Original Article

Five years' experience with a peripheral veno-arterial ECMO for mechanical bridge to heart transplantation

Vitaly Poptsov[1], Ekaterina Spirina[2], Anastasiya Dogonasheva[2], Elizaveta Zolotova[2]

[1]Department of Anesthesiology of Russia Federation, Moscow, Shukinskaya 1, Russia; [2]Shumakov National Medical Research Center of Transplantology and Artificial Organs, Moscow, Russia

Contributions: (I) Conception and design: V Poptsov; (II) Administrative support: V Poptsov; (III) Provision and study material or patients: All authors; (IV) Collection and assembly of data: V Poptsov; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Vitaly Poptsov, MD. Professor, Department of Anesthesiology of Russia Federation, Moscow, Shukinskaya 1, Russia. Email: poptsov_vit@mail.ru.

Background: Mechanical circulatory support (MCS) is the only way to save a life for heart transplant candidates and to decrease of waiting list mortality. The choice between short- or long-term pretransplant MCS depends on of type and severity of CHF. One of the most frequently used methods of temporary MSC before orthotopic heart transplantation (OHTx) is veno-arterial extracorporeal membrane oxygenation (VA ECMO). The aim of this study was to analyze own experience of peripheral VA ECMO (pVA ECMO) in heart transplant candidates needed in urgent HT.

Methods: This study included 182 pts [160 (87.9%) men and 22 (12.1%) female, age 43±1.2 yrs] supported with pVA ECMO in the period from 01. 01. 2013 to 31. 12. 2017 or 23.2% from all waiting list (n=786).

Results: During VA ECMO, 16 (8.8%) of the 182 pts died. In most pts [n=13 (81.3%)] multiorgan failure/sepsis were the cause of death. One hundred and sixty-six (91.2%) pts were successfully bridged to OHTx or 27.9% from all heart transplant recipients (n=594) (2013–2017 yrs). The duration of pVA ECMO before OHTx (n=166) was 5.8±3.2 days. One hundred and forty-three (86.1%) from 166 pts were discharged to home. Post-transplant survival among heart transplant recipient with pre-transplant MCS by pVA ECMO was in comparison with recipients without pretransplant MCS [84.2% *vs.* 90.1% (6 months), 83.3% *vs.* 91.8% (1 years), 75.1% *vs.* 86.1% (2 years), 74.2% *vs.* 85.8% (3 years), 72.3% *vs.* 84.7% (4 years), 72.3% *vs.* 83.5% (5 years) respectively (P<0.0001)].

Conclusions: pVA ECMO is a useful tool of treatment of patients with INTERMACS profile 1/2. Results of OHTx at recipients bridged with VA ECMO are less successful that recipients without pre-transplant MCS. VA ECMO should be considered as a direct bridge to OHTx in conditions of limited financial resources of health care and high availability of donor's hearts.

Keywords: Heart transplantation; mechanical circulatory support; extracorporeal membrane oxygenation

Submitted Oct 17, 2018. Accepted for publication Feb 22, 2019.
doi: 10.21037/jtd.2019.02.55
View this article at: http://dx.doi.org/10.21037/jtd.2019.02.55

Introduction

Orthotopic heart transplantation (OHTx) remains the gold standard for the therapy of patients with advanced heart failure (HF), having a 10-year survival rate of 50% and a satisfactory quality of post-transplant life (1). However, in conditions of increased demand for donor hearts, OHTx is available only for small and strictly selected patient pool with advanced HF (2,3). In the case of donor heart shortage and an expanding the pool of patients waiting for OHTx, it is necessary to apply the alternative approach to decrease the mortality rate in heart transplant waiting list (4). Implantable long-term left ventricular assist device (LVAD) is the leading method of MCS not only for heart

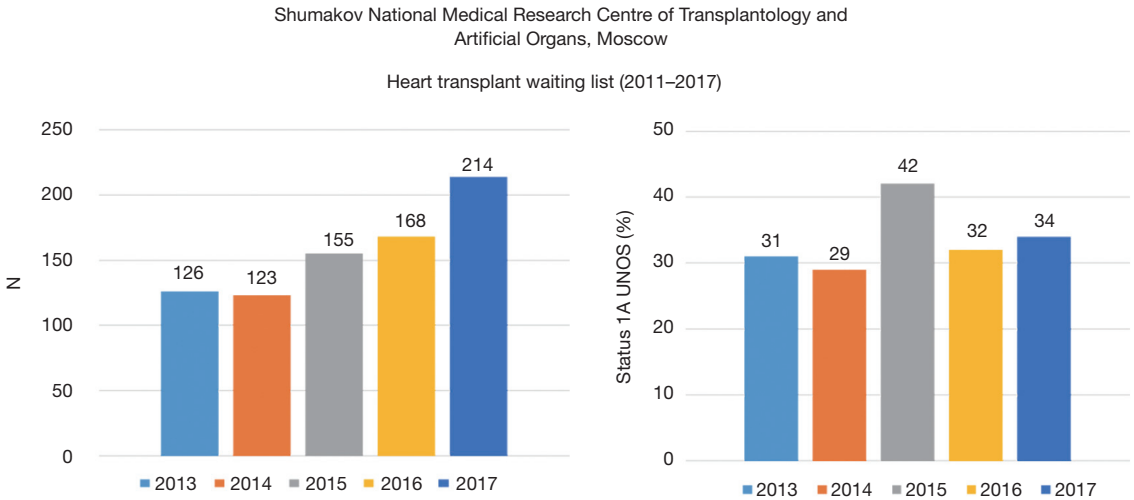


Figure 1 Shumakov center heart transplant waiting list (n=786).

transplant candidates but also patients that are ineligible for OHT (destination therapy) (5,6). More than 40% of heart transplantation has been performed in patients with LVAD according to ISHLT registry data (7). However, in some clinical situations, it is impossible for LVAD to significantly improve hemodynamics such as biventricular CHF (8). LVADs is associated with a risk of thromboembolic, hemorrhagic, infectious, and other complications (9). The high acquisition cost of the device and post-implantation management are also limiting factors due to economic considerations (10,11). In guaranteed availability of donor hearts short-term (temporary) MCS may be an alternative approach for heart transplant candidates who need an urgent OHTx procedure (12,13). One of the most frequently used methods of temporary MSC before heart transplantation is veno-arterial extracorporeal membrane oxygenation (VA ECMO) (13,14). In the last few years, heart transplant team of Shumakov National Medical Research Center of Transplantology and Artificial Organs (Moscow, Russian Federation) began to apply peripheral VA ECMO (pVA ECMO) as the leading method of pretransplant short-term MSC.

The goal of study was to estimate results of using pVA ECMO as a method of short-term MCS in heart transplant candidates requiring urgent HT.

Methods

This study included 182 heart transplant candidates (160 (87.9%) men and 22 (12.1%) female, age from 12 to 76 (43±1.2) years) treated with a peripheral VA ECMO in our center in the period from 01. 01 .2013 to 31. 12. 2017 or 23.2% from all (n=786) patients included in our heart transplant waiting list from analyzed period (*Figure 1*).

Etiology of the advanced CHF was dilated cardiomyopathy [n=119 (65.4%)], coronary artery disease [n=46 (25.3%)], chronic cardiac allograft dysfunction [n=7 (3.8%)], congenital or acquired valve diseases [n=5 (2.7%)], peripartum cardiomyopathy [n=3 (1.6%)], hypertrophic cardiomyopathy [n=1 (0.5%)], restrictive cardiomyopathy [n=1 (0.5%)].

Sixteen patients (8.8%) underwent surgery in past: coronary artery grafting with/without LV reconstruction or with/without mitral valve repair [n=4 (2.2%)], heart valve repair [n=5 (2.7%)], and primary OHTx [n=7 (3.8%)].

Other comorbidities were hypertension [n=33 (18.1%)], chronic obstructive pulmonary disease [n=16 (8.8%)], non-hemodialysis-dependent chronic renal disease with estimated glomerular filtration rate (GFR) ≤40 mL/min/1.73 m^2 [n=7 (3.8%)], carotid disease [n=12 (6.6%)], diabetes mellitus [n=4 (2.2%)], gastric or duodenum ulcer [n=6 (3.3%)], stroke [n=5 (2.7%)], pulmonary thromboembolism [n=4 (2.2%)], hepatitis B/C [n=2 (1.1%)], Dreifuss muscle dystrophy (c.de1619C mutation in EMD exon 6) [n=1 (0.5%)].

Transpulmonary gradient (TPG) and pulmonary vascular resistance (PVR), respectively, were 4–20 (11.2±2.5) mmHg and 1.9–5.6 (3.54±1.62) Wood's Units. Thirty-four (18.7%) heart transplant candidates had TPG ≥15 mmHg and PVR ≥4 Wood's Unit.

Seven (3.8%) patients were under mechanical ventilation, 6 (3.3%) noninvasive ventilator support, 4 (2.2%) intra-aortic balloon pump (IABP).

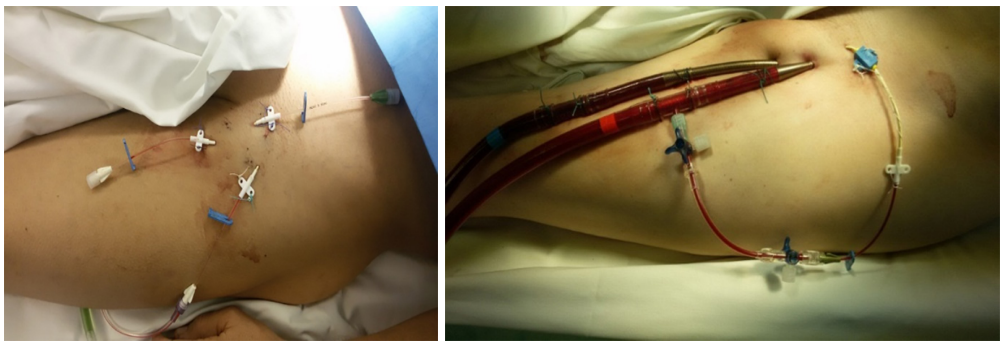


Figure 2 Percutaneous cannulation technique of pVA ECMO. pVA ECMO, peripheral veno-arterial extracorporeal membrane oxygenation.

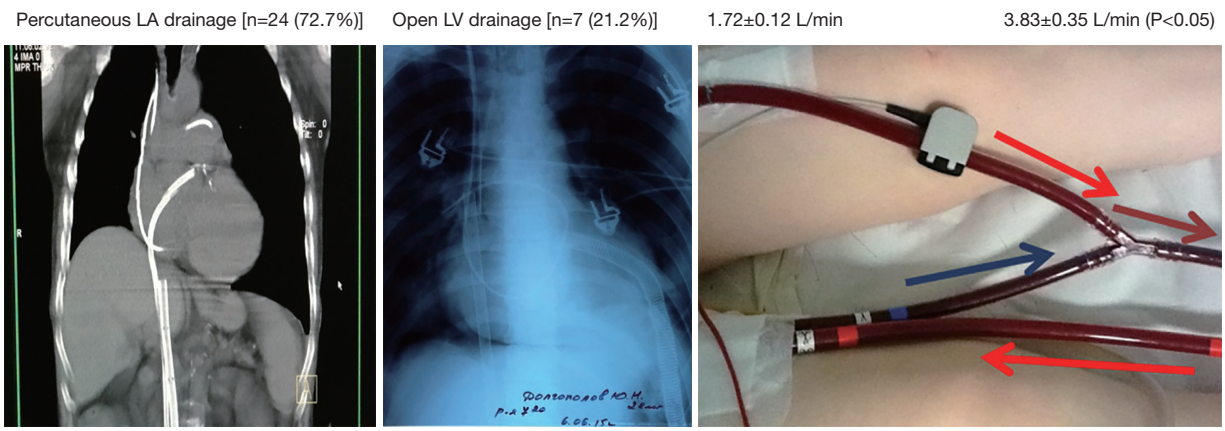


Figure 3 Left heart unloading following pVA ECMO (n=31). LA, left atrium; LV, left ventricle; pVA ECMO, peripheral veno-arterial extracorporeal membrane oxygenation.

The indication for VA ECMO was rapidly progressing congestive heart failure (CHF) of Class 1 or 2 by the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) scale or cardiac arrest with the need of cardio-pulmonary resuscitation (CPR).

Open (surgical) or transcutaneous technique was used for installation of ECMO-cannulae in femoral vessels: arterial cannula (15–17 F) and venous cannula (21–28 F). In all cases, to prevent leg ischemia catheterization (single-lumen catheter 14 G) or cannulation (arterial cannula 8 or 10 F) was performed on the side of the femoral artery cannulation (*Figure 2*).

Continuous infusion of unfractionated heparin was used for anticoagulation during pVA ECMO. The activated clotting time (ACT) was maintained at a level of 130–150 s.

In cases of left ventricle (LV) distention and pulmonary edema, percutaneous transfemoral transseptal cannulation of the left atrium (LA) by additional venous ECMO-cannula (15–17 F) or direct left ventricle cannulation by additional single-lumen venous CPB-cannula (28–30 F) via left thoracotomy was used for unloading of left heart (*Figure 3*).

Statistical analysis

Continuous variables are presented as the means ± standard deviations for continuous variables and percentages for the qualitative variables. An unpaired t-test was used for normally distributed data, after assessment of the equality of the variances. All P values were two-tailed. Categorical variables are reported as percentages and compared using the Chi-square test. Univariate analyses were performed using Chi-square and Fisher's exact tests for categorical variables. Survival and event-free survival were calculated using the Kaplan-Meier method. Statistical significance was defined as $P<0.05$. Statistical analyses were performed with the Biostat statistical software and the IBM SPSS version 20.0 software.

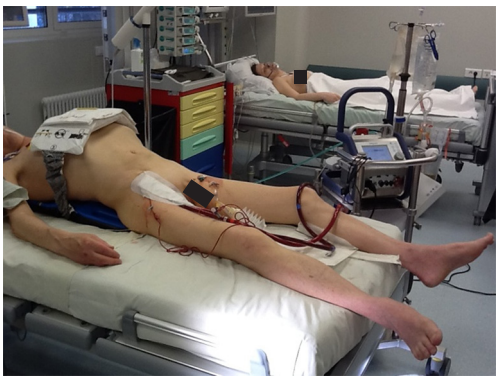


Figure 4 pVA ECMO installation under mechanical (AutoPulse system) chest compressions. pVA ECMO, peripheral veno-arterial extracorporeal membrane oxygenation.

Table 1 Parameters of VAEMO at heart transplant candidates (n=182)

Parameter	M ± σ
Revolution per minute (rpm)	3,719±137
Q, L/min	3.59±0.28
Q, L/min/m^2	1.84±0.22
Sweep gas, L/min	3.2±0.4
Sweep gas, FiO_2	0.74±0.03

VA ECMO, veno-arterial extracorporeal membrane oxygenation.

Results

In 100% (n=182) the peripheral cannulation technique via femoral vessels was used for installation of VA ECMO.

125 (68.7%) had clinical and hemodynamic indication for temporary MCS via VA ECMO corresponding to INTERMACS class 1, whereas 52 (28.6%) were in INTERMACS class 2. In several individual cases the indication for VA ECMO was extracorporeal CPR (ECPR) accounting for in 5 (2.7%) patients with in-hospital cardiac arrest. In these cases, cannulation was performed during manual (n=1) or mechanical (AutoPulse system) (n=4) chest compressions (*Figure 4*).

Surgical and percutaneous techniques of femoral cannulation were used in 29 (15.9%) and 153 (84.1%) patients, respectively. Femoral vessels of a single leg or both legs were used for cannulation in 120 (65.9%) and 62 (34.1%) patients, respectively.

Most patients [n=153 (84.1%)] were extubated within 1 hour after commencement of VA ECMO therapy. Twenty-nine pts (15.9%) were mechanically ventilated for more than 12 h after the initialization of VA ECMO. Four (2.2%) pts were later percutaneously tracheostomized for long-time invasive mechanical ventilation. Thirty-one (17.0%) patients were reintubated due to lung edema developed as a consequence of left heart overdistention (see below).

During VA ECMO, the extracorporeal blood flow was 2.2 to 4.5 (3.59±0.28) L/min or 1.84±0.22 L/min/m^2 (*Table 1*). Inotropes were used in 100% of cases to maintain the residual heart pump function.

Twenty-nine (15.9%) patients required continuous venovenous hemofiltration (CVVH) for correction of hypervolemia or hyperhydration (anasarca), metabolic, electrolyte, and multiple organ dysfunction.

Despite the additional target therapeutic options (inotropic, diuretics, CVVH and noninvasive mechanical ventilation) 31 (17.0%) patients demonstrated lung edema ("white" lungs) due to LV overdistention and needed mechanical left heart volume decompression. Lung edema developed in 3.1±1.1 days after commencement of VA ECMO therapy. Percutaneous transfemoral cannulation of the LA (n=24) and LV drainage (n=7) were used for left heart decompression (*Figure 2*). LA and LV drainage was 1.72±0.12 and 3.60±0.38 L/min, respectively. LV drainage provided a more significant reduction of PCWP in comparison with LA drainage: from 35±5 to 13±6 mmHg versus from 29±3 to 17±3 mmHg (t=2.438, P=0.024). However, 4 (57.1%) from 7 patients with LV drainage were re-operated on had to be reopened due to significant postoperative blood loss (1,312±161 mL).

During VA ECMO, 16 (8.8%) of the 182 patients died. 3 (18.8%) patients with preexisting (before VA ECMO) massive LV thrombosis died from brain death after an acute thromboembolic cerebrovascular event. In most patients [n=13 (81.3%)] multiorgan failure and sepsis were the leading cause of death. Those patients (n=13) had more severe pre-MCS clinical status (*Table 2*).

Significant (P<0.05) pre-MCS risk factors for the lethal outcome of heart transplant candidates supported by pVA ECMO were: creatinine ≥140 μmol/L, blood urea ≥15 mmol/L, total bilirubin ≥120 μmol/L, ALT ≥300 U/L, AST ≥300 U/L, INR ≥3.0, procalcitonin ≥3.0 ng/mL, and preexisting left ventricle thrombosis complicated by thromboembolic stroke with brain death following VA ECMO. Also, statistically significant factors for the fatal outcome following VA ECMO procedure were: transthoracic left ventricle drainage for left heart decompression and free hemoglobin ≥300 mg% (*Table 3*).

One hundred and sixty-six (91.2%) heart transplant

Table 2 Parameters of hemodynamic, organ function, electrolytes, acid-base status composition before the beginning of MCS in patients with different VA ECMO outcomes (n=182)

Variables	Heart transplant candidates		P
	Death during VA ECMO (n=16)	Successful bridge to OHTx (n=166)	
CVP, mmHg	23±5	18±6	0.001
PAWP, mmHg	36±7	28±6	<0.001
CI, L/min/m^2	1.2±0.5	1.5±0.4	0.006
Dopamine/dobutamine, μg/kg/min	8.7±4.6	5.9±3.9	0.008
Blood creatinine, μmol/L	146±31	112±25	<0.001
Urea, mmol/L	16±10	12±8	0.064
Total bilirubin, μmol/L	83±24	56±20	<0.001
ALT, IU/L	318±86	85±39	<0.001
AST, IU/L	376±72	71±29	<0.001
INR, IU	3.1±0.8	1.7±0.6	<0.001
Serum albumin, g/L	26±9	32±11	0.036
Serum sodium, mmol/L	126±6	133±9	0.003
pHa	7.31±0.04	7.34±0.03	<0.001
BEa, mmol/L	–6.3±2.9	–3.3±1.8	0.006
Blood lactate, mmol/L	6.4±3.2	3.5±2.6	<0.001
Procalcitonin, ng/mL	2.8±1.4	0.3±0.8	<0.001

MCS, mechanical circulatory support; VA ECMO, veno-arterial extracorporeal membrane oxygenation; CVP, central venous pressure; PAWP, pulmonary artery wedge pressure; CI, cardiac index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio.

candidates were successfully bridged to OHTx. The duration of VA ECMO before OHTx (n=166) ranged from 8 h to 40 (5.8±3.2) days. In 161 of those 166 patients, the length of VA ECMO was determined by the donor heart waiting time. In 5 patients, OHTx was delayed with the view to improving the pretransplant status and regression of multiorgan dysfunction.

Peri-operative period

One hundred and sixty-six OHTs were performed in heart transplant recipients with pretransplant VA ECMO {27.9% from all OHT (n=594) in the analyzed period [2013–2017] (*Figure 5*)}, whereas 143 (86.1%) from 166 heart transplant recipients were discharged home. Twenty-three (13.9%) recipients died during the hospital period after OHT. Twenty-one (91.3%) from 23 recipients with pretransplant VA ECMO who died from multiple organ failure developed early cardiac allograft dysfunction. In this cohort of recipients pre-transplant levels of urea and total bilirubin were significantly higher (P<0.0001) (*Table 4*). Heart donors in the group of deceased recipients were also older (P=0.036), and more donors were of age 55 and older (21.1% *vs.* 14.3% (P=0.026). Also a perioperative period was associated with more blood loss and higher need for transfusion therapy with more severe renal and hepatic dysfunction, and higher need for renal replacement therapy.

Comparison of heart transplant recipient cohorts with (n=166) and without (n=428) pretransplant VA ECMO demonstrated that recipients with pretransplant VA ECMO were younger (P=0.001), more frequently suffered from dilated cardiomyopathy (P=0.002), had higher preoperative levels of PVR (P=0.021), bilirubin (P=0.002) and INR (P=0.001) (*Table 5*). Cardiac donors in the cohort of pretransplant VA ECMO recipients were older (P=0.004), had significantly higher vasoactive-inotropic support (P=0.012) and lower LV ejection fraction (P=0.041). In the cohort of pre-transplant VA ECMO recipients perioperative

Table 3 Pre-MCS and procedure univariable predictor of mortality for heart transplant candidates supported with pVA ECMO

Variables	Odds ratio (OR)	95% confidence interval (CI)	P
Pre-MCS mortality predictor			
Total bilirubin ≥120 μmol/L	21.61	5.98–78.11	0.0010
ALT ≥300 IU/L	22.500	6.32–80.05	0.0001
AST ≥300 IU/L	18.45	5.32–64.00	0.0001
INR ≥3.0	9.26	2.86–29.96	0.0003
Serum urea ≥15 mmol/L	10.48	2.76–39.76	0.0002
Serum creatinine ≥140 μmol/L	6.88	2.03–23.30	0.0013
Procalcitonin ≥3.0 ng/mL	9.92	3.05–32.28	0.0002
Preexisting LV thrombosis	18.14	2.73–120.34	0.0060
BMI <20 kg/m^2	13.10	2.84–60.39	0.0028
Procedure mortality predictor			
Free hemoglobin ≥300 mg%	88.67	15.37–511.56	0.004
Pneumonia	33.00	6.94–156.92	0.0001
Transthoracic LV drainage	17.60	3.45–32.28	0.0015
VA ECMO installation during cardiopulmonary resuscitation	2.52	0.26–24.25	0.3938
Transcutaneous transfemoral transseptal LA drainage	3.39	0.33–34.94	0.3290

MCS, mechanical circulatory support; pVA ECMO, peripheral veno-arterial extracorporeal membrane oxygenation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; BMI, body mass index.

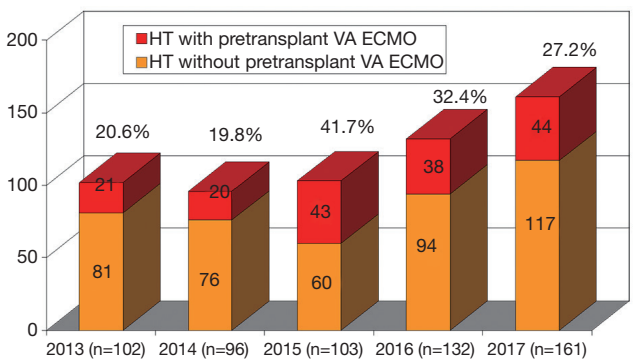


Figure 5 Annual volume of OHTx at recipients with pre-transplant pVA ECMO and without pretransplant MCS [2013–2017] (n=594). VA ECMO, veno-arterial extracorporeal membrane oxygenation; OHTx, orthotopic heart transplantation; MCS, mechanical circulatory support.

period was characterized by the higher rate of early cardiac allograft dysfunction [91.3% *vs.* 65.4% (P=0.068)], higher blood loss and transfusion therapy. Hospital mortality was higher in the cohort with pre-transplant VA ECMO [13.9% *vs.* 6.1% (P=0.003)]. ICU and hospital stay among survived recipients was also longer (P<0.05) in the cohort with pre-transplant VA ECMO (*Table 5*, *Figure 6*). Nine significant factors predictive of hospital mortality were identified (*Table 6*). Early, mid-term and late results of OHTx in recipients bridged with VA ECMO were less promising (P<0.001) compared to recipients without pre-transplant MCS (*Figure 6*).

Discussion

According to the data from the ISHLT registry, approximately 50% of heart transplant recipients are treated with pretransplant MCS (7). Forty-two percent OHTx are performed after implantable LVADs. Taking into consideration potential risks and high costs of LVAD some heart transplant centers widely use methods of temporary MCS in heart transplant candidates requiring urgent OHTx (12,15). Results of OHTx in recipients with short-term pretransplant MCS are controversial, whereas some

Table 4 Pre-transplant VA ECMO and different outcomes after OHT (n=166)

Variables	Heart transplant recipients		[t], χ^2	P
	Survivors (n=143)	Dead (n=23)		
Recipient's characteristics				
Recipient's age (years)	43.0±13.6	46.5±14.8	1.132	0.259
Recipients age ≥ 60 years (n/%)	18/12.6	5/21.7	1.859	0.173
Female (n/%)	23/16.1	3/13.0	0.004	0.949
Dilated cardiomyopathy (n/%)	99/69.2	10/43.5	4.742	0.029
Ischemic cardiomyopathy (n/%)	29/20.2	11/47.8	4.290	0.009
Prior heart transplantation (n/%)	5/4.2	2/8.7	0.351	0.552
PVR (Wood's Unit)	3.2±2.2	3.5±2.4	0.599	0.549
PVR ≥ 4 Wood's Unit	17/11.9	9/39.1	9.165	0.002
Creatinine (μmol/L)	85.4±55.4	112.8±83.1	2.037	0.043
Urea (mmol/L)	7.4±4.8	12.8±7.5	4.584	<0.0001
Total bilirubin (μmol/L)	47.8±24.4	77.5±59.3	4.208	<0.0001
ALT (U/L)	59.0±170.9	47.1±67.9	0.329	0.7425
AST (U/L)	64.0±136.6	71.8±62.4	0.273	0.785
INR (IU)	1.66±0.47	1.66±0.28	0.000	1.000
LA/LV drainage for left heart decompression (n/%)	23/16.1	3/13.0	0.369	0.544
Pre-OHT VA ECMO (days)	5.6±6.0	5.1±4.2	0.384	0.701
Donor's characteristics				
Age (years)	46.2±11.1	49.3±9.1	2.116	0.036
Age ≥55 years (n/%)	23/16.1	12/52.2	17.417	<0.0001
Female sex (n/%)	35/24.5	5/21.7	0.000	0.982
Female donor—male recipient (n/%)	22/15.4	7/30.4	2.156	0.142
Donor weight (kg)	85.9±20.2	79.0±13.5	1.580	0.116
Donor weight—recipient weight (n/%)	1.1±0.4	1.0±0.3	1.147	0.253
Non-traumatic cause of brain death (n/%)	72/50.3	19/82.6	7.073	0.008
Cardiopulmonary resuscitation (n/%)	5/3.4	1/ 4.3	0.064	0.800
Hg, g/dL	11.8±3.0	11.8±3.2	0.004	1.000
Total protein, g/L	60.0±11.6	58.2±12.6	0.683	0.496
Blood sodium, mmol/L	147±11	148±9	0.414	0.882
Blood sodium>160 mmol/L	11/7.7	2/8.7	0.028	0.868
Vasoactive-inotropic support (n/%)	123/86.0	23/100	2.457	0.117
Vasoactive-inotropic support score (max) (units)	15.3±12.3	21.4±13.3	2.183	0.030
IVS (cm)	1.29±0.31	1.30±0.32	0.143	0.887
IVS ≥1.5 cm	31/21.7	8/34.8	1.234	0.267

Table 4 (*continued*)

Table 4 (*continued*)

Variables	Heart transplant recipients		[t], χ^2	P
	Survivors (n=143)	Dead (n=23)		
LVEF (%)	62.5±9.9	63.0±9.3	0.227	0.821
LVEF <40% (n/%)	5/3.5	1/ 4.3	0.260	0.610
donor-transmitted coronary atherosclerosis treated via stenting after OHTx	13/9.1	2/8.7	0.001	0.970
Perioperative characteristics				
Ischemic time, min	164±58	176±50	1.030	0.304
CPB, min	120±41	145±55	2.873	0.005
Dopamine (max), μg/kg/min	5.2±2.1	6.8±3.1	3.086	0.003
Dobutamine (max), μg/kg/min	4.8±1.6	5.1±1.5	0.761	0.448
Epinephrine (max), ng/kg/min	58.0±22.6	67.0±29.6	3.554	0.0005
Vasoactive-inotropic support score (max) (units)				
VA ECMO after OHT >2 days (n/%)	28/19.6	21/91.3	18.434	<0.0001
Intraoperative free hemoglobin, mg%	53±87	207±107	5.095	<0.0001
Perioperative bleeding, mL	3,513±2,737	5,033±4,590	2.419	0.017
Fresh frozen plasma, mL	3,244±1,930	3,903±2,423	1.648	0.101
Red blood cell, mL	1,712±1,146	2,228±1,353	2.164	0.032
Renal replacement therapy (CVVH, HDF) (n/%)	29/20.3	19/82.6	46.169	<0.0001
Leukocytes (max), $\times 10^9$/L	16.8±5.5	22.5±5.9	3.886	0.0002
Platelets (min), 10^9/L	61.6±33.7	38.8±22.8	2.702	0.008
Hemoglobin (min), g/dL	7.6±1.7	7.7±0.5	0.245	0.807
Total protein (min), g/L	62.0±5.8	61.6±5.0	0.233	0.816
Urea (max), mmol/L	17.1±6.8	20.2±8.1	1.670	0.301
Creatinine (max), umol/L	141.4±99.2	177.6±100.7	1.392	0.168
Total bilirubin (max), umol/L	88.6±50.8	189.5±137.8	4.890	<0.0001
ALT (max), u/L	104.6±293.7	402.0±643.8	2.853	<0.0001
AST (max), u/L	151.7±120.9	750.6±1270.4	3.769	0.0003
INR (max)	1.50±0.25	1.84±0.39	4.557	<0.0001

VA ECMO, veno-arterial extracorporeal membrane oxygenation; OHTx, orthotopic heart transplantation; PVR, pulmonary vascular resistance; max, maximal value; min, minimal value; IVS, interventricular septum; LVEF, left ventricle ejection fraction; CVVH, continuous veno-venous hemofiltration; HDF, hemodiafiltration in online; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio.

studies showed comparable early and long-term outcomes in recipients with pre-transplant temporal MCS (16,17).

In last time VA ECMO has been increasingly used for the treatment of critically ill patients with life-threatening pulmonary and cardiac disorders. One of the clinical applications of VA ECMO is MCS in heart transplant candidates (18). VA ECMO is a unique method of MCS that can be used in the same recipient before and after OHTx. It is suitable for urgent OHTx from donors with extended criteria and risk of early cardiac allograft dysfunction.

Transplant centers with expertise in urgent OHTx perform high numbers (10–38%) of OHTx in recipients

Table 5 Heart transplant recipients with and without pretransplant VA ECMO (n=594)

Variables	Recipients		[t]/Хи-квадрат	P
	With pretransplant VA ECMO (n=166)	Without pretransplant MCS (n=428)		
Recipient's characteristics				
Recipient's age (years)	43.7±13.9	47.6±12.8	3.252	0.001
Recipients age ≥60 years (n/%)	23/13.9	79/18.4	0.473	0.225
Woman/man	26/15.7	75/17.5	0.251	0.617
Dilated cardiomyopathy (n/%)	109/65.7	218/50.9	9.898	0.002
Ischemic cardiomyopathy (n/%)	40/24.1	171/39.9	12.448	<0.001
PVR (Wood's Unit)	3.2±2.3	2.8±1.7	2.319	0.021
PVR ≥4 Wood's Unit	21/12.7	78/18.2	2.246	0.134
Blood creatinine (μmol/L)	91.9±63.6	100.2±65.8	0.5782	0.564
Urea (mmol/L)	8.7±6.0	7.5±3.9	0.9269	0.355
Total bilirubin (μmol/L)	54.8±37.6	29.0±22.3	3.196	0.002
ALT (U/L)	56.2±152.6	37.7±61.9	0.5727	0.568
AST (U/L)	65.8±121.2	31.5±38.0	1.344	0.181
INR (IU)	1.66±0.42	1.31±0.38	3.541	0.001
Donor's characteristics				
Age (years)	45.2±10.9	41.2±11.9	3.762	<0.001
Age ≥55 years (n/%)	35/21.1	57/14.3	4.935	0.026
Female sex(n/%)	40/24.1	101/23.6	0.000	0.984
Female donor – male recipient (n/%)	29/17.5	69/16.1	0.075	0.784
Donor weight (kg)	84.5±19.1	81.8±16.9	1.605	0.109
Donor weight/recipient weight	1.1±0.4	1.0±0.3	1.411	0.159
Non-traumatic cause of brain death (n/%)	91/50.8	192/44.9	0.007	0.932
Cardiopulmonary resuscitation (n/%)	6/3.4	18/4.2	0.335	0.563
Hg, g/dL	11.8±3.0	11.0±3.2	2.559	0.011
Total protein, g/L	59.7±11.7	59.8±13.7	0.075	0.940
Blood sodium, mmol/L	148±10	149±13	1.507	0.132
Blood sodium >160 mmol/L	13/7.3	79/15.7	7.314	0.007
Vasoactive-inotropic support (n/%)	146/93.4	391/91.4	1.229	0.268
Vasoactive-inotropic support score (max) (units)	16.5±13.6	13.5±12.7	2.532	0.012
IVS (cm)	1.29±0.31	1.25±0.28	1.554	0.121
IVS ≥1.5 cm (n/%)	39/23.5	86/20.1	0.156	0.693
LVEF (%)	62.6±9.8	64.3±8.8	2.045	0.041
LVEF <40% (n/%)	6/3.6	8/1.9	0.916	0.339
donor-transmitted coronary atherosclerosis treated via stenting after OHTx (n/%)	15/9.0	26/6.1	1.204	0.273

Table 5 (*continued*)

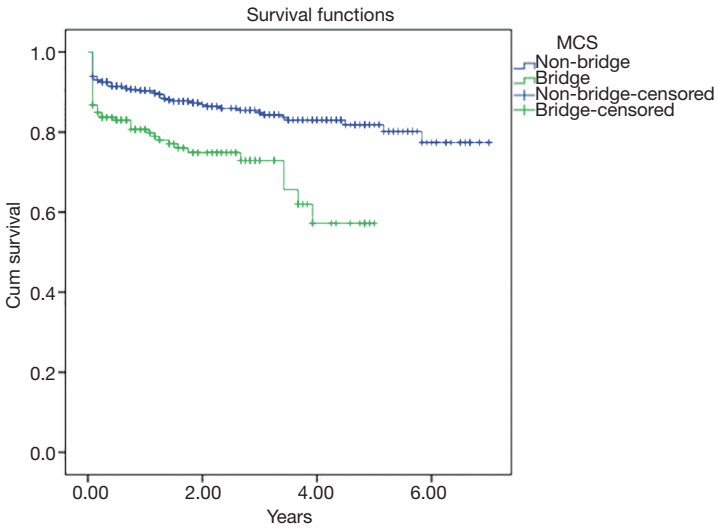
Table 5 (*continued*)

Variables	Recipients		[t]/Хи-квадрат	P
	With pretransplant VA ECMO (n=166)	Without pretransplant MCS (n=428)		
Perioperative characteristics				
Ischemic time, min	166±57	168±58	0.387	0.699
CPB, min	125±45	129±47	0.961	0.337
Vasoactive-inotropic support score (max) (units)	15.7±6.6	15.1±5.9	1.075	0.283
VA ECMO for early allograft dysfunction (n/%)	49/29.5	56/13.1	22.546	<0.001
Intraoperative free hemoglobin, mg%	183±78	193±70	1.551	0.121
Perioperative bleeding, ml	3,823±3,250	1,098±1,015	16.551	<0.001
Fresh frozen plasma, ml	3,389±2,047	1,297±931	17.995	<0.001
Red blood cell, ml	1,828±1205	748±736	13.784	<0.001
Renal replacement therapy (CVVH, HDF) (n/%)	59/35.5	139/32.5	0.3808	0.537
Leukocytes (max), $\times 10^9$/L	17.9±6.2	19.2±5.7	2.493	0.013
Platelets (min), 10^9/L	55.9±33.7	86.5±22.8	13.191	<0.001
Hemoglobin (min), g/dL	7.6±1.5	8.5±2.3	4.721	<0.001
Total protein (min), g/L	61.8±5.6	64.2±5.3	4.989	<0.001
Urea (max), mmol/L	17.8±7.2	15.3±7.2	3.880	0.001
Creatinine (max), umol/L	149.3±99.5	156.5±84.8	0.908	0.365
Total bilirubin (max), umol/L	115.8±96.2	56.0±59.4	9.505	<0.001
ALT (max), IU/L	171.1±413.7	176.0±585.5	0.100	0.921
AST (max), UI/L	309.5±955.0	286.1±651.9	0.3541	0.723
INR (max)	1.58±0.32	1.43±0.24	6.397	<0.001
Hospital mortality (n/%)	23/13.9	26/6.1	8.567	0.003
Hospital mortality associated with early allograft dysfunction (n/%)	21/91.3	17/65.4	3.338	0.068
ICU stay (survived recipients), days	8.3±10.2	5.7±5.2	4.083	<0.001
Hospital stay (survived recipients) after OHTx, days	27.6±8.3	21.1±6.9	9.715	<0.001

VA ECMO, veno-arterial extracorporeal membrane oxygenation; MCS, mechanical circulatory support; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; PVR, pulmonary vascular resistance; max, maximal value; min, minimal value; IVS, interventricular septum; LVEF, left ventricle ejection fraction; CVVH, continuous veno-venous hemofiltration; HDF, hemodiafiltration in online.

with pretransplant VA ECMO (19,20). In our series, the annual amount of OHTx with pretransplant VA ECMO ranged from 19.8% to 41.7%. Such a high volume of OHTx in VA ECMO-supported patients was caused by an 8.6-fold increase in the number of patients on the waiting list and 6.7-fold increase in a proportion of patients requiring urgent OHTx (status 1A UNOS).

The duration of pretransplant VA ECMO can vary from several hours to several weeks, depending on the clinical status of the heart transplant candidate and availability of acceptable donor heart. The duration of VA ECMO treatment should not exceed 7–14 days. This duration of VA ECMO support may be sufficient to improve the pretransplant clinical status of patients without complications (bleeding, thromboembolism, infection, sepsis), that can have an unfavorable effect on the post-transplant outcomes or be fatal (21). However, patients with liver dysfunction and pulmonary complications (e.g.,



Overall comparisons			
	Chi-square	df	Sig.
Log rank (Mantel-Cox)	16.156	1	0.000

Case processing summary				
MCS	Total N	N of Events	Censored	
			N	Percent
Non-bridge	428	60	368	86.0%
Bridge	166	42	124	74.7%
Overall	594	102	492	82.8%

Number	N	0.5 y	1 y	2 y	3 y	4 y	5 y
Bridge	166	84.2%	83.3%	75.1%	74.2%	72.3%	72.3%
		(82.1–86.3%)	(81.9–84.7%)	(73.2–77.5%)	(72.8–76.9%)	(70.6–74.5%)	(70.6–74.5%)
Number of patients		138	135	129	128	124	124
Nonbridge	428	90.1%	91.8%	86.1%	85.8%	84.7%	83.5%
		(87.4–92.5%)	(90.1–93.2%)	(84.2–88.5%)	(84.1–87.2%)	(83.1–85.8%)	(84.1–85.2%)
Number of patients		391	388	378	374	371	369

Figure 6 Post-transplant survival of heart transplant recipients with and without pre-transplant mechanical circulatory support by pVA ECMO. MCS, mechanical circulatory support; pVA ECMO, peripheral veno-arterial extracorporeal membrane oxygenation.

Table 6 Univariable predictor of hospital mortality for recipients bridged with pVA ECMO

Variables	Odds ratio (OR)	95% confidence interval (CI)	P
Recipient predictors of hospital mortality			
Urea >10 mmol/L	7.0	1.57–31.87	0.0120
Heart donor predictors of hospital mortality			
Age >50 years	3.049	1.16–8.01	0.0290
Norepinephrine >600 ng/kg/min	3.818	1.17–12.5	0.0300
Procedure predictors of hospital mortality			
Early graft failure	21.4	2.39–191.5	0.0020
Vasoactive-inotropic score >20 UI	4.92	1.32–18.39	0.0230
Blood loss >2.5 L	8.56	2.39–30.62	0.0002
Red blood cells >6 packs	2.83	1.12–7.17	0.0400
FFP >10 packs	2.96	1.16–7.57	0.0240
Resternotomy	5.409	2.137–13.609	0.0005

pVA ECMO, peripheral veno-arterial extracorporeal membrane oxygenation.

Table 7 Post-transplant survival of heart transplant recipients bridged with VA ECMO in previous publication

Publication	Population	Period	30-day survival	1-year survival
Barth *et al.* [2012]	8	2004–2009	100%	–
Cho *et al.* [2015]	25	2004–2013	–	72%
Jasseron *et al.* [2016]	55	2010–2011	79.7%	70.4%
Lechiancole *et al.* [2018]	32	2005–2017	81.3%	–
Barge-Caballero *et al.* [2017]	169	2010–2015	67.6%	54.4%

VA ECMO, veno-arterial extracorporeal membrane oxygenation.

pneumonia) may demand more time for recovery and more extended MCS. In our study, preexisting liver dysfunction was a significant predictor of mortality for heart transplant candidates with VA ECMO (total bilirubin ≥120 μmol/L (21.61 OR, P=0.010), INR ≥3.0 UI (9.26 OR, P=0.0003).

The effectiveness of the pretransplant bridge with VA ECMO is variable. Chung *et al.* demonstrated that only 44% (31 out of 70) of patients were successfully bridged to OHTx (22). In a multicenter study by Barge-Caballero *et al.* 129 (76.3%) from 169 patients listed for urgent OHTx were successfully bridged by VA ECMO (13). In our study, the rate of the successful bridge to OHTx was 91.2% that may be explained by the high volume of VA ECMO procedures performed in our institution and center-specific management of patients with temporary MCS.

Our goal was to start VA ECMO before the development of severe multi-organ dysfunction, especially liver and renal dysfunction with their negative effects on pre-transplant MCS course and post-transplant survival. Preexisting liver dysfunction was shown to be a significant predictor for lethal outcomes in patients bridged to OHTx (23). Lechiancole *et al.* estimated that OHTx was associated with high early mortality in recipients bridged with VA ECMO and had high levels of multiorgan compromise (APACHE IV score ≥47 points) (20). In research, authors demonstrated that preexisting renal dysfunction was a significant predictor of post-transplant mortality for patients supported with VA ECMO (13,14,20,24). Cho *et al.* also demonstrated that post-transplant survival was low in recipients bridged with VA ECMO and patients had severe organ deteriorations [MELD UNOS score >24 (P=0.001), SOFA score >13 (P=0.068)] and duration of pre-transplant MCS was more than 5 days (P=0.056) (23).

Most studies on the use of VA ECMO as a bridge to transplantation have demonstrated poor early and long-term survival in heart recipients (13,14,24). We also found that early (hospital) and mid-term survival was worse than in recipients without pre-transplant MCS, however was comparable or even better than in other studies (*Table* 7).

In conclusion, VA ECMO is a useful tool of treatment of heart transplant candidates with life-threatening hemodynamic compromise (INTERMACS class 1 or 2). VA ECMO is a unique method of temporary MCS which may be extended for the early post-transplant period in the same recipient with early cardiac allograft dysfunction. It may be of high clinical significance particularly for urgent OHT from donors with extended criteria. However, early, mid-term and late results of OHTx in recipients bridged with VA ECMO are poorer than in recipients without pre-transplant MCS. Nevertheless, the volume of VA ECMO performed and centers expertise in VA ECMO management may be of paramount value significantly increasing survival of these demanding patients.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by ethics committee of Shumakov National Medical Research Center of Transplantology and Artificial Organs (No. 21.12.12-1) and written informed consent was obtained from all patients.

References

1. Ammar KA, Jaconson SJ, Maloney DW, et al. Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/

American Heart Association heart failure staging criteria in the community. Circulation 2007;115:1563-70.
2. Buchholz S, Guentther SPW, Michel S, et al. Ventricular assist device therapy and heart transplantation: Benefits, drawbacks, and outlook. Herz 2018;43:406-14.
3. Mehra MR, Canter CE, Hannan MM, et al. The 2016 International society for heart lung transplantation listing criteria for heart transplantation: a 10-year update. J Heart Lung Transplant 2016;35:1-23.
4. Garbade J, Barten MJ, Bittner HB, et al. Heart transplantation and left ventricular assist device therapy: two comparable options in end-stage heart failure? Clin Cardiol 2013;36:378-82.
5. Gustafsson F, Rogers JG. Left ventricular assist device therapy in advanced heart failure: patient selection and outcomes. Eur J Heart Fail 2017;19:595-602.
6. Puehler T, Ensminger S, Schoenbrodt M, et al. Mechanical circulatory support devices as destination therapy-current evidence. Ann Cardiothorac Surg 2014;3:513-24.
7. Lund LH, Edward LD, Kucheryavaya AY, et al. The registry of the international society for heart and lung transplantation: thirty-second official adult heart transplantation; focus theme: early graft failure. J Heart Lung Transplant 2015;34:1244-54.
8. Deschka H, Holthaus AJ, Sindermann JR, et al. Can Perioperative Right Ventricular Support Prevent Postoperative Right Heart Failure in Patients With Biventricular Dysfunction Undergoing Left Ventricular Assist Device Implantation? J Cardiothorac Vasc Anesth 2016;30:619-26.
9. Robertson J, Long B, Koyfman A. The emergency management of ventricular assist devices. Am J Emerg Med 2016;34:1294-301.
10. Tadmouri A, Blomkvist J, Landais C, et al. Cost-effectiveness of left ventricular assist devices for patients with end-stage heart failure: analysis of the French hospital discharge database. ESC Heart fail 2018;5:75-86.
11. Baras Shreibati J, Goldhaber-Fiebert JD, Banerjee D, et al. Cost-Effectiveness of Left Ventricular Assist Devices in Ambulatory Patients With Advanced Heart Failure. JACC Heart Fail 2017;5:110-9.
12. Barth E, Durand M, Heylbroeck C, et al. Extracorporeal life support as a bridge to high-urgency heart transplantation. Clin Transplant 2012;26:484-8.
13. Barge-Caballero E, Almenar-Bonet L, Gonzales-Vilchez F, et al. Clinical outcomes of temporary mechanical circulatory support as a direct bridge to heart transplantation: a nationwide Spanish registry. Eur J Heart Fail 2018;20:178-86.
14. Jasseron C, Lebreton G, Cantrelle C, et al. Impact of heart transplantation on survival in patients on venoarterial membrane oxygenation at listing in France. Transplantation 2016;100:1979-87.
15. Barge-Caballero E, Almenar-Bonet L, Villa-Arranz A, et al. Impact of short-term mechanical circulatory support with extracorporeal devices on postoperative outcomes after emergency heart transplantation: data from a multi-institution Spanish cohort. Int J Cardiol 2014;176:86-93.
16. Jeevanandam V, Song T, Onsager D, et al. The first-in-human experience with a minimally invasive, ambulatory, counterpulsation heart assist system for advanced congestive heart failure. J Heart Lung Transplant 2018;37:1-6.
17. Umakanthan R, Hoff SJ, Solenkova N, et al. Benefits of ambulatory axillary intra-aortic balloon pump for circulatory support as bridge to heart transplant. J Thorac Cardiovasc Surg 2012;143:1193-7.
18. Sauer CM, Yuh DD, Bonde P. Extractorporeal membrane oxygenation use has increased by 433% in adults in the United States from 2006 to 2011. ASAIO J 2015;61:31-6.
19. D'Alessandro C, Golmard JL, Lebreton G, et al. High-urgency waiting list for cardiac recipients in France: single-centre 8-year experience. Eur J Cardiothorac Surg 2017;51:271-8.
20. Lechiancole A, Sponga S, Isola M, et al. Heart transplantation in patients supported by ECMO: is the APCHE IV score a predictor of survival? Artif Organs 2018;42:670-3.
21. Wang SS, Ko WJ, Chen YS, et al. Mechanical bridge with extracorporeal membrane oxygenation and ventricular assist device to heart transplantation. Artif Organs 2001;25:599-602.
22. Chung JC, Tsai PR, Chou NK, et al. Extracorporeal membrane oxygenation bridge to adult heart transplantation. Clin Transplant 2010;24:375-80.
23. Cho YH, Yang JH, Sung K, et al. Extracorporeal life support as a bridge to heart transplantation: importance of organ failure in recipients selection. ASAIO J 2015;61:139-43.
24. Zalawadiya S, Fudim M, Bhat G, et al. Extracorporeal membrane oxygenation support and post-heart transplant outcomes among United States adults. J Heart Lung Transplant 2017;36:77-81.

Cite this article as: Poptsov V, Spirina E, Dogonasheva A, Zolotova E. Five years' experience with a peripheral veno-arterial ECMO for mechanical bridge to heart transplantation. J Thorac Dis 2019;11(Suppl 6):S889-S901. doi: 10.21037/jtd.2019.02.55

