

ABSTRACT

of the dissertation work of Bakytzhanuly Abay for the degree of Doctor of Philosophy (PhD) in the 6D110100 – "Medicine" specialty entitled: "Improving the tactics of managing atypical atrial flutter using innovative technologies"

The relevance of research

Currently, atrial fibrillation (AF) is a very common arrhythmia. Around the world there are about 2 million people with AF. In relation to AF, many studies have been carried out, algorithms for diagnosis and treatment have been developed [Bun S.S. et al. 2015; Bochoeyer A. et al., 2003]. In recent years, special attention has been focused on atypical atrial flutter (AAFL), which remains complex and clinically significant heart rhythm disorder сердца [Ardashev A.V., 2001; Pokushalov E.A., 2004]. Due to the insufficiently widespread use of AAFL, the tactics of managing such patients have not been given due attention; the tactics of treating AAFL remain undifferentiated from the tactics of treating AF.

For many years there has been a scientific debate about whether atrial flutter (AFL) is focal or re-entry tachycardia [Rosenblueth A. et al., 1953; Olgin J.E. et al., 1995; Chen J. Et al., 2003]. The use of new computerized systems made it possible to determine that typical atrial flutter (TAFL) was re-entry tachycardia, the depolarization of which occurred in the right atrium (RA) both clockwise and counterclockwise. At the same time, the cavotricuspid isthmus (CTI) was necessarily involved in the re-entry circle, which makes it possible to eliminate the re-entry circulation in TAFL by catheter ablation of CTI, which is of undoubted practical significance.

With the development of cardiac surgery and an increase in the volume of surgical interventions on the heart, in particular operations for congenital and valvular heart diseases, the number of substrates for the development of AAFL has also increased. Often an atriotomy, a surgical "Maze" procedure, or monopolar radiofrequency isolation of the pulmonary vein ostia is required. Such AAFL after the above mentioned interventions on the heart is called incisional AFL, since the arrhythmia substrate is a scar in the myocardium [Ouyang F. et al., 2002; Markowitz S.M. et al., 2002; Akar J.K. et al., 2007]. Patients after surgical correction of heart defects are considered unpromising in terms of radiofrequency ablation (RFA) of AAFL, not only because of the high risk of AF in the postoperative period, but also because of the difficulties of conducting the RFA technique itself. In this category of patients, as a rule, there are several circles of re-entry, i.e. in addition to the most common TAFL, there is atypical incisional and atypical left AFL. Clinically, patients with AAFL are qualitatively different, more complex and severe patients. Mapping and ablation of these complex cardiac arrhythmias is a difficult task for every arrhythmologist, electrophysiologist. At the same time, this category of patients often remains without attention: in particular, in Kazakhstan due to the lack of approved algorithms and clinical protocols for the diagnosis and treatment of such patients.

Often, with long-term persistence of AAFL, it is not possible to maintain sinus rhythm only with the help of drug treatment, and unfortunately, a heart rate control strategy is chosen, drug-induced (bringing heart contractions to a normosystolic variant) or implantation of a pacemaker (PM) with the creation of an artificial atrioventricular blockade. However, this approach to the treatment of this category of patients is not justified in this situation and is practically ineffective. With the development of new technologies in medicine, it is possible to avoid artificial atrioventricular blockade.

In our practice, we have made the most of the possibilities of radical elimination of arrhythmia using catheter techniques, which allows us to restore and maintain sinus rhythm in a large category of patients. Modern RFA techniques make it possible to effectively diagnose, localize, and interrupt the re-entry cycle [Brugada J. et al., 2019]. Thus, the use of a combination of an activation, bipolar, and “stimulation” map [Hindricks G. et al., 2020] makes it possible to understand the mechanism of re-entry tachycardia and clarify the localization of pathological activity and perform the necessary ablation in this area. The combination of AAFL RFA procedure and drug therapy (hybrid therapy) allows most patients to achieve restoration of sinus rhythm.

Having sufficient experience in managing such patients, we conducted research on the scientific and practical substantiation of the above methods and optimization of the tactics of treatment and management of patients with AAFL in patients after cardiac surgery and catheter ablations.

Purpose of the study

Evaluation of improved management of patients with atypical atrial flutter after cardiac surgery and catheter ablation using innovative technologies.

Research objectives

1. To assess the clinical and hemodynamic features of the course and electrophysiological characteristics in patients with atypical atrial flutter after cardiac surgery and catheter ablations.

2. To determine the clinical and electrophysiological predictors of the development of atypical atrial flutter and evaluate the role of the cardiomechanical marker NT-proBNP in patients with atypical atrial flutter after cardiac surgery and catheter ablations.

3. To substantiate the use of a new module of the Carto3-ablation index navigation system for radiofrequency ablation and intracardiac echocardiography during transseptal puncture in patients with atypical atrial flutter after cardiac surgery and catheter ablation.

4. To develop tactics for managing patients with atypical atrial flutter after cardiac surgery and catheter ablations.

Object of study

Prospective group (107 patients) and retrospective group (101 patients) with atrial flutter after cardiac surgery and catheter ablation.

Materials of two data were analyzed: retrospective (non-AI group), 101 cases of RFA using the Carto3 navigation system (Biosense Webster, Diamond Bar, CA) without the ablation index (AI) function in the period from January 2015 to December 2017; prospective (AI group) - 107 cases of RFA using Carto3 navigation system with AI function between January 2018 and December 2020.

Subject of study

Adult patients (18 years and older, regardless of gender) with various types of AFL after previous cardiac surgery and catheter ablation.

Criteria for inclusion of patients in the study:

- Patients over 18 years of age;
- Established diagnosis of atypical and typical AFL;
- Signed informed consent of patients for EPS, RFA;

Criteria for exclusion of patients from the study group:

- Patients under 18 years of age;
- Decompensation of concomitant diseases;
- Thrombosis of the left atrial appendage, left atrial thrombosis, left atrial appendage stump thrombosis;
- Mechanical mitral valve in left AFL;
- Refusal of the patient from EFI, RFA;

Research methods

1. General clinical examination: collection of complaints, anamnesis of the disease and life, an objective examination of organs and systems.
2. Laboratory research methods:
 - general blood analysis;
 - a biochemical blood test - a study of the level of glucose, electrolyte (potassium, sodium, calcium);
 - analysis of the NT-proBNP cardiomarker;
 - coagulogram (prothrombin time, prothrombin index, international normalized ratio, activated partial thromboplastin time, fibrinogen);
 - thyroid hormones (free triiodothyronine, free thyroxine), thyroid-stimulating hormone, antibodies to thyroperoxidase;
3. Instrumental examination methods:
 - twelve-channel resting electrocardiography;
 - Holter ECG monitoring;
 - transthoracic echocardiography;
 - transesophageal echocardiography;
 - fibrogastroduodenoscopy;
 - Doppler ultrasound of the peripheral vessels of the lower extremities (triplex scanning);
4. Electrophysiological study of the heart.
5. Statistical method for processing the obtained data.

Scientific novelty of the research

1. The electrophysiological characteristics of atypical atrial flutter in patients after cardiac surgery and interventional interventions have been studied for the first time in the Republic of Kazakhstan.
2. Module of navigation system Carto3 - Ablation Index in ablation of atypical atrial flutter in patients after cardiac surgery and catheter ablation was adapted and introduced.
3. High levels of the cardiac marker NT-proBNP are a prognostic marker for the development of atrial arrhythmias and subsequent recurrences of atypical atrial flutter in patients after cardiac surgery and catheter ablation.
4. High correlation positive relationship between the level of cardiac marker NT-proBNP and left atrial pressure index; and weak reliable positive relationship with RASDL index in patients with atypical atrial flutter after cardiac surgery and catheter ablation;

Practical Significance

In patients with atypical atrial flutter after cardiac surgery and catheter ablation it is necessary to consider that this cohort of patients is burdened with background diseases and the presence of myocardial scarring and belongs to a more complex category of patients with arrhythmias.

In case of increase of cardiac marker NT-proBNP quantity more than 125 pg/ml it is recommended to manage patient with atypical atrial flutter according to the European Guidelines for the Diagnostics and Treatment of Acute and Chronic Heart Failure.

Conducting early RFA in patients with atypical atrial flutter after cardiac surgery and interventional interventions reduces the risks of recurrence of atrial flutter, development of atrial fibrillation and heart failure.

The main statements made for the defense

1. The study included 208 patients with diagnosed atrial flutter. Atypical atrial flutter is a frequent supraventricular arrhythmia in patients after cardiac surgery and catheter ablation (73%). Moreover, atypical atrial flutter, according to our study, is 77.6% of 107 patients in the group using AI and 68.3% of 101 patients in the group without AI.
2. The use of Carto3- ablation Index module in RFA for atypical atrial flutter is effective in the early and distant postoperative period.
3. Use of intracardiac Echo during catheter ablation in complicated atrial rhythm disturbances allows to reduce radiation exposure, fluoroscopy time and exclude use of contrast agent, increases safety of RFA and prevents development of contrast-induced nephropathy.
4. Proved prognostic significance of risk of atypical atrial flutter is associated with high indices of cardiac marker NT-proBNP and increased left atrial pressure.

Conclusions

1. In patients after cardiac surgery and catheter ablations in the first 8-12 months the development of TP is observed. The incidence of TAFL in the AI group (22.4%) and in the Non-AI group (31.7%) is less than the incidence of AAFL in these groups (77.6% and 68.3%, $p=0.001$).
2. Cardiac surgery with atriotomy was the leading cause of AAFL in AI and Non-AI groups (58.9% and 45.5, $p=0.054$) and caused perimetric and atriotomy reentry tachycardia in 47% and 41%. Two or more reentry tachycardias were observed in 21% of right atria and 19% of left atria.
3. We found a strong direct correlation between the amount of cardiac marker NT-proBNP and LA pressure ($r=0.761$, $p<0.001$), as well as a positive significant relationship of these parameters with increasing LA diameter ($r=0.512$, $p=0.0001$) and positive significant relationship of LA diameter with ePASP ($r=0.314$, $p=0.011$).
4. The number of atrial scar zones and mechanisms of macro reentry tachycardia, increased NT-proBNP level over 125 pg/ml in combination with increased LA pressure over 15 mmHg and increased ePASP over 28 mmHg are prognostically significant signs of atrial arrhythmias after cardiac surgery and catheter ablation. Elevation of NT-proBNP level more than 125 pg/ml is a marker of HF development in patients after cardiac surgery and catheter ablations.
5. Use of intracardiac Echo allows to reduce radiation load, fluoroscopy time and to exclude use of contrast agent that increases safety of RFA and prevents development of contrast-induced nephropathy.
6. AAFL RFA using the new Carto3- ablation index module in patients after cardiac surgery and catheter ablation reduces the risk of recurrence and prolongs AAFL -free survival ($p=0.001$).
7. An algorithm for management tactics of patients with AAFL and TAFL after cardiac surgery and catheter ablation has been developed and implemented into clinical practice.

Practical recommendations

1. Patients after cardiac surgery and catheter ablation should undergo Holter ECG and Echo in 1, 3, 6, 9, 12 months. Thereafter, if there are no cardiac rhythm abnormalities, these examinations should be performed once a year.
2. In patients after cardiac surgery and catheter ablation with sustained (more than 30 seconds) episodes of atrial arrhythmias electrophysiological examination of the heart and radiofrequency ablation should be performed preferably using 3D navigation systems.
3. Conservative therapy is recommended for unstable (less than 30 seconds) atrial arrhythmias. If conservative therapy has no effect, cardiac electrophysiological study and radiofrequency ablation are indicated, preferably using 3D navigation systems.
4. In complex types of heart rhythm disturbances such as atypical atrial flutter with several types of mechanisms and/or a complicated surgical history, use

diagnostic high-density mapping catheters (PentaRay, HD GRID) for more detailed and rapid diagnosis and effective catheter ablation.

5. In atypical left atrial flutter in patients with a poor surgical history and comorbidity, the use of intracardiac Echo is preferable to reduce radiation exposure, fluoroscopy time, increase procedure safety and prevent the development of contrast-induced nephropathy.

Approbation of the thesis

The main results of the study and provisions of the dissertation were reported:

- The 10th International Congress "Cardiology at the Crossroads of Sciences" together with the XIV International Symposium on Echocardiography and Vascular Ultrasound XXVI Annual Scientific and Practical Conference "Topical Issues of Cardiology" (Tyumen, 2019-22-24 May);

- 14th International Congress "Cardiostim" (St. Petersburg, 2020-27-29 February);

- International scientific-practical conference of young scientists and students devoted to 30th anniversary of Independence of the Republic of Kazakhstan (Nur-Sultan: Astana Medical University, 2021 - December 9-10)

- International Congress "EHRA 2022" (Copenhagen, 2022 - April 2-6);

Publications on the topic of the dissertation

According to the results of the thesis research, 25 printed papers were published, including 5 articles in the journals recommended by the Committee for the Control of Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan, 4 articles in peer-reviewed international scientific journals: Journal of arrhythmia Journal (impact factor 2.4, Q2), indexed in Web of Science and Scopus database (percentile 47%); Pacing and clinical electrophysiology (impact factor 2.7, Q2), indexed in Web of Science and Scopus database (percentile 55%); and 2 articles in the journal "Georgian Medical News," which was included in the Scopus database at the time the article was published (impact factor 0.3, percentile 26%). Published 16 theses in the materials of national and international scientific conferences, including foreign countries (Azerbaijan, Europe, Russia, Uzbekistan, Tajikistan, Kazakhstan).

Three certificates on inclusion of information in the state register of rights to objects protected by copyright, three notifications of a positive result of formal examination of the "National Institute of Intellectual Property" of the Ministry of Justice of Kazakhstan patents for invention, five certificates of introduction in the department of interventional arrhythmology JSC "National Research Cardiosurgical Center" were received.

Dissertant's personal contribution

The work was performed in accordance with the direction of science development in the field of "Life and Health Sciences" approved by the Higher

Scientific and Technical Commission under the Government of the Republic of Kazakhstan. The dissertant independently conducted recruitment of research participants, collection of material, performed clinical examination of patients with atrial flutter, independently performed radiofrequency ablation of typical and atypical atrial flutter using new technologies. Dissertant independently analyzed and summarized the results of the study, conducted statistical data processing, wrote articles under the supervision of the supervisor and consultants, independently translated the articles into English.

Structure and volume of the thesis.

The dissertation is presented on 114 pages of computer text; it consists of an introduction, review of literature sources, the main part, where the obtained results are presented and discussed, a conclusion, practical recommendations, a list of references, and appendices. The material is presented in Russian, illustrated with 47 figures and contains 11 tables. The list of the analyzed literature consists of 179 sources.