# Carbogen for Apnea Testing During the Brain Death Declaration Process in Subjects on Extracorporeal Membrane Oxygenation

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**BACKGROUND: The use of extracorporeal membrane oxygenation (ECMO) in adult patients continues to increase. Suspicion of brain death while on ECMO creates a conundrum. The American Academy of Neurology states that apnea testing is a critical component of the process to declare brain death. However, there is a paucity of literature on apnea testing for confirmation of brain death in patients on venoarterial ECMO and venovenous ECMO. Traditional apnea testing does not consider ECMO physiology or de-recruitment of the lungs in this subset of critically ill patients. Complications with traditional apnea testing include hemodynamic instability that may lead to cardiac arrest and death. METHODS: We conducted a retrospective review of apnea tests using the carbogen method performed for brain death determination on 5 subjects on ECMO. A positive apnea test was used in confirmation of brain death in all 5 subjects on either venovenous ECMO ($n = 2$) or venoarterial ECMO ($n = 3$) while remaining on mechanical ventilation. A formula was used to calculate the subject's target value for $CO_2$ production and completion of the apnea test. RESULTS: In all 5 cases, the carbogen method resulted in 100% accuracy of the targeted $CO_2$ goal, and apnea testing was confirmed with no adverse events. CONCLUSIONS: In 5 subjects on ECMO, the carbogen method for apnea testing as part of the process to declare brain death was accurate in predicting the end point of the apnea test. With the increased use of ECMO in adults and the ongoing need for organs, methods to confirm brain death with apnea testing while on ECMO should be further studied.** *Key words: ECMO; apnea tests; brain death; mechanical ventilation.* [Respir Care 2020;65(1):75–81. © 2020 Daedalus Enterprises]

## Introduction

The use of extracorporeal membrane oxygenation (ECMO) in adults has risen since 2002, with a statistically significant increase from 2006 to 2011.[1] ECMO is currently used as a form of partial cardiopulmonary bypass in cardiac surgery, pulmonary blood flow (venoarterial) and primary gas exchange (venovenous) support, and in patients awaiting heart and lung transplantation, where its use has increased 4% and 6%, respectively. However, the greatest increase in the use of ECMO has been in cases of respiratory failure, doubling from 8% in 2002 to 16% in 2012.[2] As of July 2017, the Extracorporeal Life Support Organization (ELSO) has reported > 100,000 patients on ECMO, and > 50% were for pulmonary indications. Although ECMO can be initiated as a life-saving therapy, complications may lead to devastating long-term neurologic sequelae, such as seizures, hemorrhage, infarction, and brain death.[3,4] If brain death is suspected, clinicians are confronted with the need to conduct apnea testing on patients receiving ECMO. Nasr and Rabinstein[5] examined

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the rates and outcomes of neurologic complications of subjects receiving ECMO during hospitalization. Subjects were selected from the Nationwide In-patient Sample between 2001 and 2011. Of 23,951 patients who received ECMO, 2,604 (10.9%) suffered neurologic complications of seizure (4.1%), stroke (4.1%), or intracranial hemorrhage (3.6%). Brain death is reported to have occurred in 7–21% of adults receiving ECMO in some academic centers.[6-9] With the increasing use of ECMO, the need for accurate apnea testing is paramount to confirm brain death and the possibility of increasing organ procurement.

The American Academy of Neurology (AAN) guidelines provide recommendations for the determination of brain death, including detailed checklists for prerequisites, examination, and apnea testing. Confirmatory testing is recommended if the clinical examination cannot be fully performed due to patient factors, or if apnea testing is inconclusive or aborted.[10] Ancillary testing has limitations when used as an alternative to a complete clinical exam.[11] First, ancillary testing only evaluates the cerebral cortex, whereas the most common definition of brain death refers to the absence of brainstem reflexes. Therefore, ancillary testing is not a substitute for assessing brainstem function.[11] Second, confirmatory testing may require transportation to a location outside the ICU, which is typically difficult for patients on ECMO and mechanical ventilation.

We developed a protocol for determining brain death utilizing the AAN guidelines with a clinical exam (Fig. 1). The clinical exam includes patient history, physical examination, neuroimaging, and laboratory tests to determine the presence of irreversible neurologic insults prior to apnea testing. Once a clinical exam has confirmed the absence of brainstem reflexes, an apnea test is performed to assess the final aspect of brainstem function.

In 2012, we began using carbogen during apnea testing in adult patients undergoing brain death declaration. Traditionally, apnea testing for brain death declaration is performed by disconnecting the patient from mechanical ventilation and inserting oxygen tubing to the level of the carina through the artificial airway to provide oxygen during the exam.[10,12] During this time, an assessment for unassisted breaths takes place. Per AAN guidelines, the checklist for apnea testing includes a baseline arterial blood gas (ABG) to be drawn prior to apnea testing to confirm whether the $P_{aCO_2}$ level is within the normal range (35–45 mm Hg).[10] A positive apnea test in adults is declared if the $P_{aCO_2}$ rises to $\geq$ 60 mm Hg or if there is a rise of $\geq$ 20 mm Hg above the baseline $P_{aCO_2}$ and no evidence of spontaneous respirations. This considers the fact that $P_{aCO_2}$ rises in a linear fashion by $\sim$ 3–5 mm Hg/min when a patient is removed from mechanical ventilation. $CO_2$ production at the cellular level is significantly reduced with brain injuries and brain death, making the timing of the accurate blood sampling difficult to predict.[13]

**QUICK LOOK**

**Current knowledge**

The use of extracorporeal membrane oxygenation (ECMO) in adults has risen since 2002, with a statistically significant increase from 2007 to 2011. Although ECMO can be initiated as a life-saving therapy, complications may lead to devastating long-term neurologic sequelae, such as seizures, hemorrhage, infarction, or even brain death. Brain death determination on ECMO is complicated by altered physiology.

**What this paper contributes to our knowledge**

The carbogen method may provide a safer method of effective apnea testing and can be used to confirm brain death in patients on venovenous and venoarterial ECMO. In the small number of subjects studied, the use of carbogen was successful in achieving pH and $P_{aCO_2}$ goals with continuous monitoring using $P_{ETCO_2}$.

Disconnecting a critically ill patient from mechanical ventilation to perform apnea testing has several risk factors, including hemodynamic instability and even cardiac arrest. These reasons often lead physicians to forgo apnea testing as part of the brain death evaluation.[11,13-16] This reluctance is increased in patients on ECMO who require apnea testing.[7] The purpose of this retrospective case series was to analyze whether the carbogen method was a safe and reliable apnea test to determine brain death in subjects on ECMO.

## Methods

### Study Design

This study is a retrospective review conducted on patients in the ICUs at the University of Maryland Medical Center and the R. Adams Cowley Shock Trauma Center, which are urban tertiary centers, between April 2012 and November 2014. Our institutional review board approved a retrospective chart review to evaluate apnea tests performed with carbogen while on ECMO. A chart review was completed on 5 subjects where apnea testing was performed using the carbogen method while the subjects were on ECMO.

### Carbogen Method

The carbogen method for apnea testing as a confirmation of brain death introduces carbogen, which is exoge-

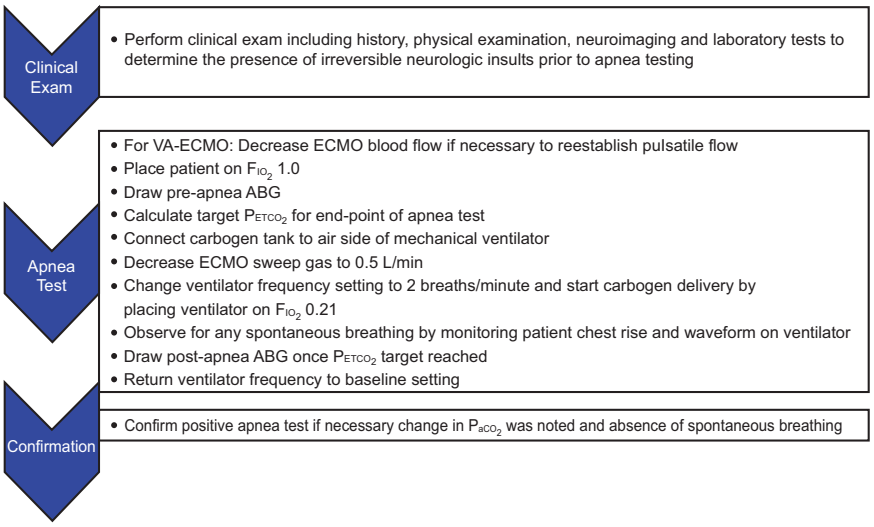


Fig. 1. Carbogen Apnea Test protocol for ECMO Patients. VA-ECMO = venoarterial extracorporeal membrane oxygenation; ABG = arterial blood gases.

nous $CO_2$ with a mixture of 3% $CO_2$ and 97% $O_2$ delivered through a ventilator. A calculation is used to predict the end point of the apnea exam by targeting an end-tidal carbon dioxide pressure ($P_{ETCO_2}$) goal: (pre-apnea pH − 7.20)/0.006.[17] This formula yields the necessary increase in $P_{aCO_2}$ to meet the requirements of a positive apnea test. Adding the sum plus the baseline $P_{ETCO_2}$ (ie, the displayed $P_{ETCO_2}$ at the time that the pre-apnea ABG was drawn) provides the $P_{ETCO_2}$ target to complete the exam with a positive apnea test.[17] For example: [(7.40 − 7.20)/0.006 = 33.33] + 40 mm Hg $P_{ETCO_2}$ = 73 mm Hg, which becomes the $P_{ETCO_2}$ target.[17] The formula is based on the relationship between $P_{aCO_2}$ and pH: for every 1 mm Hg increase in $P_{aCO_2}$, there is a corresponding 0.006 decrease in pH.[17] In addition, the formula targets a pH goal of 7.20, which should trigger spontaneous respiration if the patient is not brain dead.[18] Even if there is a large gradient between the $P_{aCO_2}$ and the $P_{ETCO_2}$, as the $P_{ETCO_2}$ increases, so will the $P_{aCO_2}$. Therefore, the $P_{ETCO_2}$ is the target to complete the apnea test that will result in a $P_{aCO_2}$ that meets the requirements for a positive apnea test.

To begin the exam, the patient is preoxygenated on an $F_{IO_2}$ of 1.0. After 10–15 min, an ABG sample is drawn to calculate the $P_{ETCO_2}$ goal. The carbogen tank is then connected to the high-pressure air inlet of the ventilator, and the ventilator is set to an $F_{IO_2}$ of 0.21 to deliver the carbogen mixture. The ECMO sweep gas is decreased to 0.5 L/min to minimize $CO_2$ clearance. The set breathing frequency is decreased to 2 breaths/min during the exam to deliver the carbogen mixture. The 2 breaths/min do not contribute much to $CO_2$ removal and also allows for an $P_{ETCO_2}$ measurement with each breath, which increases as the carbogen is delivered and the patient's $P_{aCO_2}$ increases. During the exam, the patient is monitored for any spontaneous efforts through analysis of ventilator $P_{ETCO_2}$ waveforms and by observation of the patient's chest and abdomen for any spontaneous breathing efforts. Throughout the apnea test, the patient is monitored for hemodynamic stability and oxygenation (ie, should maintain $S_{pO_2} > 85\%$). The apnea test is terminated if the $S_{pO_2}$ is $< 85\%$ for 30 s, systolic blood pressure decreases to $\leq 90$ mm Hg, or there is evidence of spontaneous effort. Once the target $P_{ETCO_2}$ is reached and no spontaneous breathing is detected, a post-apnea ABG is drawn to confirm a positive apnea test. An ABG is required to demonstrate that the $P_{aCO_2}$ has reached the AAN requirements for a positive apnea test (Fig. 1). Once the post-apnea ABG is drawn, the patient should be returned to previous ECMO and ventilator settings.

## Results

In this retrospective review, we evaluated 5 ECMO cases to determine brain death. All 5 subjects were clinically assessed to determine the need for brain death declaration per AAN guidelines. Once brain death criteria were met, including evidence of unresponsiveness and absence of brainstem reflexes, apnea testing proceeded.

The 5 subjects on ECMO ranged in age from 20 to 35 y with various diagnoses that led to an average Sequential Organ Failure Assessment (SOFA) score of 11.2. Three of the 5 subjects were on venoarterial ECMO, and the remaining 2 subjects were on venovenous ECMO. Four of the 5 subjects required a sweep gas $< 1$ L/min, whereas the fifth patient required a sweep gas of 14 L/min.

All subjects remained on the ventilator during apnea testing with the set frequency decreased to 2 breaths/min

($T_{high}$ increased to 30 s for the subject on airway pressure release ventilation (APRV)), to deliver the carbogen mixture to the patient through the ventilator. Increasing the $T_{high}$ from 8.1 s to 30 s slightly increased the mean airway pressure from 26.0 to 26.6 cm $H_2O$.

The average time to complete the apnea tests was 12.5 min with no recorded adverse events. All 5 subjects remained hemodynamically stable during the apnea test with a systolic blood pressure $\geq$ 105 mm Hg and $S_{pO_2}$ $>$ 93%. All 5 subjects were declared brain dead based on the AAN guidelines with clinical testing and positive apnea exams.

## Discussion

These data describe an effective method of apnea testing utilizing the carbogen method in subjects supported with venovenous and venoarterial ECMO. As described in a previous study,[17] we used a carbogen mixture and mathematical formula to calculate a target $P_{ETCO_2}$ to determine the completion of the apnea test. Sharpe et al[17] reported how this method eliminated the need to withhold life support (ie, mechanical ventilation) during apnea testing on 60 subjects. Our results in only 5 subjects indicate that this method may also be used to perform an apnea exam in critically ill patients requiring ECMO. The only other published studies on the use of carbogen for apnea tests during brain death determination are abstracts that were presented at scientific meetings.[19-21]

With the increased use of ECMO, it is vital to have a safe and efficient method of apnea testing.[21] Critically ill and injured patients who progress to brain death are typically unstable, requiring vasoactive agents and increased ventilatory support. Therefore, the traditional method of disconnecting critically ill patients from mechanical ventilation for apnea testing may be risky in terms of increasing instability and adverse events, such as hypotension, hypoxia, acidosis, arrhythmias, and asystole, which may lead to cardiopulmonary arrest and cardiac death.[1,15,16,22,23] Since there is a rise in the need for organ donation, the goal is to minimize adverse events since they may affect organ viability and successful organ procurement.[24,25]

Clinicians are often reluctant to perform apnea testing on patients on ECMO due to instability and the risk of adverse events, including cardiac death.[1] We have used carbogen in $>$ 200 patients to determine brain death (unpublished observations) without significant reported adverse events. Our data indicate the accuracy of using the carbogen formula to predict the $P_{ETCO_2}$ target necessary to reach the desired $P_{aCO_2}$ level. We feel this accuracy was crucial in confirming the apnea exam by ABG in the absence of spontaneous breathing effort in an effort to eliminate unguided and potentially repeated blood sampling, minimize the time the patient was removed from the ventilator and the need to repeat apnea testing, and thereby increase efficiency and reduce potential adverse events. In addition, because the patient remains on the ventilator with the carbogen protocol, airway pressure and PEEP are maintained to limit hypoxemia, which may otherwise jeopardize the completion of an apnea test.

### Venoarterial ECMO Patients

Because pulmonary blood flow is preserved during venovenous ECMO, carbogen ventilation will increase $P_{aCO_2}$ and stimulate respiratory drive in a patient who is not brain dead. However, in venoarterial ECMO, pulmonary blood flow may be completely diverted, and carbogen ventilation would not be effective to increase $P_{aCO_2}$. Therefore, in cases where a patient has no pulsatile flow while on venoarterial ECMO, blood flow through the ECMO circuit can be decreased, if the patient remains stable, to allow native cardiac function and lung perfusion, thus allowing delivery of carbogen into the circulation. Decreasing the portion of venous return used for ECMO support (ie, ECMO blood flow) could result in patients without pulsatile flow, potentially creating hemodynamic instability. In these instances, patients would not be considered for apnea testing using the carbogen method; this is a limitation of this method. Only patients who exhibit pulsatile flow when decreasing the amount of ECMO assistance are considered candidates to continue with carbogen apnea testing, as noted in the first case where the blood flow was decreased from 3.5 L/min to 3.0 L/min (Table 1). Reestablishing pulmonary blood flow can be confirmed by pulsatile blood flow on the arterial tracing and an increase in $P_{ETCO_2}$.

### Sweep Gas on ECMO

In subject #1, the sweep gas was decreased to 0 L/min and the patient was monitored for hemodynamic stability. Within 8 min, the targeted $P_{ETCO_2}$ goal of 69 mm Hg was reached, and the post-apnea ABG was drawn. The post-apnea $P_{aCO_2}$ of 84 mm Hg confirmed a positive apnea test for declaration of brain death, which was accurate based on the formula to calculate a predictable end point. Even though there was a large gradient between the $P_{ETCO_2}$ and $P_{aCO_2}$, the formula still predicts when the desired $P_{aCO_2}$ should be reached. The post-apnea ABG also demonstrated how quickly the $P_{aO_2}$ decreased, dropping from 322 mm Hg to 86 mm Hg within 8 min. It was decided after this first ECMO apnea test not to decrease the sweep level to 0 L/min to preserve the capability of providing oxygen to the patient via ECMO. In subject #2, the sweep gas was 1 L/min and was not decreased further; it took 22 min to reach the $P_{ETCO_2}$ goal. Therefore, it was decided to decrease the sweep gas flow to 0.5 L/min and to set inspired oxygen connected to oxygenator at 100% for future tests.

Table 1. Pre-Apnea and Post-Apnea Test Results for 5 Subjects Requiring ECMO and Mechanical Ventilation

| Pre-Apena Test Results | Subject 1 | Subject 2 | Subject 3 | Subject 4 | Subject 5 |
|---|---|---|---|---|---|
| Subject age, sex | 25 y old female | 20 y old male | 35 y old female | 21 y old female | 24 y old male |
| Diagnosis | Diabetic ketoacidosis | Traumatic brain injury | Pulseless electrical activity arrest | Pulmonary embolism | Motorcycle collision |
| SOFA Score | 9 | 13 | 12 | 10 | 12 |
| ABG results | | | | | |
| pH | 7.38 | 7.38 | 7.35 | 7.38 | 7.43 |
| $P_{aCO_2}$, mm Hg | 36 | 46 | 40 | 38 | 37 |
| $P_{aO_2}$, mm Hg | 322 | 201 | 141 | 367 | 60 |
| $HCO_3$ | 22 | 26 | 22 | 22 | 24 |
| $S_{pO_2}$, % | 97 | 97 | 95 | 100 | 87 |
| $P_{ETCO_2}$, mm Hg | 36 | 25 | 22 | 19 | 24 |
| ECMO type | Venoarterial | Venovenous | Venoarterial | Venoarterial | Venovenous |
| ECMO sweep gas flow, L/min | 0.75 | 1 | 2.0 | 0.5 | 14 |
| ECMO blood flow, L/min | 3.5 | 4.2 | 5.3 | 5.16 | 6.13 |
| ECMO $F_{IO_2}$ | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Ventilator mode | APRV | VC-AC | PC-AC | PC-AC | PC-AC |
| Breathing frequency (f) prior to apnea test, breaths/min | $T_{high}$ 8.1 s<br>$T_{low}$ 0.5 s<br>f = 7 | f = 18 | f = 10 | f = 12 | f = 18 |
| $V_T$, mL/kg or PC, cm $H_2O$ | ND | $V_T$ = 360 | PC: 14 | PC: 10 | PC: 18 |
| $P_{high}/P_{low}$ (in APRV mode) | 27/0 | NA | NA | NA | NA |
| PEEP, cm $H_2O$ | $T_{low}$ set to maintain 75% PEF | 10 | 10 | 10 | 18 |
| $F_{IO_2}$ for pre-apnea ABG | 1.0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Heart rate, beats/min | 120 | 99 | 130 | 80 | 80 |
| Blood pressure, mm Hg | 110/80 | 121/64 | 135/65 | 103/63 | 105/50 |

| Post-Apnea Test Results | Subject 1 | Subject 2 | Subject 3 | Subject 4 | Subject 5 |
|---|---|---|---|---|---|
| ABG results* | | | | | |
| pH | 7.22 | 7.21 | 7.15 | 7.15 | 7.03 |
| $P_{aCO_2}$, mm Hg | 61 | 69 | 61 | 64 | 89 |
| $P_{aO_2}$, mm Hg | 86 | 159 | 209 | 335 | 86 |
| $HCO_3$ | 24 | 27 | 20 | 23 | 26 |
| $S_{pO_2}$, % | 93 | 97 | 95 | 100 | 98 |
| $P_{ETCO_2}$, mm Hg | 70 | 55 | 47 | 53 | 63 |
| Time required to reach $P_{ETCO_2}$ goal, min | 8 | 22 | 10 | 37 | 10 |
| ECMO sweep gas flow, L/min | 0 | 1 | 0.5 | 0.5 | 0.5 |
| ECMO blood flow during apnea test, L/min | 3.0 | 4.2 | 5.3 | 5.16 | 6.13 |
| ECMO $F_{IO_2}$ during apnea test | 0 | 1.0 | 1.0 | 1.0 | 1.0 |
| Ventilator mode | APRV | VC-AC | PC-AC | PC-AC | PC-AC |
| Breathing frequency (f) during apnea test and ABG to confirm brain death | $T_{high}$ 30 s<br>f = 2 | f = 2 | f = 2 | f = 2 | f = 2 |
| Breathing frequency (f) and $T_{high}/T_{low}$ after apnea test was completed | $T_{high}$ 8.1 s<br>$T_{low}$ 0.5 s<br>f = 7 | f = 18 | f = 14 | f = 12 | f = 18 |
| Ventilator delivered gas mixture during apnea test and ABG, % | 97 | 97 | 97 | 97 | 97 |
| Heart rate, beats/min | 117 | 105 | 132 | 92 | 92 |
| Blood pressure, mm Hg | 94/60 | 110/54 | 140/65 | 97/60 | 130/62 |

* ABG sample drawn after $P_{ETCO_2}$ target was reached.
ECMO = extracorporeal membrane oxygenation
SOFA = Sequential Organ Failure Assessment
ABG = arterial blood gas
$V_T$ = tidal volume
APRV = airway pressure release ventilation
f = breathing frequency
PEF = peak expiratory flow
VC = volume controlled
PC = pressure controlled
AC = assist-control
NA = not applicable
ND = no data

The remainder of the subjects were completed with a sweep gas flow of 0.5 L/min, which minimized $CO_2$ clearance and allowed oxygen to be delivered to the patient via ECMO without decreasing the post-apnea test $P_{aO_2}$ significantly. With a sweep gas flow of 0.5 L/min, the post-apnea $P_{aO_2}$ only decreased by 15% with 2 of the subjects and increased by 21% with the remaining 2 cases.

### Timing of the Tests

The addition of exogeneous carbogen contributes to decreasing the time to complete the apnea test. This is beneficial because brain-damaged patients may have a decrease in $CO_2$ production in addition to a perfusion injury. The average time to complete the apnea test in our subjects was 12.5 min, excluding subject #4, in which the apnea test was safely conducted but required 37 min on venoarterial ECMO. It was postulated in this case that low $CO_2$ production and significant reduction in lung perfusion related to the subject's massive pulmonary embolism resulted in minimal gas exchange, resulting in the extensive time to reach the $P_{ETCO_2}$ goal.

### pH Goal

Using the carbogen formula as previously published, the pH goal is 7.20, although this is not a requirement in the AAN Guidelines for declaration of brain death.[11,17] The purpose of targeting a pH of 7.20 is an additional element to minimize doubt that a patient is brain dead because a rise in $P_{aCO_2}$ of 60 mm Hg by itself may not suffice as an adequate respiratory stimulant for all patients, such as those with COPD or metabolic derangements.[16,17] A decrease in pH in addition to a rise in $P_{aCO_2}$, however, should serve as sufficient respiratory stimulus in the brainstem respiratory center.[17,18] A positive apnea test is determined based on the $P_{aCO_2}$ requirements per the AAN guidelines even though we had a pH target of 7.20.[11,17,18] The carbogen formula did create a pH $\leq$ 7.20 in 2 of the 5 subjects in this study, while the remainder were 0.01–0.02 away from the pH target of 7.20.

There are several limitations to our retrospective review. This review is limited to only 5 subjects on ECMO who required an apnea test for brain death evaluation. A prospective multicenter trial is needed with more subjects on ECMO to determine the safety and accuracy of the carbogen method for brain death declaration. Although this may be completed as a multi-center trial, the enrollment numbers may still be small because this is a unique group of patients (ie, on ECMO and requiring a brain death evaluation). Another limitation is that vasopressors and their dosage were not noted in the data collection, which could have demonstrated the vasoactive dependence index of these subjects.

## Conclusions

With the increasing use of ECMO in adults and the ongoing need for donor transplant organs, methods to accurately and successfully confirm brain death with apnea testing while maintaining venovenous or venoarterial ECMO must be studied and validated. In our 5 subjects, the carbogen method for apnea testing during brain death declaration was accurate and successful in predicting the end point of the apnea test. Alternative methods to safely confirm brain death with apnea testing while on ECMO should be further studied.

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