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## CIRCULAR SYMPATHETIC PULMONARY ARTERY DENERVATION IN CARDIAC SURGERY PATIENTS WITH MITRAL VALVE DEFECT, ATRIAL FIBRILLATION AND HIGH PULMONARY HYPERTENSION

<i>Objective</i>	Investigate the influence of the sympathetic denervation of the pulmonary trunk and the orifices of the pulmonary arteries on the degree of pulmonary hypertension (PH) and outcomes of the surgical treatment of atrial fibrillation (AF) in patients with mitral valve defects, complicated AF, and high PH.
<i>Material and methods</i>	We analyzed the surgical treatment of 140 patients with mitral valve defect, concomitant AF, and high PH – pulmonary artery systolic pressure (PASP) gradient more than 40 mm Hg. The group of interest included 51 patients (46 patients with severe mitral stenosis and five patients with grade 4 mitral valve regurgitation). All patients underwent mitral valve correction (47 valve replacement surgeries and 4 valve-sparing interventions), biatrial Maze IV procedure, and additionally, denervation of the pulmonary trunk and the orifices of the pulmonary arteries. The control group included 89 patients diagnosed with mitral valve defect, AF, and PH with PASP > 40 mm Hg. However, unlike in patients of interest, denervation of the pulmonary arteries was not performed.
<i>Results</i>	Circular radiofrequency denervation of the pulmonary trunk and the orifices of the pulmonary arteries using a clamp-destroyer is an effective and safe method, significantly reduces secondary PH (p=0.018), promotes reverse remodeling of the heart chambers, left atrium in particular (p=0.01), and improves outcomes of the Maze IV procedure (p=0.022) by restoring sinus rhythm in patients with mitral valve defects, complicated AF, and high PH.
<i>Conclusion</i>	This technique must be studied further involving a more significant number of patients, analyzing long-term results, and using this technique in patients with non-valvular causes of secondary PH.
<i>Keywords</i>	Secondary pulmonary arterial hypertension; pulmonary ablation; ganglionated plexus denervation; mitral valve disorder; atrial fibrillation
<i>For citation</i>	Trofimov N. A., Medvedev A. P., Babokin V. E., Efimova I. P., Kichigin V. A., Dragunov A. G., Nikolskiy A. V., Tabaev R. G., Preobrazhenskiy A. I. Circular Sympathetic Pulmonary Artery Denervation in Cardiac Surgery Patients with Mitral Valve Defect, Atrial Fibrillation and High Pulmonary Hypertension. <i>Kardiologiya</i> . 2020;60(1):35–42. [Russian: Трофимов Н. А., Медведев А. П., Бабкин В. Е., Ефимова И. П., Кичигин В. А., Драгунов А. Г., Никольский А. В., Табаев Р. Г., Преображенский А. И. Циркулярная симпатическая денервация легочных артерий у кардиохирургических пациентов с пороком митрального клапана, фибрилляцией предсердий и высокой легочной гипертензией. <i>Кардиология</i> . 2020;60(1):35–42]
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Atrial fibrillation (AF) is one of the most common cardiac arrhythmias. Its incidence is 2% of the population, and it has been tending to increase in the past decade [1, 2]. This type of arrhythmia is detected in 30–84% of patients with cardiac valvular disease. AF reduces the effectiveness of surgical treatment and quality of life of these patients, increases the risk of thromboembolic complications, promotes worsening of heart failure, and ultimately increases mortality [2–5]. The natural course of mitral valve defect promotes dilation and

structural changes of the left atrial walls, which leads to the formation of pathological re-entry circles due to the electrical and morphological remodeling and the formation of electrical conduction blocks [6, 7]. Thus, correction of the valve apparatus is a priority for successful treatment of AF [2, 8]. However, even adequate correction of mitral valve defects in patients with preoperative AF restores sinus rhythm in only 8.5–20% of patients; other patients require additional surgery [9–11].

In the natural course of mitral valve defects, the incidence of which reaches 8% of the population [12], various structural changes develop, so an individual approach is required in each case [13]. The primary complications of mitral valve defects are AF, worsening of secondary pulmonary hypertension (PH), dilation of the heart chambers, and the onset of comorbidities [14, 15]. Worsening of secondary PH during progression of the mitral valve defect contributes to an overload on the right heart, onset of relative tricuspid insufficiency, and consequently, poor prognosis of the disease. Quality of life decreases and chances of premature death increase [16].

The modern classification of mitral valve defects specifies the presence of PH with an increase in resting pulmonary artery pressure > 25 mm Hg, according to magnetic resonance imaging (MRI) and echocardiography (EchoCG) [17, 18]. At a 2013 Congress held in Nice, a classification of PH was proposed with five main groups of pulmonary hypertension: 1) pulmonary arterial hypertension; 2) PH due to hypoxia and/or chronic lung disease; 3) PH due to left heart disease; 4) chronic thromboembolic PH; 5) idiopathic PH [19]. The onset of severe PH in patients with heart valve diseases reduces the effectiveness of surgical treatment of mitral valve defects, prolongs remodeling of the heart chambers, and reduces the effects of surgical correction of AF [20]. Pathomorphological aspects of severe PH are due to an imbalance between vasodilators and vasoconstrictors in the presence of morphological remodeling of the vessel wall [21–23].

In 1962, Osorio and Russek [24] first proved the presence of sympathetic plexuses in the pulmonary artery adventitia, which produce spasm of pulmonary arterioles and increase pressure in the pulmonary circulation. Subsequently, these data were confirmed by Baylen et al. [25] and by Juratsch et al. [26]. Effective treatment of severe PH remains a challenge of modern medicine. Medicinal drugs are expensive and are not always effective in reducing PH [27].

The first techniques of surgical correction of PH were attempted in 2013 by Chen et al. [28], who proposed denervation of pulmonary arteries using an endovascular catheter, and they achieved a significant reduction in pulmonary arterial pressure. Briongos Figuerro et al. [29] also demonstrated the feasibility of surgical denervation of the sympathetic plexuses of the pulmonary arteries and showed that a high preoperative degree of secondary PH closely correlates with persistent severe PH in the postoperative period, even after correction of the mitral valve defect (odds ratio of 1.761;  $p=0.03$ ). Techniques for surgical treatment of PH are also used in

cardiopulmonary bypass for the concomitant correction of heart valve disease. These techniques include epicardial ablation of the anterior wall of the pulmonary trunk and of the pulmonary arterial orifices with a monopolar electrosurgical cautery pencil [30], and also circular ablation of the pulmonary trunk and the orifices of the pulmonary arteries with a bipolar destructor [13, 31]. Despite these research reports, there is currently no standard technique for the surgical treatment of PH, which is why an optimal algorithm for surgical treatment of PH patients must be found.

**Objective:** Investigate the influence of the sympathetic denervation of the pulmonary trunk and the orifices of the pulmonary arteries on the degree of PH and on outcomes of the surgical treatment of AF in patients with mitral valve defects, complicated AF, and severe PH.

## Material and Methods

We analyzed the surgical treatment of 140 patients with mitral valve defect, concomitant AF, and severe PH, i.e., pulmonary artery systolic pressure (PASP) gradient more than 40 mm Hg. The surgical intervention in these patients included the correction of the mitral valve defect, specifically valve replacement or reconstructive surgeries, and Maze IV biatrial radiofrequency ablation with a bipolar AtriCure clamp.

The experimental group (Group 1) included 51 patients, 46 patients with severe mitral stenosis and five patients with grade 4 mitral valve regurgitation. All of these patients underwent correction of mitral valve defect (47 valve replacements and four valve-sparing surgeries), biatrial Maze IV procedure, and denervation of the pulmonary trunk and the orifices of the pulmonary arteries (PADN).

Criteria for inclusion in the experimental group included mitral valve defect, AF, severe PH (PASP > 40 mm Hg), and postembolic secondary PH. All patients were informed preoperatively about a planned additional PADN procedure, which was scheduled with the main stage of the surgical correction. Informed consent for additional radiofrequency ablation of the pulmonary trunk and the orifices of the pulmonary arteries was signed according to Good Clinical Practice (GCP) and the Declaration of Helsinki.

The control group (Group 2) included 89 patients with the same diagnosis of mitral valve defect, complicated AF, and severe AF. However, these patients did not undergo the PADN procedure.

Statistical data analysis was carried out using Statistica 12.0. Quantitative data are presented as mean and standard deviation ( $M\pm SD$ ). For rank values or for non-normal distributions, median, upper, and lower quartiles

(Me [Q1; Q3]) are presented. Due to the non-normal distribution of the rank and quantitative data, statistical significance of differences was calculated using the Mann-Whitney test (pm-u). The differences between relative values of qualitative data were assessed using the  $\chi^2$  test. When at least one cell of a  $2 \times 2$  table had less than five observations, the Fisher's exact test was used. Differences in mean values were considered statistically significant if error probability (p) was less than 0.05.

The main clinical and demographic characteristics of the subjects in Group 1 and Group 2 are listed in Table 1. Intergroup comparisons show more severe conditions in Group 1 subjects, specifically age, EUROSCORE score, left ventricular dilatation, right heart dilatation, left ventricular contractility, and degree of PH.

Denervation of the pulmonary trunk and the orifices of the pulmonary arteries was performed circularly using a bipolar radiofrequency AtriCure ablation clamp. During cardiopulmonary bypass, the pulmonary trunk bifurcation was isolated, and two circular ablation lines were made in the distal pulmonary trunk with three applications of the ablation clamp.

Next, orifices of the right and left pulmonary arteries were isolated, followed by applying similar ablation lines (two lines with three clamp applications on each). The orifice of the right pulmonary artery was isolated to the right of the aorta, in the projection of the transverse sinus.

Ultimately, the pulmonary artery denervation procedure included six ablation lines: two lines in the distal pulmonary artery and two lines in the orifices of the right and left pulmonary arteries.

The average time of the pulmonary artery denervation procedure was  $5.5 \pm 1.5$  min. It was followed by antegrade cardioplegia by introduction of Custodiol solution into the aortic root. The main stage of the surgery, i.e., correction of heart valve disease and Maze IV, was performed after cardiac arrest.

The duration of myocardial ischemia was  $85.2 \pm 26.6$  min, and the duration of cardiopulmonary bypass was  $114.1 \pm 33.4$  min.

The duration of patients' stay in the intensive care unit was  $2.4 \pm 3.1$  days. The postoperative management of the experimental group did not differ from that of the control group. Transthoracic EchoCG was performed in 3, 6, 12, and 24 mos after the surgery to monitor the dynamics of PH regression.

## Results

One patient in each group died due to acute heart failure in the early postoperative period. No specific complications associated with the proposed technique of surgical treatment of severe PH were observed in any group. All patients had positive postoperative dynamics of echocardiographic parameters (Table 2).

**Table 1. Clinical and demographic characteristics of patients before the surgery (n=140)**

Parameters, unit of measurement		Group 1 (n=51)	Group 2 (n=89)	P <sub>m-u</sub>
Sex (male /female)		23/28	28/61	0.108
Age, years		59.4±5.2	55.8±8.3	0.005
Nosology, %	RHD	76	85	0.072
	IE	20	9	0.072
	CTDS	4	6	0.657
Type of AF, %	Long-persistent	86	84	0.751
	Persistent	8	2	0.117
	Paroxysmal	24	13	0.164
Duration of arrhythmia, years		2.63±1.37	2.74±1.74	0.688
Atrial flutter, %		14	20	0.337
Brachiocephalic atherosclerosis with more than 50% stenosis, %		18	17	0.905
History of CVA, %		8	8	0.996
EUROSCORE score, points		5 [4; 8]	4 [3; 6]	0.004
Duration of cardiopulmonary bypass, min		111 (87-130)	136 (118-151)	<0.001
Duration of aortic clamping, min		79 (67-102)	107 (92-128)	<0.001
Tricuspid insufficiency, degree		2 (1-3)	2 (2-3)	0.095
CHF, NYHA functional class		3 (3-4)	3 (3-4)	0.058

Values are means±SD, means with (range), or median (Me) and upper, and lower quartiles (Me [Q1; Q3]). Group 1 = Experimental Group; Group 2 = Control Group. Intergroup differences were calculated with the Mann-Whitney test. CVA, cerebrovascular accident; IE, infective endocarditis; CTDS, connective tissue dysplasia; RHD, rheumatic heart disease; CHF, chronic heart failure.

**Table 2.** Changes of echocardiographic parameters in patients of interest

Parameters, a unit of measurement		Group 1 (group of interest; n=51)	Group 2 (control group; n=89)	P <sub>m-u</sub>
Tricuspid insufficiency, degree	Baseline	2 [1; 3]	2 [2; 3]	0.095
	At 24 months	0 [0; 0]	1 [1; 1]	<0.001
CHF, NYHA functional class	Baseline	3 [3; 4]	3 [3; 4]	0.058
	At 24 months	2 [2; 2]	2 [2; 3]	0.023
LVEDD, cm	Baseline	5.6 [5.4; 6.4]	5.5 [5.2; 5.7]	0.014
	At 24 months	4.6 [4.5; 5.3]	4.8 [4.6; 5.1]	0.896
LVESD, cm	Baseline	4 [3.8; 4.8]	3.8 [3.6; 4.1]	<0.001
	At 24 months	3.2 [3; 3.6]	3.3 [3.1; 3.7]	0.625
LVEDV, cm	Baseline	153.66 [135.34; 208.52]	143.2 [130.4; 160.04]	0.016
	At 24 months	97.34 [93.8; 135.34]	105.85 [97.34; 123.81]	0.858
LVESV, cm	Baseline	70 [61.95; 107.52]	61.95 [54.43; 71.2]	<0.001
	At 24 months	42.55 [35; 54.43]	44.13 [36.46; 57.71]	0.691
LVEF, %	Baseline	52.18 [49.11; 55.12]	56.26 [53.1; 57.98]	<0.001
	At 24 months	58.2 [56.26; 60.09]	57.94 [54.38; 63.27]	0.857
RVESD, cm	Baseline	3.6 [3.4; 4]	3.4 [3.2; 3.7]	0.003
	In 24 months	2.9 [2.8; 3.2]	3 [2.9; 3.1]	0.156
LA ESD, cm	Baseline	5.5 [5.3; 5.7]	5.4 [5.2; 5.6]	0.600
	At 24 months	4.1 [3.8; 4.3]	4.3 [4; 4.6]	0.010
RA ESD, cm	Baseline	5.8 [5.6; 6]	5.6 [5.2; 5.9]	0.095
	At 24 months	4.5 [4.4; 5]	5 [4.4; 5.3]	0.073
PASP gradient, mm Hg	Baseline	48 [45; 60]	46 [44; 50]	0.018
	At 24 months	23 [21; 28]	26 [23.5; 29.4]	0.519
AF, %	Baseline	100	100	>0.05
	At 24 months	16±37	34±48	0.022

Values are means±SD or median (Me) and upper, and lower quartiles (Me [Q1; Q3]). Intergroup differences were calculated with the Mann-Whitney test. EDD, end-diastolic dimension; LV, left ventricle; ESD, end-systolic dimension; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; RV, right ventricle; LA, left atrium; RA, right atrium; PASP, pulmonary artery systolic pressure; CHF, chronic heart failure; AF, atrial fibrillation.

Results shown in Table 2 demonstrate reverse remodeling of the heart chambers, increased contractile function of the left ventricle, and decrease in PH in the experimental group (Group 1). In these patients, the pulmonary trunk and the orifices of the pulmonary arteries were denervated, in addition to the main stage of the surgery. Although baseline performance was worse (EchoCG measurements and age of the patients were significantly different), the results in the experimental group were comparable with those achieved in the control group.

Blocking the sympathetic ganglia in the pulmonary arteries eliminates spasms of small arteries and arterioles, thus increasing the total capacity of the pulmonary circulation, which resulted in a decrease in postoperative PH.

Changes in the mean values of PH in both study groups are provided in Figure 1. These data demonstrate the benefits of a comprehensive approach to the correction of mitral valve defects, complicated AF, and severe PH. Denervation of the pulmonary arteries of the Group 1 patients with more severe PH produced a

significant reduction in pulmonary atrial pressure within 3 mos that was comparable to that in the control group. However, the baseline pulmonary artery pressure was significantly higher in the experimental group.

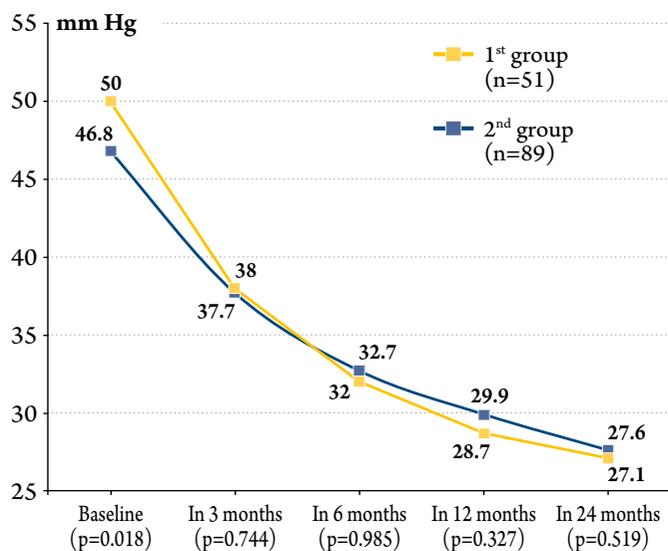
The reduction in PH with elimination of pulmonary vascular spasm contributed to the reduction of left atrial pressure.

Figure 2 shows the dynamics of postoperative left atrial remodeling.

This diagram shows the most favorable results of the reverse left atrial remodeling in the experimental group (Group 1) within 12 months after the surgery. These results were associated with blockade of the sympathetic noradrenergic ganglia located in the distal pulmonary trunk and in the orifices of the pulmonary arteries, reduction of spasm in the hypertrophied muscle layer of the arterioles, and vasodilation in the postoperative period. The result was an increase in the vascular capacity of the pulmonary circulation.

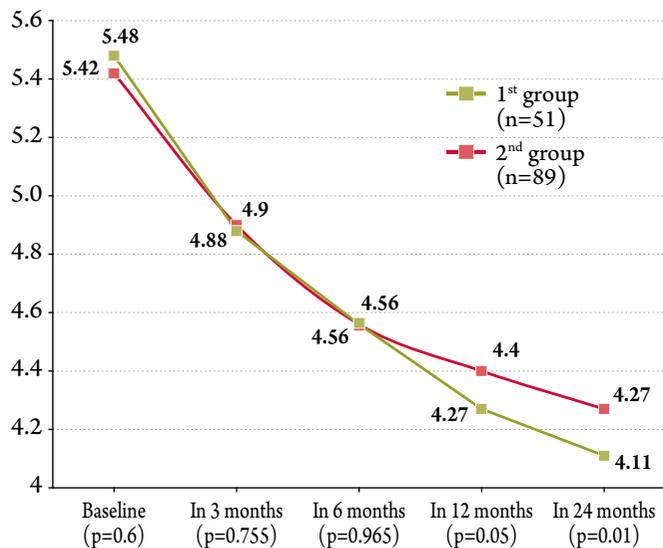
The complex cardiac remodeling increased the effectiveness of the Maze IV procedure by reducing the

**Figure 1. Dynamics of pulmonary hypertension in the experimental and control groups**



Statistical significance was assessed using the Mann-Whitney test

**Figure 2. Dynamics of the left atrial remodeling in the experimental and control groups (left atrial end-systolic dimension, cm)**



number of arrhythmias during the postoperative period. Figure 3 shows the restoration of sinus rhythm after the surgical correction of AF. Data show the percentage of patients with sinus rhythm in each group.

These data demonstrate better recovery and preservation of sinus rhythm in the experimental group (Group 1), in which denervation of the pulmonary arteries was performed in addition to correction of the valve defects and surgical treatment of AF. The comprehensive treatment applied to the experimental group produced 96.9% effectiveness of the Maze IV procedure in 3 months vs. 80% in the control group (Group 2;  $p=0.008$ ).

СКОРАЯ ПОМОЩЬ ГИПЕРТОНИКУ



П N 013055/01

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- 1 Показан большинству гипертоников при внезапном повышении артериального давления<sup>1</sup>
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<sup>1</sup>Гипертонические кризы / Под ред. С.Н. Терещенко, Н.В. Плаунова. – М.: Медпресс-информ, 2013. – С. 21-23.

<sup>2</sup>Приказ Минздрава России от 05.07.2016 N 470н "Об утверждении стандарта скорой медицинской помощи при гипертонии" (Зарегистрировано в Минюсте России 18.07.2016 N 42897)

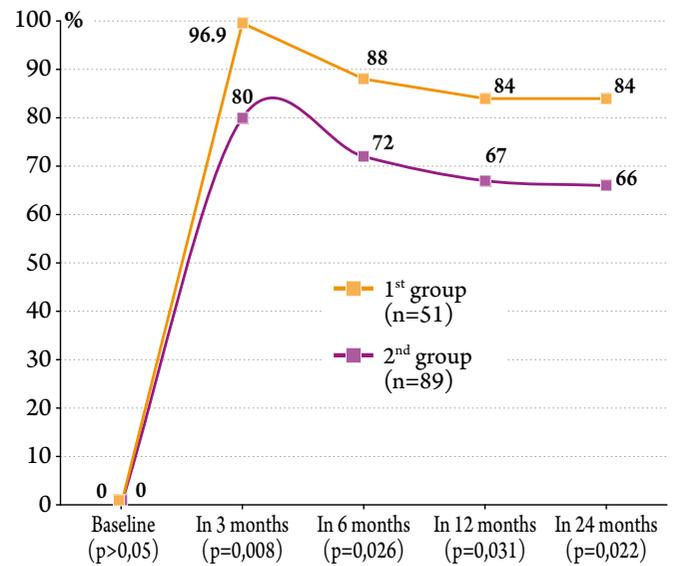
## Discussion

In this investigation, we analyzed the outcomes of surgical treatment of high-degree secondary PH by radiofrequency denervation of the distal pulmonary trunk and the orifices of the right and left pulmonary arteries in patients with mitral valve defects, AF, and severe PH. The control group was composed of an identical cohort of patients who also underwent the correction of the mitral valve dysfunction and AF, but without the correction of PH. Despite the short period of observation and the small number of patients, the data demonstrate more favorable results in left atrial reduction, elimination of relative tricuspid insufficiency, restoration and preservation of sinus rhythm, and as a consequence, elimination of heart failure phenomena in Group 1, in which a comprehensive surgical approach was applied. At baseline, the experimental group was comprised of critical patients, who were different from control group patients in age, EUROSCORE score, dilatation of the left and right ventricles, myocardial contractility, and degree of PH. Echocardiography demonstrated improved cardiac dynamics in the experimental group patients after complex surgery. Thus, values became comparable for the experimental and control groups with regard to size of right and left ventricular chambers, myocardial contractility, and degree of PH. Destruction of sympathetic nerve plexuses in the pulmonary trunk and in the orifices of the pulmonary arteries by the radiofrequency ablation relaxes the smooth muscle of the small pulmonary arteries and arterioles. This results in vasodilation similar to that observed in the lower limb vessels after lumbar sympathectomy. Overall, there was an increase in pulmonary vascular capacity and a decrease in PH. The decrease in the pulmonary artery pressure in experimental patients of Group 1 was due not only to the correction of mitral valve defects and arrhythmias but was due also to the effects of the PADN procedure.

The literature provides evidence of positive results of both endovascular radiofrequency ablation [28] and anterior wall ablation with a monopolar electro-surgical pencil [6]. The technique employed in the current investigation involved circular radiofrequency denervation not only of the pulmonary trunk but also of the orifices of the left and right pulmonary arteries. This allowed maximum denervation of the sympathetic nerve plexuses located in the adventitia of the pulmonary arteries.

The proposed technique is technically straightforward, does not affect the duration of myocardial ischemia, is performed during cardiopulmonary bypass without increasing the duration of aortic clamping, and caused no

**Figure 3.** The effectiveness of surgical treatment of atrial fibrillation in the experimental group (% of patients with sinus rhythm)



Statistical significance was calculated using the  $\chi^2$  test.

complications. The denervation procedure was completed in 5–7 minutes.

This research demonstrates the effectiveness, safety, and practical implications of the proposed technique. Moreover, when the concomitant Maze IV procedure is performed, the same bipolar AtriCure clamp-destructor is used for both surgical treatment of AF and the additional correction of high-degree PH.

## Conclusion

This investigation demonstrated that circular radiofrequency denervation of the pulmonary trunk and the orifices of the pulmonary arteries with a clamp-destructor significantly reduced secondary pulmonary hypertension, promoted reverse remodeling of the heart chambers, particularly the left atrium, and improved outcomes of the Maze IV procedure. These benefits resulted from restoring and preserving sinus rhythm in patients with mitral valve defects, complicated atrial fibrillation, and severe pulmonary hypertension. This technique must be studied further in a larger number of patients in which long-term results are analyzed. In addition, and using this technique in patients with non-valvular causes of secondary pulmonary hypertension should be evaluated.

*No conflict of interest is reported.*

The article was received on 08/08/19

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