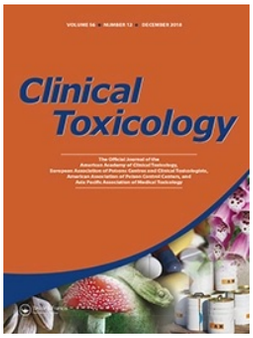

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CLINICAL RESEARCH

Clinical utility of venoarterial-extracorporeal membrane oxygenation (VA-ECMO) in patients with drug-induced cardiogenic shock: a retrospective study of the Extracorporeal Life Support Organizations' ECMO case registry

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ABSTRACT

Background: Venoarterial-extracorporeal membrane oxygenation (VA-ECMO) is increasingly utilized to treat severe or refractory drug-induced cardiovascular shock. There is limited evidence regarding VA-ECMO's clinical utility in poisoning. Therefore, we investigated the clinical benefit of VA-ECMO use in drug-induced cardiovascular shock using the Extracorporeal Life Support Organization (ELSO)'s ECMO case registry.

Methods: The ELSO registry was systematically searched retrospectively, using ICD-9/10 codes for poisoning-related cases from January 1, 2003 to July 30, 2018. All adult cases (age $\geq$ 18 years) that received VA-ECMO for cardiac support were included. Cardiogenic shock was defined as systolic blood pressure (SBP) <90 mmHg, mean arterial pressure (MAP) <65 mmHg, or requiring infusion of $\geq$2 vasopressor agents. Study outcomes included survival to discharge (i.e., from the ECMO center), changes in metabolic (acid/base), hemodynamic and ventilatory status, and complications related to ECMO support. Demographic and clinical characteristics of pre-ECMO and 24-h after VA-ECMO cannulation were compared between survivors *vs.* non-survivors.

Results: A total of 113 cases were identified from the ELSO registry; 9 cases were excluded because cardiogenic shock was not related to poisoning, leaving 104 cases for analysis. The median age was 34 years and 53.5% ($n = 54$) were male. Cardiovascular agents were involved in 47.1% ($n = 49$) of the cases followed by opioids ($n = 9$, 6.7%); 34 cases experienced pre-ECMO cardiac arrest. About 92.4% of the cases ($n = 85$) received vasopressor infusion for hemodynamic support, most frequently norepinephrine (83.7%). Median duration of VA-ECMO was 68 h (interquartile range [IQR]: 48, 113 h); 52.9% ($n = 55$) of the cases survived to discharge. VA-ECMO significantly improved hemodynamics (MAP, SBP, and DBP), acidemia/acidosis (pH, HCO_3 level) and ventilatory parameters (pO_2, SpO_2, and SvO_2). Non-survivors showed persistent acidemia/acidosis at 24-h after VA-ECMO cannulation compared to survivors. Renal replacement therapy (50.9%) and arrhythmia (26.3%) were the most frequently reported complications.

Conclusions: VA-ECMO improved hemodynamic and metabolic parameters in patients with drug-induced cardiogenic shock (DCS).

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Introduction

Overdose of agents affecting the cardiovascular system (e.g., calcium-channel blockers and cardiac sodium-channel blocking agents) results in significant morbidity and mortality from drug-induced cardiogenic shock (DCS) [1]. Therapeutic interventions such as vasopressor/inotropic infusion, high-dose insulin therapy, and sodium bicarbonate infusion are frequently initiated to treat patients with DCS. However, refractory hypotension or cardiac arrest can still occur even when medical management is optimized. Recently, there has been a growing interest in extracorporeal life support or extracorporeal membrane oxygenation (ECMO) to manage patients with DCS when other treatment modalities have failed [2–4].

ECMO was initially developed in the 1950s to provide cardiopulmonary support during cardiac bypass surgery; since then, non-surgical use of ECMO has been gaining wider acceptance [5,6]. There are two available modalities of ECMO. Veno-venous (VV)-ECMO is used to improve oxygenation in patients with isolated pulmonary failure, whereas veno-arterial (VA)-ECMO provides systemic circulatory support in patients with refractory cardiogenic shock, as a bridge to myocardial recovery, heart transplantation, or durable mechanical circulatory support [7]. In poisoning,

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VA-ECMO can play an important role in providing cardiovascular support while the offending agent is metabolized and eliminated from the body.

VA-ECMO was first used to treat quinidine-induced cardiogenic shock in 1997 [8]. Since then, literature has accrued to support the use of VA-ECMO in acutely poisoned patients with DCS [9–16]. However, the majority of the published literature is limited to case reports and small case series, limiting VA-ECMO's clinical role and application in acute poisoning. Therefore, we conducted our study to characterize the use of VA-ECMO in patients with DCS. Our goal was to assess the clinical benefits of VA-ECMO and to characterize the change in clinical parameters (e.g., metabolic, hemodynamic status, etc.), including adverse events, associated with VA-ECMO support. We hypothesized that acutely poisoned patients with DCS who survived ECMO would show improvement in early clinical parameters, compared to patients who did not survive ECMO therapy.

Methods

Study design

We conducted a retrospective cohort study using the ECMO case registry maintained by the Extracorporeal Life Support Organization (ELSO), Ann Arbor, Michigan. ELSO is an international consortium of health care institutions that promotes ECMO-related education, training, guideline development, and research. The ELSO registry, established in 1984, collects data on ECMO cases from 390 U.S. and international ECMO centers using a standardized data collection form [17,18]. Data collected by the ELSO registry include patient demographic information (gender and race), pre-ECLS and 24-h post ECLS cannulation clinical assessment – acid/base markers (e.g., pH and bicarbonate level [HCO_3] from blood gas analysis), ventilatory status (e.g., oxygenation, ventilator setting, etc.), hemodynamic data (e.g., systolic/diastolic and mean arterial blood pressures) – complication during EMCO support, and clinical outcomes (i.e., survival to hospital discharge *vs.* death). The ELSO registry was systematically searched using International Classification of Diseases (ICD), 10th Revision codes for poisoning (T36 to T65), including ICD-9 equivalent codes (960–989) from January 1, 2003 to July 30, 2018 to identify all poisoning-related cases. We included patients with age of 18 years and over who received VA-ECMO for cardiac support/suspected DCS. Cardiogenic shock was defined by systolic blood pressure (SBP) $<$ 90 mmHg, mean arterial pressure (MAP) $<$65 mmHg or requiring two or more vasopressor infusion for hemodynamic support. Cases were excluded if VA-ECMO support was initiated for non-poisoning related cardiogenic shock. The agents involved in poisoning/toxicity were classified as cardiovascular (i.e., anti-hypertensive and vasodilatory agents), opioids (including illicit and prescribed opioids), antidepressants, etc., when appropriate as specified by ICD-9/ICD-10 codes. The de-identified data from the systematic search were obtained from the ELSO in Microsoft Excel format. Written informed consent was not obtained as the study was not a human subject research. The Institutional Review Board at the University of Maryland, Baltimore exempted the study.

The outcomes in our study were hemodynamic parameters (SBP, diastolic blood pressure [DBP] and MAP), survival to discharge, defined as discharged home or to another hospital from the ECMO center, metabolic (acid/base) and ventilatory parameters, and complications related to VA-ECMO support. Descriptive analysis was performed to assess the characteristics of the study participants, and to determine the frequencies and median values of dichotomous and continuous variables, respectively. The Chi-square test or Fisher's Exact Test, as appropriate, was performed to evaluate the differences between dichotomous variables, while Student's *t*-test (for normal distribution) or the Wilcoxon rank-sum test (for non-normal distribution) was performed for continuous variables (e.g., blood pressure). Univariate analysis was performed to identify variables that were associated with increased odds of death. Subgroup analysis was performed to compare variables between survivors and non-survivors. All statistical analysis was performed using SAS version 9.3 (SAS Corp. Cary, NC).

Results

During our study period, a total of 113 VA-ECMO cases were identified in the ELSO registry. Nine patients were excluded because they involved non-poisoning related indications for their VA-ECMO cannulation, leaving 104 cases for analysis. All cases met our definition of cardiogenic shock. The median age of the study population was 34 years; males accounted for 53.5% ($n = 54$) of the cases (Table 1). The first poisoning-related VA-ECMO case was identified in 2009 and increased during the study period with the majority of cases reported in 2017 ($n = 51$; 49.0%) (Figure 1). Exposure to 20 different classes of agents, were documented. Outside of illicit substances (e.g., cocaine and heroin), the specific name of the exposed agent suspected of contributing to the DCS was not documented. The majority of cases involved poisoning from cardiovascular agents (47.1%), followed by opioids, cocaine, and antidepressants (Table 1). Agents involved in 15 cases were documented as "unspecified." The remaining 23 cases were exposed to 15 different agents (Supplementary material, Appendix A). These cases were classified as "Other" for the purpose of analysis.

Of the 92 cases with pre-ECMO support/intervention data, 85 patients (92.4.%) received vasopressor infusion for hemodynamic support; 85.9% ($n = 73$) of the patients were infused 2 or more agents, and 45.9% ($n = 39$) received 3 or more agents. Norepinephrine (83.7%) was the most commonly infused vasopressor/inotropic agent, followed by epinephrine, dobutamine, and vasopressin (Table 1). Approximately 50% of patients received bicarbonate infusion. Transvenous pacemaker and intra-aortic balloon pump were placed in 7 and 5 cases, respectively. Approximately one-third of the study cohort ($n = 34$) experienced cardiac arrest prior to cannulation for VA-ECMO. The median duration of VA-ECMO support was 68 h (IQR: 48, 113 h) and 52.9% of the cases survived to discharge. Demographic information, types of agent

Table 1. Demographic and clinical characteristics of cases that received VA-ECMO for drug-induced cardiovascular toxicity.

	Study cohort ($N = 104$)	Survivors ($n = 55$)	Non-survivors ($n = 49$)	p Values[#]
Median age, years (IQR)	34 (26, 49)	33 (25, 47)	35 (27, 52)	0.31
Gender, male (%)	54 (53.5)	24 (43.6)	30 (61.2)	0.07
Body weight, kg (IQR)	77 (65, 90)	75 (65, 90)	80 (65, 87)	0.86
Type of agent in poisoning, *N* (%)				0.63
Cardiovascular	49 (47.2)	29 (52.7)	20 (40.8)	–
Opioid	9 (8.7)	3 (5.5)	6 (12.2)	–
Cocaine	4 (3.8)	2 (3.6)	2 (4.1)	–
Antidepressant	4 (3.8)	2 (3.6)	2 (4.1)	–
Other	23 (22.1)	10 (18.2)	13 (26.6)	–
Unspecified	15 (14.4)	9 (16.4)	6 (12.2)	–
Pre-ECMO cardiovascular arrest, *N* (%)	34 (32.7)	16 (29.1)	18 (36.7)	0.41
Pre-ECMO interventions, *N* (%)[a]				
Norepinephrine	77 (83.7)	44 (88.0)	33 (78.6)	0.22
Epinephrine	62 (67.4)	32 (64.0)	30 (71.4)	0.45
Dobutamine	41 (44.6)	24 (48.0)	17 (40.5)	0.47
Vasopressin	24 (26.1)	17 (34.0)	7 (16.7)	0.06
Milrinone	5 (5.4)	2 (4.0)	3 (7.1)	0.51
Levosimendan	5 (5.4)	3 (6.0)	2 (4.8)	0.79
Bicarbonate	45 (48.4)	25 (50.)	20 (47.6)	0.82
Renal replacement therapy	33 (35.5)	21 (42.0)	12 (28.6)	0.18
Pacemaker insertion	7 (7.5)	2 (4.0)	5 (11.9)	0.15
Intra-aortic balloon pump	5 (5.4)	0	5 (11.9)	0.02*
ECMO duration, median hour (IQR)	68 (48, 113)	73 (56, 120)	55 (32, 94)	0.004*

ECMO: extracorporeal membrane oxygenation; IQR: interquartile range [25%, 75%].
[a]Pre-ECLS intervention data was only available for 92 cases.
[#]p Value represents the comparison between survivors and non-survivors.
*Statistically significant.

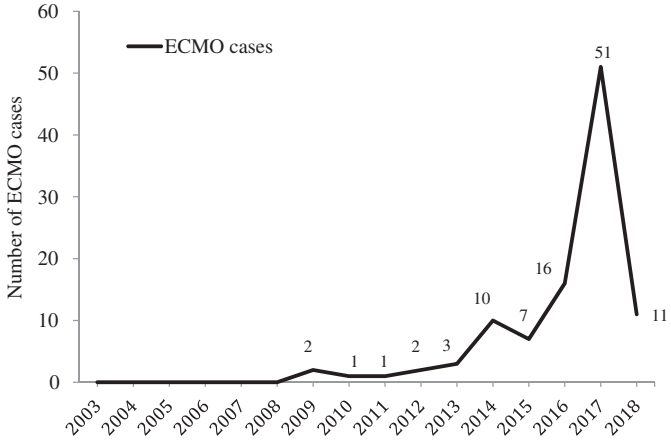

Figure 1. Venoarterial-ECMO cases for drug-induced cardiogenic shock reported to Extracorporeal Life Support Organization between 2003 and 2018. Note: the number of cases for 2018 is incomplete as extracorporeal membrane oxygenation (ECMO) cases were requested from January 1, 2003 to July 30, 2018.

involved in poisoning and pre-ECMO support/intervention between survivors and non-survivors were similar except a larger proportion of non-survivors had intra-aortic balloon pump placement (Table 1). The median duration of VA-ECMO was longer among survivors (73 h) compared non-survivors (55 h; $p = .004$).

The majority of the metabolic, hemodynamic, and ventilatory parameters showed significant improvement at 24 -h after VA-ECMO cannulation (Table 2). Initiation of VA-ECMO resulted in improvement in acidemia (pH), acidosis (bicarbonate level), oxygenation parameters, and hemodynamic status. Only the partial pressure of CO_2 did not show a significant change. There was no significant difference between survivors and non-survivors in respect to the pre-ECMO clinical parameters. However, non-survivors showed significantly lower pH and serum bicarbonate levels compared to survivors 24-h after ECMO cannulation (Table 3).

Data regarding adverse events during VA-ECMO were available for 57 of 104 cases (Table 4). Renal replacement therapy (50.9%) was the most common adverse event, followed by arrhythmia (26.3%) and infection (22.8%). The adverse event rates between survivors and non-survivors were mostly similar except for brain death, which occurred in non-survivors only, and hemolysis (Table 4). Univariate analysis of demographic, pre-ECMO clinical characteristics, and end organ injury during ECMO did not showed any association with mortality (Table 5).

Discussion

Over the past decade, there has been a growing interest in and utilization of ECMO for the management of patients with cardiovascular or/and respiratory failure from diverse medical and surgical conditions [2]. ECMO is also gaining attention within the medical/clinical toxicology community as a potentially life-saving intervention in refractory DCS providing cardiovascular support to acutely poisoned patients while their bodies metabolize and eliminate the cardiotoxic agent(s). During our study period, 15,511 adult VA-ECMO cases for cardiac support were reported to the ELSO registry. Our cohort represents only a fraction (0.067%) of these cases, indicating that VA-ECMO is not widely utilized for acute poisoning. But, VA-ECMO utilization has been increasing for DCS over the past 5 years, with the largest number of cases reported in 2017 (Figure 1).

To our knowledge, this is the largest study of VA-ECMO in acutely poisoned patients with DCS to date. The ELSO registry has been previously used to study the clinical outcomes of ECMO in adult patients with toxic exposure/poisoning.

Table 2. Hemodynamic and metabolic parameters before and 24-h after ECMO cannulation .

Variable	Pre-ECMO	24-h post-ECMO	*p* Value
pH	7.21 [7.10, 7.32]	7.38 [7.27, 7.45]	<.0001*
pO_2 (torr)	110 [62, 225]	168 [92, 247]	.004*
pCO_2 (torr)	49 [38, 60]	38 [34, 68]	.06
HCO_3 (mmol/L)	16 [13, 22]	22 [18, 26]	<.0001*
SBP (mmHg)	77 [70, 90]	96 [88, 110]	<.0001*
DPB (mmHg)	45 [39, 52]	60 [55, 68]	<.0001*
MAP (mmHg)	51 [45, 65]	70 [65, 80]	<.0001*
SpO_2 (%)	96 [87, 99]	99 [96, 100]	.0004*
SvO_2 (%)	48 [26, 51]	75 [71, 83]	.005*

ECMO: extracorporeal membrane oxygenation; pO2: partial pressure of O_2; pCO_2: partial pressure of CO_2; MAP: mean arterial pressure; SpO_2: pulse oximetry; SvO_2: mixed venous oxygen saturation.
*Statistically significant.

Table 3. Hemodynamic and metabolic parameters before and 24-h after ECMO cannulation for survivors and non-survivors.

Variable	Survivors ($n = 55$)	Non-survivors ($n = 49$)	*p* Values
Pre-ECMO			
pH	7.22 [7.14, 7.28]	7.21 [7.08, 7.34]	.64
pO_2 (torr)	114 [64, 225]	108 [61, 212]	.77
pCO_2 (torr)	53 [42, 60]	45 [32, 60]	.20
HCO_3 (mmol/L)	15 [13, 22]	17 [13, 21]	.78
MAP (mmHg)	57 [48, 63]	50 [45, 68]	.32
SpO_2(%)	97 [90, 99]	96 [85, 100]	.62
24-h after ECMO initiation			
pH	7.42 [7.35, 7.46]	7.30 [7.21, 7.44]	.003*
pO_2 (torr)	165 [88, 244]	168 [97, 248]	.79
pCO_2 (torr)	38 [35, 75]	40 [32, 53]	.83
HCO_3 (mmol/L)	24 [20, 26]	20 [16, 24]	.005*
MAP (mmHg)	68 [65, 83]	70 [64, 80]	.67
SpO_2 (%)	99 [96, 100]	99 [96, 100]	.61

Note: data represent median (interquartile range: 25%, 75%). Pre-ECMO data are reported data at the time of cannulation.
ECMO: extracorporeal membrane oxygenation; pO2: partial pressure of O_2; pCO_2: partial pressure of CO_2; MAP: mean arterial pressure; SpO_2: pulse oximetry.
*Statistically significant.

Table 4. Adverse events during ECMO.

Complications[a]	Study cohort *n* (%)	Survivors *n* (%)	Non-survivors *n* (%)	*p* Value
Renal replacement therapy	29 (50.9)	10 (43.5)	19 (55.9)	.36
Cr 1.5–3.0	14 (24.6)	6 (26.1)	8 (23.5)	.83
Cr >3.0	12 (21.1)	3 (13.0)	9 (26.5)	.32
Arrhythmia	15 (26.3)	6 (26.1)	9 (26.5)	.97
Infection	13 (22.8)	5 (21.7)	8 (23.5)	.87
Limb ischemia	10 (17.5)	3 (13.0)	7 (20.6)	.46
Hyperbilirubinemia	6 (10.5)	1 (4.4)	5 (14.7)	.21
Brain death	5 (8.8)	0 (0)	5 (14.7)	.05*
Hemolysis	3 (5.3)	3 (13.0)	0 (0)	.03*
Pulmonary hemorrhage	3 (5.3)	2 (8.7)	1 (2.9)	.34
Compartment syndrome	2 (3.5)	0 (0)	2 (5.9)	.24
Ischemic stroke	1 (1.8)	0 (0)	1 (2.9)	.41

ECMO: extracorporeal membrane oxygenation.
[a]Complication data were available for 57 patients.
*Statistically significant.

Table 5. Univariate tests of association for in-hospital mortality.

Variables	OR [95% CI]
Demographic	
Age	1.02 [0.99–1.05]
Male gender	1.96 [0.88–4.33]
Pre-ECMO variables	
CV agent vs. non-CV agent	0.64 [0.29–1.40]
pH at cannulation	0.38 [0.03–5.44]
HCO_3 at cannulation	1.01 [0.97–1.05]
MAP at cannulation	0.99 [0.96–1.02]
Pre-ECMO arrest	1.47 [0.64–3.34]
Intra-aortic balloon pump	13.72 [0.74–254.84]
Pacemaker insertion	3.01 [0.56–16.29]
Organ failures during ECMO	
Renal replacement therapy	0.57 [0.24–1.37]
Hyperbilirubinemia	3.92 [0.43–35.71]

ECMO: extracorporeal membrane oxygenation; CV: cardiovascular; MAP: mean arterial pressure.

Ramanathan et al. showed a survival to discharge rate of 59% in adult patients who received VV- or VA-ECMO for acute poisoning [19]. Although similar survival rates were reported between our two studies, there were several notable differences. Our cohort consisted of only DCS cases that required ECMO for cardiogenic shock. The majority of the cases in our study involved exposure to cardiovascular agents (47.2%) compared to the study by Ramanathan et al. (6.0%; $n = 5$ of 83) with lower median hemodynamic parameters (SBP, DBP, and MAP). The duration of ECMO was also shorter among survivors in our study (73 h *vs.* 155 h), likely due to fact that indication and modality of ECMO support was different between the two cohorts; the majority of the poisoned cases in the study by Ramanathan et al. received VV-ECMO for pulmonary support [19].

Others have also attempted to characterize and evaluate the clinical utility of ECMO using various sources of data including a poisoning-related case registry and regional poison control system data [2,9,11,20–22]. The available literature shows a wide range of survival to discharge rates (25–86%) in patients who received ECMO support for DCS

[9,15,19–22]. It is difficult to extrapolate an evidence-base assessment of VA-ECMO's clinical utility in DCS from these studies due to differences in their study designs (retrospective *vs.* observational study), small sample size with diverse demographic/clinical characteristics, and heterogeneity of the agents involved in the poisoning [9]. Currently, there is no randomized controlled trial of ECMO in human subjects. But even with these limitations, available literature, including our study, suggests that there is a potential survival benefit with VA-ECMO in a select group of patients with severe or refractory DCS. In animal studies of lidocaine [10] and amitriptyline [16] induced cardiogenic shock, the ECMO group had a higher survival rate compared to the group supported by traditional advanced cardiac life support interventions. Additionally, a retrospective study of patients with recurrent cardiac arrest and severe shock due to cardiotoxicity showed 86% survival when ECMO was initiated compared to the non-ECMO group (48%; p=.02) [22]. But further research is needed to solidify the role of VA-ECMO in poisoning and for this modality to become a standard of care in the management of severe or refractory DCS.

The majority of clinical and demographic characteristics of survivors and non-survivors were similar in our study. We did not observe a difference in survival by gender as previously reported [23]; but neurological complications (i.e., brain death) were associated with mortality [19]. All cases that required intra-aortic balloon pump died; however, no association with death was noted (odds ratio, 13.72; 95% confidence interval: 0.74–254.84), likely due to infrequent intra-aortic balloon pump insertion (Table 5). Although there were no clear pre-ECMO clinical characteristics that were associated with an increased risk of death, we found that persistent acidemia/acidosis at 24-h after ECMO initiation was associated with death even though there were no significant differences in hemodynamic and ventilatory parameters between survivors and non-survivors. The cause of the persistent acidemia/acidosis could not be determined, and is beyond the scope of our study, as we did not have access to complete clinical data of each case. We could speculate that this may be due to the severity of the poisoning, characteristics of exposure and the types of agents involved (i.e., multiple substance exposure) or from potential variability in patient care and ECMO initiation. Currently, there is no standardized clinical guideline or set of indications to initiate VA-ECMO in poisoning. ELSO provides a non-specific recommendation to consider VA-ECMO when "shock persists" despite optimization of medical management. The fact that survivors had a significant improvement in metabolic parameters at 24 h compared to non-survivors and median ECMO duration of 68 h suggests that VA-ECMO may allow for identification of patients with DCS who are at a higher risk of mortality and that prolonged ECMO runs may not be needed in acutely poisoned patients.

There are several limitations to our study. We conducted a retrospective study using data from the ELSO registry. The reporting of ECMO cases to the registry is voluntary by the participating institutions. Therefore, it is unlikely that all VA-EMCO cases involving DCS were reported. Reporting bias could also be present where cases with positive clinical outcome may be reported more frequently. The case identification was performed using ICD-9 and ICD-10 codes. As a result, we were not able to identify the specific agent(s) involved in the majority of the cases. Additionally, any coding error by the reporting institutions would have led to exclusion or misclassification of cases that could influence our findings. The data reported to and obtained from the ELSO registry did not require or include confirmatory test of patients' suspected toxicologic exposure. Therefore, we are unable to determine if the cardiogenic shock in each case was due to drug exposure. Our dataset did not include complete data for all cases; for example, pre-ECMO support/intervention data were available for 92 cases. This limitation of our data could have led to either under or overestimation in some of our study findings. The multicenter source of our data affords our finding to be generalizable. But at the same time, we are unable to control or account for variability in patient care in ECMO centers, and differences in patient care between countries that could have potentially impacted our cases' clinical outcomes. Finally, our study was not a randomized control trial. Therefore, we cannot infer a direct survival benefit of VA-ECMO even though our study suggested a potential survival benefit of VA-ECMO in patients with DSC.

Conclusions

This is the largest study evaluating the clinical utility of VA-ECMO support in acute poisoning. Our findings show that there is a potential clinical benefit, i.e., improvement in hemodynamic and metabolic status, for VA-ECMO in acutely poisoned patients with DCS who are refractory to conventional medical therapy. Our data also suggest that VA-ECMO may allow for rapid triaging of patients (i.e., identify patients with higher risk of mortality) with DSC. Further research is needed with randomized clinical trials to elucidate survival benefit and to help develop clinical guidelines and indications for VA-ECMO initiation in poisoning.

Disclaimer

Finding of this study was presented at the 39th Congress of European Association of Poisons Centres and Clinical Toxicologists. Naples, Italy. May 2019.

Disclosure statement

No potential conflict of interest was reported by the authors.

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