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PRACTICAL PEARL

The Physiology of the Apnea Test for Brain Death Determination in ECMO: Arguments for Blending Carbon Dioxide

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Introduction

Extracorporeal membrane oxygenation (ECMO) is a form of extracorporeal life support which can be utilized as a rescue modality in patients with treatment refractory cardiac or respiratory failure. ECMO removes deoxygenated blood from the venous circulation via large bore cannula where it is pumped through a membrane oxygenator which adds oxygen (O_2) and removes carbon dioxide (CO_2). The blood is then returned back to the circulation. Depending on the type of organ failure, the oxygenated blood can be returned to the venous circulation or the arterial circulation (VA ECMO). The patient's underlying physiologic derangement ultimately determines the type of ECMO [1].

ECMO is becoming an increasingly common supportive modality. From 1998 to 2015, the Extracorporeal Life Support Organization collected data on 65,171 patients undergoing support with ECMO with 53% neonates, 25% pediatric, and 23% adults. The indications for ECMO were respiratory failure (63%), cardiac failure (29%), and as a last resort in cardiopulmonary resuscitation (8%). The rate of extracorporeal cardiopulmonary resuscitation (CPR) is also increasing. Although it may be associated with a survival rate of 27%, one in four patients may progress to brain death [2].

ECMO complicates not only traditional apnea testing as guided by the American Academy of Neurology guidelines, but also ancillary cerebral blood flow tests such as a cerebral angiogram. As part of the examination, an apnea test is performed using a CO_2 rise to stimulate the respiratory centers. This is accomplished with O_2 diffusion and has remained a safe method [3]. If clinical examination is inconclusive, ancillary testing may be considered. Transportation of ECMO patients can be difficult. Additionally, the perturbations in cerebral blood flow caused by ECMO have not been adequately investigated and will vary depending on the ECMO cannulation strategy [4].

In patients on ECMO, the aforementioned protocol for apnea test is not feasible as CO_2 levels and oxygenation are related to both ECMO circuit and patient characteristics. The majority of ECMO centers in the USA use polymethylpentene (PMP) hollow fiber oxygenators. Blood flow passes on one side of the membrane, while sweep gas flows in the opposite direction. Via this cross-current exchange mechanism, O_2 is added to the blood, while CO_2 is removed. CO_2 is twenty times more soluble than O_2 and is transferred more easily through any type of membrane than O_2 [5]. CO_2 transfer is related to "sweep" gas flow (expressed in liters/minute), temperature, and pH [6, 7]. O_2 transfer is governed by blood flow, hemoglobin concentration, blood temperature, "sweep" gas fraction of O_2, and pre-membrane O_2 saturation. The high degree of CO_2 solubility combined with the high efficiency of CO_2 removal of modern PMP hollow fiber oxygenators means that attempts at decreasing sweep gas

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flow often lead to a greater effect on oxygenation than CO_2 [1, 8, 9].

We describe a case where apnea testing was performed on a patient on VA ECMO by adding CO_2 in a controlled manner to the ECMO circuit. The ultimate outcome was a successful apnea test with a predictable rise in $paCO_2$.

Case Report

A 45-year-old man suffered a cardiac arrest at home followed by recurrent ventricular fibrillation requiring cumulatively more than 60 min of CPR. Initial computed tomography (CT) scan of the head was normal. He was transferred to our tertiary care hospital and subsequently had recurrent arrest ultimately requiring VA ECMO which was initiated via femoral vein and femoral artery cannulation using a Maquet Cardiohelp device (Maquet Rotaflow Centrifugal Pump with Quadrox-I Oxygenator, Maquet Getinge, Gothenburg, Sweden). Transesophageal echocardiogram revealed biventricular akinesis. Because of the lack of left ventricular (LV) ejection, he was then taken to the operating room for central ECMO cannulation via right atrium and aorta. Due to LV distension, an additional cannula was placed into the LV to facilitate decompression. His chest was left open, and he returned to the intensive care unit (ICU).

In the ICU, temperature was targeted at 36 °C. Initially, he was sedated with propofol and fentanyl. Rhythm was controlled with lidocaine and procainamide. Low-dose norepinephrine and vasopressin were used to support his blood pressure. An endocardial biopsy was performed given uncertainty regarding etiology of cardiac arrest. When sedation was stopped, he remained comatose. His neurologic examination revealed absent motor response to pain stimuli but preservation of pupillary, corneal, and cough reflexes. Electroencephalography showed a burst suppression pattern without generalized periodic epileptic activity. Approximately 18 h later, he was noted to acutely have fixed and dilated pupils, loss of roving eye movements and no cough. Emergent CT scan of the head revealed new multifocal infarcts and diffuse cerebral edema with sulcal effacement and loss of the basal cisterns. This prompted a more formal examination.

A brain death assessment was performed after excluding possible confounders. There were no brainstem reflexes, no motor responses, and no evidence of spontaneous breathing effort. At that time, he was receiving ECMO support via VA ECMO with 60% FiO_2, sweep gas flow of 2 L/min, pump speed of 3700 RPM, pump flow of 5.32 L/min, and ECMO cardiac index of 2.11 L/m^2/min. Mechanical ventilator was set to controlled mode, tidal volume of 400 mL, respiratory rate of 12 breaths per minute, PEEP 5 cmH_2O, 50% FiO_2. Infusions included norepinephrine 0.1 mcg/kg/min, vasopressin 0.04 units/min, lidocaine 2 mg/min, procainamide 6 mg/min, heparin 5 units/kg/min, and insulin 0.5 units/h. He had pulsatility (cardiac ejection) above the ECMO circuit, and arterial blood pressure was 114/78 (89) mmHg, atrially paced rhythm at 80 beats per minute, and temperature of 37.2 °C.

Apnea testing was performed. Baseline arterial blood gas: pH 7.3, $paCO_2$ 46 mmHg, paO_2 113 mmHg, and HCO_3 26. A D-size CO_2 tank used a CGA 940 Insufflation Yoke attached to a Western Medica Regulator connected to a Cole Palmer Flowmeter with a 0–200 mL/min range which was attached to the Sechrist Air–O_2 mixer (Model 3500). The ECMO sweep flow and FiO_2 were maintained at previous settings. The patient was removed from the mechanical ventilator, and no supplemental O_2 was supplied. 100% CO_2 was added to the ECMO circuit at an 8% sweep volume ratio (160 mL/min). The basis for this value is described in the discussion. He was closely observed for respiratory effort. Five minutes into the test, an arterial blood gas revealed a pH of 7.24, $PaCO_2$ 63 mmHg, PaO_2 70 mmHg, and bicarbonate 27. The patient was observed for an additional 4 min, and no respiratory effort was noted. Throughout the test, the patient had no significant change in heart rate or arterial blood pressure. The patient was declared brain dead.

The family was subsequently consented for organ donation, and the patient was able to donate both kidneys and liver.

Discussion

Due to the complexities added to the brain death assessment of patients on ECMO, there continues to be uncertainty regarding the optimal approach to apnea testing and some patients who undergo brain death assessment may not undergo this essential test [10]. Our case report illustrates that by adding an 8% CO_2 volume to the ECMO circuit, an arterial $CO_2 > 60$ mmHg will reliably be obtained (Fig. 1). This finding should be independent of patient size, ECMO circuit volume or oxygenator surface area. This technique works without changing any of the ventilator settings although removal of the patient from the mechanical ventilator should still occur to simplify observation for respiratory efforts, and the addition of supplemental O_2 via the endotracheal tube will lead to less chance of desaturation in patients with residual pulmonary blood flow. This technique leads to rapid change

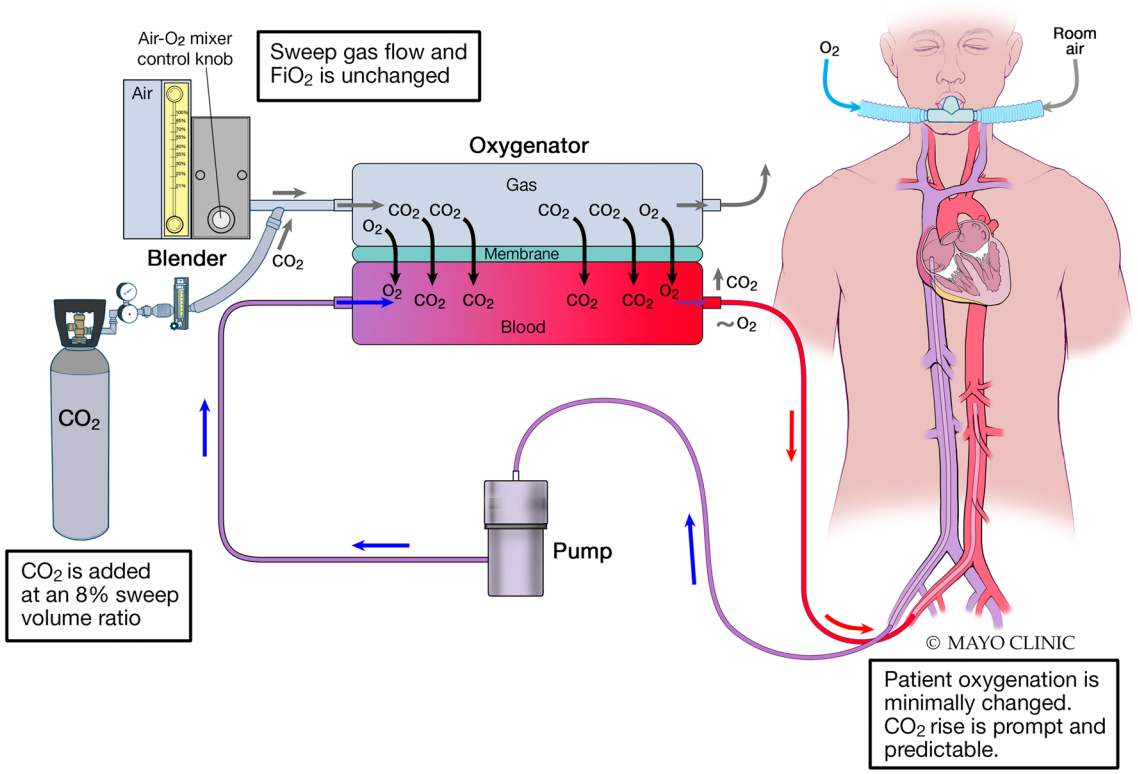

Fig. 1 An alternative approach to apnea testing on ECMO involves the addition of CO_2 into the ECMO circuit as illustrated in this figure. This method should provide a reliable increase in CO_2, and because ECMO sweep gas flow is not altered, oxygenation should be maintained

in CO_2 and eliminates the "guessing" of how much the sweep gas flow needs to be lowered, which usually results in multiple blood gasses being drawn. Knowing reliably that a target CO_2 levels will be reached allows efficient use of clinicians' time and limits unnecessary serial blood draws. Once brain death is determined, these patients are well supported, while potential for organ donation is discussed with pertinent decision makers (Fig. 2).

The blending of CO_2 and O_2 into the gaseous phase of an extracorporeal oxygenator has a long proven history of being a safe practice [11]. In cardiac surgery, the addition of CO_2 enables a normal CO_2 level in the blood of extracorporeal circuits with oxygenators and continues to be commonly performed today, especially when implementing deep hypothermic circulatory arrest with the pH stat method. During hypothermic cardiopulmonary bypass, an arterial pH of approximately 7.40 and $PaCO_2$ of 40 mmHg is maintained and corrected to the patient's actual temperature. Because of the alkaline shift in pH during cooling due to increased CO_2 solubility, CO_2 is added to the sweep gas in order to maintain the constant "normal" range of values CO_2. The total content of CO_2 in the blood increases, producing a relative hypercarbia and respiratory acidosis. The percentage of CO_2 in the ventilating gas that is necessary to maintain the $PaCO_2$ at 40 mmHg in a normothermic patient is found by dividing 40 mmHg by the atmospheric pressure. At sea level, this is 40/760 or approximately 5–6%. If a $PaCO_2$ of 65 is desired, as in apnea testing, then 65/760 denotes 8–9% CO_2 endogenous mix.

Previous descriptions of apnea testing in ECMO have advocated for decreasing sweep gas flow which subsequently relies upon a passive increase in CO_2 due to decreased CO_2 removal by the ECMO oxygenator (Fig. 3). Using this methodology, a eucapnic state is first obtained by adjusting sweep flow. Subsequently, the patient is removed from the mechanical ventilator and connected to an inflating bag with continuous positive

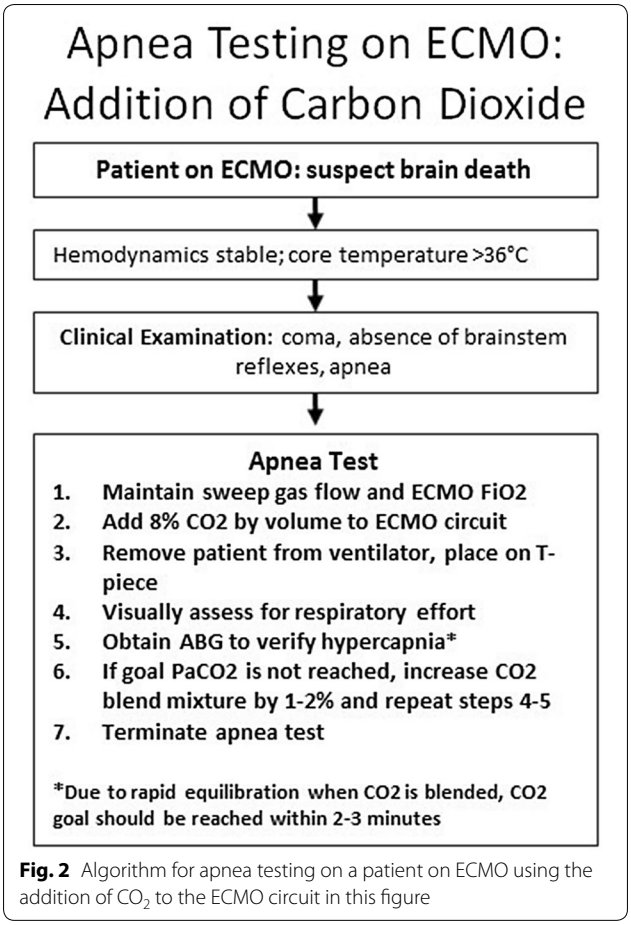

Fig. 2 Algorithm for apnea testing on a patient on ECMO using the addition of CO_2 to the ECMO circuit in this figure

airway pressure. The ECMO sweep is then decreased to 0.5–1 L/min. Serial ABGs are performed to document hypercapnia, while the patient is observed for respiratory effort [12, 13]. Variations to this protocol include alternative forms of O_2 delivery during the apnea test such as use of T-piece [14, 15], passing an O_2 tube down the endotracheal tube [16], and foregoing the addition of supplemental O_2 [17]. Yang et al. describe turning sweep flow to zero, but this method will likely lead to severe hypoxemia in most patients on VA ECMO [18]. In the largest reported series, 25 patients underwent brain death assessment while on ECMO by decreasing the sweep gas flow. Although hemodynamics and heart rhythm were relatively stable during the brain death assessments, severe hypoxia ($paO_2 < 40$ mmHg) occurred in a considerable number (8%) of patients [19]. A report by Jarrah et al. outlines specific challenges in the pediatric population. One-third of the pediatric patients who underwent brain death assessment and apnea testing by decreasing sweep gas flow experienced severe hemodynamic instability and hypoxia [13]. The alternative approach involving the addition of exogenous CO_2 to the ECMO circuit has also been discussed as a possibility by multiple authors [10, 17, 20]. Pirat et al. describe a case in which exogenous CO_2 was slowly titrated into the ECMO membrane oxygenator. In this report, the patient was left on the mechanical ventilator and end-tidal CO_2 was monitored, while exogenous CO_2 was slowly titrated into the circuit [21]. Champigneulle et al. reported a similar protocol where CO_2 is introduced via an 18 G needle inserted into the hose between the gas blender and oxygenator, while transcutaneous partial pressure of CO_2 is monitored to assist in CO_2 titration prior to obtain an arterial blood gas. In the eight patients, described minimal effects on oxygenation or hemodynamics occurred during the test. [22].

Conclusion

The utilization of ECMO to support patients with circulatory or respiratory compromise is becoming increasingly common. The apnea test is a key component of the evaluation for brain death. The majority of previous protocols for apnea testing while on ECMO involve turning ECMO sweep gas flow down to low levels which can lead to patient hypoxemia and difficulty in predicting when goal $PaCO_2$ will be reached. The addition of 8% CO_2 by volume to the ECMO circuit is a method to reliably increase $PaCO_2$ by 20 mmHg without having to decrease sweep gas flows and compromise oxygenation.

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Author Contributions
WBB helped in the care of the patient in the case report and preparation of manuscript; PS helped in the care of the patient in the case report and preparation of manuscript; EW helped in the care of the patient in the case report and preparation of manuscript.

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Upon admission the patient's family consented to review of medical chart and extraction of information for research purposes.

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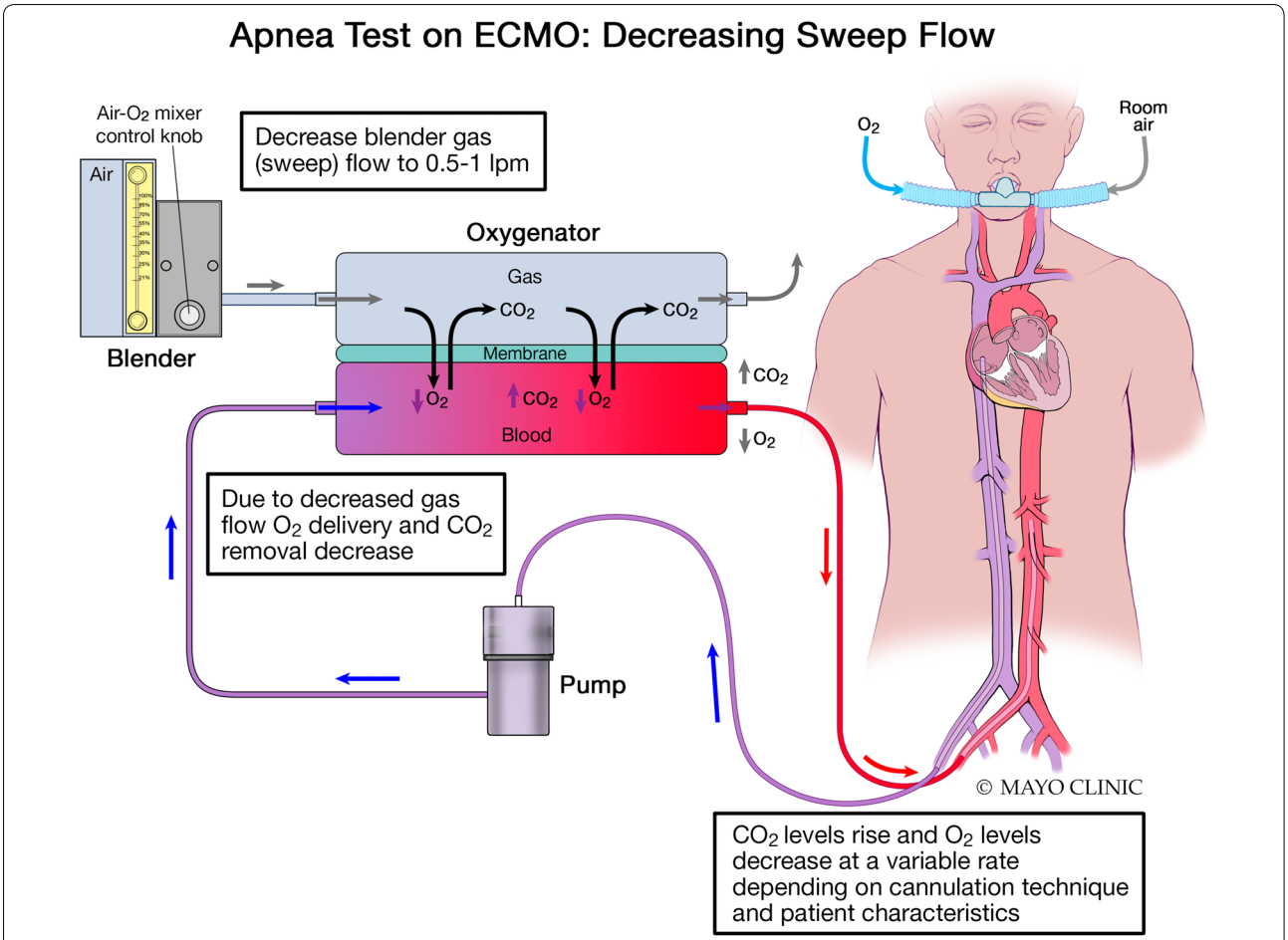

Fig. 3 In order to increase CO_2 levels to adequate levels to perform a brain death assessment apnea test while the patient is on ECMO, sweep gas flow can be decreased with goal of decreased removal via membrane oxygenator. With decreased sweep gas flow, the delivery of O_2 may be compromised

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