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FUNCTIONAL STATE OF THE CARDIORESPIRATORY SYSTEM AFTER ORTHOTOPIC HEART TRANSPLANTATION WITH PROLONGED COLD ISCHEMIA TIME

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Objective: to assess the functional state of the cardiorespiratory system in the long term after orthotopic heart transplantation (HT) with prolonged cold ischemia time. **Materials and methods.** The results of 60 orthotopic HTs performed at Meshalkin National Medical Research Center were analyzed. A comparison was made of the immediate and long-term outcomes of HTs in the group with cold ischemia time lasting for less than 240 minutes and in those with farther distance between donor and recipient sites with cold ischemia time of 240 minutes or more. In the long-term follow-up after HT, all patients underwent cardiopulmonary exercise testing, body plethysmography, assessment of the diffusing capacity of the lungs, and quality of life assessment. **Results.** Prolonged cold ischemia showed a negative effect on the early postoperative period – decreased myocardial contractility on postoperative day 1 and longer duration of inotropic support. At the same time, the survival rate and incidence of graft rejection reactions in the early and late post-HT periods in the studied groups did not differ significantly. Peak oxygen consumption in the general group in the long term after HT was 17 (14.7–21.0) mL/kg/min, VE/VCO_2 slope was 30 (29–36) at 100 (90–120) W threshold load power. All the parameters of pulmonary function tests did not differ significantly depending on cold ischemia duration. Quality of life also did not show significant differences depending on the duration of graft ischemia in terms of both physical and psycho-emotional health components of the SF-36 questionnaire. **Conclusion.** Long-term cold ischemia of the graft did not show any negative impact on the functional state of the cardiorespiratory system and quality of life in the long term after HT. The studied group of recipients was characterized by high efficiency of pulmonary ventilation and gas exchange, as well as high tolerance to physical activity in the long-term post-HT period.

Keywords: heart transplantation, cold ischemia time, cardiopulmonary exercise testing.

INTRODUCTION

Heart transplantation (HT) is the "gold standard" for terminal heart failure treatment [1]. According to international registries, the survival rate in the first year after HT is currently 85 to 93%, and the ten-year survival rate is 69% [2].

Despite the development of the legal framework for organ donation and an increase in the efficiency of the organization of the transplantation service, there remains a significant shortage of donor organs, forcing to come back to the issue of expanding the criteria for organ donation, in particular, the use of organs with prolonged cold ischemia [2, 3]. Thus, besides the publications of individual researchers [4–6], the report of the International Society for Heart and Lung Transplantation (ISHLT) in 2017 highlighted the topic of the duration of transplant ischemia as a priority for further study [2].

The transplant ischemia time depends on numerous logistic and technical factors. The recommended maximum duration of cold ischemia of the donor heart is 240 minutes [7, 8]. An increase in ischemic time affects the viability of the graft and, according to many authors, increases the risk of an unfavorable HT outcome [4, 7]. However, a number of studies have shown that prolonged time of cold ischemia does not significantly affect the early and long-term results of HT [9, 10]. The cases with extremely prolonged ischemia of the donor organ and satisfactory HT results in the long-term follow-up were described [5, 10].

Thus, the results of studies on the effect of graft ischemia duration on HT outcome are ambiguous. It is of interest to conduct further studies on this issue, including an assessment of the functional state of the organism of recipients in the long-term follow-up. The purpose of the present study is to assess the functional state of the cardiorespiratory system in the long term after orthotopic HT with prolonged cold graft ischemia.

MATERIALS AND METHODS

The study included 60 patients who underwent HT at the Meshalkin National Medical Research Center (Minis-

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try of Health of Russia; Novosibirsk, Russian Federation) from 2013 to the present. The study was performed in accordance with Good Clinical Practice and the principles of the World Medical Association Declaration of Helsinki. The study protocol was approved by the local ethics committee. Written informed consent was obtained from all patients prior to inclusion.

The inclusion criterion was the HT in history. The exclusion criteria were refusal to participate, age under 18, musculoskeletal disorders that made it difficult to perform the cardiopulmonary exercise testing (CPT).

Orthotopic HT was performed by the common bicaval technique. The hearts were retrieved by the standard method, with conservation with "Custodiol" cold cardioplegic solution. In some cases, donor hearts from remote regions, Altai Kraj, Kemerovo Oblast, Krasnoyarsk Kraj were used.

In the postoperative period, all recipients received combined immunosuppressive therapy with calcineurin inhibitor (cyclosporin 4–6 mg/kg/day or tacrolimus 0.05–0.1 mg/kg/day), mycophenolate and prednisolone 1 mg/kg/day with a gradual dose reduction to 0.1–0.2 mg/kg/day. The target level of cyclosporine was 250–300 ng/ml, the concentration of tacrolimus was 15–20 ng/ml, with a gradual decrease in therapeutic concentration in the long term after HT.

The examination protocol after HT included virological and bacteriological examination, general clinical and biochemical blood analysis, determination of the concentration of tacrolimus and cyclosporine in blood, hemocoagulation parameters, and general urine analysis. Electro- and echocardiographic examination, CPT, endomyocardial biopsy with morphological and immunohistochemical analysis, coronary angiography were performed. Endomyocardial biopsy in the first 2 months after transplantation was performed every 10 days, then after 3 months, and later once a year. The graft rejection rate was determined in accordance with the ISHLT recommendations.

The analysis included anthropometric, demographic parameters, functional class (FC) of angina pectoris by NYHA, myocardial infarction in history, acute cerebrovascular accident, previous cardiac surgery, indicators of myocardial contractility, the presence of concomitant pathology. Intraoperative characteristics included the duration of cardiopulmonary bypass, aortic occlusion, the total surgery time, and the duration of graft cold ischemia. In the early postoperative period, the duration of stay in the intensive care unit (ICU), the need and duration of inotropic support, prolonged mechanical ventilation, the need for mechanical circulatory support, myocardial contractility (the first day after HT), and adverse outcomes including graft dysfunction and hospital mortality. In the long-term follow-up, survival, cases of cardiovascular accidents, repeated cardiac surgery, the presence and severity of graft rejection, myocardial contractility, parameters of pulmonary functional tests, including CPT, and quality of life were assessed.

CPT was performed on an OXYCON Pro bicycle ergospirometric system (Jaeger, Germany) with the RAMP protocol until maximum oxygen consumption or limiting symptoms followed by a recovery period. The analysis included the following CPT parameters: threshold load power (W), peak oxygen consumption (VO_2 peak, ml/min/kg) and its metabolic equivalent (MET, RVU), respiratory ratio (RER), ventilation equivalent by carbon dioxide (VE/VCO_2 slope), oxygen pulse at maximum load (O_2-pulse), partial pressure CO_2 in the final portion of expiration ($PetCO_2$, mmHg) at rest and at the anaerobic threshold level, recovery time of oxygen consumption, and heart rate. Anaerobic threshold level was determined by the V-slope. Arterial saturation (%) was measured using pulse oximetry.

Using the methods of body plethysmography and assessment of the diffusion capacity of the lungs (Master Screen, Jaeger, Germany), the absolute and assigned to due values (with accounting for anthropometric parameters and age) of respiratory function were studied. The analysis included the forced expiratory volume in the first second (FEV1, L), Tiffeneau index (%), and diffusive capacity of lungs (DLCO, mmol/L/kPa).

The quality of life was analyzed by the results of the SF-36 questionnaire; for the analysis, summary scales characterizing the physical component of health and the psychoemotional component of health were used.

The results were statistically analyzed with the Statistica 6.1 software package (StatSoft, USA). Quantitative variables are presented as median and interquartile range (Me (Q25–Q75), qualitative variables – as frequency of occurrence and / or percentage. Intergroup comparison of indicators was performed using the Mann – Whitney test or Fisher's exact test. Survival curves were plotted by the Kaplan–Meier method with an assessment of the significance of differences by the log-rank test. p value <0.05 was considered statistically significant for all kinds of analysis.

RESULTS

To assess the effect of the duration of cold graft ischemia on HT results, all patients were divided into two groups: in the first group, the duration of graft ischemia did not exceed 240 minutes, in the second, with remote removal, 240 minutes or more. The basic characteristics of the recipients are presented in Table 1. Average age, anthropometric parameters, the presence of concomitant pathology did not differ in the study groups. In both groups, male patients slightly predominated.

Percutaneous transluminal angioplasty with stenting of the affected coronary arteries prevailed in the previous cardiac surgeries. For health reasons, a left ventricular bypass system was installed in 8 patients prior to heart transplantation.

Table 1

Baseline recipient characteristics

Parameter		General group (n = 60)	Duration of graft cold ischemia		
			<240 min. (n = 35)	≥240 min. (n = 25)	p
Age, years		42 (33–50)	46 (40–51)	40 (30–48)	0.093
Male gender, n (%)		50 (83%)	31 (89%)	19 (76%)	0.062
BMI, kg/m^2		27 (19–33)	26 (19–31)	27 (20–34)	0.288
Etiology	ischemic, n (%)	24 (40%)	14 (40%)	10 (40%)	0.545
	non-ischemic, n (%)	36 (60%)	21 (60%)	15 (60%)	
Functional class by NYHA	III, n (%)	39 (65%)	20 (57%)	19 (76%)	0.324
	IV, n (%)	21 (35%)	15 (43%)	6 (24%)	
Acute myocardial infarction in history, n (%)		8 (13%)	5 (14%)	3 (12%)	0.683
Cerebrovascular accident in history, n (%)		9 (15%)	6 (17%)	3 (12%)	0.256
Diabetes mellitus, n (%)		3 (5%)	2 (6%)	1 (4%)	0.692
Chronic lung diseases, n (%)		2 (3%)	1 (3%)	1 (4%)	0.643
Chronic kidney disease >C3A, n (%)		1 (%)	1 (3%)	0 (0%)	0.380
Previous INCOR installation, n (%)		8 (13%)	4 (11%)	4 (16%)	0.150
Previous cardiac surgery, n (%)		23 (38%)	13 (37%)	10 (40%)	0.412
LVEF, %		22 (19–25)	20 (18–26)	22 (19–24)	0.443
Right ventricle FAC, %		30 (20–38)	31 (18–36)	33 (25–39)	0.267
Systolic pressure in the pulmonary artery, mm Hg		40 (33–48)	42 (35–50)	39 (30–48)	0.252
Time in WL, days		240 (48–376)	240 (143–359)	239 (24–368)	0.592

Table 2

Intraoperative characteristics and the early postoperative period after orthotopic heart transplantation

Parameter	General group (n = 60)	Duration of graft cold ischemia		
		<240 min. (n = 35)	≥240 min. (n = 25)	p
Duration of graft ischemia, min	210 (175–340)	180 (158–190)	350 (300–430)	<0.001
Duration of artificial blood circulation, min	191 (165–240)	182 (156–210)	193 (184–241)	0.624
Duration of aortic occlusion, min	105 (90–130)	102 (94–126)	105 (86–128)	0.814
Total operation duration, min	420 (360–525)	395 (360–510)	460 (330–540)	0.326
Duration of ICU stay, days	8 (6–10)	7 (6–10)	9 (5–10)	0.375
Duration of inotropic support, h	72 (34–96)	56 (34–77)	96 (57–139)	0.014
Duration of ventilation >24 h, n (%)	9 (15%)	4 (11%)	5 (20%)	0.245
MCS after surgery, n (%)	6 (10%)	1 (3%)	5 (20%)	0.032
Repeated surgical interventions, n (%)	8 (13%)	5 (14%)	3 (12%)	0.221
LVEF, %	59 (45–63)	62 (58–65)	56 (43–58)	0.030
Right ventricle FAC, %	40 (36–45)	46 (40–51)	37 (32–40)	0.017
Systolic pressure in the pulmonary artery, mm Hg	30 (26–35)	29 (24–33)	33 (27–38)	0.269
Primary graft dysfunction, n (%)	8 (13%)	3 (8.6%)	5 (20%)	0.163
Mortality associated with primary graft dysfunction, n (%)	1 (1.7%)	1 (2.9%)	0 (0%)	0.361
30-day mortality, n (%)	5 (8%)	2 (5.7%)	3 (12%)	0.502

Against the background of the absence of differences in the initial clinical and functional state of patients and the parameters of the intraoperative period, the differences in the characteristics of the early postoperative period are noteworthy (Table 2). Thus, in the group of remote graft removal, the duration of inotropic support was significantly higher. On day 1 after HT, a significant decrease in myocardial contractility was noted, followed by restoration to normal values by days 5–7 after surgery.

As a result of primary graft dysfunction, one patient died from the group with a graft ischemia duration of less than 240 minutes. The overall 30-day mortality rate was 8% (5 patients), with no significant differences between the groups. In 4 cases, mortality was not associated with graft dysfunction.

The long-term follow-up after HT averaged 3.0 (1.9–4.8) years (Table 3). Most of the patients were FC I – II by NYHA. Myocardial contractility in the long-term

Table 3

Clinical and functional characteristics of patients at long-term follow-up after orthotopic heart transplantation

Parameter		General group (n = 60)	Duration of graft cold ischemia		
			<240 min. (n = 35)	≥240 min. (n = 25)	p
Follow-up duration, years		3.0 (1.9–4.8)	3.0 (1.7–4.8)	3.1 (1.8–4.9)	0.845
Functional class by NYHA	I, n (%)	13 (25%)	7 (23%)	6 (27%)	0.413
	II, n (%)	37 (71%)	21 (70%)	16 (73%)	
	III, n (%)	2 (4%)	2 (7%)	0 (0%)	
Diabetes mellitus, n (%)		5 (10%)	3 (10%)	2 (9%)	0.828
Chronic kidney disease >C3A, n (%)		4 (8%)	1 (3%)	3 (14%)	0.126
Cardiac surgery, n (%)		1 (%)	1 (3%)	0 (0%)	0.551
Graft rejection reaction	1A–1B, n (%)	6 (11.5%)	3 (10%)	3 (14%)	0.236
	2A–2B, n (%)	7 (13.5%)	4 (13%)	3 (14%)	
	3A–3B, n (%)	1 (1.9%)	0 (0%)	1 (4.5%)	
Mortality, n (%)		8 (13%)	5 (14%)	3 (12%)	0.575
LVEF, %		65 (63–67)	65 (64–67)	65 (60–68)	0.501
Right ventricle FAC, %		46 (42–52)	47 (45–52)	46 (39–55)	0.523
Systolic pressure in the pulmonary artery, mm Hg		31 (28–35)	31 (28–35)	31 (30–34)	0.743

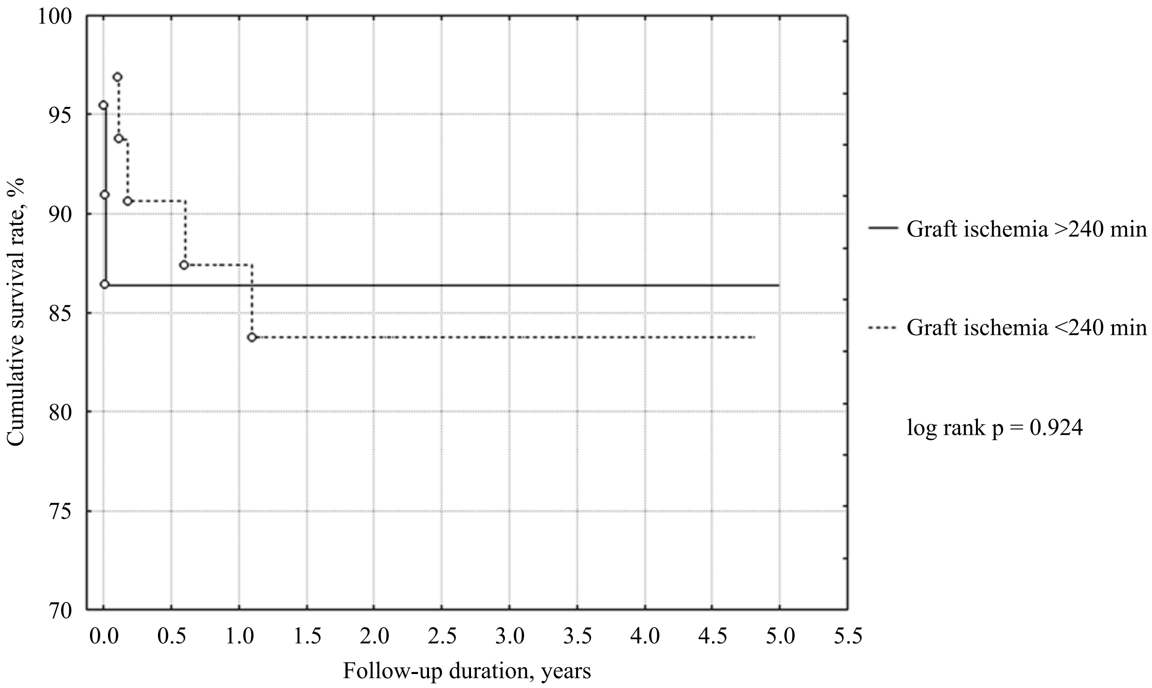

Fig. 1. Survival after orthotopic heart transplantation depending on the duration of cold transplant ischemia

period after HT corresponded to normal values, without significant differences between the groups.

During the follow-up, two patients developed diabetes mellitus, one – coronary artery disease of the transplanted heart, which required endovascular surgery.

Graft rejection grade 3A–3B was registered in 1 patient during the first year after HT, grade 2A–2B – in 7 patients. Rejection was successfully stopped after pulse therapy with methylprednisolone at a dose of 1000 mg/day for 3 days, followed by endomyocardial biopsy control. Graft rejection 1A–1B was registered in 6 patients and did not require radical correction of immunosuppressive therapy. The overall mortality rate was 13%, with no significant differences between the groups (Fig. 1). All mortality cases in the long-term follow-up period were not associated with graft dysfunction.

With improved hemodynamics after HT, all patients showed a high exercise tolerance (Table 4).

The parameters of pulmonary ventilation and gas exchange, including those during provoking physical activity, did not differ in patients with remote transplant removal. The peak oxygen consumption in the general group averaged 17 (14.7–21.0) ml/min/kg, 5.2 (4.2–6.0) MET, with a threshold load power of 100 (90–120) W.

Table 4

The results of pulmonary functional tests in the long-term follow-up after orthotopic heart transplantation

Parameter	General group (n = 60)	Duration of graft cold ischemia		
		<240 min. (n = 35)	≥240 min. (n = 25)	p
Load threshold power, W	100 (90–120)	110 (100–140)	100 (90–110)	0.146
VO_2 peak, ml/min/kg	17 (14.7–21.0)	19 (15.6–21.0)	16 (14.1–21.5)	0.269
VE/VCO_2 slope	30 (29–36)	32 (29–36)	30 (29–36)	0.458
RER peak	1.15 (1.05–1.18)	1.11 (1.06–1.16)	1.06 (1.02–1.18)	0.433
O_2-pulse peak	11.4 (9.6–12.7)	11.5 (9.6–12.6)	10.9 (10.5–12.8)	0.922
MET, conv. units	5.2 (4.2–6.0)	5.5 (4.5–6.0)	4.6 (4.0–6.1)	0.270
$PetCO_2$ at the level of the anaerobic threshold, mm Hg	37 (35–39)	36 (35–38)	38 (33–39)	0.775
$PetCO_2$ gain during exercise, mm Hg	6.3 (5.2–8.5)	5.8 (5.2–7.7)	7.0 (3.1–9.5)	0.628
VO_2 recovery time, min	6 (5–8)	7 (5–8)	6 (4–7)	0.536
HR recovery time, min	9 (7–10)	7 (6–10)	9 (8–10)	0.268
Arterial saturation, %	96 (95–97)	96 (95–97)	95 (94–97)	0.182
FEV1, % of reference	95 (84–103)	98 (92–106)	93 (76–100)	0.136
Tiffeneau Index, %	81 (77–89)	82 (75–90)	81 (76–87)	0.979
DLCO, % of reference	77 (64–85)	72 (61–80)	81 (67–87)	0.859

Note. VO_2 – oxygen consumption; VO_2 peak – peak oxygen consumption; VE/VCO_2 – ventilation coefficient of carbon dioxide; RER peak – respiratory coefficient during exercise; O_2 pulse – oxygen pulse during exercise; MET – metabolic equivalent; $PetCO_2$ – end tidal carbon dioxide partial pressure; HR – heart rate; FEV_1 – forced expiratory volume in 1 second; DLCO – lung diffusion capacity.

The absence of significant differences in the study groups was also seen for the main parameters of the quality of life, which was assessed using the SF-36 questionnaire in the long term after HT (Fig. 2).

The level of quality of life in the general group for the physical and psychoemotional components of health of the SF-36 questionnaire was above average and amounted to 53 (50–55) and 52 (50–56) points, respectively.

Thus, in the studied group of patients, long-term cold ischemia of the graft did not show a significant effect on the functional state of the cardiorespiratory system and quality of life in the long term after HT.

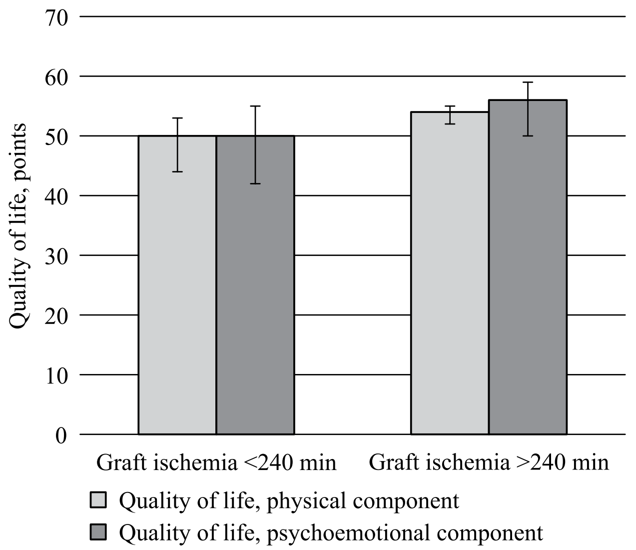

Fig. 2. Quality of life in the long-term follow-up after heart transplantation, SF-36 questionnaire results

DISCUSSION

The duration of graft cold ischemia is considered one of the most important factors determining the effectiveness of HT [2, 11, 12]. According to many authors, exceeding the safe time threshold increases the risk of postoperative allograft dysfunction and the death of the recipient [4, 13]. Destabilization of biological membranes, generation of reactive oxygen species, disturbances in electrolyte balance, energy supply, coagulation hemostasis that occur during hypoxia and subsequent tissue reperfusion play a great role in the mechanisms of allograft damage [13, 14].

However, the increase in the number of patients on the HT waiting list dictates the need to change strategies to increase the donor pool. Our study analyzed the results of long-term follow-up after HT in two groups: with allograft ischemia duration less than 4 hours, on average 180 (158–190) minutes, and exceeding the safe ischemia threshold (average ischemia time 350 (300–430) minutes).

The results of the study showed that the adverse effect of long-term cold ischemia of the allograft affects the early postoperative period after HT. Myocardial injury during prolonged cold ischemia and its subsequent reperfusion injury led to contractile dysfunction of the donor heart on the first day after HT, which required more prolonged inotropic support in the group with graft ischemia of more than 4 hours. It should be noted that by the end of hospitalization the myocardial contractility in this group corresponded to normal values and did not differ from the group with the duration of allograft ischemia less than 4 hours. Mortality in the study groups in the early postoperative period also had no significant differences, including cases associated with primary graft dysfunction. These data are comparable with the results of other researchers [15].

Numerous studies show improvements in physical performance, peak oxygen consumption and other parameters of pulmonary ventilation and gas exchange in the general cohort of patients undergoing HT [16–19]. However, when analyzing the effect of long-term allograft ischemia, the authors, as a rule, use only the main characteristics of clinical outcomes, such as graft rejection reactions, survival [4–6, 15]. In particular, the current international recommendations do not analyze the potential interactions between the ischemic time of the allograft and the characteristics of the clinical and functional state of the recipient's body and do not assess the role of the ischemic time of the allograft in any specific subgroups [2].

The advantage of the present study was a comprehensive assessment of the functional state of the cardiorespiratory system in the long term after HT, depending on the duration of graft ischemia.

Patients of both studied groups in the long term after HT corresponded mainly to FC I–II by NYHA and were characterized by normal myocardial contractility. There were no differences in the incidence of graft rejection reactions and patient survival.

The effect of the duration of graft cold ischemia on exercise tolerance and other CPT parameters was not noted. All patients in the long term after HT were characterized by high efficiency of pulmonary ventilation and gas exchange, high physical performance. The level of peak oxygen consumption in the general group, equal to 17 (14.7–21.0) ml/min/kg and VE/VCO_2 slope equal to 30 (29–36), as well as an increase in $PetCO_2$ during exercise over 5 mm Hg. Art. obtained in our study indicate a good long-term prognosis in patients undergoing HT. The kinetics of heart rate recovery and oxygen consumption after stress testing also did not depend on the duration of graft ischemia.

Quality of life, being an important indicator of the effectiveness of treatment, in our study did not show significant differences depending on the duration of graft ischemia and corresponded in the long term after HT to a level above the average for both physical and psychoemotional health components of the SF-36 questionnaire.

The findings are comparable to those of large studies. Despite the fact that the overall risk of graft dysfunction increases with an increase in the duration of ischemia beyond 4 hours, many authors believe that it is possible to safely increase the threshold to at least 5 hours without compromising HT results [20]. According to other authors, exceeding the safe time threshold has a negative value only for an allograft obtained from an older donor, since, due to age-related changes, the heart of an elderly donor may be especially susceptible to hypoxic and reperfusion damage and have a lower ability to regenerate [6, 21]. In addition, in the future, the role of the ischemic time of the allograft may change as a result of the possible introduction of new perfusion systems for the preservation of donor organs [22].

The limitation of this study was the relatively small number of observations after HT with prolonged cold ischemia of the allograft. However, the results obtained in this cohort of patients indicate the need for further study of this issue from the standpoint of a comprehensive assessment of the functional state of the organism of recipients after HT.

CONCLUSION

The study showed that long-term cold ischemia of the donor heart has a negative effect on the early postoperative period of HT in the form of a decrease in myocardial contractility on the first day after surgery and an increase in the duration of inotropic support. The survival rate and the incidence of graft rejection reactions in the early and late periods after HT were comparable in the groups with graft ischemia of less than 240 minutes and with prolonged ischemia of more than 240 minutes.

Long-term cold ischemia of the graft did not show a negative effect on the functional state of the cardiorespiratory system and quality of life in the long term after HT. The study group of recipients was characterized by high efficiency of pulmonary ventilation and gas exchange, as well as high exercise tolerance in the long term after HT.

The authors declare no conflict of interest.

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