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Early fluid resuscitation and volume therapy in venoarterial extracorporeal membrane oxygenation

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ABSTRACT

Purpose: For circulatory support, venoarterial extracorporeal membrane oxygenation (VA-ECMO) is dependent on sufficient venous drainage ensured by fluid therapy. Volume overload however is linked to poor prognosis. This study therefore evaluates volume therapy in VA-ECMO.
Material and methods: We report data of a single center registry of all patients after VA-ECMO implantation treated between 2010 and 2015.
Results: A total of 195 patients were included in this registry with a medium age of 58.2 ± 1.1 years, 71.8% were male. A positive fluid balance was detected in 94.7% at day 1 (day 2: 93.7%, day 3: 92.6%). Consistently, survivors had a lower fluid balance when compared to non-survivors ($P < .001$). Three hours post-implantation, patients above the 75th percentile had a hazard ratio of 6.03 when compared to average survival ($P < .05$). AUC at that time point was 0.726 as calculated by ROC. Patients below the 50th percentile (fluid balance below 8500 mL after 24 hours) had the best prognosis after VA-ECMO implantation ($P < .001$).
Conclusions: Higher fluid balance was consistently linked to poor survival. We found no evidence to support a liberal fluid therapy in VA-ECMO patients, especially not the early after implantation. With a retrospective study, one cannot clarify if lower fluid balance might improve outcomes or represents a prognostic marker.

1. Introduction

There are several indications for venoarterial extracorporeal membrane oxygenation (VA-ECMO) [1-4] including shock with low cardiac output [4] or patients after cardiopulmonary resuscitation [3]. Venous drainage of the VA-ECMO is dependent on sufficient supply of blood drawn from the large veins, typically the vena cava [5]. Due to an endothelial cell damage, a sepsis like syndrome is frequent in diseases like cardiogenic shock and the post resuscitation syndrome [6,7]. As part of a sepsis like syndrome, capillary leakage can induce an intravascular hypovolemia. These facts might trigger a liberal intravenous fluid therapy to VA-ECMO patients. While a more liberal fluid therapy might be lifesaving in the initial phase of sepsis, several studies suggest adverse outcome associated with excessive fluid balance during the intensive care unit stay [8-10]. In a targeted temperature study of patients after out of hospital cardiac arrest, high intravenous fluid therapy early after return of spontaneous circulation was associated with more rearrests and increased pulmonary edema [11]. This might be less relevant for prognosis in case of extracorporeal therapy if organ perfusion and oxygenation can be insured by sufficient VA-ECMO blood flow. We therefore analyzed all VA-ECMO patients treated at our institution in order to evaluate fluid balance and volume therapy in respect of outcome focusing on the early time period after implantation.

2. Methods

We report retrospective data of a single center registry of patients on VA-ECMO. All patients presented at the Heart Center Freiburg University between October 2010 and November 2015. Data derived from the registry was blinded to patient identity and covered by an ethics approval (EK-Freiburg 151/14). For data analysis t-test, ANOVA, χ^2-test or Mantel-Cox were employed as applicable and a $P \leq .05$ was considered statistically significant. All values are given as mean ± SEM if not otherwise stated.

2.1. Patient selection

Within October 2010 and November 2015, a total of 230 VA-ECMO implantations were performed at the Heart Center Freiburg University. Indication for VA-ECMO was driven by the clinical judgment of the responsible physicians being part of our ECMO response team. Typical indications for VA ECMO support were cardiogenic shock with mean arterial blood pressure below 60 mmHg despite high doses of at least two vasopressors or ongoing cardiopulmonary resuscitation without return of spontaneous circulation. Indication of VA-ECMO therefore was

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not standardized. Thirty-five implantations had to be excluded for this analysis (20 patients with a time on VA-ECMO below 3 hours, 13 patients due to VVA-ECMO therapy und 2 implantations due to second VA-ECMO implantation in the same intensive care unit stay). Therefore a total of 195 patients were considered in this study.

2.2. VA-ECMO implantation and management

Cannulation for VA-ECMO was performed bi-femoral in Seldinger technique without primary surgical cut down by two experienced intensivists and one perfusionist as previously reported [12]. Typical venous (draining) cannulas were either 21F or 23F in diameter while arterial (returning) cannulas were either 15F or 17F in diameter. Packed red blood cell transfusion was performed in case of a hemoglobin level below 8.0 g/dL. For patients without active bleeding, anticoagulation was provided by unfractionated heparin aiming at a partial thromboplastin time of 50 to 60 seconds. The decision to employ continuous renal preplacement therapy made as team decision including a nephrologist and an intensivist. Typical indications were potassium levels above 6.0 mmol/L after conservative treatment or clinically significant organ edema in patients without the need of high volume therapy.

2.3. Volume therapy

The management of vasopressors and fluid therapy was driven by clinical judgment of the treating ECMO experienced intensivist. Mean arterial pressure target in all VA-ECMO patients was 60–65 mmHg. ECMO draining pressures were regularly monitored aiming at pressure levels above - 100 mmHg. Presumed intravascular hypovolemia including findings like hypotension, ECMO suction events and excessive lactate levels were typical drivers for volume therapy. Crystalloid solutions were almost exclusively used for fluid therapy. Total fluid balance is calculated by the electronic patient chart and includes all fluids given to our patients as well as all excretion including dialysis, perspiration, blood loss, punctured fluids and urine. For the calculation of the volume therapy, total fluid balance was added to the urine output and dialyzed volume for each given day or added up for total volume infused.

3. Results

3.1. Studied population

A total of 195 patients were included in this registry. Medium age at time of VA-ECMO implantation was 58.2 ± 1.1 years and a total of 71.8% of all patients were male. Most of the patients treated were either after in-hospital our out-of-hospital cardiac arrest (78 and 71 respectively) while 42 patients received the VA-ECMO for profound shock without preceding cardiopulmonary resuscitation. The average time on VA-ECMO therapy was 65.2 ± 4.6 hours in all patients while time on mechanical ventilation was 86.4 ± 12.0 hours. A total of 24.6% of all patients survived the index hospital stay. Most of the non-survivors died while on VA-ECMO therapy while only 10.3% of all patients died after successful weaning of the device. Patients' characteristics are given in Table 1. Comparing patients surviving the index hospital stay to non-survivors, survivors were less frequently male (56.3 vs. 79.9%, $P < .001$). All other patients' characteristics including age, body weight and height, preexisting coronary or peripheral artery disease, diabetes mellitus or kidney and liver disease were not different between the groups. Also the SAPS2 score at admission was comparable. Survivors had longer VA-ECMO therapy durations however not reaching statistical significance (74.3 ± 8.5 versus 62.1 ± 5.4 hours, $P = .250$). Time on mechanical ventilation however was significantly longer in survivors when comparing to non-survivors (151.2 ± 26.4 versus 62.4 ± 12.0 hours, $P < .001$).

3.2. Volume therapy

VA-ECMO patients in this registry had a maximum positive fluid balance of 13 147 ± 994 mL at day two which slightly decreased thereafter. A positive fluid balance was detected in 94.7% of all patients at day 1 (day 2: 93.7%, day 3: 92.6%). Stating at the earliest investigated time point of three hours after implantation, survivors had a significantly lower total fluid balance when compared to non-survivors ($P < .0001$ for trend). Exact values are given in Table 1.

When dividing all patients by quartiles of total fluid balance, patients ending up in the fourth (highest) quartile had a very poor chance of survival when compared to patients in the first and second quartile. At the first investigated time point of 3 hours post implantation, chance of survival of patients in the fourth quartile was as low as 4.08% resulting in a relative hazard ratio of death of 6.03 when comparing to average survival chance of all patients (24.6%). Quartiles and risk values are given in Table 2. At all investigated time points, patients in the first and second quartile had the best prognosis while patients in the fourth quartile presented with the worst prognosis as highlighted by Kaplan Meier curves (Fig. 4, $P < .001$). The predictive value of fluid balance after 3 hours for survival was calculated by receiver operating characteristic to have an AUC of 0.726 (6 h: 0.689, 12 h: 0.677, 24 h: 0.648).

3.3. Urine output and dialysis

Survivors after VA-ECMO therapy had a significantly higher total urine output when compared no non-survivors ($P < .001$ for trend, see Table 1 and Fig. 1). The number of patients on dialysis during VA-ECMO however was not significantly different between survivors and non-survivors (18.8% versus 26.6%, $P = .271$). The number of anuric patients (urine production <100 mL/d) and oliguric patients (urine production <500 mL/d) is given in Table 1 and was statistically higher in the non-surviving patients. (See Fig. 2.)

4. Discussion

There is ample evidence in literature that fluid accumulation and positive balance after the initial phase of fluid resuscitation is associated with poorer outcomes [7,8,10,13,14]. Schmidt et al previously reported in a mixed collective of veno-arterial and veno-venous ECMO patients that survivors had a lower fluid balance when compared to non-survivors [15]. The published data on fluid balance in ECMO patients however only evaluated 24 hour time points and included only patients surviving at least 3 days on ECMO therapy. This resulted in a 90-day mortality of 24% in this trial [15]. Since at least one third of all VA-ECMO patients have an ECMO therapy duration of 2 or less days [16], a significant proportion of patients were excluded for the analysis [15]. Our study therefore focused on the early time period after ECMO implantation (the time of a potential need for a fluid resuscitation) and excluded venovenous ECMO patients in order to better define the notoriously heterogeneous ECMO population.

4.1. No evidence supporting a liberal fluid therapy

Cardiac arrest and shock frequently presents with a sepsis-like syndrome [7,17]. In sepsis, volume therapy has to be adjusted over the time course of therapy [7,8,10,13,14]. There is data suggesting that high volume therapy in sepsis within the first 6 hours is not associated with worse outcome [10,14]. In a retrospective analysis of the Vasopressin in Septic Shock Trial, patients in the second quartile with an fluid balance of 3000 mL after 12 hours had the best outcome [10]. Taking into account that patients were enrolled 12 hours after presentation with an average fluid balance of 4200 mL at enrollment, best survival in sepsis was seen with a fluid balance of 7200 mL after 24 hours [10]. This is surprisingly similar to the fluid balance of the second quartile in our registry with a fluid balance below between 3345 and 8755 mL after 24