DOI: 10.15825/1995-1191-2023-1-99-105

MID-TERM AND LONG-TERM OUTCOMES FOLLOWING HEART TRANSPLANTATION WITH PROLONGED COLD ISCHEMIA

A.V. Fomichev[1], V.N. Poptsov[2], D.A. Sirota[1], M.O. Zhulkov[1], A.G. Edemskiy[1], A.V. Protopopov[1], V.Y. Kliver[3], A.I. Skokova[2], A.M. Chernyavskiy[1], D.S. Khvan[1], K.A. Agayeva[1]

[1] Meshalkin National Medical Research Center, Novosibirsk, Russian Federation
[2] Shumakov National Medical Research Center of Transplantology and Artificial Organs, Moscow, Russian Federation
[3] Novosibirsk State Medical University, Novosibirsk, Russian Federation

Objective: comparative analysis of long-term outcomes following heart transplantation (HT) with prolonged and short cold ischemia. **Materials and methods.** We analyzed the data of 29 orthotopic HT with >4 hours of cold ischemia. The transplant surgery was performed at Meshalkin National Medical Research Center between 2013 and the present time. Organs were obtained from donors from other regions. The control group consisted of 29 HTs with cold ischemia <4 hours, performed in the same period. The minimum distance between the transplant center and the donor base was about 250 km (Barnaul); the maximum distance was about 850 km (Krasnoyarsk). Recipient survival and postoperative peculiarities were analyzed. **Results.** In-hospital survival in the prolonged cold ischemia group was 89.7% (n = 26) with 3 deaths (10.3%). In the second group (<240 min), in-hospital survival was 79.3% (n = 23) with 6 (20.7%) deaths. The Kaplan-Meier survival analysis showed no difference between the groups (Log-Rank Test, P 1/4 0.59). In addition, cold ischemia time did not increase the risk of graft rejection and the risk of transplant coronary artery disease (TCAD). **Conclusion.** HT with cold ischemia >4 hours did not have worse outcomes than in short graft ischemia. This provides grounds for further accumulation of experience in the use of heart donors from remote locations.

Keywords: heart transplantation, cold ischemia time.

INTRODUCTION

Today, more and more people are in need of heart transplantation due to progression and decompensation of chronic heart failure (CHF) [1]. The low level of organ donation and critical shortage of donor pool remain a stumbling block for organ and tissue transplantation in Russia. Despite some recent improvements, Russia is still very far from the leading positions in the organ donation ranking. A large number of regions are not involved in the organ donation and transplantation program at all. The real level of development of organ donation and transplantology depends only on a few regions; in most of the rest, there are single organ transplants [2]. This necessitates the search for optimal use of unclaimed organs from regions with poorly developed organ donation. The use of organs from remote regions is related to a number of limiting factors associated with the difficulty of assessing the quality of the donor heart, longer transportation, logistics difficulties and, of course, prolonged ischemia time. It is well known that prolonged cardiac ischemia is accompanied by high risk of graft dysfunction and high mortality [3]. According to the Russian national HT guidelines, cold ischemia >4 hours is a risk factor for impaired myocardial function, and only young donors should be considered when using hearts with prolonged ischemia time [4]. In available publications, there is no consensus on a particular safe cold cardiac ischemia threshold; there is also no agreement on the criteria for selection of donors and recipients for longer transportation.

Currently, there are no clear criteria that would help to reliably say that longer cold ischemia time can lead to mortality; risk factors have not been studied. The paper presents an analysis of the experience of Meshalkin National Medical Research Center. The specifics of donor service involve constant interaction with neighboring regions and longer transportation of donor hearts.

MATERIALS AND METHODS

A retrospective analysis of 58 heart transplants performed between July 20, 2012 and October 23, 2019 was carried out. Patients were divided into two groups depending on cold ischemia time. The first group of the study consisted of 29 recipients who underwent orthotopic HT with cold ischemia time >240 minutes, the

Corresponding author: Alexey Fomichev. Address: 15, Rechkunovskaya str., Novosibirsk, 630055, Russian Federation.
Phone: (913) 487-29-65. E-mail: a_fomichev@list.ru

Table

Patient characteristics

Characteristics	Group 1 (>240 min)	Group 2 (<240 min)
Age, years	42 [33–51]	47 [36–50]
BMI (kg/m²)	24.8 [23.3–31]	26.4 [22.4–29.5]
Gender		
Men	20 (69%)	27 (93.1%)
Women	9 (31%)	2 (6.9%)
Diagnosis		
DCM	25 (86.2%)	15 (51.7%)
ICM	3 (9.6%)	12 (37.9%)
HCM	0	1 (3.4%)
Rheumatism	0	1 (3.4%)
CHD	1 (3.4%)	0
Cold myocardial ischemia time, min	350 [300–390] (240–456)	165 [150–180] (135–240)
Urgency status (UNOS)		
1a	3 (10.3%)	2 (6.9%)
1b	5 (17.2%)	2 (6.9%)
2	21 (72.4%)	25 (86.2%)
LVAD	6 (20.6%)	3 (10.3%)
ECMO	4 (15.4%)	2 (6.9%)

second group – 29 recipients with short cold ischemia time (<240 minutes). Baseline data of the recipients are presented in Table.

Mechanical circulatory support (VAD) as bridge to transplantation was performed in 8 group 1 patients (27.6%) and 3 group 2 patients (9.6%). Extracorporeal membrane oxygenation (ECMO) as a bridge to OHT was performed in 4 group 1 patients (13.7%) and two group 2 patients.

Prolonged graft ischemia was as a result of longer transportation from neighboring regions: Kemerovo Oblast, Krasnoyarsk Krai, and Altai Krai. Transportation from Kemerovo Oblast and Altai Krai was on official vehicles (cars); Transportation from Krasnoyarsk Krai was by civil aviation.

Selection criteria for postmortem donors were standard. In all cases, single-group transplants were performed taking into account donor/recipient matching by constitution. The gender distribution of donors did not differ significantly. Donors with inotropic support >20 mg/kg/min (dopamine or dobutamine) or similar doses of other adrenergic drugs, despite aggressive optimization of pre- and postload, were not considered. The median age of donors in the prolonged ischemic group was 40 (34–46) years, in the short ischemic group 43 (40–51) years. Criteria for donor heart evaluation were standard, expanded criteria donor were not considered. The harvesting technique and method of heart preservation were standard.

A bicaval approach was used for OHT. To assess volumetric characteristics of the recipient heart after transplantation and pulmonary artery pressure, all patients underwent follow-up transthoracic echocardiography (EchoCG) immediately after surgery, at day 5–10, and month 1 after surgery. The risk of donor heart rejection was also analyzed based on endomyocardial biopsy results according to the recommended ISHLT WF 2004 classification (International Society for Heart and Lung Transplantation – working formulation, 2004).

Overall recipient survival was taken as the primary endpoint. Maximum follow-up period was 137 weeks in the long graft ischemia group and 124 weeks in the short graft ischemia group. Inotropic index values at the time of disconnection from the heart-lung machine, differences in the frequency of graft dysfunction and the need for mechanical circulatory support in the perioperative period, graft rejection, as well as risk factors of postoperative complications were also analyzed.

Taking into account small sample size and non-normal distribution (according to Shapiro–Wilk test), data were presented as median, 1st, 3rd quartile. Nonparametric statistical criteria were used: Mann–Whitney U test for comparison of independent samples. Single-factor regression analysis was used to identify predictors of mortality.

STUDY RESULTS

Duration of inotropic support

Primary graft dysfunction and the need for continued mechanical circulatory support in the postoperative period was observed for only 4 patients (15.4%) in the prolonged graft ischemia group and 3 patients (11.5%) in the short cold ischemia group (Fig. 1). These patients underwent peripheral ECMO cannulation. The level of inotropic support at the time of circulatory arrest was represented by the inotropic index, with no significant difference between the two groups ($p = 0.13$) (Fig. 2). Median inotropic index was 8 (4–14.75) in group 1 and

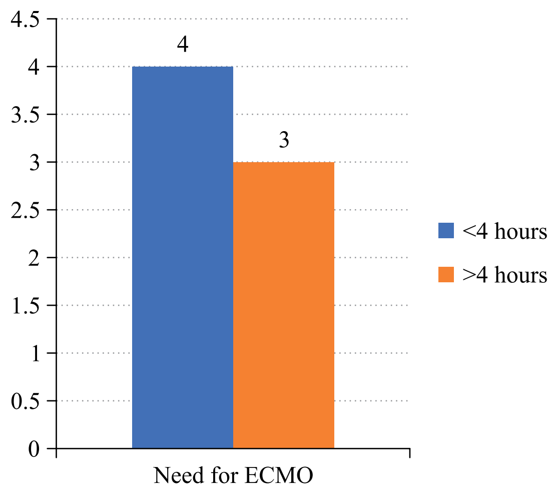

Fig. 1. Need for ECMO in the postoperative period in the study groups

6.75 (3.25–8) in group 2. Total duration of inotropic support was slightly longer in the prolonged graft ischemia group ($p < 0.05$) (Fig. 3).

In-hospital survival in the prolonged cold ischemia group was 89.7% (n = 26) with 3 deaths (10.3%). Mortality structure in the prolonged cold ischemia group was as follows: 1 patient died from primary graft dysfunction and 2 patients died from initial severe condition (desperate surgery), IA(UNOS) (Fig. 4). In one case, death was caused by severe right ventricular failure after switching off ECMO. In the other case, intraoperative massive diffuse bleeding against coagulopathy, which was caused by extremely severe pre-transplant condition of the recipient. In the second group (<240 minutes), in-hospital survival was 79.3% (n = 23) with 6 (20.7%) deaths, respectively. The mortality structure is shown in Fig. 5. The causes of mortality were acute rejection, graft dysfunction, ischemic stroke, hospital-acquired pneumonia, and tricuspid regurgitation (TR). Thus, 1 patient in each group died from primary graft dysfunction in the early postoperative period. The Kaplan–Meier survival analysis showed no difference between the groups (Log-Rank Test, P 1/4 0.59) (Fig. 6).

In the long-term postoperative period, 3 patients from the short graft ischemia group died of unknown causes, 1 died due to severe TR after iatrogenic damage to the tricuspid valve chordal apparatus during myocardial biopsy, 2 patients died due to severe coronavirus infection, 1 died from abdominal infection (Fig. 5). In the prolonged cold ischemia group, 1 patient died of unknown causes, 1 died from progression of cancer at month 1 and 3, respectively. In the mid-term and long-term, 1 patient died from cancer, 4 patients died from COVID-19.

In the mid- and long-term period, significant TCAD was detected in 3 patients from the prolonged ischemia

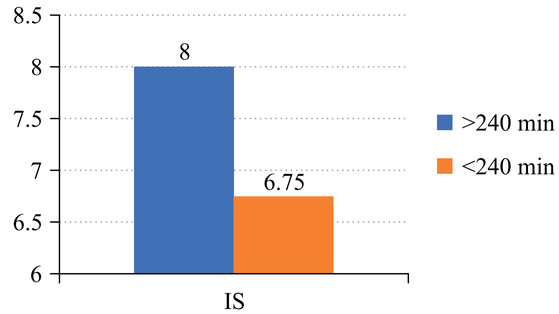

Fig. 2. Inotropic score in the study groups

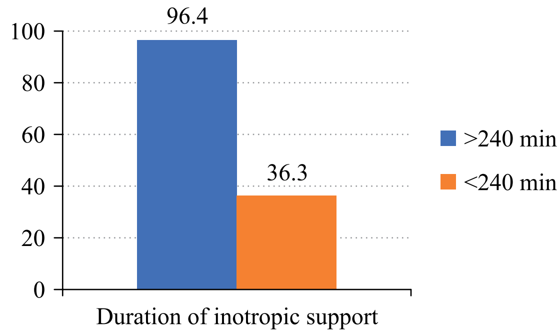

Fig. 3. Duration of inotropic support in the study groups

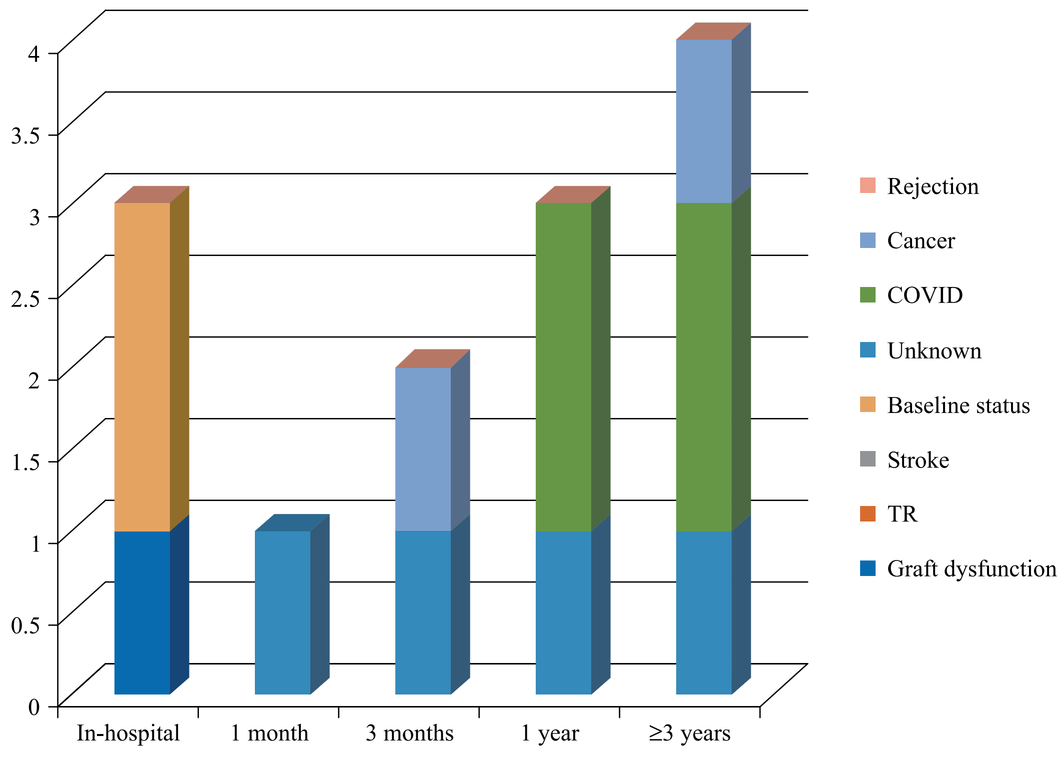

Fig. 4. Mortality patterns in the prolonged graft ischemia group

group and in 6 patients from the short ischemia group (Fig. 7).

When analyzing the frequency and degree of acute cellular rejection in the study groups in the first 30 days after transplantation based on the classification of the International Society for Heart and Lung Transplantation (ISHLT, 2004), it was shown that cold ischemia time had no adverse effect on HT outcomes in the 30-day follow-up period. The study groups of recipients were characterized by a dominant mild rejection (G1R), which did not require radical adjustment of immunosuppressive therapy.

DISCUSSION

Despite active development of perfusion technologies and attempts to optimize the organ donor pool, the issue of the use of expanded criteria heart donors and, in particular, hearts with prolonged cold ischemia, remains relevant [5].

Given the fact that in a number of cases, donor hearts from expanded criteria donors were implanted in urgent recipients after longer transportation, the initial severity of patients in the study group was slightly higher than in the comparison group. Two deaths were related specifically to the terminal state of the recipients, for whom HT

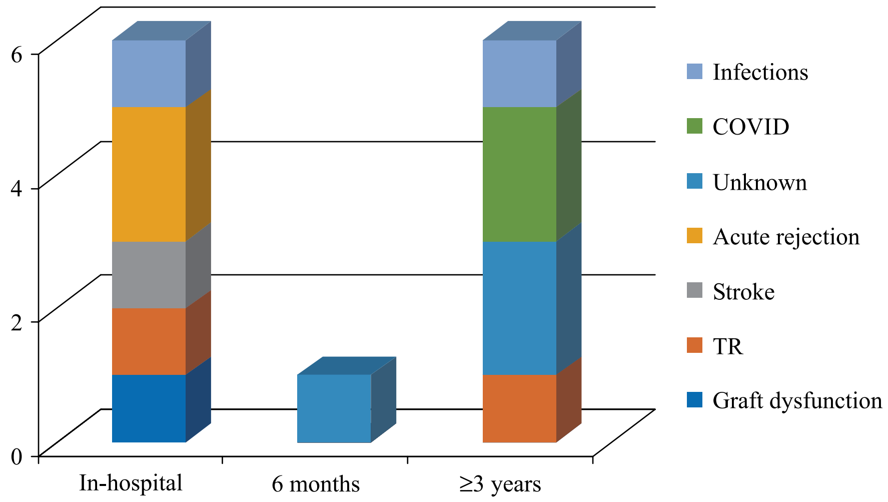

Fig. 5. Mortality patterns in the short graft ischemia group

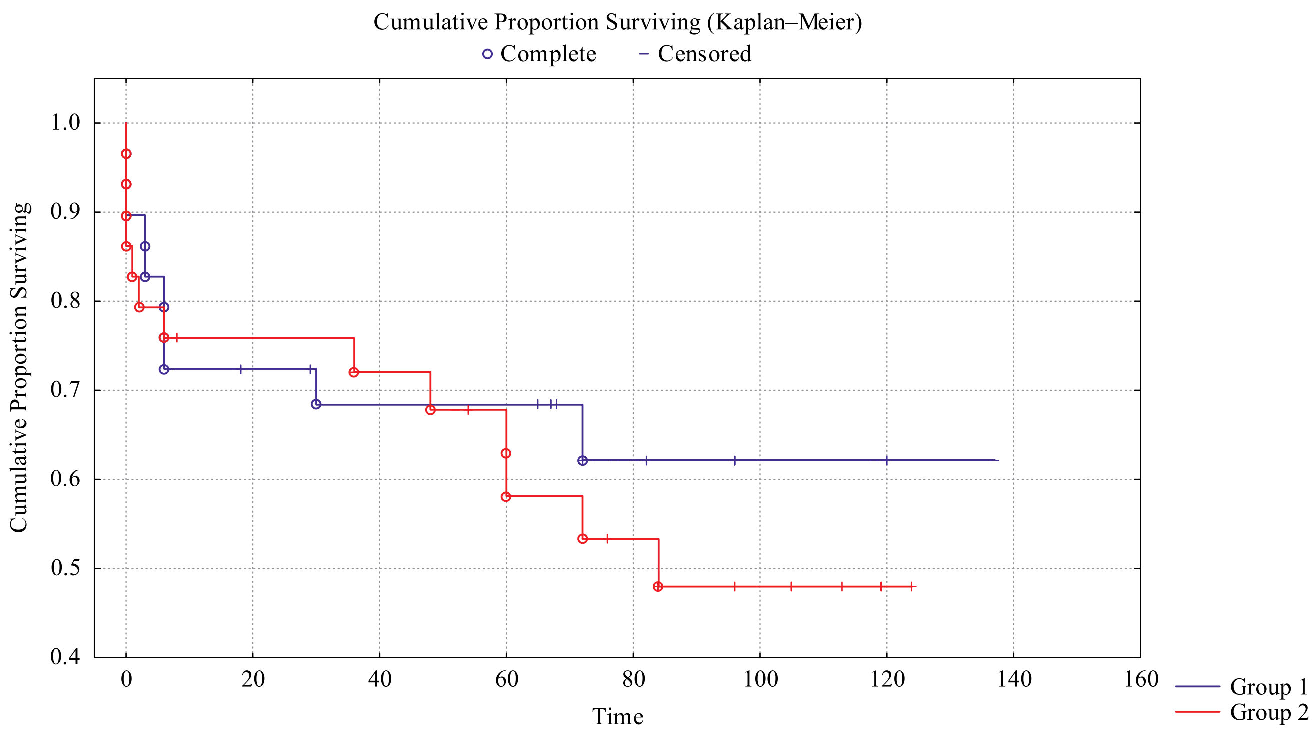

Fig. 6. Recipient survival for the entire follow-up period (months). Log-Rank Test (Spreadsheet1) WW = –1.376 Sum = 21.231 Var = 5.4010 Test statistic = –0.592046 p = 0.55382

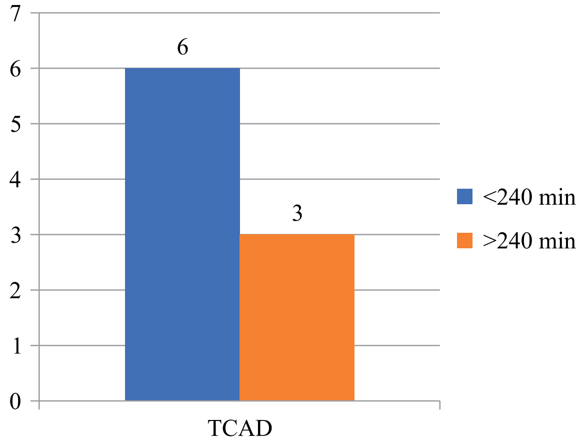

Fig. 7. Transplant coronary artery disease in the study groups

was performed as a desperate surgery. However, it did not lead to higher mortality in the prolonged ischemia group. Some authors single out prior mechanical support as a risk factor for adverse outcome [6].

Undoubtedly, modern realities contributed to the course of the post-transplant period. A total of 6 people in both groups died due to COVID-19 complications. Despite the fact that 4 people died from COVID-19 in the prolonged ischemia group and two in the comparison group, we did not obtain a significant difference in recipient survival in the groups. Analysis of one of the main potential negative factors of prolonged ischemia, primary graft dysfunction requiring mechanical circulatory support, also showed no advantage of short graft ischemia.

One of the identified consequences of the negative impact of prolonged donor heart ischemia was the duration and higher doses of inotropic support in the early postoperative period.

Unfortunately, we were unable to determine the threshold of safe cold ischemia time, probably because of the small sample of observations.

Available reports contain a lot of data on the adverse effect of cold ischemia >240 minutes on transplant outcomes. Similar results were obtained by authors from Spain, who analyzed HT outcomes in 17 centers in Spain for 2008–2018. They concluded that cold ischemia >4 hours has an adverse effect on 1-month and 1-year mortality [5].

In analyzing 317 heart transplant outcomes, a group of authors from the United States determined that each hour of cold ischemia increases the risk of primary graft dysfunction 1.8-fold [6].

Undoubtedly, there are a number of reports showing that HT with graft ischemia >300 minutes or more is possible.

Scientists from the USA have established that HT with cold ischemia >5 hours is accompanied by worse survival in the presence of such risk factors, ECMO and dialysis in the preoperative period, diagnosis of ischemic cardiomyopathy, as well as when using group 0(I) donors [7].

Authors from Botkin Hospital and the Shumakov National Medical Research Center of Transplantology and Artificial Organs distinguish between optimal (<180 minutes) and prolonged (>240 minutes) cold ischemia time. The threshold value is considered to be 300 minutes; in the presence of risk factors (advanced age, high doses of inotropic support, etc.), this threshold should not be exceeded [8].

Through analysis of 323 HT outcomes, the safe cold ischemia threshold for HT was established at ≤300 minutes [9].

An interesting analysis of the outcomes of 25,996 HTs (UNOS) was performed by authors from the USA. Patients were stratified by distance between the transplantation center and the donor base. 134 transplants were performed with a long transport of more than 1,500 miles and cold ischemia time of 7.5 hours. There was no significant difference in 1-year and 5-year survival between the groups [10].

Analysis of literature data is hampered by the heterogeneity of studies – different geography, principles of organ distribution, peculiarities of individual centers, and experience.

Despite the external factors influencing data analysis, as experience is gained, taking into account the peculiarities of the organ donation system in Siberian Federal District, the immediate and long-term outcomes of HT with prolonged cold ischemia are comparable with HT outcomes with ischemia <240 minutes. Obviously, the use of donor organs with prolonged cold ischemia has its own inclusion and exclusion criteria and risk factors. However, a clear algorithm for using this donor category, which will take into account all possible features of the regions and individual transplantation centers, is required.

CONCLUSION

HT with cold ischemia >4 hours did not show worse HT outcomes than short graft ischemia. Given the small experience, we were not able to identify the ischemic threshold and mortality predictors. However, survival after heart transplantation with prolonged cold ischemia provides grounds for further accumulation of experience in the use of heart donors from remote regions.

The authors declare no conflict of interest.

REFERENCES

1. *Shafiq F, Wang Y, Li G et al.* Clinical outcome of donor heart with prolonged cold ischemic time: A single-center study. *J Card Surg*. 2019; 35 (2): 397–404. doi: 10.1111/jocs.14404.
2. *Gautier SV, Khomyakov SM.* Organ donation and transplantation in the Russian Federation in 2020 13th Re-

port from the Registry of the Russian Transplant Society. *Russian Journal of Transplantology and Artificial Organs*. 2021; 23 (3): 8–34. https://doi.org/10.15825/1995-1191-2021-3-8-34.
3. *Nicholas R, Thomas Helen L et al.* The importance of cold and warm cardiac ischemia for survival after heart transplantation. Original articles. *Clinical transplantation*. 2008 Aug 27; 86 (Issue 4): 542–547. doi: 10.1097/TP.0b013e31818149b9.
4. Heart transplantation. National clinical guidelines. 2013.
5. *Valero-Masa MJ, González-Vílchez F, Almenar-Bonet L et al.* Cold ischemia >4 hours increases heart transplantation mortality. An analysis of the Spanish heart transplantation registry. *Int J Cardiol*. 2020; 319: 14–19.
6. *Nicoara A, Ruffin D et al.* Primary graft dysfunction after heart transplantation: Incidence, trends, and associated risks. *American Journal of Transplantation*. 2018; 18 (Issue 6): 1461–1470. https://doi.org/10.1111/ajt.14588.
7. *Tang P, Lei L et al.* Risk factors for heart transplantation survival with greater than 5 h of donor heart ischemic time. *Journal of Cardiac Surgery*. 2021 Aug; 36 (8): 2677–2684. doi: 10.1111/jocs.15621.
8. *Tenchurina EA, Minina MG.* Modern ideas in heart donor selection criteria. *Russian Journal of Transplantology and Artificial Organs*. 2020; 22 (3): 174–181. https://doi.org/10.15825/1995-1191-2020-3-174-181.
9. *Yeen W, Polgar A, Guglin M et al.* Outcomes of adult orthotopic heart transplantation with extended allograft ischemic time. *Transplant Proc*. 2013; 45 (6): 2399–2405.
10. *Gaffey AC, Chen CW, Chung JJ et al.* Extended distance cardiac allograft can successfully be utilized without impacting long-term survival. *J Heart Lung Transplant*. 2017; 36 (9): 968–972. doi: 10.1016/j.healun.2017.04.002.

The article was submitted to the journal on 25.08.2022