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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.

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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 ≥ 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.

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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

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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.