ELSEVIER

The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

Extracorporeal membrane oxygenation with multiple-organ failure: Can molecular adsorbent recirculating system therapy improve survival?

Bailey E. Sparks, BSN, Nicholas C. Cavarocchi, MD, and Hitoshi Hirose, MD

From the Division of Cardiothoracic Surgery, Department of Surgery, Thomas Jefferson University, Philadelphia, Pennsylvania.

KEYWORDS:
ECMO;
multi-organ failure;
liver failure;
MARS

BACKGROUND: Liver dialysis, molecular adsorbent recirculating system (MARS) particularly, has been used in liver failure to bridge to transplantation. We expanded the indication for MARS to patients with acute shock liver failure and cardiopulmonary failure on extracorporeal membrane oxygenation (ECMO), aiming to improve survival to wean from ECMO.

METHODS: Retrospective chart analysis of patients on ECMO between 2010 and 2015 found 28 patients who met the criteria for acute liver failure, diagnosed by hyperbilirubinemia (total bilirubin $\geq$10 mg/dl) or by elevated transaminase (alanine transaminase $>$1,000 IU/liter). Of these patients, 14 underwent MARS treatment (Group M), and 14 were supported with optimal medical treatment without MARS (Group C). Patient characteristics, liver function, and survival were compared between groups.

RESULTS: Demographics, clinical risk factors, and pre-ECMO laboratory data were identical between the groups. MARS was used continuously for 8 days $\pm$ 9 in Group M. Total bilirubin, alanine transaminase, and international normalized ratio were improved significantly in Group M. There were no MARS-related complications. Survival to wean from ECMO for Group M was 64% (9/14) vs 21% (3/14) for Group C ($p = 0.02$). Mortality related to worsening liver dysfunction during ECMO was 40% (2/5 deaths) in Group M and 100% (11/11 deaths) in Group C ($p = 0.004$). The 30-day survival after ECMO was 43% (6/14) in Group M and 14% (2/14) in Group C ($p = 0.09$).

CONCLUSIONS: MARS therapy in patients on ECMO safely accelerated recovery of liver function and improved survival to wean from ECMO, without increasing complications.

J Heart Lung Transplant 2017;36:71–76

In cases of acute-on-chronic liver failure, liver dialysis, specifically the molecular adsorbent recirculating system (MARS), has been used to bridge patients to liver transplantation and is known to improve outcomes of liver transplantation.[1,2] MARS therapy consists of filtering blood through a specialized albumin-containing dialysate to remove protein-bound toxins. Blood is filtered in-line through a charcoal column and an anion exchanger column before return. This system allows for the removal of molecules such as bile acids, bilirubin, and cytokines and water-soluble toxins such as creatinine and ammonia.[3] By removing both protein-bound and water-soluble toxins, MARS facilitates liver recovery and may prevent further deterioration of other organ systems.[4]

Overall mortality from extracorporeal membrane oxygenation (ECMO) is reported to be 47%–61%,[5] and a primary cause of death in patients on ECMO is refractory multiple-organ failure including acute liver failure (ALF). ALF occurs in approximately 13%–19% of patients on

Reprint requests: Hitoshi Hirose, MD, Department of Surgery, Thomas Jefferson University, 607 College Building, 1025 Walnut Street, Philadelphia, PA 19107. Telephone: 215-955-6925. Fax: 215-925-6010.

E-mail address: Hitoshi.Hirose@jefferson.edu

1053-2498/$ - see front matter
http://dx.doi.org/10.1016/j.healun.2016.09.014

ECMO.[6] In our institution, we expanded the indication for MARS to another patient population—patients with cardiopulmonary failure requiring ECMO who have developed ALF. This retrospective study was performed to evaluate whether MARS can improve ALF safely in patients on ECMO and to evaluate the survival of the patients on ECMO with or without MARS treatments.

Methods

After obtaining approval from the institutional review board, medical records of consecutive patients on ECMO between August 2010 and March 2015 were retrospectively reviewed to identify the incidence of liver dysfunction while on ECMO. The only exclusion criterion was any patient on ECMO in whom treatment was deemed futile within the first 24 hours of cannulation. Venoarterial ECMO was primarily used for refractory cardiac failure,[7] and venovenous ECMO was primarily used for refractory respiratory failure,[8] detailed in previous publications.

Among the 133 patients on ECMO during the study period, 28 patients (21%) were found to have ALF, defined as total bilirubin $\geq$10 mg/dl or alanine aminotransferase (ALT) $\geq$1,000 IU/liter (Table 1). Patients were included if they met the criteria for liver failure despite correction of an underlying process, such as hemolysis or obstructive cholangitis. The rounding attending physician made the decision for the initiation of MARS. Of the 28 patients included in the study, 14 patients (Group M) underwent liver dialysis using MARS (Gambro BCT, Inc, Lakewood, CO), and 14 patients (Group C) were supported with optimal medical therapies. Medical therapies for Group C and Group M included maintenance of appropriate ECMO flow (body surface area $\times$ $\geq$2.2 liter/min); lactulose treatment; nutrition support (via either enteral tube feeding or total parenteral nutrition); and avoidance of hepatotoxic medications, including statins and amiodarone. In Group M, MARS was run with blood flow rates of 100–150 ml/min using a standard dual-lumen dialysis catheter placed in the femoral vein, using a 25% albumin dialysate. Treatment was continued until recovery of liver function (specifically, total bilirubin returned to $\leq$7 mg/dl and/or ALT returned to $\leq$500 IU/liter) or the time of ECMO removal. No patient was placed on MARS with the intention to bridge to liver transplantation. The MARS circuit was maintained continuously except for circuit changes needed every 24 hours. Anti-coagulation was maintained for a partial thromboplastin time of 45–55 seconds for ECMO regardless of the presence of MARS.

Primary study end-points were survival to wean from ECMO and 30-day survival after ECMO decannulation. A secondary end-point was the trend of liver function (total bilirubin, ALT, and international normalized ratio [INR]) during treatments. In addition, bleeding complications and disseminated intravascular coagulopathy (DIC) were monitored during ECMO.

Data were expressed as number with percent and mean $\pm$ SD. Statistical analysis consisted of 2 group comparisons between Group M and Group C using Student's *t*-tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. A p-value < 0.05 was considered to be significant.

Results

There were 14 patients in Group M and 14 patients in Group C. Baseline characteristics, pre-ECMO clinical risk factors, and laboratory data were compared and were similar between the 2 groups (Table 2). Group C and Group M both include patients from overlapping time frames—Group C was not from an era before availability of MARS therapy.

The laboratory values for the patients at the time criteria of ALF were met are shown in Table 3. MARS therapy was initiated at a mean 5 $\pm$ 4 days after ECMO was started in Group M. The length of ECMO before the patients in Group C met the criteria for ALF was 7 days $\pm$ 6. The average length of MARS on ECMO was 8 days $\pm$ 9 (range, 1–32 days). After 3 days, total bilirubin average for Group M ($n = 12$) had decreased by 5.1 mg/dl $\pm$ 12, and for Group C ($n = 9$), average total bilirubin had increased 2.6 mg/dl $\pm$ 9 ($p = 0.11$). By Day 7, average total bilirubin for Group M ($n = 11$) had decreased by 7.9 mg/dl $\pm$ 15, while in the same time period, the average bilirubin for Group C had increased by 7.5 mg/dl $\pm$ 6 ($p = 0.01$). By Day 3, ALT in Group M had decreased by 1,310 IU/liter $\pm$ 1,851, and in Group C, the ALT had increased by 320 IU/liter $\pm$ 733 ($p = 0.01$). Similarly, by Day 3, INR for Group M had decreased by 0.32 $\pm$ 0.5, whereas for Group C, the INR had decreased only by 0.05 $\pm$ 0.4 ($p = 0.19$). These trends are shown in Figure 1. The trends continued for the duration of ECMO, as shown in Figure 2.

Bleeding complications on ECMO, defined as bleeding that required invasive intervention, were 79% ($n = 11$) in both groups. The most common etiologies were gastrointestinal bleeding, epistaxis, and cannula site bleeding; this breakdown was consistent across both groups. Incidence of DIC was 14% ($n = 2$) for Group M vs 21% ($n = 3$) for Group C ($p = 0.62$). The causes of DIC were multifactorial and did not appear to be related to MARS treatment. There was no MARS-related sepsis. There were no mechanical ECMO complications, such as flow competition, during MARS.

Survival to wean from ECMO was 64% (9/14) in Group M and 21% (3/14) in Group C ($p = 0.02$) (Figure 3). Mortality related to worsening liver dysfunction was 40% (2/5 deaths) in Group M and 100% (11/11 deaths) in Group C ($p = 0.004$). Of the patients who survived to wean off of ECMO, only 2 patients (22%) in Group M continued MARS treatment, and in both of these patients, liver function was

Table 1 Inclusion Criteria for MARS With ECMO

	Group M ($n = 14$)	Group C ($n = 14$)	p-value
Hyperbilirubinemia (>10 mg/dl)	11	14	0.0668
Increased ALT (>1,000 IU/liter)	3	0	0.0668
Hyperbilirubinemia (>10 mg/dl) and increased ALT (>1,000 IU/liter)	4	2	0.3570

ALT, alanine aminotransferase; ECMO, extracorporeal membrane oxygenation; MARS, molecular adsorbent recirculating system.
Data expressed as number.

Table 2 Baseline Demographics and Indications for ECMO

	Group M ($n = 14$)	Group C ($n = 14$)	p-value
Age, years	44 ± 16	54 ± 13	0.0811
Male	5 (36%)	9 (64%)	0.1306
Body mass index, kg/m^2	27 ± 6	28 ± 5	0.6359
Weight, kg	76 ± 26	78 ± 21	0.8246
Clinical risk factors			
Smoker	5 (36%)	3 (21%)	0.4028
E-CPR	3 (21%)	2 (14%)	0.6217
Diabetes mellitus	4 (29%)	4 (29%)	1.0000
Coronary artery disease	4 (29%)	8 (57%)	0.1266
Acute myocardial infarction	3 (21%)	1 (7%)	0.2801
Primary respiratory failure	3 (21%)	4 (29%)	0.6625
Primary diagnosis for ECMO			
Acute on chronic heart failure	4 (29%)	3 (21%)	0.6625
Malignant arrhythmia	2 (14%)	0 (0%)	0.1422
Takotsubo cardiomyopathy	0 (0%)	2 (14%)	0.1422
Bacterial pneumonia	0 (0%)	1 (7%)	0.3085
Interstitial pneumonitis	1 (7%)	0 (0%)	0.3085
Aspiration pneumonia	0 (0%)	2 (14%)	0.1422
Viral pneumonia	0 (0%)	1 (7%)	0.3085
Post-cardiotomy failure	5 (35%)	4 (29%)	0.6857
Acute myocardial infarction	2 (14%)	1 (7%)	0.5412
Pre-ECMO laboratory data			
Creatinine, mg/dl	1.7 ± 1	1.8 ± 0.99	0.7522
Total bilirubin, mg/dl	2.9 ± 3.1	3.3 ± 3.2	0.7611
AST, IU/liter	3,198 ± 9,997	784 ± 1,610	0.3984
ALT, IU/liter	770 ± 1,884	351 ± 751	0.4642
ALP, IU/liter	139 ± 100	107 ± 78	0.3704
Lactate, mg/dl	7.4 ± 7.5	6.6 ± 5.2	0.7521
INR	1.99 ± 1.10	1.98 ± 0.89	0.9589
ECMO data			
Venoarterial ECMO	11 (79%)	11 (79%)	1.0000
Venovenous ECMO	3 (21%)	3 (21%)	1.0000
Length of ECMO, days	17 ± 9	12 ± 10	0.1761
ECMO complications			
Bleeding	10 (71%)	11 (79%)	0.6625
DIC	2 (14%)	3 (21%)	0.6217

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DIC, disseminated intravascular coagulopathy; E-CPR, extracorporeal membrane oxygenation–assisted cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; INR, international normalized ratio. Data are expressed as mean ± SD or as number (percentage).

Table 3 Laboratory Data at Inclusion

	Group M ($n = 14$)	Group C ($n = 14$)	p-value
Duration of ECMO before MARS in group M and before met criteria of ALF in group C, days	5 ± 4	7 ± 6	0.31
On CVVHD before MARS	6 (43%)	9 (64%)	0.2556
Creatinine, mg/dl	1.3 ± 0.5	1.3 ± 0.7	1.0000
Bilirubin, mg/dl	10.5 ± 3.3	11.8 ± 1.9	0.2128
AST, IU/liter	9,412 ± 13,430	492 ± 698	0.0199
ALT, IU/liter	2,271 ± 2,577	193 ± 210	0.0058
ALP, IU/liter	162 ± 83	113 ± 47	0.0656
Lactate, mg/dl	8.2 ± 8.0	6.8 ± 7.5	0.6369
INR	1.86 ± 0.57	1.52 ± 0.43	0.0865
MELD score	29 ± 6	30 ± 5	0.6359

ALF, acute liver failure; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CVVHD, continuous venovenous hemodialysis; ECMO, extracorporeal membrane oxygenation; INR, international normalized ratio; MARS, molecular adsorbent recirculating system; MELD, Model for End-Stage Liver Disease.
Data expressed as mean ± standard deviation or as number (percentage).

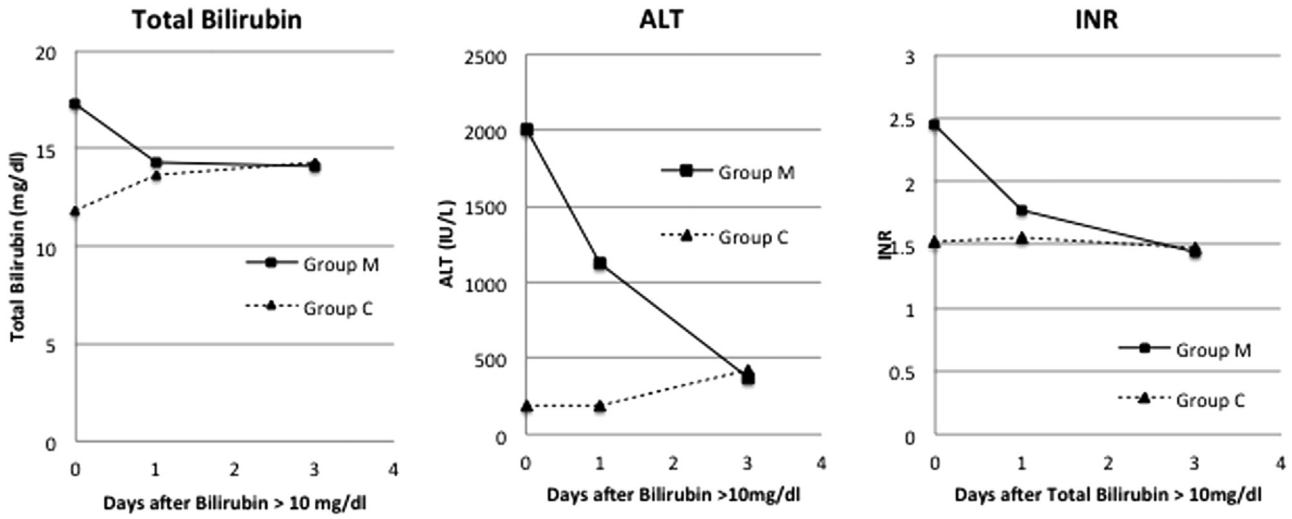

Figure 1 (Left) Trends of total bilirubin. (Middle) Trends of ALT. (Right) Trends of INR.

eventually normalized. In Group M, 5 patients (56%) weaned to a permanent mechanical circulatory support device vs only 1 patient (33%) in Group C ($p = 0.06$). The 30-day survival after ECMO decannulation was 43% (6/14) in Group M and 14% (2/14) in Group C ($p = 0.09$) (Figure 3). The patients in Group M who survived to wean off of ECMO all recovered liver function; therefore, liver failure was not a contributing factor to their deaths.

Discussion

The research on MARS for patients with cardiopulmonary failure requiring ECMO is very sparse. Zitterman et al[9] used MARS for liver failure resulting from cardiogenic shock after cardiac surgery. The study involved 197 post-operative patients with bilirubin >6 mg/dl, of which 20 (10%) required ECMO. The authors reported many complications (e.g., gastrointestinal, respiratory, infectious) and had an in-hospital mortality rate of 66% ($n = 129$) after MARS initiation. Total bilirubin did not decrease in their cohort overall, although the survivors showed a significant decrease compared with non-survivors. Based on scores on Acute Physiology and Chronic Health Evaluation II, Sequential Organ Failure Assessment, and Simplified Physiology Score II, Zitterman et al[9] determined a predicted mortality of 100%, which improved to 34% ($n = 68$) with MARS use. Survival within the ECMO population specifically was not discussed. In the only study specifically involving patients on ECMO, Peek et al[10] reviewed their series of ECMO before the use of MARS and found that no patients on ECMO at their institution survived when severe liver dysfunction (total bilirubin >23 mg/dl) developed, and only 10% survived if bilirubin was >17 mg/dl. With these prior survival data, Peek et al[10] changed their indication to initiate MARS to include patients with bilirubin >17 mg/dl. Using MARS with this indication, 2 of 5 (40%) patients survived compared with a prediction of 100% mortality.

While we were able to show that survival was improved in Group M vs Group C, it is equally important to note that complications from using the treatment did not arise. In the 2 cases of DIC within the treatment group, the causes were multi-factorial and did not appear to be related to MARS. One of the patients had an acetaminophen overdose and was never stabilized after cardiac arrest and ECMO, whereas in the other patient, DIC was due to possible hemolysis after a prolonged course on ECMO requiring 3 different mechanical circulatory support devices. Complications occurring in the intensive care unit course for both groups were similar; specifically, the incidence of DIC was similar, with no indication that MARS was the cause of any case of DIC.

In another study, Rittler et al[11] reviewed 5 patients after undergoing a Whipple operation or liver transplantation complicated with liver failure and gram-negative sepsis and/

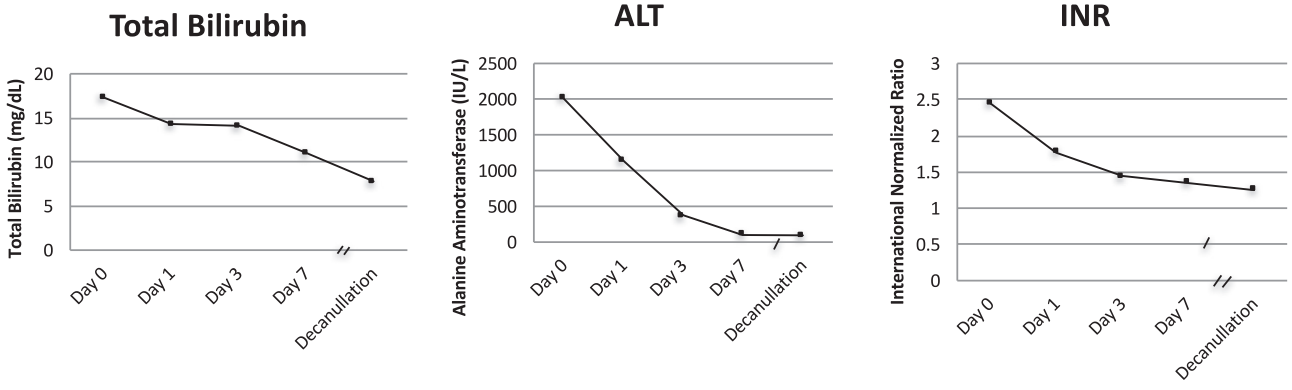

Figure 2 (Left) Trends of total bilirubin in Group M. (Middle) Trends of ALT in Group M. (Right) Trends of INR in Group M.

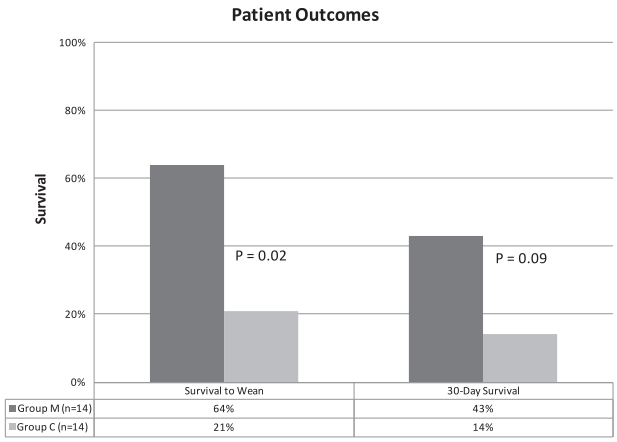

Figure 3 Survival data.

or fungemia. Despite the use of MARS, no patients survived in that particular population with liver failure accompanied by sepsis. The authors also reported significant bleeding side effects in this group, although they were using heparin to maintain partial thromboplastin time >50 seconds to anti-coagulate the MARS system. Rittler et al[11] concluded that sepsis-related liver failure might not be an indication for MARS therapy. In our study, sepsis was not the primary cause of shock liver, but 2 patients in Group M (14%) and 3 patients in Group C (21%) were septic during the study. The patients in Group M did not have any of the complications seen in the study by Rittler et al. The 2 patients in Group M survived, whereas none of the 3 septic patients in Group C survived to wean off of ECMO ($p = 0.03$).

Prior studies on the effectiveness of MARS in patients with acute-on-chronic liver failure have found that treatment can improve hemodynamic status or have an effect on coagulation.[1,12] We found an improvement of INR while on MARS (Figures 1 and 2); however, we were unable to identify the hemodynamic improvement, possibly because hemodynamics were already supported by ECMO.

Our study indicates that ALF during ECMO can be supported with MARS and that once liver functions are normalized, no additional MARS treatments are necessary. Additionally, the fact that 5 of the patients in Group M were implanted with ventricular assist devices points to recovery of end organ function, without any neurologic deficits. Without recovery of liver function, these patients would not have been candidates for ventricular assist devices.

The decision to start MARS treatment was most often based on increased total bilirubin. However, we found the Group M had significantly higher liver enzymes as well. Group M also met criteria for ALF sooner after ECMO initiation (3 days ± 3) than Group C (6 days ± 7). By Day 3 after inclusion, only 70% (10/14) of the patients in Group C were alive, with survival decreasing to 36% (5/14) by Day 7 compared with 79% (11/14) survival by Day 7 in Group M ($p = 0.02$). This illustrates that medical therapy alone is not enough to stop the progression from ALF to death in this patient population. All patients in the treatment group showed total bilirubin that trended downward by Day 3 and continued downward until MARS was stopped (Figure 2), suggesting that liver function recovered.

The main limitations of this study were small sample size, retrospective design, and single-center experience. The decision to initiate MARS therapy was a clinical judgment based on the attending physician's assessment at the bedside, and thus randomization of the 2 groups was not done. This study did not address discharge survival data. Because many surviving patients in Group M went on to receive permanent mechanical circulatory support devices, they required a more prolonged hospital stay. Survival to discharge data in that group would have many other confounding variables from those other forms of mechanical support as well as from the prolonged hospital stay. Going forward, research is needed to further refine the appropriate patient selection criteria and to initiate optimal treatment guidelines as well as to determine if MARS therapy increases survival to discharge.

Study highlights

Currently the MARS liver dialysis has been used for mainly acute-on-chronic liver failure to prolong survival until transplantation. However, the research on expanding the use of MARS to other patient populations has demonstrated mixed results regarding both safety and efficacy. Our study looked at a specific population—patients with multiple-organ failure on ECMO with ALF—to determine if MARS could improve survival to wean off ECMO. The results showed that without increasing complications, MARS could safely improve survival outcomes and accelerate liver recovery within this patient population. ECMO is widely used to support patients while the heart and/or lungs recover; the results of this study indicate that the liver can recover in the same manner if the patient is supported with MARS liver dialysis.

In conclusion, the results of this study show that MARS liver dialysis can safely and effectively be used for patients with ALF and cardiopulmonary failure who are being supported on ECMO to accelerate liver recovery. Survival benefit as a result of MARS was clearly demonstrated, without any additional increase in complications.

Disclosure statement

No conflicts of interest to disclose for any authors. No funding was received for this research.

This study was presented at the Thirty-sixth Annual Meeting and Scientific Sessions of the International Society of Heart and Lung Transplantation, in Washington, DC, April 27–30, 2016.

References

1. Olin P, Hausken J, Foss A, Karlsen TH, Melum E, Haugaa H. Continuous molecular adsorbent recirculating system treatment in 69 patients listed for liver transplantation: a meta-analysis of complications and mortality of extracorporeal membrane oxygenation. Scand J Gastroenterol 2015;50:1127-34.
2. Khuroo MS, Khuroo MS, Farahat KL. Molecular adsorbent recirculating system for acute and acute-on-chronic liver failure: a meta-analysis. Liver Transpl 2004;10:1099-106.
3. Tabata S, Cavarocchi NC, Hirose H. Successful management of severe liver failure on venoarterial extracorporeal membrane oxygenation

using molecular adsorbent recirculating system. J Heart Lung Transplant 2012;31:1322-3.
4. El Banayosy A, Kizner L, Schueler V, Bergmeier S, Cobaugh D, Koerfer R. First use of the molecular adsorbent recirculating system technique on patients with hypoxic liver failure after cardiogenic shock. ASAIO J 2004;50:332-7.
5. Zangrillo A, Landoni G, Biondi-Zoccai G, et al. A meta-analysis of complications and mortality of extracorporeal membrane oxygenation. Crit Care Resusc 2013;15:172-8.
6. Combes A, Leprince P, Luyt CE, 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.
7. Lamb K, Hirose H, Cavarocchi NC. Preparation and technical considerations for percutaneous cannulation for veno-arterial extracorporeal membrane oxygenation. J Cardiac Surg 2013;28:190-2.
8. Shaheen A, Tanaka D, Cavarocchi NC, Hirose H. Veno-venous extracorporeal membrane oxygenation (VV ECMO): indications, pre-procedural considerations and technique. J Card Surg 2016;31:248-52.
9. Zittermann A, Engel M, Hohnemann S, Kizner L, Gummert JF. Molecular adsorbent recirculating system technique for liver failure due to cardiogenic shock. Thorac Cardiovasc Surg 2013;61:522-9.
10. Peek GJ, Killer HM, Sosnowski MA, Firmin RK. Modular extracorporeal life support for multi-organ failure patients. Liver 2002; 22(suppl 2):69-71.
11. Rittler P, Ketscher C, Inthorn D, Jauch K, Hartl WH. Use of the molecular adsorbent recycling system in the treatment of postoperative hepatic failure and septic multiple organ dysfunction—preliminary results. Liver Int 2004;24:136-41.
12. Mitzner SR, Klammt S, Peszynski P, et al. Improvement of multiple organ functions in hepatorenal syndrome during albumin dialysis with the molecular adsorbent recirculating system. Ther Apher 2001;5:417-22.