Central Extracorporeal Membrane Oxygenation Support Following Calcium Channel Blocker Overdose in Children

Robert A. Sorabella,* William H. Gray,* Robert J. Dabal,* Luz A. Padilla,* Kristal Hock,† Matthew G. Clark,† Carlisle O'Meara,‡ Jeremy Hawkins,‡ Robert P. Richter,§ Santiago Borasino,† and Jonathan W. Byrnes†

Refractory vasodilatory shock (RVS) following massive calcium channel blocker (CCB) overdose remains a challenging clinical entity. Peripheral venoarterial extracorporeal membrane oxygenation (ECMO) has proven useful in several cases of CCB intoxication, however, its use in the pediatric population poses unique challenges given the generally small size of pediatric peripheral vasculature in comparison to the high flow rates necessary for adequate mechanical circulatory support. As a result of these challenges, our group has adopted a "primary" central ECMO cannulation approach to the treatment of children and adolescents admitted to our center with profound RVS after CCB ingestion. We present four cases within the last year using this approach. All patients were successfully discharged from the hospital with no late morbidity at most recent follow-up. Central ECMO support in cases of massive vasodilatory shock following CCB overdose is safe and effective and should be considered early in the clinical course of these critically ill patients. *ASAIO Journal* 2023; XX:XX–XX

Key Words: pediatric, extracorporeal membrane oxygenation, calcium channel blocker, critical care, overdose

Nonaccidental massive ingestion of calcium channel blockers (CCBs) can lead to rapidly progressive hypotension, cardiac arrhythmias, refractory vasodilatory shock (RVS), and circulatory collapse. Given the rarity of nonaccidental CCB overdose in the pediatric population, the majority of recommendations on treatment algorithms are extrapolated from adult literature and include mechanical ventilation, calcium infusion, high-dose insulin therapy, inotropes, vasopressors, and intravenous lipid emulsion.[1–3] However, a subset of patients progress to RVS despite conventional supportive therapy. While classical dogma cautions against the use of extracorporeal membrane oxygenation (ECMO) support in cases of primary vasodilation, several centers have reported the use of ECMO to treat RVS following CCB overdose with generally good results.[4–6]

Pediatric patients with RVS following CCB overdose present a unique management challenge. These situations are characterized by a high cardiac output state given the profound drug-induced vasodilation combined with massive doses of vasoactive medications to maintain end-organ perfusion pressure. For ECMO support to be advantageous in these clinical settings, supraphysiologic flow rates are essential to wean vasoactive support and improve perfusion of distal capillary beds. In the majority of pediatric patients, the peripheral vasculature is not large enough to accommodate ECMO cannulas that can support these supraphysiologic flow rates. Therefore, to place the largest possible ECMO cannulas that permit maximum flow rates, we have adopted a strategy of "primary" central ECMO cannulation for pediatric patients following massive CCB overdose presenting with RVS.

Materials and Methods

Patient Selection

All patients were admitted through the Children's of Alabama emergency department or transferred from other facilities to the pediatric intensive care unit at Children's of Alabama. At the time of consultation, all patients were being supported with mechanical ventilation, calcium infusion, high-dose insulin therapy, and had escalating doses of vasoactive drug infusions to maintain physiologic mean arterial pressure. Extracorporeal membrane oxygenation referral was left to the intensivist's discretion but was generally informed by escalating vasoactive support in the setting of known CCB overdose and indications of end-organ hypoperfusion. Upon referral, each patient was evaluated by a multidisciplinary ECMO team to determine candidacy. Vasoactive-inotropic scores (VISs) were calculated for each patient according to the method used in Gaies *et al*.[7]

Central Extracorporeal Membrane Oxygenation Cannulation

Once candidacy for central ECMO was determined, all patients were taken to the cardiovascular operating room with cardiovascular anesthesia. Median sternotomy was performed and as little dissection as possible was carried out to prevent the presence of raw surfaces that could pose a bleeding risk. Arterial and venous cannula sizes were left to the discretion of the surgeon and guided by the size of the patient's aorta, right atrium, and a goal ECMO flow index of greater than 3 L/min/

From the *Division of Cardiothoracic Surgery, Section of Pediatric Cardiac Surgery, University of Alabama at Birmingham School of Medicine, Birmingham, Alabama; †Division of Pediatric Cardiology, Section of Cardiac Critical Care Medicine, University of Alabama at Birmingham School of Medicine, Birmingham, Alabama; ‡Department of Cardiovascular Perfusion, Children's of Alabama, Birmingham, Alabama; and §Division of Pediatric Critical Care, University of Alabama at Birmingham School of Medicine, Birmingham, Alabama.

Submitted for consideration September 2023; accepted for publication in revised from November 2023.

Disclosure: The authors have no conflicts of interest to report.

Internally funded.

Correspondence: Robert A. Sorabella, Section of Pediatric Cardiac Surgery, University of Alabama at Birmingham School of Medicine, 1700 6th Avenue South, Suite 9100, Birmingham, AL 35249. Email: rsorabella@uabmc.edu.

DOI: 10.1097/MAT.0000000000002102

m^2. One hundred units per kilogram of heparin were administered before placement of the cannulas in the ascending aorta and right atrial appendage. Temporary epicardial pacing wires were placed given the increased risk of junctional rhythm and complete heart block in CCB overdose. Following initiation of central ECMO support, the chest was left open and patients were transferred to the cardiovascular intensive care unit for ongoing support. Tunneling of the cannulas through the chest wall with chest closure would also be an appropriate maneuver which we have not yet employed in this patient population.

Extracorporeal Membrane Oxygenation Support Strategy

Extracorporeal membrane oxygenation was performed with Nautilus oxygenators (Medtronic, Minneapolis, MN) and Quantum centrifugal pump heads (Spectrum Medical, Fort Mill, SC). Anticoagulation was converted to bivalirudin in all patients with an activated partial thromboplastin time goal of 70–100 seconds, which has become our standard ECMO anticoagulation strategy.[8] All circuits were monitored by an ECMO specialist continuously. All patients underwent slow continuous ultrafiltration, whereas on ECMO support for volume removal. Vasoactive support was weaned as tolerated over the course of the ECMO run, and a 1 hour clamp trial was carried out once vasoactive support was in a mild to moderate range. Assuming hemodynamics were appropriate with only modest vasoactive support and no lactate production, the patient was returned to the operating room for ECMO decannulation and chest closure. Upon medical clearance for discharge, all patients were transferred to an inpatient psychiatric unit until deemed stable for discharge from the psychiatry service.

Data Collection and Analysis

All data related to clinical presentation, symptoms, details of overdose medication, laboratory and hemodynamic variables at various points, ECMO cannulation and support details, patient survival, and details on morbidity associated with the index hospitalization and ECMO support course were collected from electronic medical records. No statistical analysis was performed due to the small cohort and the observational nature of our study. The study was approved by the Institutional Review Board of the University of Alabama at Birmingham and need for informed consent for study participation was waived.

Results

Patient Demographics

All patients presented here were admitted to our intensive care unit between November 2022 and July 2023. Demographics are shown in Table 1. The majority of patients were female and presented with complaints including nausea, vomiting, abdominal pain, and altered mental status. All patients had nonaccidental massive ingestion of CCBs. All cases except case 2 had an overdose with only one drug, whereas case 2 additionally ingested an unknown quantity of fluoxetine and mirtazapine. Determining specific dosage of ingestion was difficult in each case, but it is suspected that the three patients overdosing on amlodipine had ingested approximately 200–300 mg of the drug. We could not verify dosage of the various drugs taken by case 2. In cases 2–4, ECMO cannulation occurred quite rapidly following admission to our center due to rapidly escalating vasoactive drip requirements and lactic acidosis. In case 1, the presumptive diagnosis was septic shock until evidence of CCB overdose was found in the patient's personal belongings. No patient underwent peripheral ECMO cannulation before being considered for central ECMO cannulation, and no patient experienced a cardiac arrest before ECMO cannulation.

Extracorporeal Membrane Oxygenation Initiation and Support

Details of ECMO support are shown in Table 2. All four patients had a rising lactate level and profoundly elevated VIS score at the time of ECMO cannulation (Figures 1 and 2). All patients were supported on high-dose epinephrine, norepinephrine, and vasopressin infusions at the time of cannulation. There were no complications associated with the ECMO cannulation procedure, and there were no circuit changes required during the duration of ECMO support. Additionally, there were no periods of concerning chest tube output or returns to the operating room for mediastinal bleeding during ECMO support. However, case 4 did require a return to the operating room to reposition the arterial cannula as she began to experience high arterial line pressures several days into her ECMO course. While on ECMO, case 2 experienced periods of complete heart block and junctional rhythm interspersed with normal sinus rhythm for which he required temporary pacing *via* epicardial wires. We were able to achieve a cardiac index of greater than 3 L/min/m^2 in all cases except case 3 who had a weight of 129 kg, body mass index (BMI) of 52.5 kg/m^2, and a body surface area (BSA) of 2.38 m^2. However, her calculated ideal body weight was 50 kg which would translate to a maximum cardiac index on ECMO of 3.9 L/min/m^2.

Table 1. Patient Demographics

Variables	Case 1	Case 2	Case 3	Case 4
Age (years)	12	17	14	15
Sex	Female	Male	Female	Female
Weight (kg)	63	85	129	49
Body mass index (kg/m^2)	28.3	30.4	52.5	20.1
Body surface area (m^2)	1.67	1.93	2.38	1.48
Drug ingested	Amlodipine	Verapamil*	Amlodipine	Amlodipine
Admission to ECMO time (hours)	48	7	8	8

*Patient overdose also included fluoxetine and mirtazapine.

ECMO, extracorporeal membrane oxygenation.

Table 2. ECMO Support Variables

Variables	Case 1	Case 2	Case 3	Case 4
VIS at cannulation	175	242	90	75
Lactate at cannulation (mmol/L)	4.2	9.1	6.4	6.4
pH at cannulation	7.22	7.16	7.14	7.21
Arterial cannula	22 EOPA®	22 EOPA®	20 EOPA®	20 EOPA®
Venous cannula	36/46 Fr	36/46 Fr	29/37 Fr	29/37 Fr
Max ECMO flow (L/min)	6.57	6.05	5.86	5.3
Max cardiac index on ECMO (L/min/m^2)	3.9	3.1	2.5	3.5
Duration of ECMO support (days)	6.8	4.0	7.1	8.9
Return to OR on ECMO	No	No	No	Yes

ECMO, extracorporeal membrane oxygenation; EOPA®, Elongated One-Piece Arterial Cannula; OR, operating room; VIS, vasoactive-inotropic score.

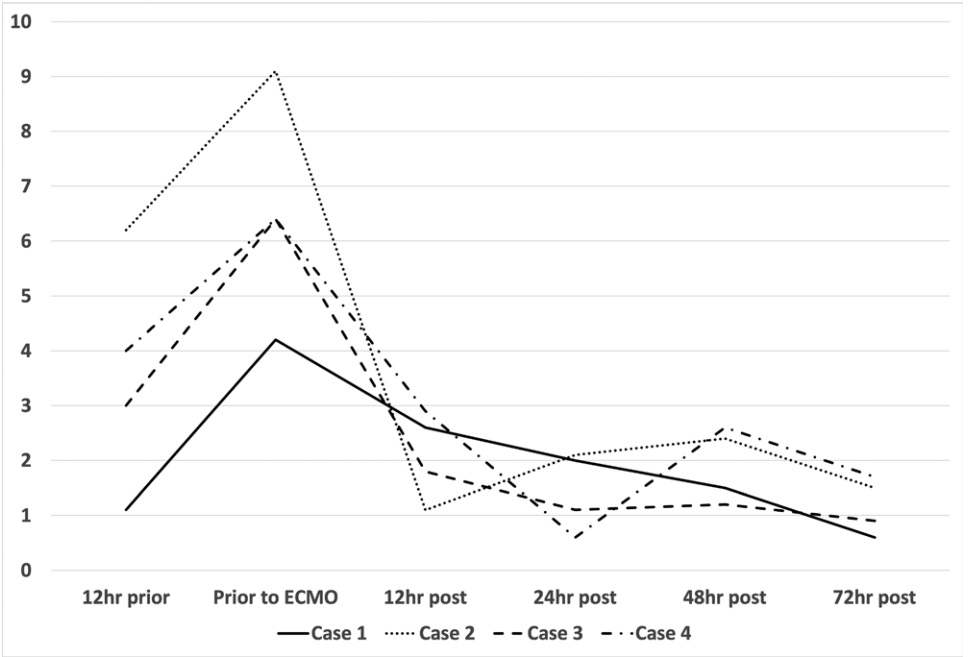

Figure 1. Serum lactate level in pericannulation period (mmol/L). Prior/post denote before cannulation and postcannulation, respectively. ECMO, extracorporeal membrane oxygenation.

Patient Outcomes

All patients survived to hospital discharge and their clinical outcomes are seen in Table 3. There were no neurological, limb, or wound complications noted during admission. Case 3 was treated for a course of tracheitis during her intensive care unit stay following ECMO decannulation and chest closure. Case 4 was treated for macrophage activation syndrome with anakinra following her ECMO decannulation. She also developed acute kidney injury that required continuous renal replacement therapy which was eventually weaned off with normal renal function. All patients were discharged from the medical unit to the inpatient psychiatric unit where they stayed for a duration of 6, 24, 74, and 10 days, respectively.

Discussion

Although rare, massive CCB overdose presents a true medical emergency that can result in RVS and rapidly impending circulatory collapse. Extracorporeal membrane oxygenation support has been shown to have reasonable outcomes for advanced CCB poisoning, mostly in the adult population. However, given the high ECMO flow rates required to support patients in a high output, vasodilated setting seen after such an overdose, peripheral ECMO use to support a pediatric patient suffering from a massive CCB ingestion is limited by the smaller size of peripheral access points in children and adolescents. To overcome this challenge in the pediatric population, we have adopted a support strategy of primary central ECMO cannulation for patients admitted to our center suffering from RVS associated with massive CCB overdose. In this report, we present four cases over a 10 months time period with 100% survival and no long-term morbidity as a result of the index hospitalization.

This is not the first report of central ECMO use following CCB overdose. Several case reports have identified patients who underwent central ECMO cannulation, however, all were done following a cardiac arrest as part of resuscitative measures or as a conversion once peripheral ECMO was determined to provide inadequate support.[6,9,10] Although these patients survived, we believe once a patient reaches massive vasodilation, it is more advantageous to pursue "elective" central ECMO cannulation than waiting for a

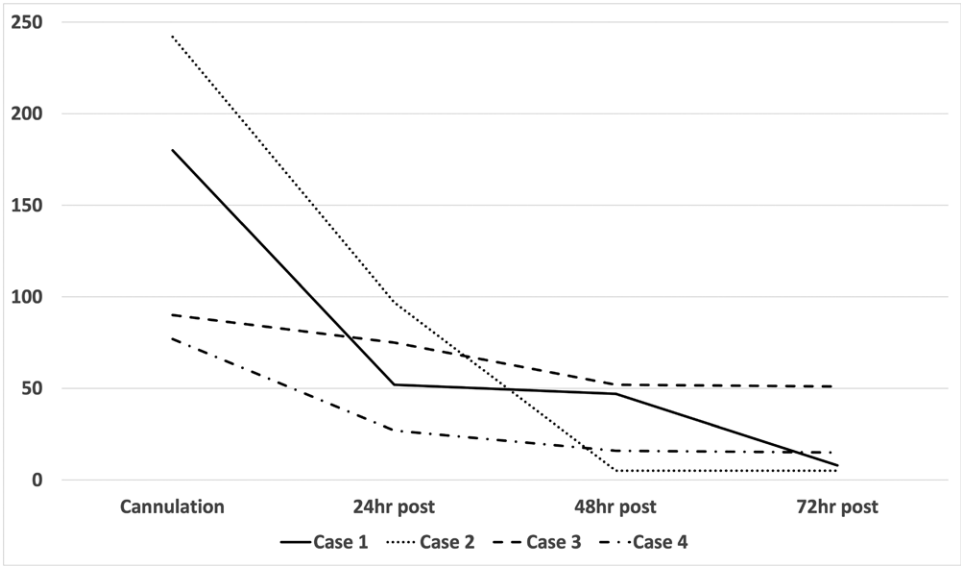

Figure 2. Vasoactive-inotropic score in pericannulation period. Post denotes postcannulation.

Table 3. Outcomes

Variables	Case 1	Case 2	Case 3	Case 4
Survival to discharge	Yes	Yes	Yes	Yes
Duration of intubation (days)	5	11	10	26
Hospital length of stay (days)	20	29	102	58
Discharge disposition	Home	Home	Home	Home
Need for CRRT after ECMO	No	No	No	Yes
Neurological complications	No	No	No	No
Limb complication	No	No	No	No
Sternal wound complication	No	No	No	No

CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

peri-arrest situation, which dramatically increases morbidity and mortality.

Over the last decade, there has been renewed interest in supporting RVS due to sepsis with central ECMO in the pediatric population. As the group from Australia notes, survival from peripheral ECMO support for children suffering from RVS was less than 50%. With their adaptation of primary central ECMO in this population, they achieved a hospital discharge rate of 74%.[11] Likewise, the group from Houston reported a hospital discharge rate of 66% in centrally cannulated pediatric patients suffering from septic shock.[12] Undoubtedly, RVS from sepsis is not the same as RVS from CCB overdose. However, we would argue the entity seen following CCB toxicity is, in fact, a model condition for which central ECMO can be most advantageous as it is a rapidly progressive and rapidly (generally <7 days) reversible process that requires very high flow rates which are unachievable even with the largest peripheral ECMO cannulas in adult patients.

Once a patient reaches the need for ECMO support following CCB ingestion, an important risk *versus* benefit analysis should ensue in considering central cannulation. Benefits include dramatically higher flow rates, more rapid weaning of high-dose vasoactive drips (confers protection to distal capillary beds), and avoidance of the peripheral vasculature to prevent neurologic (neck) or limb (groin) complications. The downsides of central cannulation are a period of open chest requirement and the risk of mediastinal reexploration for bleeding. Our patients suffered no important morbidity other than a sternal scar. In our experience, the benefits of central cannulation outweighed the risks in the case of CCB overdoses.

There are certainly limitations to our study. This is a single center case series that reflects the treatment biases of our intensivists, toxicologists, and surgeons. Perhaps the biggest limitation is our uncertainty of what would have happened to these patients if they were not placed on ECMO and thus may represent a survival bias. Additionally, one might question what would have happened if they had been placed on peripheral ECMO first instead of proceeding directly to primary central ECMO cannulation.

In conclusion, we have presented four patients who were successfully treated for profound RVS with the use of primary central venoarterial ECMO cannulation. Given these successes, our center has functionally adopted a "call for central ECMO" into the algorithm for treatment of massive CCB overdose at our children's hospital. While these events remain rare, the incidence sadly seems to be increasing as all four of these patients were treated within the last year. Clearly every patient with CCB overdose does not need ECMO support, but in those who do demonstrate profound RVS and worsening acidosis, primary central ECMO support affords excellent survival with low rates of morbidity.

References

1. St Onge M, Anseeuw K, Cantrell FL, et al: Experts consensus recommendations for the management of calcium channel blocker poisoning in adults. *Crit Care Med* 45: e306–e315, 2017.
2. Bartlett JW, Walker PL: Management of calcium channel blocker toxicity in the pediatric patient. *J Pediatr Pharmacol Ther* 24: 378–389, 2019.
3. Christensen MB, Peterson KM, Bogevig S, et al: Outcomes following calcium channel blocker exposures reported to a poison information center. *BMC Pharmacol Toxicol* 19: 78, 2018.
4. Maskell KF, Ferguson NM, Bain J, Wills BK: Survival after cardiac arrest: ECMO rescue therapy after amlodipine and metoprolol overdose. *Cardiovasc Toxicol* 17: 223–225, 2017.
5. Wang GS, Levitan R, Wiegand TJ, Lowry J, Schult RF, Yin S; Toxicology Investigators Consortium: Extracorporeal membrane oxygenation for severe toxicological exposures: Review of the toxicology investigators consortium. *J Med Toxicol* 12: 95–99, 2016.
6. Vignesh C, Kumar M, Venkataraman S, et al: Extracorporeal membrane oxygenation in drug overdose: A clinical case series. *Indian J Crit Care Med* 22: 111–115, 2018.
7. Gaies MG, Gurney JG, Yen AH, et al: Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. *Pediatr Crit Care Med* 11: 234–238, 2010.
8. Hamzah M, Seelhammer TG, Beshish AG, et al: Bivalirudin or heparin for systemic anticoagulation during pediatric extracorporeal membrane oxygenation: Multicenter retrospective study. *Thromb Res* 229: 178–186, 2023.
9. Durward A, Guerguerian AM, Lefebvre M, Shemie SD: Massive diltiazem overdose treated with extracorporeal membrane oxygenation. *Pediatr Crit Care Med* 4: 372–376, 2003.
10. Kolcz J, Pietrzyk J, Januszewska K, et al: Extracorporeal life support in severe propranolol and verapamil intoxication. *J Int Care Med* 22: 381–385, 2007.
11. MacLaren G, Butt W, Best D, Donath S: Central extracorporeal membrane oxygenation for refractory septic shock. *Pediatr Crit Care Med* 12: 133–136, 2011.
12. Ruth A, Vogel AM, Adachi I, Shekerdemian LS, Bastero P, Thomas JA: Central venoarterial extracorporeal life support in pediatric refractory septic shock: A single center experience. *Perfusion* 37: 385–393, 2022.