The last ray of hope in drug overdose : ECMO

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CASE SERIES…

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Extracorporeal Membrane Oxygenation in Drug Overdose: A Clinical Case Series

C. Vignesh, Madhan Kumar,[1] Ramesh Venkataraman, Senthilkumar Rajagopal, Nagarajan Ramakrishnan, and Babu K. Abraham

Introduction

- Overdose of cardiovascular medications such as **beta blockers and calcium channel blockers** cause impaired cardiac contractility, vasoplegia and/or rhythm disturbances.
- In addition to **conventional management** of limiting absorption, increasing elimination and hemodynamic support by intravenous (IV) calcium infusion, hyperinsulinemia-euglycemia therapy, glucagon infusion have been tried.
- Extracorporeal circulatory Life support(ECLS) has been reported as a **rescue therapy in overdose refractory to maximal medical therapy.**

- We report three patients with cardiovascular medication overdose presenting **with profound cardiovascular instability refractory** to medical therapy.
- Venoarterial extracorporeal membrane oxygenation support **(VA ECMO)** was initiated to provide hemodynamic support.
- Despite the occurrence of device-associated complications, the outcome was good and all patients survived.
- **VA ECMO may be considered in patients with severe refractory shock** due to cardiotoxic medication overdose.

- Cardiovascular medication overdose constitutes about **3.5% of all drug overdoses** and it carries a mortality of about 16%.

- Calcium channel blockers (CCBs) and beta blockers alone account for **more than 65%** of these deaths.

- Treatment with volume resuscitation, vasopressors, hyperinsulinemia-euglycemia therapy, glucagon, and temporary pacing has been successful when the overdose is **mild to moderate**.
- **In severe overdose**, with shock refractory to maximal medical therapy, **circulatory assist device has been used successfully.**
- This case series describes the use of venoarterial extracorporeal membrane oxygenation **(VA ECMO) circulatory support as a salvage therapy in patients resistant to maximal medical management.**

Case -1

A 29-year-old female was admitted to the emergency department with severe hypotension and vomiting, 8 h following ingestion of 40 tablets of **amlodipine** (10 mg each; **total 400 mg).**

She was conscious, oriented with blood pressure **(BP) of 70/40 mmHg**; heart rate (HR) of 55/min; respiratory rate (RR) of 30/min; oxygen saturation (SpO_2) of 92% and warm peripheries.

Gut decontamination with activated charcoal and resuscitation with boluses of **intravenous (IV) crystalloids, calcium gluconate, and norepinephrine infusion was done.**

- On arrival to Intensive Care Unit (ICU), her BP was **80/40 mmHg.** Arterial blood gas (ABG) analysis revealed **metabolic acidosis** with pH of 7.25 and serum lactate of 5.2 mmol/dL. Her **echocardiography** showed normal left ventricular (LV) function.
- She was electively intubated and ventilated and resuscitated with a total volume of 5.94 L of IV crystalloids. She was also initiated **on standard doses of IV 10% calcium gluconate ; IV insulin, and IV glucagon.**

- **Despite 9 hours of aggressive resuscitation**, her metabolic acidosis and hemodynamics worsened requiring **high doses of triple vasopressors** (noradrenaline, adrenaline, and vasopressin).

- At this point of time, a decision **to initiate peripheral VA ECMO** was made. A 17-French cannula was inserted into the left femoral artery and a 19-French cannula into the right femoral vein. An additional 7-French cannula was placed in the left femoral artery **to facilitate distal perfusion**

- VA ECMO was initiated at a flow of 3.7 L/min, and within **2 h,** her vasopressor requirement decreased significantly .
- Over **the next 6 h**, her acidosis settled and lactate levels decreased.
- By the 2nd day, despite significant improvement in her hemodynamics, her oxygenation worsened with clinical and radiological features suggestive of **acute respiratory distress syndrome(ARDS).**

- By the **4th day**, she was changed over to a veno-venous ECMO, and by the 6th day, it was decannulated.

- She was successfully weaned off the ventilator and **extubated by the 8th day** and discharged from the hospital on the 11th day.

Case 2

- A 19-year-old male was admitted to the ICU about 24 h after having ingested **30 tablets each of amlodipine 5 mg and atenolol 25 mg**.
- He was resuscitated in another hospital before the transfer. On arrival to the ICU, he was on high dose of **multiple vasopressors** (noradrenaline, adrenaline, dopamine, and vasopressin) and had a **temporary transvenous pacer *in situ*.**
- His HR was **80/min** (pacing rate); BP was **74/44mmHg**; SpO_2 98% on 40% FiO_2 with cold peripheries.

- Echocardiogram showed normal LV function. Baseline ABG showed **metabolic acidosis** with a pH of 7.16 and lactate level of 4.59 mmol/dL.
- He was resuscitated with **standard doses** of IV calcium gluconate, insulin, glucagon, and sodium bicarbonate

- Despite **14 hours of aggressive resuscitation**, his vasopressor requirements increased and his shock worsened leading to **initiation of a peripheral VA ECMO.**
- The cannulation technique was similar to that used for case 1 and the ECMO flow was set at 4 L/min. Over **the next 24 h, his vasopressor requirements reduced significantly** and he was completely weaned off vasopressor support.

- Urine output and lactate levels improved immediately.
- By the **4th day**, the calcium, insulin, and glucagon infusions were sequentially stopped.
- **ECMO was decannulated on the 5th day** and he was extubated on the **6th day**.
- However, on the **7th day**, he developed swelling and tenderness in the left lower limb over the arterial cannulation site, requiring fasciotomy for **impending compartment syndrome**. He responded well to treatment and was moved out of ICU on the 13th day.

CASE 3

- A 17-year-old female was admitted following ingestion of **multiple drugs (propranolol 40 mg – 10 tablets**; amitriptyline 10 mg – 4 tablets; gabapentin 300 mg – 2 tablets). Her initial resuscitation was done at an outside hospital.
- She arrived to our hospital 36 h following ingestion of the drugs, intubated, and she was **in severe shock**.
- She was **volume resuscitated** and initiated on the standard doses of IV calcium gluconate, insulin infusion, glucagon.

IN SPITE OF ABOVE EFFORTS, she had **refractory shock**

- **Refractory shock necessitating initiation of peripheral VA ECMO** and her vasopressor requirements decreased almost immediately
- By the 4th day, her **hemodynamics improved** to a level that the ECMO was weaned off and decannulated with minimal vasopressor support.

- Her stay in the ICU was a stormy and complicated by **development of multiorgan failure – acute renal failure** requiring renal replacement therapy, ischemic hepatitis, **coagulopathy** requiring multiple blood product transfusions, and **ventilator-associated pneumonia** requiring broad-spectrum antibiotics.
- She required **renal replacement therapy till day 10** and was extubated on day 10.
- On the **20th day**, she was shifted out of ICU and discharged from hospital on the **29th day.**

Discussion

- The toxic effects of cardiac medication overdose are primarily an **extension of their pharmacological activity.**
- Beta blockers and Calcium Channel Blockers inhibit calcium influx into the cells, though by different mechanisms.
- The hemodynamic effects seen in their overdose are **due to impaired cardiac contractility, vasoplegia and/or rhythm disturbances.**

- The cornerstone of medical management for these drug overdoses consists of **limiting their absorption and hemodynamic support** until they are metabolized and eliminated from the body.

- **Gastric decontamination with activated charcoal** to limit the absorption can be attempted when done early.

- **Volume resuscitation with fluids** to overcome the relative hypovolemia associated with vasodilation and inotropic/vasopressor use are the mainstay.

- **In Calcium Channel Blockers overdose,**

  calcium infusion can be initiated in an attempt to overcome the calcium channel antagonism. The increased transcellular calcium gradient drives calcium intracellularly and antagonizes the effect of CCBs.

- In patients **not responding to fluid resuscitation and inotropic support, IV glucagon** can be tried.
- Glucagon exerts its inotropic effects by activating adenylyl cyclase directly. The recommended dose is 5–10 mg IV bolus followed by infusion at the rate of 2–10 mg/h.
- The **potential adverse effects** include dose-dependent nausea, vomiting, hyperglycemia, and allergic reactions.

- **High-dose insulin** also has been used and this improves **the hemodynamics by exerting a direct inotropic effect** and also by improving the carbohydrate metabolism in the myocardium.
- The recommended dose is 1 U/kg/h following a bolus of 1 U/kg. The infusion rate may be increased by 2 U/kg/h every 10 min to a maximum dose of 10 U/kg/min.
- **Close monitoring** of serum glucose, potassium, magnesium, and phosphorus is very important.

- In this case series of three patients, various **combinations of cardioactive drug overdoses** have been described. Patient 1 had taken CCB, patient 2 presented with a combination of beta blocker and CCB, while patient 3 had taken a combination of beta blocker and other agents.

- Compared to other reported case series, this series had patients who were **younger and no any major comorbidities** which could potentiate the cardiotoxic effects of the drugs.

- All three patients were absolutely refractory to medical therapy and was in **refractory shock with high lactate levels.**
- The average time of arrival to the hospital was 18 h. All of them received primary aid in another hospital and was referred for further care.
- The **principle** of extracorporeal support in cardiovascular medication overdose is **to support the hemodynamic and vital organ perfusion, until the medications have been eliminated from the system.**

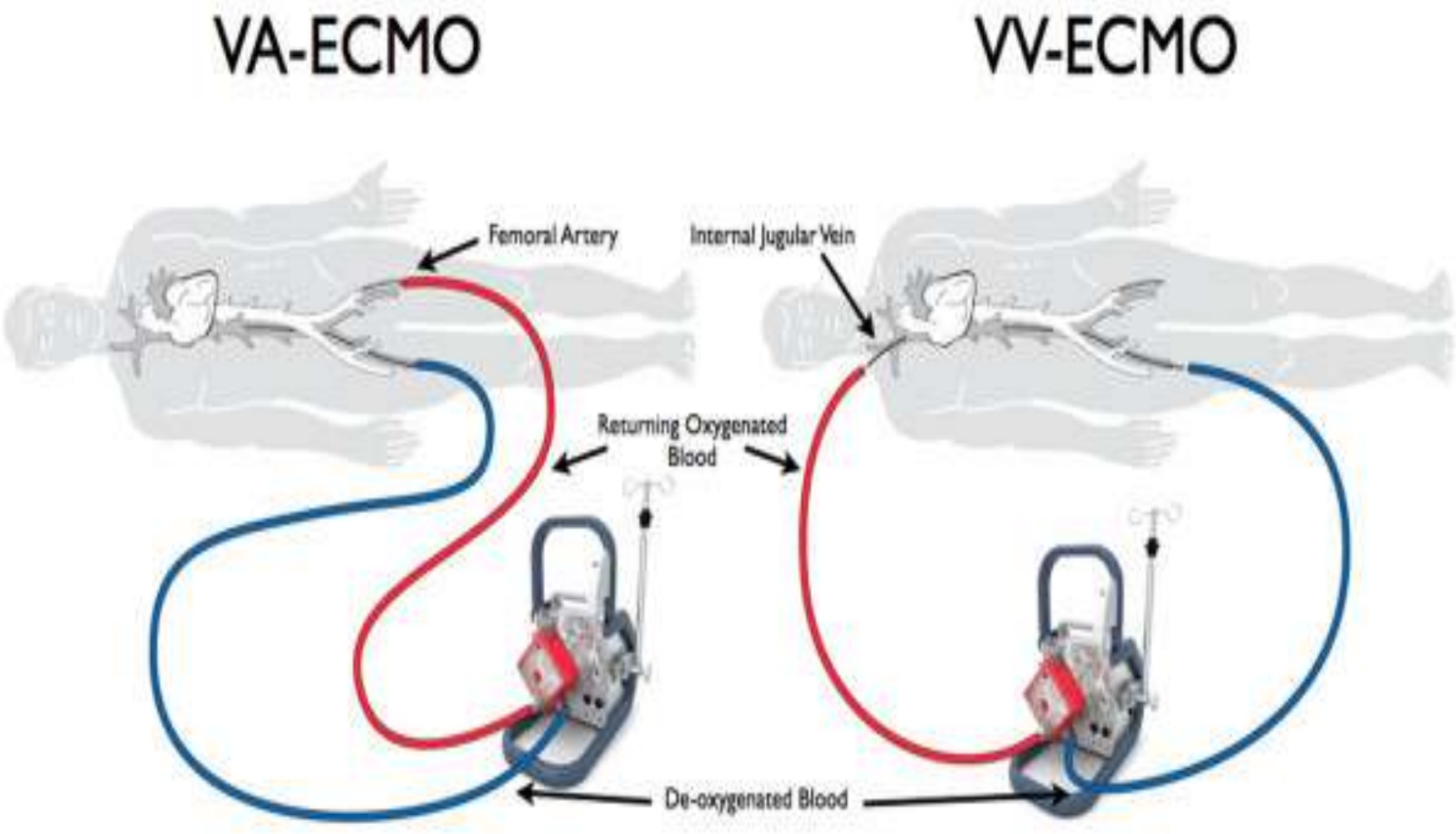
- ECMO flow was initiated at 3.5–4 L along with **vasopressors support** to maintain adequate mean arterial pressure.
- All patients were **mechanically ventilated** and other organ supports were provided as indicated.
- Once the hemodynamics improved**, ECMO flow was gradually reduced** and hemodynamic stability was assessed.
- If patient remained hemodynamically stable, **ECMO was weaned off.**

- The average admission to ECMO initiation time in this series was **15.3 h.**
- **Daubin *et al.*,** in a larger series of seventeen patient, reported admission to ECMO initiation time of 6.4 ± 2.6 h.
- One of the patients, in this series, had developed multiorgan failure requiring organ supports including renal replacement therapy.
- In all the three patients, **percutaneous peripheral arterial cannulations** were performed bedside in the ICU.

VV ECMO for ARDS..

- Extracorporeal membrane oxygenation (ECMO) is used to **treat refractory hypoxemia induced by the acute respiratory distress syndrome**, It is a venous-venous method providing oxygenation of venous blood; thus, there is no circulatory support.
- But VA ECMO is used for circulatory support.

VA ECMO & VV ECMO.



VA ECMO

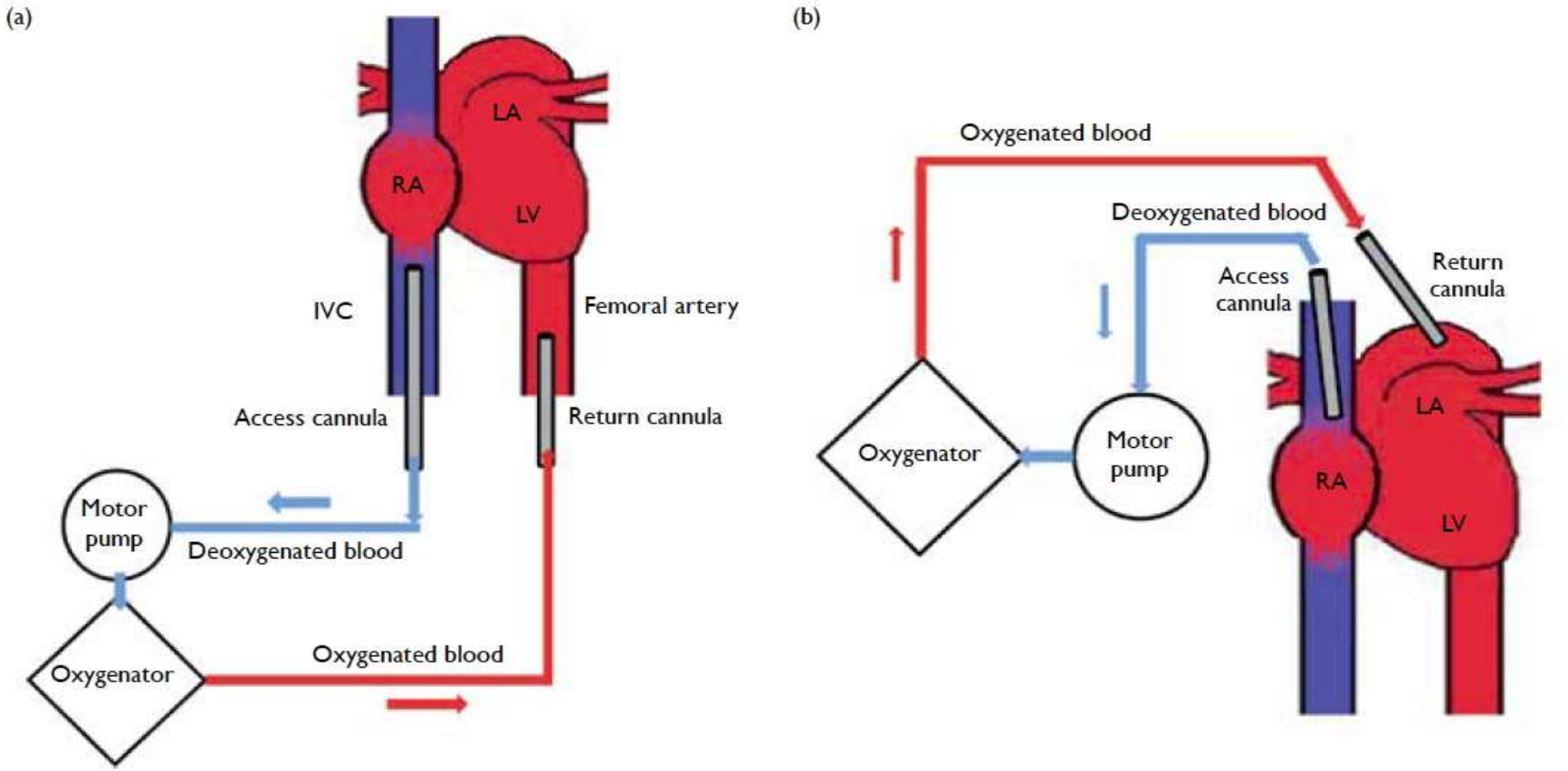


FIG 1. Two different configurations of venoarterial extracorporeal membrane oxygenation (VA-ECMO)
(a) Peripheral and (b) central VA-ECMO
Abbreviations: IVC = inferior vena cava; LA = left atrium; LV = left ventricle; RA = right atrium

IABP(Intra Aortic Balloon counter Pulsation) and drug overdosage

Intra aortic balloon counter pulsation(IABP):

Temporary support for the left ventricle by mechanically displacing blood within the aorta

Most common and widely available methods of mechanical circulatory support

Concepts:

- Systolic unloading
- Diastolic augmentation

IABP:Haemodynamic effects-

- Augmentation of diastolic pressure
- Increase coronary perfusion
- Increase Myocardial Oxygen Supply

- Decrease afterload
- Decrease cardiac work
- Decrease myocardial oxygen consumption
- Increase cardiac output

IABP: TRIGGER MODES --

Trigger modes

Trigger :

- Event the pump uses to identify the onset of cardiac cycle (systole)
- Pump must have consistent trigger in order to provide patient assist
- If selected trigger not detected, counter pulsation will interrupted

1.ECG

- uses the slope of QR segment to detect triggering point

2. AP(Arterial pressure wave)

- Systolic upstroke of the arterial pressure wave form is the trigger

IABP in drug overdosage…

- IABPs provides **limited support of cardiac output** and helpful **for mechanical circulatory support** and do play a certain beneficial role in the management of cardiogenic shock .
- **BUT,** IABPs do **not work** in patients **with cardiac arrest**. So **major limitation** in cardiotoxic poisonings are **refractory asystole, PEA(pulseless electrical activities), pulseless ventricular arrhymias.**

CPB(Cardio-Pulmonary Bypass) in drug overdose.

- CPB(Cardio-Pulmonary Bypass)basically **provides circulatory support**, although it collects venous oxygen-desaturated blood in the right atrium and, thus, always requires an oxygenator, which is integrated within the circuitry.
- CPB requires **sternotomy** and both atrial and aortic cannulations so CPB procedure **restricted to the operating room.**
- CPB has been performed in cases of diltiazem and verapamil poisonings, and has been used in combination with an IABP in a **cardioactive drug overdoses** .
- CPB is an invasive method resulting in a number of potentially life-threatening **complications** LIKE BLEEDING, COAGULOPATHY,MEDIASTINAL HAEMOATOMA .

CPB & ECMO…

- In contrast with CPB, ECMO can be performed using **peripheral cannulations** of both arterial and venous vessels.
- Percutaneous cannulation of femoral vessels is used. However, a blinded approach of vessels may cause laceration resulting in **severe occult local bleeding**.
- Furthermore, due to the size of the arterial cannula of about 15 to 17 F gauge, the occlusion of the vessel lumen by the cannula may result in **arterial ischemia BUT DISTAL PERFUSION by retrograde cannula prevent ischemia.**
- ECMO has been used sucessful used in imipramine , carbamazepine, propranolol , CCBs ,quinidine, flecainide , verapamil , digoxin and chloroquine poisonings.

- Peripheral ECMO has been used in combination with an IABP in a case of organophosphate poisoning .
- **Babatasi & colleagues and Massetti & colleagues** published a series of **seven consecutive severe poisonings** involving cardiac drugs and treated with ECLS using the **peripheral bypass to prevent limb ischemia.** Circulation in the cannulated limb was provided by a tube inserted distally into the superficial femoral artery and connected to the side port of the ECLS arterial line(to maintain distal perfusion).

- The average duration of ECMO support in this series was **74 h.**
- In the series reported by **Daubin *et al.*,** the duration of ECMO was **4.5 ± 2.4 days**.
- There was a **rapid decrease in the inotropic requirements after initiation of ECMO**, however, a small dose was continued to maintain a target mean arterial pressure. These findings are very similar to other reports.

- In another case report, **Weinberg *et al.*** described successful use of ECMO in **two patients with refractory vasodilatory shock associated with amlodipine poisoning.**

  Like any other invasive devices, ECMO too comes with its **set of complications**. Limb ischemia is a well-documented complication of ECMO support.

- **Daubin *et al.*** reported ischemic complications in 10 of the 17 patients in their case series.
- However, **Mégarbane *et al***. have reported lesser ischemic complications.
- One of the three patients in this case series developed limb ischemia in the cannulation side requiring fasciotomy, **despite ensuring distal limb perfusion with additional distal cannulation**
- The other major reported complication of ECMO support is **bleeding**.
- Despite these complications all three patients survived and were discharged successfully.

Some more case series from all around world

Daubin *et al.*

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Crit Care. 2009; 13(4): R138.
Published online 2009 Aug 25. doi: 10.1186/cc8017

PMCID: PMC2750196

Extracorporeal life support in severe drug intoxication: a retrospective cohort study of seventeen cases

Cédric Daubin,[✉1] Philippe Lehoux,[2] Calin Ivascau,[3] Marine Tasle,[2] Mehdi Bousta,[1] Olivier Lepage,[3] Charlotte Quentin,[1] Massimo Massetti,[3] and Pierre Charbonneau[1]

Daubin *et al.* - Results.

Fifteen patients had ingested cardiotoxic drugs and two patients had non-cardiac drugs overdosage. **(TOTAL-17)**

Time from hospital **admission to initiation** of ECLS was 6.4 ± 2.6 hours.

The **mean ECLS flow rate** was 3.45 ± 0.45 L/min.

The **average ECLS duration** was 4.5 ± 2.4 days.

Early complications included limb ischemia (n = 6), femoral thrombus (n = 1), cava inferior thrombus (n = 1), and severe bleeding at the site of cannulation (n = 2).

13 (76%) out of 17, were discharged to hospital without sequelae.

Daubin *et al.* concludes…

- Based on our experience, we consider ECLS as a **last resort, efficient** and relatively safe therapeutic option in this population. However, the uncontrolled nature of our data requires careful interpretation.

Another review article…ToxIC

J Med Toxicol. 2016 Mar; 12(1): 95–99.
PMCID: PMC4781808
Published online 2015 May 27. doi: 10.1007/s13181-015-0486-8

Extracorporeal Membrane Oxygenation (ECMO) for Severe Toxicological Exposures: Review of the Toxicology Investigators Consortium (ToxIC)

G. S. Wang,✉ R. Levitan, T. J. Wiegand, J. Lowry, R. F. Schult, S. Yin, and on Behalf of the Toxicology Investigators Consortium.

Author information ▶ Copyright and License information ▶

- Retrospective review of the ToxIC Registry from **January 1, 2010 to December 31, 2013.**

- There were **26,271 cases of toxic drug exposures** (60 % female) reported to the ToxIC Registry, **10 (0.0004 %) received ECMO:** 4 pediatric (< 12 years), 2 adolescent (12–18 years), and 4 adults (>18 years).

ToxIC Registry concludes…

- ECMO was **rarely used** for toxicological exposures in the ACMT ToxIC Registry , **BUT When utilized**, in most cases, ECMO was **administered prior to cardiac arrest and the survival rate was high.**
- If available, ECMO may be a **valid treatment modality for severe poisoning exposures prior to cardiovascular collapse.**

Another case report …

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Successful extracorporeal life support in a case of severe flecainide intoxication

Auzinger, Georg M. MD; Scheinkestel, Carlos D. MB BS, FRACP

Critical Care Medicine: April 2001 - Volume 29 - Issue 4 - p 887-890
Case Reports

Flecainide – pharmacodynamics..

- Flecainide is is a **class Ic antiarrhythmic** agent and as such, it is used for paroxysmal supraventricular tachycardias (PSVT)
- Flecainide is a **sodium channel blocker**, binding to voltage gated sodium channels.
- It **stabilizes the membrane** by inhibiting the ionic fluxes required for the initiation and conduction of impulses.
- **Ventricular excitability is depressed** and the stimulation threshold of the ventricle is increased during diastole.

- A 30-yr-old male with a history of **severe flecainide overdose**. At presentation, the patient was **in refractory cardiocirculatory collapse** and was successfully resuscitated with ECMO. **Twenty-six hours** later, extracorporeal support could be discontinued after achieving hemodynamic stability.
- **Conclusion :** In patients with severe but potentially reversible cardiac dysfunction attributable to flecainide intoxication, **ECMO can maintain cardiac output and vital organ perfusion** while allowing time for drug redistribution, metabolism, and clearance.

Baud et al.

Critical Care

Review | Open Access

Clinical review: Aggressive management and extracorporeal support for drug-induced cardiotoxicity

Frédéric J Baud ✉, Bruno Megarbane, Nicolas Deye and Pascal Leprince

Critical Care 2007 **11**:207

https://doi.org/10.1186/cc5700

Published: 12 March 2007

Baud et al. - concludes…

The **renewed interest regarding** the efficiency and safety of temporary mechanical assistance in form ECLS in posioning due to cardiotoxic drugs.

- There is a **need for more aggressive treatment** in the subset of patients not responding to conventional treatment so **ECLS remain last promising modality.**
- In contrast, the majority of human cases are single/few cases reports, except for one series .
- Appealing clinical results have been reported supporting the assumption that **further studies are needed to clarify prognostic factors of cardiotoxic drug poisonings** and, therefore, **to clarify the indications and usefulness of peripheral ECLS.**

In our scenario – Feb 22,2018 : IJCCM

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Conclusion ..

Based on the **limited evidence**, there may be a role for the use of **VA ECMO** in patients with **severe cardioactive drug overdose refractory to the medical therapy.**

Early initiation of ECMO support before organ failure or cardiac arrest sets in should be considered and may **ensure the better overall outcome.**

so EARLY initiation in REFRACTORY SHOCK


Hope
THANK YOU