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ENDOVASCULAR OCCLUSION OF THE PATENT FORAMEN OVALE AS PART OF ANTIARRHYTHMIC TREATMENT OF A PATIENT WITH PERSISTENT ATRIAL FIBRILLATION (CASE REPORT)

Below is a case report of treatment of a patient with persistent tachysystolic atrial fibrillation (AF), chronic heart failure (CHF) with a moderately reduced left ventricular ejection fraction (EF) and patent foramen ovale (PFO) with an atrial septal aneurysm. A 58-year-old man (with body mass index of 27.8 kg/m2) with tachysystolic persistent AF (duration 3 months) was hospitalized due to an increase in CHF symptoms (CHF functional class according to NYHA is II-III). The patient had been constantly receiving therapy in accordance with current recommendations (angiotensin receptor blockers, diuretics, beta-blockers, amiodorone and rivaroxaban). Transthoracic echocardiography showed a moderate decrease in ejection fraction (EF) (41%), an increase in the left (47 mm) and right (51x74 mm) atria. The patient underwent AF radiofrequency catheter ablation (RFA) in the left atrium, which identified PFO. The final stage of RFA was performed by external electrical cardioversion with successful restoration of sinus rhythm. Four months after RFA, despite a stable sinus rhythm, the patient maintained a moderately reduced LV EF (44%) and dilatation of the left (44 mm) and right (43x65 mm) atria. Transesophageal echocardiography revealed an aneurysmally altered atrial septum and a positive bubble test with a large number of bubbles. In accordance with current recommendations, the patient had indications for primary prevention of stroke – endovascular occlusion of the PFO, which was performed. Three months after PFO closure, the patient discontinued diuretics, amiodarone, and rivaroxaban. Combined therapy in a patient with persistent AF, with a moderately reduced EF and verified PFO, which included pathogenetic therapy for CHF, prescription of antiarrhythmic drugs, RFA of the AF substrate, and interventional closure of the PFO, made it possible to effectively control sinus rhythm, significantly reduce the manifestations of CHF and provide primary prevention of embolic disorders.

Key words: atrial fibrillation, endovascular occlusion of patent foramen oval, primary prevention of stroke, reverse atrial remodeling, radiofrequency ablation, heart failure.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia, the incidence of which in the population can reach 1-2%. In most patients, AF develops against the background of an already existing pathology [1].

Defining a priority strategy for patients with AF between cardiac rhythm management and heart rate control strategies has long been controversial regarding their impact on the endpoints of reduced mortality, improved quality of life and reduced unplanned hospitalizations [2]. In recent years, publications have begun to appear indicating that there is a positive relationship between the strategy aimed at maintaining sinus rhythm and survival in patients with AF [3]. Currently the most effective method for implementing this strategy is radiofrequency catheter ablation (RFA) [4]. The long-term success of the procedure is determined, among other things, by adequate correction of concomitant pathology and modification of AF risk factors (heart failure, arterial hypertension, thyroid dysfunction, apnea/hypopnea, obesity) [5–8].

In recent years, there has been evidence that patent foramen ovale (PFO) may be a pathogenetic factor contributing to the progression of arrhythmic syndrome [9-12]. PFO is formed as a result of failure in fusing (adhesion) of the septum primum and septum secundum in the interatrial septum, which leads to the formation of the so-called valve through which shunting from right to left (usually transient) can occur when the pressure in the right atrium exceeds the pressure in the left atrium. In the population PFO is detected in 17–57% of cases [9] and can cause paradoxical embolism [13].

In this regard, it is relevant to think of the need for correction (modification) of this risk factor in the treatment program for patients with AF.

Here we present a clinical case of staged treatment of a patient with persistent AF, heart failure with a moderately reduced left ventricular ejection

fraction and PFO, whose restoration of sinus rhythm by RFA and subsequent interventional closure of the PFO resulted in effective control of the arrhythmic syndrome, elimination of manifestations of heart failure and normalization of echocardiographic parameters.

Materials and Methods

Description of the Clinical Case.

Stage 1 – RFA AF (June 2019). Patient T., 58 years old, body mass index 27.8 kg/m2, was admitted to the clinic in early June 2019 complaining of shortness of breath, feeling short of breath, decreased exercise tolerance, increased fatigue. According to the anamnesis since April 2019 he has been diagnosed with a persistent form of AF with severe ventricular tachysystole (Fig. 1), which led to the development of heart failure in both circles of blood circulation (hepatomegaly, ascites, hard breathing during auscultation of the lungs). These complaints gradually intensified and corresponded to the II–III functional class (FC) of CHF according to the NYHA classification. According to transthoracic echocardiography there was a pronounced dilatation of the left atrium (anteroposterior size – 47 mm) and a decrease in systolic function of the left ventricle (EF was 41%) (Table 1).

Table 1 – Comparative table of echocardiographic parameters

Echocardiographic parameters	Values		
	Before RFA	3 months after RFA	1 year after the closure of the PFO
Left ventricular end-diastolic dimension	56 mm	58 mm	57 mm
Left ventricular end diastolic diameter	139 ml	141 ml	139 ml
Left ventricular end-systolic diameter	82 ml	73 ml	63 ml
Left ventricular ejection fraction	41%	44%	55%
Right ventricle	32 mm	32 mm	31 mm
Anteroposterior dimension of the left atrium	47 mm	44 mm	41 mm
Left atrial volume	131 ml	96 ml	83 ml
Apical position of the right atrium	51x74 mm	43x65 mm	43x63 mm
Expanding of aortic opening	18 mm	18 mm	18 mm
Aortic insufficiency	0-1 degree	0-1 degree	0-1 degree
Mitral insufficiency	2 degrees	2 degrees	1st degree
Tricuspid insufficiency	2 degrees	2 degrees	1-2 degrees
Pressure in the pulmonary artery	40 mmHg	45 mmHg	30 mmHg

Blood tests show an increase in the level of the N-terminal natriuretic peptide precursor (NT-proBNP) to 912 pg/ml. During the hospital stay the patient underwent an examination (including coronary angiography), which made it possible to exclude an unstable variant of the course of coronary artery disease, myocarditis (according to magnetic resonance imaging with contrast), thyroid dysfunction (thyroid-stimulating hormone level upon admission to the hospital was 4.2 mU/l).

Affected by drug therapy (bisoprolol 5 mg/day, amiodarone 200 mg/day, diuver 10 mg/day, verospiron 50 mg/day, xarelto 20 mg/day), the symptoms of heart failure decreased in the patient (EF 41%, there was a decrease in liver size).

According to current recommendations for the treatment of AF, the patient had class IIA indications for radiofrequency ablation (RFA) of the AF substrate [5]. In order to get prepared for RFA, the patient received amiodarone 200 mg/day for 4 weeks. At the beginning of July 2019, an intervention was performed. During transseptal puncture, the patient was diagnosed with a patent foramen ovale (catheterization of the left atrium was noted with a guidewire of the delivery system without the use of a transseptal needle). RFA of the AF substrate was performed using the non-fluoroscopic CARTO system (Fig. 1), which included antral isolation of all pulmonary veins, linear RF exposure in the area of the mitral isthmus and LA fornix, as well as modification of the arrhythmia substrate along the posterior wall (the total RFA time was 43 min, power 40 W, temperature 45 °C, irrigation rate 17 ml/min). At the final stage of the procedure, sinus rhythm was restored by electropulse therapy (one time, 250 J) (Fig. 1). The patient was discharged on the second day after surgery in a satisfactory condition.

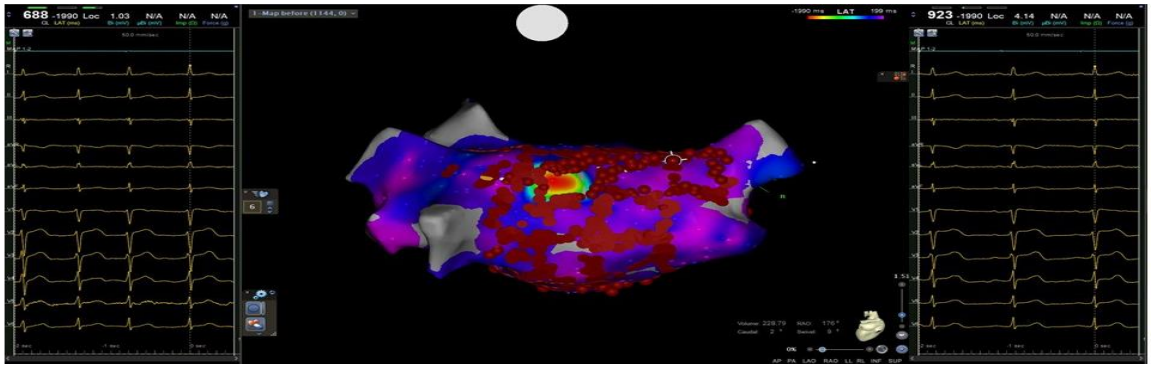

Figure 1 – 12-lead surface ECG before (left) and after radiofrequency ablation in the left atrium (right) and electroanatomical voltage-amplitude (EAVA/EAVM) 3-D reconstruction of the left atrium (posterior view) performed during radiofrequency ablation (in the center of the picture).

Stage 2 – Closure of the PFO (January 2020). In November 2019 the patient was again admitted to our clinic with complaints of reduced exercise tolerance. Despite a stable sinus rhythm for 4 months after RFA, the patient retained a moderately reduced LV EF (44%), left atrial dilatation (44 mm), moderate pulmonary hypertension (PAP 45 mm Hg) (see Table 1). Though blood tests show a decrease in the level of NT-proBNP, nevertheless, its value remained quite high and amounted to 518 pg/ml.

The patient underwent transesophageal echocardiography during the treatment, an aneurysmally altered atrial septum and a positive bubble test (bubble test) with a large number of bubbles (more than 20) were detected (Fig. 2).

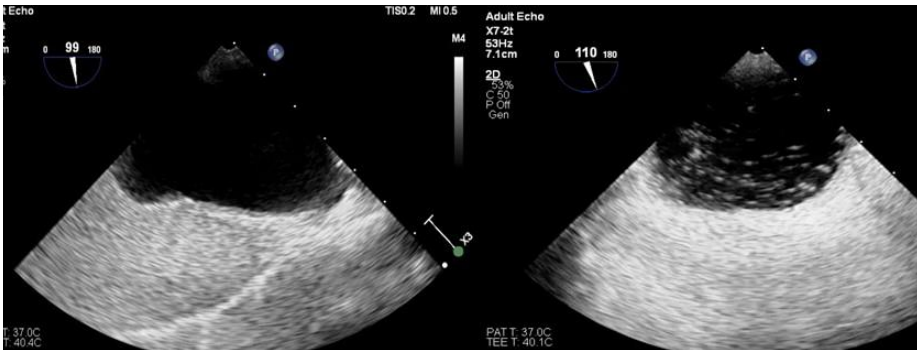

Figure 2 – Bubble test during transesophageal echocardiography. In the right part of the figure, the agitated solution is detected only in the cavity of the right atrium. In the right part of the figure, when performing a bubble test with a Valsalva test, a large number (more than 20 bubbles) passes through the PFO into the cavity of the left atrium.

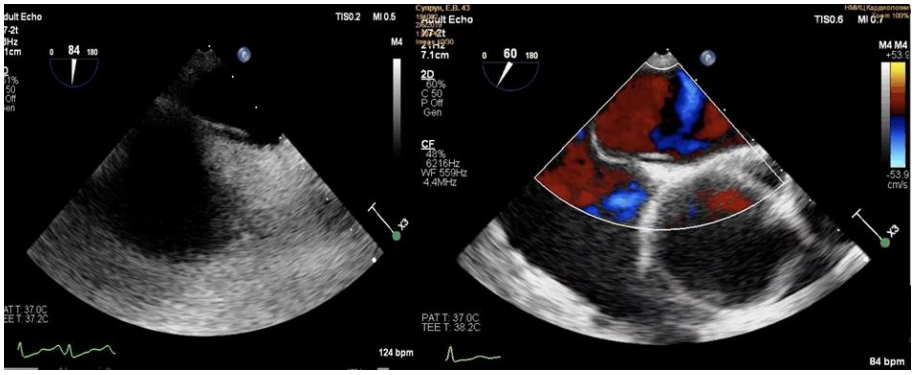

Figure 3 – Patent foramen ovale on transesophageal echocardiography. Long tunnel (10 mm) with a diameter of 4 mm (left), atrial septal aneurysm (right)

PFO folds was 10 mm, and the diameter was 4 mm. (Fig. 3)

The above data testified to the potentially malignant nature of PFO due to the high risk of thrombotic mass migration from the venous system to the systemic circulation with the subsequent development of embolic complications [14, 15].

To date there is no absolute indication for percutaneous PFO closure for the primary prevention of stroke. However, according to the recommendations of the Society for Cardiovascular Angiography and Interventions (SCAI), in patients with aneurysm of the IAS and a positive bubble test there are class 2 indications for interventional closure of the PFO [15]. After obtaining informed consent from the patient, it was decided to perform interventional closure of PFO with the FIGULA FLEX II PFO 23/25 mm occluder, which was performed in January 2020 (Fig. 4)

Figure 4 – Installed occluder FIGULA FLEX II PFO 23/25 mm. Radiography of the heart in the left anterior oblique (LAO 45). On the left is a stability check (lifting). On the right is the result of the implantation of the occluder

The procedure went without complications and the patient was discharged the next day. In the postoperative period, the patient got triple therapy (clopidogrel 75 mg per day, acetylsalicylic acid 75 mg per day and rivaroxaban 15 mg per day). One month after the intervention, acetylsalicylic acid was canceled, and three months later, rivaroxaban was cancelled as well.

Stage 3 – Control Examination.In January 2021 the patient underwent a follow-up examination after the treatment, which showed that associated with a stable sinus rhythm after RFA and PFO closure, the patient had a significant increase in exercise tolerance. Blood tests showed normal levels of NT-proBNP (110 pg/ml) and there were no manifestations of CHF. During the comparison ECHO-CG the size of the left atrium (41 mm) and PAP (30 mm Hg) decreased, and LV systolic function improved significantly (EF 55%) (see Table 1). Three months after PFO closure, the patient discontinued diuretics and amiodarone. Comparison Holter ECG monitoring showed no episodes of atrial fibrillation. The patient continues therapy with clopidogrel, beta-blockers, ACE inhibitors.

Results and Discussion

1.PFO as a factor in the pathogenesis of AF

Back in 2000 data were published that among patients who had a cryptogenic stroke or a transient ischemic attack with PFO verified by transesophageal echocardiography during an endocardial electrophysiological study, AF was significantly more often induced, and the parameters of refractoriness and conduction velocity in both atria were lower (indicates a high vulnerability of the atria) than in patients without PFO [10].

However, until recently, PFO was not considered as a factor associated with the progression of AF. So, in 2008 Knecht S. et al., demonstrated in a group of 203 patients with paroxysmal AF that the presence of PFO did not affect the results of RF isolation of the pulmonary veins in maintaining a stable sinus rhythm during 50 months of follow-up [16]**.**

Relatively recently data were published that PFO is one of the independent predictors of arrhythmia recurrence after cryoablation of persistent AF [11]. The authors suggested that PFO may be a trigger for atrial extrasystoles that trigger AF, and the functioning of

the right-left shunt in the atria leads to the entry of biologically active substances (serotonin, etc.) and platelet aggregates into the LA, which under normal conditions undergo "detoxification" in the lungs , and if it enters the LA, it can lead to the development of fibrosis, atriopathy, and the progression of AF [12].

In the above patient at the stage of preparation for the intervention, all modifiable risk factors for AF were assessed and corrected, and in our opinion, other factors, in addition to PFO, which were identified during the RFA procedure, were insignificant. PFO was probably the main pathogenetic basis for the progression of arrhythmic syndrome resistant to drug antiarrhythmic therapy and the subsequent development of CHF in our patient.

2.Influence of PFO closure on the arrhythmic syndrome

Data on the effect of PFO closure on the course of AF are contradictory. Thus, according to the CLOSURE-1 study which included 860 patients with PFO post-intervention, the incidence of AF in the first year after the procedure was 5.7%, while in the group of patients who underwent drug prevention of AF episodes, there were no episodes of AF. The authors suggested that the development of AF in the early postoperative period may be associated with inflammatory processes in the atrial myocardium associated with intervention. This hypothesis is indirectly supported by the fact that at follow-up, the incidence of AF decreased to 3.9 **%** [17].

On the other hand, there is an assumption that the closure of the PFO may have an antiarrhythmic effect on AF. In this regard, the results of several meta-analyses including over 5000 patients who underwent interventional or surgical closure of the PFO or atrial septal defect, deserve attention, which indicate a significant decrease in the prevalence of AF after the intervention in the follow-up period of up to 5 years [18, 19**].** In 2019 Carpenter A. et al. published the results of a long-term follow-up of 384 patients with an atrial septal defect who underwent interventional closure. AF was detected in 74 (20%) patients, and 15 of them underwent RFA in the LA prior to insertion of an occluder in the MPS. The follow-up results indicated that 36% of patients with AF who did not undergo RFA did not have AF recurrence within one year after closure, and out of 289 patients (80%) without pre-existing AF, the incidence of this arrhythmia during the year observation was surprisingly low (0.3%) [20].

3.Primary prevention of stroke in PFO

To date a large evidence base has been accumulated on the secondary prevention of cryptogenic strokes in patients with patent foramen ovale. The large randomized international trials like RESPECT, REDUCE, DEFENCE-PFO and CLOSE demonstrated superiority of endovascular isolation of the foramen ovale over medical therapy in patients with previous cryptogenic strokes and patent foramen ovale [21-24].

In 2013 a paradoxical embolism risk scale (risk of paradoxical embolism (RoPE) score) [25] was developed. Based on the obtained score on the RoPE scale, patients can be identified who have the highest relationship between the cryptogenic stroke that has occurred and the patent foramen ovale. The presence of 7, 8 and 9 points corresponds to 72%, 84% and 88% of the relationship. Such patients belong to the group of high correlation and endovascular closure of the PFO is shown according to the recommendations of the American Society of Cardiology from 2021 [26].

In addition to scoring on the paradoxical embolism risk scale, when selecting patients as a secondary prevention of cryptogenic stroke to close the patent foramen ovale, it is necessary to focus on the anatomy and morphology of the foramen ovale and atrial septum, as well as the result of the bubble test. So, the study of S. Homma et al showed that the size of the foramen ovale was significantly larger in patients with cryptogenic stroke compared with patients with an identified cause of stroke (2.1 ± 1.7 mm vs. 0.57 ± 0.78 mm; $P < 0.01$). The number of microbubbles was also greater in patients with cryptogenic stroke compared with those with an identifiable stroke cause (13.9 ± 10.7 vs. 1.6 ± 0.8 [mean ± SD]; $P < 0.0005$) [13].

The study of Jong – Young Lee et al. shows that out of 1,014 patients with ischemic stroke referred for transesophageal echocardiography, 184 patients had PFO associated with cryptogenic stroke. During follow-up (median 3.5 years), 14 patients (7.7%) had recurrent stroke. Multivariate analysis demonstrated that an atrial septal aneurysm or atrial septal hypermobility (hazard ratio 6.04, 95% CI 1.84 to 19.86, $p = 0.003$) and PFO size (hazard ratio 3.00, 95% CI from 1 .96 to 4.60, $p<0.0001$) were independent predictors of recurrent stroke. The PFO threshold for predicting recurrent stroke for 3 years had been 3.0 mm (95% confidence interval 2.1–3.7 mm, area under the curve 0.889, $p<0.001$) with a sensitivity and specificity of 90.0% and 79. 4%, respectively [14].

Thus, the criteria for high-risk PFO were identified, which are independent predictors of the development of stroke. According to the recommendations of the American Society of Cardiology, patients should be treated with PFO closure only as a secondary prevention of cryptogenic stroke. The big challenge now is to determine the role of primary prevention of cryptogenic stroke in patients with high-risk patent foramen ovale.

One of the few references to the primary prevention of cryptogenic strokes in patients with PFO is found in the recommendations of the Society for Cardiovascular Angiography & Interventions – Management of Patent Foramen Ovale [15]. The paper states that in patients with systemic embolism and no history of PFO-related stroke, who have other embolic etiologies ruled out, the SCAI guidelines suggest the closure of PFO, and not just providing medical therapy. The recommendation is based on a low evidence base and additional large-scale studies are needed to identify patients with indications for primary prevention of various embolic complications, including strokes due to patent foramen ovale. Since in our case the patient had an interatrial septum aneurysm in combination with a positive bubble test and had all the signs of a high-risk PFO, he/she underwent interventional PFO occlusion as part of the primary prevention of stroke.

4.Echocardiographic changes after PFO closure.

In the study of Aslan M. et al. echocardiographic parameters were evaluated before and 6 months after interventional closure of the interatrial septum defect with a verified left-to-right shunt in 41 patients. After interventional closure of the interatrial septum defect there was a significant decrease in the end-diastolic dimension of right and left ventricles, dimension of the right atrium, and a decrease in atrial electromechanical delay, although the dimension of the LA itself did not change significantly. The dynamic assessment of echocardiographic parameters over time in our patient is consistent with the research data and essentially indicates the reverse remodeling of the atria and ventricles, thus eliminating the structural basis for the development and progression of AF [27].

We assumed that the interventional closure of PFO in our patient would be of key importance in improving his clinical status and quality of life, would ensure long-term maintenance of sinus rhythm, and would also be justified in relation to the primary prevention of stroke due to the "malignant" morphological characteristics of the PFO. Our assumptions turned out to be true.

Conclusion

Combination therapy in a patient who has persistent AF, a moderately reduced EF and verified PFO with right-to-left shunt flow arteriovenous, including pathogenetic therapy for CHF, prescription of antiarrhythmic drugs, RFA of the AF substrate, and interventional closure of PFO, allowed for effective control of sinus rhythm and significant reduction of HF cases, development of reverse remodeling of the heart chambers, as well as for providing primary prevention of embolic disorders.

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