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A CASE OF SUCCESSFUL ORTHOTOPIC HEART RETRANSPLANTATION IN AN 11-YEAR-OLD CHILD

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Objective: to present a clinical case of an 11-year-old child who underwent repeat heart transplantation (HT) at Almazov National Medical Research Centre in St. Petersburg, Russia. **Materials and methods.** A case of successful heart retransplantation in an 11-year-old child with cardiac allograft vasculopathy (CAV) is presented. **Results.** The postoperative period after heart retransplantation had no significant differences with the postoperative period of primary heart recipients. The complexity of the intraoperative stage was determined by pronounced adhesions. As part of preoperative preparation, the patient underwent chest CT scan, which, in our experience, allows us to evaluate the heart syntopy and, in turn, is an important preparatory stage in planning repeat interventions. **Conclusion.** Our first experience of cardiac retransplantation in pediatric patients suggests that repeat HT is the most optimal treatment for pediatric patients with CAV and requires more thorough preoperative preparation.

Keywords: heart retransplantation, orthotopic heart retransplantation, artificial circulation.

INTRODUCTION

HT is the gold standard for the treatment of American College of Cardiology/American Heart Association (ACC/AHA) stage D heart failure (HF). For HF, 35,703 adult HTs were performed worldwide from 2009 to 2017, and about 5800 heart transplants are performed annually [1]. Between 2009 and 2022, 2224 HTs were performed in the Russian Federation. The median survival after adult HT exceeds 12 years, the survival rate depends on the 1-year survival rate, which exceeds 50% after 14 years of follow-up [1], and the unadjusted 1-year survival rate after HT is 85% [2]. Post-transplant complications include graft failure, rejection, and CAV.

According to world reports, the number of HTs performed is increasing annually and averages 100 to 120 per year worldwide or 2% to 4% of all HTs in adults. In 2010, a repeat HT was performed for the first time in the Russian Federation. Today, the number of such operations remains sporadic.

INCIDENCE AND EPIDEMIOLOGY OF REPEAT HEART TRANSPLANTATION

Compared to primary HT recipients, retransplant recipients are on average younger, more sensitized, and tend to be more acutely ill with worsening renal function, increased likelihood of hospitalization, dialysis, intubation, inotropic support, or extracorporeal membrane oxygenation (ECMO) [3]. Between 2006 and 2013, 51.6% of adult heart transplant recipients were hospitalized at the time of retransplantation, 48% received inotropic therapy, 6.7% were implanted with left ventricular assist device, 4.6% with right ventricular assist device, 7.2% with intra-aortic balloon pump counterpulsation, 8% with mechanical ventilation, 2% with total artificial heart, and 5.8% with ECMO [3].

The three main indications for heart retransplantation (RTx) are acute rejection, early graft failure, and CAV [4].

Although RTx accounts for no more than 5% of all HTs, it was important to review the outcomes of repeat HTs in critically ill patients. There were marked clinical differences between patients who required cardiac RTx with and without CAV. However, RTx with CAV should be considered as the optimal treatment option in this group of patients. Various options for mechanical circulatory support in patients scheduled for surgical treatment should be considered as a way to stabilize the patient as well as a bridge to RTx. There has been an annual improvement in survival in patients undergoing RTx for CAV [4].

A study by N.K. Chou et al. that was conducted from March 1995 to May 2005, featured 8 patients with cardiac allograft failure, of whom 6 (75%) had CAV and 2 (25%) had acute rejection. The mean interval to RTx was 32 to 84 months. CAV was diagnosed on the basis of any localized coronary artery anomalies or diffuse coronary artery narrowing. A left main trunk lesion ≥70% of the primary vessels with stenosis ≥70%, or isolated branch stenosis ≥70% in all three systems was classified as a severe NYHA class III to IV lesion for which re-transplantation should be considered. These patients underwent heart RTx. As a control for acute graft rejec-

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tion, endomyocardial biopsy was performed weekly for the first month, then every 3 months for the first year, and then annually thereafter. Coronary angiography was performed 1 month after RTx. Acute rejection was defined as acute humoral or cellular rejection grade 3A or higher using the International Society for Heart and Lung Transplantation (ISHLT) classification criteria [4].

Of 628 HTs in 606 patients in the Russian Federation, operated on between 1986 and early 2016, 22 patients (3.63%) required repeat heart transplantation. The mean age of recipients for the RTx was 45.59 ± 14.66 years. In 8 (36.4%), the reason for performing RTx was chronic persistent graft rejection with hemodynamic disorders; in 10 (45.6%) recipients, RTx was performed early due to primary graft dysfunction. Two recipients (9.0%) had secondary graft dysfunction resulting from heart transplant coronary artery disease (TxCAD), and two had acute graft myocarditis (9.0%). The interval between the primary and the repeat HT was 734.59 ± 1235.4 days. All recipients received triple-drug immunosuppressive therapy, including tacrolimus or cyclosporine, mycophenolate mofetil and methylprednisolone [5].

By 2018, the experience of performing heart RTx at Shumakov National Medical Research Center of Transplantology and Artificial Organs had reached 27 surgeries in patients for periods from 1 day to 15 years after primary transplantation [5].

The most common indications for RTx are CAV and allograft rejection. While primary graft failure is the most common cause in the first month after HT, CAV is the most common cause after the first year. Other causes include graft rejection or heart valve defect [6]. A group of scientists led by Syed-Saif Abbas Rizvi in 2017 conducted a systematic review of 11 studies that included 7,791 patients, of which 7,446 patients underwent primary HT, whereas 345 required RTx. Indications for RTx were CAV (60.2%), acute rejection (20.7%), and early graft failure (19.1%) [7].

An earlier analysis of the ISHLT/UNOS registry for all cardiac retransplants performed in the United States from 1987 to 1998 showed that the time from primary transplant to RTx ranged from 1 day to 15.5 years, with 56% undergoing RTx for chronic rejection or CAV, 18% for primary or nonspecific graft failure, 9% for acute rejection, and 3% due to hyperacute rejection. Most of these patients (60%) were in the intensive care unit at the time of RTx, and 40% were on some form of life support (e.g., ventricular assist device, inotropic therapy) [8].

The presence of severe CAV (left coronary artery stenosis ≥50% or stenosis of two or more primary vessels ≥70% or branch stenosis ≥70% in all 3 systems) is associated with poor 1-year survival and high mortality. Such patients should be considered for RTx [9, 10].

The aim of the study was to present a clinical observation of a patient who underwent repeat heart transplantation at Almazov National Medical Research Centre.

MATERIALS AND METHODS

An 11-year-old child, on April 12, 2021, was urgently hospitalized at Almazov National Medical Research Centre due to increasing chronic heart failure on the background of dilated cardiomyopathy, CAV. From the anamnesis: supraventricular extrasystoles were detected from the age of five after an acute respiratory viral infection, left ventricular ejection fraction (LVEF) 54%. In April 2015, he was hospitalized at Children's Republican Clinical Hospital in Saransk for decompensated chronic heart failure (DCHF), as well as rhythm disturbances such as supraventricular extrasystoles and unstable paroxysmal supraventricular tachycardia. He was discharged on the background of improved diagnosis: chronic non-rheumatic carditis with lesions of the cardiac conduction system, with rhythm disturbances – ventricular polymorphic extrasystoles, ventricular tachycardia with a probable outcome in dilated cardiomyopathy (DCM). In March 2016, after recurrent arrhythmic syncope, it was decided to implant a Protecta DR D 364 DRG implantable cardioverter-defibrillator. He was discharged with recommendations to continue sotalol, metoprolol, captopril, verospiron, diuver, carbamazepine, and prednisolone.

From June 2016, the patient's condition deteriorated, and there was increasing heart and respiratory failure. According to data from 24-hour ECG monitoring: 15,819 polymorphic ventricular extrasystoles, decreased left ventricular ejection fraction (LVEF) according to echocardiography (EchoCG) up to 10% (Simpson). In January 2017, he was consulted by a council of physicians at Almazov National Medical Research Centre due to severe CHF on the background of dilatation of heart chambers: left ventricular end-diastolic diameter (LVEDD) 61 mm, decrease in myocardial contractility up to 10% (Simpson), formation of mitral and tricuspid regurgitation, life-threatening rhythm disturbances and low effectiveness of drug therapy, the only possible treatment for this patient is heart transplantation.

The child was admitted to Fortis Malar Hospital, Chennai, India from November 10, 2017 to March 20, 2018. During hospitalization, several cardiac arrest episodes were recorded, after which ECMO machine was connected. On January 17, 2018, orthotopic donor HT surgery was performed for health indications. The postoperative period was complicated by episodes of severe hypotension, as well as left ventricular dysfunction. Against the background of increasing left ventricular failure, a decision was made to reimplant the ECMO system. In view of inotropic therapy, the patient's hemodynamic state stabilized, LV contractility improved. On January 20, 2018, the ECMO system was explanted. On February 15, 2018, the cardiac monitor showed ventricular fibrillation with transition to asystole, cardiopulmonary resuscitation (CPR) was initiated. Acute rejection

was suspected and pulse therapy with glucocorticoids was initiated.

Coronary angiography was performed – a three-vessel lesion of the coronary arteries was detected, and percutaneous transluminal angioplasty of the right coronary artery and anterior interventricular coronary artery was performed. The diagnostic procedure was complicated by acute thrombosis in the right coronary arterial wall, CPR was initiated, and thrombolysis (eptifibatide) was performed. Due to unstable hemodynamics with a tendency to hypotension, the ECMO system was implanted again. Positive dynamics was observed for six days; against this background, the ECMO system was removed. Endomyocardial biopsy was performed – no signs of rejection. In March 2018, he was discharged due to his stabilized condition.

In May 2018, he suffered an ischemic stroke: mixed tetraparesis, seizure syndrome, asthenic syndrome in the early recovery period. Anticonvulsant therapy Kepra 33 mg/kg was prescribed; subsequently, positive dynamics were noted during the therapy; seizures did not recur, the therapy was discontinued.

According to EchoCG studies dated December 19, 2018, there was moderate dilatation of the left heart chambers (left atrium (LA) 30 mm, LVEDD 43 mm). LVEF 57%. Mitral valve (MV) leaflets of increased echogenicity. Slight acceleration of transmittal blood flow 1.6 m/s. Moderately dilated aortic root lumen, prolapse of aortic valve (AV) flaps, regurgitation grade 1. Estimated systolic pressure in the pulmonary artery (PA) 30 mm Hg. Moderate LV myocardial hypertrophy (interventricular septum (IVS) up to 8–9 mm, left ventricular posterior wall (LVPW) up to 9 mm).

The patient was re-hospitalized for evaluation at Fortis Malar Hospital, Chennai, India from February 17, 2019 to February 21, 2019. This hospitalization included percutaneous transluminal coronary angioplasty with left coronary artery stenting and anterior interventricular artery restenosis. The postoperative period was uneventful. According to EchoCG data over time, grade II mitral regurgitation, tricuspid insufficiency (TI) grade 2, pulmonary hypertension (LA pressure 51 mm Hg, inferior vena cava (IVC) 1.1 cm, collapsing more than 50%). LVEF 65%. He was discharged in stable condition with recommendations to continue immunosuppressive and antimycotic therapy, as well as statins.

As part of preoperative preparation, coronary angiography was performed on February 11, 2021 – a multivessel coronary lesion was determined (Fig. 1).

Chest CT scan shows that the right atrium and right ventricle are directly adjacent to the sternum in the lower

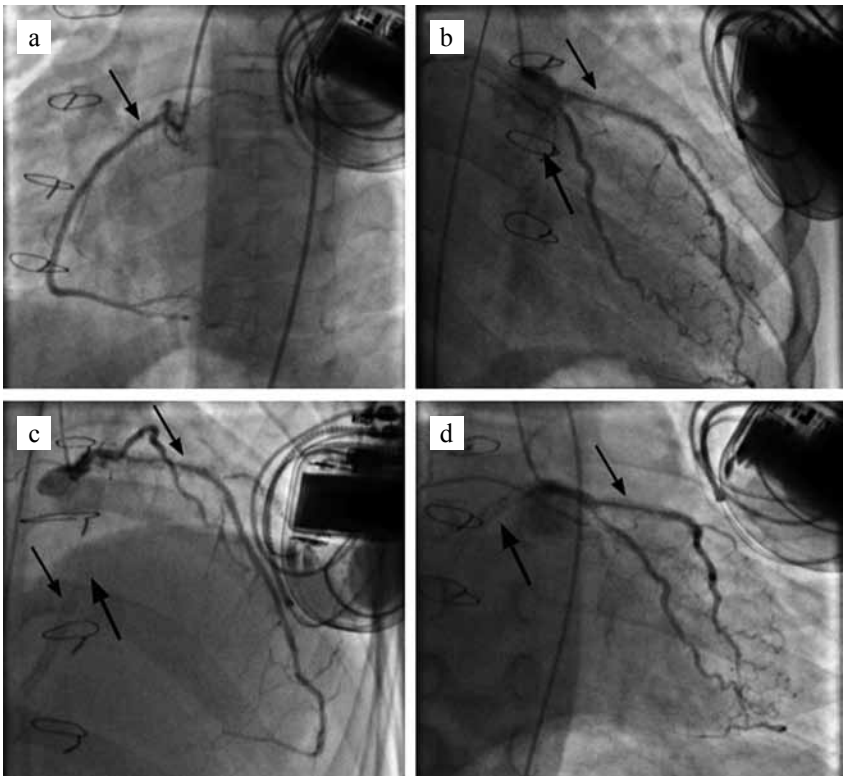

Fig. 1. Preoperative coronarography. The right coronary artery basin was previously stented, diffuse loss of stent lumen up to 40% maximum (a); left coronary artery basin, anterior interventricular artery (AIA): post-stenting condition in the proximal third from the orifice – up to 70% restenosis, the periphery is satisfactory. Circumflex artery (CA): represented by the main branch and the marginal artery (MA). The main branch is occluded in the proximal third, the periphery is hypoperfused, filled through intrasystem collaterals. MA – post-stenting condition – up to 70–80% restenosis, the periphery is satisfactory (b, c, d)

third, no focal and infiltrative changes were detected (Fig. 2).

On April 12, 2021, surgical treatment was performed in the scope of resternotomy, orthotopic heart transplantation by bicaval technique. After performing resternotomy and cardiolysis, the main stage of surgical intervention was performed according to the standard technique, it proceeded without peculiarities. Extracorporeal circulation lasted for 92 minutes, aortic clamping time was 63 minutes, and graft ischemia time was 155 minutes. The intraoperative stage proceeded without complications, and custodiol cardioplegia was used. After removing the aortic clamp, spontaneous recovery of cardiac activity was noted, no rhythm disturbances were registered. After control transesophageal echocardiography, decannulation was performed. At the end of extracorporeal circulation, we measured central hemodynamics: heart rate 125 beats/min, sinus rhythm, blood pressure 85–95/60–65 mmHg, cardiac index 2.53 l/min/m^2, stroke volume 24.5 ml, total peripheral resistance 1808 dyn·sec·cm^5, central venous pressure 4 mmHg, and pulmonary artery pressure 20/7 mmHg. On the background of inotropic therapy were dobutamine 5 mcg/kg/min and norepinephrine 0.6 mcg/kg/min.

The patient was then transferred to the aseptic ward of the Department of Anesthesiology and Reanimation in a stable condition, received dobutamine 5 mcg/kg/min, noradrenaline 0.6 mcg/kg/min as inotropic and vasopressor therapy. He was extubated 8 hours after the end of the operation, without any peculiarities. Subsequently, positive dynamics was noted in the form of decreasing doses of inotropic and vasopressor therapy; from day 2, the patient was activated within the bed, verticalization was also performed. Tacrolimus levels were monitored daily and immunosuppressive therapy was adjusted. On the 10th day after surgical treatment, the patient was transferred to the specialized department, where further rehabilitation and optimization of therapy was carried out. According to the standard protocol, endomyocardial biopsy was performed every 14 days. Histological examination revealed no signs of rejection (AMR0), EchoCG showed LVEF 70%, blood flow on the aortic valve was not accelerated, mitral regurgitation up to grade I, tricuspid regurgitation up to grade I, grade I pulmonary regurgitation, left ventricular global contractility was not reduced, no asynergy zones were reliably detected, right ventricular myocardium contractility was moderately reduced (TAPSE = 12 mm, S' = 8 cm/sec).

During hospitalization, immunosuppressive therapy was adjusted: gradual reduction of metipred to 10 mg per day, tacrolimus depending on serum levels (target values by the time of discharge), mycophenolate mofetil under control of white blood cell/neutrophil count. After administration of a course of granulocyte colony-stimulating factor (leukostim), the neutrophil level normalized. Mycophenolate mofetil was resumed. After a course of rehabilitation and adjustment of immunosuppressive therapy, the patient was discharged for outpatient follow-up.

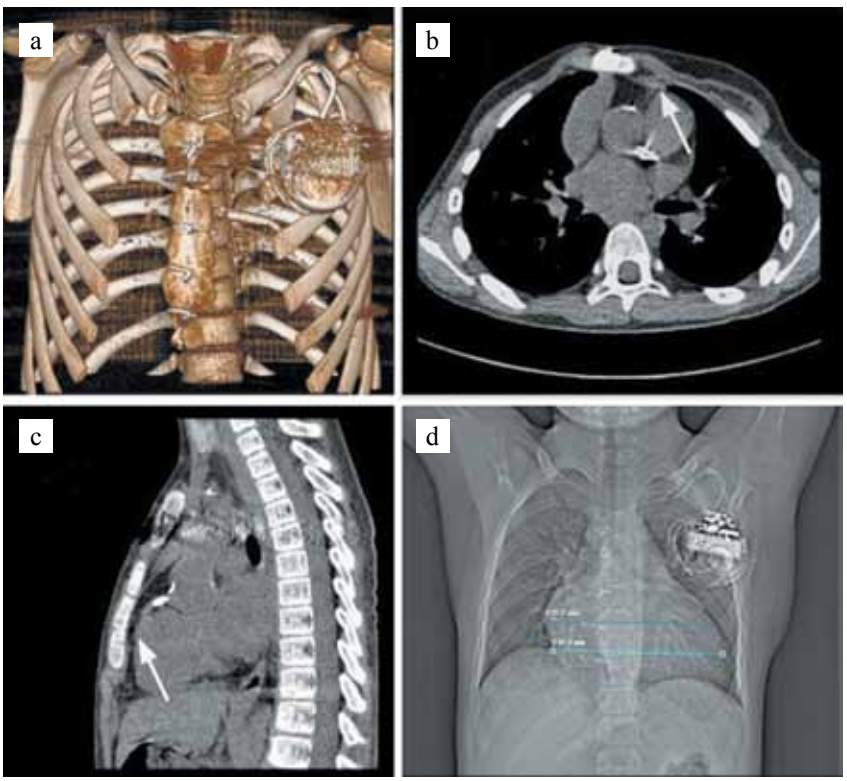

Fig. 2. Preoperative chest CT scan. CT volume rendering (a); transverse image (b); sagittal image (c); frontal image showing the transverse dimensions of the transplanted heart (d)

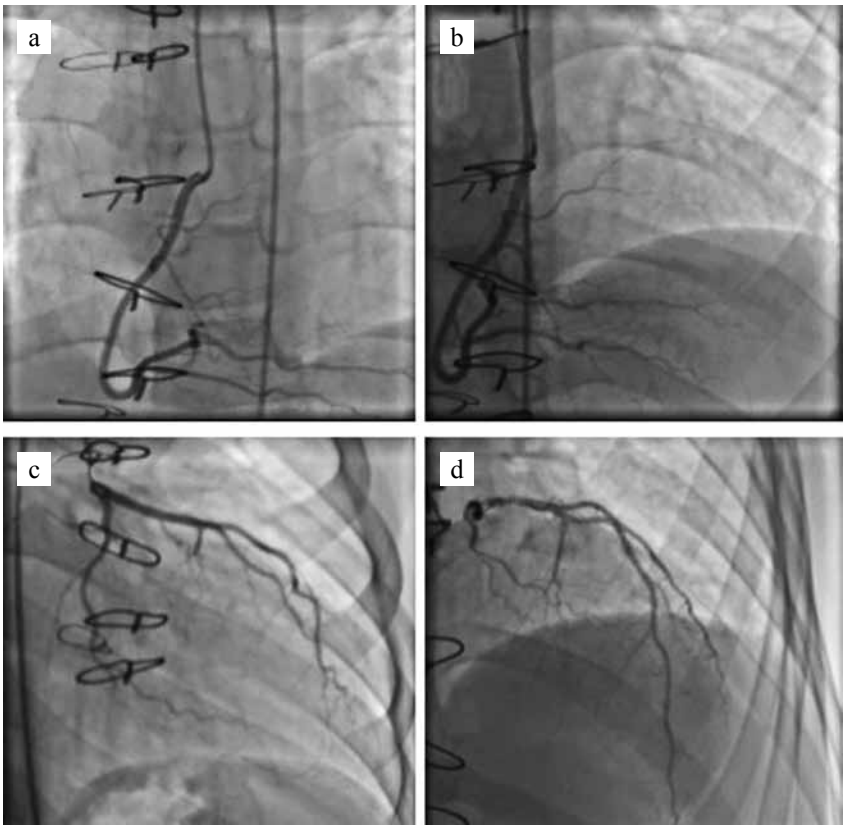

Fig. 3. Postoperative (12 months later) coronarography. Right and left coronary artery basin, without signs of atherosclerotic lesion of the coronary bed

Thereafter, planned hospitalizations and therapy adjustments, as well as examinations were carried out. On May 27, 2022, control coronarography was performed – coronary arteries without angiographic signs of atherosclerotic lesions. Blood flow through the coronary arteries was satisfactory (Fig. 3).

DISCUSSION

This case report describes a patient with CAV, one of the possible complications after heart transplantation. Patients with such a diagnosis are rarely helped by drug therapy; the most optimal treatment is surgical – heart retransplantation. According to the world literature, the number of repeated interventions does not exceed 5% in the age group from 18 to 39 years, but there is an increasing trend every year. However, the number of repeated HTs in the pediatric population in the Russian Federation, as well as in the world, still amounts to dozens of cases, which reflects the clinical significance of such reports.

As part of the preoperative preparation, the patient underwent chest CT scan, which, in our experience, allows us to assess cardiac syntopy and, in turn, is an important preparatory stage in planning repeat interventions. Preoperative preparation of the patient is also important, namely CHF compensation in a specialized department, if the severity of the patient's condition allows it.

The second stage of cardiac rehabilitation took place at the cardiology department. This clinical case demonstrates successful treatment of a CAV patient, in which case repeat HT was the optimal treatment.

CONCLUSION

The management of patients indicated for retransplantation, both preoperatively, as well as intraoperatively and postoperatively, requires multidisciplinary involvement. Repeat heart transplantation is the most optimal treatment modality for pediatric patients with CAV. However, further clinical evidence needs to be accumulated from which clear guidelines for this approach should be developed.

The authors declare no conflict of interest.

REFERENCES

1. *Chambers DC, Cherikh WS, Harhay MO, Hayes D Jr, Hsich E, Khush KK et al*. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult lung and heart-lung transplantation Report-2019; Focus theme: Donor and recipient size match. *J Heart Lung Transplant*. 2019 Oct; 38 (10): 1042–1055. doi: 10.1016/j.healun.2019.08.001.
2. *Barghash MH, Pinney SP.* Heart Retransplantation: Candidacy, Outcomes, and Management. *Curr Transplant*

Rep. 2020; 7 (1): 12–17. doi: 10.1007/s40472-019-00257-y. Epub 2019 Dec 17. PMID: 32435573; PMCID: PMC7223608.

3. *Lund LH, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dipchand AI et al.* International Society of Heart and Lung Transplantation. The registry of the International Society for Heart and Lung Transplantation: thirty-first official adult heart transplant report – 2014; focus theme: retransplantation. *J Heart Lung Transplant*. 2014 Oct; 33 (10): 996–1008. doi: 10.1016/j.healun.2014.08.003. Epub 2014 Aug 14. PMID: 25242124.
4. *Chou NK, Chi NH, Chen YS, Yu HY, Lee CM, Huang SC et al*. Heart retransplantation for heart allograft failure in Chinese heart transplant recipients: NTUH experience. *Transplant Proc*. 2006 Sep; 38 (7): 2147–2148. doi: 10.1016/j.transproceed.2006.06.109. PMID: 16980027.
5. *Gautier SV, Poptsov VN, Saitgareev RSh, Shumakov DV, Zakharevich VM, Khalilulin TA i dr.* Strategiya retransplantatsii serdtsa: rezul'taty i problemy. *Vestnik transplantologii i iskusstvennykh organov*. 2016; 18 (Prilozhenie): 32.
6. *Lund LH, Edwards LB, Kucheryavaya AY, Dipchand AI, Benden C, Christie JD et al.* International Society for Heart and Lung Transplantation. The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Official Adult Heart Transplant Report – 2013; focus theme: age. *J Heart Lung Transplant*. 2013 Oct; 32 (10): 951–964. doi: 10.1016/j.healun.2013.08.006. PMID: 24054804.
7. *Rizvi SA, Luc JGY, Choi JH, Phan K, Moncho Escrivà E, Patel S et al*. Outcomes and survival following heart retransplantation for cardiac allograft failure: a systematic review and meta-analysis. *Ann Cardiothorac Surg*. 2018 Jan; 7 (1): 12–18. doi: 10.21037/acs.2018.01.09. PMID: 29492380; PMCID: PMC5827127.
8. *Srivastava R, Keck BM, Bennett LE, Hosenpud JD.* The results of cardiac retransplantation: an analysis of the Joint International Society for Heart and Lung Transplantation/United Network for Organ Sharing Thoracic Registry. *Transplantation*. 2000 Aug 27; 70 (4): 606–612. doi: 10.1097/00007890-200008270-00013. PMID: 10972218.
9. *Costanzo MR, Naftel DC, Pritzker MR, Heilman JK 3rd, Boehmer JP, Brozena SC et al*. Heart transplant coronary artery disease detected by coronary angiography: a multiinstitutional study of preoperative donor and recipient risk factors. Cardiac Transplant Research Database. *J Heart Lung Transplant*. 1998 Aug; 17 (8): 744–753. PMID: 9730422.
10. *Mehra MR, Crespo-Leiro MG, Dipchand A, Ensminger SM, Hiemann NE, Kobashigawa JA et al*. International Society for Heart and Lung Transplantation working formulation of a standardized nomenclature for cardiac allograft vasculopathy – 2010. *J Heart Lung Transplant*. 2010 Jul; 29 (7): 717–727. doi: 10.1016/j.healun.2010.05.017. Erratum in: *J Heart Lung Transplant*. 2011 Mar; 30 (3): 360. PMID: 20620917.

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