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BASELINE PULMONARY HYPERTENSION IN HEART TRANSPLANT RECIPIENTS: 9 YEARS OF EXPERIENCE AT ALMAZOV NATIONAL MEDICAL RESEARCH CENTRE

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Objective: to assess the impact of baseline pulmonary hypertension (PH) on early and long-term outcomes following heart transplantation (HT). **Materials and methods.** From January 2010 to December 2018, 112 HTs were carried out. Based on right heart catheterization results, all recipients were divided into 2 groups: Group 1 – with PH (n = 76; mean pulmonary arterial pressure (mPAP) ≥25 mm Hg), Group 2 – without PH (n = 36; MPAP <25 mm Hg). The average age of Group 1 patients was 46.4 ± 14.9 years, baseline pulmonary vascular resistance (PVR) was 3.5 ± 1.5 Wood units, PVR after reversion test (nitric oxide – 80 ppm, iloprost 20 μg) – 2.8 ± 1.0 Wood units, systolic PAP (sPAP) – 50.1 ± 13.4 mm Hg. The average age in Group 2 was 47.3 ± 12.2 years, baseline PVR – 2.1 ± 0.8 Wood units, sPAP – 27.4 ± 5.3 mm Hg. The dynamics in indicators of early postoperative period (duration of mechanical ventilatory support, use of vasodilators and inotropic support and the length of stay in intensive care unit (ICU), 30-day mortality) and long-term post-HT echocardiography results were assessed. **Results.** Due to acute right-ventricular failure (RVF) developing after heart transplantation, veno-arterial extracorporeal membrane oxygenation (VA-ECMO) was done in 8 patients (11%) from Group 1 and one patient (3%) from Group 2. Presence of PH did not affect duration of mechanical ventilatory support, inotropic support, and length of stay in ICU. Levosimendan therapy in the early postoperative period was more often performed in Group 1 (n = 29) than in Group 2 (n = 6) (p = 0.048). Nitric oxide inhalation was also more often administered in Group 1 (n = 54); Group 2 (n = 7), (p = 0.003). Sildenafil therapy after HT was comparable in both groups Group 1 (n = 25); Group 2 (n = 6), (p = 0.048). In early post-HT stages, 14 patients died, 30-day mortality was comparable in both groups (p = 0.12). Six months after HT, no differences were found in the sPAP (p = 0.21) and PVR (p = 0.07) levels. **Conclusion.** Patients with baseline PH after HT have a more severe early postoperative period, including a higher RVF incidence, with the need for ECMO implantation. A PVR level >3.5 Wood units is not a threshold for HT. Patients with baseline PVR >3.5 Wood units following HT show comparable results with patients without baseline PH. This allows such patients (baseline PVR >3.5 Wood units) to be considered for inclusion in the heart transplant waiting list. In addition, 30-day mortality and duration of mechanical ventilatory support after HT in patients with and without baseline PH did not differ. Regardless of the baseline level of sPAP and PVR, all patients showed improvement in these parameters after HT. Six months after HT, no differences were found in sPAP and PVR levels in the patients, regardless of whether there was baseline PH or not.

Keywords: heart transplantation, heart failure, pulmonary hypertension, PH, pulmonary artery pressure, PAP, pulmonary vascular resistance, PVR, vasodilators.

INTRODUCTION

Selecting a therapeutic tactics for managing patients with severe cardiac pathology and associated pulmonary hypertension (PHT) remains one of the unresolved issues involved in choosing candidates for the heart transplant waitlist. According to ESC (European Society of Cardiology) guidelines, PHT is defined by elevated mean pulmonary artery pressure (mPAP) ≥25 mmHg [1]. C. Roldaan divides PHT into 3 groups: mild (sPAP 35–45 mmHg), moderate (sPAP 46–60 mmHg), and severe (sPAP >60 mmHg) [2]. There is no common opinion among researchers that could help to identify contraindications for heart transplantation (HT) in PHT. G.F. Delgado et al. and M.C. Deng et al. consider 2.5 WU as the limit value for pulmonary vascular resistance (PVR) when wait listing HT candidates [3, 4]. H. Ross et al. suggest that sPAP >50 mmHg and PVR >3–4 WU, measured after pharmacological test, should be considered a contraindication for HT [5]. According to J. Kettner et al., severe PHT (sPAP >50 mmHg) is no longer a contraindication for HT [6]. According to S. Klotz et al., HT candidates with pre-HT reversible PHT can be comparable with patients without PHT, since, despite a significantly higher risk of complications, long-term

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survival after orthotopic cardiac transplantation was not affected [7].

PHT increases the risk of early post-transplant acute right ventricular failure (RVF), which often requires the use of auxiliary circulatory devices (extracorporeal membrane oxygenation (ECMO) devices) and levosimendan. It is associated with severe complications [8, 9]. For instance, in a study by M.V. Mogollón Jiménez et al., which analyzed 39 heart transplantations in recipients with PHT (mPAP exceeded 35 mmHg in 30.8% of patients), early postoperative mortality increased to 50% [10]. In a study by S. Klotz et al., within 30 days after HT, RVF manifestations developed in 64% of recipients with PHT, and only 27% of patients without PHT [7]. Z. Zeng et al. found no significant difference in mortality rates in the PHT and non-PHT groups [11]. S. Klotz et al. found that PHT was reversible in most patients after HT [12]. In this case, there was no statistically significant difference in survival rates among the PHT and non-PHT groups [12, 13]. E. Gude et al. showed that a year after HT, recipients with mPAP >20 mmHg had a lower survival rate than those with mPAP <20 mmHg [14]. Currently, there is no clear consensus on PHT severity threshold values for wait-listing cardiac transplant candidates.

In PHT patients, B. Lindelow et al. observed rapid positive dynamics starting from the early post-transplant period – decreased PAP – without any other concomitant therapy [15]. After HT, all parameters normalize in patients (decreased PAP and PVR) [16]. In addition, HT outcome in PHT patients depended on different approaches and had no single relationship with the borderline values of these indicators for wait-listing cardiac transplant candidates. Various studies have demonstrated the inexactness of the effect of baseline PHT on the early post-transplant period and on mortality. Thus, issues related to selection and management of patients with associated PHT after HT require further investigation. The work was aimed at evaluating the effect of baseline PHT on early and long-term survival after heart transplantation.

MATERIALS AND METHODS

From January 2010 to December 2018, 112 orthotopic cardiac transplantations were performed via a bicaval technique. The recipients included 82 men and 30 women. Their average age was 46.7 ± 14.0 years. Before HT, the left ventricular ejection fraction (LVEF) was 22.3 ± 10.1%. Heart failure was caused by: coronary heart disease – 49% (n = 55), dilated cardiomyopathy – 28% (n = 31), non-compact myocardium – 8% (n = 9), arrhythmogenic right ventricular dysplasia – 3.6% (n = 4), congenital heart defect (CHD) – 3.6% (n = 4), chronic rheumatic heart disease – 2.7% (n = 3), hypertrophic cardiomyopathy (HCM) – 2.7% (n = 3), cardiac sarcoidosis – 0.9% (n = 1), cardiac amyloidosis – 0.9% (n = 1) and restrictive cardiomyopathy (RCM) – 0.9% (n = 1). Prior to HT, 13 recipients were implanted with mechanical circulatory support (MCS) devices: extracorporeal membrane oxygenation system (n = 6), biventricular MCS Berlin Heart EXCOR (n = 8). This group of patients had signs of NYHA FC II–III chronic heart failure (Simpson LVEF – 8 to 29%, TAPSE <10 mm), multiple organ failure (MOF).

Prior to HT, all patients underwent right heart catheterization in order to assess PVR level and central hemodynamics indicators. The patients were divided into 2 groups: group 1 – with pulmonary hypertension (mPAP ≥25 mmHg), group 2 – without pulmonary hypertension (mPAP <25 mmHg). In group 1, 47% (n = 36) of patients underwent a test for PHT reversibility with inhalation of nitric oxide (80 ppm) or iloprost 20 μg [17].

The average age of patients in group 1 (n = 76) was 46.4 ± 14.9 years, PVR value was 3.5 ± 1.5 (1.25 to 8.30) WU, PVR value after reversibility test was 2.8 ± 1.0 (0.7 to 5.0) WU, sPAP – 50 ± 13 (27 to 97) mmHg. In 6 patients from group 1 who were implanted with MPC Berlin Heart EXCOR as a bridge before HT, the average age was 19 to 39 years, PVR value was 2.9 to 4.5 WU, PVR value after reversibility test was 2.5 to 4.6 WU, sPAP – 42 to 58 mmHg. In group 2 (n = 36), the average age was 47.3 ± 12.2 years, PVR – 2.1 ± 0.8 (0.8 to 3.7) WU, sPAP – 27.4 ± 5.3 (14 to 36) mmHg. The age of patients between the two groups did not differ (p = 0.096). Pulmonary wedge pressure (PWP) in group 1 was 20.7 ± 6.8 (4 to 32) mmHg (including for recipients with Berlin Heart EXCOR – 19 to 28 mmHg), in group 2 – 11.1 ± 4.4 (3 to 20) mmHg (p = 0.023).

Also, 23 patients from group 1 were treated with levosimendan [18] and 4 with sildenafil before HT; 20 of them had PHT during surgery. Among associated diseases, it is necessary to note that 15 patients had chronic obstructive pulmonary disease while 33 had a history of pulmonary embolism.

Immediate outcomes were evaluated based on duration of inotropic support, mechanical pulmonary ventilation (MPV), being in the intensive care unit (ICU), frequency of deaths, use of levosimendan, sildenafil or inhaled nitric oxide. The use of dopamine, dobutamine and epinephrine was considered an inotropic support after HT. Vasopressor support was performed with norepinephrine.

To assess long-term results, transthoracic echocardiography (echocardiography) was performed 6 months after HT. The formula $10 \times (Vmax \times Th/VTI_{RVOT}) + 0.16$ was used to calculate PVR, while S.P. Nagueh 1.24 × E/Em + 1.9 was used to calculate PWP [19]. Echocardiography also assessed the presence of tricuspid valve regurgitation and mitral valve regurgitation.

Statistical data processing was performed using the SPSS 21.ORU program. In cases of normal distribution of indicators, the Student's t-test was used to evaluate the statistical significance of differences between groups. Data were presented in the form of "mean value ± stan-

dard deviation (M ± SD)". For a distribution other than normal, the nonparametric The Mann–Whitney U test was used to estimate differences; data were presented as median (Me) [25th; 75th percentile]. When describing groups of less than 20 patients, data were presented as median, minimum and maximum values of the symptom. Fisher's exact test was used to evaluate the differences in qualitative parameters. The criterion of statistical significance of findings was considered $p < 0.05$. This study was conducted in accordance with the principles of the Helsinki Declaration.

RESULTS

Early postoperative period in all patients had manifestations of biventricular heart failure. There was no significant difference in duration of patients' inotropic support in the early postoperative period (5 [4; 10] and 5 [3; 7] days, Mann–Whitney U test $p = 0.21$). Presence of PHT did not affect length of MPV after heart transplantation (1 [1; 2] and 1 [1; 2] days, Mann–Whitney U test $p = 0.8$). Due to post-HT acute RVF, 8 patients (11%) from group 1 and 1 patient (3%) from group 2 were implanted with ECMO systems using veno-arterial technique; 3 patients (4%) from group 1 and 1 (3%) from group 2 underwent tricuspid valve replacement (TVr) (Batista procedure) due to development of post-HT degree 4 tricuspid regurgitation (TR). Two recipients from group 1 had early graft dysfunction; there was no such complication in group 2. Endomyocardial biopsy in patients who underwent a TVr revealed no signs of rejection in the first follow-up month.

The study showed that the number of patients who had a complicated post-HT period and were in ICU for more than 10 days were more in group 1 (39%, n = 30) than in group 2 (19%, n = 7), chi-square $p = 0.04$. There were no statistically significant differences in the length of stay in ICU between the two groups – 8 [6; 13] and 7 [6; 10] days, respectively, $p = 0.18$.

However, in the early postoperative period, levosimendan therapy was more often performed in group 1 (n = 29) than in group 2 (n = 6), chi-square $p = 0.048$. Also, a significantly larger number of patients received nitric oxide inhalations in group 1 (n = 54) than in group 2 (n = 7), chi-square $p = 0.003$. Six-month outcomes of the use of sildenafil in the early postoperative period after transplantation were comparable in both groups: in group 1 – 25 patients, in group 2 – 6 patients, chi-square = 0.048.

In early post-HT stages, 14 patients died in the study population; 30-day mortality was comparable in both groups: group 1 – 12 (15%) recipients, group 2 – 2 (6%) recipients, chi-square $p = 0.12$. The difference in group 1 was that within 1 month after HT, five recipients died against the background of ECMO implanted due to acute RVF.

Six months after HT, the groups showed no differences in sPAP (34.2 ± 7.1 and 33.8 ± 4.8 mmHg, $p = 0.21$) and PVR (1.8 ± 0.6 and 1.5 ± 0.4 WU, $p = 0.07$) levels. In group 1, there was decreased sPAP in all patients after HT (48.3 ± 12.5 and 34.0 ± 7.0 mmHg, respectively, $p < 0.001$). In this case, 32% (n = 24) from group 1 still had PHT (sPAP 40.4 ± 4.8 mmHg) 6 months after HT. Patients from group 1 experienced decreased PVR level (3.7 ± 1.4 and 1.8 ± 0.5 WU, respectively, $p < 0.001$) six months after HT. In particular, positive dynamics were detected in recipients who before HT were on MPC Berlin Heart EXCOR: sPAP with 50 (42 to 58) mmHg. to 36 (29 to 38) mmHg; PVR from 4.1 (2.9 to 4.50) to 2.1 (1.9 to 3.4) WU. Six months after HT in patients from group 2, there was no evidence suggesting PHT; sPAP and PVR were within normal limits.

After 6 months, post-HT PWP levels in both groups did not significantly differ (12.4 ± 6.1 and 11.1 ± 4.7 mmHg, respectively, $p = 0.27$). However, in group 1, post-HT PWP levels were significantly lower than pre-HT PWP levels (17.0 ± 7.9 and 11.5 ± 5.3 mmHg, respectively, $p < 0.001$).

Six months after HT, incidence and severity of mitral regurgitation (MN) and TR were comparable – MN was detected in a quarter of patients in both groups: 26% (16 of 61) in group 1, 21% (7 of 34) in group 2, chi-square $p = 0.64$, and TR was found among most patients: 64% (39 of 61) in group 1, 65% (19 of 34) in group 2, chi-square $p = 0.44$. Incidence of MN (grade 2–4) in group 1 was 31% (5 of 16), in group 2 – 29% (2 of 7) and TR (grade 2–4): in group 1 – 36% (14 of 39), in group 2 – 32% (6 of 19), chi-square $p = 0.75$.

DISCUSSION

Irreversible PHT in patients undergoing pharmacological therapy is a contraindication for HT due to the high risk of postoperative RVF [6, 8]. HT surgeries at Almazov National Medical Research Centre has shown that the risk of early post-transplant complications is higher in recipients with baseline PHT. Some studies have demonstrated that despite the high risk of RVF, long-term survival after orthotopic cardiac transplantation is not affected by baseline PHT [7, 12]. This is consistent with our findings at Almazov National Medical Research Centre. We found out that PVR >3.5 WU is not a contraindication for heart transplantation. Besides, post-transplant outcomes in these patients are comparable to those with no baseline PHT.

Baseline PHT increases the risk of acute RVF in the early postoperative period after HT [15, 20]. The use of nitric oxide and other vasodilators perioperatively can be effective in reducing the risk of post-transplant RVF [12, 21]. TR is one of the most common post-HT complications [20]. It can be caused by various factors. At the same time, some studies attribute TR to progression of cell rejection [20, 22]. In our study, only 4 out of 89 pa-

tients needed TVr; they had no histological signs of graft rejection in the early postoperative period. Increased TR in a follow-up long-term period may be associated with the risk of tricuspid valve injury during endomyocardial biopsies, which requires further investigation.

Developing PHT long after HT is associated with decreased survival rate [14, 23]. According to B. Lindelow et al., all HT recipients have lower PVR levels [15]. In turn, Gude et al. claim that RVF and increased PVR levels at 6 months, 2 and 3 years after HT are prognostically unfavorable factors [14]. S. Klotz et al. claim that reversible PHT patients have similar outcomes with non-PHT patients [12]. Moreover, the presence of combined (pre-capillary and post-capillary) PHT before HT is attributed to persistence of increased PVR 1 year after surgery [24]. According to retrospective evaluation of our results, in 32% (n = 24) of patients with baseline PHT, sPAP levels were above 35 mmHg 6 months after heart transplantation, despite positive dynamics.

The use of sildenafil, levosimendan, and nitric oxide in patients with heart failure brings down PAP and PVR levels [25, 26]. Possible use of vasodilators after cardiac transplantation has not been sufficiently studied. A retrospective evaluation of our findings showed that the use of various tactics (levosimendan, sildenafil, nitric oxide) for treating PHT patients is effective in the early post-transplantation period.

CONCLUSION

1. Patients with baseline PHT after HT have a more severe early postoperative period, including higher incidence of RVF, which require ECMO implantation.
2. A PVR >3.5 WU is not a contraindication for heart transplantation. Patients with baseline PVR >3.5 WU after HT achieves comparable results compared with patients without baseline PHT. This makes such patients potential cardiac transplant candidates.
3. However, 30-day mortality and length of ventilator support after HT did not differ in patients with and without baseline PHT.
4. Regardless of baseline sPAP and PVR levels, these indicators improved significantly in all patients after HT.
5. 6 months after HT, no differences were found in the sPAP and PVR levels, regardless of whether the patient had baseline PHT or not.

The authors declare no conflict of interest.

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