

# Apnea Test on Extracorporeal Membrane Oxygenation: Step Forward with Carbon Dioxide

Ozlem Saritas Nakip, MD; Selman Kesici, MD; Kivanc Terzi, MD; Benan Bayrakci, MD

*Department of Pediatric Critical Care Medicine and Life Support Center, Hacettepe University Faculty of Medicine, İhsan Doğramacı Children's Hospital, Ankara, Turkey*

**Abstract:** Apnea test must be performed to confirm brain death in patients meet clinical criteria. But the increment of carbon dioxide is generally not achievable because of the diminished production of carbon dioxide and additional sweep in extra corporeal membrane oxygenation (ECMO). We report three children with congenital heart disease treated with ECMO and had brain death during follow-up. All met clinical criteria but apnea test cannot be achieved in classical way because of prolonged duration and hemodynamic compromise. Therefore, we

used external carbon dioxide to achieve desired levels of oxygen and carbon dioxide safely. Because of the lack of protocols for pediatric patients on ECMO, apnea test with exogenous carbon dioxide may be a reliable and rapid test in such patients. Especially cardiac patients, in whom classical apnea test can cause rapid deterioration, exogenous carbon dioxide may serve as an alternative. **Keywords:** apnea test, brain death, carbon dioxide, cardiomyopathies, extracorporeal membrane oxygenation. *J Extra Corpor Technol. 2022;54:83-7*

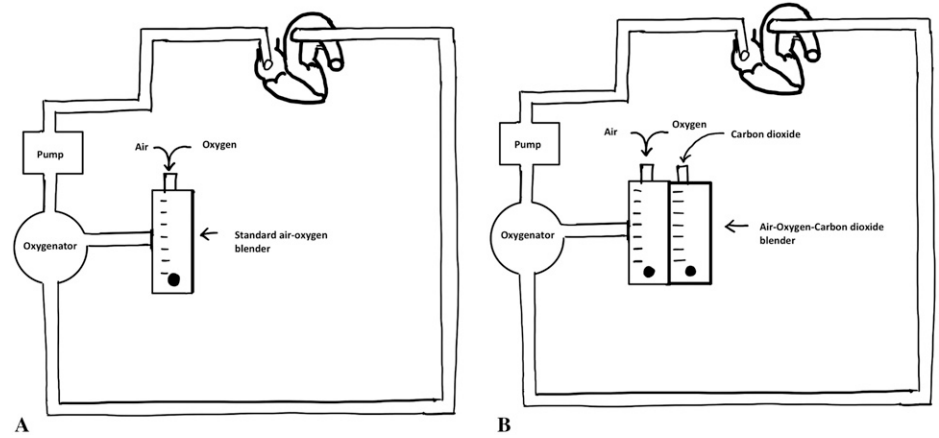
Determination of brain death in children depends on the absence of neurologic function with a known irreversible cause of coma. Coma and apnea must co-occur to diagnose brain death. Apnea testing (AT) must be performed safely and requires documentation of an arterial  $\text{PaCO}_2 > 60$  mmHg or increasing 20 mmHg above the baseline with no respiratory effort during the testing period to support the diagnosis of brain death. If the AT cannot be achieved or completed because of hemodynamic instability, a supplementary study should be made (1,2). The classical method of AT is performed using a T-piece for  $\text{O}_2$  insufflation when  $\text{PaCO}_2$  level is above 60 mmHg or increased 20 mmHg above baseline (1). However,  $\text{CO}_2$  removal continues through the membrane in extra corporeal membrane oxygenation (ECMO) patients and that leads to inadequate raise in  $\text{CO}_2$  levels. We here reported three patients that AT was achieved with  $\text{CO}_2$  insufflation.

## DESCRIPTION

Patient 1 (6 months, boy) was admitted to pediatric intensive care unit (ICU) with decompensated heart failure. He was diagnosed with noncompaction cardiomyopathy in newborn period. Because of ejection fraction was persistently below 20% despite medical therapy, heart transplantation decision was made by the local committee. While he was waiting for transplantation in hospital, he had pulseless ventricular tachycardia and central (right atrium-aorta) venoarterial ECMO treatment was started during cardiopulmonary resuscitation (E-CPR) as a bridge to transplantation. On the 10th day of ECMO, severe intraventricular hemorrhage was demonstrated by bedside cranial ultrasonography. After discontinuation of all sedatives his comatose status persisted, and two neurologic examinations with an interval of 24 hours revealed absence of brain stem reflexes and persistent coma. For the declaration of brain death, we performed an AT in a classical manner when patient's clinical condition was most appropriate (normothermia, 55 mmHg of mean arterial pressure, no electrolyte and blood glucose abnormalities). We turned off sweep gas without any change in blood flow rate (0.55 LPM) to achieve increment in  $\text{PaCO}_2$  after  $\text{PaO}_2$  reached 488 mmHg, disconnected him from ventilator using a T-piece for oxygen insufflation. At the 5th minute,

Received for publication July 30, 2021; accepted February 7, 2022.  
Address correspondence to: Ozlem Saritas Nakip, Department of Pediatric Intensive Care, Hacettepe University Faculty of Medicine, İhsan Doğramacı Children's Hospital, Altındağ, Ankara, 06230, Turkey.  
E-mail: saritasnakipozlem@gmail.com  
The senior author has stated that the authors have reported no material, financial, or other relationship with any healthcare-related business or other entity whose products or services are discussed in this paper.

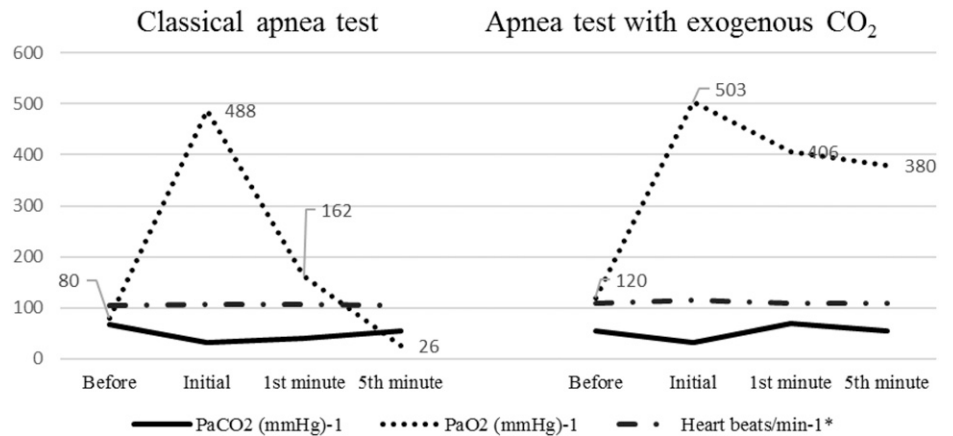
**Figure 1.** Schematic view of extracorporeal membrane oxygenation (ECMO) circuit. (A) The classical ECMO circuit with air and oxygen blender. (B) ECMO circuit with an air-O<sub>2</sub>-CO<sub>2</sub> mixer that used in apnea test with exogenous CO<sub>2</sub>.



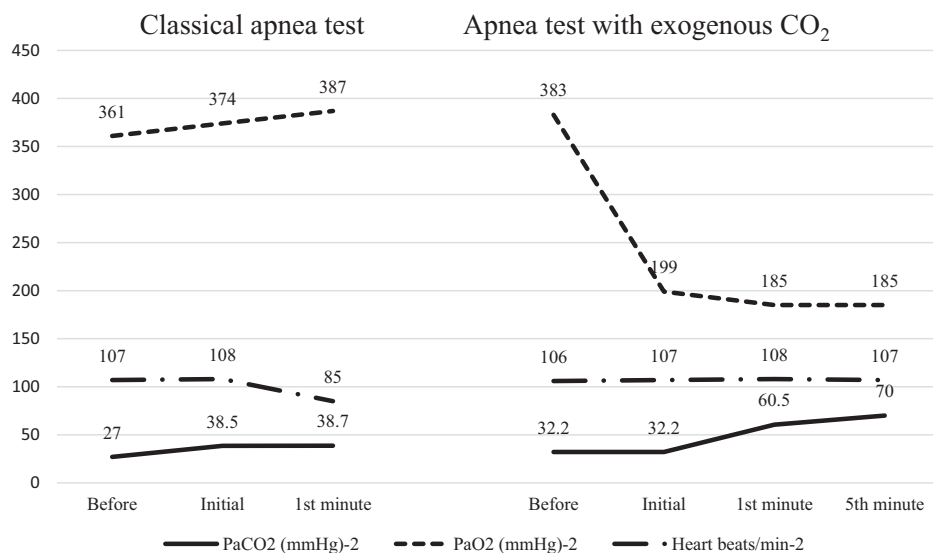
he had severe hypotension and hypoxia and arterial blood gas revealed severe lactic acidosis with severe hypoxemia (PaO<sub>2</sub> = 26 mmHg, PaCO<sub>2</sub> = 55 mmHg, and lactate level was high). His pulse rate did not change because he had an internal pacemaker. The test was not completed because of hemodynamic instability. We gave him inotropes to stabilize blood pressure and started continuous veno-venous hemodiafiltration via ECMO circuit to treat severe metabolic acidosis rapidly. After 4 hours from the first AT, we performed a second one using a carbon dioxide insufflation through the air blender of ECMO circuit to accelerate the test by achieving desired CO<sub>2</sub> level without hemodynamic compromise (Figure 1). In the way of AT with exogenous CO<sub>2</sub>, we started to give CO<sub>2</sub> at a rate of 0.1 L/min and measure arterial PaCO<sub>2</sub> in every minute via blood gas analyzer. During the CO<sub>2</sub> insufflation, sweep gas flow was 0.2 L/min, blood flow was 0.55 LPM with 1,660 RPM, and FiO<sub>2</sub> was 60% on ECMO. After first 1 minute of CO<sub>2</sub> insufflation, arterial pH was 7.15, PaCO<sub>2</sub> was 69 mmHg, and PaO<sub>2</sub> was 406 mmHg. We stopped CO<sub>2</sub>, while the ECMO sweep gas flow was 0.2 L/min and FiO<sub>2</sub> was 100%, we separated the patient from the ventilator and observed him for 5 minutes.

At the end of the 5 minutes, PaCO<sub>2</sub> was still above 50 mmHg, his mean arterial pressure was 58 mmHg, SpO<sub>2</sub> was 99%. Figure 1 shows the arterial blood gas results and heart rates before and during both AT. He showed no respiratory movement and the test was consistent with brain death. We declared that he had brain death without neuroimaging study and withdrawal the treatment because he was not suitable for organ donation. In this method of AT, hypoxia and hemodynamic instability did not appear (Figure 2) and only in 5 minutes the test was completed without hemodynamic compromise. An informed consent form was obtained from the patient's parents for this study.

Patient 2 (2.5 years, boy) who admitted to pediatric ICU (PICU) after a Sano Shunt operation. Shortly after, he had cardiac arrest and went through a central (right atrium-aorta) VA-ECMO due to low cardiac output syndrome. On second day of ECMO, his pupils were become dilated and unresponsive to light. After discontinuation of all sedatives neurological examination was consistent with absolute coma. Cranial computerized tomography showed diffuse ischemia, edema, and cerebellar tonsillar herniation. An AT was performed in



**Figure 2.** Arterial pO<sub>2</sub> and pCO<sub>2</sub> values of Patient 1 during classical apnea test and with exogenous CO<sub>2</sub>. \*Heart rate did not change with hypoxia because of the internal pacemaker device.



**Figure 3.** Arterial pO<sub>2</sub> and pCO<sub>2</sub> values of Patient 2 during classical apnea test and with exogenous CO<sub>2</sub>.

classical way (ECMO blood flow: 0.2 LPM reduced from 1.2 LPM, FiO<sub>2</sub>:100%, positive end expiratory pressure (PEEP): 8 cm/H<sub>2</sub>O, respiratory rate (RR): 2 breaths/min). However, the test was failed after the first minute because hypoxia and hypotension occurred. We turned all the treatment parameters right before the test, so Figure 3 did not show any hypoxia. After fluid boluses and inotropes, he stabilized. A second apnea test was performed using external CO<sub>2</sub>. For this purpose, in addition to the above mentioned parameters, CO<sub>2</sub> was given at a rate of 0.1 L/min while 1.2 LPM of blood flow rate and 0.2 LPM of gas flow rate. After the first minute, his pH was 7.23, PaO<sub>2</sub> was 199 mmHg, and PCO<sub>2</sub> was 60.5 mmHg. He was separated from the ventilator, given 10L/min oxygen through a T-piece. He showed no respiratory movement and the test was consistent with brain death.

Patient 3 (7 months old, girl) with a tetralogy of Fallot was transferred into the cardiac ICU after a total repair surgery. The surgery lasted unexpectedly long because of a variation of left pulmonary artery originated from aorta that was not seen in angiography. After 12 hours of surgery, systemic inflammatory response syndrome with low cardiac output occurred. Despite medical treatment, systemic hypotension was refractory, she went through central (right atrium-aorta) VA-ECMO after E-CPR of approximately 50 minutes. After 2 days, she lost all her brainstem reflexes and her comatose status persisted after discontinuation of sedative drugs. An AT was performed in classical way (ECMO blood flow: 0.2 LPM reduced from 0.8 LPM, turned off sweep flow, FiO<sub>2</sub>:100%, PEEP: 8 cm/H<sub>2</sub>O, RR: 2 breaths/min). The test was disrupted because of severe hypoxia and hypotension right after the first minute. After supported with the proper parameters, exogenous CO<sub>2</sub> was used to

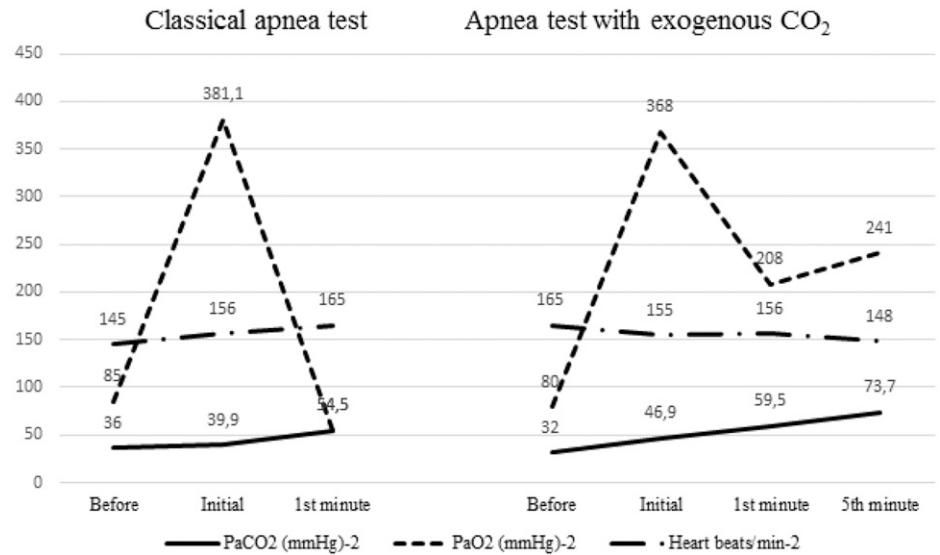
perform AT again. In the second AT, 0.8 LPM (calculated based on patient size) of a blood flow, 0.4 LPM of a sweep gas flow, and 0.1 LPM of a CO<sub>2</sub> flow rate were adjusted after pre-oxygenation through both ventilator and ECMO and achieving high pO<sub>2</sub> level (Figure 4). As shown in Figure 4, the desired CO<sub>2</sub> level was achieved quickly without hypoxia and hemodynamic compromise. She was observed for any respiratory movements, which did not occur. The AT was consistent with brain death and supported with a CT angiography.

All three patients were treated with the same ECMO equipment (Dideco Perfusion Tubing Systems, Sorin Group Italia, S.r.l, Mirandola, Italy), Sechrist 3500 low flow air-oxygen mixer (Sechrist Industries, Inc., Anaheim, CA), and Stockert® SCPC centrifugal pump system console (Stockert GmbH Inc., Baden-Württemberg, Germany).

## COMMENT

Intracranial hemorrhage is the most serious and fatal complication of ECMO because of mandatory anticoagulation. It is recommended extracorporeal life support should be discontinued promptly if there is no hope for healthy survival or chance to be organ donor (3). Determination of brain death is crucial to decide what next step is. There is no specific guideline for AT for ECMO patients. ECMO is an artificial life support system in which CO<sub>2</sub> and oxygen exchange is made externally and the most common cause of death is intracranial hemorrhages (parenchymal or ventricular). In ECMO patients, AT is a controversial issue (4,5). The AT is based on the patient's inability to change the CO<sub>2</sub> and no central respiratory response to elevated blood CO<sub>2</sub> level. This period

**Figure 4.** Arterial pO<sub>2</sub> and pCO<sub>2</sub> values of Patient 3 during classical apnea test and with exogenous CO<sub>2</sub>.



may be longer for patients on ECMO since the CO<sub>2</sub> removal achieved mostly by ECMO membrane. While waiting for the increase of CO<sub>2</sub>, the possibility of developing tissue hypoxia appears to be problematic in patients with unstable hemodynamic condition. A close monitoring of the patient is necessary for the completion of the test safely. But many children who undergone cardiac surgery have internal or external pacemaker because of postoperative rhythm alterations. As in our Patient 1 whom heart rates controlled with such device, heart rate is not a reliable monitor parameter during the AT.

The protocols for AT in VA-ECMO patients (both pediatric and adult) has been suggested to be safely and successfully applicable (6,7). If no adjustments to blood flow are performed, it is not possible to evidence hypercapnia above the threshold required for validation of the AT, so it is recommended to reduce blood flow rate with a 75–80% of calculated cardiac output of the patient in adults (8). However, children, especially with congenital cardiac heart surgery, were more susceptible to a decrease of cardiac output and decreasing blood flow rate may result hemodynamic instability.

AT can be performed with decreased sweep gas flow with 100% of FiO<sub>2</sub> (9). Even though partial CO<sub>2</sub> pressure is theoretically zero when applying 100% FiO<sub>2</sub> through the ECMO air blender, there is still CO<sub>2</sub> removal on some levels. Therefore, it is possible to reach the desired CO<sub>2</sub> level by giving CO<sub>2</sub> externally (10). Pirat et al. declared that addition of exogenous CO<sub>2</sub> to the gas blender is a valid method for conducting apnea tests during ECMO (11). Harrar et al. also reported AT with using exogenous CO<sub>2</sub> in two children (12). As there is no well-defined protocol for this scenario, the gas flow rates, blood flow rates, and mechanical ventilation settings during the test vary widely.

Performing the AT seems to be a safe option by closely monitoring the patient and slowly titrating the treatment variables.

When brain, which is the main factory of CO<sub>2</sub> does not work, CO<sub>2</sub> increment which is crucial for brain death confirmation via AT cannot be achieved. It requires more time to achieve desired CO<sub>2</sub> levels. Meanwhile, hemodynamic compromise occurs and the test could not be completed. When the classical technique failed for our patients, it was necessary to find another fast and safe way. CO<sub>2</sub> insufflation thru ECMO membrane shortened the time for increment of arterial CO<sub>2</sub> pressure allowing the patient to be stable during the AT. When we performed the test in classical way, it could not be completed because of severe hypoxia in the 1st minute, however, we reached the desired level with using external CO<sub>2</sub> insufflation in 1 minute so, had the opportunity to complete the AT without hypoxia and clinical compromise.

Brain death diagnosis is troublesome under ECMO and yet should take a place with a standardized protocol for a decent management and possible organ donation (13). The main diagnostic tool is AT, but the increment of CO<sub>2</sub> is generally not achievable because of the diminished production of CO<sub>2</sub> and additional sweep via ECMO membrane. This results in failed AT attempt due to prolonged duration (14). To overcome this problem, AT with exogenous CO<sub>2</sub> insufflation is a reliable tool for brain death confirmation under ECMO.

## REFERENCES

1. Nakagawa TA, Ashwal S, Mathur M, et al. Medicine SoCC. Guidelines for the determination of brain death in infants and children: An

- update of the 1987 Task Force recommendations. *Am Acad Pediatrics*. 2011;128:e720–40.
2. Busl KM, Lewis A, Varelas PN. Apnea testing for the determination of brain death: A systematic scoping review. *Neurocrit Care*. 2021;34:608–20.
  3. Organization ELS. ELSO Guidelines for Cardiopulmonary Extracorporeal Life Support, General Guidelines for all ECLS Cases. Ann Arbor, MI: ELSO organization; 2017.
  4. Sahu MK, Vaswani P, Bipin C, et al. Enigma of apnea test for brain death on ECMO-an ongoing discussion-case study and review of literature. *Indian J Thorac Cardiovasc Surg*. 2020;37:1–4.
  5. Virupakshaiah A, Ichord R, Topjian AA, et al. A review of current controversies in determining death by neurologic criteria in children. *Curr Opin Pediatr*. 2020;32:759–64.
  6. Jarrah RJ, Ajizian SJ, Agarwal S, et al. Developing a standard method for apnea testing in the determination of brain death for patients on venoarterial extracorporeal membrane oxygenation: A pediatric case series. *Pediatr Crit Care Med*. 2014;15:e38–43.
  7. Muralidharan R, Mateen FJ, Shinohara RT, et al. The challenges with brain death determination in adult patients on extracorporeal membrane oxygenation. *Neurocrit Care*. 2011;14:423–26.
  8. Sady ERR, Junqueira L, Veiga VC, et al. Apnea test for brain death diagnosis in adults on extracorporeal membrane oxygenation: A review. *Rev Bras Ter Intensiva*. 2020;32:312–18.
  9. Giani M, Scaravilli V, Colombo SM, et al. Apnea test during brain death assessment in mechanically ventilated and ECMO patients. *Intensive Care Med*. 2016;42:72–81.
  10. Champigneulle B, Chhor V, Mantz J, et al. Efficiency and safety of apnea test process under extracorporeal membrane oxygenation: The most effective method remains questionable. *Intensive Care Med*. 2016;42:1098–9.
  11. Pirat A, Kömürçü Ö, Yener G, et al. Apnea testing for diagnosing brain death during extracorporeal membrane oxygenation. *J Cardiothorac Vasc Anesth*. 2014;28:e8–9.
  12. Harrar DB, Kukreti V, Dean NP, et al. Clinical determination of brain death in children supported by extracorporeal membrane oxygenation. *Neurocrit Care*. 2019;31:304–11.
  13. Bein T, Muller T, Citerio G. Determination of brain death under extracorporeal life support. *Intensive Care Med*. 2019;45:364–66.
  14. Migdady I, Stephens RS, Price C, et al. The use of apnea test and brain death determination in patients on extracorporeal membrane oxygenation: A systematic review. *J Thorac Cardiovasc Surg*. 2021;162:867–77.e1.