator individually after 10 "blinded" procedures. The median

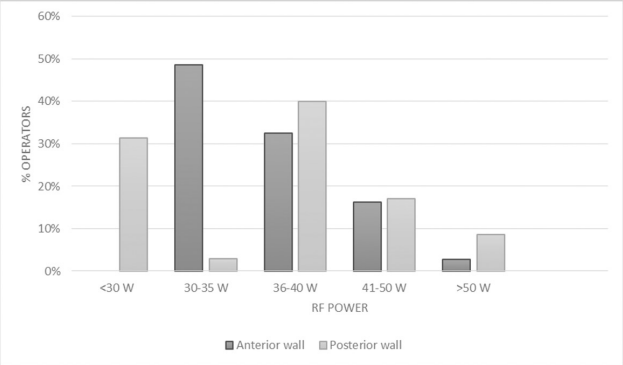

Fig. 9. Differences in the radiofrequency (RF) power parameter along the left atrium anterior and posterior walls.

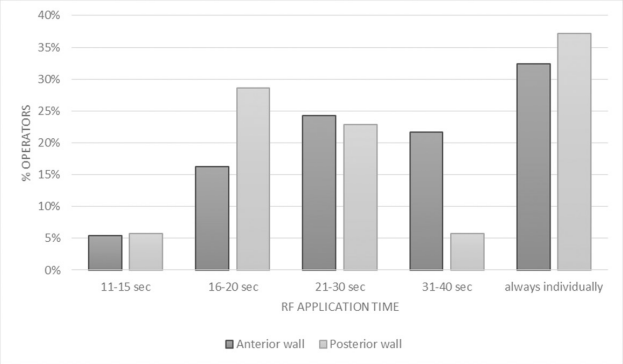

Fig. 10. Differences of the radiofrequency (RF) application time for the left atrium anterior and posterior walls.

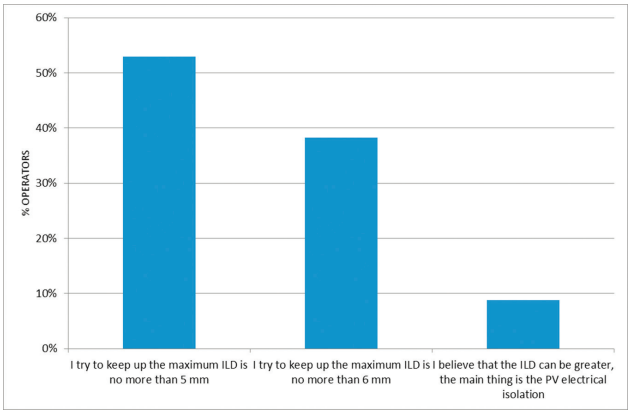

Fig. 11. Maximum interlesion distance (ILD) around the pulmonary vein (PV) to which operators aim.

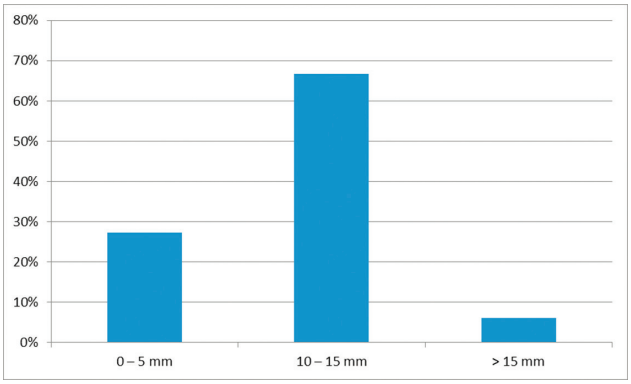

Fig. 12. Distance from the pulmonary vein' ostia to the ablation points.

value of the AI is calculated for each segment of the PV. The same AI value can be obtained for different values of contact force, time, and power.

There is significant variation in technology use, adaptation of different ablation parameters to achieve similar AI values and pronounced variation in target index values across operators. The predictive power of the AI has been shown in several studies: M. Das et al. demonstrated that an AI value of >480 for the LA anterior wall and roof and> 370 for the posterior wall is associated with a low probability of reconnection when followed for two months [56]. In the OPTIMUM study, similar efficacy was obtained with AI values ≥ 450 and ≥350 for the anterior and posterior walls, respectively [55]. In studies using the "CLOSE" protocol, a cutoff AI value of ≥550 for the anterior LA wall and ≥400 for the posterior LA wall was used [57]. Thus, the spread in the AI values is obvious. Since the AI correlates with the transmurality of RF lesion, an insufficient AI value may be associated with a high frequency of PV reconnection, and if its value is too high, the risk of myocardial overheating, collateral damage, and myocardial perforation increases. Optimal values of the AI are currently being studied in a multicenter prospective register [58].

Most of the survey participants noted that the introduction of AI technology made it possible to improve the results of AF CA (Table 2). Most experts are guided by the following AI parameters: 400-500 for the anterior LA wall and 350-450 for the posterior LA wall (Fig. 13).

Table 1.

Expert opinions on the benefit of CF-sensing catheters

Answer options	Response rate, %
No benefits	0
Moderate benefits over standard RF ablation catheters for AF	5,4
Significant benefits over standard RF ablation catheters for AF	40,5
The introduction of this technology has fundamentally changed the practice of AF CA, significantly improved treatment outcomes	51,4
Harm has been done	2,7

Hereinafter: AF - atrial fibrillation, CA - catheter ablation, CF - contact force, RF - radiofrequency

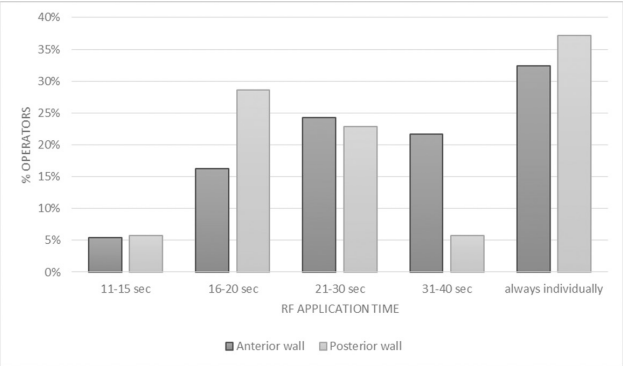

Fig. 13. Frequency of application of a particular ablation index value among responders.

PVI separately or carina ablation between ipsilateral veins

Earlier, in some studies, it was shown that the carina between the upper and lower PV can be the source of trigger arrhythmias that induce and maintain AF [59, 60]. It was also noted that considering the likelihood of PV reconnection through the ablation lines, isolation of two PV using one circle of ablation may be associated with reconnection from two PVs at once. Thus, separate isolation of each PV or routine carina ablation between the superior and inferior PV may be associated with a lower risk of reconnection from two PV simultaneously [61, 62]. At the same time, transmural and continuous myocardial injury using one circular line around two ipsilateral PV should be sufficient for persistent bidirectional conduction block two PV at once. A third of the experts participating in the survey do not perform carina ablation in their clinical practice. Experts' views on routine ablation between ipsilateral veins are summarized in Table 3.

Additional linear lesion in the left atrium

Several studies have shown a relationship between the occurrence and presence of AF with LA electrical and

Table 2.

Benefits of using modules for standardization of RF pulmonary vein isolation (for example, Ablation Index)

Answer options	Response rate, %
No benefist	2,7
Moderate benefits over standard RF ablation catheters for AF	10,8
Significant benefits over standard RF ablation catheters for AF	56,8
The introduction of this technology has fundamentally changed the practice of AF CA, significantly improved treatment outcomes	27
Harm has been done	2,7

Table 3.

Routine performance of the carina ablation between the ipsilateral vein

Answer options	Response rate, %
Almost always do	22
Sometime do	46
Almost never do	32
Never do	0
I consider it harmful	0

Table 4.

Frequency of use of the esophagus temperature control during radiofrequency ablation

Answer options	Response rate, %
Never	86,5
Rarely	8,1
Personalized decision making	2,7
Often	2,7
Always	0

structural remodeling [63, 64]. Based on the magnetic resonance tomography data with late gadolinium enhancement, a group of authors led by N.F.Marrouche formed LA fibrosis degree score UTAH. According to the UTAH score, LA fibrosis can be minimal, which corresponds to UTAH I (≤5% of the LA myocardium), mild or UTAH II (from 5%-20%), moderate or UTAH III (20-35%), and severe or UTAH IV (> 35%) [65]. Myocardial fibrosis can be indirectly detected by determining the atrial electrical activity amplitude. Thus, with the LA voltage mapping, areas with a reduced amplitude of electrical potentials may reflect the presence of myocardial fibrosis.

It is known that the presence and severity of the electroanatomical substrate are responsible for AF recurrence after PVI alone [66]. On the other hand, empirical linear lesion, in the hope of modifying an additional arrhythmia substrate, in patients with persistent AF does not lead to an improvement in sinus rhythm maintenance [67, 68]. At the same time, voltage-oriented RF modification of areas with a low signal amplitude (<0.5 mV at three nearby points) is associated with high rates of freedom from arrhythmia after one ablation procedure in patients without antiarrhythmic therapy during one year of follow-up and represents a personalized AF treatment approach [69].

The unanimous opinion of experts is that it is necessary to achieve complete electrical PV in all AF CA procedures. Opinions were divided regarding additional substrate ablation outside the PV. Thus, the expediency of catheter ablation of areas with complex fractionated atrial electrograms in some patients (mainly with persistent AF) is recognized by a minority of specialists (24%). In paroxysmal AF, the need for empirical linear ablation in the LA is denied by almost all specialists (94%). Personalized ablation/ablation of LA low-amplitude activity areas is considered appropriate by 30 out of 37 (81%) experts during the primary ablation procedure.

Most respondents believe that in paroxysmal AF, the primary catheter ablation strategy should be only PV electrical isolation of the - 35/37 experts. In non-paroxysmal AF, the primary catheter ablation strategy was distributed as follows:

- only PV isolation and cardioversion to restore sinus rhythm - 31/37 specialists;
- routine additional substrate ablation outside the PV - 8/37 specialists;
- after PV isolation with ineffective cardioversion or induction of atrial tachycardia, a combined approach to substrate ablation (search for arrhythmia triggers, linear ablation) - 22/37 specialists;
- personalized decision on additional ablation outside the PV for each patient based on clinical, echocardiographic and electrophysiological patterns (LA voltage map) - 22/37 specialists.

Table 5.

Frequency of use of acute efficacy control technics

Answer options	Response rate, %
Pulmonary vein perimeter stimulation	60
Stimulation by ablation points	5,7
Adenosine	2,9
Multiple approaches	23
Other	8,4

Table 6.

Necessary of the ablation protocol standardization (power, RF application time, catheter stability, circular and / or linear lesions)

Answer options	Response rate, %
Mandatory	16,2
Rather needed	18,9
Rather not needed	16,2
Harmful	2,7

Safety: temperature control in the esophagus during ablation on the LA posterior wall

When performing RF ablation, there is a risk of heating the esophagus anterior wall. The significance of this complication varies from the degree of subsequent damage to the esophageal mucosa; in the most severe cases, an extremely rare but catastrophic complication can develop - an atrioesophageal fistula. Esophageal temperature monitoring is used to control RF energy, early detection of potentially dangerous overheating of the posterior LA wall and extracardiac structures damage and has a high level of recommendation from the professional community (Class IIa C-EO) [10]. When registering an increase in temperature on the sensor by 1-2 °C or up to a level of 39-40 °C, it is recommended to stop the ablation. However, there are technical difficulties in using the temperature sensor due to the anatomical features of the esophagus, which can give a false impression of safe RF exposure. On the other hand, the cessation of energy supply results in low efficacy of the ablation itself. In addition, cases of development of esophageal fistula are known even with satisfactory temperature control [70]. There are various types of temperature sensors, differing in size, the number of sensors, however, due to the low incidence of complications associated with overheating of the LA posterior wall, it is not possible to assess the significant efficacy of the sensors. In the Russian Federation, esophagus temperature control is rarely used for several reasons. To prevent esophagus damage, other approaches have been proposed: active cooling of the esophageal mucosa [71], mechanical displacement of the esophagus with a guided probe [72]. The effectiveness and safety of these techniques have been little studied. According to this survey, esophagus temperature control during AF ablation is very rarely used in the Russian Federation (Table 4).

RF ablation acute effectiveness

There are several generally accepted and recommended techniques for assessing the acute efficacy of AF CA, which include (1) waiting 20 minutes after PV isolation to determine early conduction recovery and assessing the need for additional applications (Class IIa), (2) adenosine / ATP test (Class IIb), as well as electrical stimulation of the PV perimeter along with the ablation points and a combination of techniques [10]. The effectiveness of the above techniques for long-term maintenance of sinus rhythm is still questionable [73, 74]. There is no single consensus among operators on this issue, and each operator applies or adapts one or another methodology following personal

experience. In our survey, operators to assess bidirectional conduction block more often use PV stimulation by diagnostic catheters (Table 5).

Anesthesia and mechanical ventilation for AF ablation

Several studies have shown that mechanical ventilation with deep anesthesia is associated with a more stable position of the ablation catheter, which leads to a more continuous ablation line around the PV [75]. However, deep anesthesia may be associated with a higher risk of severe complications esophagus damage [76]. Deep sedation without mechanical ventilation can be accompanied by a periodic awakening of the patient, irregular breathing, making it difficult to stable positioning of the ablation catheter. In a survey of 6/37 operators during AF ablation, they routinely use deep sedation with mechanical ventilation, while 23/37 experts routinely use light sedation during RF PVI, and in 20% of cases deep anesthesia may be required due to the painfulness of the ablation, the duration of the procedure or the patient's fatigue.

AF ablation standardization

The existing dispersion in the values of AF CA efficacy and safety among different operators and centers predetermines the importance of the ablation protocol standardization [9, 77, 78]. The implementation of the CLOSE protocol [57] became the starting point for standardization, the goal of which is reproducibility and achievement of the same high level of ablation success in the hands of different operators. A standardized and optimized approach to ablation, maintaining RF application continuity and achieving the AI target values (Ablation Index, AI, Biosense Webster, USA) led to PV reliable isolation and was associated with acute and long-term efficacy [79-81]. Most experts (81%) note that PVI standardization is rather necessary or even mandatory to obtain reproducible and stable results of AF treatment (Table 6).

Among the arguments against total standardization is the limitation of the possibility of further development of the methodology, since changing the exposure parameters to try to further improve the results will be limited by the adopted intervention protocols. Another argument against the complete standardization of the ablation approach is the need to consider the clinical features of arrhythmia and electrophysiological remodeling of the atrial myocardium.

CONCLUSION

This paper presents an analysis of Russian specialists' opinions on the factors influencing the results of AF CA. A variety of parameters used for RF PVI and additional ablation approaches of the arrhythmogenic atrial substrate are presented. It should be noted that a survey was conducted of specialists who perform RF PVI, who has experience working with technologies for controlling the contact force and the Ablation Index. Thus, the opinion of specialists, to a greater extent using other ablation technologies, could not be sufficiently considered. Such areas as standardization of the ablation protocol, standardization of the protocol of antiarrhythmic therapy in the post-ablation period require further research and evaluation of the efficacy and safety in randomized and/or observational multicenter studies.

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APPENDIX
ONLINE QUESTIONNAIRE ON ASPECTS OF ATRIAL FIBRILLATION ABLATION

1. Please indicate your age:
2. How many years have you been performing atrial fibrillation (AF) ablation?
3. In my clinical practice (the practice of my department), paroxysmal AF catheter ablation efficacy (single ablation, 12 months follow-up, without antiarrhythmic therapy) is:
   A. <50%
   B. 51-65%

C. 66-75%
D. 76-85%
E. >85%

4. In my clinical practice (the practice of my department), persistenr AF catheter ablation efficacy (single ablation, 12 months follow-up, without antiarrhythmic therapy) is:
A. <40%
B. 40-50%
C. 51-65%
D. 66-75%
E. 76-85%
F. >85%

5. In my practice (the practice of my department), the proportion of patients with non-paroxysmal AF in relation to all patients with AF ablation is:
A. ≤10%
B. 11-20%
C. 21-30%
D. 31-40%
E. 41-50%
F. >50%

6. Number of AF ablation performed by me during the year:
A. <50
B. 51-100
C. 101-150
D. 151-200
E. 201-300
F. >300

7. Number of AF ablation performed in my department per year:
A. <50
B. 51-100
C. 101-200
D. 201-500
E. 501-1000
F. >1000

8. Maximum inrerlesion distance between ablation points around the pulmonary vein:
A. I try to keep up the maximum ILD is no more than 5 mm
B. I try to keep up the maximum ILD is no more than 6 mm
C. I believe that the ILD can be greater, the main thing is the PV electrical isolation

9. Approximate distance from the ostia of the pulmonary vein to the ablation line:
A. 0-5 mm
B. 10-15 mm
C. >15 mm

10. The preferred, in my opinion, RF power for ablation along the left atrium anterior wall:
A. <30 W
B. 30-35 W
C. 36-40 W
D. 41-50 W
E. >50 W

11. The preferred, in my opinion, RF power for ablation along the left atrium posterior wall:
A. <25 W
B. 25-29 W
C. 30-35 W
D. 36-40 W
E. 41-50 W
F. >50 W

12. Flow (irrigation) rate of the ablation catheter for ablation along the left atrium anterior wall:
A. <17 ml/min
B. 17-30 ml/min
C. >30 ml/min

13. Flow (irrigation) rate of the ablation catheter for ablation along the left atrium posterior wall:
A. <17 ml/min
B. 17-30 ml/min
C. >30 ml/min

14. Application time at one ablation point along the left atrium anterior wall:
A. <5 sec
B. 6-10 sec
C. 11-15 sec
D. 16-20 sec
E. 21-30 sec
F. 31-40 sec
G. >41 sec
H. always individually

15. Application time at one ablation point along the left atrium posterior wall:
A. <5 sec
B. 6-10 sec
C. 11-15 sec
D. 16-20 sec
E. 21-30 sec
F. 31-40 sec
G. >41 sec
H. always individually

16. Acute control of pulmonary vein isolation:
A. Using a multipolar diagnostic catheter (circular or otherwise)
B. Using only ablation catheter
C. I believe that after ablation around the pulmonary vein, control is not needed
D. Other (indicate)

17. Additional control of ablation around the pulmonary vein:
A. I stimulate pulmonary vein with a diagnostic electrode
B. I perform stimulation at the ablation points
C. With adenosine
D. Multiple approaches
E. Other (indicate)

18. Do you perform routine ablation between the ipsilateral vein (carina between the superior and inferior pulmonary vein on the right and left side) to improve the overall efficacy of ablation?
A. I almost always do
B. Sometime I do
C. I almost never do
D. I never do
E. I consider it harmful

19. Is it necessary to fully standardize (on a national level) the ablation protocol (power, RF application time, catheter, circular and / or linear lesions)?
A. Mandatory

B. Rather needed
C. Rather not needed
D. Harmful

20. Is it necessary, in your opinion, to routinely perform LA voltage mapping to identify low-amplitude and / or fragmented activity areas (regardless of the inducibility of atrial tachycardia or AF) in patients with paroxysmal AF, in addition to pulmonary vein isolation?
A. Mandatory
B. Rather needed
C. Rather not needed
D. Harmful

21. In patients with paroxysmal AF, in the case of low-amplitude and / or fragmented activity (regardless of the inducibility of atrial tachycardia or AF) areas:
A. Need to ablate
B. Rather, should be ablated
C. Rather, should not be ablated
D. Additional ablation is harmful

22. Is it necessary, in your opinion, to routinely perform LA voltage mapping to identify low-amplitude and / or fragmented activity areas (regardless of the inducibility of atrial tachycardia or AF) in patients with persistent AF, in addition to pulmonary vein isolation?
A. Mandatory
B. Rather needed
C. Rather not needed
D. Harmful

23. In patients with persistent AF, in the case of low-amplitude and / or fragmented activity (regardless of the inducibility of atrial tachycardia or AF) areas:
A. Need to ablate
B. Rather, should be ablated
C. Rather, should not be ablated
D. Additional ablation is harmful

24. Do you routinely perform additional ablation (linear lesions, ganglionic plexus ablation, CFAE ablation) in patients with paroxysmal AF in addition to pulmonary vein isolation?
A. Never
B. Rarely
C. Personalized decision making
D. Often
E. Always

25. Do you routinely perform additional ablation (linear lesions, ganglionic plexus ablation, CFAE ablation) in patients with persistent AF in addition to pulmonary vein isolation?
A. Never
B. Rarely
C. Personalized decision making
D. Often
E. Always

26. Do you routinely use deep sedation for AF catheter ablation?
A. Never
B. Rarely
C. Personalized decision making
D. Often
E. Always

27. Do you use esophagus temperature control for RF ablation along the LA posterior wall?
A. Never
B. Rarely
C. Personalized decision making
D. Often
E. Always

28. Do you perform paroxysmal AF ablation with IC or III class antiarrhythmic drugs?
A. Never
B. Rarely
C. Personalized decision making
D. Often
E. Always

29. Do you perform persistent AF ablation with IC or III class antiarrhythmic drugs?
A. Never
B. Rarely
C. Personalized decision making
D. Often
E. Always

30. Do you recommend for patients to modify cardiovascular risk factors before AF ablation (body weight reducing, blood glucose controlling, blood pressure controlling, aerobic exercise, HF therapy optimization, etc.)?
A. Never
B. Rarely
C. Personalized decision making
D. Often
E. Always

31. In my clinical practice (the practice of my department), the percentage of patients with paroxysmal AF who require redo ablation to achieve an acceptable clinical effect:
A. <5%
B. 5-10%
C. 11-20%
D. 21-30%
E. 31-40%
F. 41-50%
G. >50%

32. In my clinical practice (the practice of my department), the percentage of patients with persistent AF who require redo ablation to achieve an acceptable clinical effect:
A. <5%
B. 5-10%
C. 11-20%
D. 21-30%
E. 31-40%
F. 41-50%
G. >50%

33. What systems do you use in your clinical practice (practice of your department) for the AF treatment?
A. Encite Velocity / Precision (Abbott)
B. Rhythmia (Boston Scientific)
C. CARTO 3 (Biosense Webster)
D. Cryocath (Medtronic)
E. Other

34. Do you use catheters with contact force control (for example, Smart Touch) for AF ablation in your clinical practice (practice of your department)?
A. Never
B. Rarely

C. Personalized decision making
D. Often
E. Always

35. Do you use in your clinical practice (practice of your department) modules for standardization of RF AF ablation (for example, Ablation Index)?
A. I apply Ablation Index
B. I apply LSI
C. I apply other one (indicate)

36. The Ablation Index value on the LA anterior wall in your clinical practice:
A. <300
B. 300-350
C. 351-400
D. 401-450
E. 451-500
F. 500-550
G. 551-600
H. 601-650
I. >650
G. Do not apply

37. The Ablation Index value on the LA posterior wall in your clinical practice:
A. <250
B. 250-300
C. 301-350
D. 351-400
E. 401-450
F. 451-500
G. 500-550
H. 551-600
I. 601-650
G. >650
K. Do not apply

38. What percentage of AF ablation procedures in your clinical practice (the practice of your department) are performed using the Ablation Index technology?
A. 0-20%
B. 20-40%
C. 40-60%
D. 60-80%
E. 80-100%

39. How significant, in your opinion, are the benefits of using catheters with contact force control for the AF treatment:
A. No benefits
B. Moderate benefits over standard RF ablation catheters
C. Significant benefits over standard RF ablation catheters for AF
D. The introduction of this technology has fundamentally changed the practice of AF CA, significantly improved treatment outcomes
E. Harm has been done (please clarify)

40. How significant, in your opinion, are the benefits of using modules for standardizing RF and pulmonary vein isolation (for example, Ablation Index):
A. No benefits
B. Moderate benefits over standard RF ablation catheters
C. Significant benefits over standard RF ablation catheters for AF
D. The introduction of this technology has fundamentally changed the practice of AF CA, significantly improved treatment outcomes
E. Harm has been done (please clarify)

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MULTIMARKER APPROACH FOR ASSESSING EFFICIENCY OF CARDIAC RESYNCHRONIZATION THERAPY IN PATIENTS WITH SINUS RHYTHM

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Purpose. To design a mathematical model, that can predict a positive response to cardiac resynchronization therapy (CRT) in patients with congestive heart failure (CHF) and sinus rhythm, according to complex analysis of neurohumoral and immune activation biomarkers, fibrosis, renal dysfunction, echocardiography.

Methods. Parameters of echocardiography, plasma levels of NT-proBNP, interleukins-1β, 6, 10, tumor necrosis factor α, C-reactive protein (CRP), matrix metalloproteinase-9 (MMP-9), tissue inhibitors of metalloproteinase 1 and 4, cystatin C (CYSTATIN) were studied in 40 CHF patients with sinus rhythm (65% coronary artery disease patients, 75% males, mean age 54.8±10.6 years old) during the period of maximum decrease of left ventricular end-systolic volume (LVESV) (mean duration 27.5 [11.1; 46.3] months). Responders (decrease in LVESV ≥15%) and non-responders (decrease in LVESV <15%) were identified.

Results. The number of responders was 26 (65%). The initial set of variables included: age, left ventricular ejection fraction (EF), pulmonary artery systolic pressure, right ventricle size and NT-proBNP, CRP, MMP-9, CYSTATIN. According to logistic regression analysis, a prediction model of positive CRT response was created. The specificity of the model was 92.9%, sensitivity - 83.3%, AUC=0.952 ($p<0.001$).

Conclusion. The proposed model, based on the assessment of left ventricle EF and circulating biomarkers of inflammation, fibrosis, and renal function, strongly suggests a higher possibility of response to CRT.

Key words: cardiac resynchronization therapy; immune inflammation; fibrosis; renal dysfunction

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With an increasingly aging population, the prevalence of congestive heart failure (CHF) in the Russian Federation is steadily growing and amounts to more than 14 million people, which allows us to call the disease a global problem of modern cardiology [1]. CHF is a disease with a complex set of pathophysiological mechanisms, the study of which is accompanied by the improvement of treatment methods. Cardiac resynchronization therapy (CRT) has revolutionized the treatment of patients with reduced left ventricular (LV) systolic function and widened QRS complex due to improved quality and longer life expectancy, reduced hospitalization rates and mortality [2].

Currently, there is no unified approach to assess the efficacy of CRT. Along with the use of indicators of clinical response, functional criteria, laboratory markers, as well as their various combinations, the most often there used reduction of LV end-systolic volume (LVESV) by 15% or more [3]. Despite the constantly changing selection criteria for implantation of CRT devices, its efficiency is about 70% [4]. Non-responders compared to responders have a higher risk of ventricular arrhythmias, cardiovascular events, and overall mortality [5]. In this connection the ineffectiveness of CRT is a serious clinical problem, which is probably multifactorial and can be caused by suboptimal positioning of the electrodes and programming of the device, the presence of postinfarction scar, the absence of "corrected dyssynchrony", as well as the presence of concomitant diseases [6], among which renal insufficiency plays a major role [7].

Deterioration of renal function in patients with CHF occurs from 40% to 70% and is a predictor of disease progression and mortality in patients, including those receiving CRT [8]. The molecular mechanisms of CRT influence are being actively studied. The association of cardiac remodeling in connection with CRT with a decrease in the activity of immune inflammation, neurohumoral activation, and fibrosis has been established [9-11]. However, none of the studied biomarkers can predict a positive response to CRT. In this connection, the search for predictors of a favorable response to CRT is highly relevant. The modern direction of research is a multimarker approach with an assessment of various pathophysiological mechanisms of the pathogenesis of CHF.

The aim of our study was to create a mathematical model capable to predict a favorable response to CRT in patients with CHF and stable sinus rhythm based on complex analysis of biomarkers of neurohumoral and

immune activation, fibrosis, renal dysfunction, echocardiographic parameters.

MATERIAL AND METHODS

Forty patients with CHF from the "Register of performed operations of cardiac resynchronization therapy" (Certificate of state registration of the database No. 2010620077 dated February 1, 2010) (65% of ischemic, 75% men) and stable sinus rhythm aged 30 to 74 years (mean age 54.8±10.6 years) were included in the study consecutively from 2003 to 2017. Patients signed an informed consent to conduct the study, which was approved by the ethics committee. To select patients for CRT devices implantation, we used the presence of intraventricular and/or interventricular dyssynchrony according to echocardiography (EchoCG), LV ejection fraction (LVEF) less than or equal to 35%, II-IV functional class of CHF, the width of QRS complex on ECG more than 120 ms.

The criteria for intraventricular dyssynchrony diagnosis in M-mode was a time delay between peaks of LV posterior wall contraction amplitude and interventricular septum over 130 ms. To diagnose intraventricular dyssynchrony, pulsed-wave Doppler in the LV outflow tract was used. Intraventricular dyssynchrony was indicated by prolongation of the pre-ejection period from left ventricle more than 140 ms, interventricular dyssynchrony - by prolongation of interventricular mechanical delay time more than 40 ms. Intraventricular dyssynchrony was determined by tissue Doppler imaging by interval difference between basal segments of LV lateral wall and interventricular septum more than 60 ms. The study was conducted at baseline, 1, 3, 6 months and every 6 months after the implantation of CRT devices. If necessary, the parameters of the CRT device were optimized. The period of the best response to CRT was estimated retrospectively according to the maximal decrease of LVESV and was 27.5 [11.1; 46.3] months. Heart failure functional class (FC) was determined based on the result of the 6-minute walk test and clinical criteria according to the New York Classification (NYHA). EchoCG was performed using a stationary Philips IE-33 ultrasound device (USA). LV end-diastolic volume (LVEDV) and LVESV, pulmonary artery systolic pressure (PASP), left atrial (LA) size and right atrial (RA) volume and right ventricular (RV) size were calculated. LVEF was assessed by the Simpson method. Plasma levels of the N-terminal fragment of natriuretic peptide (NT-proBNP), interleukins (IL)-1b, IL-6, IL-10, TNF-α, matrix metalloproteinase 9 (MMP-9) and tissue inhibitors of metalloproteinases (TIMP-1 and TIMP-4) MMP-9 were studied by solid-phase chemiluminescence enzyme immunoassay (sandwich method) on IMMULITE 1000 analyzer (Siemens Diagnostics, USA). MMP-9/TIMP-1 and MMP-9/TIMP-4 coefficients were calculated. High-sensitivity C-reactive protein (CRP) in blood serum was determined by an immunoturbidimetric method using analytical kits C-REACTIVE PROTEIN hs (BioSystems, Spain) on a Clima MC-15 analyzer (Spain). Quantitative determination of cystatin C in blood serum was performed by the sandwich method using analytical kits Human Cystatin C Elisa (BioVendor, Czech Republic). Optical density was measured using a StatFax 4200 reader.

Table 1.

Clinical characteristics of groups with different response to CRT

	I group responders (n=26)	II group non-responders (n=14)	p
Time for best response, month	31.0[22.0;50.0]	12.0[5.0;26.7]	0.005
Mean age, years	58.0±7.4	50.4±12.8	0.022
Men, n (%)	16 (69.6)	14 (82.4)	0.356
CAD, n (%)	16 (69.6)	10 (58.8)	0.481
PMI, n (%)	6 (26.1)	7 (41.2)	0.502
CABG, n (%)	3 (13.0)	0	0.124
PCI, n (%)	4 (17.4)	5 (29.4)	0.208
II FC HF (NYHA), n (%)	13 (56.6)	8 (47.1)	0.144
III FC HF (NYHA), n (%)	7 (30.4)	6 (35.3)	
IV FC HF (NYHA), n (%)	3 (13.0)	3 (17.6)	
Hypertension, n (%)	20 (87.0)	9 (52.9)	0.017
PAF	4 (17.4)	5 (29.4)	0.345
DM, n (%)	2 (8.7)	2 (11.8)	0.480
Obesity, n (%)	13 (56.5)	9 (52.9)	0.987
BMI, kg/m^2	30.7±5.5	29.3±6.2	0.492
The mean QRS duration, ms	174.7±26.3	154.7±20.1	0.011
CLBBB, n (%)	20 (87.0)	10 (58.8)	0.042
Antiarrhythmic drug use, n (%)	3 (13.0)	9 (52.9)	0.021
MRA, n (%)	20 (87.0)	15 (88.2)	0.904
Diuretics, n (%)	19 (82.6)	16 (94.1)	0.277
Calcium channel blockers, n (%)	7 (16.7)	0	0.070
BB, n (%)	20 (87.0)	15 (88.2)	0.904
Digoxin, n (%)	4 (17.4)	1 (5.9)	0.277
ACEI, n (%)	16 (69.6)	14 (82.4)	0.356
ARB, n (%)	6 (26.1)	2 (11.8)	0.263
Statins, n (%)	19 (82.6)	5 (29.4)	0.001

Notes: CAD - coronary artery disease; PMI - previous myocardial infarction; CABG - coronary artery bypass grafting; PCI - percutaneous coronary intervention; FC HF (NYHA) - functional class of congestive heart failure according to the New York Heart Association classification; PAF - paroxysmal atrial fibrillation; DM - diabetes mellitus; BMI - body mass index; CLBBB - complete left bundle branch block; MRA - mineralocorticoid receptor antagonists; BB - beta-blockers; ACEI - angiotensin converting enzyme inhibitors; ARB - angiotensin II receptor blockers.

Statistical analysis was performed using the SPSS 21 software package (SPSS Inc., Chicago, IL, USA). The distribution normality was assessed using the Kolmogorov-Smirnov method. If the distribution is normal, the results are presented as M±SD, where M is the mean value, SD is the standard deviation; if the distribution is not normal, the results are presented as the median and interquartile range (Me [25; 75]). The chi-square test was used to analyze qualitative data in unrelated groups. To compare quantitative indicators in unrelated groups with their normal distribution, the Student's t-test was used, with a distribution other than normal - the Mann-Whitney test, in related groups - paired Student's t-test or Wilcoxon's test. The mathematical model was constructed using logistic regression. ROC analysis was used to find the optimal diagnostic point of separation (threshold value) of the indicators and assess the diagnostic significance of the model. Differences were considered significant at $p<0.05$.

RESULTS

According to the dynamics of LVESV in connection with CRT, 2 groups of patients were distinguished: group 1 (n=26; 65%) - responders (decrease in LVESV >15%); group 2 (n=14; 35%) - non-responders (decrease in LVESV <15%). Clinical characteristics of the study groups are presented in Table 1. Patients of group 2 were younger, they are less likely to suffer from arterial hypertension and took antiarrhythmic drugs and statins. In group 2, a shorter period of better response to CRT was revealed, lower incidence of complete left bundle branch block (CLBBB) and the duration of QRS complex was noted.

Table 2.

Dynamics of echocardiographic parameters and exercise tolerance

		I group responders (n=26)	II group non-responders (n=14)	P between groups
6MWT, m	initially	292.6±100.8	302.7±128.8	0.797
	follow-up	379.5±83.8	339.7±75.0	0.145
p in group		<0.001	0.450	
LA, mm	initially	46.8±5.1	49.6±5.7	0.123
	follow-up	43.3±7.5	48.4±5.3	0.016
p in group		0.027	0.251	
RA, ml	initially	61.6±19.0	68.6±20.4	0.292
	follow-up	51.7±17.5	78.1±15.9	<0.001
p in group		0.018	0.198	
RV, mm	initially	28.0±3.2	31.3±3.8	0.007
	follow-up	26.2±17.5	30.8±3.6	<0.001
p in group		0.014	0.661	
LVESD, mm	initially	56.9±6.9	61.3±9.3	0.276
	follow-up	43.2±9.1	56.9±6.3	0.001
p in group		0.010	0.419	
LVEDD, mm	initially	65.4±6.0	68.8±8.1	0.158
	follow-up	56.8±7.8	67.9±7.8	0.001
p in group		<0.001	0.573	
LVESV, ml	initially	150.8±39.8	178.4±55.4	0.091
	follow-up	82.8±39.1	168.6±51.7	<0.001
p in group		<0.001	0.010	
LVEDV, ml	initially	220.7±46.5	249.7±69.1	0.147
	follow-up	150.2±49.8	242.2±65.2	<0.001
p in group		<0.001	0.047	
EF, %	initially	32.3±5.1	29.0±4.6	0.042
	follow-up	46.9±8.6	30.9±5.0	<0.001
p in group		<0.001	0.022	
PASP, mmHg	initially	39.5±8.8	50.1±11.2	0.011
	follow-up	29.9±13.1	46.9±11.6	0.001
p in group		0.193	0.036	

Notes: 6MWT - 6-minute walk test; LA - left atrium; RA - right atrium; RV - right ventricle; LVESD - left ventricular end-systolic dimension; LVEDD - LV end-diastolic dimension; LVESV - LV end-systolic volume; LVEDV - LV end-diastolic volume; LVEF- LV ejection fraction; PASP - pulmonary artery systolic pressure.

The dynamics of echocardiographic parameters and exercise tolerance according to the 6-minute walk test are presented in Table 2. While there were no dynamics of exercise tolerance according to the 6-minute walk test in group 2, there was a highly significant increase in group 1.

According to EchoCG, patients in group 2 initially and in dynamics had larger RV sizes and PASP, initially a tendency towards greater LVESV and significantly lower LVEF. In dynamics in connection with CRT, in group 2 there was a significant decrease only in LVESV, LVEDV, PASP and an increase in LVEF.

In group 1, there was a significant decrease in LA, RA, RV, LV end-systolic dimension (LVESD), LV end-diastolic dimension (LVEDD), LVESV, LVEDV, and increase in LVEF. The degree of RA change was significantly opposite in the groups. The degree of decrease in LVESD, LVEDD, LVESV, LVEDV and increase in LVEF were more significant in group 1.

The results of the analysis of the dynamics of biomarkers of immune inflammation, neurohumoral activation and fibrosis, as well as cystatin C in groups with different responses to CRT are presented in Table 3. Initially, group 2 patients had significantly higher levels of CRP, cystatin C, MMP-9, and a tendency to higher values of NT-proBNP.

Analysis of biomarkers of immune inflammation did not reveal significant dynamics in group 2. Only a tendency to decrease in TNF-α concentration was noted. A significant decrease in the levels of IL-1β, IL-6, IL-10, TNF-α was detected in group

1 in connection with CRT. No differences, dynamics and degree of change in galectin-3 were revealed in the groups.

In the dynamics, there was a tendency for a decrease in MMP-9 levels in group 2, while there were no significant changes in MMP-9 concentration in group 1. The degree of change in MMP-9 was significantly opposite in the groups (37.9[-48.3;106.1] ng/mL in group 1 vs -73.2[-108.9;8.6] ng/mL in group 2; p=0.017). MMP-9 concentration was significantly higher in group 1 in connection with CRT. There were no differences between the groups in the dynamics of TIMP-1 and TIMP-4 levels. While there were no dynamics of MMP-9/TIMP-1 and MMP-9/TIMP-4 ratios in group 2, there was a significant increase in the MMP-9/TIMP-1 ratio in group 1, as well as a tendency to higher MMP-9/TIMP-4 in connection with CRT.

ROC analysis was used to investigate the prognostic significance of all biomarkers studied. For optimal recognition of patients with a likely favorable response to CRT, threshold values of the following parameters were established: NT-proBNP (1432.0 pg/mL, sensitivity 86.7%, specificity 63.6%, AUC=0.745, p=0.012), CRP (4.29 mg/mL, sensitivity 80.0%, specificity 77.3%, AUC=0.753, p=0.010), MMP-9 (155.75 ng/mL, sensitivity 78.6%, specificity 61.1%, AUC=0.706, p=0.048), cystatin C (0.395 mg/L, sensitivity 85.7%, specificity 65%, AUC=0.759, p=0.011).

When conducting multivariate analysis (binary logistic regression), the initial set of variables included signs that were significantly different or tended to differ in the studied groups of patients, such as age, RV size, PASP, LVEF, MMP-9, CRP, cystatin C, NT-proBNP.

As a result of the analysis, a model with four variables was created. The technical result is expressed by the formula for calculating the value of the function F: F = 3.231 + 0.344 x EF - 3.479 x CYSTATIN - 0.039 x MMP9 - 0.638 x CRP, where EF is the LVEF in %; CYSTATIN is the cystatin C level in mg/l; MMP9 - the level of matrix metalloproteinase 9 in ng/l; CRP is the level of C-reactive protein in ng/L.

The prediction of the response to CRT is carried out according to the formula: P=1/(1e (-F)), where P is the probability that the event of interest will occur (develop-

Table 3.

Biomarkers of immune and neurohumoral activation, fibrosis, cystatin C in groups with different response to CRT

		I group responders (n=26)	II group non-responders (n=14)	P between groups
IL-1β, pg/mL	initially	3.8[2.9;4.4]	3.9[3.2;4.4]	0.996
	follow-up	2.7[2.4;3.2]	3.7[3.2;5.3]	0.028
p in group		0.022	0.598	
IL-6, pg/mL	initially	2.6[2.4;3.3]	3.3[2.8;5.3]	0.108
	follow-up	2.3[1.7;2.5]	3.7[2.1;8.0]	0.002
p in group		0.010	0.388	
IL-10, pg/mL	initially	2.4[1.6;5.0]	3.1[2.4;4.8]	0.408
	follow-up	1.9[1.6;2.2]	3.7[2.1;4.7]	0.004
p in group		0.045	0.814	
TNF-α, pg/mL	initially	8.3[6.4;10.1]	8.6[6.7;11.2]	0.527
	follow-up	5.4[4.1;7.9]	5.6[4.5;9.2]	0.501
p in group		0.021	0.066	
CRP, mg/mL	initially	2.4[0.9;4.3]	7.2[4.5;10.1]	0.010
	follow-up	1.4[0.8;3.6]	6.2[3.4;10.1]	0.002
p in group		0.514	0.670	
Cystatin C, mg/L	initially	0.2[0.2;0.4]	0.9[0.4;1.8]	0.011
	follow-up	0.5[0.2;1.8]	0.3[0.2;1.9]	0.553
p in group		0.212	0.731	
NT-proBNP, pg/mL	initially	1044.5[673.5;2786.0]	2794.5[1499.3;5230.3]	0.094
	follow-up	518.0 [174.5;1894.5]	2232.5[1140.8;4155.0]	0.155
p in group		0.335	0.946	
MMP-9, ng/mL	initially	144.4[110.4;203.7]	190.2[157.2;255.2]	0.038
	follow-up	218.2[145.1;264.6]	130.6[101.8;236.3]	0.022
p in group		0.119	0.078	
TIMP-1, ng/mL	initially	297.4[201.8;471.5]	409.4[272.3;473.4]	0.649
	follow-up	240.9[163.3;358.2]	354.5[205.0;441.5]	0.107
p in group		0.107	0.649	
TIMP-4, ng/mL	initially	2203.0[1461.1;2686.8]	2138.6[1665.6;2082.8]	0.900
	follow-up	2067.1[1570.7;2495.3]	2301.9[1860.4;2715.1]	0.410
p in group		0.624	0.736	
MMP-9/ TIMP-1, n	initially	0.5[0.3;0.8]	0.5[0.4;0.7]	0.774
	follow-up	0.7[0.5;1.5]	0.5[0.2;0.7]	0.014
p in group		0.045	0.651	
MMP-9/ TIMP-4, n	initially	0.07[0.05;0.1]	0.09[0.07;0.1]	0.336
	follow-up	0.1[0.08;0.1]	0.07[0.03;0.1]	0.065
p in group		0.232	0.480	

Notes: IL - interleukin; TNF-α - tumor necrosis factor α; CRP - C-reactive protein; NT-proBNP - N-terminal fragment of the prohormone brain-type natriuretic peptide; MMP-9 - matrix metalloproteinase 9; TIMP-1 & TIMP-4 - tissue inhibitors of matrix metalloproteinase 1 and 4.

ment of a response to CRT); e is a mathematical constant equal to 2.718; F is the value of F function. If the P-value is less than 0.696, then the non-responder group is determined, and if the P-value is greater than or equal to 0.696, then the responder group is determined and the response to CRT is predicted. The specificity of this model was 92.9%, and sensitivity was 83.3%. The area under the ROC curve was 0.952 ($p<0.001$), which corresponds to the excellent quality of the model (Fig. 1).

DISCUSSION

We believe that for adequate assessment of the effectiveness of CRT, it is necessary to use not a fixed time frame, but the time frame for the best response to CRT to maximize the reduction of LVESV, which makes it possible to take into account the individual adaptive capabilities of patients. We have previously shown that in several patients, during the first year of follow-up, there are no positive dynamics of LVESV. However, in later terms, these patients more often become super-responders (decrease of LVESV >30%) [12]. The results of this study again confirmed significantly longer term of the best response on CRT in the group of responders in comparison with non-responders.

According to EchoCG data, group 2 patients had an initially larger size of RV, the prognostic significance of which is discussed in the literature [13], as well as significantly higher values of PASP initially and in dynamics, were revealed. In connection with CRT, the degree of change in RA volume was the opposite in the groups: it decreased in group 1 and increased in group 2. Previously, the association of decreased RV function with increased levels of creatinine and brain natriuretic peptide has been revealed [14]. In our study, there was a tendency for higher basal NT-proBNP levels in patients of group 2. Possible mechanisms of the negative effect of enlarged right parts of the heart are the increase in stagnation, reduction of renal blood flow, with the subsequent development of renal dysfunction. In connection with CRT in patients of group 1 echocardiographic parameters improved not only in the left but also in the right parts of the heart, confirming the literature data on the ability of CRT to cause favorable RV remodeling [15].

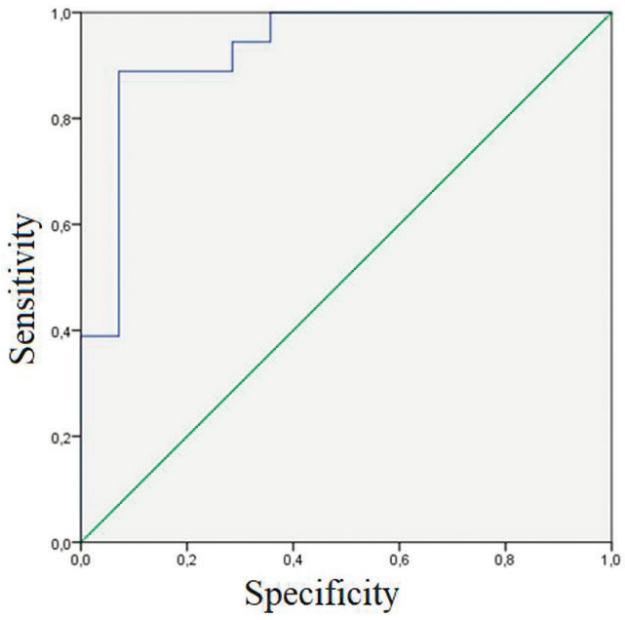

Fig. 1. ROC-curve of logistic regression (AUC=0.952, p<0.001).

It is known that activation of immune inflammation mediated by IL-1β, IL-6, IL-10, CRP, TNF-α plays a central role in the development of heart failure [16]. A close association of cytokine levels with the severity of clinical manifestations of CHF has been revealed [17]. The association of the effectiveness of CRT with a decrease in immune activation has been established [9], which is confirmed by the results of our study - a significant decrease in IL-1β, IL-6, IL-10, TNF-α was detected in the group of responders. We did not reveal any significant dynamics of CRP in the studied groups. However, its significantly higher level in the non-responders group and inclusion in a model capable of predicting response to CRT indicates an important role of CRP as a marker of immune activation, as well as the importance of immune inflammation in the effectiveness of CRT.

It was found that inflammatory mediators, through the activation of cell signaling pathways such as TGF-β/Smad and Notch [18], contribute to the activation of matrix metalloproteinases (MMPs) that play a key role in extracellular matrix (ECM) reconstruction. ECM is a dynamic environment. Being an important adaptive factor at the initial stages of the disease, the reorganization of ECM becomes a factor in pathogenesis during the progression of CHF. The activity of MMPs can be blocked by tissue inhibitors of MMPs - TIMPs. The imbalance between MMPs and TIMPs, assessed by the ratio of MMPs/TIMPs, leads to uncontrolled activation of MMPs, imbalance between ECM synthesis and degradation, fibrogenesis, cardiac remodeling, and progression of CHF. The true function of MMPs and TIMPs is still not well understood. There is little information about the specific types of MMPs and TIMPs involved in the processes of tissue remodeling in CHF, and in some cases, it is contradictory, which may be due to different expression patterns of hormones, growth factors, inflammatory mediators, and the stage of the disease.

The relationship between the increase in the concentration of MMP-9, TIMP-1 [19, 20], and the severity of CHF has been established. The available information regarding their predictive usefulness in CHF and CRT is controversial [21]. In some studies, there was no change in the level of MMP-9, TIMP-1 in connection with CRT [22], while others showed a significant decrease [23]. In the study by M. Szulik et al. significant decrease in the expression of MMP-9 in connection with CRT was observed only in 67% of patients with ischemic cardiomyopathy and was associated with a lower baseline concentration of CRP [24]. In most studies, no correlations between the levels of MMP-9, TIMP-1, and LV geometry parameters were found, and therefore the exact relationship between collagen turnover and response to CRT remains unclear. We did not find in the literature data on the effect of CRT on the TIMP-4 level.

According to our study, there were no significant dynamics in the level of MMP-9, TIMP-1, TIMP-4 in the studied groups. However, the degree of MMP-9 change in

the groups was the opposite - it increased in responders and decreased in non-responders. In connection with CRT, the group of responders tended to have a higher MMP-9/TIMP-4 ratio and a significantly higher MMP-9/TIMP-1 ratio. Since this pattern of changes in fibrosis biomarkers was detected in the group of favorable responses to CRT, it probably has a positive physiological meaning. In the study by D. D. Bonnema et al. decrease in the ratios MMP-9/TIMP-1, MMP-9/TIMP-4, and MMP-2/TIMP-4 during aging was found, which indicates a reduced ability to degrade ECM with age and contributes to the development of interstitial fibrosis [25]. MMP-9/TIMP-1 and MMP-9/TIMP-4 coefficients likely reflect the preserved ability to reconstruct ECM and the higher adaptive capacity of responders, despite their older age.

It is known that renal function is an important predictor of adverse clinical course of CHF, mortality, response to CRT [7]. A sensitive marker of early renal dysfunction is cystatin C, the biological role of which is associated with inhibition of extracellular cathepsin activity. A baseline cystatin C level above 1 mg/L was found to be associated with a fourfold increased risk of non-response to CRT, as well as an increased risk of developing significant cardiovascular events within two years [26]. Probably, the level of cystatin C is linearly related to the risk of progression of heart failure due to its revealed correlation with the level of NT-proBNP [27]. The combination of high levels of cystatin C and NT-proBNP is associated with a ninefold increase in the risk of non-response to CRT [28]. According to our study, the baseline level of cystatin C in non-responders was significantly higher than in responders, which confirms the effect of renal function on the effectiveness of CRT.

In the presented model, the combination of MMP-9, CRP and cystatin C demonstrates a close relationship between three key mechanisms of CHF pathogenesis - immune inflammation, fibrosis and renal dysfunction, which determine the severity of the disease and the response to CRT. In this model, inflammatory mediators induce the activity of MMPs. Gelatinases, which include MMP-9, through various interactions with TNF-α and TNF-β, monocytic chemoattractant proteins, growth factors, oxidative stress, affect the development and progression of renal dysfunction [29], contributing to the reconstruction of ECM, the development of renal fibrosis, blocking of the interstitial capillary beds and kidney hypoxia. There were no significant dynamics of NT-proBNP level in the studied groups, which was probably due to the small number of patients, as well as their severity. As an example of the use of the obtained mathematical model, we present 2 clinical cases.

Patient K., 64 years old, complained of dyspnea, various pains in the chest area, occurring without clear association with physical and emotional stress. Her blood pressure increased to 180/120 mm Hg within a year. She did not take hypotensive medications regularly. The deterioration of health was noted within three months. Initially, ECG revealed CLBBB (QRS-160 ms). According to echocardiography: aortic atherosclerosis, sclerosis of the aortic valve cusps with minor regurgitation; dilatation of predominantly left parts with signs of moderate mitral regurgitation; along with diffuse hypokinesis, a moderate decrease in the contractile function of the heart (LVEF-35%), LVESV-120 ml; signs of minor pulmonary hypertension, intraventricular dyssynchrony. Selective coronary angiography revealed no data for hemodynamically significant stenotic lesions of the coronary arteries. The patient was discharged with a diagnosis: Arterial hypertension, stage III, grade 3, risk of cardiovascular complications 4 (very high). CLBBB. CHF IIA FC III (NYHA). After 3 months of optimal drug therapy, complaints of shortness of breath on light physical activity, edema of the lower extremities, general weakness and fatigue, periodically varied pains in the precordial region, occurring unrelated to physical activity and relieved independently, persisted. Laboratory examination: cystatin C level - 0.21 ng/L, MMP-9 - 62.45 ng/L, CRP - 4.09 ng/L. Using available data, we calculated the F function value of 8.134 and the probability P-value of 0.999.

The obtained P-value allowed the patient to assume the development of a favorable response to CRT at the preoperative stage in addition to the generally accepted criteria. Considering clinical and anamnestic data, progression of CHF symptoms, the ineffectiveness of drug therapy, and high risk, the patient was implanted with a permanent biventricular pacemaker - Consulta Medtronic with endocardial electrodes. One week after the implantation of the CRT device, the patient noticed an improvement in her well-being. After 6 months EchoCG data showed positive dynamics in the form of volume reduction (LVESV up to 105 ml), an increase of LVEF up to 43%, a decrease of NYHA FC. After 12 months, according to EchoCG: LVESV - 85 ml, LVEF - 45%; NYHA FC II. After 18 months - LVESV - 55 ml, LVEF - 49%, in dynamics normalization of the left heart size, NYHA FC II. After 30 months - LVESV - 49 ml, LVEF - 55%, NYHA FC I. The proposed method made it possible to predict a favorable response to CRT.

Patient C., 37 years old, was observed in Tyumen Cardiology Research Center since 2005 with the diagnosis: Coronary artery disease. Previous myocardial infarction (2005). Postinfarction apical LV aneurysm. Ventricular fibrillation. Paroxysms of unstable ventricular tachycardia. CHF IIA. FC III (NYHA). Dyslipidemia. Coronary angiography was performed twice (2006, 2009): no data for stenotic lesions of the arteries were found. In 2009, the patient was implanted with a Medtronic Virtuoso DR cardioverter-defibrillator with Medtronic endocardial electrodes. In 2011 he was admitted with complaints of shortness of breath, palpitations and pressing pains in the region of the heart during exertion (going upstairs to the 2nd floor), general weakness, rapid fatigability. The arrhythmia counter of the implanted device recorded 2 episodes of unstable ventricular tachycardia (5-65 complexes). According to ECG data, CLBBB was registered (QRS - 160 ms.) According to EchoCG: increased echogenicity of the aortic walls; extensive circular cicatricial changes of LV myocardium with signs of postinfarction apical LV aneurysm; severe dilatation of the left heart with signs of moderate mitral regurgitation; LVEF - 31%; signs of intra- and interventricular dyssynchrony. Laboratory examination: cystatin C level - 0.41 ng/L, MMP-9 - 318.3 ng/L, CRP - 4.49 ng/L. Using available data, we calculated the F function value of -2.809 and probability

P-value of 0.057. The obtained P-value allowed the patient with the presence of classic criteria for implantation (NYHA FC III CHF, LVEF - 31%, CLBBB, QRS - 160 ms) to assume no responsibility to CRT. The patient was implanted with the CRT-P CONTAK RENEWAL Boston Scientific device. According to EchoCG after 6 months: LVESV - 189 ml, LVEF - 33%; NYHA FC III. After 12 months, in dynamics there was an increase in the heart cavities, LVESV - 239 ml, LVEF - 31%, NYHA FC III. Optimization of the parameters of the CRT system was carried out: AV delay - 120 ms, VV delay - 30 ms. After 18 months: LVEF - 33%, sizes of the heart cavities without significant dynamics, LVESV - 230 ml, NYHA FC III. Optimization of the parameters of the CRT system was performed: AV delay - 120 ms, VV delay - 0 ms. After 30 months: LVEF - 30%, without significant dynamics, LVESV - 232 ml, NYHA FC III. Thus, the patient was predicted to have no favorable response to CRT at the preoperative stage. However, considering available indications, the patient was implanted with a CRT-D device, but no positive effect was obtained.

STUDY LIMITATIONS

Considering our experience in the implantation of CRT devices since 2003, when there were no modern recommendations, the study included patients with QRS complex duration >120 ms. Until 2013, for referral to cardiac resynchronization, the protocol of St. Mary's Hospital (London) was used, which is based on the data of spectral tissue Doppler studies [30]. The limitation of our work is the retrospective design and the small number of patients.

CONCLUSION

Thus, our proposed method for predicting a possible response to CRT includes assessment of LVEF, as well as laboratory parameters reflecting the key mechanisms of the development and progression of CHF - immune inflammation, fibrosis, renal dysfunction. The results of the study emphasize the necessity of comprehensive examination of a patient with CHF who is a candidate for implantation of a CRT device. The use of the method suggests a response to CRT and may improve the quality of patient selection.

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IMPROVEMENT OF CARDIAC MULTISPIRAL COMPUTED TOMOGRAPHY PROTOCOL FOR PLANNING INTERVENTIONAL ARRHYTHMIA MANAGEMENT

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Purpose. The study aimed at the comparison of computed tomography (CT) contrast enhancement (CE) protocols for optimal visualization of cardiac chambers, evaluation of their impact on results of non-invasive superficial cardiac mapping.

Methods. The study included 93 patients with heart rhythm disorders in whom catheter ablation of arrhythmia was planned. Noninvasive cardiac mapping for arrhythmia localization was performed and included multichannel ECG-registration and CT with intravenous CE (1st group - monophasic (50 patients), 2nd group - split-bolus (18 patients), 3rd group - with pre-bolus (25 patients). Qualitative and quantitative (measurement of mean blood attenuation in four chambers, calculation of ventricular-myocardial [VM] contrast-to-noise ratio VM-LV и VM-RV for the left ventricle [LV] and right ventricle [RV], respectively) parameters were compared between the groups. Fusion of ECG and CT data was carried out a semi-automatic mode with a non-invasive imaging complex.

Results. Regardless of CE technique, sufficient and homogeneous contrast attenuation was obtained for the left atrium (LA) and LV (mean blood attenuation in LA more than 278 HU, LV 250 HU, VM-LV 0,582). In most cases, the enhancement of the right heart was insufficient with the monophasic protocol; the average CT density was lower than 200 HU, VM-RV 0,256. The split-bolus protocol improved visualization of the right atrium (RA) and RV (blood density in RA 258HU, RV 227HU, VMRV 0,541); however, there was a heterogeneity of the RA cavity due to artifacts from the superior vena cava (VC) and unenhanced blood from the inferior VC. Pre-bolus administration increased the contrast ratio between RA myocardium and blood due to the improvement of blood CT density in the inferior VC (blood density 294 HU). The quality of RV CE was similar to 2nd group (blood density 264 HU, VM-RV 0,565).

Conclusion. The split-bolus and with pre-bolus CE protocols improve visualization of the RV, supporting the high-level enhancement of the left heart. The protocol with a pre-bolus is preferable for exact differentiation of the right atrial endocardial contour.

Key words: computed tomography; radiofrequency ablation; noninvasive cardiac mapping; arrhythmia

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Catheter techniques used to treat cardiac arrhythmias have been actively developed in recent years. The ablation procedure is carried out under X-ray control, intracardiac echocardiography or 3D electroanatomic mapping [1]. Since the 2000s, multichannel non-invasive cardiac mapping systems are available in addition to standard intraoperative mapping [2-4]. Key advantages of such systems include non-invasive nature, the possibility of simultaneous mapping of all four cardiac chambers, the possibility of not only endocardial, but also epicardial mapping [5]. The data of the surface non-invasive cardiac mapping contribute to faster and more precise imaging of the arrhythmogenic substrate area, selection of the optimal catheter ablation technique, as well as reduction of surgery duration [6, 7].

Global scientific sources provide detailed data on surface mapping techniques with a comparison of accuracy with invasive electrophysiological and electroanatomical mapping and the impact of preoperative data on the ablation procedure. Availability of high-quality computed tomography (CT) scans is an important factor for obtaining highly reliable anatomical data at superficial mapping. This depends not only on computed tomography machine capability and scan settings but also on the selected contrast enhancement (CE) technique that allows immediate obtaining of high contrast between the myocardium and the blood in the atrium or ventricle. Global literature describes many studies concerning the search for the optimal contrast enhancement technique for CT coronary angiography, CT of the left atrium (LA) and pulmonary veins; less material is available for the right atrium (RA) and right ventricle (RV) imaging. However, there is no scientific data concerning the impact of the quality of the computed tomography cardiac images on non-invasive mapping results.

Aim. To compare CT contrast enhancement protocols to determine the best optimal contrasting technique

for cardiac cavities and to assess its impact on the quality of 3D reconstructions based on non-invasive surface cardiac mapping.

MATERIAL AND METHODS

In the FSBI "A.V.Vishnevsky National Medical Research Center of Surgery" 93 patients with different types of cardiac arrhythmias were hospitalized for catheter ablation of arrhythmia from April 2018 until March 2020. Most patients had atrial arrhythmias - 73 patients (78.5%) and 20 patients (21.5%) had ventricular arrhythmias. Among the patients, males predominated: 57 patients (61%), the mean age was 56±12.3 years. Preprocedural all patients underwent contrast-enhanced CT of the cardiac chambers and 3D modeling of the cardiac chambers using the standard CT software: Philips Intellispace Portal. The patients were divided into 3 groups depending on the contrast enhancement technique used. Demographic characteristics were balanced between the groups (Table 1).

All patients underwent a non-contrast low-dose CT scan of the chest with capturing all surface mapping electrodes and examining the cardiac area with intravenous contrast enhancement and ECG synchronization (the arterial phase of the scan was performed to obtain anatomical data and the delayed phase of the scan was conducted to exclude intracardiac thrombosis). The scan was performed using Philips Brilliance 64 and Philips Ingenuity 64 tomographs. Three contrast enhancement techniques were used: standard monophasic, split-bolus, and pre-bolus.

Contrast agent (CA) injection technique in group 1: monophasic CA injection at the rate of 1 mL per 1 kg of body weight, then 40 mL of saline (50 patients).

CA injection technique in group 2: fractional injection using the split-bolus technique. Phase 1 - 2/3 of the undiluted CA volume, phase 2 - 1/3 of the CA volume diluted with the saline at a 1:1 ratio, phase 3 - 40 mL of the saline (18 patients).

CA injection technique in the group 3: phase 0 - 50 mL pre-bolus, then, after a 50-sec delay, phase 1 - 2/3 of the undiluted CA volume, phase 2 - 1/3 of the CA volume diluted with the saline at a 1:1 ratio, phase 3 - 40 mL of the saline (25 patients).

The contrast agent injection rate was 3.5-4 mL/sec in all three groups.

The scan starts parameters were similar in all three groups: a locator on the ascending aorta, the absolute threshold for achieving contrast was 150 HU, a minimum delay of the scan beginning from reaching the threshold was 4.2 sec; delayed phase - after 90 sec. The "bolus tracking" mode in groups 1 and 2 was started simultaneously with the CA injection initiation, in groups 3 - 50 seconds after the end of the pre-bolus injection.

Contracting of the cardiac chambers was assessed qualitatively (visual assessment of homogeneous contract filling and the quality of 3D cardiac models) and quantitatively (measurement of chamber content density at three levels, as well as calculation of the ventricular-myocardial contrast ratio for the right and left ventricles using the formula:

$VM = (HU_{ventr} - HU_{mio}) / HU_{aorta}$ [8].

Immediately before the tomography, all patients underwent synchronous ECG recording in 6 standard leads from the extremities and in 224 leads from the chest surface using the "Amycard 01K" diagnostic complex. The electrocardiographic and tomographic data were combined semi-automatically using the same diagnostic complex (Fig. 2).

To verify the arrhythmogenic substrate, isochronous activation maps (for ventricular arrhythmias) and phase maps of the right and left atria (for atrial fibrillation and flutter) were built. In the final 3D models of surface mapping, a visual assessment of the right cardiac chambers was performed using a scoring scale of 1 to 3 points, where 1 score reflected the unsatisfactory quality of reconstruction, the impossibility to obtain diagnostic information; 2 scores reflected the good quality of reconstruction, the model was close to an anatomical one with the presence of artifacts that do not interfere with the diagnostic information interpretation; 3 scores reflected the excellent quality of reconstruction. Then, an electrophysiological examination, electroanatomical invasive mapping and radiofrequency

Table 1.

Patients' characteristics

	Total	Group I	Group II	Group III
Number of patients, n	93	50	18	25
The mean age, years	56,4±12,3	55,1±12,3	59,2±10,8	54,8±13,7
Male, n (%)	57 (61)	35 (70)	8 (44,4)	14 (56)
Females, n (%)	36 (39)	15 (30)	10 (55,6)	11 (44)
Atrial arrhythmias, n (%)	73 (78,5)	43 (86)	13 (72,2)	17 (68)
Ventricular arrhythmias, n (%)	20 (21,5)	7 (14)	5 (27,8)	8 (32)

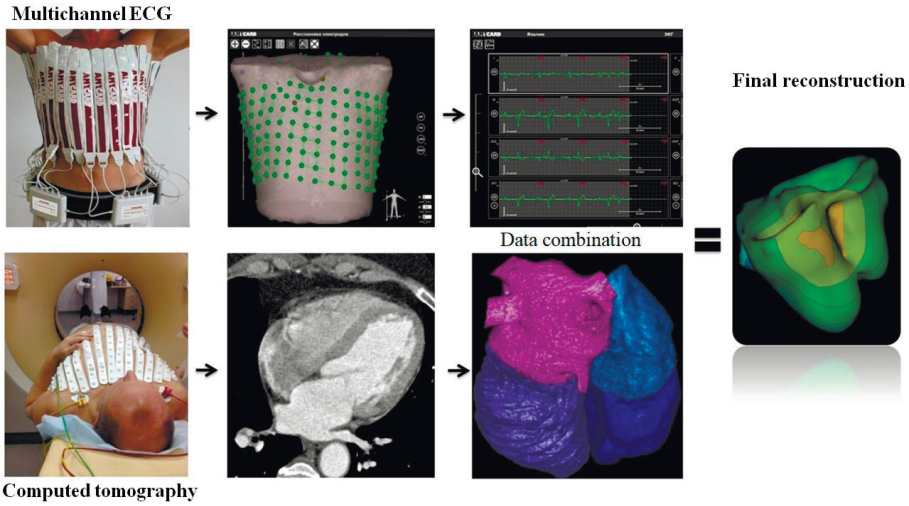

Fig. 1. Stages of non-invasive surface cardiac mapping.

ablation of arrhythmia were conducted in the X-ray operating room.

RESULTS

Table 2 shows the quantitative analysis results for the contrast enhancement of cardiac chambers.

The parameters of the mean contrasted blood density in the LA lumen were significantly higher in group 1 and were similar in group 2 and group 3. There was no significant difference in density in the left ventricle (LV) cavity between groups. Ventricular-myocardial contrast ratio shows the extent of cardiac cavity contrasting in relation to the wall. The larger the ratio, the better the contrasting difference between the ventricular wall and the blood filling its lumen, which makes it easier to identify the endocardial contour when building 3D images. For the LV, this parameter was comparable and did not differ significantly between groups. Regardless of the contrast enhancement technique, there was sufficient contrasting of the coronary arteries, high contrast between the myocardium and the blood in the left cardiac chambers, with good visualization of papillary muscles, aortic and mitral valves, additional septa, mass lesions and thrombotic masses.

With the monophasic contrast enhancement protocol (group 1), the contrasting of the right cardiac chambers was not sufficient to obtain diagnostic information: mean blood density in the RA was 176±102 HU, in the RV 172±86 HU. Nearly in all cases, mean density of the contrasted blood in the chamber cavity was below 200 HU, a minimum threshold value allowing differentiation of the myocardium internal contour from low-contrasted blood filling the right ventricle and atrium [17]. This is due to the flow of a new portion of non-contrasted blood from the inferior vena cava (IVC) with each cardiac cycle. Subsequently, this led to inaccurate automatic identification of the RV and RV endocardium borders when constructing epi-endocardial cardiac models, their distortion, and required manual processing of 3D reconstructions during surface mapping (Fig. 2).

Due to prolonged CA injection time the split-bolus contrast enhancement technique (group 2) prevented its rapid washout from the right cardiac chambers; this improved the images of the tricuspid and pulmonary valve, papillary muscles, myocardium of the right atrium and ventricle (mean blood density in RA was 258±59 HU, in RV - 227±45 HU). However, the heterogeneity of the RA cavity contrast enhancement was maintained due to artifacts from the CA bolus tail and lowdensity blood from the IVC. This also resulted in less accurate identification of the RA endocardium borders and sometimes required manual correction of reconstructions (Fig. 3).

The CE technique with pre-bolus injection (group 3) increased the contrast between the RA myocardium and the blood (mean blood density in the RA was 294±88 HU, in the RV 264±74 HU, (Fig. 4).

The homogeneity of the RV contrast enhancement was like that in group 2. The VM-RV values for the 2nd and 3rd types of protocols were more than 2 times higher than the values for the monophasic protocol. Atrial mapping using a pre-bolus protocol subjectively required the least amount of time (Fig. 5).

The operator noted that ventricular mapping in the patients from groups 2 and 3 was easier and took less time than in the patients from group 1.

As stated above, the qualitative analysis of the reconstructions was carried out based on the ability of imaging to provide diagnostic information from the final isochronous activation and phase maps of the right cardiac chambers. According to the data obtained, shown in the diagram (Fig. 6), in the monophasic contrast enhancement group, only 18% of cases (9 patients) had "good" quality of the right cardiac chambers' reconstruction and the other cases of reconstruction were scored 1. On the contrary, in the split-bolus contrasting group, only 16.7% of reconstructions (3 patients) were considered "unsatisfactory". In the pre-bolus contrasting group, all 100% of the right cardiac chambers reconstructions were scored 2 or 3, without unsatisfactory results ($p < 0.001$).

Table 2.

Results of quantitative analysis of the heart chambers contrast enhancement (HU)

Measurement level	Group I	Group II	Group III	P-value*
LA	305.9±75.4	260.3±72.3	277.6±40.8	0.044
LV	293.8±72.2	248.1±64.2	269.7±40.3	0.051
RA	176.0±101.8	257.6±58.7	293.7±88.0	< 0.001
RV	171.6±86.0	227.1±45.1	263.6±73.5	< 0.001
VM-LV	0.628±0.13	0.582±0.09	0.586±0.131	0.312
VM-RV	0.256±0.265	0.541±0.236	0.565±0.267	< 0.001

Notes: LA - left atrium, LV - left ventricle, RA - right atrium, RV - right ventricle, VM-LV - ventricular-myocardial contrast ratio for the left ventricle, VM-RV - ventricular-myocardial contrast ratio for the right ventricle, * - significance at $p < 0.05$.

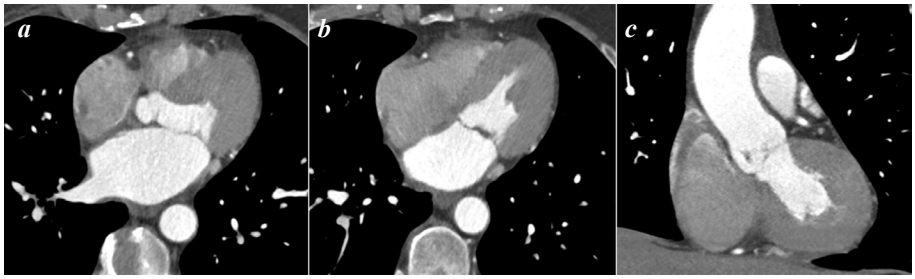

Fig. 2. Cardiac CT, monophasic contrast enhancement, arterial phase (a, b - axial reconstructions, c - coronal reconstruction). High contrast between the myocardium and the blood in the left cardiac chambers. Contrasting of the right cardiac chambers insufficient for surface mapping due to the constant flow of non-contrasted blood from the IVC.

DISCUSSION

The standard CE protocols in cardiac studies (in particular, CT coronary angiography, as the most performed tomographic

procedure) have been optimized for the left cardiac chambers and are applicable when imaging of the LA and the pulmonary veins is required prior to ablation of atrial fibrillation. This protocol is a monophasic contrast agent injection at the rate of 1 ml per kg of patient body weight or the addition of a second phase with injection of small saline volume [9]. However, in this case the amount of CA being injected, and the infusion duration have not been optimized to assess abnormalities of the right chambers, the constant flow of non-contrasting blood from the IVC and the extension of the CA bolus tail in the superior vena cava (SVC) leads to significant inhomogeneity of the chamber contents and low contrast in relation to the myocardium; besides a significant part of the CA has time to leave the right chambers. The contrast enhancement of the right atrium and ventricle varies widely, which we observed in arm 1 (Fig. 2).

When planning catheter ablation, it is important to obtain sufficient and homogeneous contrasting of the left and right cardiac cavities, since the arrhythmogenic activity areas may be localized in any myocardial area [1, 10]. The imaging of right cardiac chambers can be improved by adjusting the amount and rate of CA injections to prolong the duration of CA flow and maintain adequate contrast of the whole heart during scanning [11]. However, monophasic injection of the CA only at a constant rate does not allow sufficient homogeneous contrasting of the right cardiac chambers and often leads to the emergence of linear artifacts from high-density blood in the SVC, shading adjacent structures and distorting 3D reconstructions [12-14].

The use of dual volume contrast media injectors allowing simultaneous injections of the CA and the saline allowed significant changes in the approach to the intravenous contrasting technique [15]. It has been demonstrated that the use of a bolus chaser, i.e. the saline, reduces the frequency of streak artifacts from highly contrasted blood and also reduces the total CA amount required for optimal contrasting [12, 14, 16, 17], while maintaining high and homogeneous contrasting of the arterial system [12, 18]. On the other hand, in many cases, the bolus chaser and the accompanying decrease in the volume of the CA injected and the modernization of the scanning duration leads to an accelerated CA washout from the right cardiac chambers and reduce the attenuation ratio in the RA and RV. This makes it difficult to trace the endocardium contours, to analyze the anatomy and abnormal changes in the right cardiac chambers and the pulmonary trunk [12, 14].

Clinical tasks have stimulated a discussion about a switch from the monophasic contrast protocol to more complex combinations of the CA, saline, and their mixture for adequate contrast enhancement of the cardiac chambers of interest during the scanning.

The fractional contrast agent injection, i.e. split bolus, was initially applied for imaging the urinary system [19], then researchers began to use it to improve cardiac imaging. This protocol is currently used with the following stages included: 1) CA injection, 2) CA-saline mixture injection in various ratios, 3) saline solution injection. In our study, the split-bolus technique used allowed improving right ventricle imaging quality by increasing the contrast of the myocardium-chamber cavity border (Fig. 3).

D.Utsunomiya et al. were among the first to compare monophasic contrast enhancement, with (group B) and without a bolus chaser (group C), and a split-bolus protocol (group A) for imaging the cardiac chambers and the coronary arteries. The split bolus included a CA: saline dilution in a 50:50 ratio in the second phase and a slow injection at a rate of 1.5 ml/sec. It was observed that the highest attenuation ratio in the RV cavity was obtained with the split-bolus protocol; however, the differences were not statistically significant. The difference between the maximum and minimum attenuation values in the LV cavity for all three protocols varied slightly; it was comparable in the RV and the LV when protocol A was used and varied significantly for protocols B and C. Thus, the best contrast enhancement of the LV and RV chambers with clear imaging of the endocardial contour of the interventricular septum was observed with a prolonged fractional CA injection. In the case of a monophasic injection with or without a bolus chaser in half of the patients, precise identification of the interventricular

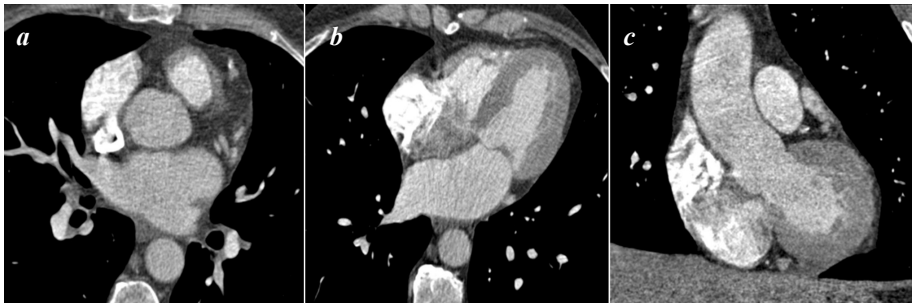

Fig. 3. Cardiac CT, split-bolus contrast enhancement, arterial phase (a, b - axial reconstruction, c - coronal reconstruction). Sufficient and homogeneous contrasting of the left cardiac chambers and the right ventricle. Heterogeneity of contrast agent filling in the RA is maintained due to artifacts from the bolus "tail" in the SVC and non-contrasted blood flow from the IVC.

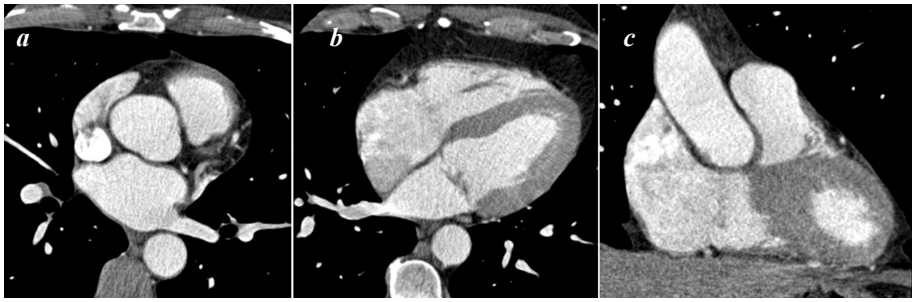

Fig. 4. Cardiac CT, pre-bolus contrast enhancement, arterial phase (a, b - axial reconstruction, c - coronal reconstruction). Increased extent of contrasting and homogeneity of the right cardiac chambers. Sufficient and homogeneous CA filling is maintained in the left cardiac chambers.

septum borders is challenging due to the low contrast of the myocardium/RV cavity [8].

J.M.Kerl et al. retrospectively analyzed data of cardiac CT scan in 75 patients obtained using three contrast enhancement protocols similar to those of Utsunomiya [8], but the split-bolus protocol included a CA: saline mixture injection in a 70:30 ratio, at a rate of 5 ml/sec. Although a monophasic CA injection without saline resulted in a high level of contrast enhancement of the left and right cardiac chambers (which may be associated with the application of the test-bolus technique to determine the scan start delay time), the frequency of artifacts reached 100% in the SVC and 94% in the RA. In the bolus chaser and split-bolus groups, the incidence of SVC/RA artifacts accounted for 34%/59% and 91%/67%, respectively. The image of the left cardiac chamber structures (papillary muscles, aortic valve, LV myocardium) and the coronary arteries generally had similar quality between the three arms. The right cardiac structures (papillary muscles, moderator band, tricuspid and pulmonary valves, RV myocardium) were visualized much better in the split-bolus group [12].

Due to variation in the contrasting extent for the right cardiac chambers depending on the CA dilution ratio for fractional injection, J.G.Lu et al. compared different versions of the split-bolus protocol with each other, changing the CA concentration in the mixture from 30% to 70%, as well as with a monophasic injection to establish the optimal technique. As a result, the mean blood density in the coronary arteries was significantly higher for monophasic injection with a saline chaser and was not significantly different for split-bolus protocols, and this did not affect the quality of vascular imaging. The saline chaser used also minimized the incidence of streak SVC artifacts (2.1%) in contrast to the monophasic CE without any saline (41.7%). With the split-bolus protocols, artifacts emerged in 12.5-23%, the incidence was not significantly different when the CA dilution ratio was changed. When assessing the intracardiac structures, the researchers noted that fractional CA injections lead to a more prolonged contrast enhancement of the RA, RV, and LA cavities; clear imaging of the right chambers structures was obtained with all split-bolus protocols. However, the greater the CA dilution ratio is in the second phase, the lower the attenuation ratio is in these chambers, while the blood density in the LV and the ascending aorta did not differ significantly [14].

M.Kok et al. have also obtained high quality of RV contrasting using the split-bolus protocol: the mean attenuation ratio of more than 200 HU was recorded in almost 80% of cases (372/472 scans). The contrasting was conducted with an individual selection of the amount of CA injected (108±24 mL) and the injection rate (6.1±2.2 ml/sec) based on the body weight and the proposed scan duration, the CA: saline ratio accounted for 20:80 [20].

D.Gopalan has highlighted the key factors allowing the optimal contrast enhancement of the right ventricle. They include: 1) use of a contrast agent with a high concentration of iodine (320-370 mg/ml); 2) split-bolus CA injection. If simultaneous contrasting of the pulmonary trunk is required, the injection of the bolus chaser should be skipped; 3) maintaining a high injection rate (at least 5 ml/sec) during the entire infusion period to reduce the effect of a venous return from the IVC; 4) coordination of the saline solution and contrast agent injection rates in multiphase protocols to reduce the phenomenon of "dead space" (a small portion of the CA, lingering between the brachiocephalic and superior vena cava, especially with decreased injection rate at the second stage of the split-bolus) [13].

The pre-bolus technique was introduced relatively recently. Initially, it was intended to optimize the radiation exposure on the patient during examinations of the pulmonary veins and the left atrium, namely, to exclude intracardiac thrombosis. Filling pseudo defects arising from incomplete mixing of the CA and the blood at impaired atrial contractility, increased trabeculation and large pectineus muscles can mimic thrombotic masses [21, 22]. A delayed scan with high sensitivity allows differentiating these changes, but increases the patient's radiation exposure [23, 24]. J.Hur et al. have used this technique to detect left appendage thrombosis in patients with ischemic stroke, as well as before catheter ablation for atrial fibrillation. Two CA boluses were used: 1) 50 ml test bolus; 2) 70 ml main bolus injected 180 seconds after the test bolus injection. The scan started simultaneously with the start of the main bolus injection; thus, in one scan cycle, an

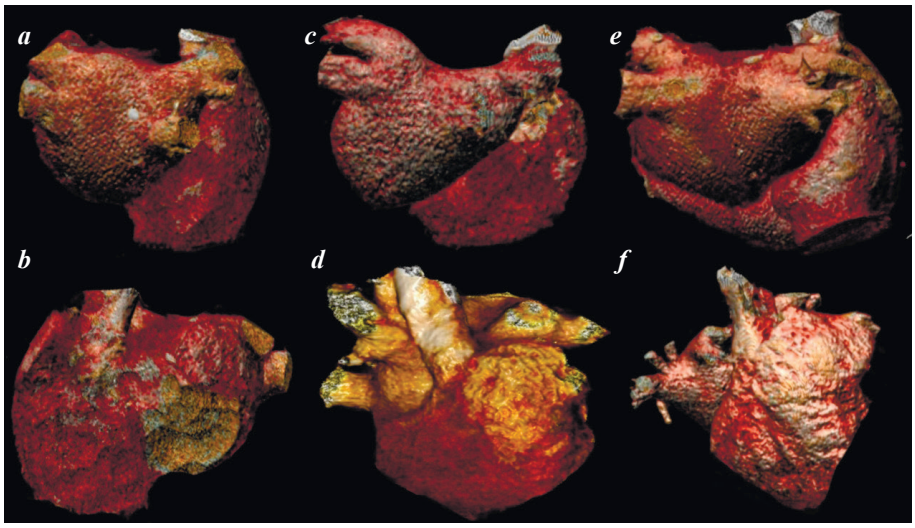

Fig. 5. Intermediate result of non-invasive cardiac mapping: volumetric epicardial atrial models (a, c, e - left atrium, b, d, f - right atrium) at monophasic contrast enhancement (a, b), split-bolus (c, d), with a pre-bolus technique (e, f). With the monophasic protocol, the right atrium (5b) is not contrasted, which is why it is displayed as non-volumetric in the final reconstructions. With the split-bolus and pre-bolus protocols, the right atrium is more contrasted (5d and 5f). However, with the pre-bolus protocol (5f), a more homogeneous contrast filling (by a lower difference in color spectrum) and a more detailed display of the right atrium structures are reflected.

arterial phase was obtained for imaging the LA cavity and the pulmonary vein ostia, and a delayed one - for the LA appendage [25, 26].

W.Staab et al. have also used the protocol with a pre-bolus of 30 mL CA at a slow injection rate (2 mL/sec), and then, after 20 seconds pause, the injection of 70 mL CA at a normal rate (4 mL/sec) to examine patients before AF ablation. In all studies, almost 100% values of sensitivity, specificity, positive and negative predictive values for imaging of thrombotic masses were obtained. However, the impact of this contrast enhancement technique on the imaging quality of right chambers has not been assessed [27].

Our previous study assessed the RA contrasting quality before atrial fibrillation catheter ablation using a pre-bolus technique. Since the main problem preventing homogeneous contrast enhancement of the RA is a hypodense blood flow from the IVC, we assumed that due to recirculation during the pause the pre-bolus would increase the IVC density at the start of the main bolus injection, as well as at the start of the scanning. The study results demonstrated increased homogeneity of the RA contents resulting from mixing of the contrasted blood from the SVC and IVC in the cavity. By reducing the CA volume in the main bolus injection, the risk of artifacts from SVC is minimized with a sufficient quality of left cardiac chambers contrasting preserved [28].

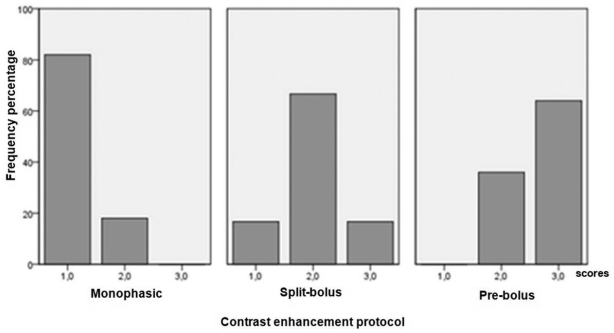

Fig. 6. Bar chart reflecting the qualitative scoring of the final surface mapping reconstructions and the distribution of the results in each arm (in percentage).

This study is an extension of the previous one. For a more detailed assessment of the modified contrast enhancement protocol and its impact on the surface mapping results, it was necessary to compare it with the split-bolus technique. Both protocols provided a high contrast between the myocardium and the blood in the right ventricular cavity; the quality of 3D surface mapping models did not differ significantly. However, the pre-bolus significantly increased the right atrial cavity homogeneity and the contrast of the myocardial-chamber cavity border; this allowed obtaining more detailed anatomical models and the time spent on mapping was subjectively lower with this type of contrast enhancement.

Thus, the protocols of prolonged fractional injection of the contrast agent using the split-bolus technique and with a pre-bolus increase the quality of right ventricle structures imaging, with a high level of CE maintained in the left cardiac chambers. In clinical cases, when precise differentiation of the internal contours of the right atrium is required for the surface mapping of the atrial arrhythmia sources, it is preferable to use a pre-bolus technique, ensuring higher homogeneity of cavity contrasting compared to the monophasic and split-bolus protocols. If reduced contrast agent exposure is required in patients with a high risk of acute renal injury or other contrast-induced conditions, it is possible to use the contrasting protocol with the split-bolus technique for preoperative topical diagnosis of the atrial arrhythmia due to a smaller volume of the contrast agent required.

CONCLUSION

Split bolus and pre-bolus contrast enhancement protocols improve right ventricle imaging while maintaining high contrasting levels of the left chambers. This ensures a precise and reproducible assessment of the volume and function of the right and left ventricles, anatomical structures, and pathological changes. However, in case when precise differentiation of the internal contours of the right atrium is required at surface mapping of the atrial arrhythmia, it is preferable to use a pre-bolus.

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GROWTH DIFFERENTIATION FACTOR 15 AS AN INTEGRAL MARKER OF CLINICAL AND FUNCTIONAL STATUS OF PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION

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Aim. To study the relationship between growth differentiation factor 15 (GDF-15) level in blood serum and patient clinical and functional status parameters, and to determine predictors of GDF-15 level in pts with non-valvular atrial fibrillation (AF).

Material and methods. Eighty-seven pts (with the mean age of 56.9±9.2 years) with non-valvular AF were studied. A general clinical examination, as well as echocardiography and laboratory tests were performed. These included fasting serum glucose (mmol/l), highly sensitive C-reactive protein (h/s CRP) (mg/l), creatinine level (μmol/l) and subsequent calculation of glomerular filtration rate (ml/min/1.73m^2), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) (pg/ml). The level of GDF-15 (pg/ml) in blood serum was determined using an enzyme immunoassay with a human ELISA analytical kit.

Results. An increase in GDF-15 level was associated with age, ischemic heart disease, severity of hypertension, and heart failure, resulting in a higher risk of stroke, according to the CHA_2DS_2 -VASc score, carbohydrate metabolism disorders and obesity, increased h/s CRP and NT-proBNP levels, enlargement of the right and left atria, signs of diastolic left ventricular dysfunction and structural remodeling in the form of eccentric hypertrophy. Multiple linear regression analysis revealed 2 independent predictors of GDF-15 levels: age and fasting glucose.

Conclusion. GDF-15 is an integral biomarker of age-related metabolic disorders and structural and functional changes in the heart, which opens up prospects for further study of its prognostic significance in pts with non-valvular AF.

Key words: non-valvular atrial fibrillation; growth differentiation factor 15; structural remodeling of left ventricle; heart failure with preserved left ventricular ejection fraction

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Atrial fibrillation (AF) is the most common type of arrhythmia and is associated with a two-fold increased risk of death and a five-fold increased risk of stroke [1]. Since the number of AF in recent decades has increased significantly [2], the search for predictors of adverse outcomes in patients (pts) with AF is vital. Currently, the CHA_2DS_2-VASc clinical score is used for stroke risk stratification in non-valvular AF [3, 4]. There is plenty of evidence, however, that the assessment of clinical factors alone is not sufficient to determine risk in patients with AF.

Recently, much research has been done on risk stratification of adverse cardiovascular events in pts with AF various biomarkers circulating in their blood [5, 6]. Thus, in a subanalysis with RE-LY biomarkers, it has been shown that increased levels of certain biomarkers, namely N-terminal pro-B-type natriuretic peptide (NT-proBNP) and highly sensitive troponin I, is associated with higher rates of cardiovascular death and thromboembolic complications. Their addition to CHA_2DS_2-VASc therefore helps in improving its predictive value [7]. Subanalysis with ARISTOTLE biomarkers in pts with AF demonstrated the potential use of growth differentiation factor 15 (GDF-15) in risk stratifying - not only for cardiovascular and overall mortality, but also of major bleeding [8].

It is well-known that various cardiovascular risk factors, including age, arterial hypertension (HTN), obesity, and diabetes mellitus, are involved in the pathogenesis of AF through diastolic left ventricular (LV) dysfunction [9, 10] and eventual congestive heart failure (CHF) with preserved LV ejection fraction (LVEF). Since GDF-15 is expressed by many different types of cells in response to inflammation and myocardial stress [11, 12] and has great prognostic potential in pts with AF, it was interesting to study which clinical and functional parameters cause an increase in GDF-15 levels in pts with non-valvular AF and preserved LVEF.

This work aimed to study the relationship between GDF-15 level in blood serum and clinical and functional status parameters and to determine independent predictors of GDF-15 level in pts with non-valvular AF.

MATERIAL AND METHODS

A single-stage cohort study included 87 pts with non-valvular AF aged 27 to 72 years (mean age 56.9±9.2) consisted of 32 women and 55 men hospitalized at Tyu-

men Cardiology Research Center from April 2018 to October 2019 for primary radiofrequency pulmonary vein isolation. The exclusion criteria were thrombosis of left atrial appendage according to transesophageal echocardiography (EchoCG), acute or decompensated chronic comorbidities, chronic obstructive pulmonary disease, pregnancy, and patient refusal to participate in the study. The clinical characteristics of the patients are presented in Table 1.

Table 1.

Clinical characteristics of patients

Characteristics	Indicators
Age (years)	56.9±9.2
Female, n (%)	32 (37%)
HTN, n (%):	74 (85%)
HTN 1 stage, n	10
HTN 2 stage, n	32
HTN 3 stage, n	32
IHD, n (%):	31 (35.6%)
IHD + HTN, n	29
Previous MI, n	4
CHF, n (%)	68 (78.2%)
CHF I FC, n	30
CHF II FC, n	34
CHF III FC, n	4
Paroxysmal AF, n (%)	62 (71.3%)
Persistent AF, n (%)	25 (28.7%)
Lone AF, n (%)	11 (12.6%)
HD AF<1 year, n	10
HD AF from 1 to 3 years, n	29
HD AF >3 years, n	48
No CM disorders, n (%)	74 (85.1%)
Impaired fasting glycemia, n (%)	3 (3.4%)
Impaired TT to glucose, n (%)	4 (4.6%)
Diabetes mellitus type 2, n (%)	6 (6.9%)
Obesity:	
No obesity, n (%)	42 (48.3%)
Obesity I degree, n (%)	27 (31.0%)
Obesity II degree, n (%)	17 (19.5%)
Obesity III degree, n (%)	1 (1.2%)
CHA_2DS_2-VASc (average score)	1.9
CHA_2DS_2-VASc 0 score, n	5
CHA_2DS_2-VASc 1 score, n	28
CHA_2DS_2-VASc 2 score, n	29
CHA_2DS_2-VASc 3 score, n	18
CHA_2DS_2-VASc 4 score, n	5
CHA_2DS_2-VASc 5 score, n	1
CHA_2DS_2-VASc ≥2 score, n	53
HAS-BLED 0 score, n	65
HAS-BLED 1 score, n	18
HAS-BLED 2 score, n	4

Notes: HTN - arterial hypertension, IHD - ischemic heart disease, MI - myocardial infarction, CHF - congestive heart failure, FC - functional class, AF - atrial fibrillation, HD - history of disease, CM - carbohydrate metabolism, TT - tolerance test.

All pts had symptomatic AF, including 71.3% with paroxysmal AF and 28.7% with persistent AF. The majority suffered from HTN - 74 (85%). Lone AF was observed in 11 pts (12.6%). Sixty-eight pts (78.2%) had signs of CHF, in which I and II functional class of CHF prevailed (73.5%).

Drug therapy included oral anticoagulants (OAC), antiarrhythmic drugs (AAD), and basic therapy for underlying diseases. OAC therapy was started in all pts before hospitalization and continued throughout their stay at the clinic. The distribution by type of OAC was as follows: dabigatran - 23 pts, rivaroxaban - 26, apixaban - 21, warfarin (with the maintenance of target INR level from 2 to 3) - 17 pts. Regarding AAD, 14 pts took amiodarone, 18 - propanorm (propafenon), 20 - sotalol, 6 - allapinin (lappaconitine hydrobromide), 21 - β-blockers and 8 pts did not take AAD. Angiotensin-converting enzyme inhibitors or sartans were taken as baseline therapy by 59 pts, diuretics by 24 pts, statins by 59 pts, and calcium antagonists by 11 pts.

All pts underwent detailed transthoracic EchoCG with assessment of chamber size and volume, structural and functional state of the heart, type of heart geometry [13], as well as LV diastolic function following the recommendations of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACI) [14]. The studies were performed using a Vivid E9 ultrasound scanner (General Electric Medical Systems, USA) with subsequent recording on a hard disk and calculation of the mean values for 3 consecutive cardiac cycles. The type of LV geometry was determined based on calculations of LV myocardial mass index (MMI) and LV relative wall thickness (RWT) according to ASE and EACI Guidelines [13]. The following types of LV geometry were distinguished: type 1 (normal heart geometry): normal LVMMI (≤95 g/m^2 for women and ≤115 g/m^2 for men) and RWT ≤0.42; type 2 (concentric remodeling): normal LVMMI and RWT >0.42; type 3 (concentric hypertrophy): increased LVMMI (>95 g/m^2 for women and >115 g/m^2 for men) and RWT >0.42; type 4 (eccentric hypertrophy): increased LVMMI and RWT ≤0.42.

Laboratory methods of investigation included complete blood count and biochemical blood test including fasting glucose levels (mmol/L), creatinine (μmol/L), followed by calculation of glomerular filtration rate (GFR) using CKD-EPI formula (ml/min/1.73 m^2), NT-proBNP (pg/mL), high-sensitivity C-reactive protein (h/s CRP) (mg/L).

Determination of GDF-15 level venous blood was taken on an empty stomach; after centrifugation for 15 minutes at 2500 rpm, blood serum was aliquoted for further freezing (at -70 °C). GDF-15 level (pg/ml) in blood serum was determined by a quantitative method using a direct enzyme immunoassay. We used a Stat Fax 4200 microplate photometer (USA), an analytical kit «Human

GDF-15/MIC-1 ELISA» (BioVender, Czech Republic), intended for research purposes, with determination range from 35 to 2240 pg/ml. Median values in different age groups were taken as indicative reference values (according to the instructions): 378-648 pg/ml for men, 444-653 pg/ml for women.

Statistical data analysis

The data were statistically processed using Statistica 12.0 software package. The distribution of continuous variables was investigated using the Kolmogorov-Smirnov test. Data were presented as median (Me) and interquartile range [25%; 75%]. The Mann-Whitney U-test was used when comparing indicators in 2 independent groups concerning abnormal distribution; when comparing 3 or more independent groups, the Kruskal-Wallis test with Bonferroni correction was used. Qualitative indicators were compared using the χ^2 test and Fisher's exact test. Evaluation of correlations between pairs of quantitative characteristics was carried out with normal distribution using Pearson's correlation coefficient, and, in the absence of normal distribution, using Spearman's rank correlation coefficient. Multiple linear regression with stepwise inclusion of variables was used to determine independent predictors of GDF-15 level. The results were assessed as statistically significant at $p < 0.05$; at $p \leq 0.1$ - as a statistical trend.

The study complies with the provisions of the Declaration of Helsinki and the study protocol has been approved by the local ethics committee. Informed consent was obtained from all subjects.

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RESULTS

GDF-15 levels in pts in the study ranged from 204 to 1752 pg/mL, with a median of 767.5 [590.0; 951.0] pg/mL. Correlation analysis of GDF-15 levels with clinical and demographic parameters showed a positive moderate relationship between GDF-15 and age: r=0.5262 (p=0.00002) (Fig. 1a). Comparative analysis showed no significant differences in the level of GDF-15 between men and women: 750.0 [546.0; 924.5] and 788.0 [665.0; 988.0] pg/mL, respectively (p=0.2471). Higher levels of GDF-15 were observed in pts with cardiovascular diseases (CVD) compared to pts with isolated AF: 810.7 [630.0; 965.0] and 590.0 [381.0; 759.0] pg/mL, respectively (p=0.023112). There was a tendency towards higher levels of GDF-15 in pts with ischemic heart disease compared to those who did not have it: 838.3 [692.0; 951.0] and 720.0 [504.0; 961.5] pg/mL, respectively (p=0.0729). No association of GDF-15 level with such clinical characteristics as history and form of AF was found. There was also no correlation between GDF-15 level and such factors as smoking and history of anemia.

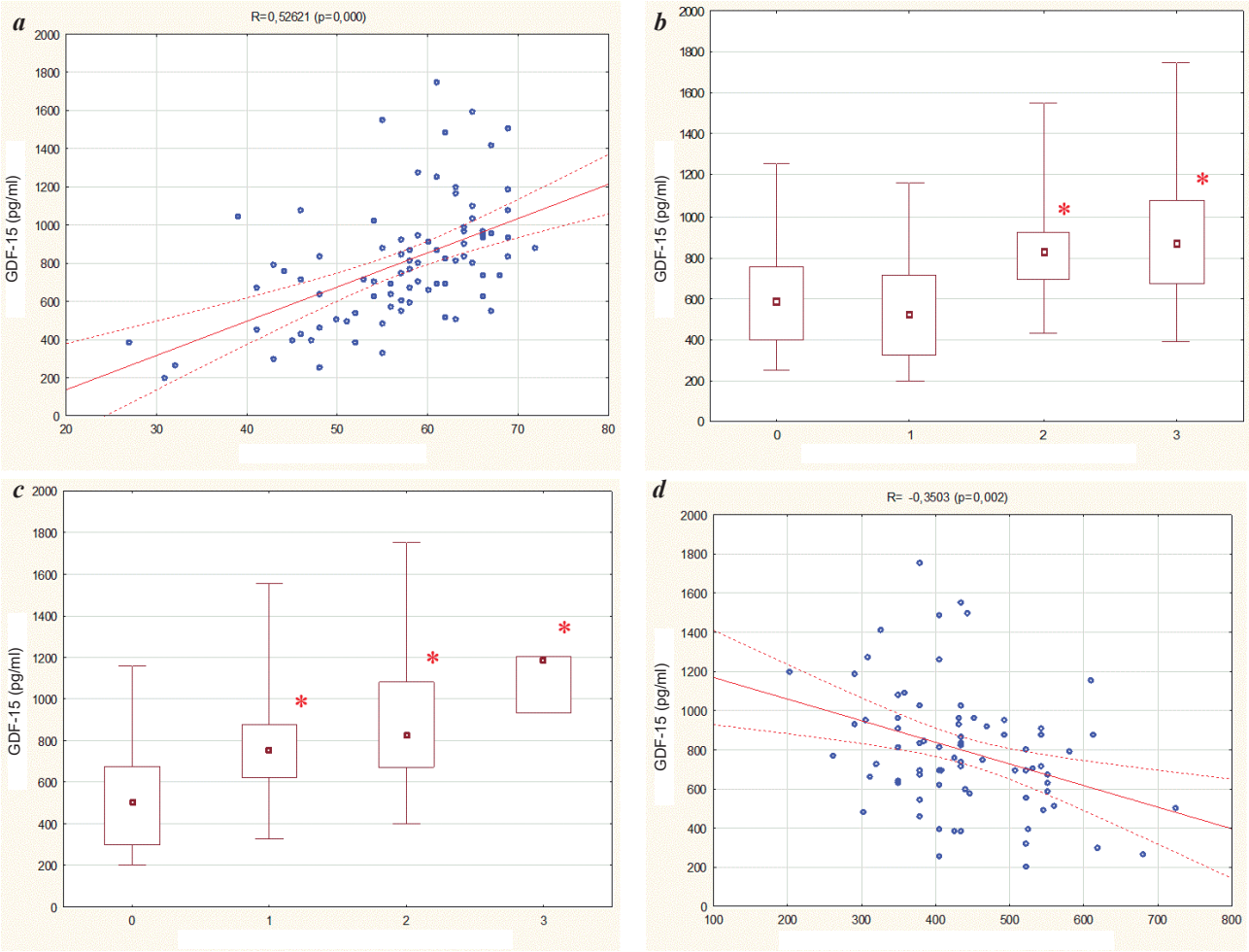

Fig. 1. Data of correlation and comparative analysis characterizing the relationship between the level of GDF-15 with: a - age, b - presence and stage of arterial hypertension (HTN), c - functional class (FC) of congestive heart failure (CHF), d - distance in 6-minute walk test; * - p<0.05 compared to the absence of HTN or CHF.

An increase in GDF-15 level was found in the presence of HTN, gradually rising with the progression of the disease (p=0.0126) and the grade of HTN (p=0.0024) (Fig. 1b). Also, GDF-15 level increased in the presence and severity of CHF (Fig. 1c), a weak negative relationship between the level of GDF-15 and the distance in 6-minute walk test was found: r=-0.35 (p=0.002) (Fig. 1d). Following the above correlations, GDF-15 levels statistically significantly increased with rising risk of thromboembolic complications (TEC) according to the CHA_2DS_2-VASc scale (p=0.0041) (Fig. 2). However, there was no correlation between GDF-15 level and HAS-BLED score. This may be because there were no pts with a high risk of bleeding in the study group.

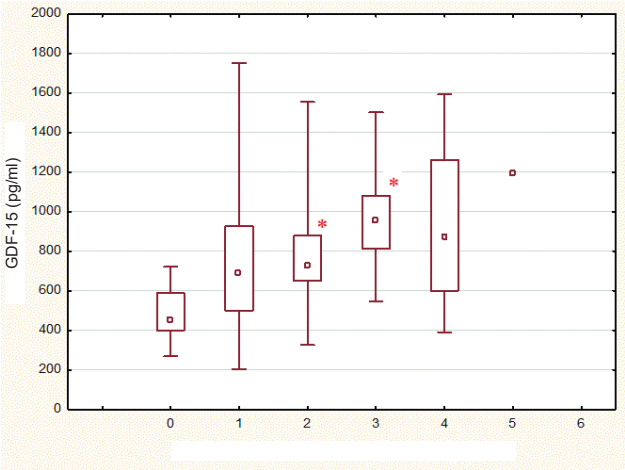

Fig. 2. GDF-15 level depending on the risk on CHA_2DS_2-VASc score, where * - p<0.05 compared to 0 score.

There was a tendency towards a higher level of GDF-15 in pts with diabetes mellitus compared to those without it: 1074.0 [910.0; 1487.0] and 754.7 [582.3; 941.5] pg/mL, respectively (p=0.0760), as well as a moderate positive correlation with fasting blood glucose: r=0.4048 (p=0.0001). As for the association of GDF-15 level with disorders of fat metabolism, a weak positive association of GDF-15 level with body mass index (BMI) was found r=0.21 (p<0.05). When studying the relationships between GDF-15 level and other biomarkers, weak positive relationships were found with the level of h/s CRP (r=0.2924, p=0.01) and NT-proBNP (r=0.2407, p=0.03), as well as a weak negative relationship with GFR (r=-0.2832, p=0.009). No significant relationship with blood creatinine level was noted.

The study of the relationship between GDF-15 level and echocardiographic parameters did not reveal any correlations with LV systolic function sizes and indices, mean LVEF was 64.6±7.8%. At the same time, there was a weak positive correlation between GDF-15 and right atrial volume (Fig. 3a) and left atrial size (Fig. 3b), as well as a moderate negative correlation with such indices of LV diastolic function as the velocity of septal (Fig.3c) and lateral parts of the fibrous ring of the mitral valve in diastole (Fig. 3d).

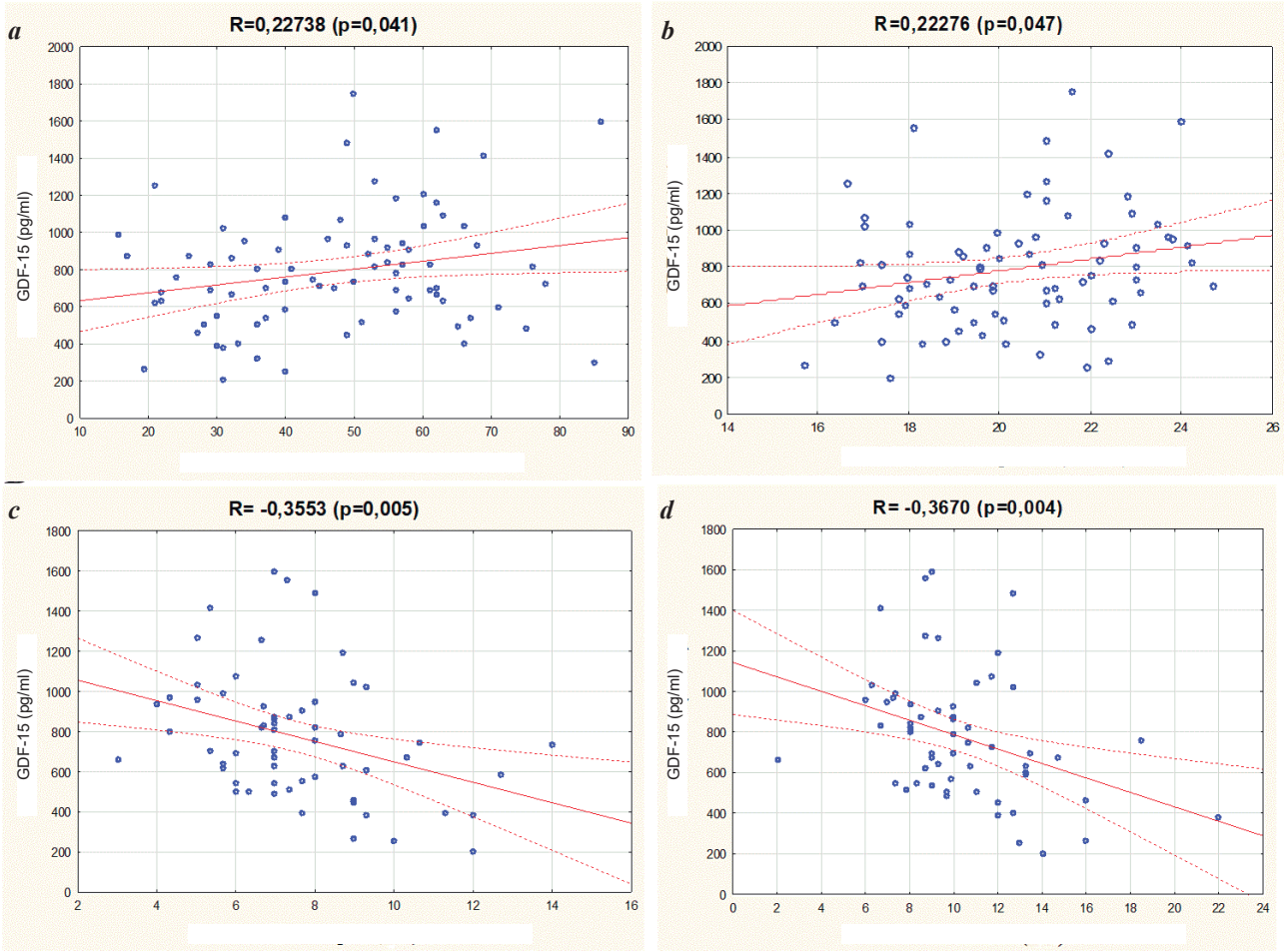

Fig. 3. Correlations between GDF-15 level and echocardiographic parameters: a - right atrial (RA) volume, b - left atrial (LA) size, velocity of septal (c) and lateral (d) parts of mitral valve fibrous ring in diastole.

It was of interest to study the relationship between the level of GDF-15 in the blood and structural LV remodeling since we previously demonstrated that the severity of LA fibrosis depended on the type of heart geometry [15]. According to the above criteria, pts were grouped according to the type of heart geometry: normal geometry - 46 people, concentric remodeling - 20, concentric hypertrophy - 7, eccentric hypertrophy - 14. GDF-15 level in pts with normal heart geometry was conventionally taken as the reference GDF-15 level. Comparative analysis showed higher GDF-15 levels only in pts with eccentric hypertrophy compared to patients without structural heart remodeling (Fig. 4), which agrees with our previously published data: it was eccentric LV hypertrophy that was an independent predictor of severe fibrosis, ≥35% of LA area [15].

To compare the contribution of all the above factors that have significant associations with GDF-15 level in its variance as well as identify independent predictors of GDF-15 level, we applied multiple linear regression analysis with the method of stepwise inclusion of variables. GDF-15 level was taken as a dependent variable, while all variables (clinical and demographic, biomarkers, EchoCG data) which showed a significant correlation with GDF-15 level, were taken as independent factors. The results are presented in Table 2.

As shown in the table, the independent predictors of GDF-15 level were two variables that had the greatest effect on the dispersion of GDF-15 value: age and fasting blood glucose level. The predictors were ranked in descending order by the significance of their influence on GDF-15 level and are as follows: age (regression coefficient β=0.5017, p=0.0001), fasting blood glucose level (β=0.2757, p=0.0254). A positive regression coefficient for both predictors means that blood GDF-15 levels increase with age and fasting blood glucose.

DISCUSSION

GDF-15 (MIC-1) is a member of the cytokine superfamily of transforming growth factor β (TGF-β) [16, 17]. It is expressed by many different types of cells, including adipocytes and myocytes, in response to inflammation and stress: e.g., cell ischemia, mechanical and oxidative stress [6, 11, 12]. Although GDF-15 is widely expressed in various tissues under physiological conditions, its expression level increases in response to pathological stress associated with inflammation or tissue damage [18, 19].

According to our data, the GDF-15 level correlates both with risk factors and severity of CVD, which, in turn, are closely associated with the development of AF. Thus, statistically significant correlations of GDF-15 with such factors as age, BMI, the severity of HTN, CHF, GFR, and NT-proBNP confirm this. Our results correspond with the data of other researchers who proved that the level of GDF-15 was associated with almost all risk factors for CVD (age, carbohydrate metabolism disorders, GFR, obesity) [8, 19]. The difference in our data was that we did not obtain an association of GDF-15 level with male gender, smoking, and persistence of AF [8]. This may be due to the small size of the study group.

Similar to ARISTOTLE biomarker subanalysis [8], we obtained a significant correlation of GDF-15 level with CHA_2DS_2-VASc score; moreover, GDF-15 level increased progressively with increasing risk of TEC. In contrast to our data, Tong Liu et al. in their study on the association of GDF-15 with the CHA_2DS_2-VASc scale found no difference in GDF-15 level in low-risk and high-risk patients, explaining this by the peculiarities of the Chinese population and the small size of the study group [20]; at the same time, the predictive value of GDF-15 levels did not depend on the CHA_2DS_2-VASc score.

Our data on the relationship between the level of GDF-15 and impaired carbohydrate and fat metabolism, as well as with h/s CRP, are consistent with the results of other researchers. Thus, according to I. Dostalova et al., an increase in the concentration of GDF-15 in blood serum was associated with an increase in BMI, adipose tissue mass, and levels of triglycerides, glucose, glycated hemoglobin, and CRP in blood serum [19]. The co-authors believe that MIC-1 (GDF-15) can be considered as "a possible etiopathogenetic candidate and/or metabolic marker of obesity and such associated diseases as insulin resistance or type 2 diabetes mellitus" [19]. M. Carstensen et al. published the results of a prospective cohort study showing that base-

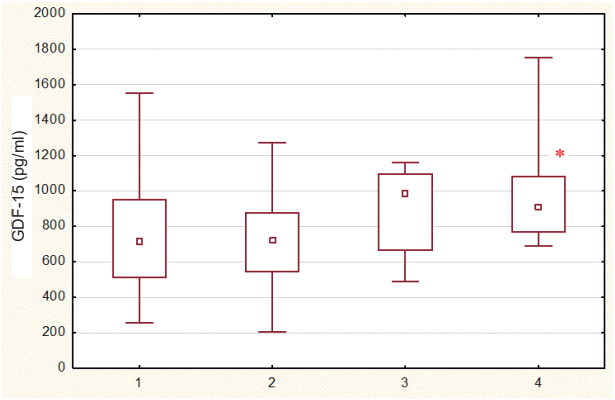

Fig. 4. Comparison of GDF-15 level between patients with different types of heart geometry, where 1 - normal geometry, 2 - concentric remodeling, 3 and 4 - concentric and eccentric hypertrophy, * - p=0.0161 between geometry types 1 and 4.

Table 2.

Results of multiple linear regression analysis

Predictors	R=0.6045, R2=0.3854 F(3.45)=8.4340 p<0.00015					
	β	Standard error β	B	Standard error B	t (45)	p
Free term			-994.07	389.56	-2.55	0.0142
Age (years)	0.5017	0.1193	17.83	4.24	4.21	0.0001
FBG (mmol/l)	0.2757	0.1193	126.01	54.51	2.31	0.0254

Note: FBG - fasting blood glucose.

line GDF-15 levels were significantly higher in individuals who subsequently developed type 2 diabetes mellitus compared to those who did not [21]. The relationship between GDF-15 and h/s CRP revealed in our study can also confirm the concept of the role of immune inflammation in the development and progression of CHF with preserved LVEF [22], including pts with AF.

As it has been already noted above, many risk factors of AF realize their role in the pathogenesis of AF through the development of diastolic LV dysfunction [9], leading, to progressive heart failure with preserved LVEF. This was reflected in the results we obtained. GDF-15 level correlated positively with indicators characterizing the volume and size of the right and left atria but negatively with the velocity of septal and lateral parts of the fibrous ring of the mitral valve in diastole. At the same time, an increase in GDF-15 level was associated with a rise in the functional class of CHF, a decrease in the distance in the 6-min walk test, and an increase in NT-proBNP level. This data corresponds with the results of other researchers. Thus, according to R. Stahrenberg et al. increased GDF-15 levels correlated with certain markers, namely LV diastolic dysfunction as E/e' and LA volume index and LVMMI and was independently associated with decreased distance in 6-min walk test [23]. A study by O.M.Drapkina et al. showed a negative association of GDF-15 level with the ratio of peak E to peak A of trasmitral blood flow in diastole (r=-0.26) [22]. These studies, as well as our data, show that GDF-15 may be a potential indicator of a grade of diastolic dysfunction and may also serve as an additional biomarker for the diagnosis of CHF with preserved LVEF.

When studying the relationship between the level of GDF-15 and LV structural remodeling, an increase in GDF-15 levels was found in pts with eccentric LV hypertrophy. As mentioned above, this type of geometry combines 2 features: the presence of LV myocardial hypertrophy and RWT ≤0.42.

LV hypertrophy is known to be a strict marker of adverse outcomes in various populations: from the general population to the population of persons affected by CVD [24], but it is not included in the risk assessment score for TEC in non-valvular AF [4]. According to RE-LY analysis, it was found that LV hypertrophy detected by electro-, or echocardiography is a marker of increased risk of adverse outcomes in pts with AF [25]. Subanalysis RE-LY with biomarkers investigated the association of cardiac biomarkers and LV hypertrophy with adverse outcomes in patients with non-valvular AF [24]. It was found that the GDF-15 level in pts with LV hypertrophy was higher than in pts without it, although LV hypertrophy yielded biomarkers including GDF-15 in predicting the risk of death and stroke; when considered together as predictors, it lost its independent predictive value. We did not find statistically significant correlations between GDF-15 level and the thickness of the interventricular septum, LV posterior wall, and LVMMI, but we found a relationship between GDF-15 level and the presence of eccentric LV hypertrophy which, along with hypertrophy, is characterized by the initial signs of LV dilatation. Moreover, we did not find any data in literature indicating the association of GDF-15 level with the presence of a certain type of heart geometry and, in particular, eccentric LV hypertrophy.

Age was the most significant and independent predictor of GDF-15 level. This corresponds with a large amount of evidence that GDF-15 is a marker of body aging and is associated with the deterioration of biological functions [18, 19, 26]. There is evidence that mitochondrial dysfunction is one of the signs of aging associated with the pathogenesis of many age-related disorders [26]. Another independent predictor of GDF-15 in our study was fasting blood glucose level. It should be noted that the presence of signs of mitochondrial dysfunction was also found in insulin resistance and diabetes mellitus [27]. It has been shown that GDF-15 can be used as a diagnostic marker of mitochondrial diseases - congenital disorders caused by mitochondrial and nuclear genomic mutations that lead to defective mitochondrial oxidative phosphorylation and impaired energy production [27]. It can be assumed that the predictors of increased GDF-15 level that we identified may, in turn, be united by the presence of mitochondrial dysfunction, which is one of the manifestations of an organism aging.

Thus, our data confirm that GDF-15 is an integral marker of cellular stress, organ dysfunction and biological aging of the cardiovascular, endocrine, and renal systems [6, 28]. Further studies are needed to determine the reference levels of GDF-15 in different age groups with and without CVD [28], to study the prospects for using GDF-15 in the search for new targets and the choice of a treatment strategy for CVD, including AF [29].

STUDY LIMITATIONS

The single-stage study included a small number of pts. There was no control group of pts without AF, which made it impossible to study the contribution of AF to the variance of GDF-15 level in blood. When determining the level of GDF-15, an analytical assay for research purposes was used, which dictates the need to expand the scope of the study and determine its reference values.

CONCLUSION

The results of our study confirm that GDF-15 manifests itself as an integral biomarker of age-associated metabolic disorders and structural and functional changes of the heart, which opens prospects for further study of its prognostic significance in pts with non-valvular AF.

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ASSESSMENT OF THE FREQUENCY AND POSSIBLE RISK FACTORS FOR PAROXYSMAL ATRIAL FIBRILLATION IN THE EARLY POSTOPERATIVE PERIOD AFTER TRANSAPICAL IMPLANTATION OF THE MEDLAB-CT VALVE

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Aim. To study the incidence and possible risk factors for atrial fibrillation (AF) in the early postoperative period after transapical implantation of the first Russian aortic valve (TAP-AVI).

Methods. The study included 118 patients after successful TAP-AVI. Patients with open aortic valve replacement due to dislocation of the prosthesis were excluded, as well as subjects with permanent AF and who died in the early postoperative period. The mean age of the patients was 71.1±4.9 years, body mass index 31.1±5.9 kg/m^2 , males - 39.8%, hypertension was present in 93.2%, diabetes mellitus (DM) - in 27.9%, paroxysmal AF - in 12.7%, coronary artery disease (CAD) was in 56.7%, 8.4% were smokers. The median follow-up time corresponded to the hospital stay - 9.5 days. To identify cardiac arrhythmias, regular daily ECG recording in 12 leads was initiated from the first day after TAP-AVI. In the presence of palpitations, 24-hour ECG monitoring was performed. Indicators such as age, male gender, DM, history of AF, interatrial block before surgery, CAD, and echocardiographic parameters were studied as possible predictors of AF development in the early postoperative period after TAP-AVI. There were no significant differences in the baseline parameters in patients with AF paroxysms and sinus rhythm.

Results. In the early postoperative period, AF was encountered in 46 (39%) of patients. New-onset AF occurred in 38 (32.2%) patients. No cerebrovascular event occurred in patients with post-surgery AF. The only statistically significant risk factor for AF in the postoperative period was CAD (OR 5.756; 95% CI 1.009-8.132; p = 0.048).

Conclusion. In the early postoperative period, the only significant predictor of AF was the presence of documented CAD.

Key words: atrial fibrillation; aortic stenosis; transapical aortic valve replacement

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In the last decade, transapical aortic valve implantation (TAP-AVI) has established itself as an alternative to open aortic valve replacement in patients with a high risk of perioperative complications [1, 2].

Specific complications of TAP-AVI include atrial fibrillation (AF) [3-5] and different conducting system disorders in the form of incomplete and complete left bundle branch block, up to a complete atrioventricular (AV) block, requiring the implantation of a permanent pacemaker [6, 7].

There are no data on the frequency of AF in the early postoperative period after TAP-AVI of the domestic prosthesis 'MedLab-CT' in the literature.

Aim. To study the incidence and possible risk factors of atrial fibrillation in the early postoperative period after transapical implantation of the first domestic aortic valve 'MedLab-CT'.

MATERIALS AND METHODS

From October 2015 to December 2019, 173 patients underwent TAP-AVI 'MedLab-CT' by the transapical method. Clinical selection of patients has carried out following ESC/EACT 2017 recommendations for the treatment of valvular heart disease. The study was of a prospective observational character. The study included 118 patients.

Inclusion criteria:

- successful operation of TAP-AVI 'MedLab-CT' by the transapical method,
- the ability to assess rhythm disturbances before and after surgery.

Exclusion criteria:

- open prosthetic aortic valve implantation due to dislocation of the MedLab-CT prosthesis,
- severe intraoperative complications that led to the death,
- permanent atrial fibrillation.

All patients underwent 12-lead electrocardiography (ECG), Holter monitoring, transthoracic and transoesophageal echocardiography (EchoCG), heart multispiral computed tomography with contrast (MSCT), and coronary angiography before surgery.

EchoCG is an important diagnostic method. This method confirms the presence of aortic stenosis and the degree of its calcification; additionally, the function of the left ventricle (LV) is evaluated, and concomitant diseases of the valve or aortic pathology are detected. Transoesoph-

ageal EchoCG provides an additional assessment of concomitant mitral valve disease and allows for a more accurate calculation of the estimated size of the aortic valve prosthesis and the distance to the mouths of the coronary arteries. MSCT provides additional information about the size and geometry of the aortic root, the ascending aorta and the severity of calcification.

All our patients had severe aortic stenosis with various clinical variants of its manifestation, a preserved ejection fraction without a moderate or pronounced degree of mitral regurgitation. In case of the detection of coronary artery stenosis >70% of the diameter in the proximal segments according to the results of coronary angiography in patients with primary indications for TAP-AVI, preliminary/simultaneous percutaneous coronary intervention with stent implantation of the coronary arteries was performed.

To detect AF in the postoperative period, patients were evaluated daily with regular ECG recordings in 12 leads from the first day after TAP-AVI and 24-hour Holter ECG monitoring after transfer from the intensive care unit and before discharge. Also, a blood test for the determination of blood potassium was performed in the intensive care unit. The potassium level in the blood was in the reference range of 3.5-5.5 mmol/l. The scope of preoperative examination, implantation technique and postoperative management was described in detail above [1, 2, 7].

The mean age of patients was 71.1±4.9 years, including 47 men (39.8%), with a body mass index of 31.1±5.9 kg/m^2. In this cohort, 33 (27.9%) patients had diabetes mellitus, 67 (56.7%) had coronary heart disease (CHD) 109 (93.2%) had hypertension and 10 (8.4%) had chronic obstructive pulmonary disease. EuroSCORE was 7.8 [5.1-11.2] % and coronary artery complexity the Syntax Score scale was 5 [0-13] points. Paroxysmal AF before surgery was detected in 15 (12.7%) patients and interatrial block in 23 (19.5%) patients.

The following EchoCG parameters have been recorded: the LV end-diastolic volume was 103.5 [88-125] ml, the LV end-systolic volume was 35.8 [28-49] ml, the LV ejection fraction was 60.5±11.5%, the thickness of the posterior wall of the LV was 14.1±2.5 mm, the interventricular septum was 14.7±2.4 mm, the anteroposterior size of the left atrium was 39.3±5.1 mm, and the volume of the left atrium was 76.5[62-95.2] ml.

All patients received anticoagulant therapy (direct and indirect-acting anticoagulants until the target level of the international normalized ratio was reached), anesthesia and anti-inflammatory drugs (if indicated), angiotensin-converting enzyme inhibitors, beta-blockers, antiarrhythmic drugs according to indications and as cardioversion (amiodarone), gastroprotective therapy, and antiplatelet agents (if indicated), and attended physical rehabilitation classes. Upon discharge, all patients were prescribed indirect-acting anticoagulants (warfarin) with recommendations for maintaining an international normalized ratio within 2.0-3.0 for 6 months, followed by switching to monotherapy. The median duration of follow-up in the hospital was 9.5 days.

Statistical analysis

All clinical data of patients were taken from the electronic medical history (‘Medialog 7.10 B0119’). Statistical processing of the results was carried out using IBM® SPSS® Statistics Version 21 (21.0.0.0). All quantitative variables were checked for the type of distribution using the Kolmogorov-Smirnov criterion, graphically using quantile diagrams, as well as indicators of asymmetry and kurtosis. With a symmetric distribution, the results are expressed as the arithmetic mean and standard deviation (M±SD). If the distribution was not symmetric, then the values are represented by the median (Me) and the interquartile range in the form of the 25thand 75thpercentiles. Qualitative data are described using frequencies (n) and fractions (as a percentage).

The risks were assessed using step-by-step multivariate logistic regression analysis. The latter was used to select a set of independent predictors included in the statistical model that affects the dependent variable (the probability of AF in the postoperative period). The data are represented by the achieved significance level (p) and a 95% confidence interval (95% CI). The critical significance level was assumed to be ≤0.05.

RESULTS AND DISCUSSION

The paroxysmal form of AF in the postoperative period after TAP-AVI ‘MedLab-CT’ was detected in 46 patients, which required electrical or drug cardioversion in 3 patients. In other cases, spontaneous relief of arrhythmia was noted. During hospitalization, no cerebrovascular events were recorded. In the early postoperative period, hemorrhagic complications were noted in three patients (2.5%) in the form of postoperative bleeding (two cases of hemopericardium and one case of haemothorax), which required resternotomy and surgical hemostasis. All of them were observed in a group of patients without documented episodes of AF.The assessment of the estimated risk factors for AF in the early postoperative period was carried out by a step-by-step multivariate logistic regression analysis (Table 1). The only statistically significant risk factor for AF in the postoperative period after TAP-AVI ‘MedLab-CT’ in our series of observations was the presence of CHD in the patient (OR 5.756; 95% CI 1.009-8.132; p=0.048).

Degenerative aortic stenosis is one of the most frequent valvulopathies in our time, requiring surgical correction in patients with severe aortic stenosis and the presence of clinical manifestations [8, 9]. Both classical open prosthetics of the aortic valve and TAP-AVI can be accompanied by complications associated with this procedure, including bleeding, vascular damage, thromboembolic complications (in particular, stroke) and arrhythmias [3, 4, 10-13].

First-time AF episodes in the early postoperative period after TAP-AVI attract attention, may require antiarrhythmic and anticoagulant therapy, and may also cause an increase in the duration of hospitalization [3,4]. The first time AF was defined by us as stable AF recorded on an ECG during hospitalization or AF more than 30 seconds was recorded on the Holter ECG monitor, detected in patients after TAP-AVI without a previously documented history of arrhythmia.

In some clinical studies, it has been reported that the prevalence of AF before open prosthetics of the aortic valve is 7-43% and 22-41% before TAP-AVI [5, 10, 11, 14-16]. A similar prevalence was described in a meta-analysis which revealed preprocedural AF in 18% and

31% of patients respectively [17] and in the results of the FRANCE-2 registry preprocedural where AF was diagnosed before TAP-AVI in 25.8% of patients [18]. In our case, preprocedural AF was diagnosed in 18.6% (22 people) of patients, while 15 people had a paroxysmal form of AF and 7 (they were excluded from the study) had a permanent form. Thus, AF is observed in a significant proportion of patients before surgery.

According to some of the authors, the frequency of new episodes of AF after open prosthetics of the aortic valve and after TAP-AVI is 31-64% and 4-32%, respectively [3-5, 10, 11, 13-16, 19]. Also, according to the results of the FRANCE-2 registry, the first occurrence of AF after TAP-AVI was observed in 6% of patients [18]. According to M.Vavuranakis et al, who analyzed published articles on the PubMed and Embase databases, the appearance of new AF episodes in the early postoperative period after TAP-AVI reaches from 1 to 32% [20]. In our study, AF developed in 39.0% (46 patients), and first-time AF was observed in 32.2% (38 patients). At the same time, the presence of paroxysmal AF before surgery was not a significant risk factor for AF in the early postoperative period.

Table 1.

Assessment of the estimated risk factors for AF in the early postoperative period (n=118).

Parameter	95% Confidence Interval	P
Male	0.114-1.176	0.091
Age	0.911-1.137	0.758
BMI	0.919-1.112	0.826
Diabetes mellitus	0.315-3.407	0.954
Hypertension	0.384-2.451	0.293
CHD	1.009-8.132	0.048
COPD	0.085-3.881	0.568
Atherosclerosis	0.224-2.017	0.478
CKD	0.361-3.753	0.799
Preprocedural AF	0.713-11.425	0.139
Syntax Score	0.935-1.019	0.270
EuroScore	0.894-1.074	0.666
Duration of follow-up	0.966-1.137	0.256
CDS	0.978-1.024	0.113
EDV	0.982-1.030	0.643
Posterior wall of the left ventricle	0.748-1.360	0.956
Interventricular septum	0.643-1.216	0.449
LA diameter	0.934-1.199	0.375
LA volume	0.975-1.017	0.724
Interatrial block	0.132-1.551	0.207

Note: BMI - body mass index, CHD - coronary heart-disease, COPD - chronic obstructive pulmonary disease, CKD - chronic kidney disease, EuroScore - risk assessment scale for cardiac surgery, Syntax Score - scale for assessing the severity of coronary artery damage when using various tactics of myocardial revascularisation in patients with multivessel coronary artery damage, CDS - course-diastolic-size, EDV- end diastolic volume, AF - atrial fibrillation, LA - left atrial.

There is a risk of overestimating the incidence of first-time AF in this group of patients. The exclusion of patients with preprocedural AF is often based on a history of previously documented heart rhythm disorders or a short preprocedural screening. But, in 12% of patients, AF may be asymptomatic [21] and the development of heart rhythm disorders in the postoperative period may be a verification of a previously preprocedural unknown AF [3].Increased knowledge about predisposing factors, optimal post-treatment monitoring, and preventive antiarrhythmic and antithrombotic therapy can reduce the risk of developing secondary complications in relation to new episodes of AF. Despite the wide variety of reasons for the development of AF after surgical correction of aortic stenosis, to date a marker with the maximum prognostic ability has not yet been found.

In the literature, independent predictors of the occurrence of AF after open aortic valve surgery include a preoperative age of more than 70 years, history of AF, elongation of the dispersion of the P wave and the filtered P wave, an increase in the thickness of the posterior wall of the LV, the thickness of the interventricular septum ≥1.8 cm; a decrease in the maximum blood flow rate in the left atrium appendage, prolonged artificial circulation, a low body mass index, a maximum transvalvular gradient of ≥85 mm Hg, a history of heart failure, as well as left ventricular ejection fraction before surgery and in the early postoperative period ≤50% [19, 22, 23].

The pathogenesis of arrhythmias during the mini-invasive TAP-AVI procedure is not well-described, although according to some authors, a greater increase in markers of myocardial damage is observed with transapical access, which indicates more extensive myocardial damage compared to transfemoral transcatheter aortic valve implantation [24]. Also, transapical access and preprocedural dilatation of the left atrium are associated with an increased risk of developing new episodes of AF [3, 5].

In our study, TAP-AVI was carried out by the transapical method. In our series of observations, possible predictors of the development of AF in the postoperative period after TAP-AVI 'MedLab-CT' included only chronic coronary heart disease (p=0.048) with statistical significance.The mechanisms of the development of AF in uncomplicated CHD and the interaction between AF and coronary perfusion have not been established. But, from the point of view of the probability of developing AF in CHD, according to some authors, the main importance is not the fact of detecting coronary atherosclerosis, but rather the presence of complications of CHD. In patients with coronary artery disease confirmed by coronary angiography but without signs of HF, AF is found in only 0.2-0.8%. In the presence of clinical manifestations of HF, mitral regurgitation, large postinfarction zones, as well as in asymptomatic systolic dysfunction of the left ventricle, the probability of detecting AF increases to 25% [25-27]. There is also a clear pattern between the duration of the history of coronary heart disease and AF, since the duration of coronary heart disease up to 10 years increases the risk of AF by 2.6 times, and more than 10 years increases the risk of AF by 4 times.

The prevalence of AF in CHD increases with age: in men over 60 years of age, the incidence of AF increases by 3.6 times compared to middle-aged patients and for women the same indicator increases by 7 times [27].

The main mechanism of AF development in elderly patients with severe degenerative aortic stenosis is chronic pressure overload of the left ventricle and left atrium at later stages of aortic stenosis. As a result, according to Manolis et al. [28], the compliance of the left ventricle decreases and the stiffness of the left ventricle increases, the filling pressure increases, the reserve of coronary blood flow decreases, the tension of the heart walls increases and the sympathetic nervous system and the renin-angiotensin-aldosterone system are activated [28, 29]. A distinctive feature of this process is fibrosis and increased proliferation of connective tissue. Structural rearrangement leads to the fact that there is an electrical dissociation between the muscle bundles, which facilitates the occurrence and maintenance of AF. Over time, tissue remodeling occurs, which contributes to the development and maintenance of AF by changing the atrial structure. Atrial remodeling consists of three components:

1. Electrical remodelling: with the rapid frequency of atrial contractions observed during AF attacks, there is a decrease in the duration of the action potential due to changes in the content of intracellular calcium. Even with a prolonged AF paroxysm after the recovery of the sinus rhythm, electrical remodelling quickly and completely regresses.
2. Contractile remodelling is a decrease in the contractility of the LA because of changes in the content of intracellular calcium against the background of a high heart rate in AF, leading to blood stagnation and thromboembolic complications, in particular stroke.
3. Structural remodelling of tissues occurs after weeks and months. In this case, macro-and microscopic changes occur in the myocardium, which lead to the development of contractile dysfunction and a decrease in heart output.

During transcatheter TAP-AVI, high-frequency stimulation of the ventricles is performed, which can also lead to an imbalance of intracellular calcium, and in the presence of concomitant diseases, structural changes to the myocardium and electrolyte imbalance in the early recovery period after surgery can lead to AF.

Atrial fibrillation is associated with increased mortality, a higher frequency of stroke and other thromboembolic complications, heart failure, decreased quality of life, decreased exercise tolerance, impaired left ventricular function and the development of cognitive dysfunction [25]. According to some authors, new episodes of AF after surgery are also independently associated with adverse events such as stroke, death, and an increase in the length of hospital stay [4, 19, 20].

According to M.Vavuranakis et al., patients with a history of AF have a higher mortality rate in the early postoperative period after TAP-AVI than individuals with first-time AF paroxysms. According to the same authors, patients with first-time AF paroxysms have at least twice the risk of cerebrovascular events occurring in the subacute phase (1-30 days) after TAP-AVI [20]. According to other authors, the occurrence of asymptomatic AF in the early postoperative period after TAP-AVI is not associated with a deterioration in the short-term prognosis [30].

In our study, no cerebrovascular events were recorded during follow-up, either in the group of patients without a history of AF or in the group with AF. The absence of cerebrovascular events may be associated with anticoagulant therapy with warfarin at that time for 6 months from the first day after TAP-AVI with the achievement of the target INR (2.0-3.0). Currently, the general approach is to double antiplatelet therapy up to 6 months after TAP-AVI except for patients with AF, who are recommended to combine warfarin with one of the antiplatelet drugs (aspirin or clopidogrel).

CONCLUSIONS

In our series of observations, the paroxysmal form of AF occurred in 46 (39.0%) patients after TAP-AVI ‘MedLab-CT’. AF was detected in 38 (32.2%) patients for the first time. Cerebrovascular events were not detected in patients with paroxysmal AF in the early postoperative period. The only significant predictor of the occurrence of AF in the early operational period was the presence of coronary heart disease.

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EXPERIMENTAL USE OF STEREOTACTIC RADIOSURGERY FOR NON-INVASIVE INTERVENTIONS IN ARRHYTHMOLOGY

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Purpose. The experimental study aimed to study the effects of stereotaxic radioablation of various doses on the myocardium of the atria, ventricles and atrioventricular (AV) node in the long term (up to 6 months); as well as assessment of collateral damage during radioablation.

Methods. The study comprised 4 domestic pigs. The animals were 10-12 weeks old, the average weight was 30±2.7 kg. A linear accelerator was used for the experiment. Each animal underwent radiation exposure in different areas: 1st animal - AV node (dose 35 Gy), 2nd animal - AV node and the apex of the left ventricle (LV) (dose 40/35 Gy, respectively), 3rd animal - pulmonary veins (PV) and left atrium (dose 30 Gy), 4th - AV node and LV free wall (dose 45/40 Gy). Under intravenous sedation with hemodynamic monitoring, contrast-based CT of the heart was performed to assess the degree of displacement of the heart chambers in one respiratory and cardiac cycle and to assess the anatomy of the chambers of the heart and adjacent organs. The allocation and the contouring of the target zones were carried out in three projections: axial, frontal and sagittal. For electrocardiographic control, a loop recorder was implanted in each animal. The average exposure time was 11±7 minutes. After a follow-up period, morphological examination of the autopsy material was performed.

Results. The average follow-up period after ablation was 134.75±77.34 days. The electrophysiological effect of the ablation was achieved in cases of complete AV-block development. This effect was developed in 2 out of 3 animals, where AV-node was exposed: 2nd animal - 40 Gy on 108th day of observation and 4th animal - 45 Gy on 21st day of observation. No cardiac tachyarrhythmia was recorded in the animals. The results of myocardium macro- and microscopic examination showed significant changes in the target zones. These areas had precise but uneven damage boundaries, which were within the planned ones (conformal exposure with a high degree of precision). The transmural nature of the changes was noted as well. Massive fields of fibrous tissue of various degrees of maturity (with a predominance of subepicardial localization) with focal hemorrhages of various ages and granulations were detected, which were surrounded by cardiomyocytes with coagulated and vacuolated cytoplasm.

Conclusion. The use of non-invasive stereotactic treatment of tachyarrhythmias has high prospects in modern electrophysiology as an alternative ablation method.

Key words: stereotactic radioablation; ventricular tachycardia; noninvasive ablation

Conflict of Interests: nothing to declare
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The high prevalence of tachyarrhythmias has emerged the need of developing novel treatment approaches. They are primarily focused on optimizing the existing methods by improving their efficiency and ensuring their safety.

The introduction of catheter ablation in the early 1990s has revolutionized treatment for tachyarrhythmia and shown superior clinical outcomes. It is almost 100% effective for treating patients with Wolff-Parkinson-White syndrome. Catheter ablation is recommended to patients with arrhythmias in the national and international clinical guidelines with a high level of evidence and clinical support for efficacy and safety. However, catheter ablation may be furtherly optimized [1] for patients with long-standing, persistent, and paroxysmal atrial fibrillation (AF). The long-term success of interventional catheter ablation for treating long-standing AF varies from 10% to 15% and for paroxysmal AF - from 50% to 70% [1, 2]. Radiofrequency ablation (RFA) is used to perform an electrophysiological examination, treat and prevent ventricular tachycardia (VT) in patients with ischemic cardiomyopathy [3]. RFA is the first-line treatment for polymorphic and monomorphic VT in patients with implantable cardioverter-defibrillators (ICD) and repeated shocks from ICD due to sustained VT [4]. The 3-year freedom from VT recurrence in patients with ICD varies from 20 to 48%. RFA can fail because of inaccessibility to the VT substrate, the large volume of interest, the transmural heterogeneity of ventricular myocardium with the thickness over 30 mm [4]. Hemodynamic instability precludes mapping during VT and may require the placement of the patient on extracorporeal circulation [5].

These patients commonly suffer from severe concomitant diseases, such as chronic heart failure, respiratory and renal failure. The presence of comorbidities increases the risk of procedure or becomes an absolute contraindication to RFA.

Mechanical trauma to the atria and ventricles (resulting in cardiac tamponade) and adjacent organs (atrial-oesophageal fistula, phrenic nerve) are recognized as the major risks of catheter ablation of tachyarrhythmias. It is also associated with an increased risk of periprocedural stroke, transient ischemic attack, and air embolism. The incidence of these complications can range from 0.6% to 3% with a mortality rate of 0.1% [6]. In addition, interventional procedures are time-consuming and require the need of fluoroscopy.

Recently stereotactic radiotherapy of malignant foci using cobalt-60 machines, medical linear accelerators (LIBAC) and heavy charged particles has become a promising modality for treating oncology. Novel technologies allow shaping the high-dose radiation beam to conform to the target volumes with high precision and selectivity. The delivery of conformal radiation minimizes the radiation exposure on the adjacent healthy tissues and minimizes acute and delayed radiation complications [7]. Jean Regis and John Adler, well-known experts in stereotactic surgery, have proposed the concept of neuromodulation to provide the rationale for functional radiosurgical interventions for hyperkinesis and pain syndromes. The radiation-induced neuromodulation principle suggests that the delivery of high doses of ionizing radiation allows both, the formation of a focus of destruction and the modulation of the function. Non-invasive stereotactic treatment using linear electron accelerators can be considered as a promising alternative to catheter ablation in patients with tachyarrhythmias. The beneficial potential of stereotactic therapy has been demonstrated in several experimental and clinical studies [8].

The high efficacy and safety of stereotactic radiotherapy using electron and proton accelerators, accurate navigation systems, digital methods for dose planning and distribution, precisely delineating anatomical structures, and motion tracking have opened new horizons in the treatment of respiratory and cardiovascular disease. Since oncologists and arrhythmologists share the single task to damage pathological tissues, promote the progression of fibrosis with the resultant conduction block, the green light has been given to the experimental and preclinical studies on radioablation to treat tachyarrhythmias. Several research groups have shown promising results of radiation-induced damage to arrhythmogenic cardiac tissues in animal experimental studies.

Our study is aimed at developing a novel radioablation technique to perform radiation-induced damage to arrythmogenic cardiac tissues and assessing the long-term accuracy, efficacy, and safety of radiation exposure in a porcine model.

MATERIAL AND METHODS

The experimental study was performed in the A.V.Vishnevsky National Medical Research Center of Surgery and N.N.Burdenko National Medical Research Center of Neurosurgery following the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes and the requirements of the All-Union State Standard ISO 10993-2.

A total of four pigs, two males, and two females Sus scrofa domesticus pigs, were used in the study. Animals were aged 10-12 weeks with a mean weight of 30±2.7 kg. Radioablation was performed in the period from December 2019 to February 2020. All animals underwent irradiation at the predetermined target zones. Animal 1 was irradiated with 35 Gy at the AV node. Animal 2 received radiation exposure at the AV node area and the left ventricular apex with a 40/35 Gy dose of radiation, respectively. Animal 3 underwent radioablation of the pulmonary vein orifice and left atrium with 30 Gy dose exposure. Animal 4 underwent radioablation of the AV node and the left ventricular free

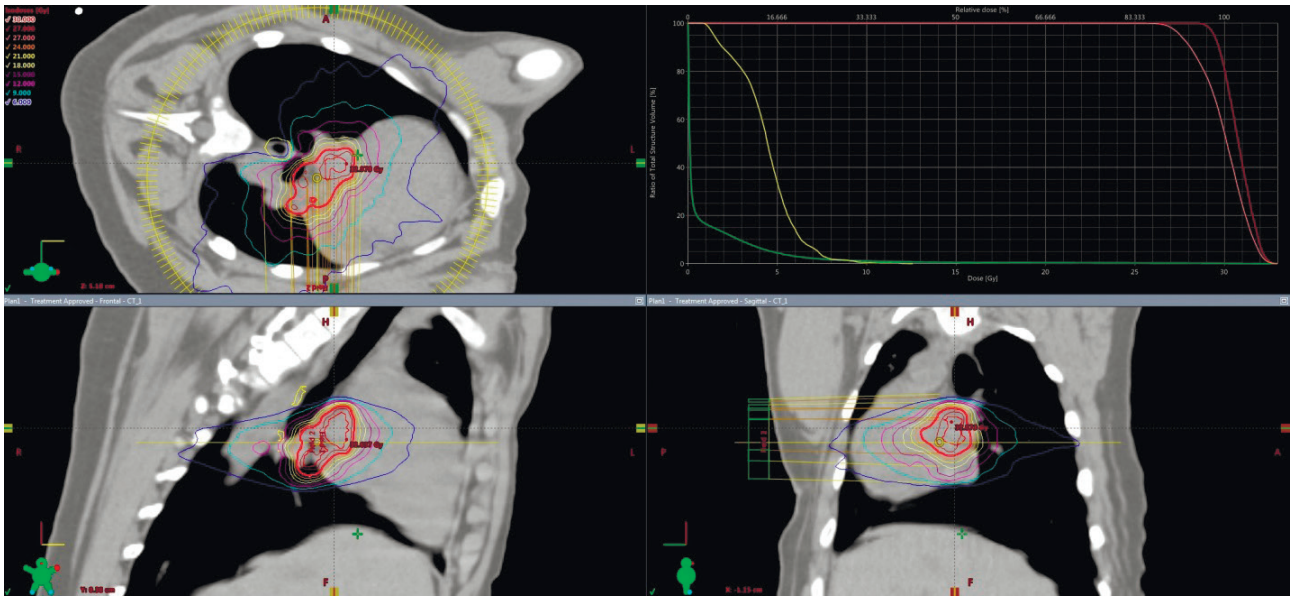

Fig. 1. Radioablation planning. Contouring of the target exposure area (pulmonary veins). The figure shows a series of CT scans of a pig's heart in three planes. The esophagus is marked with a yellow outline. According to the dose planning and distribution, the target volume (red curve) is irradiated with a given high dose, creating a dose fall-off at the esophagus (yellow curve) and minimizing the radiation exposure.

wall with 45/40 Gy dose exposure, respectively. Stereotactic radiosurgery doses were delivered by a TrueBeam STx linear accelerator (Varian, USA).

Animals were sedated with i.v. ketamine 4.4 mg/kg, zoletil 2 mg/kg. Animals were on spontaneous breathing with the supply of humidified oxygen. The following hemodynamic parameters were monitored: blood pressure, heart rate, SaO_2, and respiration rate. Laboratory animals were then immobilized on a special vacuum mattress. First, multislice computed tomography (MSCT) was performed. To ensure accurate target tracking during cardiorespiratory motion, native CT scans were recorded to mark the region of interest (Fig. 1). Contrast-enhanced CT scans were recorded to assess the anatomy of the heart chambers and adjacent organs. The tracking of the target zone was then performed using the MSCT image series in the axial, frontal, and sagittal planes. Treatment planning was performed with the Eclipse Treatment Planning System software (Varian, USA). The target zone was marked on each series of images with a step of 1.25-1.3 mm. A margin of up to 5 mm was extended from the target outline for untracked respiratory and cardiac motion (Fig. 2-5). The target zone was then assessed using the following parameters: gross target volume (GTV, the volume of the target zone that can be seen with the help of imaging), planning target volume (PTV, the final volume containing GTV and the additional margin of up to 5 mm), the proximity of critical structures to the region of interest (esophagus, lung tissue) (Fig. 1).

After all the parameters had been calculated, animals underwent radiation exposure. The characteristics of the target zones and exposure parameters are presented in Table 1. The mean exposure time was 11±7 minutes. There were no intraoperative complications. The next step included the implantation of a loop recorder (Reveal, Medtronic, USA) into the right lateral region of the chest to monitor the rhythm remotely during the follow-up (transmission of recordings every 14 days). The device programming parameters were as follows: pause episode detection - 1,5 sec, AT/AF detection, VT detection >300 ms.

The follow-up period was 6 months. At the end of the follow-up, animals were sacrificed. Biopsied tissues were referred to as morphological, macroscopic, and microscopic studies. All samples were documented by photographs, cut transversely into slices through 1,5 cm, and then fixed in 10% formalin solution buffered to pH 7.0-7.2 for 48 hours.

Biopsied tissues were taken from the target zones (a full-thickness sample of the heart, including the pericardium, myocardium, and endocardium, cardiac conduction system, including AV node, coronary arteries, and heart veins) and adjacent organs and tissues (lungs, esophagus, bronchi, peribronchial lymph nodes). A total of 167 samples were collected. Samples were placed in tissue cassettes and fixed then in 10% formalin solution buffered to pH 7.0-7.2 for 24 hours, washed with running tap water, and dehydrated with graded series of alcohol. Samples were embedded into paraffin blocks according to the standard protocol and then cut into 3-μm thick sections using an automatic rotary microtome HM 355 S (Thermo Scientific, Germany). Samples were mounted onto glass slides (Gerhard Menzel GmbH, Germany) and stained with hematoxylin and eosin according to the standard protocol. In addition, Masson trichrome staining and van Gieson's staining were performed to identify type I-IV collagen fibers. Periodic acid Schiff staining was performed to detect glycopolysaccharides in the cells of the cardiac conduction system.

The main objectives of the histological assessment included the examination of the conformity and homogeneity of exposure, as well as the evaluation of the electrophysiological effects following stereotactic radioablation.

RESULTS

The mean follow-up period after the indexed procedure was 134.75±77.34 (max. 189 days - min. 20 days) days. Animals 1, 2, 3 underwent the entire follow-up period of 6 months.

AV node radioablation

Macroscopic findings suggested that the presence of evident changes in the AV node area induced by radiation exposure. The changes had clear but rough boundaries that did not exceed the PTV. The exposure zone calculated in the planning system completely coincided with the resultant exposure zone, i.e. radiation exposure was precise

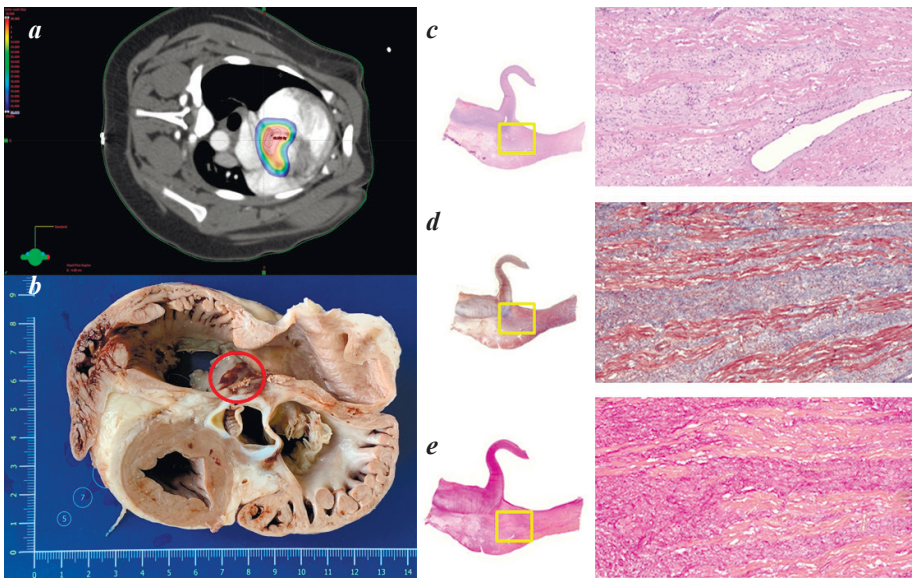

Fig. 2. a: Dose distribution in the target zone (AV node) and adjacent tissues on a series of contrast-enhanced CT scans of the pig heart in the axial plane calculated in the treatment planning system. b: A macroscopic sample of the porcine heart. The red circle marks the irradiation area. A microscopic sample of the AV node tissue after radiation exposure. c: hemotoxylin-eosin staining. d: Masson's trichrome staining. e: van Gieson's staining. Magnification: 40-200. AV node - atrioventricular node, CT - computed tomography.

(Fig. 2 a, b). Conformity of irradiation was achieved in all animals (animals 1, 2, 4).

Microscopic examination reported evident changes in all layers of the AV node area with mature granulation tissue among unchanged myocardial fibers (Masson trichrome staining and van Gieson's staining (Fig. 2 c, d, e). AV node samples proved that some cardiomyocytes were completely torn with resultant coagulation and vacuolization of the cytoplasm, suggesting acute stress response. Histological changes were more pronounced at a maximum radiation dose of 45 Gy.

Single intact cardiomyocytes from the conduction system were determined in the same zones.

The Reveal Insertable Cardiac Monitor showed that animals 2 and 4 had third-degree AV block. None rhythm or conduction disturbances were recorded in animal 1 within the follow-up. Animal 2 had transient third-degree AV block mainly overnight: the minimum heart rate was 16 beats per minute with the rhythm pauses over 2 secs. A total of 1,868 episodes were recorded within 173 days. The maximum duration of transient third-degree AV block was 42 mins. The AV block was first detected on day 108 after the implantable cardiomonitor implantation (Fig. 3). Animal 4 died on day 21 from asystole due to the development of a complete AV block.

Pulmonary vein radioablation

Macroscopic examination reported the presence of hemorrhagic impregnation and calcification deposits. The exposure zone in the planning system completely coincided with the resultant radiation exposure proving its high conformity.

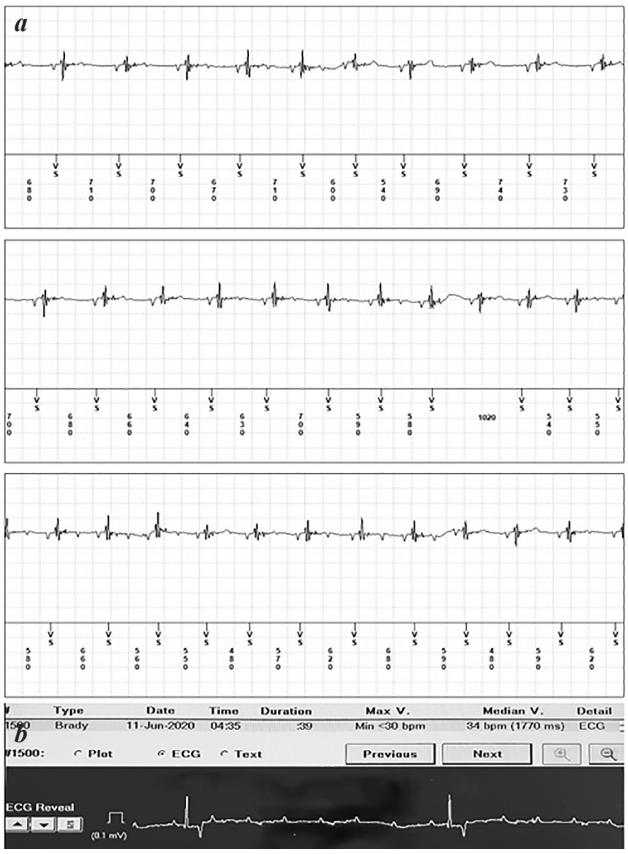

Fig. 3. a: ECG recorded with the Reveal ICM on day 1 of the experiment. The rhythm is sinus, the heart rate is 100 bpm. b: a single-channel ECG was recorded with the Reveal ICM on day 108. An episode of transient complete AV block is recorded with a heart rate of less than 30 bpm.

Histological findings of the sample collected from the pulmonary vein orifice area and the thickness of the left atrial wall showed the presence of calcification foci, edema, and loose connective tissue after radiation exposure. Focal edema was found in the region of the myocardial stroma. None necrotic and fibrotic regions were found in the adjacent organs (lungs, esophagus, bifurcation lymph nodes) (Fig. 4).

No rhythm or conduction disturbances were recorded in animal 3 within the follow-up.

Left ventricular free wall and interventricular septum radioablation

Macroscopic examination reported clear boundaries of the exposure area, almost consistent with the PTV calculated before the procedure (animal 2 underwent the irradiation at the left ventricular apex and the part of the interventricular septum; animal 4 underwent the irradiation at the LV free wall (Fig. 5).

Histological examination of the myocardium at the left ventricular apex and interatrial septum (animal 3) reported transmural fibrosis of varying maturity degrees (mostly subepicardial) with hemorrhages of multiple ages and granulations surrounded by cardiomyocytes with coagulation and vacuolization. Samples collected from animal 4 reported the presence of granulations, necrosis, transmural fibrosis with the regions of calcification and hemorrhages (Fig. 5). Importantly, the anterior interventricular artery, partially passing through the exposure target zones, had no signs of damage and was not thrombosed. However, edema and partial destruction of the integumentary plate were found in the subendothelial zone increasing the risk of parietal thrombosis in the long-term period (Fig. 5).

No ventricular arrhythmias were recorded with the Reveal device in animals 2 and 4. Animal 4 died from asystole due to a complete AV block on day 21 of the follow-up.

Macroscopic examination confirmed high-precision radiation treatment with superior conformity.

Microscopic examination reported the presence of transmural lesions with necrosis and calcification, suggesting the production of homogeneous damage to the myocardium, followed by the formation of fibrosis.

The loop recorder reported that the radiation exposure at a dose of 35 Gy did not allow achieving stable electrophysiological effects, whereas 40-45 Gy doses produced AV blocks of varying severity.

DISCUSSION

The first report on the use of radiosurgery for treating arrhythmias in the experimental study was published by Sharma et al. in 2010. Sixteen mini pigs underwent radioblation with 25-80 Gy doses of exposure using the CyberKnife robotic stereotactic system (Accuray Inc., USA) with predetermined targets at the cavotricuspid isthmus, AV node, the left ventricular free wall, pulmonary veins, and left atrial appendage. Electrophysiological mapping was performed with the epi-endo approach using the navigation mapping system CARTO (Biosense Webster. USA) before and after the procedure. Two animals in the group

of AV node exposure underwent pacemaker implantation. The long-term follow-up period was 6 months. The bidirectional cavotricuspid block was seen at 40 Gy one month after exposure. Energy ranged from 38Gy to 80 Gy and pulmonary vein–left atrial junction and left atrial appendage showed marked voltage reduction to less than 0.05 according to EPI data at 35 days. AV block was produced in one animal with a radiation exposure dose of 70 Gy at 49 days (one of the two animals was excluded from the study due to the infection at the site of pacemaker implantation). No other organ damage was seen. Despite the exact underlying mechanism affecting tissues and promoting cell damage that had not been determined, it provoked cell apoptosis and immune-inflammatory processes. Histological examination reported vacuolization, eosinophilic infiltration, vasculitis, ischemic damage with the development of fibrosis, and subsequent calcification of the exposure substrate. The absence of the thermal damage suggested the preservation of the vascular endothelium preventing capillary and arterial bed thrombosis [9]. In our study, the alteration of electrophysiologic properties was achieved earlier at a lower exposure dose (transient AV block was produced at 40 Gy within 108 days. A dose of 45 Gy resulted in the animal death from sudden cardiac arrest (third-grade AV block) on day 21 day. Histological examination revealed similar changes in the affected areas as reported by Sharma et al.

M.Refaat et al. (2017) assessed the effectiveness of the stereotactic radioablation of the AV node with various loading doses from 35 Gy to 40 Gy in a porcine model. Alterations of electrophysiological properties were recorded by the implanted pacemaker. AV block was produced within 2 months after stereotactic radioablation. Biopsied tissues included AV node tissues and adjacent organs. The histological assessment reported severe architectural disruption with loss of the smooth cellular organization, in addition to cellular necrosis and extensive fibrin deposition in the area. Sections from the surrounding tissues, however, including the liver, esophagus, and lungs, showed normal architecture [10].

P.C.Zei et al. (2018) assessed the feasibility of performing stereotactic radioablation of the pulmonary vein orifices with treatment doses ranging from 15-35 Gy using a canine and swine model. Before and after stereotactic irradiation, electroanatomic mapping of spike activity zones in the pulmonary vein orifices was performed with Carto 3 (Biosence Webster, USA). Control electroanatomical mapping was performed at months 3 and 6 after the indexed procedures. The effectiveness of pulmonary vein isolation was 100% in the groups with exposure doses of 25 and 35 Gy, while reduced to 80% in the group with an exposure radiation dose of 20 Gy. Stereotactic radioablation was ineffective at a dose of 15 Gy [11].

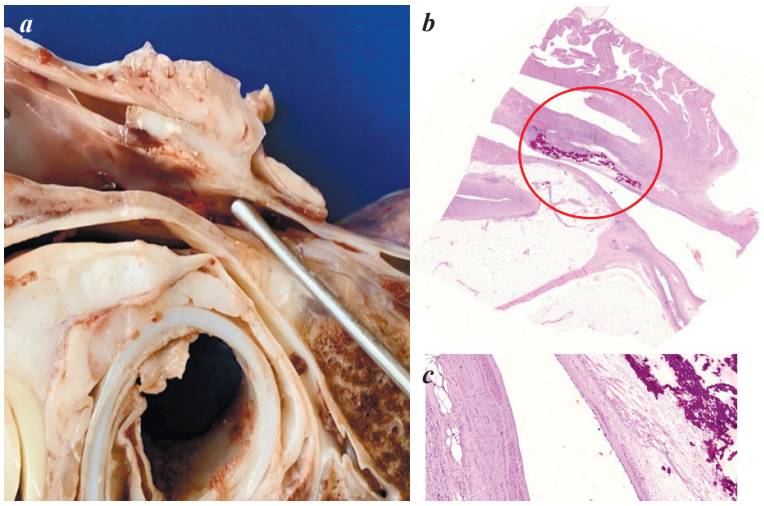

Fig. 4. a: A macroscopic sample of the pulmonary vein orifice after radioablation. b: A microscopic sample stained with hematoxylin-eosin. c: A magnified region marked with the red circle represents the affected area, stained with hematoxylin-eosin. Magnification: 40-200.

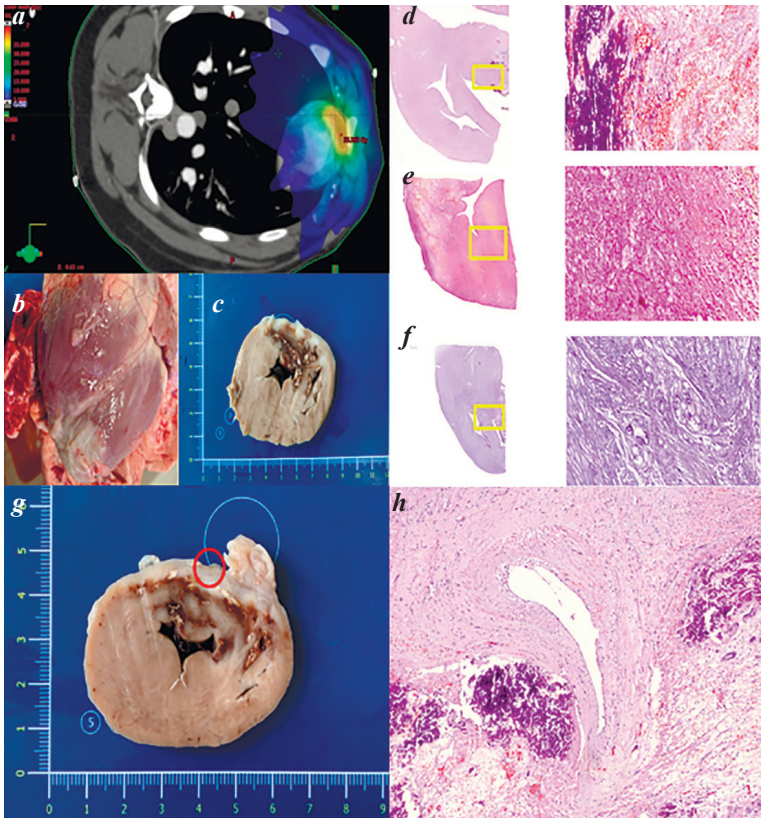

Fig. 5. Left upper images: a: The porcine left ventricular apex on contrast-enhanced CT scan in the treatment planning system. b: A macroscopic sample of the porcine heart. Fibrosis in the area of the apex. c: A macroscopic sample after radioablation. The modified area corresponds to the affected area. Right upper images: a microscopic sample of the left ventricular apex after radioablation. d: hematoxylin-eosin staining. e: van Gieson's staining. Magnification: 40-200. f: PAS staining. Bottom images: g: A macroscopic sample of the porcine left ventricle after radioablation. The red circle denotes the LAD projection. h: A microscopic sample of the left ventricular wall at the LAD level. Hematoxylin-eosin staining. Magnification: 200. LAD – left anterior descending artery.

Two studies conducted by research groups from Germany and the United States described similar effects. They used a porcine model (n = 17) and the same study design to assess the effectiveness of stereotactic radioablation using a linear carbon beam. I.Lehmann et al. (2016) divided 17 pigs into 4 groups according to the pretreatment zones. Group 1 underwent the radioabaltion of AV node with the application of 25, 40, and 55 Gy doses of (n = 8). Group 2 underwent irradiation of the right superior pulmonary vein with an exposure dose of 30-40 Gy (n = 3). Group 3 received irradiation of the left ventricular free wall with an exposure dose of 40 Gy (n = 3). Three animals were included in the control group. Irradiation was performed at the GSI Helmholtz Centre for Heavy Ion Research (Darmstadt, Germany) using a single horizontal beam line. The median follow-up was 20.3 weeks. Long-term results were assessed using positron emission tomography and electrophysiological studies at 1, 3, and 6 months after the indexed exposure. Histological assessment was performed to determine achieved effects. In two out of six animals, both irradiations with 55 and 40 Gy led to complete AV block. In the animal that developed complete AV block following 40 Gy, the block was not persistent until the end of follow-up at six months. Three animals were excluded from the study due to the infection at the site of pacemaker implantation. Researchers supposed that the obtained results were associated with the target contouring complexities (AV node). The pulmonary vein exposure resulted in a decrease in spike activity, including in the acute period at all doses delivered. When exposed to the left ventricular free wall, the accuracy of exposure was assessed using positron emission tomography and histological examination. Ablation lesions of the left ventricle were consistent with those of radiation exposure [12].

F.Rapp et al. focused on the pathology and pathomorphology of radiation injury. No radiation-induced effects on the esophagus, trachea, phrenic nerve, and skin were observed by histological and immunohistochemical examination suggesting the precision and selectivity of stereotactic radioablation. Coronary arteries in the treated area were not damaged and thrombosed. Hemorrhagic impregnation of the myocardium at the treated area with the migration of macrophages and sideroblasts was found. This finding positively correlated with radiation exposure. Immunohistochemical stainings were used to identify activated T-cells (CD45+), demonstrating that inflammatory reactions were mostly present in tissues irradiated with higher doses, and in regions where the tissue was visibly damaged. It is typical for the severity of fibrosis (the degree of collagen deposition) and myocytolysis [13].

Stereotactic radioablation has shown promising results in the treatment of tachyarrhythmias and may be considered as an alternative method for treating patients refractory to the catheter and medical treatment and those with contraindications to interventional procedures. Further development of this technology requires both experimental and extended clinical studies to accurately determine its effectiveness and safety. There are still gaps that should be addressed in further studies: the required therapeutic doses to produce functional and homogeneous damage to the myocardium at different localizations; ensuring the accuracy of irradiation concerning cardiorespiratory motion; possible reversibility of the produced myocardial injury; possible proarrhythmia of the treatment; the potential of producing a true (pathogenetic) antiarrhythmic effect.

LIMITATIONS

Our study had several limitations: a small number of animals included in the study, a significant difference in the anatomy of the heart and the location of adjacent organs from the human heart, although the pig heart is a generally accepted model for experimental research in cardiac surgery and arrhythmology, and delayed radiation side effects that are needed to be assessed when calculating the risks-benefit ratio. We did not use radiation doses over 50 Gy. Since the loop recorders were implanted immediately after the intervention, we could not exclude the presence of rhythm disturbances in animals before the procedure. We could evaluate the postmortem autopsy material, but could not monitor radioablation effects in the PV and ventricles using electrophysiological control in the mid- and long-term period. Electrophysiological control will be implemented in our future study.

Table 1.

Treatment planning parameters for all dose groups and targets

	№1	№2		№3	№4	
Date of experiment	7.12.2019	21.12.2019		18.01.2020	1.02.2020	
Gender	male	female		male	female	
Target zone	AV node	AV node	LV apex	PV	AV node	LVFW
Doze of radiation, Gy	35	40	35	30	45	40
GTV, cm3	2.4	3.7	2.4	5.6	7.9	1.9
GTV-PTV +margins, mm	3	3	3	3	2-3	5
PTV, cm3	7.9	9.6	7.5	15.2	20.9	13
Beam energies, MeV	6x	6x-FFF		6x-FFF	6x-FFF	
Beam intesity, me/min	600	1400		1400	1400	
Treatment time	23 min 44 sec	8 min 20 sec		6 min 16 sec	9 min 38 sec	

Note: AV node - atrioventricular node, PV - pulmonary veins, LV - left ventricle, GTV - gross target volume, PTV - planning target volume, FFF - flattening filter-free, LVFW - left ventricle free wall.

CONCLUSION

Each group demonstrated safe and precise radiation exposure. Histological examination confirmed alteration of electrophysiological properties produced at all applied radiation doses. We produced transient AV block at a dose of 40 Gy within 108 days of the follow-up and third-stage AV block at 45 Gy within 21 days using a 6 MeV photon beam. However, the dose of 35 Gy was not sufficient to promote electrophysiological changes when targeted at the AV node. Histological examination reported that ablation lesions were consistent with those of radiation exposure that was conformal and precise. Our experimental study along with other research groups has proven that stereotactic radioablation demonstrates high effectiveness and safety for producing persistent myocardial damage.

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CRYOBALLOON PULMONARY VEIN ISOLATION IN A PATIENT WITH PAROXYSMAL ATRIAL FIBRILLATION AFTER ATRIAL SEPTAL DEFECT CLOSURE USING THE "AMPLATZER" OCCLUDER

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A case report of cryoballoon ablation for atrial fibrillation in a patient after atrial septal defect closure is presented.

Key words: atrial septal defect; occlude; atrial fibrillation; cryoballoon isolation

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Atrial septal defect (ASD) accounts for 30-40% of all cases of congenital heart defects in adults. ASD is commonly accompanied by the volume overload of the right atrium (RA) and right ventricle (RV) promoting alterations in the left atrium (LA) electrophysiological properties. These alterations underlie the development of heart rhythm disturbances [1]. ASD is treated either by open-heart surgery or by an endovascular approach using various occluder devices. Atrial fibrillation (AF) occurs in 25% of patients with ASD before surgery and 60% of patients in the long-term period after surgery [2, 3]. Interventional treatment of AF is effective in patient's refractory to antiarrhythmic therapy [4]. Since interventional procedures require access to the LA, an implanted occluder limits the manipulations of operators during the intervention. We aim to report an effective and safe method of treating paroxysmal AF in the patient after endovascular ASD closure with the "Amplatzer" occluder.

A patient was admitted to the hospital with paroxysmal atrial fibrillation, a tachysystolic pattern (CHA_2DS_2-VASc score of 1, HAS-BLED score of 0). EHRA III. The patient had secondary ASD closed with the "Amplatzer" occluder in 2001. The patient had concomitant NYHA class 1 chronic heart failure. According to transthoracic echocardiography (TTE), the RA and LA were enlarged. There was no dislocation of the occluder and both discs were deployed. There were no blood shunts across the atrial septum. Multislice computed tomography (MSCT) of the LA and pulmonary veins (PV) reported an LA volume of 105 mL. The venous connection was without any alterations and the occluder was visualized along the entire atrial septum (Fig. 1).

To minimize the number of surgical accesses to the LA and considering the presence of previously implanted occluder, we performed cryoballoon PV isolation.

The Seldinger technique was employed to perform the venous access under local anesthesia in the cath-lab. A decapolar electrode was positioned through the left subclavian vein into the coronary sinus. A quadropolar electrode for temporary stimulation was positioned through the left femoral vein into the right ventricular cavity. The Swartz introducer sheath with a transseptal needle was passed through the right femoral vein into the RA cavity.

Under transesophageal echocardiography (TEE) (Fig. 2), the atrial septum and the implanted occluder were visualized. We evaluated the atrial septum and selected the free area of the posterior inferior margin of the occluder to perform the transseptal puncture under TEE monitoring.

After the access to the LA was achieved, we performed cryoballoon PV isolation according to the standard protocol. The Swartz introducer was replaced with a FlexCath Advance controlled delivery system, followed by positioning of the cryoballoon and multipolar circular electrode in each PV. Additionally, 3D reconstruction of the LA anatomy was performed using the Astrocard Navigation System (Russian Federation) to achieve better visualization of the PV and construct voltage maps before and after PV isolation. Before isolation, spike activity in each

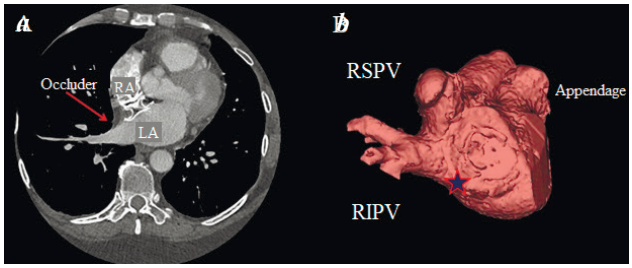

Fig.1. MSCT findings: a) Axial plane - left atrial level: the atrial septum with the implanted device; b) 3D reconstruction of the LA from side of the atrial septum, the occluder's shadow is visualized. The asterisk denotes the native area of the atrial septum suitable for the transseptal puncture. RA - right atrium, LA - left atrium, RSPV - right superior pulmonary vein, RIPV - right inferior pulmonary vein.

PV was assessed. After the balloon inflation, optimal PV occlusion was assessed by contrast injection. Cryoapplication time was 180 seconds and then was followed by cooling and deflation of the balloon. The minimum temperature in the upper left PV and the lower left PV was 55ºC and 42ºC, respectively. Before cryoablation of the right PVs, the quadropolar electrode was positioned in the superior vena cava to stimulate the phrenic nerve. The minimum temperature in the upper right PV and the lower right PV was -44 ºC and -50 ºC, respectively (Fig. 3). The PV was successfully isolated when the spike activity was verified by the multipolar circular electrode recordings. There were no technical difficulties associated with balloon positioning. The procedure lasted for 110 minutes and the fluoroscopy time was 20 minutes.

There were no complications in the postoperative period. The control TTE was performed after 2 hours of the intervention, and days 1 and 2 confirmed the absence of any devices damages and blood shunts across the atrial septum. The patient was discharged 2 days after the intervention.

DISCUSSION

There are few studies on treating AF in patients after endovascular ASD closure. Santangeli et al. [5] reported the outcomes of 39 patients with previously implanted occluders treated for AF. Of them, 33% of patients had paroxysmal AF, 51% - persistent AF, and 16% - long-term persistent AF. The transseptal puncture in the area of the native interatrial septum was performed in 35 patients. Four patients required the puncture to be performed through an occluder. When the introducer and the needle were positioned in the center of the occluder, the traction was performed. After contrast injection, the needle was replaced with a guide, and the balloon was delivered to the occluder. The puncture site was dilated and then the introducer and electrodes were inserted. Control TTE did not show any shunts across the atrial septum.

Sang et al. [6] presented a single-center experience of 16 catheter ablation procedures in patients with previously implanted occluder devices. Importantly, the operators did not use additional TEE or intracardiac ECHO control. To achieve better visualization before the transseptal puncture, the contrast was injected to evaluate the atrial septum and the implantation site of the occluder relative to the great arteries and heart valves in different planes. If the transseptal puncture in the native atrial septum area failed, the central zone of the occluder was punctured. The balloon was used to pass the introducer into the LA. Li et al. [7] reported 9 cases of catheter ablation after endovascular ASD closure. Eight patients underwent the transseptal puncture under X-ray control and 1 patient underwent intraoperative TEE. The operators performed the access to the LA along the posterior inferior margin of the occluder; in case of unsuccessful attempts, the transseptal puncture was performed through the occluder. But it increased both, the duration of fluoroscopy and the time of procedure itself. Revishvili et al. [8] reported a clinical case of a transseptal puncture approach in the occluder-free zone of the atrial septum in a patient after endovascular ASD closure. The transseptal puncture was performed under intracardiac ECHO control.

The outcomes of catheter ablations in patients after endovascular ASD closure and the rate of postoperative

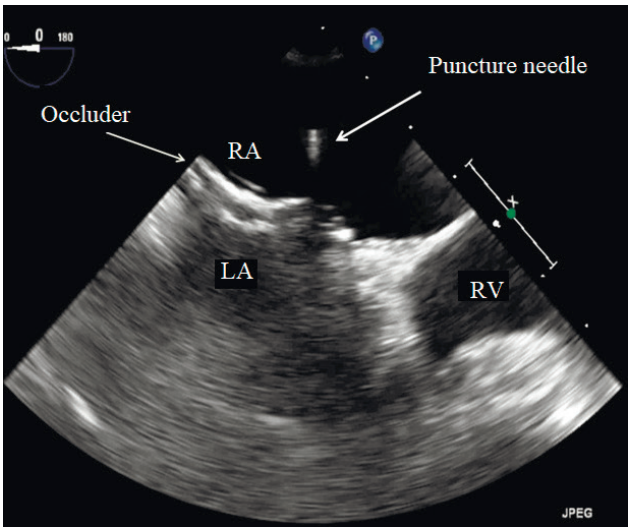

Fig. 2. The transseptal puncture under TEE monitoring: the heart chambers, the implanted occluder, the atrial septum, the puncture needle is visualized. TEE - transesophageal echocardiography, RA - right atrium, LA - left atrium, RV - right ventricle

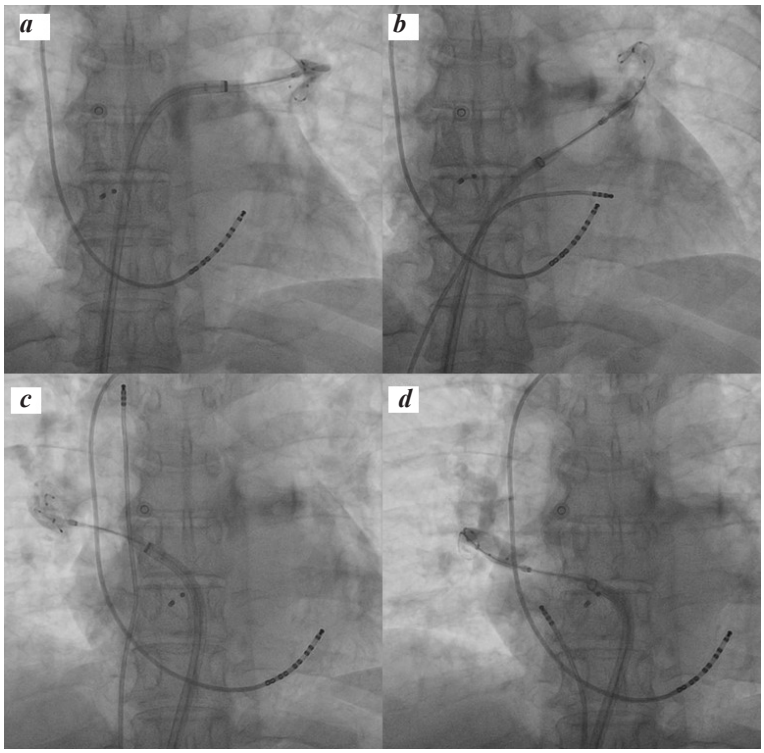

Fig. 3. a) Cryoballoon ablation of the LSPV; b) Cryoballoon ablation of the LIPV; c) Cryoballoon ablation of the RSPV; d) Cryoballoon ablation of the RIPV. A frontal plane. The balloon in the PV and the shadow of the occluder are visualized. LSPV - left superior pulmonary vein, LIPV - left inferior pulmonary vein, RSPV - right superior pulmonary vein, RIPV - right inferior pulmonary vein

complications did not differ from those reported for patients with an intact atrial septum.

CONCLUSION

Cryoballoon PV isolation can be safely performed in patients with previously implanted occluder devices in the atrial septum. The site of access in the LA does not complicate the manipulation of instruments in the LA and does not affect the positioning of the cryoballoon in the LA. Preoperative MSCT of the LA allows evaluating the size and position of the occluder in the atrial septum. Intraoperative TEE allows selecting a safe, occluder-free zone to perform the transseptal puncture.

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PROCEDURE TECHNIQUE AND A RARE INTRAPROCEDURAL COMPLICATION DURING PERMANENT HIS BUNDLE PACING

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A case of successful endocardial lead implantation into the His bundle position is presented. Procedure technique and transient atrioventricular block during implantation are described.

Key words: cardiac pacing; atrial fibrillation; heart failure; atrioventricular block; His bundle pacing; complication

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His-bundle pacing (HBP) is a new method for bradyarrhythmia management. Data in favor of using HPB with pacemaker [1] and cardiac resynchronization device [2, 3] is continuously rising. Planned AV nodal ablation for rate control in atrial tachyarrhythmias with fast AV conduction is considered as an indication for HBP since 2019 [4-6]. The risk of intraprocedural and postprocedural complications (lead dislodgement, pacing threshold rise, exit block) is an important factor precluding many electrophysiologists from the wide use of permanent HBP.

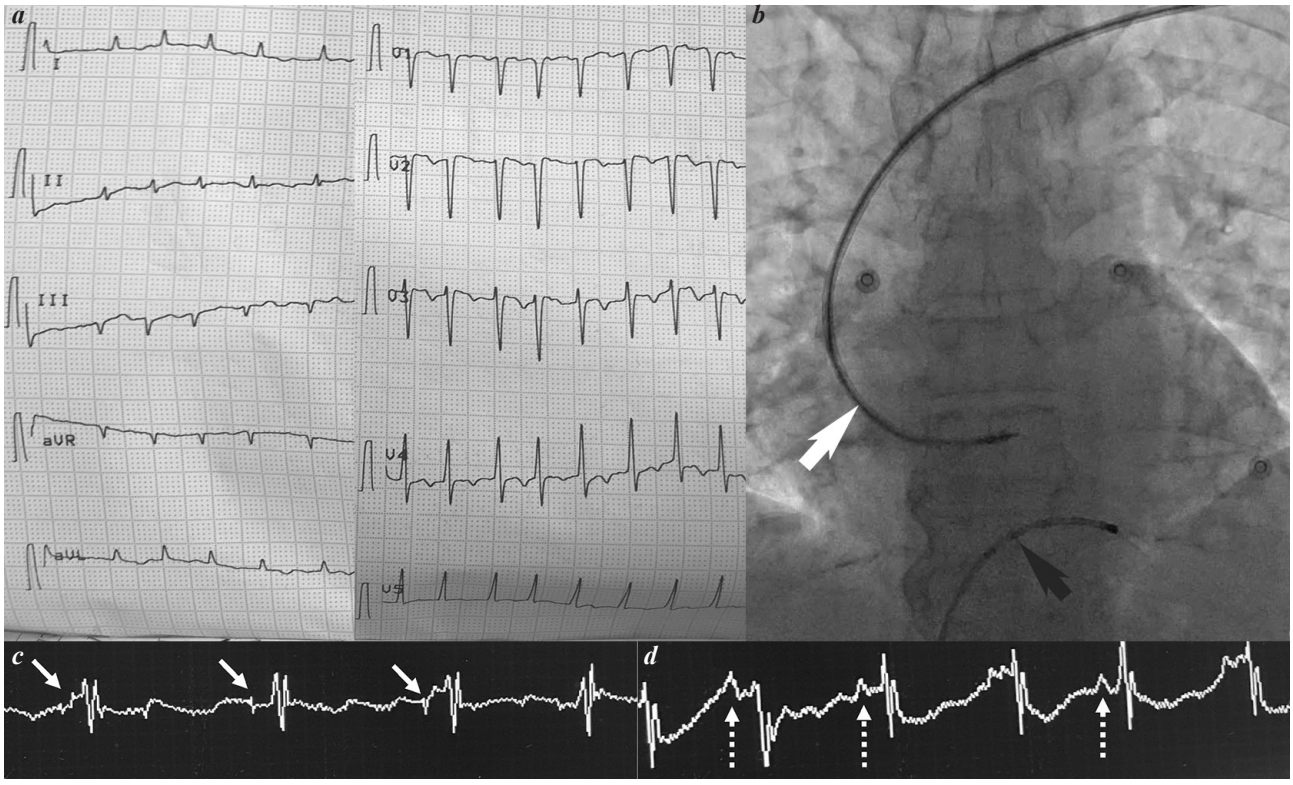

Fig. 1. a. ECG at the admission, 25 mm/s. Atrial fibrillation with the fast ventricular response, HR 168 bpm, QRS 80 ms. b. Delivery tool (white arrow) is positioned in the upper part of the triangle of Koch to register the His bundle electrogram and subsequent lead fixation (The pacing lead is inside the sheath). A steerable diagnostic catheter (grey arrow) is positioned in the right ventricle for the safety pacing in case of AV conduction disturbances during the His bundle lead fixation. c, d: Local electrogram from the His bundle pacing lead. C. His bundle EGM before the lead fixation - low amplitude fibrillatory atrial activity, irregular ventricular spikes with preceding narrow His bundle spikes (white arrows) D. His bundle EGM after the lead fixation. His bundle spikes (dotted arrows) morphology changed, current of injury is visible.

We present a rare case of transitional AV conduction impairment during HBP lead fixation in a patient with atrial fibrillation and tachy-induced cardiomyopathy.

A fifty-four-year-old male patient was hospitalized due to chronic heart failure. Atrial fibrillation of unknown duration and high ventricular rate of 168 bpm was diagnosed for the first time (Fig.1, A). Oral anticoagulation (rivaroxaban 20 mg daily), diuretic (furosemide) and rate-control (digoxin 250 μkg daily, metoprolol 50 mg daily) therapy was prescribed. Echocardiography revealed diffuse left ventricular (LV) contractility reduction with LV ejection fraction (EF) of 20%. The NT-proBNP level was increased to 3085 ng/ml.

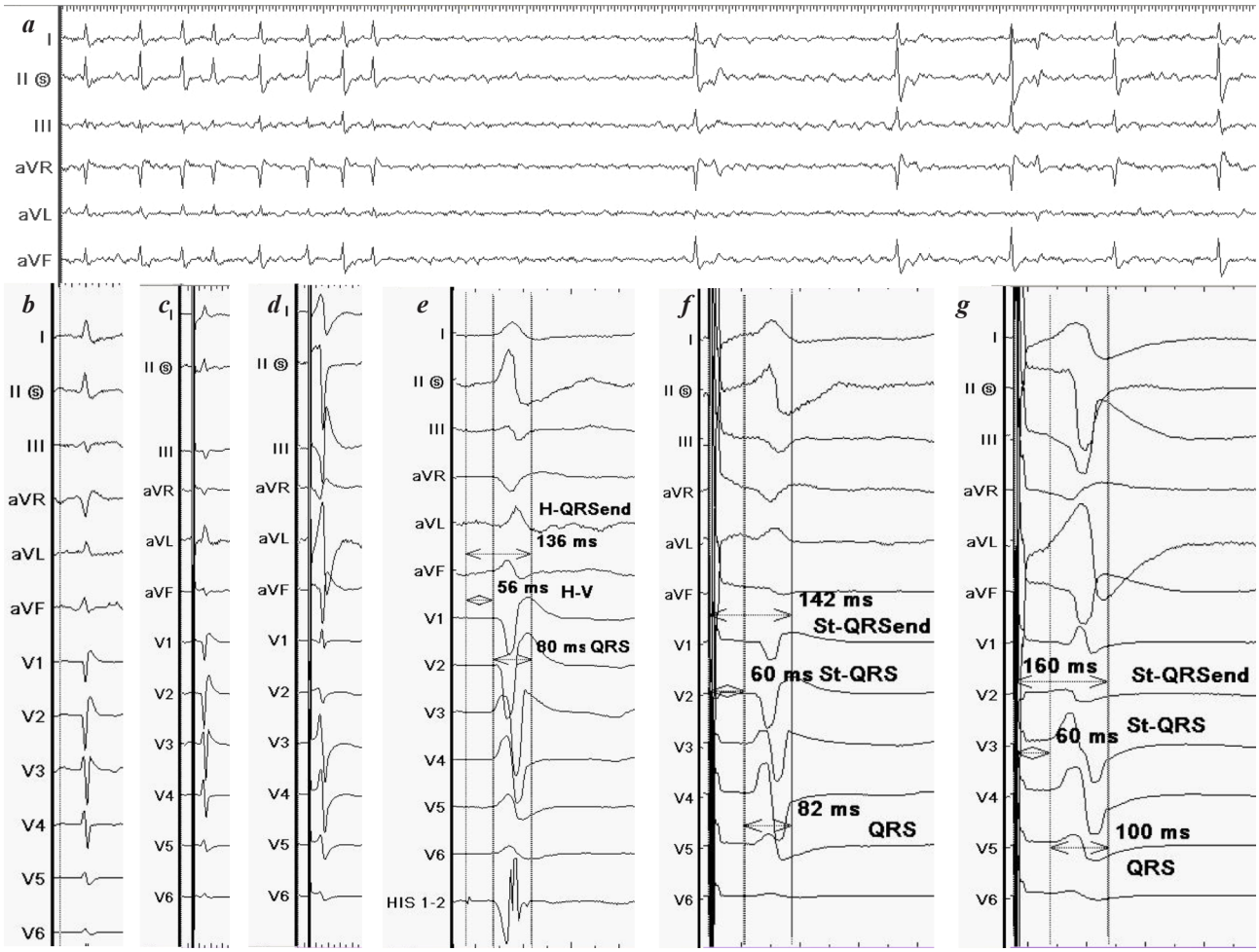

Fig. 2. a. ECG during the His bundle pacing lead fixation, 25 mm/s. Atrial fibrillation with HR 120-160 bpm is followed by 4,7 s pause and then restoration of AV conduction with HR 40-50 bpm. b-d: 12-lead ECG (25 mm/s) demonstrates similar QRS morphologies (RBBB) during spontaneous rhythm (b) and selective HBP (c). During the non-selective HBP (after the lead fixation) the RBBB is resolved but the axis becomes vertical (see the text). e-g: 12-lead ECG (100 mm/s) demonstrates similar duration of intervals H-V (56 мс)/H-QRSend (136 мс) during spontaneous conduction (e) и St-QRS (60 мс)/St-QRSend (142 мс) during selective HBP (f) before the lead fixation. QRS width (80 ms) is also similar. With nonselective HBP after the lead fixation (f), there is some change in the QRS morphology (incomplete RBBB resolution, left axis deviation) and QRS width (100 ms) and St-QRSend interval (160 ms) rise.

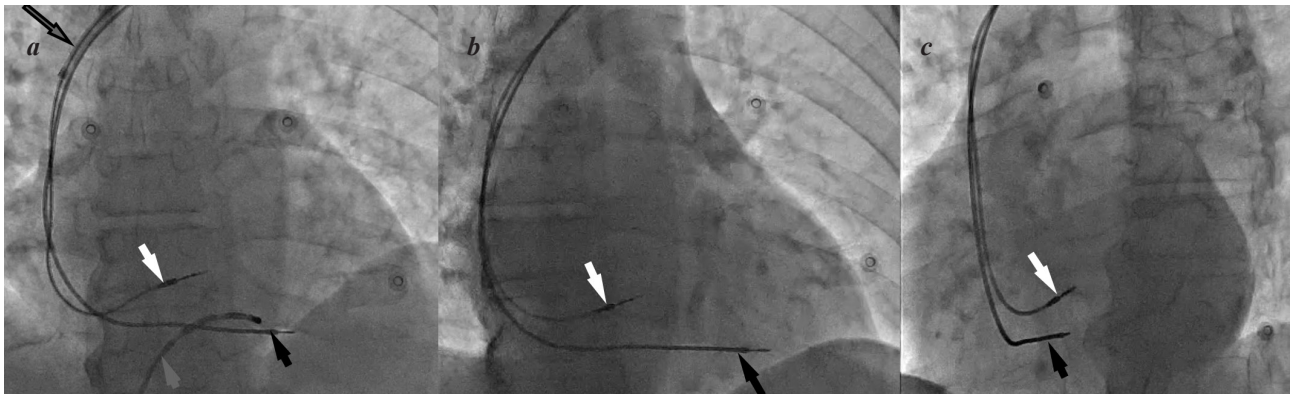

Fig. 3. Final fluoroscopy of pacing leads in the AP (A), RAO (B) and LAO (C) views. Pacing leads in the His bundle (white arrow) and the interventricular septum (black arrow), decapolar diagnostic catheter (grey arrow) and delivery sheath (figured arrow) are marked.

The attempts to lower the heart rate were ineffective due to the hypotension which became more pronounced with metoprolol doses higher than 50 mg daily. The rhythm-control strategy was not applicable due to the presence of mobile LV thrombus revealed by transthoracic echocardiography. Severe heart failure status and several prothrombotic factors (low LV EF, uncontrolled high ventricular rate) did not allow us to wait for the spontaneous lysis of the thrombus on the anticoagulant therapy. Due to the inability to effectively control heart rate or rhythm, pacemaker implantation and subsequent AV nodal ablation were decided to be a single option. As the right ventricle pacing could lead to the additional LV EF reduction and cardiac resynchronization therapy was not technically applicable, we decided to perform permanent His-bundle pacing.

Procedural data

Two endocardial leads (active-fixation CaptureFix Novus 5076 58 cm (Medtronic, USA) and passive-fixation ELBI-211 58 cm (ElestimKardio, Russia) were positioned through the left axillary vein to the right atrium. ELBI-211 lead was introduced to the right ventricle and fixed at the apical trabeculated part of the interventricular septum. The right femoral vein was canulated by the 8F hemostatic introducer and decapolar steerable diagnostic catheter CS EZSteer D-F (Biosense Webster, USA) used to map interatrial septum, Koch's triangle, and His bundle area. Then CaptureFix Novus lead was positioned in the upper part of the Koch's triangle using AcuityPro CS-EH-STR-curve (Boston Scientific, USA) (Fig. 1, B). His bundle electrogram was registered (Fig. 1, C) and selective HBP was performed with a pacing threshold of 1,7V@0,4ms (Fig. 2, C and F). His bundle injury-current was revealed during lead fixation (Fig. 1, D) [1,7] and the pacing threshold was not changed after the fixation. Before the splitting-out of the delivery sheath, all entire His pacing lead was screwed in clockwise for more durable fixation. During this manipulation, the intermittent AV block with 5-second pause and subsequent ventricular rate deceleration to 50-80 bpm was documented (Fig. 2, A). This lower heart rate stayed until the end of the procedure despite the bolus injection of 1 mg of atropine and 8 mg of dexamethasone. Effective non-selective HBP was performed after the delivery sheath removal (Fig. 2, D and G). Right ventricular myocardial and His bundle pacing thresholds did not differ and therefore the capture was lost simultaneously during threshold testing without any change in QRS morphology while the pacing amplitude was decreased. Interestingly, the St-QRSend interval duration during non-selective HBP was slightly longer than H-QRSend during the spontaneous conduction (Fig. 2, E-G). In our opinion, this phenomenon could be explained by the partial capture of His bundle fascicles responsible for the conduction to the right and left posterior bundle branches, causing the morphology of RBBB and left axis deviation. Both leads were fixed and connected to the 460 DR (ElestimKardio, Russia) dual-chamber pacemaker. The HBP lead was connected to the atrial channel. The device was programmed to DVI mode with a 60 bpm lower rate. Leads' position in the AP, LAO, and RAO fluoroscopy views is presented in Fig.3.

Postprocedural follow-up. Repeat Holter monitoring after the procedure revealed the decrease in mean daily heart rate to 80 bpm (from 40 to 100 bpm) despite the withdrawn rate-decelerating medications. Echocardiography before the discharge revealed the increase in LV EF to 25%. LV thrombosis had been also resolved probably due to the anticoagulant therapy. Repeat hospitalization was planned to perform electrical cardioversion but ambulatory ECG revealed a sinus rhythm of 72 bpm and normal AV conduction (PQ 150 ms). Taking into account the absence of implanted atrial lead, we decide not to ablate the AV node. Leads' parameters are presented in Table 1. Unfortunately, the patient was lost for follow up and catheter ablation to prevent AF recurrence was not performed.

Table 1.

His-pacing lead parameters, measured during and 1 months after the implantation.

Parameters		Intraprocedural	1 months after
His bundle lead	R-wave	3.8 mV	5.6 mV
	Impedance	425 Ohm	520 Ohm
	Threshold	1 V @ 0.4 ms	1.5 V @ 0.4 ms
Right ventricular lead	R-wave	12 mV	9,6 mV
	Impedance	550 Ohm	600 Ohm
	Threshold	0,3 V @ 0.4 ms	0,5 V @ 0.4 ms

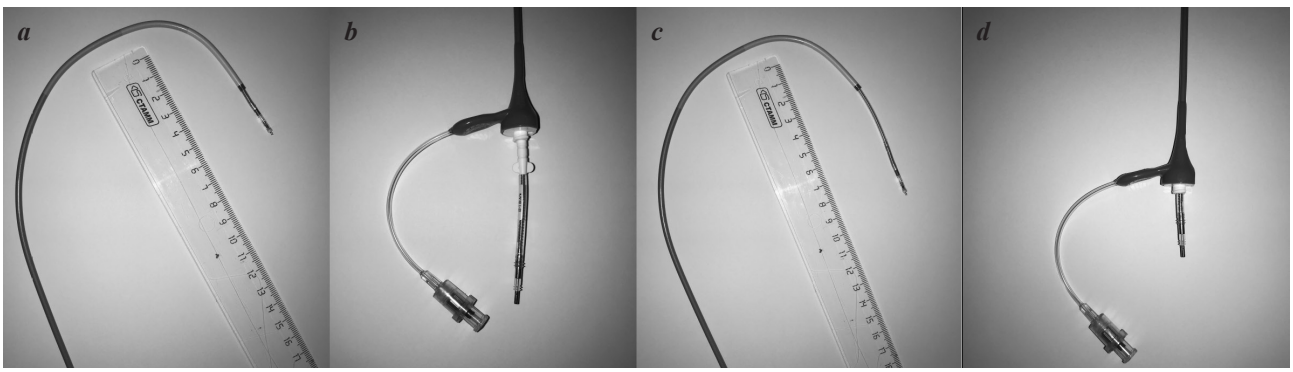

Fig. 4. The lengths of the non-steerable delivery sheath and standard active fixation endocardial pacing lead CaptureFix Novus 5076 58 cm (Medtronic). A and B. If the pacing lead is introduced with fixing cuff, its distal tip is out of the delivery tool by 3 cm. It makes pacing lead dislodgement the intracardiac manipulations and delivery sheath cutting out more probable. C and D. If the pacing lead is introduced without fixing the cuff, its distal tip is out of the delivery tool by 6 cm. It makes pacing lead dislodgement the intracardiac manipulations and delivery sheath cutting out less probable.

DISCUSSION

This case is interesting from several points of view. Firstly, this case is one of the first description conduction system pacing with standard endocardial active-fixation lead and unspecialized delivery tool. Using the lead with retractable screw and non-steerable delivery sheath, which is routinely used for CS catheterization, is not widely used. There are two techniques to deploy the pacing lead to the His bundle: through the delivery sheath and over the stylet. The last one has demonstrated relatively low effectiveness [8] but has low costs. The most widely used variant of the first approach is "classical" 3830 lead implantation using non-steerable C315 (Medtronic, USA) or steerable C304 (Medtronic, USA) delivery tools. Nonetheless, the use of unspecified delivery tools and standard endocardial leads is also possible [9]. In our case, we used endocardial active-fixation lead CapsureFix Novus 5076 58 cm (Medtronic, USA) and non-steerable delivery sheath AcuityPro CS-EH-STR-curve (Boston Scientific, USA). Lead and delivery tool lengths should be considered during the preimplantation setup. Pacing leads of 52 cm length are too short to be used. Removing the fixing cuff is useful before implantation of 58 cm leads allows more deep lead insertion into the delivery sheath and slack formation in the right atrium before slitting out the sheath (Fig. 4).

The second interesting moment is the AV nodal conduction impairment during the procedure. In our case, AV nodal conduction deficit persisted until the discharge and caused a withdrawal of beta-blockers and digoxin. The AV block could be caused by the AV nodal artery damage, or by the mechanical injury of the His bundle (or AV nodal) tissue, which is diagnosed in 1,1% of conduction system pacing cases [10,11]. Heart wall deformation in the Koch's triangle during the additional lead rotation could also be the reason for AV block. In such cases AV conduction impairment should be intermittent and resolve within several days after the injury. We consider this mode of AV conduction impairment the most probable.

Of complications, which are traditionally mentioned after HBP, the most prevalent are lead dislodgement (0,6%) and threshold rise (2,1%) [8]. Infection, exit block, and detection problems are rarer. It is known from private communication with the opinion leader in HBP that AV conduction impairment during the lead fixation is sometimes happening (with no exact prevalence), but is usually intermittent, resolves by the end of the procedure, and is not affect the final complication statistics. Nonetheless, it is considered to use the additional temporary lead in the RV during the first procedures of HBP [1,12].

LIMITATIONS

The alternative mechanism of His bundle electrogram changes after the lead fixation is the far-field potential registration. We could not differentiate those two options (injury-current and far-field electrogram) using the data we had and mentioned the most probable in our opinion.

CONCLUSION

His bundle pacing is a perspective technique to treat patients with AF and uncontrolled ventricular rate before the AV nodal ablation. HBP allows physiological synchronous excitation of ventricular myocardium over the conduction system. Intermittent AV nodal conduction impairment is a rare but possible intraprocedural complication of lead implantation into to the His bundle. It doesn't need any additional interventions but follow up.

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