Air Medical Journal 38 (2019) 178–182

Contents lists available at ScienceDirect

Air Medical Journal

journal homepage: http://www.airmedicaljournal.com/

Original Research

Long-Distance Transportation of Carbon Monoxide–Poisoned Patients on Extracorporeal Membrane Oxygenation Seems Possible: A Porcine Feasibility Study

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A B S T R A C T

Objective: Extracorporeal membrane oxygenation (ECMO) has been widely used to stabilize patients with impairment of cardiac/respiratory function, and ECMO has been used to stabilize cardiopulmonary insufficiency caused by carbon monoxide (CO) poisoning in a porcine model. Airborne transportation in fixed wing aircraft of patients suffering from CO poisoning is challenging because as the air pressure drops, the oxygen content falls correspondingly.

The aim of this study was to show the feasibility of cannulating and establishing ECMO therapy during airborne transportation after severe CO poisoning in a porcine model.

Methods: An anesthetized pig was subjected to severe CO poisoning and loaded onto a Hercules aircraft. Cardiac arrest was induced at an altitude of 8,000 feet, after which cannulation and the establishment of venoarterial (VA) ECMO were performed. Vital signs were monitored, and arterial blood samples were analyzed while airborne.

Results: CO poisoning was induced with carboxyhemoglobin at 58% before takeoff. We successfully cannulated the animal in-flight during cardiac arrest and initiated VA ECMO. The animal regained spontaneous circulation and was successfully weaned from ECMO. During VA ECMO, PaO_2 was maintained at high levels (420-615 mm Hg).

Conclusion: It is possible to cannulate and initiate VA ECMO treatment as airborne en route therapy for cardiac arrest and severe CO intoxication in a porcine model.

Carbon monoxide (CO) is highly toxic, even in small concentrations. It acts on several levels, all leading to diminished oxygen metabolism and subsequent general ischemia. Subsequent cardiac and pulmonary failure might prove fatal. CO typically forms in connection with combustion of carbon-containing materials. Major sources of exposure are fire smoke and gas containing CO.[1-3] In addition to increased levels of CO, thermal injuries on the thoracic cage, in airways, and in the lungs may prevent proper oxygenation. Hyperbaric oxygen (HBO) therapy is used in selected cases for severe CO poisoning because the half-life of carboxyhemoglobin is lowered significantly.[4,5] Whether HBO therapy decreases mortality and/or morbidity is a highly debated subject.[6-9] HBO requires expensive equipment and specialized knowledge and is usually only available at very few medical facilities in each country, whereas extracorporeal membrane oxygenation (ECMO) is accessible in mobile configurations.[10,11]

In a previous porcine study, it was shown that venoarterial (VA) ECMO may be a valuable asset in the treatment of CO poisoning.[12] By relieving strain on the heart and improving oxygenation, ECMO may serve as an alternative to or a bridge to HBO therapy. This is supported by 2 case reports in which VA ECMO was used as therapy in severe CO poisoning and 1 in which venovenous (VV) ECMO was used.[13-15] ECMO has previously been used during aerial transportation of

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1067-991X/$36.00

https://doi.org/10.1016/j.amj.2019.03.009

patients.[16,17] However, to the best of our knowledge, cannulation during flight has not been performed previously.

Aerial transportation of patients by fixed wing aircraft can be challenging. Fixed wing aircraft present hostile environments for the patient, equipment, crew, and medical personnel.[18] One of the major challenges is the reduction in air pressure with increasing altitude because this also leads to a reduction in oxygen content in the air. To some extent, the reduction in air pressure can be limited by pressurizing the cabin. However, in most pressurized cabins, the pressure will not exceed 80% of sea level pressure regardless of the altitude of flight, the equivalent of around 8,000 ft.[19] In addition to altitude, complicating factors such as vibration, noise, poor lighting, air conditioning, and the effect of gravitational forces also come into play.[20]

It is possible to minimize the impact of these stressors by placing a medical evacuation (medevac) module inside the aircraft. The Royal Danish Air Force (RDAF) has custom-made medevac modules at its disposal designed to reduce vibration and noise and to provide a temperature-controlled, air-conditioned, well-lighted environment for the medical personnel and the patient (Fig. 1). Even though this improves conditions for the patient and the staff, the impact of altitude and g-forces remains unchanged.

The aim of the present study was to show the feasibility of using ECMO as a potential en route therapy after severe CO poisoning in a porcine model and to explore the possibilities for VA cannulation and initiation of this treatment in-flight.

Methods

Ethical Statement

The experiment involving the research animal was authorized by the Danish Animal Experiments Inspectorate (J.nr. 2016-15-0201-01064). A veterinarian participated in the experiment.

Research Animals, Medication, and Instrumentation

For this experiment, we used a female Danish Landrace pig weighing 39 kg. The pig had an acclimation period of 5 days after arriving at the research facility from the farm. At the research facility, pigs are housed in groups with free access to feed and water.

On the day of the experiment, the pig was anesthetized with an intramuscular injection of 10 mL Zoletil 100 (tiletamine/zolazepam-Virbac Danmark, Kolding, Denmark). Anesthesia was continued with intravenous infusion of fentanyl (300 μg/h) and propofol (120 mg/h) for the duration of the experiment. A 6.5-mm endotracheal tube was placed and connected to a portable ventilator (Oxylog 2000; Dräger-werk AG & Co, Lübeck, Germany) using 8 mL/kg to calculate the tidal volume. Positive end-expiratory pressure was set at 5 cm H_2O but was increased intermittently for short periods to avoid atelectasis; 7F sheaths were inserted with the aid of ultrasound in both femoral arteries, in the right femoral vein, and in the right external jugular vein. The venous sheaths were used for the infusion of fluids and medications, whereas the arterial sheaths were used for blood gas

Figure 1. Photographs of key elements in the experiment. (a) The intensive care medevac module during loading onto the Hercules C130J at Aalborg Airbase. (b) A view of the intensive care medevac module inside the cargo bay of the aircraft. (c) Cannulation during chest compressions inside the medevac module at an altitude of 8000 ft. (d) Cannulation completed and extracorporeal circulation established. Cannulas are secured with sutures.

analysis and continuous invasive blood pressure measurements. The femoral sheaths were also inserted in order to prepare for emergency cannulation via the Seldinger technique for ECMO during the forthcoming flight. Electrocardiographic monitoring was performed during the experiment, and arterial blood gas samples were taken regularly and analyzed on location using portable equipment (ABL90 FLEX Series; Radiometer Medical, Brønshøj, Denmark). Technicians from Radiometer Medical were present during the entire experiment to secure correct blood gas analysis. Isotonic saline solution was infused continuously according to guidelines.[21,22] A urinary thermal catheter was used to drain urine and to monitor core temperature. For ECMO, we used a centrifugal pump (Rotaflow; Maquet, Rastatt, Germany) and an oxygenator (QUADROX Adult; Maquet, Rastatt, Germany).

Experimental Protocol

Once all sheaths and monitoring equipment were in place, the pig was transferred from the operating room in the Biomedical Research Laboratory to an ambulance provided by the RDAF and then transported to Aalborg Air Base. For safety reasons, CO poisoning could not be performed in the aircraft itself; therefore, it was carried out in a hangar at the air base. The animal was transferred to a stretcher in a designated area of the hangar and connected to a ventilator (Dameca DREAM, Rødovre, Denmark). Then, CO poisoning was initiated by adding CO from a pressurized canister to the closed circulation attached to the ventilator. CO was added in small doses, keeping the inhaled CO at a maximum of 2%. Fraction of inspired CO was controlled using an exhaust emission gas analyzer (Model SV-5Q; China Coal, Shaanxi, China). Waste air from the ventilator was led outside the hangar into free air. During intoxication, the air inside the hangar was monitored for potential leaks of CO using a CO detector. Once carboxyhemoglobin reached 50%, it was held at this level until right before departure from the hangar, at which time an extra dosage was given. The pig was transferred to and installed in a medevac module that had been loaded onto the aircraft (Hercules C-130J; Lockheed Martin, Bethesda, MD) before the experiment (Fig. 1). Aeromedical Evacuation Squadron 690 (RDAF) operated the medevac module, and Air Transport Squadron 721 (RDAF) operated the aircraft. All medical equipment was securely fastened before takeoff. After 50 minutes of flight and with a cabin pressure of 8,000 ft (also the actual altitude), cardiac arrest was induced (defined by systolic pressure < 25 mm Hg) by placing an electrode connected to a 9-V battery in the right atrium via a central venous catheter. While chest compressions were performed as part of the resuscitation efforts, a 15F arterial cannula (Novaport; Novalung, Heilbronn, Germany) and a 19F venous cannula (Medtronic, Minneapolis, MN) were placed using the Seldinger technique via the femoral sheaths placed earlier. At this time, the pig was given 20,000 IU heparin. After placement, the cannulas were connected to the extracorporeal circuit, and ECMO was started. Oxygen flow to the oxygenator was set at a constant level of 2 L/min with 100% oxygen, and blood flow was 2 L, equivalent to 3,000 rounds/min on the Rotaflow. Resuscitation was ongoing during the following time period, and after 29 minutes of ECMO, return of spontaneous circulation was obtained using direct current conversion (Zoll Pro Pac MD; ZOLL Medical Corporation, Chelmsford, MA). Nevertheless, ECMO was continued as circulatory and respiratory support. Because of other obligations on this test flight, the aircraft had a short time period at 2,500 ft. The aircraft returned to Aalborg Air Base, and the pig was transferred back to the hangar where weaning from ECMO was initiated. The pig managed 20 minutes on its own circulatory conditions (without inotropic drugs) and was then sacrificed using an intravenous injection of pentobarbital.

Results

Cannulation of the animal was performed at 8,000 ft during cardiac arrest and achieved return of spontaneous circulation 29 minutes after ECMO was established. The time in the air was 127 minutes. Weaning from ECMO was initiated and completed after landing. The time line of the experiment and the altitude curve are shown in Figure 2. Blood gas values and related events are listed in Table 1. During VA ECMO, PaO_2 was maintained at high levels (420-615 mm Hg) compared with ventilation with fraction of inspired oxygen at 100% (300-435 mm Hg).

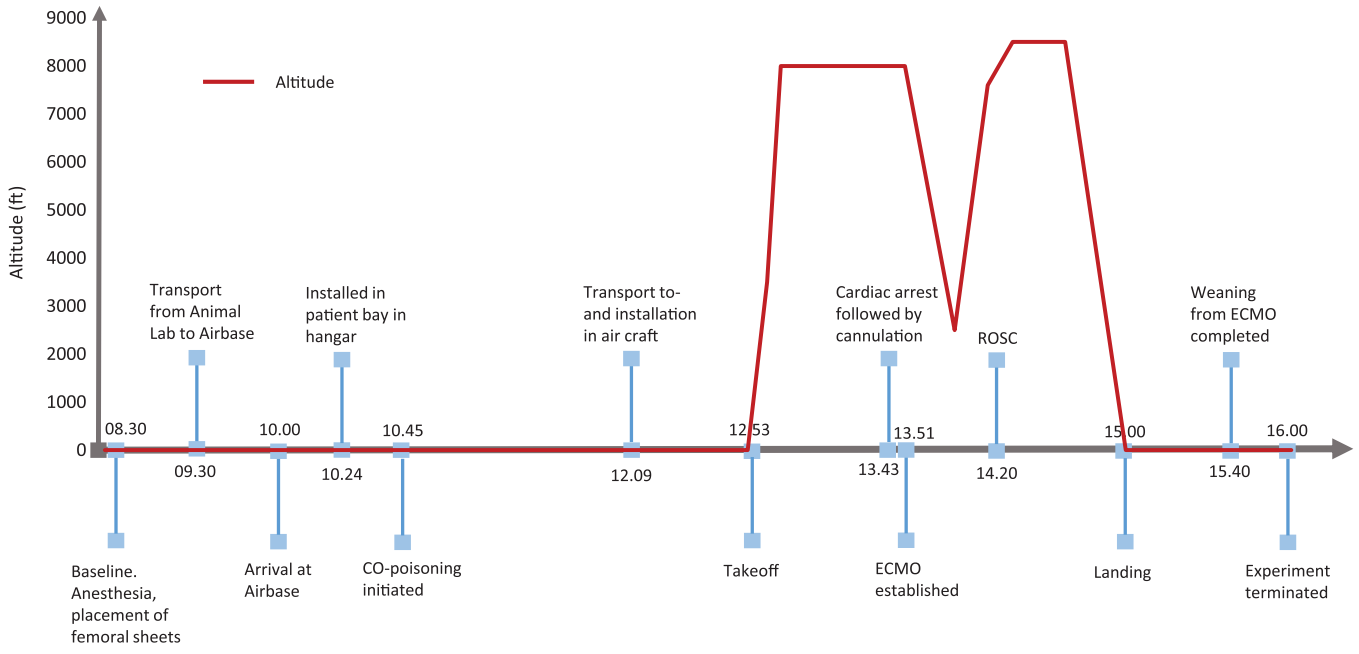

Figure 2. The time line of the experiment. Significant events plotted along the time line and corresponding altitude represented with the red line. Arterial blood gas samples are listed in Table 1.

Table 1
Time Line of Events, Arterial Blood Gas Samples, and Selected Vital Signs

Time	Event	Altitude (ft)	pH	CO_2 (mm Hg)	pO_2 (mm Hg)	Lactate (mmol/L)	HbCO (%)	BP (mm Hg)	HR (beats/min)
08.33	Baseline	0	7.46	35.7	321.0	0.8	0.3	104/58	51
10.24	Transfer to hangar completed	0	7.5	37.8	390.1	0.7	0.3	100/54	52
10.35	Arterial blood gas analysis	0	7.48	38.7	284.3	0.7	0.3	97/54	50
10.45	CO poisoning initiated	0	7.48	38.6	297.8	0.6	14.6	106/52	63
11.05	Arterial blood gas analysis	0	7.46	41.4	303.0	1.1	49.3	144/85	70
11.15	Arterial blood gas analysis	0	7.45	41.5	297.0	1.2	49.0	136/62	70
11.48	Arterial blood gas analysis	0	7.46	39.6	303.0	1.1	58.7	114/62	68
12.09	Transfer to aircraft	0							
12.20	Arterial blood gas analysis	0	7.54	28.7	381.8	1	27.5	87/47	60
12.53	Takeoff	0							
13.05	Arterial blood gas analysis	8000	7.53	32.3	68.9	0.8	12.5	93/47	46
13.06	Ventilator set at 100% oxygen	8000							
13.12	Arterial blood gas analysis	8000	7.49	33.9	433.6	0.7	11.1	95/46	45
13.25	Arterial blood gas analysis	8000	7.46	32.1	444.1	0.7	9.3	113/46	44
13.43	Cardiac arrest induced	8000						21/18	135
13.51	ECMO established	8000						76/74	VF
14.00	Arterial blood gas analysis	4000	7.31	33.0	535.6	4.1	10.9	84/82	VF
14.08	2500 ft 50 mmol K^+	2500	7.28	33.5	615.8	5.5	9.9	65/62	VF
14.20	ROSC	4500							SR
14.29	Arterial blood gas analysis	8500	7.25	35.4	419.3	7.9	7.3		62
14.38	Arterial blood gas analysis	8500	7.37	25.4	465.1	6.9	7.5		51
15.00	Wheels on ground	0	7.24	34.7	567.8	8	5.3	100/68	43
15.30	Arterial blood gas analysis	0	7.11	55.6	186.8	6.8	4.7	183/43	62
15.37	Weaning from ECMO initiated	0	7.18	41.9	469.6	6.9	4.5	181/133	112
15.40	Weaning completed	0							
15.45	Arterial blood gas analysis	0	7.15	49.7	184.5	5.7	4.4	123/70	82

BP = blood pressure; CO = carbon monoxide; ECMO = extracorporeal membrane oxygenation; HbCO = carboxyhemoglobin; HR = heart rate; ROSC = return of spontaneous circulation; SR =sinus rythm; VF = ventricular fibrilation.
Time line and significant events with corresponding arterial blood gas samples, BP, and HR.

Discussion

We showed that it is feasible to apply VA ECMO in a medevac setting onboard a fixed wing aircraft in a pig suffering from severe CO poisoning. VA cannulation while airborne is possible even during cardiac arrest. Thus, ECMO may be of potential use as rescue therapy for patients with life-threatening impairment of cardiac and/or pulmonary function and may facilitate safe transportation of such patients.

Air medical transportation is no easy task. Noise limits the ability of free communication and inhibits the use of auditory alarms on medical equipment. Vibration can potentially disturb equipment, and at frequencies between 25 and 75 Hz, it can raise muscular activity, which results in increased oxygen consumption.[18] Gravitational forces (g-forces), especially during acceleration/deceleration, displace blood, and the drop in pressure displaces body fluids to the third space.[23] Turbulence is kept at a minimum at a flight altitude of 8,000 to 10,000 ft[24]; however, fuel consumption as well as air traffic and weather are important factors when planning the altitude of transportation.[25] In a military evacuation procedure, tactical concerns regarding flight altitude and cabin pressure may overrule considerations regarding patient/staff comfort. The reduction in oxygen pressure as well as the other in-flight stressors mentioned earlier can be limiting factors when airborne transfer of a patient is needed.[20] As previously mentioned, the use of medevac modules can reduce the impact of these factors, thereby creating improved working conditions for the medical crew. The obstacles created by g-forces and the lowering of air pressure are the same and must be dealt with accordingly.

On several occasions, patients have been transported using fixed wing aircraft while on ECMO.[16,17] In these patients, ECMO was established before patient transportation. Typically, a highly specialized team will be allocated to the medical facility from where the patient is transferred, and the team will initiate or continue ECMO therapy during transportation. Mobile ECMO systems have been used for these purposes. To the best of our knowledge, no reports regarding en route cannulation and the initiation of ECMO treatment exist. During the present study, we managed to perform a successful femoral cannulation in-flight during cardiac arrest in a porcine model. When used as an in-flight rescue therapy option, ECMO may prove to be a valuable tool to make some transportation possible that otherwise would have been deemed too hazardous to attempt. However, it is important to weigh the potential complications of ECMO therapy (ie, bleeding, infection, stroke, and lower limb ischemia) against the possible benefits of initiating treatment.[26] For this reason, it may be favorable to use ECMO as a backup strategy instead of placing the patient on ECMO before departure. In this way, the risk of complications will be minimized while still achieving safe transportation of the patient.

The principles and procedures regarding cannulation and the establishment of VA ECMO for CO poisoning are not different for other patient categories. Therefore, it is reasonable to assume that cannulation in air will also be possible in these patients. Depending on the patient type, venovenous ECMO might be preferable, in which case a double-lumen cannula inserted via the external jugular vein might be sufficient. Again, intravascular sheaths placed before departure will presumably ease the in-air cannulation procedure significantly. When performing this procedure, it was a huge advantage to use the femoral arterial/venous sheaths that were placed before takeoff. This markedly limits the time consumption of the procedure and the risk of complications or failure. If in-flight cannulation is contemplated as a backup plan, we strongly suggest the placement of sheaths before takeoff.

Even though a high PaO_2 was achieved when using the ventilator at 100% oxygen (up to 443 mm Hg), an even higher PaO_2 was achievable when ECMO was applied (615 mm Hg). We speculate that these last percentages might potentially influence the outcome if the patient is in critical condition.

For safety reasons, we chose not to perform the intoxication inside the aircraft. If a leak of CO should occur, evacuation would not have been possible while in the air, endangering the entire crew. Therefore, we intoxicated the pig in a hangar close to the

runway. The disadvantage of this was that we could not intoxicate the pig to the point of severe cardiac insufficiency or cardiac arrest because the time needed for transportation, loading, and takeoff would have made it impossible to initiate ECMO in time for resuscitation. However, we did reach a very high level of CO intoxication (carboxyhemoglobin = 58%) that in normal conditions would be considered lethal; however, because of ventilation with high fraction of inspired oxygen, carboxyhemoglobin levels dropped markedly until the experiment went airborne. In order to create the intended critical situation, cardiac arrest was induced using direct current as described previously. Although we performed cannulation in a severely CO-intoxicated animal during cardiac arrest, the situation does not fully represent a CO-induced cardiac arrest. Nevertheless, the technique involved in cannulation and ECMO therapy was not different.

It is also a limitation that the pig, for ethical reasons regarding the use of animals for research, had to be euthanized after the experiment. Therefore, knowledge is lacking regarding the neurologic performance of the animal after poisoning and treatment. However, the case reports of ECMO being used in patients with CO poisoning suggest that ECMO-treated CO poisoning is possible with favorable neurologic outcomes.[13-15] Future studies exploring the effect of ECMO intervention and CO poisoning should take neurologic outcome into consideration.

We chose a pig for our animal model for several reasons; the cardiopulmonary system is similar to that of humans, and the size of the animal allowed us to use the same medical equipment/procedures that would have been used for humans.[27] The cannulation procedure is more difficult in pigs because the difference in anatomy makes the angle between the entry point of the cannulas in the skin and the blood vessels steeper than in humans. We have no reason to believe that the physiological impact during flight on the pig (ie, the impact of g-force/vibration) does not resemble that of humans. The difficulties involved in loading/unloading between the different locations is comparable with what would have been the case for humans; this is also an important factor for our feasibility evaluation.

In a military setting, the use of en route ECMO may make it possible to combine tactical and strategic medevac into 1 flight because ECMO can be used as a rescue therapy for unstable patients who would otherwise have required a stop in a role 1 to 3 facility for stabilization before strategic medevac.[28] If this is the case, the patient is repatriated sooner, which is both a medical advantage and an operational advantage because managing critically ill patients rapidly depletes the limited medical resources in a mission area.

Conclusion

In a porcine model, it is possible to cannulate and start VA ECMO treatment as an en route therapy for cardiac arrest and severe CO intoxication. The possibility of using ECMO as a backup strategy has the potential to make airborne transportation of these critical patients safer.

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