

Denervation of Pulmonary Arteries in Patients with Mitral Valve Defects Complicated by Atrial Fibrillation and Pulmonary Hypertension

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The aim of the study was to evaluate whether sympathetic denervation of the trunk and orifices of pulmonary arteries could reduce pulmonary hypertension and help in managing atrial fibrillation. In addition, we aimed to identify the main predictors of recurrent rhythm disturbances in patients with mitral valve dysfunction complicated by atrial fibrillation and high pulmonary pressure.

Materials and Methods. We analyzed the results of surgical treatment of 140 patients with mitral defects complicated by atrial fibrillation and high-grade pulmonary hypertension (more than 40 mm Hg). In the main group of patients (n=51), surgical intervention included the correction of mitral defect, the treatment for atrial fibrillation according to Maze IV, and the radiofrequency denervation of the trunk and orifices of the pulmonary artery in order to correct pulmonary hypertension. In the control group (n=89), patients with similar heart defects underwent the mitral dysfunction repair (Maze IV), but no denervation of the pulmonary trunk or orifices was performed.

Results. We found that the circular radiofrequency denervation of the trunk and orifices of the pulmonary arteries effectively reduced pulmonary hypertension in patients with mitral valve defects complicated by atrial fibrillation and high pulmonary pressure. The proposed procedure results in reverse remodeling of the heart cavities, especially the left atrium (p=0.01), a decrease in pulmonary hypertension, and permanent restoration of a sinus rhythm after the Maze IV procedure (p=0.008). The main predictors of recurrent atrial fibrillation in these patients after the combined surgical treatment are arrhythmias lasting over 5 years (p=0.04), initial pulmonary hypertension of more than 60 mm Hg (p=0.028), concomitant severe tricuspid insufficiency (p=0.006) and atherosclerotic lesions in the brachiocephalic and cerebral vessels.

Key words: pulmonary artery denervation; pulmonary hypertension; mitral defect.

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Introduction

Rhythm disturbances in the form of atrial fibrillation occur in 30–84% of patients with heart valve disease. This type of arrhythmia significantly reduces the efficacy of surgical treatment of valve defects and increases the risk of thromboembolic complications and heart failure, which affects the quality of life and survival of the patients [1–3]. Prevalence of atrial fibrillation reaches 2%, and over the past decade there has been a trend to its increase [4, 5].

The occurrence of mitral valve defects, whether stenosis or insufficiency, reaches 8% of the general population [6] and causes increased pressure in the left atrium cavity, which expands over time. In addition, these patients have morphological and electrical changes in the myocardial wall with sections of slow and fast conduction resulting in the formation of abnormal re-entry circles [7, 8]. On top of that, an increase in the left atrium pressure leads to pulmonary hypertension with subsequent structural changes in pulmonary arterial walls and an overload of the right heart [9–11].

An increase in the pulmonary circulation pressure also contributes to the development of tricuspid insufficiency and eventually to heart failure and other comorbidities associated with a poor quality of life and worsen prognosis in this group of patients [12].

In this regard, surgical correction of valve dysfunction is the main pathogenetic task in the surgical treatment of atrial fibrillation [5, 13]. Yet, the sinus rhythm is restored in only 8.5–20.0% of patients who undergo mitral valve repair. Therefore, additional efforts to treat cardiac arrhythmias are needed [14–16].

Currently, pulmonary hypertension is defined as an increase in the pulmonary artery pressure to a value more 25 mm Hg at rest [17, 18]. The latest classification of pulmonary hypertension was proposed in 2013 by Simonneau [19]: hypertension associated with diseases of the left heart, hypertension associated with respiratory diseases and hypoxia, arterial hypertension, chronic thromboembolic hypertension, and idiopathic hypertension. Pulmonary hypertension in patients with heart valve dysfunction reduces the efficacy of surgical valve repair, increases the time for rehabilitation, slows the heart chamber remodeling process, causes rhythm disturbances and reduces the efficacy of surgical treatment for atrial fibrillation [20]. The pathogenesis of secondary pulmonary hypertension is discussed within a few mechanisms: an abnormal ratio of thromboxane to prostacyclin and the resulting activation of thromboxane in the pulmonary vessel endothelium, *in situ* thrombosis, a decrease in the synthesis of endothelial nitric oxide (a powerful vasodilator), an increased production of vasoconstrictors and, as a rule, hypertrophy of smooth muscle cells with secondary chronic vasoconstriction and a proliferative reaction of the vessel intima and adventitia [21–23].

The treatment of pulmonary hypertension is

currently one of the urgent tasks of modern medicine. In this condition, drug therapy is costly and not very effective [24].

The first studies of the sympathetic regulation of the vascular tone of pulmonary arterioles and pre-capillaries were performed in 1962 by a group of Osorio [25]. They demonstrated the presence of sympathetic nerve plexuses in the adventitia of the pulmonary trunk and orifices of the pulmonary arteries; stimulation of these nerves apparently caused the contraction of smooth muscle cells and eventually led to a spasm of pulmonary arterioles and increase in the pulmonary blood pressure. Later, these data were confirmed by other authors [26, 27].

Surgical correction of secondary pulmonary hypertension (except for pulmonary artery banding) was first proposed in 2013 by Chen et al. [28]. Their technique was based on radiofrequency ablation of pulmonary arteries (with the help of an endovascular catheter) aiming at denervation of the sympathetic plexuses. Their encouraging results prompted us to study this technique in more detail. Other studies on the endovascular radiofrequency denervation of sympathetic ganglia in the trunk and orifice of the pulmonary arteries [29, 30] confirmed the efficacy of the technique. In a study by Briongos Figuero et al. [31], patients with initially high-grade pulmonary hypertension tended to retain the similarly high pulmonary pressure in the postoperative period, despite surgical correction of mitral dysfunction (odds ratio 1.771; $p=0.03$). A method of surgical correction of pulmonary hypertension under cardiopulmonary bypass with simultaneous surgical intervention on the mitral valve (radiofrequency ablation of the anterior wall of the trunk and orifices of pulmonary arteries using a monopolar pen-electrode) was reported by Bogachev–Prokofiev et al. [32]. There is also a technique for circular radiofrequency denervation of the trunk and orifice of pulmonary arteries using a bipolar destructor [9, 33].

Despite the data presented above, the current medical practice does not have a generally accepted protocol for surgical treatment in patients with mitral valve dysfunction complicated by atrial fibrillation and pulmonary hypertension; therefore, a further search for an optimal algorithm for surgical correction of this pathology is needed. In addition, there is no data on the effect of the surgical treatment of high pulmonary pressure on the outcome of the Maze IV procedure and the preservation of the sinus rhythm in the postoperative period.

The aim of the study was to evaluate whether sympathetic denervation of the trunk and orifices of pulmonary arteries could reduce pulmonary hypertension and help in managing atrial fibrillation. In addition, we aimed to identify the main predictors of recurrent rhythm disturbances in patients with mitral valve dysfunction complicated by atrial fibrillation and high pulmonary pressure.

Materials and Methods

Medical histories of 140 patients with mitral defect complicated by atrial fibrillation and high-grade pulmonary hypertension (more than 40 mm Hg) were analyzed. In part of the patients (n=51), the treatment included surgical correction of the mitral defect (valve reconstruction or, in most cases, prosthetics), surgery for atrial fibrillation, i.e. bi-atrial radiofrequency ablation according to the Maze IV scheme using an AtriCure bipolar ablator (ATRICURE Inc., USA), and radiofrequency denervation of the trunk and orifices

of the pulmonary artery in order to reduce pulmonary pressure.

The control group (n=89) included patients with the same pathology — mitral valve disease complicated by atrial fibrillation and pulmonary hypertension. These patients also underwent mitral defect correction and the Maze IV procedure, however, the denervation of the pulmonary artery trunk or orifices was not performed.

The criteria for inclusion in the study group were the presence of mitral valve disease, atrial fibrillation, high-grade pulmonary hypertension (more than 40 mm Hg), the absence of hemodynamically significant damage to

Table 1

Clinical and demographic characteristics of patients prior to surgery (M±m)

Parameters (n=140)	Study group (n=51)	Control group (n=89)	p, Mann-Whitney
Sex (m/f)	23/28	28/61	0.108
Age (years)	59.4±5.2	55.8±8.3	0.005
Disease (%):			
chronic rheumatic heart disease	76	85	0.072
infectious endocarditis	20	9	0.072
connective tissue dysplasia	4	6	0.657
Type of atrial fibrillation (%):			
sustained persisting	86	84	0.751
persisting	8	2	0.117
paroxysmal	24	13	0.164
Arrhythmia history (years)	2.63±1.37	2.74±1.74	0.688
Atrial flutter (%)	14	20	0.337
Atherosclerosis of brachiocephalic vessels with stenosis of more than 50% (%)	18	17	0.905
Acute cerebrovascular accident history (%)	8	8	0.996
Risk of adverse outcome, EuroSCORE (points), Me [Q1; Q3]	5 [4; 8]	4 [3; 6]	0.004
Time of cardiopulmonary bypass (min), Me (min–max)	111 (87–130)	136 (118–151)	<0.001
Aortic clamping time (min), Me (min–max)	79 (67–102)	107 (92–128)	<0.001
Tricuspid insufficiency (degree)	II	II	0.095
NYHA chronic heart failure class	III	III	0.058
Surgical correction of mitral defect:			
prosthetics	47	84	0.605
plastic repair	4	5	
End-diastolic size of the left ventricle (cm)	5.84±0.60	5.59±0.55	0.014
End-systolic size of the left ventricle (cm)	4.25±0.54	3.92±0.52	<0.001
End-diastolic volume of the left ventricle (ml)	171.47±41.33	154.99±36.59	0.016
End-systolic volume of the left ventricle (ml)	82.52±25.26	68.45±22.52	<0.001
Left ventricular ejection fraction (%)	52.45±4.70	56.36±5.10	<0.001
End-systolic size of the right ventricle (cm)	3.63±0.33	3.46±0.30	0.003
End-systolic size of the left atrium (cm)	5.48±0.35	5.42±0.67	0.6
End-systolic size of the right atrium (cm)	5.71±0.41	5.56±0.57	0.095
Pulmonary hypertension (mm Hg)	50.02±8.67	46.87±6.78	0.018

the coronary arteries that would require revascularization, the absence of thromboembolic changes in the pulmonary arteries, and no history of chronic obstructive pulmonary disease with severe respiratory failure. In the postoperative period, none of the patients received specific medications for the correction of pulmonary hypertension. Prior to the intervention, all patients were informed about the forthcoming surgery with additional denervation of the pulmonary arteries to be performed before the main phase of the operation. In accordance with the Helsinki Declaration (2013), the patients signed the informed consent forms; the surgery team and investigators followed the principles of Good Clinical Practice (GCP).

The study group and the control group were comparable in terms of the main clinical and demographic indicators (Table 1). The patients in the study group though were significantly older and had worse cardiac manifestations in terms of EuroSCORE, dilation of the right heart and the left ventricle, the left ventricle ejection fraction, and the degree of pulmonary hypertension.

The denervation procedure on the trunk and orifices of pulmonary arteries was performed circularly using an AtriCure bipolar radiofrequency clamp-ablator. Intraoperatively, after connecting to the cardiopulmonary bypass, distal sections of the pulmonary artery trunk were isolated and two ablation lines (3 points in each) were applied to the pulmonary trunk (Figure 1).

After that, orifices of the pulmonary arteries were similarly isolated, and ablation lines applied by a radiofrequency destructor. To access the orifices of the right pulmonary artery, the aorta was pushed to the left to expose the transverse sinus of the heart (Figure 2).

In its final form, the radiofrequency denervation of the pulmonary arteries was accomplished by 6 ablation lines, two at the orifices of the left and right pulmonary

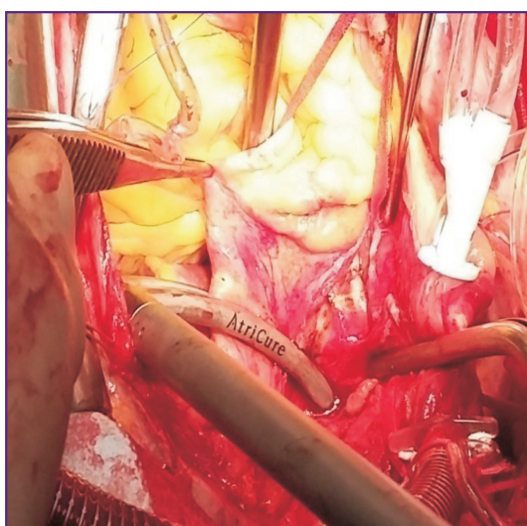


Figure 1. Pulmonary trunk denervation

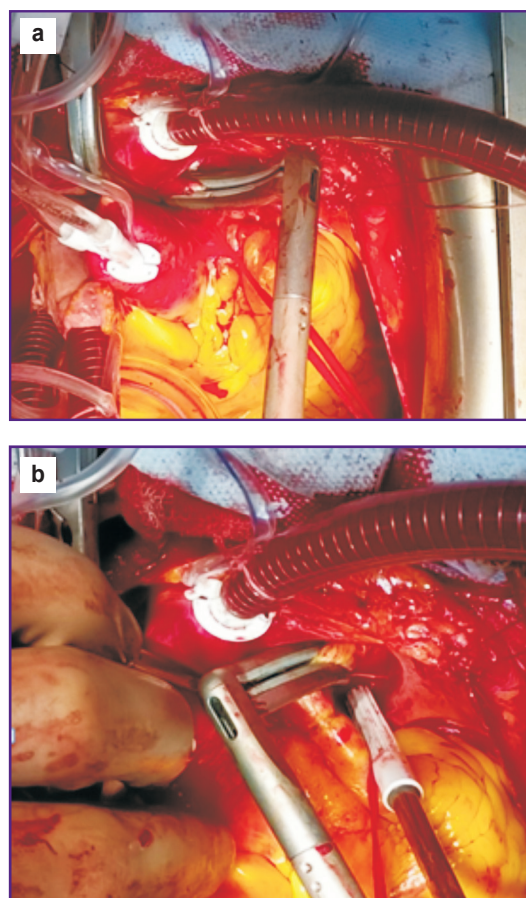


Figure 2. Denervation of the orifices of the right (a) and left (b) pulmonary arteries

arteries and two at the distal section of the pulmonary artery trunk (Figure 3).

The time to complete the radiofrequency denervation of the pulmonary arteries was 5.5 ± 1.5 min.

After introducing antegrade cardioplegia (Custodiol solution) into the aortic root and achieving cardiac arrest, the main stage of the operation — surgical intervention for mitral valve dysfunction and atrial fibrillation — was performed. The cardiopulmonary bypass lasted 114.1 ± 33.4 min, and the duration of myocardial ischemia was 85.2 ± 26.6 min.

After the denervation, patients stayed in the intensive care unit for 2.4 ± 3.1 days, which did not differ from patients in the control group (2.6 ± 2.8 days). The management of patients in the postoperative period was identical in both groups. Transthoracic echocardiography was performed 3, 6, 12, and 24 months after surgery.

Statistical analysis of the results was carried out using the Exel and Statistica 10.0 software. The data are presented by the mean values and the standard error ($M \pm m$). Statistical significance of the differences between the groups was calculated by the Mann–Whitney test. The absolute values were compared using the χ^2 criterion; if the number of samples was less

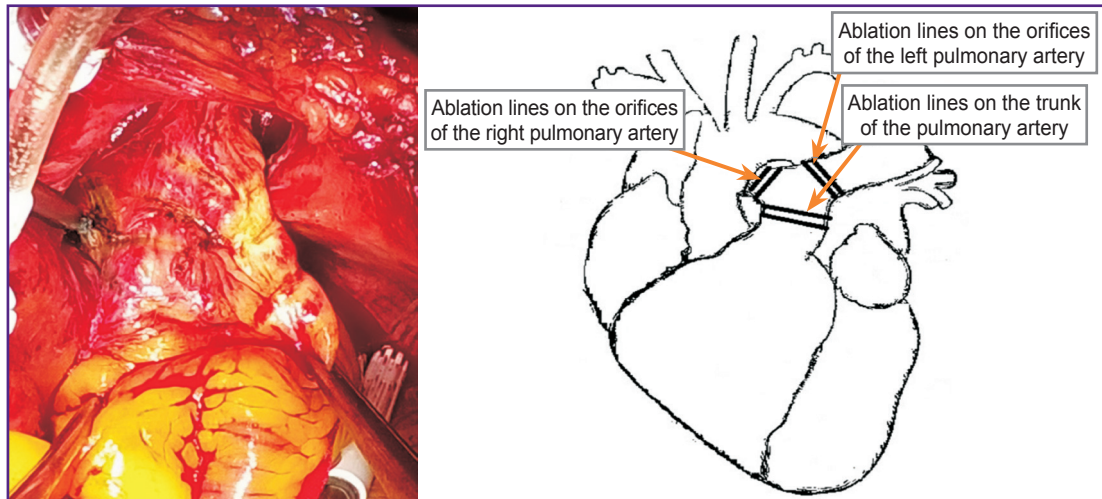


Figure 3. Ablation lines on the trunk and orifices of the pulmonary arteries

than 5, the two-sided Fisher test was used. The values of $p < 0.05$ indicated significant differences between the compared values.

Changes in the mean values of pulmonary hypertension in both groups are shown in Figure 4. Here, the advantage of this integrated approach to the surgical treatment of mitral valve disease complicated

Results and Discussion

There was 1 case of death in each group; both were due to progressive acute heart failure. No complications due to radiofrequency denervation of pulmonary arteries in the study group were observed. Positive dynamics of echocardiographic indices in the postoperative period was noted in patients of both groups (Table 2).

In the study group, patients showed significantly better results than those in control. Specifically, it manifested in a better reverse remodeling of the heart, an increased contractile function of the left ventricle, and in reduced pulmonary hypertension. With the initially worse echocardiography and the older age in the study group, 24 months after surgery, these patients reached the heart indices close to those in the control group.

Radiofrequency denervation of the sympathetic ganglia of the pulmonary trunk and pulmonary arteries promotes relaxation of smooth muscle cells in the walls of small arteries and arterioles, thus leading to vasodilation and, subsequently, to an increased capacity of the pulmonary circulation, which ultimately helps reduce pulmonary hypertension.

Table 2

Dynamics of echocardiographic parameters 24 months after surgery (M±m)

Parameters	Study group (n=51)	Control group (n=89)	p, Mann-Whitney
End-diastolic size of the left ventricle (cm):			
baseline	5.84±0.60	5.59±0.55	0.014
24 months after surgery	4.89±0.53	4.88±0.49	0.896
End-systolic size of the left ventricle (cm):			
baseline	4.25±0.54	3.92±0.52	<0.001
12 months after surgery	3.39±0.51	3.35±0.37	0.625
End-diastolic volume of the left ventricle (ml):			
baseline	171.47±41.33	154.99±36.59	0.016
24 months after surgery	114.28±30.29	113.34±27.50	0.858
End-systolic volume of the left ventricle (ml):			
baseline	82.52±25.26	68.45±22.52	<0.001
24 months after surgery	47.83±16.54	46.75±12.60	0.691
Contractility of the left ventricle (%):			
baseline	52.45±4.70	56.36±5.10	<0.001
24 months after surgery	58.72±5.88	58.89±3.55	0.857
End-systolic size of the right ventricle (cm):			
baseline	3.63±0.33	3.46±0.30	0.003
24 months after surgery	3.03±0.26	2.96±0.22	0.156
End-systolic size of the left atrium (cm):			
baseline	5.48±0.35	5.42±0.67	0.6
24 months after surgery	4.27±0.34	4.11±0.33	0.01
End-systolic size of the right atrium (cm):			
baseline	5.71±0.41	5.56±0.57	0.095
24 months after surgery	4.82±0.56	4.66±0.34	0.073
Pulmonary pressure (mm Hg):			
baseline	50.02±8.67	46.87±6.78	0.018
24 months after surgery	27.65±6.35	29.88±31.30	0.519

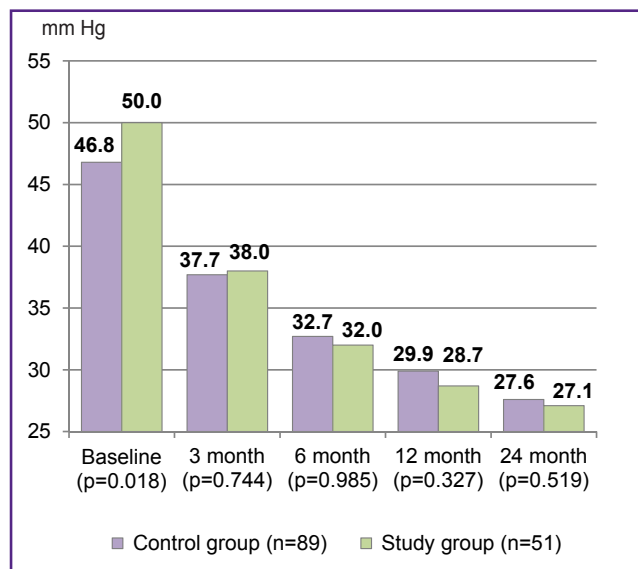


Figure 4. Dynamics of pulmonary hypertension
Statistical significance of the differences between the mean values was calculated by the Mann–Whitney test

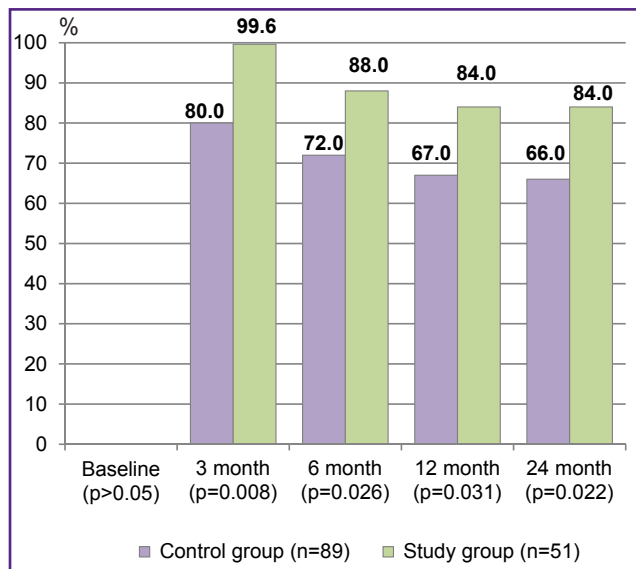


Figure 5. Preservation of the sinus rhythm in patients after surgery (statistics calculated using the χ^2 criterion)
The results are presented as a percentage of patients having a sinus rhythm

Table 3

Predictors of recurrent atrial fibrillations in patients of the study group (M±m)

Identified predictors	Sinus rhythm (n=42)	Atrial fibrillation (n=8)	p, Mann-Whitney
History of atrial fibrillation (years)	2.19±0.89	4.63±1.51	0.001
Atherosclerosis of the brachiocephalic arteries	0.12±0.33	0.50±0.53	0.009
History of acute cerebrovascular accident	0±0	0.50±0.53	0.001
EuroSCORE risk of adverse outcome	5.26±2.21	7.63±1.19	0.005
Severe tricuspid insufficiency	1.79±0.78	2.63±0.52	0.006
Chronic heart failure functional class by NYHA	3.36±0.48	3.75±0.46	0.04
End-diastolic size of the left ventricle (cm)	5.78±0.60	6.24±0.45	0.046
End-diastolic volume of the left ventricle (ml)	167.4±41.4	197.9±31.8	0.055
End-diastolic size of the right ventricle (cm)	3.57±0.32	3.95±0.23	0.002
Pulmonary pressure (mm Hg)	48.76±8.30	55.40±8.81	0.046

by pulmonary hypertension and atrial fibrillation has been clearly demonstrated. The proposed technique made it possible to achieve a significant reduction in hypertension in patients with initially high-grade pulmonary hypertension, which became similar to the control values 3 months after surgery.

Normalization of blood pressure in the pulmonary arteries against the background of vascular vasodilation helps decrease the pressure in the left atrium and stimulates the reverse remodeling (see Table 2; p=0.01). The reverse remodeling of heart cavities in the study group resulted in a more effective Maze IV procedure and preservation of the sinus rhythm after surgery.

Surgical correction of atrial fibrillation was performed in patients of both groups, but the number of recurrent

fibrillation episodes was significantly lower in the study group, 3 months after surgery (Figure 5).

Restoration and preservation of the sinus rhythm after surgery was significantly better in the study group due to the additional surgical correction of pulmonary hypertension by radiofrequency denervation of the trunk and orifices of pulmonary arteries: after 3 months, 99.6% of patients had a sinus rhythm, while in the control group this indicator was at the level of 80% (p=0.008).

In the course of this research, an analysis of unfavorable

predictors of recurrent atrial fibrillations in the study group was performed (Table 3); in patients of the control group, the rhythm failure predictors were classical and did not cause any scientific interest.

The results of the study demonstrate high rates of recurrent atrial fibrillation in patients with a long history of arrhythmia, atherosclerotic lesions in the brachiocephalic and cerebral arteries, severe tricuspid insufficiency, dilation of the left ventricle, and high-grade pulmonary hypertension.

We investigated the likelihood of recurrent arrhythmias (atrial fibrillation) in patients after mitral disease correction, the Maze IV procedure, and pulmonary artery denervation (Figure 6).

The analysis showed that a history of atrial fibrillation

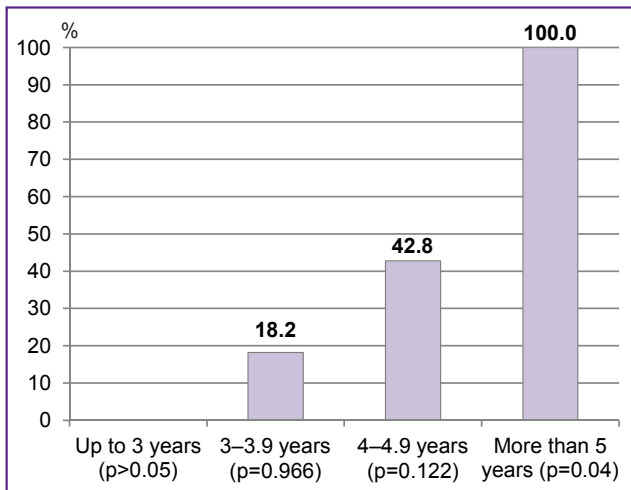


Figure 6. Recurrence rate of atrial fibrillation in patients with different arrhythmic history

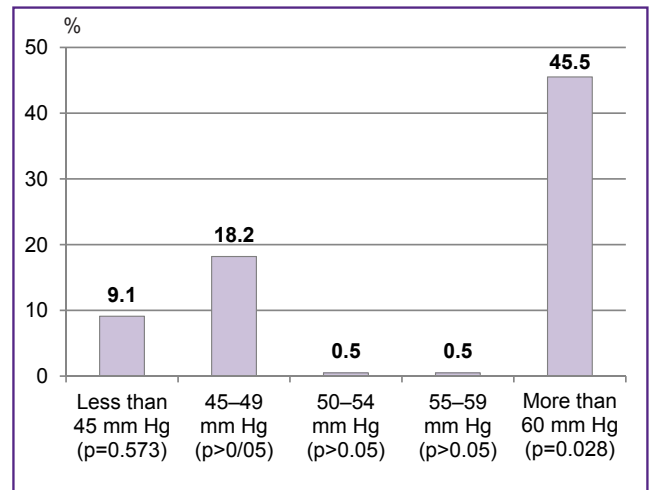


Figure 7. Recurrence rate of atrial fibrillation in patients with different pre-operative pulmonary pressure

of more than 5 years contributes to the recurrence of arrhythmia in almost all patients of the study group ($p=0.04$).

The degree of pulmonary hypertension, as the study showed, also significantly impacted the recurrence rate of arrhythmia in patients of the study group (Figure 7).

An initial value of pulmonary pressure over 60 mm Hg was an unfavorable prognostic factor for atrial fibrillation in patients with valve deficiency correction, the Maze IV procedure, and pulmonary artery denervation.

Despite the insufficiently large sample of patients and the lack of long-term results, the data obtained in this study suggest a superiority of the proposed method (compared with the control group) for remodeling the heart cavities, reducing pulmonary pressure, increasing myocardial contractility and restoring the sinus rhythm. The decrease in pulmonary hypertension in such patients occurs not only due to the elimination of mitral valve defect, but also due to vasodilation of small arteries and arterioles and an increase in the capacity of the pulmonary circulation after denervation of the sympathetic nerve fibers of the trunk and orifices of the pulmonary arteries. The denervation procedure does not increase the time of myocardial ischemia during surgery, as it is performed using a parallel circulation bypass; the denervation is simple to perform, and it was not associated with any specific complications. On average, the procedure of radiofrequency ablation of pulmonary arteries took 5–7 min.

The use of the AtriCure bipolar clamp-destructor allows for the circular denervation of pulmonary arteries, i.e., over the entire circumference of the vessels; this approach improves the efficacy of the technique (compared with ablation of the anterior wall) because the entire sympathetic nerve plexus located in the trunk and orifices of pulmonary arteries is destroyed. Our study demonstrates the practical significance, efficacy,

and safety of the proposed methodology. In addition, the same AtriCure clamp destructor can be used for both the pulmonary artery denervation and the following Maze IV procedure for atrial fibrillation.

Conclusion

Circular radiofrequency denervation of the trunk and orifices of pulmonary arteries is an effective method for surgical treatment of secondary pulmonary hypertension in patients with mitral valve defects complicated by atrial fibrillation and high pulmonary pressure. It contributes to a significant reverse remodeling of the heart cavities, in particular, the left atrium, a decrease in pulmonary hypertension, and a restoration and preservation of the sinus rhythm after the concomitant Maze IV procedure.

The main predictors of recurrent atrial fibrillation in patients with mitral valve dysfunction, combined with atrial fibrillation and pulmonary hypertension after this surgical treatment are arrhythmias of more than 5-year duration, initial pulmonary hypertension over 60 mm Hg, concomitant severe tricuspid insufficiency, and atherosclerotic lesion in brachiocephalic and cerebral vessels.

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