Plasma Free Hemoglobin Is a Predictor of Acute Renal Failure During Adult Venous-Arterial Extracorporeal Membrane Oxygenation Support

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Objective: **Hemolysis is a common and severe complication during extracorporeal membrane oxygenation (ECMO). Increased plasma free hemoglobin (PFHb) is related to renal injury. The aim of this study was to investigate whether increased PFHb during adult venous-arterial ECMO was associated with acute renal failure (ARF).**

Design: **A retrospective, observational, single-center study.**

Setting: **Fuwai Hospital in Beijing, China.**

Participants: **The study comprised 84 venous-arterial ECMO patients.**

Interventions: **None.**

Measurements and Main Results: **A total of 84 consecutive adult patients (≥18 years) with cardiac diseases requiring venous-arterial ECMO support were studied retrospectively. Demographics of patients, clinical and ECMO characteristics, and PFHb level were collected within the first 3 days after ECMO. ARF was defined as a ≥300% rise in serum creatinine from baseline or application of dialysis. Repeated measurement analysis of variance revealed that the main effect for the non-ARF group and ARF group in PFHb ($p = 0.002$) was significant. A significant main effect for time points ($p < 0.001$) and time × group interaction ($p = 0.014$) in PFHb was obtained. In a multiple logistic regression model, peak PFHb during ECMO (odds ratio 1.052, 95% confidence interval 1.016-1.089, $p = 0.005$) was a risk factor for ARF during ECMO and patients who underwent heart transplantation (odds ratio 0.240, 95% confidence interval 0.060-0.964, $p = 0.044$) experienced less ARF. There was a linear correlation between peak serum creatinine and peak PFHb (Spearman's $r = 0.223$, $p = 0.042$).**

Conclusions: **Increased PFHb is a predictor of ARF among adult patients on venous-arterial ECMO support.**

KEY WORDS: ***acute renal failure, extracorporeal membrane oxygenation, plasma free hemoglobin***

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) increasingly has been used in critically ill patients with severe cardiopulmonary failure. However, acute renal failure (ARF) as a risk factor for mortality is a severe complication during ECMO support.[1] The initial high pump speed of ECMO, which may result in hemolysis, is a risk factor of acute kidney injury (AKI) in adult patients receiving ECMO.[2] Pump and oxygenator thrombosis, negative inlet pressure, and excessive pump speed may result in elevated plasma free hemoglobin (PFHb) by destroying red blood cells.[3] Elevated PFHb is a common complication and a risk factor of mortality during ECMO support.[4] PFHb is toxic to the kidney and obstructs renal tubules, leading to renal injury. Neal et al found that 4 of 5 patients who experienced rapid increases in PFHb levels >100 mg/dL needed dialysis during ECMO or ventricular assist devices support.[5] However, the clinical evidence that increased hemolysis affects renal function in adult patients receiving ECMO is scarcely reported in the literature. The aim of this retrospective, observational, single-center study was to investigate whether increased PFHb was associated with ARF during adult venous-arterial extracorporeal membrane oxygenation (VA ECMO).

METHODS

Patients

Medical data of consecutive adult patients (≥18 years) with cardiac diseases and who required VA ECMO support between December 2010 and June 2015 in the Fuwai Hospital were retrospectively collected. Inclusion criteria included age ≥18 years, sufficient data of PFHb and serum creatinine (SCr), and every patient with 1 ECMO run. Patients with history of kidney diseases were excluded. The authors' institutional review board exempted this retrospective study from full review because there was no modified intervention and diagnostic strategy, and the requirement for patient consent was waived.

Data Collection

Patients were divided into a non-ARF group and an ARF group. ARF was defined as a ≥300% rise in SCr concentration from baseline or application of dialysis, according to RIFLE.[6] Demographics, surgery information, and laboratory characteristics were collected from an electronic medical record database in the authors' institution. Characteristics before ECMO, including initiation of cardiopulmonary resuscitation, intra-aortic balloon pump use, mean arterial pressure, and lactate level, were recorded. The worst clinical parameters, including peak SCr, peak PFHb, peak lactate level, nadir mean blood pressure (MBP), nadir flow, and per-day peak vasoactive drug dose (epinephrine, norepinephrine, dopamine) during ECMO, were recorded. When renal replacement therapy was performed, SCr measurements were disregarded. Once ARF was confirmed, the worst clinical parameters before appearance of ARF were used. The PFHb level within the first 3 days after

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ECMO initiation were extracted from the ECMO database of the authors' center.

ECMO Setup and Management

The ECMO system (Quadrox D Jostra; Medizintechnik AG, Hirrlingen, Germany) consisted of an oxygenator, a centrifugal pump, a set of polyvinylchloride tubing, a heat exchanger, and an oxygen/air blender. After initiation of ECMO, fentanyl and imidazole were used to maintain adequate anesthesia and sedation. An endotracheal intubation and protective ventilation strategy were adopted to reduce the ventilator-associated lung injury and atelectasis during ECMO. Synchronized intermittent instruction ventilation mode was applied to all patients. Heparin was administered to maintain the activated clotting time in the range of 140 to 180 seconds and activated partial thromboplastin time in the range of 50 to 70 seconds. When platelet counts were below 50,000/mm^3, a stored platelets infusion was administered. Leukocyte-reduced packed red blood cells were infused to maintain a goal hematocrit of 30% to 35%. Using hemodynamic status and blood gas analysis monitoring, the ECMO blood flow was maintained at 40 to 220 mL/kg/min to achieve adequate systemic perfusion. The inotropic agent doses were reduced to a minimum, allowing for optimal myocardial recovery once the ECMO was started. The ECMO system, patients' status, and clinical parameters were checked and recorded every 3 hours by experienced perfusionists. In addition, oxygenators were changed when impairment of the oxygenator gas exchange or severe blood destruction occurred. Oxygenator clot formation was defined as visible clots in circuits or the oxygenator. PFHb was measured at least once a day using a HemoCue Plasma/Low Hb Photometer (HemoCue AB, Ängelholm, Sweden).

Statistical Analysis

Categorical variables were expressed as frequencies with percentages and compared with chi-square test or Fisher's exact test when the expected frequency was less than 5. Continuous variables were presented as mean with standard deviation or median with interquartile range, as appropriate, and were compared using the Student's t-test or Mann-Whitney-U test. Risk factors with a $p < 0.1$ in univariate analysis were further analyzed in multivariable regression model. Backward stepwise logistic regression analysis was used to identify risk factors associated with ARF during ECMO support. A repeated measurement analysis of variance was used to compare changes in PFHb over time between the 2 groups. Spearman rank correlation coefficient (r) was applied to analyze correlation between PFHb and SCr for non-normally distributed variables. All data were analyzed using SPSS, version 21.0 (IBM, Armonk, NY). GraphPad Prism software, version 5.0 (San Diego, CA) was used to portray a line graph of changes in PFHb over time and correlation scatter diagrams between PFHb and SCr. Statistical significance was defined as 2-tailed $p < 0.05$.

RESULTS

From December 2010 to June 2015 in Fuwai Hospital, 84 adult patients (age, 48.14 ± 13.86 years; weight, 65.39 ± 13.17 kg; male/female, 66/18) supported by VA ECMO with sufficient PFHb data were included in this retrospective study. One patient with missing PFHB was excluded. Indications of VA ECMO were found in 28 (33.3%) patients after heart transplantation, 51 (60.7%) patients after other cardiac surgery, and 5 (6%) patients with medical heart failure. The mean ECMO duration was 126.28 ± 60.05 hours. The total survival rate was 41.7%. The incidence of ARF was 48.8%. Twenty-six (63.4%) cases of ARF occurred within the first day and 9 (22%) within the second day. Hemofiltration was used in 17 (41.5%) ARF patents within the first day and 13 (31.7%) within the second day during ECMO support. There was no significant difference in demographics between the non-ARF and ARF groups (Table 1).

ECMO characteristics and outcomes among the non-ARF and ARF groups are shown in Table 2. The peak lactate level during ECMO support was higher in the ARF group ($p = 0.009$). The peak PFHb during ECMO support was higher in the ARF group (45.37 ± 36.54 mg/dL) than in the non-ARF group (21.21 ± 16.88 mg/dL, $p = 0.003$). The classification of PFHb level (PFHb < 10 mg/dL, PFHb 10-50 mg/dL, PFHb > 50 mg/dL) was different between the 2 groups ($p = 0.005$). The higher dose of epinephrine was administered in patients with ARF (non-ARF group v ARF group, median [interquartile range], 0.05 [0.03-0.10] v 0.08 [0.06-0.15] μg/kg/min, $p = 0.006$). Patients with ARF needed more platelet transfusion ($p = 0.001$), and the survival rate of the ARF group was lower ($p < 0.001$).

As the result of univariate analysis, clamping time ($p = 0.080$); MBP before ECMO ($p = 0.081$); posttransplantation ($p = 0.093$); worst clinical parameters during ECMO (peak lactate, $p = 0.018$; peak epinephrine dose, $p = 0.014$; nadir

Table 1. Patient Demographics

Parameter	Non-ARF Group	ARF Group	p Value
Number of patients	43	41	
Age (years)	46.47 ± 15.54	49.90 ± 11.79	0.258
≥60 years, n (%)	9 (20.9%)	10 (24.4%)	0.705
Weight (kg)	65.40 ± 11.31	65.38 ± 15.02	0.994
Male, n (%)	36 (83.7%)	30 (73.2%)	0.239
NYHA class 2-3/class 4	30/13	32/9	0.388
Diagnosis			0.058
Congenital heart disease, n (%)	3 (7.0%)	4 (9.8%)	
Coronary heart disease, n (%)	10 (23.3%)	12 (29.3%)	
Valvular heart disease, n (%)	3 (7.0%)	11 (26.8%)	
Aortic disease, n (%)	4 (9.3%)	1 (2.4%)	
Cardiomyopathy, n (%)	15 (34.9%)	9 (22.0%)	
Fulminant myocarditis, n (%)	0	1 (2.1%)	
Pulmonary embolism, n (%)	1 (2.3%)	2 (4.9%)	
Constrictive pericarditis, n (%)	3 (7.0%)	0	
Coronary and valvular heart disease, n (%)	4 (9.3%)	1 (2.1%)	
Posttransplantation, n (%)	18 (41.9%)	10 (24.4%)	0.090
Medical heart failure, n (%)	4 (9.3%)	1 (2.4%)	0.360
Basic laboratory characteristics			
Serum creatinine (μmol/L)	88.82 ± 18.66	87.57 ± 21.99	0.791
Blood urea nitrogen (mmol/L)	7.43 ± 2.91	7.71 ± 2.77	0.677

Abbreviation: NYHA, New York Heart Association.