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The first experience of using extracorporeal membrane oxygenation in severe primary graft dysfunction following heart transplantation

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Abstract

Introduction. *The number of surgically treated cases of heart failure by means of orthotopic heart transplantation is increasing every year. At the same time, there is a shortage of optimal donors for heart transplantation, being a factor that leads to a primary graft dysfunction in the intra- and immediate postoperative period. In order to reduce the risk of complications and increase patient survival rates in primary heart graft dysfunction, a number of transplant centers resort to the choice of the treatment by means of mechanical circulatory support, such as extracorporeal membrane oxygenation.*

Clinical case. *In the early postoperative period after heart transplantation, the patient was diagnosed with developing primary graft dysfunction. The clinical response to medication support of hemodynamics was unsatisfactory. Veno-arterial extracorporeal membrane oxygenation was performed. On the 4th day, the regional contractility of the left ventricle restored, the ejection fraction of both ventricles increased, their systolic function improved. The patient was discharged on the 21st day in a satisfactory condition.*

Conclusion. *Mechanical circulatory support modalities, such as veno-arterial extracorporeal membrane oxygenation, can compensate for the emerging primary myocardial dysfunction in recipients. The efficiency of the extracorporeal membrane oxygenation is achieved not only by knowledge of current clinical recommendations, but also depends on the implementation of other clinics' experience as well as technical readiness of the center and medical personnel' qualification.*

Keywords: primary heart graft dysfunction, orthotopic heart transplantation, heart, extracorporeal membrane oxygenation

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ABB, acid-base balance

ACE, angiotensin converting enzyme

ACT, activated coagulation time

ALT, alanine aminotransferase

AST, aspartate aminotransferase

BB, buffer bases

BSA, body surface area

CHRS, centrifuge head rotational speed

CPB, cardiopulmonary bypass

CVP, central venous pressure

DBP, diastolic blood pressure

DCM, dilated cardiomyopathy

EchoCG, echocardiography

ECMO, extracorporeal membrane oxygenation

EDD, end-diastolic dimension

EDV, end diastolic volume

EF, ejection fraction

ESD, end-systolic dimension

FC, functional class

GFR, glomerular filtration rate

OHT, orthotopic heart transplantation

HF, heart failure

HR. heart rate

IVS, interventricular septum

LA, left atrium

LV, left ventricle

NYHA, New York Heart Association

PA, pulmonary artery

PASP, pulmonary artery systolic pressure

PAWP, pulmonary artery wedge pressure

P-BNP, B-type natriuretic peptide

PE, pulmonary embolism

PHGD, primary heart graft dysfunction

PTD, post-thrombotic disease

RA, right atrium

RR, respiratory rate

RV, right ventricle

s´t, tricuspid annular systolic velocity

SBP, systolic blood pressure

TAPSE, Tricuspid annular plane systolic excursion

TV, tidal volume

VPV, volumetric perfusion velocity

Introduction

The incidence of chronic heart failure (HF) in Russia continues to increase from year to year and amounts to 2.4–4.5 million patients [1]. Pharmacological therapy remains the first line of treatment for patients with heart failure, international protocols of pharmacological management of patients with various conditions in heart failure have been developed, but the mortality rate remains high, reaching up to 12% per year [1]. Orthotopic heart transplantation (OHT) is referred to as a radical treatment for end-stage heart failure. OHT is an effective method for treating an end-stage heart failure and remains one of the best treatment options with a relative decrease in 5-year mortality by 3.9 times among the operated patients [1-3]. Currently, the number of operations using organ donation is increasing. Over the recent 5 years, the number of OHT performed in the Russian Federation has grown by 42%; in 2018, 285 OHT were performed in 18 centers throughout Russia [4].

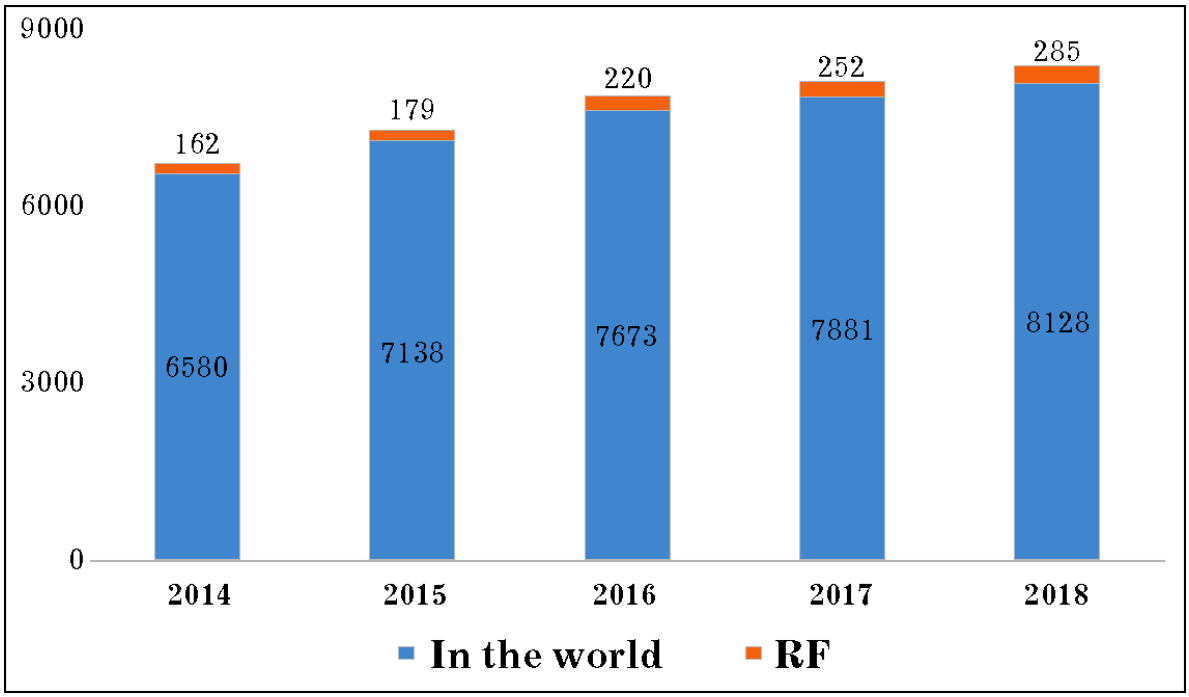

Fig. 1. The annual number of heart transplantations in the world and in Russia over the period from 2014–2018 [2, 5]

In the Republic of Tatarstan, the first heart transplantation was performed in 2011 at Interregional Clinical Diagnostic Center, Kazan; total 9 such operations had been performed for the followed 8 years. All patients had end-stage heart failure, which was qualified as functional class (FC) III in 6 patients, and FC IV in 3 patients; the causes of the end-stage heart failure were dilated cardiomyopathy in 88.8% (8 cases), and ischemic cardiomyopathy in one case; the mean left ventricular (LV) ejection fraction (EF) in the operated patients was 21.2 ± 2.7%, their mean age was 49.1 ± 11.2 years old; and as for the gender distribution, there were 7 men of 9 operated patients (78%).

Heart transplantation can be followed by complications, such as a cardiogenic shock and a cardiac arrest, which are emergencies with a high mortality rate. To maintain the necessary pulmonary gas exchange and restore the cardiac function, the temporary prosthetics of the heart and lungs are necessary when their functions are taken over by mechanical

support equipment. This is the mechanical circulatory support using extracorporeal membrane oxygenation (ECMO) devices [6]. Indications for veno-arterial ECMO include refractory low cardiac activity (the cardiac index lower than 2 L/min) and hypotension (systolic blood pressure [SBP] lower than 90 mm Hg) [7].

With the increasing number of OHT operations performed and a deficiency in optimal donor hearts, the severe clinical status of recipients and condition of donor organs proportionally increase. Factors inherent in the recipient, donor, and perioperative management can lead to a catastrophic complication, which is a primary heart graft dysfunction (PHGD). The definition of post-transplant primary graft dysfunction is based on the Consensus Statement [8] of the International Society for Heart and Lung Transplantation and is characterized as a syndrome of cardiac dysfunction that occurs in the immediate postoperative period after heart transplantation and is the main isolated cause of death within the first 30 days after transplantation. In the early period after heart transplantation, from 5–28% of recipients develop a severe PHGD refractory to combination drug therapy, requiring to use various methods of mechanical circulatory support [3, 8]. PHGD has a high 30-day mortality rate of approximately 30%, which is the result of “incorrect” cardiac perfusion or a failed selection of a suboptimal donor heart. Despite numerous advances in the field of transplantation over the recent decades, the factors involved in PHGD development and those contributing to optimal treatment of this condition still remain incompletely understood. This is partly due to the lack of a uniform definition of PHGD and, therefore, which treatments would bring the greatest benefit to the patient [9].

We present a clinical case report with a favourable clinical result of the conversion of cardiopulmonary bypass (CPB) to veno-arterial ECMO in a patient with PHGD after OHT.

Clinical Case Report

A female patient I., 30 years old, was admitted to the Interregional Clinical Diagnostic Center, Kazan, as referred from a regional hospital, having the diagnosis of dilated cardiomyopathy (DCM) that had developed as a result of viral myocarditis experienced 6 months ago. The patient's condition had been deteriorating over the previous 4 months that was manifested with pain in the cardiac region, inspiratory dyspnea at slight exertion, pain and swelling in the left lower limb. Transthoracic echocardiography (EchoCG) revealed the LV and left atrium (LA) enlargements, a decreased LV contractile function with diffuse myocardial hypokinesis, an elevated pulmonary artery systolic pressure (PASP), and a marked tricuspid and mitral valve insufficiency. At admission, the patient's condition was assessed as moderately severe, with the complaints of inspiratory dyspnea at rest and in the supine position, cough, edema of the lower extremities, decreased urine output, and heart palpitations. Diagnostic and functional tests were performed to verify the cardiac pathology.

Based on the examination performed, PE was excluded. At angiopulmonography, the pulmonary artery patency was traced to its branches of the III – IV order. EchoCG identified diffuse hypokinesis of the LV myocardium with its global contractile function being decreased; there was also a decrease in the contractile function of the right ventricle (RV) myocardium; tricuspid annular plane systolic excursion (TAPSE) was 1.0 cm. All heart chambers were enlarged and there was a marked insufficiency of the mitral and tricuspid valves caused by the dilatation of

the cardiac chambers and, as a consequence, the dilatation of the atrioventricular fibrous rings (type I, according to A. Carpentier's classification). Decreased contractile functions of the LV and RV myocardium caused an impairment of intracardiac hemodynamics, which led to a volume overload and increased intracavitary pressures in the cardiac chambers (RV and LV), which in turn entailed an increased preload on the LV, an increase in the right atrium (RA) pressure up to 21/12 (16) mm Hg, an increased afterload on the RV: the intracavitary pressure of 44/7 (25) mm Hg, an increased pressure in the pulmonary artery (PA) of 52/26 (35) mm Hg, pulmonary artery wedge pressure (PAWP) of 34/25 (29) mm Hg.

Laboratory diagnostic tests revealed hyponatremia, increased blood levels of B-type natriuretic peptide (P-BNP), anemia, and a moderate decrease in glomerular filtration rate.

To treat and control the symptoms of heart failure, slow down the progression of the disease and improve the prognosis, the patient was administered a standard drug therapy.

Four months later, when a matching donor heart became available, this patient was re-hospitalized for heart transplant surgery (Table 1).

Table 1. Clinical characteristics of the recipient and the donor

Parameter	Recipient (I.)	Donor (Kh.)
Age, years	30	20
Gender	Female	Male
Underlying disease	DCM	Brain contusion. Acute subdural hematoma.
Concomitant diseases	Recurrent deep vein	Chest trauma

	thrombosis of lower limbs. 3A degree chronic kidney disease	
SBP, mmHg	100	101
DBP, mmHg	70	63
HR, beats/min	90, sinus rhythm	107, sinus rhythm
Cardiac catheterization	Pressure (mm Hg): RA:21/12, PA: 52/26, PAWP 34/25, Cardiac output 3.75 L/s, Cardiac Index 2.32 L/min/m^2, Pulmonary vascular resistance 2 WU, Stroke volume 39.52 mL/beat	-
Echocardiography data		
LV end-diastolic dimension, cm	6.7	3.8
LV end-systolic dimension, cm	5.6	2.4
IVS thickness in diastole, cm	0.7	0.8
LV myocardium mass	235.7	
LV EDV, mL	208	60
Stroke volume, mL	-	22

LV EF according to Simpson, %	25	50
Anteroposterior LA dimension, cm	5.6	3.4
volume, mL	182	32
Right atrium volume, mL	90	69
RV, cm	3.7	2.6
RA pressure, mm Hg	15	-
PASP, mm Hg	69	30
TAPSE, cm	1.1	1.8
s´t, cm/s	8	11,5
Mitral regurgitation	Grade 3	Grade 1
Tricuspid regurgitation	Grade 3	Grade 1-2
Additional findings	Thrombi in the right ventricle	-
Complete Blood Count		
White blood cells	4.5×10^{9} /L	5.6×10^{9} /L
Hemoglobin, g/L	90	145
Red blood cells	3.94×10^{12} /L	5.6×10^{12} /L
Hematocrit	28.1	45.1
Platelets	235×10^{9} /L	242×10^{9} /L
Acid-base balance		
pH	7.323	7.148
pCO_2, mm Hg	47	26.8
pO_2, mm Hg	15.4	289.3
BB, mmol/L	-2.2	-7.3
Lactate, mmol/L	1.84	4.4

Blood Biochemistry		
P-BNP, pg/mL	26000	170
AST, U/L	11.6	106
ALT, U/L	7.5	100
Total bilirubin, mcmol/L	13.4	7.6
Total protein, g/L	72.9	62
Creatinine, mcmol/L	106	235
GFR, mL/min	53	-
Glucose, mmol/L	4.5	18.4
Urea, mmol/L	8.51	17.9
Sodium, mmol/L	139	175
Potassium, mmol/L	4.31	3.9

The indications for heart transplantation were absolute, since the patient had a decompensated form of cardiomyopathy, the end-stage HF (NYHA FC IV); she was unable to perform any physical activity and was in condition of an expected risk of death for less than a year (recommendation class I, level of evidence C). At the time of re-hospitalization, according to examination results, the diagnostic data obtained were similar to those recorded at the initial hospitalization to the Interregional Clinical Diagnostic Center, Kazan. The patient received an optimal drug therapy for heart failure: thiazide diuretics, aldosterone antagonists, angiotensin-converting enzyme (ACE) inhibitors, hybrid alpha and beta-blockers (carvedilol), direct anticoagulant: CHA_2DS_2VASc score 2.

According to EchoCG data and laboratory test results (the blood level of troponin I being 0.320 ng/mL), the donor heart had no signs of acute myocardial injury. The patient received medium doses of inotropic drugs (dofamine 6 μg/kg/h) to maintain adequate pressure and cardiac perfusion.

Cardioplegia and myocardial protection were achieved with Custodiol solution in a volume of 3000 mL. The heart was transported in a cooler bag in sterile plastic pouches filled with Custodiol solution and packed in ice. Intra- and postoperative management protocols had been standardized and were uniform for all patients. The surgery was performed according to the cava-caval technique of orthotopic heart transplantation (M. Yacoub, 1990; G. Dreyfus, 1991).

After a median sternotomy and pericardiotomy, the aorta and the main trunk of the pulmonary artery were isolated before the start of CPB. After the CPB start, a clamp was applied onto the ascending aorta. The right atrium was cut off in stages at the level of the superior and inferior vena cava; the pulmonary veins were cut off the left atrium at the site, afterwards the aorta and the pulmonary artery trunk were transected.In stages, anastomoses were made with the left atrium, venae cava, and the major main vessels. De-embolization was performed through shunts in the ascending aorta and right pulmonary vein; during the entire period until the closure of the heart cavity, carbon dioxide was supplied to the wound in a volume of 1.5 L/min. The duration of CPB and mechanical circulatory support was 435 min, and the donor heart myocardium ischemia time was 169 min. CPB was ensured using a Stockert S5 Heart-Lung Machine equipped with a Revolution centrifugal arterial pump.

After the main stage of the heart transplant surgery, when trying to wean from the CPB machine, the systemic pressure did not rise above 80/60 mm Hg. Medicinal measures were taken to improve

hemodynamics: norepinephrine 0.3 μg/kg/min, dobutamine 10 μg/kg/min. Intraoperative transesophageal EchoCG was performed, which showed a marked decrease in LV EF to 11%, visualised a limited movement of all LV and RV segments, a significant decrease in RV and LV EFs, and grade 3 tricuspid regurgitation.

Due to the development of biventricular dysfunction, there was a lack of clinical response to drug inotropic support. The decision was made to provide an assisted mechanical support. Connection to the ECMO Rotaflow Maquet System was undertaken, the arterial line was cannulated into the ascending aorta, and the venous line was passed into the inferior vena cava. Thus, the veno-arterial ECMO was started to maintain hemodynamics, the adequate perfusion of organs and tissues. After that, the patient was taken to the Intensive Care Unit. Continuous heparinization was provided to achieve the targeted activated coagulation time (ACT) value of 200 s, the parameter variation was maintained in the range from 180–220 s. The patient was sedated with propofol under mechanical ventilation by using an orotracheal tube and closed sternum to the upper third of the sternotomy wound.

The parameters of adequate blood flow for cardiac support were set on the ECMO apparatus, and are shown in Table 2.

Table 2. Changes in extracorporeal membrane oxygenation technical parameters, inotropic support, and laboratory data in Patient I. over time

Parameters	ECMO start	Day after ECMO				
		1	2	3	4	5
VPV, mL/min	4200	3900	2500	2000	2100	-
CHRS, r/min	3200	3120	2530	2300	2345	-

SBP mm Hg	72	78	108	132	125	120/78
CVP, mm Hg	10	10	9	9	12	9
O_2 flow, L/min	3	2,5	2	1	1	-
FiO_2, %	65	60	60	45	45	-
ACT, s	478	168	168	212	178	-
Dobutamine, mcg/kg	-	-	3	3	3	3
Norepinephrine, mcg/kg/min	0.1	0.1	-	-	-	0.05
TV, mL	350	350	350	350	450	450
RR, min	10	10	20	18	12	14
FiO_2, %	30	30	30	30	30	60
PEEP, cm H_2O	8	8	6	6	5	6
pO_2, mm Hg	297	173	206	134	189	145
pCO_2, mm Hg	59	41	31	40	43	43
Lactate, mmol/L	4.7	3.4	2.2	1.3	0.9	0.8
Troponins, ng/mL	-	19.2	14.3	5.8	1.0	-

Laboratory blood parameters were monitored every 4 hours, the instrumental assessment of the heart functional parameters was made daily. The ACT showed the target values during the entire period, no increase in vasopressor doses was required. The oxygen fraction (FiO_2, %) adjustment was made by checking the arterial partial oxygen pressure measurements, no lower than 150 mm Hg, with a gradual conversion from a two-phase ventilation to spontaneous breathing.

According to the EchoCG results, a positive dynamics of the heart function was noted, the LV size was gradually decreasing, and the contractile function of the LV and RV increased (Table 3). Positive dynamics was also noted in relation to regional LV contractility (Fig. 2). The general hemodynamics stabilization without using high doses of vasopressors, and the adequate oxygen saturation of arterial blood were indicative of an improvement in LV and RV systolic function, so the flow rate and the centrifuge head rotational speed were decreased. Recovery of the systolic function of both ventricles was observed starting from day 2–3 after the ECMO initiation; and on day 4, the regional LV contractility was normal.

Table 3. Dynamics of heart functional parameters according to echocardiography data during and after surgery

Parameter	Postoperative day							
	1	**5**	**6**	**9**	**11**	**19**	**23**	**27**
LV EDD, cm	5	4.3	4.2	3.9	3.9	4	4.2	4.4
LV ESD, cm	4.1	2.7	2.6	2.4	2.3	2.5	2.7	2.5
IVS thickness, cm	0.9	1.2	1.2	1.3	1.4	1.3	1.2	1
RV, cm	2.3	2.3	2.4	-	2	1.9	2.5	1.8
LA, cm	-	3.4	-	-	-	-	3.1	-
LV myocardium mass, g	162.2	176.2	169.8	181.6	192.3	167.5	169.8	150.6
LV/BSA mass index, g/m^2	95.4	103.6	99.9	106.8	113.1	98.5	99.9	88.6
LV EDV, mL	72	74	68	67	63	66	71	68

LV EF, %	23	53	58	62	62	62	62	61
TAPSE, cm	5.0	7.0	1.3	1.0	1.5	1.5	1.5	1.8
s´t, cm/s	6.0	10.0	10.0	12.0	12.0	11.0	14.0	15.0
PASP, mm Hg	44	42	41	42	35	31	24	31
RA pressure, mm Hg	20	10	10	10	5	5	5	5

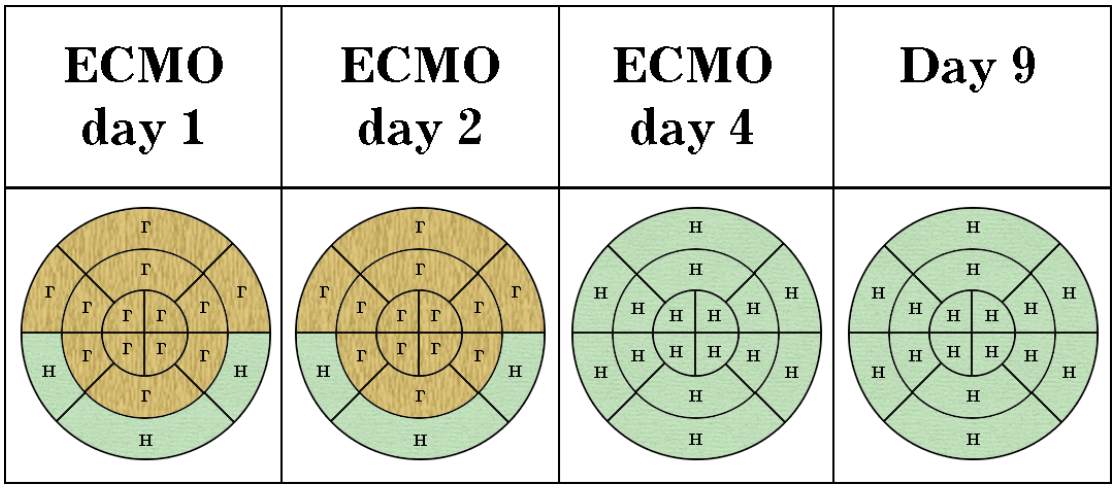

Fig. 2. Changes in the regional contractility of LV myocardium over time

On day 4, ECMO was switched off, and the patient was transferred to the operating room, where re-sternotomy and decannulation from the aorta and the right atrium were performed.

During veno-arterial ECMO, the following were transfused: packed red blood cells in a volume of 2907 mL, fresh frozen plasma 7740 mL, platelet concentrate 1200 mL. No transfusion-related adverse reactions or complications were seen, neither bleeding nor wound infection, either. The patient regularly received a calcineurin inhibitor, antiviral therapy, and corticosteroids.

The patient was discharged on day 21 when the target blood level of immunosuppressive drugs had been reached. The first endomyocardial

biopsy was performed on day 5 after surgery and revealed a mild cellular rejection without humoral crisis (1R, pAMR 0), an ischemic myocardial injury, and signs of previous pathology. Further biopsy of the myocardium did not reveal any negative dynamics.

Conclusion

The growing number of orthotopic heart transplantations for the treatment of end-stage heart failure and the limited number of optimal donor hearts made doctors to selecting suboptimal donors, which entails the risk of primary graft dysfunction development. As a result of acute myocardial ischemia-reperfusion injury with stunning, which developed during the sustained trauma, as well as the brain death and associated pathogenous events lead to a primary graft dysfunction. Therefore, in case the primary heart graft dysfunction develops, the cardiac decompression, rapid blood oxygenation, and perfusion of vital organs are important; these measures help to reduce intracavitary hypertension and limit the development of subendocardial coronary perfusion blockade. One of the methods to treat the acute hemodynamic disorder caused by biventricular dysfunction is a mechanical support of oxygenation and hemodynamics using extracorporeal membrane oxygenation (evidence class I) [8].

Our case has demonstrated new possibilities for the treatment of the donor heart (graft) primary dysfunction. The mechanical circulatory support by using extracorporeal membrane oxygenation prevents the primary heart graft dysfunction progression and the development of acute cellular rejection and leads to the recovery of the systolic function of the transplanted heart within several days.

Based on the above, we can make the following conclusions:

1. The indications for intraoperative initiation of veno-arterial extracorporeal membrane oxygenation in a patient undergoing heart transplantation include: an ineffective drug cardiotonic therapy, the decrease in systolic pressure to 70 mm Hg after cardiopulmonary bypass circuit has been turned off, or the need for a long-term assisted cardiopulmonary bypass (within 40 minutes), and also the decrease in the systolic function of the left and right ventricles, and grade 3 tricuspid regurgitation.

2. Veno-arterial extracorporeal membrane oxygenation performed in case of a developing heart graft dysfunction can improve the systolic function of the left ventricle on day 4 (over a two-fold increase in the left ventricle ejection fraction from 23% to 53%).

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