Artificial Organs

Peripheral Extracorporeal Membrane Oxygenation System as Salvage Treatment of Patients With Refractory Cardiogenic Shock: Preliminary Outcome Evaluation

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Abstract: The novel Permanent Life Support (PLS; Maquet, Jostra Medizintechnik AG, Hirrlingen, Germany) as peripheral veno-arterial extracorporeal membrane oxygenation (ECMO) support system has been investigated as treatment for patients with refractory cardiogenic shock (CS). Between January 2007 and July 2011, 73 consecutive adult patients were supported on peripheral PLS ECMO system at our institution (55 men; age 60.3 ± 11.6 years, range: 23–84 years). Indications for support were failure to wean from cardiopulmonary bypass in the setting of postcardiotomy ($n = 50$) and primary donor graft failure ($n = 8$), post-acute myocardial infarction CS ($n = 12$), and CS on chronic heart failure ($n = 3$). Mean support time was 10.9 ± 7.6 days (range: 2–34 days). Overall, 26 (35.6%) patients died on ECMO. Among survivors on ECMO, 44 (60.2%) patients were successfully weaned from support, and three (4.1%) were switched to a mid–long-term ventricular assist device. Thirty-three (45.2%) were successfully discharged. The following variables were significantly different if survivors and nonsurvivors on ECMO were compared: age ($P = 0.04$), female gender ($P < 0.01$), cardiopulmonary resuscitation before ECMO ($P < 0.01$), lactate level before ECMO ($P = 0.01$), number of platelets, fresh frozen plasma units, and packed red blood cells (PRBCs) transfused during ECMO support ($P = 0.03$, $P = 0.02$, and $P < 0.01$), blood lactate level ($P = 0.01$), and creatine kinase isoenzyme MB (CK-MB) relative index 72 h after ECMO initiation ($P < 0.001$), and multiple organ failure on ECMO ($P < 0.01$). Stepwise logistic regression identified blood lactate level and CK-MB relative index at 72 h after ECMO initiation, and number of PRBCs transfused on ECMO as significant predictors of mortality on ECMO ($P = 0.011$, odds ratio [OR] = 2.48; 95% confidence interval [CI] = 1.11–3.12; $P = 0.012$, OR = 2.81, 95% CI = 1.026–2.531; and $P = 0.012$, OR = 1.94, 95% CI = 1.02–5.21; respectively). Patients with an initial poor hemodynamic status could benefit by rapid peripheral installation of PLS ECMO. The blood lactate level, CK-MB relative index, and PRBCs transfused should be strictly monitored during ECMO support.
Key Words: Cardiogenic shock—Mechanical circulatory support—Extracorporeal membrane oxygenation.

The usage of extracorporeal membrane oxygenation (ECMO) was introduced into clinical practice by Bartlett et al. (1). Since the early 1970s, ECMO has been used in more than 170 centers worldwide and in more than 35 000 severely ill patients with refractory cardiogenic shock (CS) or respiratory failure as reported by the Extracorporeal Life Support Organization (ELSO) registry (2).

ECMO offers several advantages: (i) it provides cardiac and pulmonary support; (ii) the peripheral insertion of cannulas into vessels is simple and rapid, thus avoiding a sternotomy incision; (iii) it can be performed during cardiopulmonary resuscitation (CPR); (iv) it provides time to assess potential heart transplantation (Htx) or long-term ventricular assist device (VAD) candidates; and (v) it is less costly than other forms of mechanical circulatory support (MCS).

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Membrane oxygenators are one of the main elements of ECMO systems. After silicone and microporous hollow fibers oxygenators (3,4), recently, a new generation of polymethylpentene (PMP) membrane oxygenators has been introduced.

We report our experience in using the novel ECMO circuit Permanent Life Support (PLS; Maquet, Jostra Medizintechnik AG, Hirrlingen, Germany) consisting of a PMP oxygenator and a centrifugal pump for treatment, as peripheral setting, of adult patients with primary or postcardiotomy CS.

PATIENTS AND METHODS

ECMO system

The ECMO circuit consisted of a PMP oxygenator, Quadrox D (Maquet, Jostra Medizintechnik AG), and a centrifugal pump, RotaFlow (Maquet, Jostra Medizintechnik AG).

Peripheral veno-arterial cannulation was performed in all 73 patients by usage of an arterial return cannula, DLP Biomedicus 15 Fr–19 Fr (Medtronic, Inc., Minneapolis, MN, USA) which was inserted into the femoral artery and a venous drainage cannula, DLP Biomedicus 17 Fr–23 Fr (Medtronic, Inc.) which was inserted into the femoral vein (Fig. 1). Both insertions were performed using the Seldinger technique after anterior vessel wall exposure. In eight patients, belonging to the postcardiotomy cohort, a 19-Fr venous cannula into the right jugular vein, DLP Biomedicus (Medtronic, Inc.), was used as first inserted during cardiopulmonary bypass (CPB) installation due to reoperation procedures ($n = 18$).

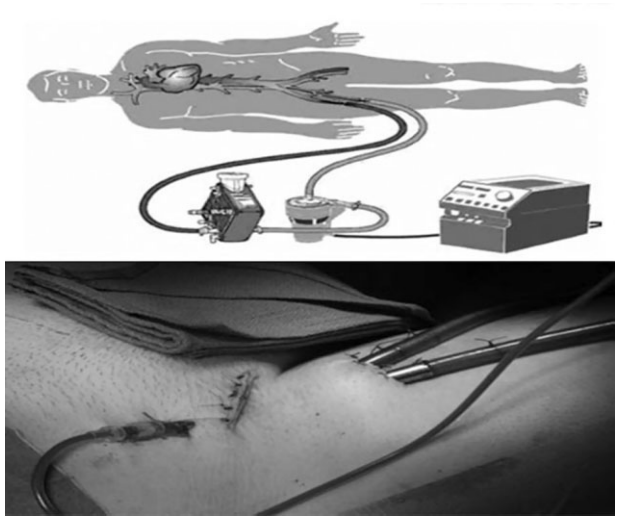

FIG. 1. Peripheral veno-arterial extracorporeal membrane oxygenation support setting.

The Quadrox D oxygenator has a PMP hydrophobic hollow fiber diffusion membrane with an effective surface area of 1.8 m^2, which allows long-term high gas exchange performance; the oxygen transfer capacity and the carbon dioxide transfer capacity are 288 and 230 mL/min, respectively; the pressure drop across the in and out lines of the device does not exceed 40 mm Hg at 4 L/min; the priming volume is 250 mL. This oxygenator is compact with a decreased heat exchange surface area of the membrane (0.6 m^2), thus reducing the risk of clot formation.

The RotaFlow is a centrifugal pump with a low prime volume (32 mL). The pump rotor is suspended by a permanent magnetic field, and four flowing channels are generated inside the housing of the pump. These allow a continuous laminar flow with minimal turbulence and a reduced risk of hemolysis.

The RotaFlow pump can provide high blood flow up to 10 L/min. The tubing, pump, and oxygenator are all coated with Bioline Coating (Maquet, Jostra Medizintechnik AG). Recombinant human albumin is adsorbed on the extrinsic surface and acts as receptor of heparin. Covalent bonds and ionic interaction occur between the heparin molecules and the albumin. By this treatment, all the surfaces in contact with the blood have highly stable covalent and ionic links with heparin. This coating provides high hemocompatibility, thus minimizing the activation of platelets, coagulation cascade, and complements.

The circuit was primed with saline. The priming procedure usually needed 4–5 min, and this proved very useful in those patients who require immediate ECMO support in other hospital places such as intensive care, emergency department, and hemodynamic laboratory.

The novel adopted circuit, named Permanent Life Support (PLS; Maquet, Jostra Medizintechnik AG), was used in all patients. In the PLS, the Quadrox D oxygenator has the housing reinforced with glass fibers to increase the mechanical resistance and the polyvinyl chloride of the circuit is DEHP-free (Bis 2-ethylhexyl-phthalate). For these characteristics, this circuit is more biocompatible and has been certified for a support period of 14 days (DEKRA Intertek Certification as a notified body of the European Union, in accordance with the Directive 93/42/ European Community).

Patients

The ECMO program was started at our institution in January 2007. Since then and until July 2011, 4322 adult patients underwent cardiac operations, mainly isolated coronary artery bypass graft (CABG). During the same period, 73 patients (1.7%)

TABLE 1. *Demographic and preimplant clinical parameters of the different cohorts of patients supported by peripheral ECMO*

	Postcardiotomy ($n = 50$)	Donor graft failure ($n = 8$)	Post-AMI ($n = 12$)	Acute on chronic HF ($n = 3$)
Mean age (years)	64.3 (40–84)	49.1 (23–63)	65.8 (40–71)	50.6 (46–55)
Male gender (*n*,%)	32 (64%)	8 (100%)	11 (91.6%)	3 (100%)
BSA (m^2)	1.8 (1.75–1.88)	1.8 (1.78–1.88)	1.9 (1.85–1.95)	1.82 (1.78–1.86)
Etiology				
Coronary disease (*n*,%)	29 (58%)	—	12 (100%)	1 (33.3%)
Valvular disease (*n*,%)	25 (50%)	—	—	—
DCMP (*n*,%)	—	—	—	3 (100%)
Preoperative LVEF (%)	48.3 (35–75)	—	—	—
Number of diseased coronaries	2.4 (2–3)	—	2.3 (2–3)	3
Previous cardiac operation	18 (36%)	3	—	—
Logistic EuroSCORE (%)	25.5 (10–45)	—	—	—
CPB time	202.4 (48–368)	227.3 (196–266)	—	—
Ischemic time	117.2 (65–199)	195.5 (177–210)	—	—
SAPS II score*	31 (28–45)	32 (26–45)	36 (28–50)	31 (15–41)
Inotropic score*	32 (20–45)	30 (20–38)	35 (20–50)	32 (15–38)
mSAP (mm Hg)	63 (50–65)	64.9 (50–68)	62.9 (48–65)	60.9 (50–70)
SvO_2 (%)	48 (40–55)	54 (48–58)	47 (40–55)	48 (45–55)
Lactate level (mg/dL)	13.6 (6.7–18.1)	12.5 (5.7–17.2)	14.8 (7.7–18.1)	12.9 (6.7–17.1)
CPR (*n*,%)	8 (16%)	—	7 (58.3%)	1 (33.3%)
CPR time (minutes)	28.1 (16–62)	—	31.5 (11–53)	25.5 (15–55)
IABP	2 (4%)	—	12 (100%)	2 (66.6%)
Mechanical ventilation	50 (100%)	8 (100%)	12 (100%)	1 (33.3%)

All values are presented as median and range or as percentage.

* Definition is given by the same authors elsewhere (5).

AMI, acute myocardial infarction; BSA, body surface area; CBP, cardiopulmonary bypass; CPR, cardiopulmonary resuscitation; DCMP, dilative cardiomyopathy; HF, heart failure; IABP, intra-aortic balloon pump; LVEF, left ventricular ejection fraction; mSAP, mean systolic arterial pressure; SAPS, simplified acute physiology score; SvO_2, mixed venous oxygen saturation.

required veno-arterial peripheral ECMO support for primary or postcardiotomy CS (Tables 1 and 2).

Central setting of ECMO support ($n = 10$) in the same period of time (initial experience) was excluded in this report. The femoral route was preferred to the open sternotomy route for ECMO support because the presence of an open sternotomy wound increased the risk of bleeding and infection, and made nursing care more difficult.

Inclusion criteria for peripheral ECMO support to treat primary refractory heart failure (HF) and CS at our institution are the following: acute myocardial infarction; acute decompensation of end-stage dilated cardiomyopathy; myocarditis; high-risk percutaneous transluminal coronary angioplasty (PTCA); failure to wean from CPB after surgery.

Patients were excluded according to the following criteria: severe peripheral arteriopathy; severe and chronic renal failure; terminal malignancy; irreversible or severe degenerative brain diseases; trauma.

ECMO support was installed mostly in the operating room ($n = 70$) and rarely in the intensive care unit ($n = 3$).

In the studied population, the vital status immediately before ECMO placement, as traditionally evaluated before any short-term mechanical support device placement at our institution (5), was

TABLE 2. *Demographic data, pretransplantation recipients characteristics, donor characteristics, and surgical times of graft failure patients cohort supported by peripheral ECMO*

	Patients ($n = 8$)
Recipient age (years)	49.1 (23–63)
Recipient gender (male)	8
Idiopathic DCMP (*n*)	3
Valvular DCMP (*n*)	2
Ischemic DCMP (*n*)	1
Restrictive CMP (*n*)	1
GUCH (*n*)*	1
Redo operation (*n*)	3
Previous TAH implantation (*n*)	1
TPG	15.3 (12–18)
Donor age (years)	39.2 (27–46)
Donor gender (male)	6
D/R size match	0.9 (0.7–0.10)
Total ischemic time (min)	195.5 (177–210)
Reperfusion time (min)	227.3 (196–266)

All values are presented as median and range.

* Tetralogy of Fallot (TOF).

CABG, coronary artery bypass grafting; DCMP, dilative cardiomyopathy; D/R, donor/recipient; GUCH, grown-up congenital heart disease; TAH, total artificial heart; TPG, transpulmonary gradient.

documented using the simplified acute physiology score II (Table 1). Briefly, the following data were collected and score points calculated: age, heart rate, systolic blood pressure, body temperature (in degrees Celsius), PaO_2/FIO_2, urine output, serum blood urea nitrogen, white blood cell count, serum potassium, sodium and bicarbonate level, bilirubin plasma level, Glasgow coma score, documented history of chronic disease (acquired immunodeficiency syndrome, hematologic malignancy, metastatic cancer), and type of admission.

The inotropic score, as calculated at our institution (5), before ECMO placement was also evaluated (Table 1). Briefly, the doses of dopamine, dobutamine, and enoximone (in micrograms per kilogram body weight per minute) were added; the doses of epinephrine and norepinephrine were multiplied by 100 and then added.

ECMO management

The ECMO blood flow was adequately adjusted during the first 24–48 h to maintain cardiac index of 2.6 L/min/m^2, mixed venous oxygen saturation (SvO_2) around 70%, and mean arterial pressure of 60–65 mm Hg.

Before cannulation, all patients received an intravenous heparin bolus (40–80 units/kg); during ECMO support, the heparin was administered continuously to achieve an activated clotting time of 140–160 s and a prothrombin time value of 50–70. Infusion of antithrombin III (AT III) was required if the AT III serum level was below 80%. In patients with a motionless left ventricle, small doses of inotropes (dobutamine) were given to obtain a minimal ventricular contraction avoiding clot formation inside the left ventricle. In four cases (5.4%), we resorted to direct left atrial venting to effectively decompress the left ventricle.

All ECMO support was conducted under normothermia. Those patients who had cardiac arrest before starting ECMO were progressively cooled to 32–34°C for 24–36 h by usage of a heater-cooler (Stockert, Munchen, Germany) (6).

Closed heart examinations by transesophageal echo were done to assess the left ventricle motion daily. Since peripheral cannulation, CW-Doppler of the tibial artery was done every 2 days to assess the leg perfusion. In all patients, a distal perfusion catheter (8-Fr flexible soft balloon-tipped coronary catheter for selective anterograde cardioplegia infusion [Maquet]) was inserted to avoid deleterious leg ischemia (Fig. 1).

All patients needed blood transfusions to achieve a hematocrit of 28–30%, and platelet infusions were given when platelet count was less than 50 000–60 000.

Mechanical ventilation was continued throughout ECMO support with the same management for every patient. Ventilator setting was commonly set at a tidal volume of 8 mL/kg, eight breaths/min, positive end expiratory pressure of 10 cm H_2O, and an FiO_2 of 0.40–0.60. Intra-aortic balloon pump (IABP) was employed in all patients with the aim of reducing the afterload to improve the coronary perfusion and maintaining a pulsatile flow.

At our institution, no attempts to wean off ECMO are usually considered for the first 72 h. Criteria for weaning include SvO_2 equal to or more than 70%, hematocrit of 28–30%, absence of bleeding or tamponade, a left ventricular ejection fraction equal to or more than 35%, absence of left heart distension, good contraction of right ventricle with absence of moderate to severe tricuspid regurgitation, normal blood lactate levels, and normal urine output.

Step-by-step weaning is our main strategy with close transesophageal echo examinations. This consists of reducing the pump flow at 0.5 L/min/m^2 for approximately 40–60 min with IABP set at 1:1. If the hemodynamics remained stable without increasing or adding doses of inotropes, heparin was stopped and ECMO was removed in the operating room within the next 1 h and rarely at bedside ($n = 3$). After ECMO removal, no patient needed subsequent ECMO support.

Among the non-weanable patients, two were switched to prolong the support to an extracorporeal third-generation continuous flow Levitronix CentriMag (Levitronix LCC, Waltham, MA, USA) left ventricular assist device (LVAD) by cannulating the left atrium and the ascending aorta with further continuous intravenous heparin administration, to maintain a thromboplastin time of 50–60 s, and one to an implantable long-term axial flow HeartMate II (Thoratec, Inc., Pleasanton, CA, USA) LVAD by cannulating the apex of the left ventricle and the ascending aorta with a postoperative anticoagulation management consisting of warfarin, to maintain an international normalized ratio of 2.5–3.0, associated with a platelet aggregation inhibitor at low dosage (aspirin, 100 mg per day).

In all patients, the IABP support was maintained for at least 5 days after ECMO removal.

Statistical analysis

Descriptive statistics are expressed as mean ± standard deviation or as median and range. A P value <0.05 was considered to have a statistical significance. Categorical variables are presented as percentages,

TABLE 3. *Outcome on peripheral ECMO support*

	Postcardiotomy ($n = 50$)	Donor graft failure ($n = 8$)	Post-AMI ($n = 12$)	Acute on chronic HF ($n = 3$)
ECMO time (days)	10.9 (2–36)	4.9 (3–7)	10.7 (6–24)	9.9 (8–13)
ECMO >6 days	38 (76%)	1 (12.5%)	9 (75%)	3 (100%)
IABP on ECMO	50 (100%)	8 (100%)	12 (100%)	3 (100%)
IABP time (days)	14.9 (2–42)	7.9 (3–12)	13.7 (6–30)	13.7 (8–18)
Intubation time (days)	20 (2–42)	10.1 (3–10)	19.2 (6–28)	19.3 (8–15)
Hospital stay (days)	41.2 (2–96)	21.6 (3–32)	38.5 (6–57)	38.4 (8–37)
Creatinine >3.5 (mg/100 mL)	19 (38%)	1 (12.5%)	5 (41.6%)	2 (66.6%)
CVVH	28 (56%)	1 (12.5%)	7 (58.3%)	2 (66.6%)
CVVH time (days)	8.3 (6–11)	3 (4–7)	8.1 (6–14)	7.6 (5–10)
Bleeding/tamponade	29 (58%)	4 (50%)	4 (33.3%)	—
Transfusion	50 (100%)	8 (100%)	12 (100%)	3 (100%)
PRBCs	18 (3–52)	16.1 (3–48)	19.3 (3–51)	17.1 (3–55)
PLT units	16.5 (6–48)	15.8 (6–50)	15.9 (6–52)	16.1 (6–47)
FFP (1000 mL/unit)	5.6 (2–15)	5.2 (2–17)	6.1 (2–18)	5.1 (2–14)
Pulmonary complications	12 (24%)	1 (12.5%)	3 (25%)	—
Liver failure	21 (42%)	2 (25%)	5 (41.6%)	2 (66.6%)
Bilirubin >15 (mg/100 mL)	19 (38%)	1 (12.5%)	5 (41.6%)	1 (33.3%)
PLT count	125.6 (40–198)	115.8 (95–188.1)	133.6 (88–177.5)	123.4 (105–166.1)
PFH (mg/dL)	46.5 (28–165)	43.5 (15–148)	48.9 (26–158)	44.3 (18–95)
CK-MB relative index (%)*	7.3 (5–28)	7.7 (4–20)	8.1 (5–25)	7.7 (5–19)
MOF	19 (38%)	1 (12.5%)	5 (41.6%)	1 (33.3%)
Sepsis	9 (18%)	—	2 (16.6%)	—
Brain death (cerebral hemorrhage)	9 (18%)	—	2 (16.6%)	—
Leg ischemia	4 (8%)	—	—	—
Survived on ECMO	31 (62%)	7 (87.5%)	7 (58.3%)	2 (66.6%)
Weaned from ECMO	30 (60%)	7 (87.5%)	6 (50%)	1 (33.3%)
Died on ECMO	19 (38%)	1 (12.5%)	5 (41.6%)	1 (33.3%)
Discharged	19 (38%)	7 (87.5%)	5 (41.6%)	2 (66.6%)
Bridge to VAD	1 (2%)	—	1 (8.3%)	1 (33.3%)
Bridge to Htx	—	—	—	—

All values are presented as mean and standard deviation or as percentage.

* Definition is given by Zhang et al. (7).

AMI, acute myocardial infarction; CVVH, continuous, veno-venous hemofiltration; CK-MB, MB isoenzyme of creatine kinase; ECMO, extracorporeal membrane oxygenation; FFP, fresh frozen plasma; HF, heart failure; Htx, heart transplantation; IABP, intra-aortic balloon pump; MOF, multiple organ failure; PFH, plasma free hemoglobin; PLT, platelet; PRBCs, packed red blood cells; VAD, ventricular assist device.

and χ^2-test was used to compare them. Analysis of variance for repeated measures was employed for numerical variables. Continuous variables were evaluated by Student's *t*-test for independent variables. A univariate analysis was used as a screening process in order to identify any possible predictor variables, which were chosen as those with $P < 0.05$. Stepwise logistic regression analysis was applied to determine the independent predictors of 30-day mortality.

All analyses were performed using SPSS for Windows Release 11.5 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Mean age was 60.3 ± 11.6 years (range, 23–84 years), and 55 patients (75.3%) were men. Forty-four patients (60.2%) were weaned off ECMO, and 26 (35.6%) died during mechanical support due to multiple organ failure (MOF). Sepsis and brain death (cerebral hemorrhage) occurred in 11 cases (15.06%) (Tables 1–3). Thirty-three patients (45.2%) were successfully discharged. Three patients were switched to Levitronix CentriMag (Levitronix LCC) LVAD, in two cases ($n = 1$, death on support due to ischemic stroke; $n = 1$, myocardial recovery after 7 days of support and discharge), and HeartMate II (Thoratec, Inc.) LVAD, in one case (discharge; 311 days of ongoing support).

Fifteen patients (20.5%) required ECMO to treat primary CS. Twelve of them, referred from other institutions, had a large anterior myocardial infarction ($n = 8$, left main) and were already treated by primary PTCA. Three patients had an acute decompensation on chronic HF due to end-stage dilative cardiomyopathy.

Fifty patients (68.4%) received ECMO support after a cardiac surgery procedure due to failure to wean from CPB. Postcardiotomy procedures included: CABG in 18; combined mitral valve replacement and tricuspid valve repair in nine; combined CABG and ascending aorta replacement in

seven; aortic valve replacement in five; Bentall procedure in four; combined CABG and aortic valve replacement in four; and mitral valve replacement in three.

Sixteen patients (21.9%) received ECMO during CPR with a mean time CPR of 31.5 ± 14 min (range, 11–62 min).

Preoperative risk profile and postoperative parameters are listed in Tables 1–3. Overall mean ECMO support time was 10.9 ± 7.6 days (range, 2–34 days).

IABP was inserted in all patients before ECMO support since we followed the IABP score by Haussman et al. (8) for mechanical support initiation.

Pressure drop never exceeded 40 mm Hg, and at posttreatment, all the components of ECMO system were macroscopically evaluated to detect eventual clots or fibrin deposits, and no circuit had macroscopic alterations.

In all patients, blood lactate, creatine kinase isoenzyme MB (CK-MB), and CK-MB relative index as the ratio of CK-MB to total CK were measured. All parameters evaluated had a significant reduction already during the first 72 h of ECMO support (Tables 1, 2, and 4).

The blood lactate level 72 h after ECMO initiation ($P = 0.01$), the MB isoenzyme of creatine kinase (CK-MB) 72 h after ECMO initiation ($P = 0.01$), and the CK-MB relative index 72 h after ECMO initiation ($P < 0.001$) had statistically significant differences if survivors and nonsurvivors on ECMO were compared (Table 4).

Logistic regression analysis revealed blood lactate levels at 72 h after initiation of ECMO and CK-MB relative index 72 h after ECMO initiation to be a significant predictor of mortality on ECMO support ($P = 0.011$, odds ratio [OR] = 2.48; 95% confidence interval [CI] = 1.11–3.12 and $P = 0.012$, OR = 2.81, 95% CI = 1.026–2.531, respectively).

All patients were transfused (Table 3) due to intravenous heparin infusion and large vessel cannulas with frequent oozing evident on daily examinations. The patients who died had a higher number of red blood cell transfusions ($P < 0.01$), a higher number of platelets ($P = 0.03$), and a higher number of units of fresh frozen plasma transfusions ($P = 0.02$) (Table 4).

The stepwise logistic regression analysis even revealed that the number of packed red blood cells transfused is an independent predictor of mortality during ECMO support ($P = 0.012$, OR = 1.94; 95% CI = 1.02–5.21).

Platelet counts were measured, and a moderate reduction was observed (overall, average 228.6 ± 82.3 K/μL, before ECMO, vs. 134.2 ± 92.8 K/μL, already at 72 h of ECMO support [$P = 0.01$], but with no significant further reduction at the overall average time of ECMO support and no significant difference between survivors and nonsurvivors). Eight patients had a significant reduction of platelet count (<50 K/μL) due to heparin-induced thrombocytopenia type II, and fundaparinux (2.5 mg, per day) was used as an alternative to intravenous heparin administration (9). Among them, one patient died of MOF and brain

TABLE 4. *Comparison of the survivors and nonsurvivors variables*

	Survivors ($n = 47$)	Nonsurvivors ($n = 26$)	P value
Age (years)	49 ± 9.8	66.1 ± 12.1	0.04
Female gender	8 (17.02%)	15 (65.2%)	<0.01
Lactate level (mg/dL) before ECMO	12.7 ± 3.7	30.5 ± 27.3	0.01
CPB time (min) in postcardiotomy cohort	172.5 ± 92.6	234 ± 122.2	0.02
Aortic cross-clamping time (min) in postcardiotomy cohort	88.2 ± 55.4	142.5 ± 76.1	<0.01
CPR before ECMO	2 (4.2%)	14 (53.8%)	<0.01
Inotropic score before ECMO*	11.2 ± 3.3	34.6 ± 7.2	0.03
Intubation time (days) on ECMO	9.9 ± 8.2	19.9 ± 7.2	0.02
MOF on ECMO	1 (2.1%)	26 (35.6%)	<0.01
PRBCs on ECMO	8.4 ± 5.5	22.6 ± 13.4	<0.01
PLT units on ECMO	14.8 ± 7.8	26.5 ± 16.8	0.03
FFP (1000 mL/unit) on ECMO	3.5 ± 3.8	9.8 ± 8.4	0.02
Blood lactate level (mmol/L) 72 h after ECMO initiation	2.2 ± 1.41	7.8 ± 5.42	0.01
Blood level of CK-MB (U/L) 72 h after ECMO initiation	146.3 ± 136.3	358.4 ± 231.2	0.01
CK-MB relative index (%) 72 h after ECMO initiation†	7.4 ± 3.52	20.7 ± 11.4	<0.001
PFH (mg/dL) 72 h after ECMO initiation	33.4 ± 11.2	94.2 ± 15.6	<0.01

All values are presented as mean and standard deviation or as percentage.

* Definition is given by the same authors elsewhere (5).

† Definition is given by Zhang et al. (7).

CBP, cardiopulmonary bypass; CK-MB, MB isoenzyme of creatine kinase; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; FFP, fresh frozen plasma; IABP, intra-aortic balloon pump; MOF, multiple organ failure; PFH, plasma free hemoglobin; PLT, platelet; PRBCs, packed red blood cells.

death (cerebral hemorrhage), while seven were successfully weaned off ECMO support (postcardiotomy cohort).

Peripheral complications of femoral access included femoral bleeding (58.5%), femoral site infection (7.2%), leg ischemia (4.5%), and we had no inferior vena cava thrombosis or femoral vein thromboses.

DISCUSSION AND CONCLUSION

Peripheral ECMO support is a well-established technology that provides full circulatory support with several advantages (10–13), and its indications are widely increasing (2).

In the early 1990s, the hollow-fiber polypropylene membrane oxygenator (Fig. 2) was introduced and showed more advantages than the old silicone membrane oxygenator (3,4) such as high gas exchange efficiency with a small change surface, low prime volume, and low pressure gradient. However, it revealed plasma leakage for periods of more than 6 h.

Recently, a novel material called polymethylpentene (PMP) (Fig. 2) represents the key to the last generation of oxygenators. Only some studies have reported the outcome of ECMO with the PMP oxygenator and mostly in pediatrics (14,15) or in patients with respiratory failure (16). Toomasian et al. (17) conducted an animal study and reported a better gas exchange, minor platelet consumption, and less pressure drop in the PMP oxygenator in comparison with the silicone oxygenator.

Several studies (7,12,13,18–27) reported the use of ECMO with the combination of a hollow-fiber microporous oxygenator and a centrifugal pump with described periodical change of both oxygenator and pump. In 2004, the ELSO registry (28) already reported a 27% oxygenator failure and a 36% pump malfunction in patients above 16 years. In our experience, we had to change the ECMO circuit and the oxygenator due to clot formation in three patients with aggressive sepsis (postcardiotomy cohort) who eventually died thereafter.

Several studies reported the mean time of ECMO duration ranging between 1.7 and 7.1 days (7,12,13,18–27). In our experience, the mean time of ECMO duration was 10.2 ± 7.3 days (range, 2–34 days).

Bleeding remains a serious problem in patients supported with ECMO (24). Magovern and Simpson (29) observed fewer units of all blood components usage in survivors on ECMO by usage of a microporous oxygenator. Ko et al. (22) described a 100% rate of transfusion without any differences among survivors and nonsurvivors. Horton et al. (15) observed a reduction of transfusions in a pediatric population using the ECMO Quadrox D/RotaFlow

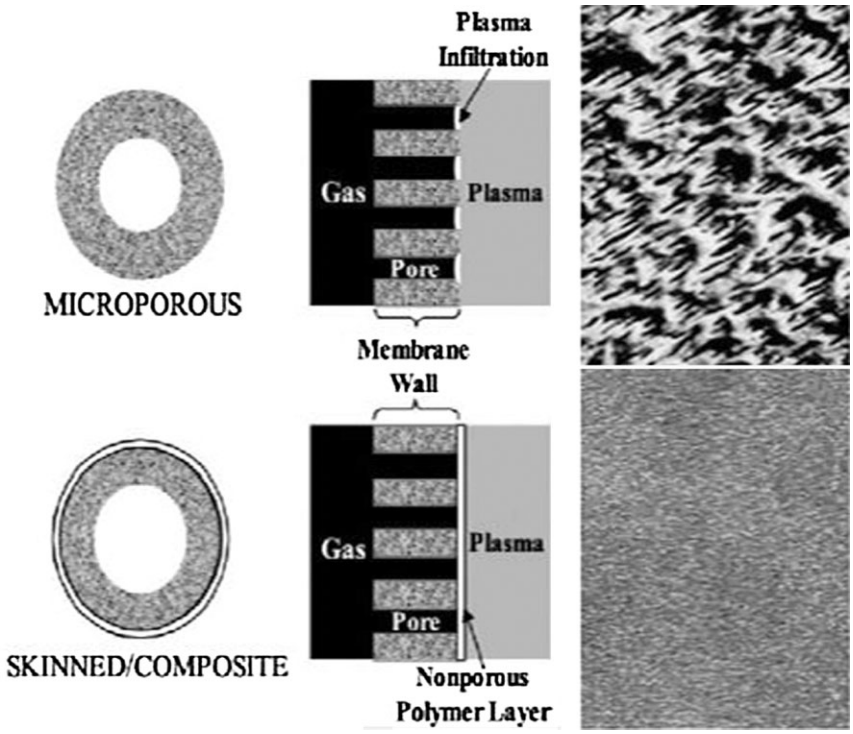

FIG. 2. Polypropylene "standard" membrane: Polypropylene fibers: Gas is in contact with the blood through a microporous hollow fiber; gas transfer is obtained by direct contact (upper panel). Polymethylpentene "plasma-tight" membrane: Polymethylpentene fibers: Hollow fibers are protected by a thin outer skin; gas transfer is obtained by gas diffusion through this thin layer (lower panel).

system. Agati et al. (14) adopted an ECMO circuit with a PMP oxygenator in pediatrics and observed low requirement of platelet replacement therapy.

In our experience, we have observed a slight reduction of blood component transfusions and lower plasma-free hemoglobin levels, in terms of hemolysis rate, in patients who survived on ECMO compared with patients who died on ECMO (Table 4).

We reported an overall mortality of 35.6% and an overall survival rate on ECMO of 64.3% (Table 3), which are similar to other reports (7,12,13,18–27), but with a longer time of ECMO duration. This could have different interpretations. On the one hand, if the patient could not be weaned off ECMO within 7 days, then Htx or a VAD implantation is required. On the other hand, the possibility of leaving the patient on ECMO for more than 7 days, before attempting weaning off support, has to be seriously considered, particularly with the PMP oxygenators.

The decisive management for optimal timing of device insertion and duration of support to either bridge or recovery is difficult to provide in a precise fashion. Moreover, the question of whether to bridge to transplant or use a long-term device has remained controversial. Our goal was to adopt an ECMO support as a bridge to Htx if there was no evidence of recovery after weaning attempt(s) following neurologic recovery and multiple-organ improvement as the average waiting time to Htx is shorter than in the USA (90 vs. 250 days).

We noticed no significant difference between the patients who survived and the patients who died on ECMO in terms of mean time of ECMO duration (9.2 ± 3.9 days vs. 10.8 ± 5.6 days, respectively; $P = 0.71$).

Regarding the ECMO outcome, the ELSO reported (2,28) the data of the international summary of extracorporeal life support (ECLS) registry, in which the percentage of survival to ECLS and survival to discharge for cardiac patients are 48 and 34%, respectively; survival to ECLS and survival to discharge for patients suffering from cardiac arrest is 36 and 27%, respectively. Some authors (7,12,13,18–27) reported a survival to discharge ranging between 24 and 41%, and percentages of weaning off ECMO between 46 and 64%.

By considering all data mentioned before, we can say that the peripheral ECMO system with PMP oxygenator Quadrox D/RotaFlow is an optimal alternative to microporous oxygenators and has to be seriously considered even when a perfusion longer than 6 days is forecast.

At the moment, there are no specific guidelines for the management of ECMO, and the decision to discontinue support is still a challenge and is entrusted to the experience of each center.

Hyperlactatemia (blood lactate >3 mM) during CPB is associated with increased mortality (6,8–10,15–25). Similarly to the study of Formica et al. (24), we clearly confirmed that the blood lactate level (>3 mM) after 72 h is a parameter to predict the probability (50%) of 30-day mortality (Table 4).

Moreover, similarly to the study of Zhang et al. (7), we observed that patients who presented an index of CK-MB (7,30) at 72 h of 10% should have a predicted probability of mortality of 50%, and patients not weaned off ECMO (mostly nonsurvivors) have a CK-MB relative index significantly higher than patients who are weaned off (Table 4).

Consequently, any eventual decision concerning the discontinuation of ECMO support can be clearly supported, according to the above-evaluated predictors. In addition, the rate of bleeding and the need for blood transfusions during ECMO remain high and confirm to be associated with an increase in mortality (24,29) (Table 4).

Peripheral veno-arterial PLS ECMO support proved to be successful even in cases of graft failure after Htx (Tables 1–3) and remain our first choice if a MCS is necessary (31).

Some studies (5,32–34) showed success in the use of the new generation CentriMag blood pumping system (Levitronix LLC). Levitronix CentriMag as VAD configuration has been used since the beginning of our experience (2002) as short-term MCS (5). Actually, we are going to adopt Levitronix CentriMag as the ECMO support system. Further analysis of our data, even comparing different ECMO circuits, will be able to help us show our own short-term MCS protocol management.

As limitations, this study is based on our single-center experience, and the included patients of this study are not many. However, outcomes correspond to those published elsewhere, and the statistic analysis still revealed a significant result.

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REFERENCES

1. Bartlett RH, Gazzaniga AB, Jefferies MR, et al. Extracorporeal membrane oxygenation (ECMO) cardiopulmonary support in infants. *ASAIO Trans* 1976;22:80–93.
2. Extracorporeal Life Support Organization. ELSO Registry. Available at: http://www.elso.med.umich.edu/Registry.html. Accessed July 2011.
3. Kolobow T, Bowman RL. Construction and elimination of an alveolar membrane artificial heart-lung. *ASAIO Trans* 1963;9:238.
4. Bramson ML, Osborn JJ, Main FB. A new disposable membrane oxygenation with integral heat exchanger. *J Thorac Cardiovasc Surg* 1965;50:391.
5. Loforte A, Montalto A, Ranocchi F, et al. Levitronix CentriMag third-generation magnetically levitated continuous flow pump as bridge to solution. *ASAIO J* 2011;57:247–53.
6. Nolan JP, Morley PT, Vanden Hoek TL, et al. Therapeutic hypothermia after cardiac arrest: an advisory statement by the advanced life support task force of the International Liaison Committee on Resuscitation. *Circulation* 2003;108:118–21.
7. Zhang R, Kofidis T, Hiroyouki K, et al. Creatine kinase isoenzyme MB relative index as predictor of mortality on extracorporeal membrane oxygenator support for postcardiotomy cardiogenic shock in adult patients. *Eur J Cardiothorac Surg* 2006;30:617–20.
8. Hausmann H, Potapov EV, Koster A, et al. Prognosis after the implantation of an intra-aortic balloon pump in cardiac surgery calculated with a new score. *Circulation* 2002;106(Suppl. 1):I203–6.
9. Pappalardo F, Scandroglio A, Maj G, Zangrillo A, D'Angelo A. Preliminary experience with fondaparinux. Treatment of heparin-induced thrombocytopenia after cardiac surgery. *J Thorac Cardiovasc Surg* 2010;139:790–2.
10. Chen JS, Ko WJ, Yu H, et al. Analysis of the outcome for patients experiencing myocardial infarction and cardiopulmonary resuscitation refractory to conventional therapies necessitating extracorporeal life support rescue. *Crit Care Med* 2006;34:950–7.
11. Doll N, Kiaii B, Borger M, et al. Five-year results of 219 consecutive patients treated with extracorporeal membrane oxygenation for refractory postoperative cardiogenic shock. *Ann Thorac Surg* 2004;77:151–7.
12. Hoefer D, Ruttmann E, Poelzl G, et al. Outcome evaluation of the bridge to bridge concept in patients with cardiogenic shock. *Ann Thorac Surg* 2006;82:28–34.
13. Combes A, Leprince P, Luyt C, et al. Outcomes and long-term quality of life of patients supported by extracorporeal membrane oxygenation for refractory cardiogenic shock. *Crit Care Med* 2008;36:1404–11.
14. Agati S, Ciccarello G, Fachile N, et al. DIDECMO: a new polymethylpentene oxygenator for pediatric extracorporeal membrane oxygenation. *ASAIO J* 2006;52:509–12.
15. Horton S, Thuys C, Bennet M, et al. Experience with the Jostra Rotaflow and Quadrox D oxygenator for ECMO. *Perfusion* 2004;19:17–23.
16. Peek GJ, Killer HM, Reeves R, et al. Early experience with a polymethylpentene oxygenator for adult extracorporeal life support. *ASAIO J* 2002;48:480–2.
17. Toomasian JM, Schreiner RJ, Meyer DE, et al. A polymethylpentene fiber gas exchange for long-term extracorporeal life support. *ASAIO J* 2005;51:390–7.
18. Saito S, Nakatani T, Kobayashi J, et al. Is extracorporeal life support contraindicated in elderly patients? *Ann Thorac Surg* 2007;83:140–5.
19. Smedira N, Moazami N, Golding CM, et al. Clinical experience with 202 adults receiving extracorporeal membrane oxygenation for cardiac failure: survival at five years. *J Thorac Cardiovasc Surg* 2001;122:92–102.
20. Sung K, Lee YT, Park PW, et al. Improved survival after cardiac arrest using emergent autopriming percutaneous cardiopulmonary support. *Ann Thorac Surg* 2006;82:651–6.
21. Zimpefer D, Heinisch B, Czerny M, et al. Late vascular complications after extracorporeal membrane oxygenation support. *Ann Thorac Surg* 2006;81:892–5.
22. Ko W, Lin C, Chen RJ, et al. Extracorporeal membrane oxygenation for adult postcardiotomy cardiogenic shock. *Ann Thorac Surg* 2002;73:538–45.
23. Tayara W, Starlng RC, Yamani MH, et al. Improved survival results after acute myocardial infarction complicated by cardiogenic shock with circulatory support and transplantation: comparing aggressive intervention with conservative treatment. *J Heart Lung Transplant* 2006;25:504–9.
24. Formica F, Leonello A, Colagrande L, et al. Extracorporeal membrane oxygenation to support adult patients with cardiac failure: predictive factors of 30-day mortality. *Interact Cardiovasc Thorac Surg* 2010;10:721–6.
25. Luo XJ, Wang W, Hu SS, et al. Extracorporeal membrane oxygenation for treatment of cardiac failure in adult patients. *Interact Cardiovasc Thorac Surg* 2009;57:612–4.
26. Bakhtiary F, Keller A, Dogan S, et al. Venoarterial extracorporeal membrane oxygenation for treatment of cardiogenic shock: clinical experience in 45 adult patients. *J Thorac Cardiovasc Surg* 2008;135:382–8.
27. Liden H, Wilklund L, Haraldsson A, Berglin E, Hultman J, Dellgren J. Temporary circulatory support with extracorporeal membrane oxygenation in adult with refractory cardiogenic shock. *Scand Cardiovasc J* 2008;16:1–7.
28. Conrad SA, Rycus PT, Dalton H. Extracorporeal life support registry. *ASAIO J* 2005;51:4–10.
29. Magovern GJ, Simpson KA. Extracorporeal membrane oxygenation for adult cardiac support: the Allegheny experience. *Ann Thorac Surg* 1999;68:655–61.
30. Capellan O, Hollander JE, Pollack D Jr, et al. Prospective evaluation of emergency department patients with potential coronary syndromes using initial absolute CK-MB vs. CK-MB relative index. *J Emerg Med* 2003;24:361–7.
31. Arpesella G, Loforte A, Mikus E, Mikus PM. Extracorporeal membrane oxygenation for primary graft failure. *Transplant Proc* 2008;40:3596–7.
32. Ang AL, Teo D, Lim CH, Leou KK, Tien SL, Koh MB. Blood transfusion requirements and independent predictors of increased transfusion requirements among adult patients on extracorporeal membrane oxygenation—a single centre experience. *Vox Sang* 2009;96:34–43.
33. Russo CF, Cannata A, Lanfranconi M, et al. Veno-arterial extracorporeal membrane oxygenation using Levitronix centrifugal pump as bridge to decision for refractory cardiogenic shock. *J Thorac Cardiovasc Surg* 2010;140:1416–21.
34. Aziz TA, Singh G, Popjes E, et al. Initial experience with CentriMag extracorporal membrane oxygenation for support of critically ill patients with refractory cardiogenic shock. *J Heart Lung Transplant* 2010;29:66–71.