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Experience of heart transplantation with an extended cold ischemic time of donor heart

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Aim. A retrospective analysis of the outcomes of heart transplantation (HT) with extended cold ischemic time of donor heart (more than 4 hours) versus heart transplantation with short cold ischemia time (less than 4 hours).

Material and methods. The retrospective analysis included 52 recipients who underwent HT in the period from July 20, 2012 to October 23, 2019 in Meshalkin National Medical Research Center. The patients were divided into two groups: group 1 (n=26) — orthotopic HT with extended cold ischemic time (more than 240 minutes), group 2 (n=26) — short cold ischemia time (less than 240 minutes). The effect of cold ischemia duration on hospital survival, the function of donor heart, and the postoperative course was assessed.

Results. A retrospective analysis revealed a higher rate of hospital survival in the group of recipients with extended cold ischemic time (more than 240 minutes) — 88,5% compared to 80,7% in the second group. There was no difference between the groups in the acute rejection rate, the need for inotropic agents, mechanical circulatory support, and cardiac pacing, as well as the incidence of postoperative renal failure and infectious complications.

Conclusion. Due to the small number of patients, our experience in HT with extended cold ischemic time does not allow us to draw global conclusions, but a preliminary comparison of HT with extended and short cold ischemic time did not reveal significant advantages in one group or another. This provides a basis for further accumulation of experience and research.

Key words: heart transplantation, cold ischemia, heart failure.

Relationships and Activities: none.

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End-stage heart failure (HF) remains a major healthcare problem. Heart transplantation (HT) is a key treatment for end-stage HF. The problem of a critical donor organ shortage and an increase in the need for HT specify the expansion of criteria for selecting donors — age, function, ischemic time of donor heart.

Currently, the recommended cold ischemia time (CIT) is <4 hours, and an increase in the heart preservation duration is associated with an increased risk of ischemia-reperfusion injury, graft dysfunction, and mortality [1].

Already in 1995, analysis of CIT effect on the short- and long-term results of orthotopic HT (oHT). It was revealed that CIT was not a predictor of graft dysfunction and did not affect short- and long-term survival [2].

US authors presented more contradictory data, where the donor older age, regardless of the CIT, was a predictor of mortality. And an increase in the CIT to 6 hours is the best option for critical recipients [3].

Despite many studies, the question of the safe CIT remains open; there is no clear limit for preservation time. At the same time, it is complicated by various methods of donor heart preservation, small numbers of studies, and the heterogeneous structure of recipients.

Which recipients need oHT with prolonged CIT? Which preservative solution is best used in this case? Are there any postoperative features? There are no definite answers to these questions yet.

There are data showing that a young donor organ tolerates prolonged ischemia better than an older one. A shorter CIT improves survival in elderly HT recipients [4, 5]. Obviously, a donor age and the estimated ischemia time should be taken into account to improve the survival of HT recipients [4-6].

Undoubtedly, promising areas are the development of more effective methods for donor organ preservation and normothermic perfusion.

At the same time, it is necessary to minimize extra- and intracellular edema, intracellular acidosis, and to reduce the free radical formation. There are many studies aimed at optimizing preservation methods in order to increase the safe CIT and to reduce myocardial damage associated with prolonged ischemia [7].

The article presents the experience of oHT with prolonged ischemia time at the E. N. Meshalkin National Medical Research Center.

Material and methods

The retrospective analysis included 52 recipients: 43 men and 9 women who underwent oHT in the period from July 20, 2012 to October 23, 2019. The patients were divided into two groups depending on the CIT. The first group of the study included 26 recipients who underwent oHT with prolonged CIT of heart (>240 min); the second group — 26 recipients with short CIT (<240 min). The baseline characteristics of the recipients are presented in Table 1. In all cases, prolonged ischemia was due to long-term transportation from remote regions: Krasnoyarsk Krai, Kemerovo Oblast, Altai Krai.

All organ harvesting was performed from brain-dead donors. The age of the donors ranged from 23 to 56 years. The median age in the prolonged CIT group was 40 (34-46) years, in the short CIT group — 43 (40-51) years. The selection criteria were standard, donors with expanded criteria were not considered. Surgical and heart preservation techniques were standard.

All patients underwent oHT using the standard bicaval technique.

All patients underwent control transthoracic echocardiography immediately after surgery, on days 5-10, and after 1 month. The function and volumetric characteristics of the recipient's heart chambers after transplantation and the pulmonary artery pressure were assessed. Based on the results of a histological study of an endomyocardial biopsy, the level of rejection was assessed according to the ISHLT-WF classification (International Society for Heart and Lung Transplantation — working formulation, 2004).

In-hospital survival was considered as the primary endpoint. Secondary endpoints included the inotropic score at the time of disconnection from the heart-lung bypass machine, differences in the graft dysfunction incidence and the need for perioperative mechanical circulatory support, graft rejection, and analysis of risk factors for postoperative complications.

Given the small sample size and non-normal distribution (according to the Shapiro-Wilk test), the data are presented as median and first and third quartiles. We used the Mann-Whitney test for comparison of independent samples. Univariate regression was used to identify predictors of mortality.

Results

In-hospital survival in the prolonged CIT group was 88,5% (n=23), where 3 deaths were recorded (11,5%). At the same time, all three deaths in group 1 was due to graft dysfunction in the early postoperative period. All three patients belonged to the urgency status 2 in accordance with the United Network of Organ Sharing guidelines (1989). In one case, the cause was severe right ventricular failure after disconnection of extracorporeal membrane oxygenation (ECMO), in another case — large intraoperative bleeding in the patient with coagulopathy and severe decompensated heart failure, which was due to the extremely severe pre-transplantation sta-

Table 1

Baseline characteristics of recipients

Parameter	Group 1 (>240 min)	Group 2 (⩽240 min)
Age, years	41,5 [32,25-48,75] (21-66)	47 [33,75-50] (13-61)
BMI, kg/m^2	25,15 [21,65-27,45]	25 [23,5-31,975]
Sex		
Men Women	19 (73%) 7 (27%)	24 (92%) 2 (8%)
Primary diagnosis		
DCM	19 (73%)	13 (50%)
ICM	5 (19,2%)	10 (38,4%)
HCM	0	1 (3,8%)
Rheumatism	0	1 (3,8%)
Myocarditis	0	1 (3,8%)
Tumor	1 (3,8%)	
Congenital heart disease	1 (3,8%)	
Cold ischemia time of allograft, min	349,5 [300-397,5] (240-456)	173,5 [155,75-185,25] (135-240)
UNOS status 1a 1b 2	 4 (15,4%) 5 (19,2%) 17 (65,4%)	 2 (7,7%) 1 (3,8%) 23 (88,5%)

Abbreviations: HCM — hypertrophic cardiomyopathy, DCM — dilated cardiomyopathy, ICM — ischemic cardiomyopathy, BMI — body mass index.

tus of the recipient. OHT for this patient was a desperate operation.

In-hospital survival in the second group (<240 min) was 80,8% (n=21), where 5 deaths were recorded (19,2%), respectively. There were following causes of deaths: multiple organ failure (n=1), sepsis (n=1), acute rejection (n=1), and graft dysfunction (n=2).

According to the Kaplan-Meier survival estimates, there was no difference between the groups (log-rank, P 1/4 0,8025) (Figure 1).

Thus, primary graft dysfunction in the early postoperative period was observed in 11,5% (n=3) in the first group, and in 19,2% (n=5) in the second group.

Mechanical circulatory support (MCS) as a bridge to transplantation was performed in 8 patients (30,7%) from group 1 and 3 patients from group 2 (11,5%).

ECMO as a bridge to oHT in the first group was performed in one patient (3,8%). Due to hemodynamic instability and high-dose inotropic support, it was decided to reconnect ECMO immediately after surgery. MCS in the early postoperative period in the prolonged CIT group was needed only by 4 patients (15,4%), in the group with short CIT — by 3 patients (11,5%).

The level of inotropic support at the time of disconnection from cardiopulmonary bypass machine is represented by the inotropic score, while no

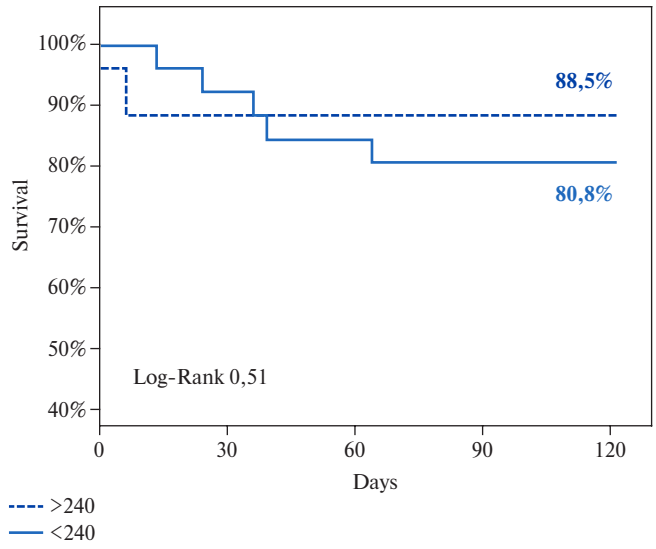

Figure 1. Kaplan-Mayer survival analysis in groups.

significant difference was found between the two groups (p=0,13). The median inotropic score in the 1st group was 8 (4-14,75), in the 2nd — 6,75 (325-8).

Univariate analysis revealed that significant predictors of in-hospital mortality were a decrease in heart graft contractility (hazard ratio, 10,97; 95% confidence interval, 2,64-54,24; p=0,0014), while

Table 2

Endomyocardial biopsy results

Results of endomyocardial biopsy according to ISHLT-WF (1990) criteria	No rejection	1A и 1B	2 и 3A	3B и 4
Perioperative period				
Group with ischemia >240 min	57,6% (n=15)	38,4% (n=10)		3,8% (n=1)
Group with ischemia ⩽240 min	73,1% (n=19)	19,2% (n=5)	3,8% (n=1)	3,8% (n=1)
One month after surgery				
Group with ischemia >240 min	61,5% (n=16)	30,7% (n=8)	7,7% (n=2)	
Group with ischemia ⩽240 min	84,6% (n=22)	11,5% (n=3)	3,8% (n=1)	

Table 3

Transthoracic echocardiography dynamics in recipients after HT

	Group with ischemia ⩽240 min	Group with ischemia >240 min	p
Indicators for 5-10 days after surgery			
LV EDV, ml	70,6 [60,25-76,25]	70 [49-90]	p=0,94
LV ESV, ml	29 [19,875-31]	15,5 [12,75-31,15]	
RV EDV, ml	35,5 [28,675-44,5]	33,5 [28,125-43,75]	
LVEF, %	60,5 [56,25-64,75]	61 [55-66]	p=0,66
RV FAC, %	41,5 [38,5-51,5]	41 [38-43]	
IVS thickness, mm	12,5 [11-14]	14 [13-16]	
LVPW thickness, mm	12 [10,25-14,5]	13 [12-15]	
Pulmonary artery pressure (mm Hg)	30 [27,5-32,75]	32 [28,5-36,5]	
Indicators 1 month after surgery			
LV EDV, ml	71 [66-74]	86 [61-90]	p=0,47
LV ESV, ml	21 [19,9-30]	29 [20,75-32,75]	
RV EDV, ml	34 [32-41,5]	36,5 [32-46]	
LVEF, %	65 [61-66]	65 [59,25-70]	p=0,86
RV FAC, %	46 [45-48]	45 [40-46]	
IVS thickness, mm	14 [12-15]	13 [13-15,75]	
LVPW thickness, mm	12,5 [12-13,5]	14 [12-15]	
Pulmonary artery pressure (mm Hg)	30 [28-33]	31 [30-33,5]	

Abbreviations: LVPW — left ventricular posterior wall, LV EDV — left ventricular end-diastolic volume, LV ESV — left ventricular end-systolic volume, RV EDV — right ventricular end-diastolic volume, IVS — interventricular septum, LVEF — left ventricular ejection fraction, RV FAC — right ventricular fractional area change.

ischemia time and mechanical support before oHT did not affect mortality.

The need for renal replacement therapy after oHT was the same in both groups — 3,8% (n=1).

There were no differences in the rates of MCS, postoperative renal failure, the need for cardiac pacing, and infectious complications.

There were no significant differences in the groups in the frequency of in-hospital acute cellular rejection. In group 1, there was 1 case of severe rejection and 2 cases of moderate rejection. In the 2nd group, there was one case of severe and moderate rejection. Endomyocardial biopsy results are shown in Table 2.

Cardiac pacing was required in two cases (7,6%) in the group of prolonged CIT and in three cases (11,5%) in the short ischemia group.

All patients underwent transthoracic echocardiography. The volumetric characteristics and mechanical activity of the recipient's heart chambers after transplantation were evaluated. The results of postoperative echocardiography are presented in Table 3.

The assessment of left ventricular (LV) end-diastolic volume and LV ejection fraction did not reveal significant difference between the groups. At the same time, there was a significant difference within the group in LV ejection fraction (p=0,03 and p=0,02, in

the 1st and 2nd groups, respectively), but there were no differences in LV end-diastolic volume (p=0,31, p=0,54, in the 1st and 2nd groups, respectively).

Discussion

HT is a key treatment for end-stage HF. The problem of a critical donor organ shortage and an increase in the need for HT specify the introduction of expanded criteria donors and donor hearts with prolonged CIT. Currently, the recommended cold ischemia time (CIT) is <4 hours. In a situation where the estimated CIT may exceed 4 hours, it is necessary to use hearts from young donors with normal function and little inotropic support [1].

According to this comparative analysis, we did not find a significant difference in in-hospital survival in the study groups. Undoubtedly, based on these data alone, we cannot recommend increasing the allowable ischemic time. A much larger-scale analysis of the effect of donor heart CIT on recipient survival after oHT is required.

According to many studies, the short- and long-term results of oHT with short- and long-term ischemia are comparable [8-11], which is consistent with our data. Univariate regression did not reveal the effect of CIT on in-hospital survival.

Shafiq F, et al. from Wuhan Union Hospital in China presented the experience of 297 HTs, evaluating the effect of CIT (>8, 6-8, 4-6 and <4 hours) on survival rates. In their opinion, donor hearts with CIT <8 h can be safely used to increase the donor pool. CIT >8 h was a predictor of a higher mortality rate compared with the other three groups during the 2-year follow-up, as well as longer cardiopulmonary bypass [10].

The interesting analysis was presented by Gaffey AC, et al. [12]. Authors analyzed the results of 25,996 oHTs conducted for the period from January 2000 to December 2013. The effect of the distance from the donor to the transplant center and the CIT on 1- and 5-year survival was evaluated. It was concluded that with the correct selection of the donor-recipient pair, the distance and CIT of the cardiac allograft does not affect 1- and 5-year survival. Also, there was no difference in the risk of stroke, the need for dialysis and reoperations in the groups [12].

The retrospective cohort study by British Columbia researchers revealed that an increase in cardiac allograft ischemia time was not associated with a significant difference in 10-year survival.

In another analysis, the total ischemic time of the cardiac allograft also did not affect survival. However, the effect of prolonged CIT on survival has been proven if the donor's age was >50 years (p=0,009) [9].

In our opinion, the interest in the prolonged CIT of cardiac allograft by foreign authors has somewhat decreased. This is due to the fact that the central ways to solve the problem of donor shortages in developed countries is the development of perfusion technologies. Promising results are demonstrated by the Transmedics organ care system (Transmedics, Inc., USA) and the LifeCradle system (Organ Transport Systems, Inc., USA) [13].

Unfortunately, the use of the above systems of normothermic perfusion in Russia is impossible due to high cost. Currently, the use of heart transplants with cold ischemia for 4-8 h may be one of the main ways to expand the donor pool and increase the availability of HT.

This suggests itself that it is necessary not only to expand the donation criteria and increase the CIT, but also optimize the technology of donor organ preservation, introducing normothermic perfusion systems, and develop methods against ischemia-reperfusion injury.

Conclusion

The short-term outcomes in recipients after HT with prolonged and short ischemia of the cardiac allograft are comparable. The use of donor hearts with long-term ischemia increases the number of HT and reducing the mortality of potential recipients included in the waiting list. According to current study, in-hospital mortality is specified by the severity of the recipient's preoperative condition. It is planned to further accumulate experience on safe CIT of cardiac allograft.

Relationships and Activities: none.

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