Extracorporeal Membrane Oxygenation With a Poly-Methylpentene Oxygenator (Quadrox D). The Experience of a Single Italian Centre in Adult Patients With Refractory Cardiogenic Shock

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Although microporous polypropylene hollow fiber oxygenators are standard devices used for extracorporeal membrane oxygenation (ECMO), they have limitations such as development of plasma leakage. Poly-methylpentene (PMP) is a new material used for the last generation of oxygenators. We reviewed our experience with a new PMP oxygenator (Quadrox D) and a centrifugal pump (RotaFlow) used to support adult patients with refractory cardiogenic shock. Between January 2000 and April 2007, 25 patients required ECMO for primary or postcardiotomy cardiogenic shock. Eighteen patients were analyzed [mean age 60.2 years; 11 (61%) men; 7 (39%) women]. Nine patients (50%) suffered primary cardiogenic shock. Cardiopulmonary resuscitation was applied in 11 patients (61%) with a mean duration time of 31.5 minutes. Mean ECMO duration time was 7.1 ± 6.3 days (range, 1–27 days). Intra-aortic balloon pump was used in 13 patients (72.2%) with a mean duration time of 7.7 ± 5 (range, 2–17 days). Twelve patients (66.7%) survived on ECMO and five patients (27.8%) were discharged. Our results indicate the PMP oxygenator and the centrifugal pump provided acceptable results in terms of surviving on ECMO and discharge. Patients with an initial catastrophic hemodynamic status could benefit by means of a rapid institution of ECMO with PMP oxygenators. *ASAIO Journal* 2008; 54: 89–94.

Extracorporeal life support (ECLS) using extracorporeal membrane oxygenation (ECMO) was introduced into clinical practice during the early 70s[1] and has become accepted worldwide. It is considered one of the fastest and cheapest methods for biventricular and respiratory support in adult and pediatric populations. Membrane oxygenators are one of the main elements of the ECMO system and outcomes depend on them. Kolobow and Bowman[2] and Bramson *et al.*[3] introduced the silicone oxygenators that were used until the diffusion of microporous hollow fibers oxygenators in the 90s. Recently, a new generation of poly-methylpentene (PMP) membrane oxygenators have been introduced with the aim of allowing longer support without the complications linked to the hollow-fiber oxygenators, such as plasma leakage.

This retrospective study aims to report our experience in using an ECMO circuit consisting of a PMP membrane oxygenator and a magnetic centrifugal pump in the treatment of adult patients with primary or postcardiotomy refractory cardiogenic shock.

Materials and Methods

Extracorporeal Membrane Oxygenation System

The ECMO circuit consisted of a PMP oxygenator, Quadrox D (Maquet, Jostra Medizintechnik AG, Hirrlingen, Germany) and a centrifugal pump, Rotaflow (Maquet, Jostra Medizintechnik AG, Hirrlingen, Germany). Peripheral veno-arterial cannulation was adopted in 13 patients: the arterial return cannula, DLP Biomedicus 17 Fr. (Medtronic Inc, Minneapolis, MN), was inserted percutaneously into the femoral artery and a venous drainage cannula, DLP Biomedicus 19 Fr.–23 Fr. (Medtronic Inc, Minneapolis, MN) was inserted percutaneously into the femoral vein (**Figure 1**). In one patient, a 19 size venous cannula was inserted into the right jugular vein (**Figure 2**) because of stenosed inferior vena cava. The rest of the patients received a central cannulation through ascending aorta, DLP 20–22 Fr and right atrium, single cannula 51 Fr, DLP (Medtronic Inc, Minneapolis, MN).

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 ml/min 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.

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Figure 1. Peripheral percutaneous cannulation through right femoral vessels.

Figure 3. Extracorporeal membrane oxygenation circuit components with Bioline treatment (Quadrox D poly-methylpentene oxygenators and centrifugal RotaFlow pump).

The RotaFlow pump can provide high blood flow until 10 L/min. Tubing, pump, and oxygenator are all coated with Bioline Coating (Maquet, Jostra Medizintechnik AG, Hirrlingen, Germany) (**Figure 3**). 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. Thus, this coating provides high hemocompatibility of the whole surface of the system minimizing the activation of platelets, coagulation cascade, and complements. In this way, clot formation and inflammatory syndrome are dramatically reduced.

The circuit was primed with Ringer's lactate, and no heparin was added to the prime volume. Priming of the circuit usually needed 4–5 minutes 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.

A new circuit named Permanent Life Support—PLS (Maquet, Jostra Medizintechnik AG, Hirrlingen, Germany) was used in the last two patients. In the PLS, the Quadrox D oxygenator has the housing reinforced with glass fibers to increase the mechanical resistance and the polyvinyl chloride (PVC) 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 European Union, in accordance with the Directive 93/42/European Community).

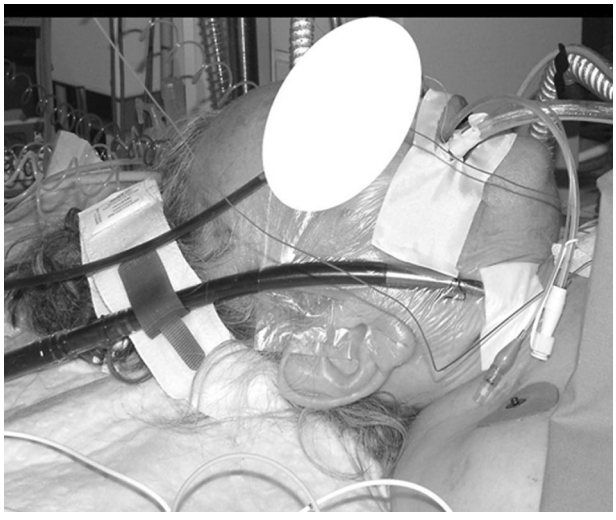

Figure 2. Right internal jugular vein percutaneous cannulation.

Patients

The ECMO program was started at our institution in January 2000. Since then and until April 2007, 2,823 adult patients underwent cardiac operations. Of these, 1,834 (65%) underwent isolated coronary artery bypass graft. During the same period, 25 patients (0.85%) required ECMO for primary or postcardiotomy cardiogenic shock. Of these, seven patients did not have indications for ECMO: three type A acute aortic dissections; one aortic rupture occurring 40 days after an aortic valve replacement operation; and three received ECMO support after 18 hours of the onset of primary cardiogenic shock. In these patients, ECMO was not useful because of catastrophic hemodynamics and poor indications for ECMO support. For these reasons, in this small group of patients, it was not possible to verify the utility of ECMO support; hence, these seven patients were excluded from the analysis.

Inclusion criteria for ECMO support to treat primary refractory cardiogenic shock at our institution are the following: age <75 years; acute myocardial infarction and its mechanical complications; pulmonary embolism; accidental hypothermia; decompression of end-stage dilated cardiomyopathy; myocarditis; high-risk percutaneous transluminal coronary angioplasty; support for high-risk resternotomy. Patients were excluded according to the following criteria: age >75 years; cardiac arrest during or after coronary angiogram without graftable coronary arteries and without indication to heart transplant; moderate to severe aortic regurgitation; severe peripheral arteriopathy; severe and chronic renal failure; terminal malignancy; irreversible or severe degenerative brain diseases; trauma; aortic dissection.

Extracorporeal membrane oxygenation support was installed in the emergency department, intensive care unit, hemodynamic laboratory, and operating room.

Extracorporeal Membrane Oxygenation Management

The ECMO blood flow was adequately adjusted during the first 24–48 hours to maintain cardiac index of 2.6 L/min/m^2, mixed venous oxygen saturation (SvO_2) around 70%, and mean arterial pressure (MAP) of 60–70 mm Hg. Continuous intravenous heparin was administered to achieve an activated clotting time (ACT) of 140–160 seconds and a prothrombin time value of 50–60. 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. All ECMO support was conducted under normothermia. Those patients who had cardiac arrest before starting ECMO were progressively cooled at 32°C–34°C for 24–36 hours.[4] Closed heart examinations by transesophageal echo were done to assess the left ventricle motion at least one time daily. In patients with peripheral cannulation, CW-doppler of the tibial artery was done every day to assess the leg perfusion. In two patients, a distal perfusion through an 8 Fr catheter was obtained until peripheral arterial cannula was removed. All patients needed blood transfusions to achieve a hematocrit of 30%–35%, 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, 4 breaths/min, positive end expiratory pressure of 10 cm H_2O, and an FiO_2 of 0.40–0.60. Intra-aortic balloon (IABP) was employed in 13 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 48 hours. Criteria for weaning include SvO_2 equal to or more than 70%, hematocrit of 30%–35%, 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, normal urine output. Step-by-step weaning is our main strategy with close transesophageal echo examinations.

Table 1. Pre-ECMO Patients characteristics (n = 18)

Variables	Data
Age	60.2 ± 11.4 (41–76)
Male/Female	11/7 (61%–39%)
BSA	1.7 ± 0.3
Hypertension	12 (66.7%)
Diabetes	2 (11.2%)
Creatinine >2 mg/100 ml	3 (16.7%)
Hyperlipidemia	6 (33.3%)
COPD	4 (22.2%)
Left main disease >70%	7 (39%)
No. diseased coronaries	2.8 ± 0.5 (1–3)
Preoperative EF (%)	43 ± 16.2 (15–73)
EUROSCORE	10.2 ± 4.3 (1–19)
Previous cardiac operation	1 (5.5%)
Primary cardiogenic shock	9 (50%)
CPR	11 (61%)
CPR time (min)	31.5 ± 14 (12–63)
ECMO on CPR	10 (55.6%)

IABP, intra-aortic balloon pump; BSA, body surface area; COPD, chronic obstructive pulmonary disease.

This consists of reducing the pump flow at 0.5 L/min/m^2 for approximately 40–60 minutes. For patients who were supported with IABP, this device was set at 1:1. If the hemodynamics remained stable without increasing or adding doses of inotropes, heparin was stopped and ECMO was removed at bedside or in the operating room within the next 1 hour. After ECMO removal, no patient needed subsequent ECMO support.

Statistic Analysis

Descriptive statistics are expressed as mean ± standard deviation. A p value ≤0.05 was considered to have a statistical significance. Categorical variables are presented as percentages. Analysis of variance for repeated-measures was employed for numerical variables measured during the time as platelet counts, blood lactate levels, creatine kinase isoenzyme MB (CK-MB) values, and CK-MB relative index. Continuous variables were evaluated by Student t test for independent variables. All statistic analysis was performed with the Statistical Package for Social Science (SPSS, version 14.0 for Windows; SPSS Inc., Chicago, IL).

Results

Mean age was 60.2 ± 11.4 years (range, 41–76 years) and 11 patients (61.1%) were men. Five patients (27.8%) were weaned off ECMO and survived to hospital discharge. Twelve

Table 2. Postoperative Variables and Postoperative Complications (n = 18)

Variables	Data
CPB time (min)	202 ± 95 (48–368)
Aortic cross clamp time (min)	117 ± 49 (65–199)
Anasthomosis	2.9 ± 0.8 (1–4)
IABP on ECMO	13 (72.2%)
IABP time (d)	7.7 ± 5 (2–17)
ECMO time (d)	7.1 ± 6.3 (1–27)
ECMO >4 d	14 (77.7%)
Intubation time (d)	12 ± 8.5 (2–32)
Hospital stay (d)	23.4 ± 23.8 (2–95)
Creatinine >3.5 mg/100 ml	5 (27.8%)
CVVH	10 (55.6%)
CVVH time (d)	7 ± 6.9 (2–25)
Bleeding/tamponade	11 (61.1%)
Transfusion	18 (100%)
Red blood cells	18.7 ± 13 (3–50)
Platelets	16.5 ± 12 (5–48)
FFP	5 ± 4.5 (1–14)
Pulmonary complications	5 (27.8%)
Liver failure	8 (44.4%)
Bilirubin >15 mg/100 ml	6 (33.3%)
MOF	6 (33.3%)
Survived on ECMO	12 (66.7%)
Died on ECMO	6 (33.3%)
Discharged	5 (27.8%)
Postoperative variables in all patients	(n = 25)
ECMO time (d)	6.5 ± 6.2 (0–27)
IABP on ECMO	13 (52%)
IABP time (d)	7.6 ± 3.3 (2–17)
ECMO <24 h	7 (28%)
Survived on ECMO	14 (56%)
Died on ECMO	11 (44%)
Discharged	5 (20%)

FFP, fresh frozen plasma; MOF, multi-organ failure.

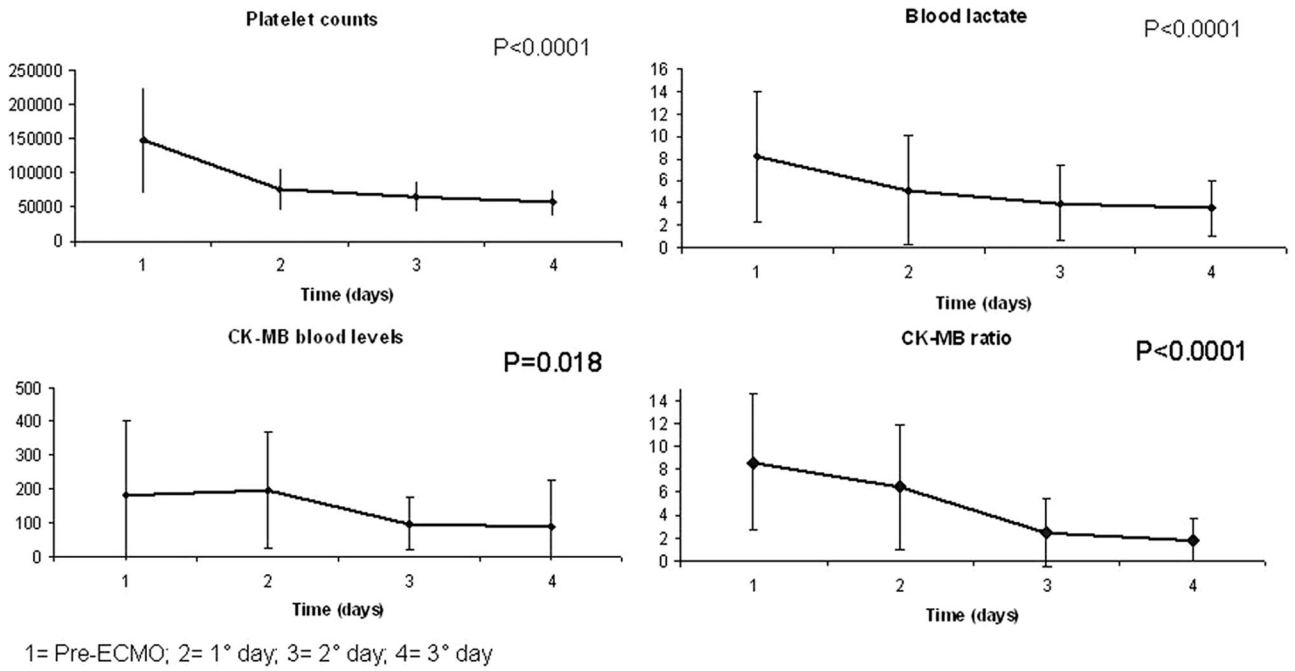

Figure 4. Time coursing of platelet counts, blood lactate levels, blood creatine kinase isoenzyme MB (CK-MB) level, and CK/CK-MB ratio.

patients (66.7%) were weaned off ECMO and six patients (33.3%) died during the support. Among the patients who were weaned off ECMO, five patients (27.8%) were discharged and the remaining seven patients died: multiorgan failure (MOF) n = 6, peritonitis n = 1, liver failure n = 2, brain death n = 2, uncontrolled bleeding n = 1, and asystole n = 1. Seven patients (38.9%) required ECMO to treat primary cardiogenic shock. Two of them had a myocardial infarction complicated by a rupture of free left ventricular wall, five had a large anterior myocardial infarction. In these seven patients, ECMO was installed in emergency room. Eleven patients received ECMO during cardiopulmonary resuscitation (CPR) with a mean time CPR of 31.5 ± 14 minutes (range, 12–63 minutes). Preoperative risk profile and perioperative parameters are listed on **Tables 1** and **2**. Mean ECMO support time was 7 ± 6.1 days (range, 1–27 days). Intra-aortic balloon was inserted in 13 patients (72.2%) with a mean support time of 7.7 ± 5 days (range, 2–17 days).

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. Only one patient required the replacement of ECMO circuit because of persistent sepsis despite aggressive antibiotic therapy after 15 days. In this case, the ECMO components were free from clots and fibrin deposits, and the oxygenator had acceptable gas exchange performance and low pressure drop. The ECMO support was continued for 12 more days, but the patient died because of MOF.

In all patients, blood lactate, CK-MB, and CK-MB relative index as the ratio of CK-MB to total CK[5] were measured at four steps: preECMO, on 1st day, 2nd day, and 3rd day. All parameters evaluated had a significant reduction during that period of time. Platelet counts were measured at the same time points, and a dramatic reduction was observed (**Figure 4**). All patients were transfused. The patients who received a central cannulation had a higher number of red blood cell transfusions (p = 0.04) and a higher number of platelet transfusions (p = 0.03) (**Table 3**). The patients who survived on ECMO needed fewer red blood cell transfusions than patients who died during mechanical support (p = 0.01) (**Table 4**).

Discussion

Acute myocardial infarction is complicated in 7%–10% of patients by cardiogenic shock that has a mortality around 80%[6]; the incidence of postcardiotomy cardiogenic shock is reported between 0.5% and 3% with a very high mortality,

Table 3. Blood Component Transfusions Between Patients With Peripheral Cannulation and Central Cannulation

	Peripheral (n = 12)	Central (n = 6)	*p*
Red blood cells	6.5 ± 12	23 ± 13	0.04
Platelets	14.8 ± 7.8	26.5 ± 30	0.08
FFP	4.5 ± 3.8	8 ± 8.4	0.03

FFP, fresh frozen plasma.

Table 4. Blood Component Transfusions Between Patients Survived on ECMO and Patients Died on ECMO

	Survived (n = 13)	Died (n = 5)	*p*
Red blood cells	9,4 ± 5.5	22.6 ± 13.4	0.01
Platelets	10.2 ± 5.2	20 ± 13.3	0.7
FFP	3 ± 2.5	6.5 ± 5.2	0.1

FFP, fresh frozen plasma.

ranging between 80% and 90%.[7] Extracorporeal membrane oxygenation support has many advantages: it is easily implantable both through femoral vessels or *via* ascending aorta and right atrium; it can be easily installed outside the operating room; generally the implantable procedure is fast; it can be used also in cardiac centers that do not have a transplant heart or ventricular assist device (VAD) program; it is cheaper than other more complex mechanical supports. For these reasons, the indications to use ECMO in adult cardiac patients are widely increasing. As recently reported by Extracorporeal Life Support Organization (ELSO) registry data,[8] the use of ECMO support is progressively growing with an overall survival on ECMO support in patients with shock of 31%.

Since the introduction of the silicone membrane oxygenator in the late 1960s, industry has directed serious efforts toward developing an ideal oxygenator that can replace the human lung with very high efficacy without increasing the inflammatory response. Indeed, the silicone membrane has shown good performance because of its high biocompatible characteristics. The silicone surface is homogeneous and does not contain micropores which can cause plasma leakage. However, the silicone oxygenator has a very large membrane surface to ensure adequate gas exchange and needs both high prime volume and high pressure drop; moreover, the procedure to optimize the efficacy of the oxygenator is cumbersome and lengthy, requiring a CO_2 gas flush. In the early 1990s, a new membrane concept was considered: the hollow-fiber polypropylene membrane. These oxygenators had advantages over the silicone oxygenators, such as high gas exchange efficiency with a smaller change surface, lower prime volume, and lower pressure gradient. However, this generation of oxygenators has micropores causing plasma leakage for periods more than 6 hours, thus reducing the gas exchange. Recently, a new concept has been introduced: to create an oxygenator with the same property as silicone in terms of diffusion membrane without the presence of micropores and the same property as polypropylene in terms of low pressure for gas exchange. The new material is poly-methyl-pentene (PMP) (**Figure 5**) which represents the key of the last generation of oxygenators. Very few studies have reported the outcome of ECMO with the PMP oxygenator and most described the use of the PMP in pediatric populations[9,10] or in patients with respiratory failure.[11] Moreover, there are no randomized studies which compare different oxygenators for ECMO support. Toomasian *et al.*,[12] conducted an animal study where silicone and PMP oxygenators were compared. In this study, 10 sheep were divided into two groups and assisted on ECMO for 72 hours. The authors reported a better gas exchange, minor platelet consumption, and less pressure drop in the PMP oxygenator, whereas the change in hemoglobin, leukocyte count, and pathological findings were not significant. Plasma leakage was not observed in either oxygenator. They concluded that the PMP oxygenator was an optimal device for long-term ECMO support. To the best of our knowledge, our study represents the first report regarding the use of a PMP oxygenator (Quadrox D) in association with a centrifugal pump (RotaFlow) for the treatment of cardiogenic shock in cardiac adult patients. Several studies[6,7,13–19] reported the use of ECMO with the combination of a hollow-fiber microporous oxygenator and a centrifugal pump. Changing of both oxygenator and centrifugal pump are described. In 2004, the ELSO registry[8] 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 only in one patient because of aggressive sepsis. The components of the ECMO circuit received a careful macroscopic examination, and no clots or other deposits were identified.

A number of studies reported the mean time of ECMO duration ranging between 1.7 days and 4.1 days.[13–23] In our experience, the mean time of ECMO duration was 7.1 ± 6.3 days which is quite higher than the values reported in the literature. We can explain this with the fact that there was no concern about the optimal performance of the Quadrox D oxygenator and the RotaFlow, so that 14 patients were supported for more than 4 days.

Bleeding remains a serious problem in patients supported with ECMO. Several studies have reported high percentages of transfusions with red blood cell units, platelets, and fresh frozen plasma. Magovern and Simpson[20] described their experience with ECMO using a microporous oxygenator and observed that patients who survived ECMO received slightly fewer units of all blood components compared with nonsurviving patients. Ko *et al.*,[18] in a group of 53 patients supported with ECMO using a microporous oxygenator, described a 100% rate of transfusion without any differences among the patients who died on ECMO or survived. Recently, Horton *et al.*,[10] observed a reduction of transfusions (19 patients out of 23) in a pediatric population using the ECMO Quadrox D/RotaFlow system. Agati *et al.*[9] adopted an ECMO circuit with a PMP oxygenator in a small group of eight pediatric patients, and they observed that five patients did not require platelet replacement therapy. In our experience, we have observed a slight reduction of blood component transfusions in patients who received a peripheral cannulation compared with patients with central cannulation and a significant reduction of red blood units transfusion ($p = 0.01$) in patients who survived on ECMO compared with patients who died on ECMO. These data could be interpreted as one of the advantages of PMP oxygenators compared with microporous devices, but at the moment, there are not enough data that could definitively confirm this hypothesis.

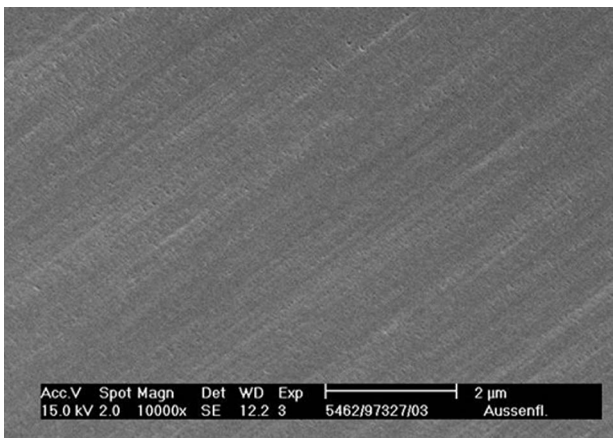

Figure 5. Electonic microscopic image of poly-methylpentene membrane.

We reported an overall mortality of 28.7% and a surviving rate on ECMO of 66.7%, which are similar to other reports,[13–23] but with a longer mean time of ECMO duration. This could have different interpretations. On the one hand, if the patient could not be weaned off ECMO within 3–4 days, then heart transplantation or a VAD is required. On the other hand, the possibility of leaving the patient on ECMO for more than 4 days, before attempting weaning off support, has to be seriously considered, particularly with the PMP membrane oxygenators, in which plasma leakage has not been documented. 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 (6.6 ± 3.9 days *vs.* 7.6 ± 9.6 days respectively, $p = 0.7$).

Regarding the ECMO outcome, the ELSO registry data of 2006 reported an ECMO survival of 61% and a survival of 33% for patients above 16 years who had cardiac arrest in European centers. The international 2006 ELSO data showed an ECMO survival of 45% and a survival of 22% for adult patients with cardiac arrest and a survival of 45% for cardiogenic shock. Other authors[13–23] reported a survival to discharge ranging between 24% and 41% and percentages of weaning off ECMO between 46% and 64%. Comparing our ECMO survival data at discharge with all data mentioned before, we can say that the ECMO system with PMP oxygenator Quadrox D/RotaFlow is an optimal alternative to other microporous oxygenators and has to be seriously considered when a perfusion longer than 4 days is forecast.

Conclusion

Extracorporeal membrane oxygenation support is now considered a valid rescue tool in patients with refractory cardiogenic shock, although the mortality is still high. Research in developing new materials could help worldwide ECMO teams to increase the survival and reduce the incidence of ECMO complications and oxygenator failure. In our experience, the Quadrox D oxygenator has demonstrated an optimal performance without occurrence of plasma leakage and necessity of replacement mainly for ECMO longer than 4 days in adult patients with cardiogenic shock. Further studies are mandatory to confirm the possibility of using this device for more days or even 2 weeks. Bleeding and transfusions remain a problem to be solved.

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