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A 5-YEAR SINGLE-CENTER EXPERIENCE IN HEART TRANSPLANTATION IN ROSTOV OBLAST

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Objective: to evaluate the outcomes of heart transplants performed at Rostov Regional Clinical Hospital within five years. **Materials and methods.** Between 2017 and 2022, 29 orthotopic heart transplants (HT) were performed in our clinic. Heart failure was caused by postinfarction cardiosclerosis (21 cases, 72.4%) and dilated cardiomyopathy (8 cases, 27.6%). Among the recipients, 27 (93.1%) were men and 2 (6.9%) were women. Mean age was 53.14 ± 8.7 years (34 to 67 years). All patients received quadruple-drug immunosuppressive therapy, including induction with monoclonal antibodies; calcineurin inhibitor, mycophenolic acid, and corticosteroid were used after HT. **Results.** In-hospital mortality was 10.34% (n = 3). The causes of death were multiple organ failure and infectious and septic complications. After discharge, 4 (13.8%) recipients died over 5 years. Rejection reaction with the development of graft dysfunction (3 recipients, 75%), infectious and septic complications (1 recipient, 25%) were the causes of death in the long-term period. The survival rate was analyzed according to the Kaplan–Meier estimate. One-year survival was 80.9%. Three-year survival rate corresponded to the 5-year survival rate – 70.56%. Five-year survival of patients surviving the first year after HT was 86.1%. Maximum follow-up period was 64 months. **Conclusion.** HT continues to be the gold standard for patients with end-stage heart failure. Five-year HT experience in our center has shown a survival rate that is comparable to that of the International Society for Heart and Lung Transplantation (ISHLT).

Keywords: heart transplantation, heart failure, immunosuppressive therapy.

INTRODUCTION

Despite the significant evolution in the treatment of heart failure (HF), in some cases, even if optimal therapy is selected, the patient's condition remains severe, quality of life is low, and prognosis is disappointing [1].

Over the last 20 years, the number of patients with functional class (FC) III–IV chronic heart failure (CHF) in the Russian Federation increased by 1.3% (from 1.8% to 3.1%), reaching 4.5 million people. Prognosis of such patients is unfavorable: the median survival time for FC III–IV CHF is 3.8 years. Annual mortality in this group, even when treated in a specialized hospital, is 10.2% [2]. In the group of patients with refractory CHF, mortality within a year can reach 50% [3].

To date, HT is the only effective method of treatment for end-stage CHF, which reliably increases survival, improves exercise tolerance and quality of life. In addition, in most cases, HT allows patients to return to active activity [4].

Currently, more than 5000 HT are performed annually worldwide [5]. Continuous development of surgical techniques and technologies, improvement and emergence of new immunosuppressive therapy regimens, have significantly improved prognosis after HT [6]. According to ISHLT reports, the survival rate of patients after transplantation has improved considerably over the last decades and today the median survival rate exceeds 12 years [5].

National healthcare has come a long way over the past decades. Due to the active development of transplantology, the number of HT has increased 10-fold in the past 14 years. For instance, the number of HTs in Russia increased from 0.2 per million population in 2008 to 2.0 in 2022. And the total number of HTs performed over 35 years was 2200 [7].

MATERIALS AND METHODS

The HT program in Rostov Oblast was started in 2017. Over five years, 29 orthotopic HTs have been performed at the cardiac surgical center of Rostov Regional Clinical Hospital. The outcomes were analyzed retrospectively.

From November 2017 to November 2022, there were 54 patients on the HT waiting list. Of these, transplantation was performed in 29 (53.7%) patients; 10 (18%)

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patients on the waitlist died from CHF progression in the absence of technical possibility to perform HT or use mechanical circulatory support as a bridge to HT. Two (4%) patients were withdrawn from the waitlist for various reasons. One patient had remission of the disease on the background of selected therapy, his hemodynamic parameters improved, ejection fraction increased, in view of which he was delisted. Thirteen (24%) patients remained in the HT waitlist at the moment of writing this paper.

Those with refractory end-stage congestive heart failure (CHF) and a prognosis of 1-year transplant-free survival <50% were selected for inclusion on the HT waiting list. Objective criteria for this prognosis include:

– <20% left ventricular ejection fraction;
– >20 mmHg pulmonary wedge pressure;
– <12 mL/kg/min decrease in peak oxygen consumption (peak VO_2) in patients not receiving beta-blockers and peak <14 mL/kg/min VO_2 against the background of maximum tolerated dose of beta-blockers;
– signs of severe myocardial ischemia in patients with coronary heart disease, which significantly limit daily activities when revascularization by coronary artery bypass grafting or percutaneous coronary angioplasty is impossible;
– recurrent life-threatening rhythm disturbances refractory to drug therapy, as well as to electrophysiological methods of treatment (catheter ablation and(or) implantation of cardioverter-defibrillator) [8].

The main contraindication for transplant listing was the detection of high vascular resistance of the small pulmonary circulation (>5 Wood's units), with no effect on inhaled vasodilators.

Among the operated patients, the etiology of end-stage heart failure was postinfarction cardiosclerosis in 21 cases (72.4%) and dilated cardiomyopathy in 8 cases (27.6%); 93.1% (n = 27) of recipients were male, 6.9% (n = 2) were female. The mean age was 53.14 ± 8.7 years (34 to 67 years).

To assess the degree of HF, a 6-minute walk test was performed, which averaged 257 ± 83.4 m: 16 (55.2) recipients had the New York Heart Association (NYHA) functional class (FC) IV, 13 (44.8%) had NYHA FC III.

Echocardiography revealed a marked decrease in left ventricular (LV) myocardial contractility – LV EF 22.11 ± 8 (10–47%), cardiomegaly (LV end-diastolic diameter 71.54 ± 8.7 mm (55–87 mm), LV end-diastolic volume 291.6 ± 79.8 ml (160–550 mL), moderate pulmonary hypertension (mean pulmonary artery pressure 32.7 ± 11.24 mmHg).

The results of right heart catheterization showed moderately elevated pulmonary artery pressure of 29.37 ± 13.28 mmHg (10 to 63), elevated pulmonary vascular resistance in Wood units of 1.58 ± 0.83 (0 to 3.1), and low cardiac index of 1.85 ± 0.58 L/min/m^2 (0.46 to 3.2).

The bicaval HT technique was used in all cases.

The time parameters were as follows: CPB 178.9 ± 38.77 min (123–273), donor heart anoxia time 144.5 ± 32.87 min (78–220), and operation time 296.39 ± 61.5 min (218–450). The mean length of stay at the intensive care unit was 7.36 ± 3.1 days.

In the postperfusion period, all patients received dopamine-based inotropic support, combined with adrenaline (91% of cases), and with vasopressor support with norepinephrine (in 79% of cases). Right ventricular failure (RVF) was managed using levosimendan, sildenafil, nitric oxide inhalation and ilprost. All the drugs were administered at moderate therapeutic doses.

After HT, all patients received triple-drug immunosuppressive therapy, which was selected to minimize the toxic effects of the drugs on the recipient. Histological evaluation of biopsy specimens was performed according to the ISHLT-2004 classification. The average length of stay at the hospital by the recipient was 36.2 ± 12.4 days.

RESULTS

All cases of orthotopic HT performed were analyzed. During the follow-up period, 24% (n = 7) of recipients died. In-hospital mortality was 10.3% (n = 3). The 30-day mortality was 3.44% (n = 1). During the follow-up period of up to 3 months, 13.8% (n = 4) of recipients died.

The main causes of early mortality were multiple organ failure (MOF) and infectious septic complications, which amounted to 100% (n = 4) in the structure of early mortality (Fig. 1). The cause of in-hospital mortality in 2 cases was MOF developing against the background of acute RVF, and 1 patient died due to a combination of sepsis and MOF. One recipient was discharged in satisfactory condition, but a month later he was re-hospitalized with double pneumonia and died of infectious septic complications.

Among non-fatal complications (Fig. 2) in the early postoperative period, RVF occurred in 18 (69.2%) patients. To correct RVF, levosimendan was used in all cases, sildenafil was used in 18 (62%) patients, nitric oxide inhalation was used in 5 (17.2%) patients, and 2 (6.9%)

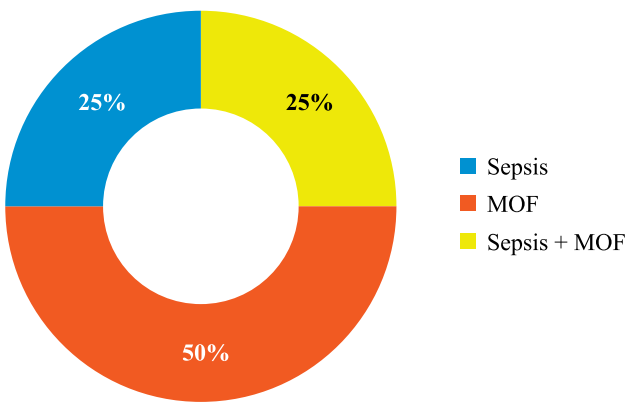

Fig. 1. Causes of early post-HT mortality

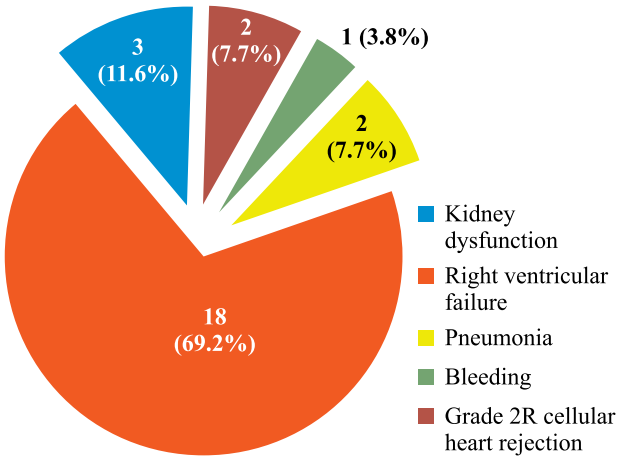

Fig. 2. Structure of non-fatal in-hospital complications

recipients required triple-drug therapy: sildenafil, nitric oxide inhalation, and ilprost.

Postoperative renal dysfunction requiring renal replacement therapy (RRT) was noted in 3 (11.6%) patients.

Infectious complications during the hospital period were represented by bacterial pneumonia in 1 (3.85%) patient.

In one case, a patient developed bleeding on day 10 after HT, which was successfully controlled. The subsequent postoperative period was uneventful, and the patient was discharged from the hospital on day 32.

One patient, operated on in 2021, was transferred to an infectious diseases hospital on day 2 after testing positive for SARS-CoV-2. The postoperative period was uneventful, therapy was monitored and coordinated remotely. After 13 days, she was transferred to the cardiology department. After the necessary instrumental examinations, including endomyocardial biopsies, and after achieving the target laboratory parameters, she was discharged on day 15.

Acute rejection reaction during the hospital period was diagnosed in 2 (7.7%) recipients.

Biopsy results were analyzed according to the ISHLT-WF 2004 (International Society for Heart and Lung Transplantation – working formulation, 2004) recommended classification of acute rejection. To manage the acute rejection crisis, pulse therapy with methylprednisolone (1.0 g, 3 times a day), plasma filtration, and immunoglobulin therapy were implemented.

At control examination at different periods after HT, coronary artery disease was detected in the transplanted heart of 5 recipients (17.2%), which in two cases required stenting of the affected coronary artery segments, and in cases where stenoses were hemodynamically insignificant, adjustment of lipid-lowering therapy.

Three recipients died in the long-term period. The cause of death in all cases was graft rejection reaction combined with other complications. So, one patient died in 7 months due to infectious septic complications on the background of acute antibody-mediated rejection (AMR). One patient died in 14 months from pulmonary thromboembolism on the background of grade 2R acute cellular rejection, acute AMR. One patient died in 24 months from myocardial infarction on the background of acute AMR.

During the entire follow-up period, grade 1R cellular rejection was diagnosed in 13 (44.8%) recipients, and grade 2R in 4 (13.8%). Grade 1 AMR was diagnosed in 3 (10.3%) recipients, all these cases were fatal.

DISCUSSION

Currently, there are two most common HT techniques: biatrial (developed in 1921 by R. Lower and N. Shumway) and bicaval (proposed in 1990 by M. Yacoub and D. Sievers) [9, 10]. Considering the advantages of the bicaval technique – maintaining the normal geometry of the right atrium, reducing the frequency of sinus node dysfunction and tricuspid regurgitation – we consider this technique to be the most optimal and use it in our center. All patients had sinus rhythm at the time of discharge.

Evaluating our HT outcomes, we see that the main cause of early postoperative mortality in patients is associated with MOF and septic complications on the background of immunosuppression.

Immunosuppressive therapy regimens used today can, in most cases, achieve a balance by adequately suppressing rejection reactions and preventing excessive immunosuppression. And the use of induction therapy can reduce the risk of acute rejection and delay the administration of nephrotoxic calcineurin inhibitors.

In our case, immunosuppression was induced via oral administration of mycophenolic acid (Mayfortic) 360–720 mg before the operation, infusion of monoclonal antibodies (basiliximab) 20 mg before aortic clamping and administration of methylprednisolone before blood flow was activated. On day 4 after HT, basiliximab was re-injected. Subsequently, the patients received a triple-drug immunosuppressive therapy: calcineurin inhibitor (tacrolimus), sodium mycophenolate (Mayfortic) and corticosteroid (prednisolone). Calcineurin inhibitors were administered from day 2–3 after surgery under the control of renal function, gradually increasing the dose of the drug to the required level. In accordance with the scheme proposed by specialists at Shumakov National Medical Research Center of Transplantology and Artificial Organs, the target tacrolimus blood trough level at year 1 after HT was considered to be a decreasing level from 15 to 5 ng/mL, and subsequently the level was maintained at 5 ng/mL [11, 12].

In our practice, there were 2 cases of seizure syndrome developing against the background of tacrolimus administration, and blood levels were within the target values, which required replacing the drug with cyclosporine.

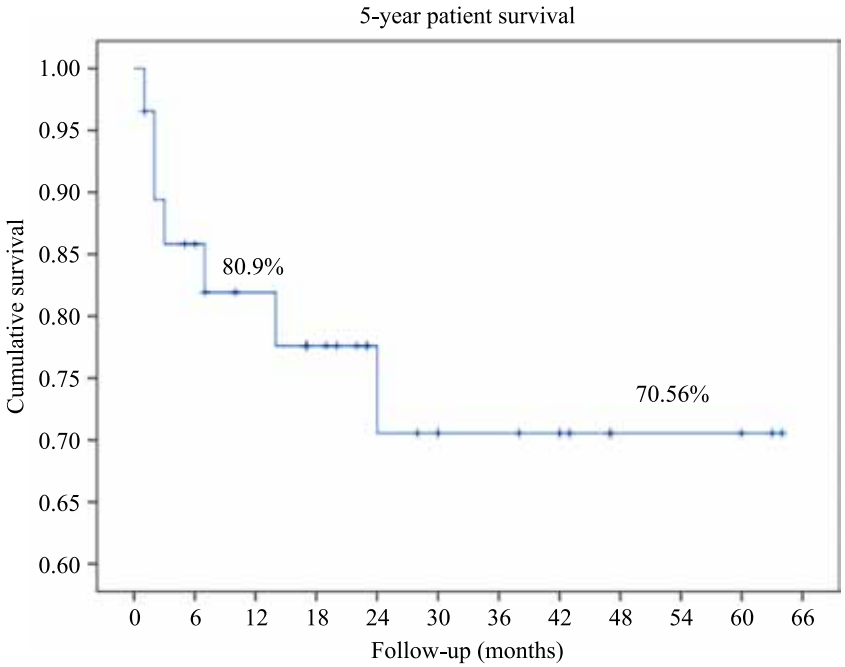

Fig. 3. Kaplan–Meier patient survival

Despite constant improvement in immunosuppressive therapy and the emergence of new drugs, there is no ideal immunosuppression regimen, and some patients require individual selection of therapy.

CONCLUSION

Summarizing the 5-year experience in our center, we can say that HT is the most effective method of treatment for end-stage CHF; it prolongs the life of patients and also improves their quality of life, and in most cases return them to active activity.

The highest rate of fatal complications is still characteristic of the first months of HT, which indicates the need for further improvement in immunosuppressive therapy regimens, to avoid both acute rejection and infectious complications. Optimization of the waiting list and the activities of district medical institutions on early detection and routing of patients with severe/end-stage CHF will reduce the proportion of MOF in the structure of early mortality and increase the survival rate of patients after surgery.

The best outcomes are achieved with careful selection of patients and strict compliance with all medical guidelines in the postoperative period.

The 1-year Kaplan–Meier survival rate in our study was 80.9% (Fig. 3). The overall 5-year survival was 70.56%. Five-year survival of patients surviving the first year after HT was 86.1%, which is comparable to ISHLT data.

The authors declare no conflict of interest.

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