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PERIOPERATIVE PERIOD IN HEART TRANSPLANTATION WITH EXTREMELY PROLONGED ISCHEMIC TIMES (>6 HOURS)

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Amidst the shortage in viable donor hearts, the use of hearts from expanded criteria donors, including those with prolonged ischemic time, remains one of the real ways to increase the donor pool and number of heart transplantations (HTx) performed. The study included 38 recipients (33 (86.8%) men and 5 (13.2%) women) aged 11 to 66 (44.7 ± 12.0 years, median 48.0 years), who underwent primary (n = 37; 97.4%) or repeat (n = 1; 2.6%) HTx (retransplantation). Donor hearts (n = 38) with ischemic time ranged from 362 (6 hours 2 minutes) to 571 (9 hours 31 minutes) or 407 ± 52 minutes (median 400 minutes). In 33 (86.8%) of 38 recipients, the early posttransplant period was characterized by satisfactory initial graft function. Five (13.1%) recipients developed severe primary graft dysfunction, requiring post-transplant venoarterial extracorporeal membrane oxygenation (VA-ECMO) (n = 4; 10.5%) or prolongation of pre-transplant VA-ECMO within 8 days of HTx (n = 1; 2.6%). In-hospital mortality was 7.9% (n = 3). Thirty-five (92.1%) of 38 recipients were discharged from the hospital. Three recipients died in the post-hospital period at day 734, 944, and 2146 after HTx. Thirty-two (84.2%) of the 38 recipients remained alive at the end of the study. Our own experience shows that HTx from donors with prolonged ischemic time could be effective.

Keywords: heart transplantation, prolonged ischemic time.

INTRODUCTION

In the context of shortage of viable donor hearts, the use of hearts from expanded criteria donors remains one of the real ways to increase the donor pool and the number of HT performed [1, 2, 3]. Suspected prolonged (>4 hours) donor ischemic time due to the time it takes to transport the donor heart to a transplant center (transport ischemia) or other reasons is one of the leading factors of expanded heart donation [4]. Despite the existing concerns on a more frequent severe primary dysfunction, HTx with prolonged ischemic time continues to be performed and is considered as one of the measures to eliminate donor organ shortage and increase the number of heart transplants [5, 6]. Studies on transplantation with ischemic time >6 hours are few and demonstrate the ambiguous influence of this expanded donation factor on immediate and long-term outcomes of HTx [7, 8].

The **objective** of the study was to determine the effect of extremely prolonged ischemic time (>6 hours) on the nature of restoration of primary function in heart transplant recipients and the immediate outcomes of HTx.

MATERIALS AND METHODS

During the period from January 1, 2011 to December 31, 2021, 1500 heart transplant surgeries were performed at Shumakov National Medical Research Center of Transplantology and Artificial Organs, Moscow. This included 38 (2.5%) with ischemic time >360 minutes. The study included 38 recipients (33 (86.8%) men and 5 (13.2%) women) aged 11 to 66 (44.7 ± 12.0, median 48.0 years), who underwent primary (n = 37 (97.4%)) or repeat (n = 1 (2.6%)) HTx (retransplantation) with a given ischemic time. In all observations, transplantation with extremely prolonged (≥6 hours) donor heart ischemic time was due to the territorial distance of the donor base from the transplant center.

Pre-transplant characteristics of the heart recipient

The main cardiac conditions that led to end-stage chronic heart failure (CHF) and the need for HTx were dilated cardiomyopathy (n = 20 (52.6%)), coronary heart disease (n = 16 (42.1%)), restrictive cardiomyopathy (n = 1 (2.6%)), and long-term irreversible heart graft dysfunction (n = 1 (2.6%)). The severity of CHF corresponded to classes IIA (n = 2 (5.3%)), IIB (n = 25 (65.8%)), and III (n = 11 (28.9%)) according to the Strazhesko–Vasilenko classification or 3 (n = 4 (10.5%)) and 4 (n = 34 (89.5%)) functional class (3.8 ± 0.4) according to the

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NYHA classification. The urgency of HTx corresponded to status IA (n = 18 (47.4%)), IB (n = 5 (13.2%)), or 2 (n = 15 (39.4%)) according to UNOS.

Eleven (28.9%) patients had heart arrhythmia in the form of permanent atrial fibrillation. A cardioverter defibrillator was implanted in 8 (21.1%) recipients. Five (13.2%) recipients had previously undergone cardiac surgery on the open chest and pericardial cavity: implantation of a long-term left ventricular bypass system (n = 3); coronary artery bypass grafting (n = 1); primary HTx (n = 1).

Concomitant conditions included: class 2 obesity (n = 8 (21.1%); arterial hypertension (n = 7 (18.4%); multifocal atherosclerosis with lesions of brachycephalic and/or lower extremity arteries (n = 7 (18.4%)); chronic bronchitis (n = 5 (13.2%)); gastric/duodenal ulcer (n = 5 (13.2%)); dyscirculatory encephalopathy (n = 4 (10.5%)); gout (n = 4 (10.5%)); subclinical hypothyroidism (n = 3 (7.9%)); cholelithiasis (n = 3 (7.9%)); urolithiasis (n = 3 (7.9%)); chronic kidney disease stage 2 and higher (n = 3 (7.9%)); condition after acute cerebrovascular disease (n = 2 (5.3%)); type 2 diabetes mellitus (n = 2 (5.3%)); condition after pulmonary embolism (n = 1 (2.6%)).

In 5 (13.2%) patients, dopamine (3–6 (3.9 ± 1.6) μg/kg/min (n = 4)) or dobutamine (4 μg/kg/min (n = 1)) cardiotonic therapy was sufficient to correct systemic hemodynamic disorders; which lasted for 4–30 (7.1 ± 10.1) days before HTx.

In 15 (39.5%)) recipients, we used short-term pre-transplant mechanical circulatory support (MSC) by peripheral venoarterial extracorporeal membrane oxygenation (VA-ECMO), in 4 (10.5%)) – prolonged MSC by implanted left ventricular bypass. VA-ECMO before HTx lasted for 1–6 (2.1 ± 0.8) days.

The clinical, laboratory, and instrumental pre-transplant examination of recipients, including the results of invasive central hemodynamic studies at the time of inclusion on the heart transplant waitlist, are presented in Table 1.

Clinical, instrumental, and laboratory examination of heart donors

Heart was harvested from brain-dead donors (n = 38), whose brain death was caused by nontraumatic (n = 30 (78.9%)) or traumatic (n = 8 (21.1%)) lesion. The harvesting was done at donor centers located in the following places: Voronezh (n = 10 (26.3%)); Tula (n = 5 (13.2%)); Arkhangelsk (n = 4 (10.5%)); Ryazan (n = 4 (10.5%)); Volgograd (n = 3 (7.9%)); Samara (n = 3 (7.9%)); Tyumen (n = 3 (7.9%)); Rostov-on-Don (n = 2 (5.3%)); Ivanovo (n = 1 (2.6%)); Kazan (n = 1 (2.6%)); Chelyabinsk (n = 1 (2.6%)); Ufa (n = 1 (2.6%)). In 28 (73.7%) and 10 (26.3%) observations, long-distance transportation of donor heart was done by air and road transport, respectively.

The age of heart donors (29 (76.3%) men and 9 (23.7%) women) was 22–60 (41.6 ± 9.7) years, including 4 (10.5%) donors aged 55 years or above; weight was 60–110 (78.4 ± 12.1) kg, and artificial ventilation (AV) lasted for 1–9 (2.2 ± 1.6) days. None of the donors had cardiopulmonary resuscitation episodes. The main parameters of clinical, laboratory and instrumental examination of the heart donors are presented in Table 2.

The donor heart was cold preserved with histidine-tryptophan-ketoglutarate (Custodiol®) solution by non-selective antegrade cardioplegia in a 3–4 L volume depending on the donor's anthropometric parameters. Repeated injection of 1 L of chilled the preservative solution was performed immediately before donor heart suturing through a cardioplegic cannula placed in the ascending aorta before the first injection of the preserving solution.

The criteria for expanded heart donation were (1) donor age >50 years; (2) left ventricular hypertrophy ≥1.4 cm; (3) left ventricular ejection fraction <50%; (4) high sympathomimetic vasopressor/cardiotonic support (norepinephrine >600 ng/kg/min or dopamine >10 μg/kg/min); (5) sustained cardiopulmonary resuscitation >5 min; (6) transient (lifetime) coronary artery atherosclerosis; (7) potentially correctable cardiac valve pathology; (8) hypernatremia >160 mmol/L; (9) methanol poisoning [9].

The following prognostic scales were used to objectively assess the degree of donor heart marginality and the risk of primary graft dysfunction: Eurotransplant Donor Heart Scale [10], Donor Risk Index Model [11], RADIAL score [12]. A heart donor was qualified as having expanded criteria if there were more than 17 points on the Eurotransplant Donor Heart Scale and 9 points or more on the Donor Risk Index Model. Incidence of primary heart graft dysfunction according to the RADIAL score was estimated according to the total score: 0 point, 2.1%; 1 point, 4.1%; 2 points, 8.1%; 3 points, 15.2%; 4 points, 27.4%; ≥5 points, 44.2% [12].

We quantified the magnitude of inotropic/vasopressor therapy using the Wernovsky-Inotropic Score (WIS) = dopamine (μg/kg/min) + dobutamine (μg/kg/min) + 100 × adrenaline (μg/kg/min) and Vasoactive Inotropic Score (VIS) = WIS + 10 × milrinone (μg/kg/min) + vasopressin (U/kg/min) + norepinephrine (μg/kg/min) [13, 14].

Early heart graft dysfunction was classified as primary or early secondary dysfunction. The diagnosis and severity of primary graft dysfunction was established in accordance with ISHLT criteria from 2010 [15]. Early secondary graft dysfunction was defined as impaired pumping function in heart transplant recipients that developed in the early post-transplant period and was due to immunological reasons, high pulmonary hypertension or errors in heart transplant surgical technique [16].

Table 1

Preoperative characteristics of heart recipients who underwent transplantation with donor heart ischemia time of more than 6 hours (n = 38)

Parameter	Value (minimum, maximum, mean)
Non-invasive and invasive (right heart catheterization) hemodynamic assessment at the time of inclusion in the waiting list	
HR, bpm	54–120 (79.3 ± 17.1)
Systolic BP, mm Hg.	86–144 (106.0 ± 14.1)
Diastolic BP, mm Hg.	48–92 (69.6 ± 11.8)
Mean BP, mm Hg.	60–101 (78.2 ± 11.7)
RAP, mm Hg.	4–19 (8.8 ± 4.5)
Systolic PAP, mm Hg.	29–51 (36.9 ± 12.1)
Diastolic PAP, mm Hg.	10–35 (20.4 ± 7.5)
Average PAP, mm Hg.	15–44 (25.1 ± 8.1)
PCWP, mm Hg.	11–32 (18.9 ± 6.6)
CO, L/min	2.2–5.1 (3.5 ± 0.9)
CI, L/min/m^2	1.82 ± 0.41 (1.2–2.3)
TPG, mm Hg.	2–12 (7.0 ± 2.8)
PVR, Wood units	0.6–5.9 (2.3 ± 1.2)
Laboratory tests within 24 hours before heart transplantation	
Hemoglobin, g/dL	11.0–16.7 (13.3 ± 2.5)
White blood cells, 10^9/L	5.7–13.6 (7.8 ± 2.7)
Platelets, 10^9/L	74–396 (173.2 ± 70.5)
Urea, mmol/L	6.0–16.7 (8.1 ± 3.3)
Creatinine, μmol/L	48–152 (100.7 ± 31.2)
Total bilirubin, μmol/L	11–95 (33.1 ± 23.3)
ALT, IU/L	22–175 (30.7 ± 31.8)
AST, IU/L	16–146 (35.7 ± 32.9)
Total protein, g/L	59–87 (72.2 ± 6.5)
Glucose, mmol/L	4.4–8.6 (5.9 ± 1.2)
PI, %	48–97 (83.3 ± 10.2)
INR	1.1–2.4 (1.38 ± 0.40)
K^+, mmol/L	3.2–4.9 (3.6 ± 0.4)
Na^+, mmol/L	126–140 (134.5 ± 3.5)
pH	7.30–7.49 (7.40 ± 0.08)
BEa, mmol/L	(–) 3.5–3.6 (0.59 ± 3.0)
Lactate, mmol/L	0.6–1.7 (1.1 ± 0.4)
Transthoracic echocardiography within one week before heart transplantation	
Ascending aorta, cm	1.8–3.5 (3.1 ± 0.6)
Left atrium, cm	4.2–6.6 (5.1 ± 0.7)
Right ventricle, cm	1.8–4.4 (3.2 ± 0.7)
LVEDD, cm	4.5–7.5 (6.3 ± 1.2)
LVESD, cm	2.9–6.8 (5.1 ± 1.5)
LVESV, mL	88–360 (231.1 ± 82.4)
LVEDV, mL	48–221 (177.9 ± 77.1)
SV, mL	18–71 (54.4 ± 23.1)
LVEF	10–33 (26.2 ± 14.1)
LVPW, cm	0.95 ± 0.17
IVS, cm	0.96 ± 0.17
Mitral regurgitation, grade	1.5–3.0 (1.9 ± 0.8)
Tricuspid regurgitation, grade	1.0–3.0 (2.1 ± 0.6)

Note: HR, heart rate; BP, blood pressure; RAP, right atrial pressure; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; CI, cardiac index; TPG, transpulmonary pressure gradient; PVR, pulmonary vascular resistance; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PI, prothrombin index; INR, international normalized ratio; BEa, base excess arterial; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; SV, stroke volume; LVEF, left ventricular ejection fraction; LVPW, left ventricular posterior; IVS, interventricular septum.

The diagnosis and severity of donor-transmitted atherosclerosis was established according to the results of the first post-transplant coronary angiography performed no later than 1 month after HTx. The diagnosis and severity of acute cellular and antibody-mediated rejection were established according to ISHLT criteria [17, 18].

Statistical processing of the study data was performed using Microsoft Excel spreadsheets and Statistica for Windows 7.0 application software package (Start Soft Inc. USA), Biostat and SPSS. Normality of distributions was assessed using the Kolmogorov–Smirnov test. Mean values of numerical parameters were presented as $M \pm \sigma$. Mean values were compared using the Mann–Whithey U-test or Student's t-test. A significant difference was considered at $p < 0.05$. Pearson's chi-squared test and Fisher's exact test were used to compare frequencies of binary outcomes. The Kaplan–Meier estimate was used to assess survival, and survival was compared using the log-rank test.

RESULTS

The ischemic time of donor hearts (n = 38) ranged from 362 (6 hours 2 minutes) to 571 (9 hours 31 minutes) or 407 ± 52 (median 400) minutes, including: 361–420 minutes (7 hours), n = 27 (71.1%); 421–480 minutes (8 hours), n = 7 (18.4%); 481–540 minutes (9 hours), n = 3 (7.9%); >540 minutes (or >9 hours), n = 1 (2.6%).

The number of expanded heart donor factors was 2.2 ± 1.2. The degree of cardiac donor marginality according to the Eurotransplant Donor Heart Score was 19.2 ± 8.2, the Donor Risk Index Model score was 6.7 ± 2.1, and the RADIAL scale score was 2.9 ± 1.0. The predicted primary graft failure rate, calculated using the RADIAL scale, was 16.4 ± 10.6%.

Table 2

Donor characteristics with ischemic time >6 hours (n = 38)

Parameter	Value (minimum, maximum, mean)
Sympathomimetic cardiotonic/vasopressor support	
No sympathomimetic support, n (%)	7 (18.4%)
Norepinephrine only, n (%)	24 (63.2%)
Norepinephrine + dopamine, n (%)	7 (18.4%)
Dopamine (max), μg/kg/min, (n = 7)	3–18 (10.1 ± 6.9)
Dopamine (before withdrawal), μg/kg/min, (n = 4)	2–15 (4.1 ± 2.8)
Noradrenaline (max), ng/kg/min, (n = 24)	50–1000 (430.0 ± 185.3)
Norepinephrine (before withdrawal), μg/kg/min, (n = 24)	100–800 (288.2 ± 146.5)
Laboratory tests	
Hemoglobin, g/dL	11.0–16.7 (13.3 ± 2.5)
Total protein, g/L	59–87 (72.2 ± 6.5)
Glucose, mmol/L	4.4–8.6 (5.9 ± 1.2)
K^+, mmol/L	2.7–5.9 (3.8 ± 0.6)
Na^+, mmol/L	126–140 (134.5 ± 3.5)
pH	7.29–7.56 (7.41 ± 0.25)
BEa, mmol/L	(–) 3.3–2.5 (0.9 ± 1.3)
Blood lactate, mmol/L	0.8–6.9 (1.8 ± 0.7)
Transthoracic echocardiography	
Ascending aorta, cm	2.4–4.7 (3.2 ± 0.7)
Left atrium, cm	2.4–5.7 (3.7 ± 0.8)
Right ventricle, cm	2.1–3.5 (2.6 ± 0.5)
LVEDV, mL	56–130 (105.5 ± 27.2)
LVESV, mL	20–58 (39.9 ± 13.5)
SV, mL	35–105 (63.9 ± 21.7)
LVEF	50–70 (61.9 ± 6.4)
LVPW, cm	0.9–1.4 (1.2 ± 0.2)
IVS, cm	0.9–1.5 (1.2 ± 0.2)
IVS ≥1.4 cm, n (%)	6 (15.8%)
Mitral regurgitation, degree	0.0–1.5 (1.1 ± 0.3)
Tricuspid regurgitation, degree	1.0–1.5 (1.2 ± 0.2)
sPAP (estimated), mm Hg.	19–42 (26.7 ± 0.7)

Note: BEa, base excess arterial; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; SV, stroke volume; LVEF, left ventricular ejection fraction; LVPW, left ventricular posterior; IVS, interventricular septum; sPAP, systolic pulmonary artery pressure.

In 31 (81.6%) of 38 recipients, HTx was performed by bicaval technique, in 7 (18.2%) – by biatrial technique. Anesthesia lasted for 6.6 ± 0.9 hours, surgical intervention lasted for 4.9 ± 0.5 hours, cardiopulmonary bypass (CPB) was 63–164 (148 ± 25) minutes, heart graft suturing lasted for 43 ± 8 minutes, the "removal of aortic unclamping – weaning from CPB" interval was 48 ± 20 minutes.

In 33 (86.8%) of 38 recipients, the early post-transplant period was characterized by satisfactory initial graft function. In this cohort of recipients, the highest adrenaline dose during follow-up was 58.7 ± 21.3 ng/kg/min, dopamine was 8.1 ± 2.5 μg/kg/min, and dobutamine was 7.0 ± 2.3 μg/kg/min, dopamine or dobutamine dose at the time of transfer from the intensive care unit (ICU) was 3.9 ± 0.3; the highest VIS score was 16.2 ± 3.9, the lowest and highest CI values were 2.6 ± 0.2 and 3.1 ± 0.3 L/min/m^2, respectively, the highest RAP/CVP value is 13.9 ± 2.1 mm Hg, average PAP 25.4 ± 6.3 mm Hg, PCWP was 16.3 ± 1.9 mm Hg, and the lowest and highest LVEF values were 52.3 ± 6.7% and 62.0 ± 4.6%, respectively. Levosimendan as an additional component of sympathomimetic cardiotonic therapy was used in 100% of cases. In 16 (42.1%) recipients, we used double sequential administration of the drug. Postoperative adrenaline administration lasted for 62.5 ± 18.7 hours; the interval to achieve a dosage of less than 5 μg/kg/min with dopamine or dobutamine monotherapy was 4.9 ± 0.8 days; postoperative AV lasted for 12.5 ± 6.7 hours; treatment in the ICU was 5.7 ± 4.4 days; cardiotonic therapy in the early posttransplant period was 9.2 ± 5.2 days.

In 10 (26.3%) patients, a sinus rhythm was registered since the initial heart graft function was restored. Due to bradyarrhythmia in the heart transplant recipients, 28 (73.7%) the patients required temporary pacing in VOO mode (n = 6), AOO mode (n = 13) or VOO with transition to AOO mode (n = 9) with a generated HR of 100 to 120 per minute.

Five (13.1%) recipients developed severe primary graft dysfunction, necessitating post-transplant VA-ECMO (n = 4 (10.5%)) or prolongation of pre-transplant VA-ECMO for 8 days after HTx (n = 1 (2.6%)) (severe according to the ISHLT Primary Graft Dysfunction classification (2010)). Four (80.0%) of 5 recipients were diagnosed with a biventricular primary heart transplant dysfunction, and 1 (20.0%) had a predominantly right ventricular variant in the absence of pre-transplant pulmonary hypertension. Persistent resolution of severe primary graft dysfunction in 4 (80%) of 5 allowed termination of VA-ECMO at days 4–8 (6.1 ± 1.6) from the start of MSC.

According to the first coronary angiographic study, donor-transmitted atherosclerosis requiring percutaneous coronary intervention was detected in 3 (7.9%) of 38 recipients and included hemodynamically significant (over 50%) narrowing of 1 (n = 2) and 3 (n = 1) coronary arteries.

According to results from the first endomyocardial biopsy, acute cellular rejection grade 2 R or higher and/or antibody-mediated rejection pAMR grade 2 or higher was not diagnosed in any of the cases.

Hospital mortality was 7.9% (n = 3). In all cases, the cause of death was progressive multiple-organ failure developed against the background of severe primary dysfunction of the heart transplant (n = 1) and purulent-septic complications (bacterial pneumonia (n = 1), pancreatic necrosis (n = 1)). Hospital mortality in the cohort of recipients with severe primary dysfunction was 20% (1 in 5).

Thirty-five (92.1%) of 38 recipients were discharged from the hospital. The duration of ICU treatment among the surviving recipients was 5.8 ± 1.4 days. The follow-up period at the end of data collection (December 31, 2021) was 1053 ± 174 days. Three recipients died in the posthospital period at days 734, 944, and 2146 after HTx. The causes of death were lung cancer (n = 1), sepsis and multiple-organ failure against the background of pneumonia developed in out-of-hospital conditions (n = 1), and sudden death (n = 1). Of the 38 recipients, 32 (84.2%) were still alive at the end of the study. The mean life expectancy of recipients with prolonged ischemic time was 70.7 ± 5.6 months at the end of the study (Fig.).

DISCUSSION

Prolonged preservation of donor heart may be due to the time it takes to transport the donor heart from the donor base to the transplant center, or due to a delay in suturing the donor heart as a result of prolonged isolation (cardiolysis) of the recipient's own heart in the repeated nature of surgical intervention (for example, explantation together with removal of the implanted assisted circulation system) or other reasons, leading to prolonged time interval between removal and beginning of suturing of the donor heart [19].

Suspected prolonged ischemic time is one of the "traditional" criteria for expanded heart donation [20]. Amid the current donor organ shortage over the last three decades, the use of hearts from expanded criteria donors, including those with prolonged ischemic time, remains a feasible way to increase the availability of heart transplantation, including in patients who need it urgently and/or have a predicted worse early and long-term post-transplant survival, independent of donor characteristics [21].

The limits of acceptable duration of donor heart ischemic time have not yet been defined and are the subject of scientific research. The threshold cold preservation time for the donor heart is considered to be 4 hours [22, 23]. According to the guidelines of the International Society for Heart and Lung Transplantation (ISHLT), transplantation with a donor ischemic time >4 hours is allowed

in certain clinical situations when other heart donor factors are ideal for effective HTx (young age, normal systolic function, no inotropic support) [22]. Earlier studies have shown that donor ischemic time >4 hours significantly increases the risk of severe primary graft dysfunction requiring the use of mechanical circulatory support (MCS) [24]. Some transplant centers consider it acceptable to perform HTx with donor ischemic time of 4–6 hours [20, 25]. Cases of HTx with donor ischemic time >6 hours are rare and, as a rule, are done at transplantation centers with experience in performing these transplants and/or heart transplants from expanded criteria donors [5, 26, 27].

It is well known that cold cardioplegia, which is the main method of donor heart preservation, does not provide complete cessation of metabolic processes in myocardium in conditions of its anoxia, leading to depletion of energy substrates, intracellular acidosis, hyperproduction of reactive oxygen species and cardiomyocyte edema [28]. Subsequent reperfusion (re-oxygenation) enhances the functional and morphological damage to the heart transplant myocardium. The leading pathogenetic mechanisms of ischemia-reperfusion injury (IRI) in heart transplant recipients are hyperproduction of reactive oxygen species and calcium overload, which leads to uncontrolled activation of calcium-dependent ion transport systems, depletion of energy reserves, disruption of cardiomyocyte metabolism and subsequent irreversible cardiomyocyte damage [29]. Disruption of mitochondrial calcium-dependent pores or mitochondrial permeability transition pores plays an important role in the chain of pathophysiological disorders caused by IRI [30, 31]. As it increases, the potentially negative influence of ischemic time on functional and morphological disorders of heart graft caused by IRI, as well as on immediate and long-term outcomes of HTx, increases [32].

Prolonged preservation increases the risk of severe primary dysfunction in heart transplant recipients. The leading cause is a combination of irreversible and reversible ischemic-reperfusion myocardial injury to the cardiac graft [33]. Primary graft dysfunction remains the most common cause of death in the early stages after HTx [34]. The risk of severe primary dysfunction increases when prolonged ischemic time is combined with other expanded heart donation factors (e.g., age of the donor) [35]. Hearts from young donors (age <34 years) are more tolerant to prolonged ischemic time compared to hearts from older donors (>34 years), which predetermines better early and long-term survival after HTx [36]. The relationship between ischemic time and the risk of acute graft rejection, as well as accelerated coronary artery disease in heart transplant recipients and chronic dysfunction in the long term after HTx has been revealed [37].

According to the multicenter, international ISHLT registry (2017), 18,772 HTx were performed between January 2009 and June 2015, of which 1.8% (n = 337) were with ischemic time >6 hours [32]. In the study we presented, the proportion of transplants with donor ischemic time >6 hours was 2.5% between January 1, 2011 and December 31, 2021. Almost half of the patients (47.4%) required urgent HTx, including 39.5% (n = 15) with short-term pre-transplant MCS and 5.3% (n = 2) with life-threatening complications of long-term MCS (implantable left ventricular bypass systems).

Severe early graft dysfunction requiring MCS developed in 13.1% of observations, corresponding to its predicted incidence according to the RADIAL scale

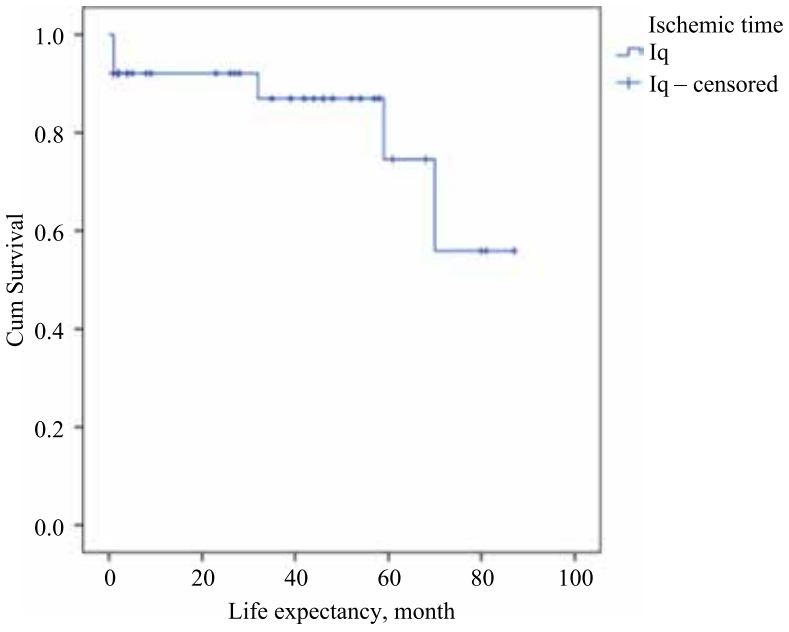

Fig. Kaplan–Meier estimates of survival in heart recipients with graft ischemic time >6 hours

(16.4 ± 4.6%). A meta-analysis by Buchan T.A. et al (2021) found that the incidence of primary graft dysfunction in heart transplant recipients was 20.5% according to ISHLT classification (2010), of which 7.7% were for severe dysfunctions requiring MCS [34]. Increasing the donor ischemic time beyond 240 minutes increases by three times the risk of primary graft dysfunction [38]. Starting from the threshold value of 240 minutes, further increase in ischemic times leads to a linear increase in the incidence of primary graft dysfunction in heart transplant recipients [34]. In an earlier study by Marasco S.F. et al (2007), increasing ischemic time from 240 minutes to 360 minutes or more increases the incidence of early graft dysfunction by 2.9 times (from 17% to 50%), the frequency of post-transplant MCS by 4.4 times (from 7% to 31%) and the median ICU treatment duration by 3.3 times (from 3 days to 10 days) [39]. Thus, according to Marasco S.F. et al (2007), every second recipient develops primary dysfunction when the ischemic time increases over 6 hours, and every 3 recipients need MCS at these graft ischemic times [39]. Buchan T.A. et al (2021) found that increasing the ischemic time by 1 hour increases the incidence of primary dysfunction by 1%, and increasing the age of the heart donor by 10 years, increases the incidence by 65% [34]. Pre-transplantation use of VA-ECMO is associated with a 10-fold increase in the incidence of primary graft dysfunction [40].

In-hospital mortality rates in recipients with primary dysfunction vary widely (from 19% to 37%) and in most studies depend on the severity of its hemodynamic manifestations [41]. In our study, the in-hospital mortality of recipients with primary graft dysfunction requiring MCS was 20% (1 of 5) or 33.3% of all cases (1 of 3) of in-hospital mortality in transplantation with donor ischemic time >6 hours.

In-hospital patient survival in extremely (>6 hours) prolonged ischemic time was 92.1%, which is comparable to those (93%) in HTx within the recommended ischemic time (<240 minutes) [39].

CONCLUSION

1. 2.53% of heart transplants were performed with an ischemic time >6 hours, which in all cases was due to the territorial distance of the donor base from the transplant center.
2. In transplantations with excessively prolonged (>6 hours) graft ischemic time, the incidence of severe early dysfunction in the heart transplant recipients, which required MCS (venoarterial extracorporeal membrane oxygenation) was 13.1%.
3. In-hospital survival of transplant recipients with excessively prolonged (>6 hours) ischemic time was 92.1%.

The authors declare no conflict of interest.

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