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The experience of 70 heart transplants in a multidisciplinary medical care facility

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Introduction. *The total number of patients with chronic heart failure in Russia had reached 15 million by 2016, including 6 million of those with the end-stage heart failure. Currently, heart transplantation (HT) provides the only possible method of a definite treatment of the disease, which allows a significant steady and long-term improvement of patient's quality of life.*

The purpose of *this article was to review the experience of heart transplantation in a multidisciplinary medical institution over an 8-year period.*

Material and methods*. Since September 2009, more than 300 patients have been studied for the presence of indications for heart transplantation in the Department of Urgent Cardiology, Assisted Circulation and Heart Transplantation of the Sklifosovsky Research Institute for Emergency Medicine. Eighty of all the screened potential recipients were included in the*

waiting list, and by the end of 2017, heart transplantations had been performed in 70 of them; the mean waiting time for transplantation was 93 ± 79 days.

Results. *The graft ischemia time averaged 174 ± 28 minutes (97 to 250 minutes). The graft ischemia time was 187 ± 36 minutes with the biatrial technique* and *169 ± 24 minutes with bicaval technique. That parameter made 184 ± 23 minutes for a distant organ retrieval, while for a local organ retrieval* it was 155 ± 29 minutes. *By the end of 2017, of 70 cardiac transplant recipients enrolled in the analyzed group, 31 patients (44%) had died, 12 of whom during their hospital stay (hospital mortality was 18%). The main cause of death was the multiple organ failure syndrome in the early postoperative period, and infectious complications in the later period.*

Conclusion*. The advantage of establishing the organ transplantation center (particularly for heart transplantation) in a multidisciplinary medical care facility lies in reduced donor organ ischemia time and starting treatment of complications without delay. The number of infectious complications, as well as complications associated with acute cellular rejection and coronary artery disease of the transplanted heart can be reduced by creating a regional system ensuring the targeted work with posttransplant patients.*

Key words: heart transplantation, heart failure, organ donation

ACE, angiotensin converting enzyme

CABG, coronary artery bypass grafting

CHF, chronic heart failure

COPD, chronic obstructive pulmonary disease

CV, cardioverter

DCMP, dilated cardiomyopathy

EchoCG, echocardiography

EIT, electroimpulse therapy

HPM, heart pacemaker

HT, heart transplantation

HTCAD, heart transplant coronary artery disease

ICMP, ischemic cardiomyopathy

ICU, Intensive Care Unit

ISHLT, International Society for Heart and Lung Transplantation

TPVR, total pulmonary vascular resistance

TV, tricuspid valve

Introduction

To date, more than 23 million people worldwide suffer from the end-stage chronic heart failure (CHF). Despite recent advances in cardiology, including the interventional cardiology, pool of such patients is steadily increasing due to growing population and population aging [1]. The prevalence of this nosology in developed countries makes 1-2% of the total adult population and increases with age; according to rough estimates, 6 to 10% of people over 65 years of age have CHF that is the main reason for their hospitalization. In addition to a high incidence, CHF has an unfavorable prognosis with high mortality due to sudden death and the disease progression. A 5-year survival rate after established CHF diagnosis is lower than 60%; and a 1-year survival in refractory CHF is approaching 25% [2]. From the beginning of the XXI century, the total number of CHF patients in Russia increased 2 times (from 7.2 to 15.0 million), while the

number of patients with end-stage CHF increased 3.4 times (from 1.76 to 6.0 million) [3].

Current standards of CHF treatment imply a combined approach, including: 1) the therapy with cardiac glycosides, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, diuretics and other drugs; 2) the resynchronization therapy involving the implantation of cardioverter-defibrillators; 3) the use of mechanical left ventricular assisted devices (VAD) [4]. Despite the available CHF treatments, the quality of life of most patients does not improve. Currently, heart transplantation (HT) provides the only possible method of a definite treatment of the disease, which allows a significant steady and long-term improvement of patient's quality of life. Other definite techniques based on the idea of assisted circulation, according to world principles, represent only a "bridge to transplantation" [4].

The Sklifosovsky Research Institute for Emergency Medicine remains the only transplant center in the structure of Moscow Healthcare Department dealing with the issues of orthotopic HT.

The purpose of this article has been to review the experience of heart transplantation in a multidisciplinary medical care facility over an 8-year period (from September 2009 to December 2017).

Material and methods

To identify those in need of HT, the patients with end-stage CHF from cardiology centers, polyclinics, and other hospitals were referred to the Sklifosovsky Research Institute for Emergency Medicine where they were evaluated from the point of potential candidates for HT and investigated on indications according to the HT Program. From September 2009, more than 300 patients were examined in *the Department of Urgent Cardiology*,

Assisted Circulation and Heart Transplantation of the Sklifosovsky Research Institute for Emergency Medicine to identify the indications for HT. The course of screening was based on the scheme developed by V.I. Shumakov in the Research Institute of Transplantology and Artificial Organs [5] that was slightly modified according to the current recommendations of the International Society for Heart and Lung Transplantation (ISHLT) [5, 6], and the modern trends and specific features of current National Healthcare System [7].

Among all potential recipients evaluated under the HT Program, 80 were included in the waiting list, and 70 of them underwent HT by the end of 2017; the average waiting time for HT was 93 ± 79 days (from 7 to 332 days). The preoperative characteristics of patients who underwent HT are presented in Table. 1.

Regular examinations and therapies for end-stage CHF in patients on the waiting list were conducted in accordance with the recommendations of the All-Russian Scientific Society of Cardiology, and ISHLT [3, 8], starting with oral cardiac glycosides, ACE inhibitors, beta-blockers, diuretics, and other medications prescribed on an outpatient basis in a stable course of end-stage CHF. When decompensated, in the cases refractory to glycoside-diuretic therapy, the non-glycoside inotropic drugs (dopamine, dobutamine, levosimendan) were parenterally administered in hospital, under monitoring of the natriuretic hormone level.

Table 1. Preoperative characteristics of recipients undergoing heart transplantation

Parameter	Number of patients	%%
Etiology: DCMP / ICMP	27/43	39/61
Gender: men / women	63/7	90/10
Age, years	55 ± 13 (19 to 67)	
Severity by UNOS: 2 / 1b / 1a	52/13/5	74/19/7
Average waiting time for HT, days	128	
TPVR, Wood units	2.7 ± 1.0	
Left ventricle ejection fraction, %	27 ± 6.0	
Total protein, g/L	73 ± 8	
Creatinine, mmol/L	108 ± 18	
Total bilirubin, μmol/L	24 ± 14	
Concomitant pathology:		
gastrointestinal tract disease	19	27th
encephalopathy of various origin	45	64
impaired renal function	15	21
COPD	10	14
diabetes	13	19
thyroid gland disease	7th	10
tuberculosis	1	1.4
Interventions prior to HT:		
coronary artery stenting	15	21
HPM, HPM-CV, EIT	9	13
CABG	3	4
implantation of a left ventricle assist device	1	1.4

Note: DCMP = dilated cardiomyopathy; ICMP = ischemic cardiomyopathy; COPD = chronic obstructive pulmonary disease; HPM = heart pacemaker; CV = cardioverter; EIT = electroimpulse therapy; CABG = coronary artery bypass grafting; TPVR = total pulmonary vascular resistance.

Organ donation management

The transplantologists of the Sklifosovsky Research Institute for Emergency Medicine were notified of an available a donor from Moscow Coordination Center for Organ Donation whose specialists established the diagnosis of brain death. During the donor conditioning phase, the heart was evaluated by echocardiography (EchoCG) results. Coronary arteriography was performed in male donors aged over 45 years and female donors aged

over 50 years. The donors were located either in other Moscow hospitals (distant organ harvesting), or in different ICUs of the Sklifosovsky Research Institute for Emergency Medicine (local organ harvesting). A multiple organ harvesting was performed in all donors, except for 2 cases of heart failure in donors with brain death caused by methanol poisoning. The characteristics of the donor pool are presented in Table 2.

Table 2. Characteristics of donors

Parameter	***Number of donors***	***%%***
Gender: men / women	*59/11*	*84/16*
Age, years:		
<20	*3*	*4.6*
20-29	*23*	*32.9*
30-39	*25*	*35.7*
40-49	*13*	*18.6*
> 50	*6*	*8.2*
Cause of death:		
traumatic brain injury	*43*	*61*
acute cerebrovascular accident	*19*	*27*
poisoning	*2*	*3*
gunshot wound	*6*	*9*
Site of organ harvesting:		
local harvesting	*30y*	*43*
distant harvesting	*40*	*57*

The donor-recipient pair was selected considering the ABO system compatibility and matching anthropometric data. Due to a small number of patients on the current waiting list, the results of the microlymphocytotoxic complement-dependent test and the pre-existing antibody levels were evaluated only retrospectively. The result of the microlymphocytotoxic test (cross-match) in all donor-recipient pairs was negative. None of the patients showed pre-existing antibodies.

A cold cardioplegic solution Custodiol was used to protect myocardium in all cases. The harvested organs were transported in isothermal boxes.

Heart implantation was performed using one of the two techniques: the biatrial technique in 10 patients (14%), bicaval technique in 59 (86%) patients. In 18 cases (26%), the HT techniques used were supplemented with the De Vega tricuspid valve (TV) repair (in 4 cases of the biatrial technique, and 14 cases of the bicaval technique).

To prevent graft rejection, a standard immunosuppressive therapy was used. At 4 hours prior to delivery to the operating room, all patients were administered mycophenolic acid or its derivatives i.e. mycophenolate mofetil. Induction in immunosuppression was performed with monoclonal antibodies (basiliximab) or rabbit antithymocyte globulin (thymoglobulin), Immunosuppression was continued with a standard three-component therapy: calcineurin inhibitors (tacrolimus), mycophenolic acid preparations (mycophenolic acid or mycophenolate mofetil), glucocorticosteroids (prednisolone). During the first year, drug doses of immunosuppressive therapy were titrated; and by the end of the first year, it became a two-component immunosuppression after the withdrawal of glucocorticosteroids.

From the early postoperative period (5-10 days), the monitoring for cellular rejection was started by making the histological examination of the right ventricle myocardium biopsy specimens obtained by transvenous endomyocardial biopsy. To exclude an acute humoral rejection, the immunohistochemical examination of biopsy specimens was performed. A coronary arteriography was performed once a year to reveal possible coronary artery pathology (the heart transplant coronary artery disease [HTCAD]) as a consequence of a chronic humoral rejection.

The severity of the cellular and humoral rejection was assessed in accordance with the ISHLT classification [9]. In 0-1A rejection grade, no therapy correction was made; in other grades, the rejection severity was assessed and either the baseline therapy was adjusted, or the pulse-therapy with glucocorticoids, or the administration of monoclonal antibodies (thymoglobulin) were used. Patients with the verified humoral rejection received proliferative signal inhibitors (everolimus), and courses of plasmapheresis.

Recipient's current state was assessed with a planned and, if necessary, emergency instrumental investigations and laboratory tests (ultrasonography, electrocardiography, coronary arteriography, laboratory blood tests, X-ray, and computed tomography, endoscopic examinations).

Results

For the analysis of the early postoperative period, we used the data that largely determine the condition of the transplanted organ and the patient as a whole in that period.

The graft ischemia time averaged 174 ± 28 minutes (from 97 to 250 minutes), while in 57% of cases (43 patients) the time of transplant ischemia was less than 180 minutes.

The graft ischemia time depended on the chosen surgical technique of transplantation and on how far was the donor from the Sklifosovsky Research Institute for Emergency Medicine: the graft ischemia time was 187 ± 36 minutes with the biatrial technique, and 169 ± 24 minutes with bicaval technique. The same parameter made 184 ± 23 minutes for the distant graft retrieval and 155 ± 29 minutes for a local retrieval. Recently there has been a tendency to decrease the graft ischemia time regardless of the distance from

the donor. So, the mean graft ischemia time for 10 most recent HTs (7 local organ retrievals, 3 distant retrievals) did not exceed 150 minutes at the end of 2017.

By the end of 2017, among 70 post-HT recipients included in the analyzed group, 31 patients (44%) had died, 12 of them died in hospital (hospital mortality made 18%). Uncontrollable intraoperative bleeding was the cause of 2 deaths. Almost 80% of all deaths were caused by either multiple organ failure syndrome with prevailing right ventricular heart failure that developed in the early postoperative period as a result of initial pulmonary hypertension, or infectious complications that developed within 3 to 6 months after surgery.

One of the integral parameters of the postoperative course assessment has been the patient's length of stay in the intensive care unit (ICU). The decision on patient's transfer from the ICU to the somatic department is generally made when hemodynamics is stable with minimal inotropic support and completed induction of immunosuppression. In our patients, that period was 8 ± 6 days (from 4 to 38 days), with 70% of the recipients requiring the ICU monitoring for no more than 5 days; and only in 2 cases, the period of ICU stay was 25 and 38 days, respectively.

Initially, the endomyocardial biopsy (EMB) was performed according to the protocol adopted by ISHLT; further, the number of planned biopsy studies was reduced in patients having no signs of rejection, since, given the high level of immunosuppression in such patients, the rejection rate was always 0 as per the ISHLT classification. According to the original protocol we adopted, the biopsy was made at the end of the first week after surgery, at the end of the first month, at 3 months, at 6 months, and further every

other year. Thus, the number of hospitalizations decreased, and the workload of the department was reduced.

In the posttransplant period, the patients on immunosuppression receiving high doses of glucocorticosteroids had the following complications: steroid-induced peptic ulcers (in 2 pts), pneumonia of various origin (in 10 pts), and oncology diseases (in 2 pts). There were also such complications as renal failure and HTCAD. In situation where complications occurred during the in-hospital stay in the Sklifosovsky Research Institute for Emergency Medicine, the necessary medical care was rendered immediately, being the specific feature of the practice in a multidisciplinary emergency care facility.

Discussion

At present, the discussions on the heart implantation technique are still going on. It is known that HT can be performed by using either of the two techniques: biatrial or bicaval. The biatrial technique was widely used in the early stages of mastering the HT operation, and later an alternative bicaval technique was proposed. Each of the techniques has its own pros and cons. The biatrial technique is more feasible, but its use is associated with the breakdown of the right atrium geometry, which is manifested by the development of specific complications in the form of a sinus node dysfunction, an early TV insufficiency, a right ventricle failure. The bicaval technique avoids many of these shortcomings, but, technically, it is more complicated for use and carries the risk of superior vena cava artificialis stenosis. Due to its simplicity, the biatrial technique has advantages in heart retransplantation. The choice of the HT technique had a certain impact on the graft ischemia time (the mean graft ischemia time was 187 ± 36 minutes

with the biatrial technique, and 169 ± 24 minutes with the bicaval technique). However, the patients undergoing the HT by means of biatrial technique more often developed the phenomena of right ventricle failure that required a prolonged administration of inotropic drugs. Also, all the recipients after the HT by biatrial technique had the need for the implantation of a permanent pacemaker. Similar complications were reported by other authors. For example, after having analyzed the results of 36 operations, R.F.Locali et al. reported significantly better, early and long-term results in patients after HT using the bicaval technique. The incidence of heart rhythm irregularities, tricuspid valve insufficiency, sudden death, thromboembolic complications, the need for permanent cardiac pacing and the length of stay in the ICU were significantly lower with bicaval technique than with biatrial technique [10].

The right ventricle failure is one of the postoperative period complications. In the present study, the analysis of the postoperative course in patients without concomitant interventions on TV demonstrated a 48% incidence of right ventricle failure. In this connection, at the initial stages of mastering the HT, its technique was supplemented with De Vega TV annuloplasty in 18 patients (12.4%) for unloading the right heart and preventing the right ventricle failure in the early postoperative period: the HT biatrial technique was used in 4 cases, and the bicaval technique in 14. The decision on the need for correcting the TV annuloectasia was made considering the presence of baseline pulmonary hypertension, and the over-expansion of the fibrous ring of the donor's heart TV and the significant regurgitation into the right atrium present after the cardiac recovery, according to transesophageal echocardiography results. The annuloplasty was aimed at narrowing the diameter of the fibrous ring to mean of 3.5 cm,

which would result in the appearance of minor diastolic transvalvular gradient limiting the preload to the right ventricle. The annuloplasty was performed before the donor's heart implantation in the biatrial group, and at the stage of warming the patient through an additional right atriotomy in the bicaval group.

After HT, the patients who underwent a suture annuloplasty had the mean diastolic transvalvular gradient on TV 2.3 ± 0.7 mm Hg, according to EchoCG; the regurgitation into the right atrium was absent in all patients; the right atrium volume was 52 ± 11 ml. In the early postoperative period, 7 patients (39%) who underwent annuloplasty (2 from the biatrial group, and 5 from the bicaval group) showed the phenomena of a right ventricle failure, and they were administered a prolonged BNP-controlled inotropic therapy (dobutamine, levosimendan). Thus, the incidence of a right ventricle failure after undertaken TV annuloplasty was 38% (vs. 48% without annuloplasty, the difference was not significant). Our obtained data suggest that the suture annuloplasty of the TV in the donor heart does not lead to a significant reduction in the incidence of an early posttransplantation right ventricle failure. The right ventricle dysfunction occurred after HT might be predetermined by such causes as the initial state of the lesser circulation, the graft ischemia time, the metabolic myocardial damage, rejection. Additional manipulations aimed at limiting the right ventricle preload do not help to reduce the incidence of the right heart chamber dysfunction after HT. On the basis of EchoCG data, H.H.Sievers et al. noted that the right atrium volume characteristics are comparable in patients after HT, regardless of whether the preventive plastic surgery on TV was performed or not ($p<0.05$). There was no difference in the incidence of TV insufficiency either [11]. According to the study by A.I. Fiorelli et al., there were no significant differences in the

severity of tricuspid insufficiency and the volume characteristics of the right heart in patients after HT [12].

Screening within the HT Program revealed pulmonary hypertension in majority of patients. Each patient, irrespective of the EchoCG data before HT, underwent a pulmonary circulation catheterization. In patients with TPVR lower 3 Wood units (60.5%), HT was not contraindicated; and there were no cases of a right ventricular heart failure in that group of patients in the posttransplant period. In patients with TPVR over 3.5 Wood units and a good response to nitric oxide (39.5 %), the phenomena of the right ventricle failure of varying severity developed in the posttransplant period, requiring a prolonged administration of inotropic drugs. For patients with TPVR over 3.5 Wood units non-responsive to nitric oxide, heart transplant was refused. Such classification of patients into groups considering the TPVR severity is presented in the ISHTL recommendations [13].

In the patients on immunosuppressive therapy, there were no signs of the graft cellular rejection, which was confirmed by endomyocardial biopsy data. The cellular rejection was observed only in those patients in whom tacrolimus was withdrawn for 3 days or more for one or another reason. In accordance with the scheme proposed by the specialists of Academician V.I. Shumakov Research Centre of Transplantology and Artificial Organs [14], the target blood level of the mean tacrolimus concentration in the 1st year after HT was considered the level decreasing from 15 to 5 ng/mL with further concentration maintenance at 5 ng/mL.

If any complications develop, in particular, such as the perforated stomach ulcer, the time factor is important, and an emergency medical care should be provided in the shortest possible time. In a multidisciplinary hospital with round-the-clock duty services, this task is fulfilled by

definition. There are also available around-the-clock laboratory and diagnostic services, consultations of various specialists, renal and hepatic replacement therapy facilities, which help to effectively prevent the development of possible complications or speed up the process of their treatment.

Conclusion

The advantage of establishing the center for organ transplantation, in particular the heart transplantation, in a multidisciplinary medical institution lies in the reduction of the donor organ ischemia time and initiating the treatment of complications without delay.

Multiple organ failure is the main cause of early postoperative mortality and is brought about by the severity of patient's initial condition. An earlier referral of patients with a chronic heart failure to transplantologists and decreased waiting time for heart transplantation through expanding the donor pool would improve the immediate results of transplantation.

Efforts to reduce a postoperative mortality in the first month after orthotopic heart transplantation should be aimed at improving the algorithms of immunosuppressive therapy, which, if adequate, would prevent both an acute rejection and infectious complications.

The number of infectious complications, and complications associated with an acute cellular rejection and coronary artery disease of the transplanted heart can be reduced through creating a regional system for targeted work with transplant patients. For this, an outpatient transplant center should be established (most likely, at a clinic performing organ transplantations), which would have all the necessary specialists trained in

the transplant patient care and being in close contact with the coordinator in each of the regional transplant centers. This will prevent complications at an early stage of their development and, accordingly, prolong the recipient's life.

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