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Supplement 7. Determination of Brain Death/Death by Neurologic Criteria in Patients on Extracorporeal Support: Extracorporeal Membrane Oxygenation

This supplementary material has been provided by the authors to give readers additional information about their work.

Determination of Brain Death/Death by Neurologic Criteria in Patients on Extracorporeal Support: Extracorporeal Membrane Oxygenation

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Abstract

Introduction Patients requiring ECMO and other forms of extracorporeal support are at high risk of complications leading to brain injury and brain death/death by neurologic criteria (BD/DNC). Performing apnea testing may be challenging under these conditions.

Methods We conducted a scoping review of apnea testing during veno-venous or veno-arterial ECMO support.

Results A review of ECMO principles, gas exchange physiology and clinical report of apnea testing with extracorporeal support is provided.

Conclusion Guidance for determination of BD/DNC on ECMO includes fulfilling fundamental principles of BD/DNC (etiology, prerequisites, clinical criteria and any indications for ancillary testing). Apnea testing should be performed by pre-oxygenation through the ventilator and ECMO sweep gas, providing CPAP while decreasing sweep gas flow to increase arterial $PaCO_2$ to traditional apnea test targets.

Patients requiring ECMO and other forms of extracorporeal support are at high risk of complications leading to brain injury and brain death/death by neurologic criteria (BD/DNC). Performing apnea testing may be challenging under these conditions. Authors conducted the initial literature searches of the Cochrane, Embase and MEDLINE databases for the time period between January 1, 1992 and July 2017. Subsequent searches were performed to capture relevant articles between July 2017 and April 2020. Because of the significant lack of data from randomized controlled trials or large studies, GRADE evaluation of the evidence was not performed. However, evidence was reviewed by a multidisciplinary group of clinicians (see Introduction chapter) and recommendations were generated according to the following criteria. Strong recommendations ("It is recommended that") were based on expert consensus that clinicians should follow the recommendation unless a clear and compelling rationale for an alternative approach was present, and where actions could be adopted as policy. Even though most evidence in this area is limited and of low-quality, strong recommendations were made as a precautionary, conservative approach, to prevent premature or erroneous determinations of death (false positives). Conditional or weak recommendations ("It is suggested that") were generated when there were potentially different options and the best action may differ depending on circumstances, patients,

resources or societal values, or where there is a need for further evidence or discussion among clinicians and stakeholders. In cases where there was insufficient evidence and the balance of benefits versus harms was neutral, no recommendations were made.

A significant number of people being treated with extracorporeal membrane oxygenators (ECMO) progress to brain death/death by neurologic criteria (BD/DNC). The etiology of BD/DNC may be related to the primary disease process, such as ECMO-CPR for refractory cardiac arrest with subsequent anoxic brain injury, or embolic or hemorrhagic complications related to extracorporeal support.[1] The same fundamentals of BD/DNC determination – etiology, prerequisites, minimum clinical criteria, and indications for ancillary testing – should be applied to adults and children on ECMO.

ECMO can be used to provide respiratory support only (Veno-Venous ECMO or V-V ECMO) for patients with refractory hypoxemia or to provide both respiratory and circulatory support (Veno-Arterial ECMO or V-A ECMO) for patients with refractory hypoxemia and severe cardiac and/or hemodynamic failure. During ECMO, the blood is essentially drained from a person's body through a large bore venous catheter placed near the right atrium or the inferior vena cava, oxygenated externally with a membrane oxygenator (that increases the O_2 and removes CO_2 and therefore acts as an "artificial lung") and then returned to the body through either a venous access (V-V ECMO) or through an arterial catheter (V-A ECMO). In V-V ECMO, the entire cardiac output is based on intrinsic cardiac function. In V-A ECMO, a pump that provides adequate "cardiac output" is added in order to provide continuous flow circulatory support that augments or replaces intrinsic pulsatile cardiac function.

With the advancement of extracorporeal technology and the development of mechanical multi-organ support, ethical dilemmas about the ultimate mechanism of death are being raised. Brain-based determinations of death are increasingly relevant when circulatory support is in place that prevents the arrest of circulation. This can be represented by patients with circulation fully supported by V-A ECMO or a Left Ventricular Assist Device (LVAD) in the absence of any effective or intrinsic cardiac output. These patients may have suffered extensive anoxic brain injury followed by diffuse cerebral edema and brain herniation (with a mechanism and neurological exam compatible with BD/DNC). The determination of death can only be brain-based while circulation is extracorporeally supported.

ECMO has been used in neonatal and pediatric care since the 1980's, but recently the use of ECMO is increasing in adults. In a study evaluating ECMO use from 2006 to 2011, there was an increase in the rate of ECMO cases per million adult discharges of 433%, i.e. from 11.4 (95% CI, 6.1-16.8) in 2006 to 60.9 (95% CI, 28.1-93.7) in 2011.[2,3] This is important to physicians who perform evaluations for BD/DNC because BD/DNC can occur as a complication associated with ECMO. In fact, in 2009, it was reported that 21% of adults treated with ECMO to support cardiopulmonary resuscitation were declared brain dead.[4]

Performing an apnea test in these persons on ECMO requires adherence to the same principles as in those not receiving ECMO, but it can sometimes be more challenging in this population, particularly because there is a lack of consistent guidance on how the test should be performed under these conditions. In a retrospective study of 26 people who were declared brain dead while on ECMO and became organ donors between 1995 and 2014, 11 (42%) did not have an apnea test. Of those, nine (82%) had one or more ancillary tests performed to confirm BD/DNC, while the other 2 (18%) underwent only a clinical

examination. Interestingly, all cases in which ECMO was documented as the reason for not doing an apnea test occurred after 2008.[3]

CO_2 clearance during ECMO depends on: a) the rate of the sweep gas flow through the oxygenator, b) the ECMO blood flow, c) the physical properties of the oxygenator (maximum CO_2 exchange rate), d) the presence of added CO_2 in the inspired gas, and e) the rate of CO_2 elimination by the mechanically ventilated acutely injured lung. If the other parameters are stable, CO_2 removal is mainly dependent on the rate of sweep gas flow through the oxygenator.[5] When performing an apnea test in patients receiving ECMO, the sweep gas flow rate is minimized to diminish CO_2 removal and therefore promote arterial CO_2 accumulation. Given the high solubility and facility with which CO_2 diffuses through the membrane oxygenator and is eliminated, very low (or non-existent) gas flow rates are required in order to allow for progressive accumulation of CO_2 in the bloodstream (hypercapnia). Unfortunately, hypoxemia can develop with very low gas flow rates, but this is not a common occurrence.

Small case series in adults [6-9] and children [10] have been published on the methodology to perform apnea testing while on ECMO. There are descriptions of apnea testing in both V-A ECMO [11-17] and V-V ECMO.[7,18,19] The most common process includes pre-oxygenation with 100% FiO_2 on the ventilator and 100% O_2 on the ECMO gas flow, reduction of the sweep gas flow to 0-1 L/min and either 1) using CPAP with a flow inflating anesthesia bag, or 2) maintaining CPAP on the ventilator, or 3) placing them on T-piece, or 4) disconnecting the ventilator and placing a cannula inside the endotracheal tube while delivering O_2 flow at a rate of 6-9 L/min.[7,19,20] In one Italian study, 144 decedents not requiring ECMO were compared with 25 decedents on V-A ECMO. Both groups were pre-oxygenated with 100% FiO_2 for 5 minutes. The apnea test was conducted via a resuscitator bag (AMBU bag) with an adjustable PEEP valve connected to 8 L/min oxygen. The PEEP in the valve was the same as the PEEP on the ventilator. For those on ECMO, the extracorporeal blood flow was not modified, but the sweep gas flow was reduced to 1 L/min, and FiO_2 was increased to 100 %. Fluid boluses and increases or initiation of vasoactive drugs were required in less than 10% and 3 %, respectively, of the apnea procedures. Severe hypoxia occurred in 2.4 % of decedents not on ECMO and 8% of those on ECMO ($p = 0.063$).[21] Another reported method utilized Carbogen (inhaled CO_2) via the ventilator circuit in a person on V-A ECMO with the goal of promoting faster arterial CO_2 accumulation and shortening of the apnea test. The target CO_2 goal was achieved within 8 minutes without hemodynamic instability.[17]

Caution has been advocated in the performance of apnea testing during V-A ECMO when intrinsic cardiopulmonary function persists.[22] Reliance on distal arterial blood gases as measurement of hypercarbia may not account for CO2 exchange in the lung which may exit the left heart, enters the proximal aorta and aortic arch and mixes with ECMO flow. This can be mitigated by ensuring simultaneous measurement of CO2 levels in post oxygenator circuit. For those VA-ECMO patients without intrinsic cardiopulmonary function and continuous flow, distal arterial blood gases remain accurate, but the validity of transcranial doppler during non-pulsatile flow has been questioned.[23]

Recommendations and Suggestions

1. It is recommended that the same fundamentals of the BD/DNC concept – etiology, prerequisites, minimum clinical criteria, apnea testing targets and indications for ancillary testing – be applied to adults and children on ECMO.

2. It is recommended that performance of an apnea test be part of BD/DNC testing in persons on V-V and V-A ECMO, unless contraindicated due to cardiopulmonary instability.
3. In persons receiving V-A ECMO for circulatory and respiratory support, it is recommended that the extracorporeal blood flow be maintained during the clinical evaluation and apnea test in order to prevent hemodynamic instability and achieve a MAP ≥ 60 mmHg in adults and age-appropriate targets in pediatrics. V-A ECMO flow rates may be increased to support the MAP if required before or during testing.
4. It is recommended that prior to apnea testing, a period of pre-oxygenation be provided for all persons on ECMO by administering 100% inspired oxygen via the mechanical ventilator and increasing the O_2 in the membrane lung from the ECMO machine to 100% for 10 minutes.
5. It is recommended that apnea testing in persons on ECMO be conducted by:
    a. Delivering 100% oxygen to the lungs via CPAP on the mechanical ventilator, a resuscitation bag with a functioning PEEP valve, or oxygen flow via a tracheal cannula,
        - Similar to apnea testing in general, the application of positive airway pressure with the use of CPAP/PEEP may prevent derecruitment.
        - It is recognized that some patients may not be mechanically ventilated during ECMO and suspected BD/DNC. Under these conditions, while an apnea test can still be conducted, maintaining oxygenation during the apnea test may be challenged due to the inability to deliver oxygen to the lower airway. Oxygenation will depend on providing 100% oxygen in the sweep gas. If oxygenation cannot be maintained appropriately, the test will need to be aborted and ancillary testing will be required.
        - In cases of VA-ECMO with intrinsic cardiac output, blood gases should be measured simultaneously from the distal arterial line and post oxygenator ECMO circuit. The apnea tests targets for *both* sampling sites should be pH < 7.30 and $PaCO_2$ of at least 60 mmHg (20 mmHg above the patient's baseline $PaCO_2$ for persons with pre-existing hypercapnia).
    b. Maintaining oxygen in the membrane lung at 100% throughout the duration of the testing,
    c. Titrating the sweep gas flow rate to 0.5-1 L/min while maintaining oxygenation,
    d. Assessing for spontaneous breathing while targeting traditional apnea test targets via serial blood gases (as described in the Minimum Clinical Criteria for Determination of Brain Death section), keeping in mind that achieving a pH < 7.30 and $PaCO_2$ of at least 60 mmHg (20 mmHg above the patient's baseline $PaCO_2$ for persons with pre-existing hypercapnia) may take longer than in a person without ECMO support,
    e. Terminating the test immediately if the person exhibits any kind of spontaneous respiratory movements or becomes unstable as described in the Minimum Clinical Criteria chapter,

f. Restarting mechanical ventilation and returning to the prior ECMO sweep gas flow rate when the pH reaches < 7.30 and $PaCO_2$ reaches 60 mmHg (20 mmHg above his/her baseline $PaCO_2$ if there is premorbid hypercapnia).

6. As described in the Minimum Clinical Criteria chapter, it is suggested that if the apnea test cannot be safely conducted or completed, an ancillary test be considered.

Questions to Inform Research Agendas

1. Are there different prerequisite hemodynamic targets for persons on V-A ECMO who are maintained on continuous blood flow?
2. Are the indications for ancillary tests different in patients on ECMO?
3. Does the addition of inhaled or sweep gas CO_2 mitigate the risks of apnea testing in ECMO patients?
4. Does non-pulsatile flow in patients on VA-ECMO impact the reliability of transcranial doppler as an ancillary test?

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