

Apnea Testing for the Determination of Brain Death in Patients Supported by Extracorporeal Membrane Oxygenation

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Abstract

The neurological criteria for brain death include coma, absent brain stem reflexes, and apnea. For patients on extracorporeal membrane oxygenation (ECMO), routine apnea testing is not possible because gas exchange occurs entirely through the membrane oxygenator. We describe the protocol we used to perform the apnea test and declare brain death in a patient on ECMO and review the literature of brain death testing in patients on ECMO. A 39-year-old female presented with cardiogenic shock followed by pulseless electrical activity (PEA) and eventually started on veno-arterial (VA) ECMO. Neurology was consulted for prognostication. Initial exam 48 hours after arrest showed absent brain stem reflexes. Another neurological exam 72 hours after arrest was compatible with brain death, so apnea test was performed. The apnea test involved preoxygenation, then she was disconnected from ventilator and the gas sweep rate decreased to 1 L/minute while maintaining the same blood flow rate. At 10 minutes, the PCO_2 level needed to declare brain death was achieved. With increasing use of ECMO to support critically ill patients, physicians should become familiar with the challenges this technology has created when testing for apnea in the determination of brain death. In this case report, we showed that apnea testing can be done in patients on ECMO without the need for ancillary testing. The mainstay of performing apnea testing on these patients is decreasing the gas sweep rate to 0.5 - 1 L/minute while maintaining the same blood flow rate.

Keywords: ECMO; Brain death; Apnea test

Introduction

The neurological criteria for brain death include coma, absent brain stem reflexes, and apnea. Apnea testing involves discon-

necting the mechanical ventilator, observing for spontaneous respirations and, if none, measuring the $PaCO_2$ after 8 - 10 min. The test is positive if the $PaCO_2$ is ≥ 60 mm Hg or has increased ≥ 20 mm Hg above the baseline. For patients on extracorporeal membrane oxygenation (ECMO), an advanced form of life support, this kind of apnea testing is not possible because gas exchange occurs entirely through the membrane oxygenator. ECMO provides oxygenation and circulatory support for patients with severe respiratory and cardiac failure. A modification of the cardiopulmonary bypass circuit is routinely used in cardiac surgery; ECMO is smaller and portable and can be used for several days to weeks in adult respiratory distress syndrome, cardiogenic shock, as a bridge to heart or lung transplantation [1], or to support in-hospital cardiac arrest [2-4]. Though early use of ECMO in the 1970s was plagued with complications [5, 6], advances in technology and safety have resulted in its increasing use over the last decade [7-10].

Configuration of the ECMO circuit

There are two configurations with ECMO: a veno-venous (VV) configuration to provide oxygenation in patients with respiratory failure and a veno-arterial (VA) configuration to provide both oxygenation and circulation in patients with respiratory and cardiac failure [11] (Fig. 1). For both, the circuit is composed of vascular access catheters and heparin coated tubing, a blood pump, membrane oxygenator and a temperature control system. In VV ECMO, de-oxygenated blood is removed from a venous catheter placed in the femoral vein (extending into the inferior vena cava) and passively drained by gravity into a reservoir. A pump then either pushes (using a roller pump) or draws (using a centrifugal pump) the blood from the reservoir and through a membrane oxygenator and heat exchanger before returning to the internal jugular vein (extending into the right atrium) [12] (Fig. 2).

Typically, the membrane oxygenator is manufactured with microporous polypropylene material to create hollow, capillary fibers or capillary membranes, which provide a blood-gas interface for the diffusion of gases. Specifically, blood flows inside the capillary fibers while gas flows outside in the opposite direction. The composition of the gas on the gas side of the oxygenator membrane is determined by adjustment of a blender that mixes room air with oxygen for delivery into the

Manuscript accepted for publication February 26, 2016

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doi: <http://dx.doi.org/10.14740/jnr376w>

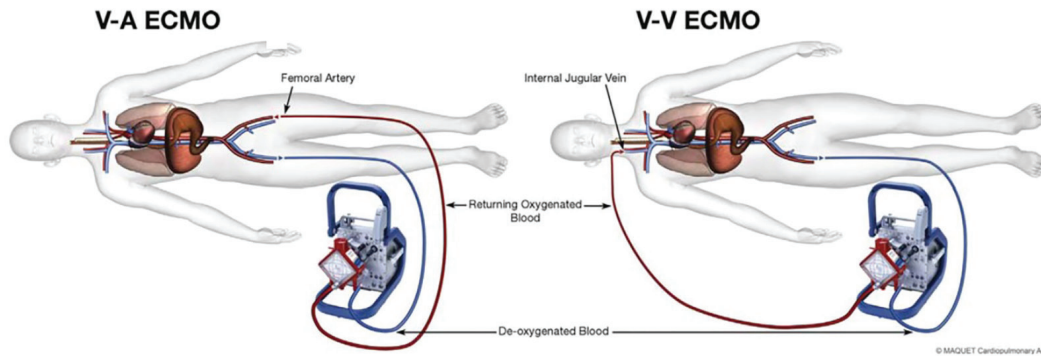


Figure 1. Illustration of VA ECMO and VV ECMO. Example of the cannulation sites for VA ECMO (femoral vein-femoral artery) and VV ECMO (femoral vein-internal jugular vein) with blood flow through the oxygenator.

oxygenator. The membrane oxygenator acts as the “artificial lung” adding oxygen (O₂) and removing carbon dioxide (CO₂) from the blood. That is, though patients are usually mechanically ventilated, because venous blood is being diverted away from the lungs and through the membrane oxygenator, adjusting the ventilator settings will not affect the PaO₂ or PaCO₂. Oxygenation is determined mainly by the fraction of oxygen delivered through the oxygenator and rate of blood flow through the circuit. Clearance of CO₂ depends mainly on the rate of sweep gas flow through the oxygenator [13]. Because of the high solubility and fast diffusion property of CO₂, removal is very efficient and can occur at lower blood flow rates needed for adequate oxygenation.

For VA ECMO, it is the same process just that the blood is returned to the femoral artery. Initial cardiac output targets of 1.5 - 2.0 L/min are acceptable but are titrated up gradually to

3.0 - 6.0 L/min. Because arterial flow will be continuous and non-pulsatile, a pulse pressure of approximately 10 - 15 mm Hg is considered acceptable [14]. Though usually not necessary, sometimes vasopressors and inotropic agents can be used to achieve a specific target blood pressure and cardiac output (VV ECMO does not support the circulation and thus has no effect on cardiovascular hemodynamics) (Table 1) [15].

Brain death

The neurological criteria for brain death were defined by the American Academy of Neurology Practice Parameter in 1995 [16] and updated in 2010 [17]. They include the following clinical prerequisites: irreversible and proximate cause of coma documented by either clinical or neuroimaging evidence

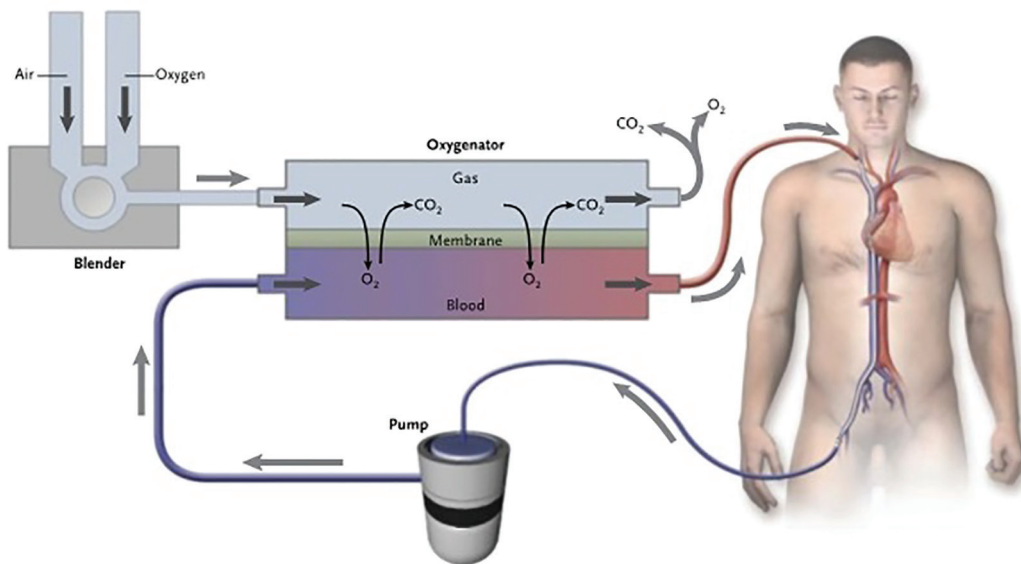


Figure 2. The membrane oxygenator in ECMO. The extracorporeal membrane oxygenation pump delivers venous blood to the oxygenator. This device is divided into two chambers by a semipermeable membrane. The venous blood enters the oxygenator and travels along one side of the membrane (the blood side), while fresh gas known as sweep gas is delivered to the other side (the gas side). Gas exchange (oxygen uptake and carbon dioxide elimination) takes place across the membrane. The oxygenated blood reinfused into the patient’s venous system.

Table 1. The Standard Initial Settings and Goals for ECMO [15]

Circuit flow	50 - 80 mL/kg/min
Sweep gas flow	50 - 80 mL/kg/min
Fractional inspired oxygen	100%
Oxygen saturation (drainage cannula)	> 65%
Oxygen saturation (return cannula)	100%
Arterial oxygen saturation	VA: > 95%; VV: 85-92%
Arterial carbon dioxide tension	35 - 45 mm Hg
Mean arterial pressure	65 - 95 mm Hg

of catastrophe along with exclusion of confounding factors that could be contributing to coma such as severe electrolyte, acid base, or endocrine abnormalities, CNS-depressant drugs, hypothermia (core temperature < 36 °C) and hypotension (systolic blood pressure < 100 mm Hg). In adults, a single careful neurological examination is required to document the presence of coma and the absence of brain stem reflexes. After that an apnea test is performed to document the absence of spontaneous respirations. First, a baseline arterial blood gas is obtained to ensure eucapnea and then the patient is removed from the mechanical ventilator and observed for any evidence of spontaneous respirations. If no respirations are observed, a repeat blood gas is obtained after approximately 8 min. The test is considered positive if the PaCO₂ is ≥ 60 mm Hg or has increased at least 20 mm Hg above the baseline PaCO₂. The time of death is declared to be the time the PaCO₂ reached the target value.

For patients with severe respiratory or cardiac failure supported on ECMO, the practice parameter does not provide a process for apnea testing. Unlike patients on mechanical ventilation alone, gas exchange for patients supported on ECMO occurs mainly through the membrane oxygenator. Carbon dioxide elimination is dependent on the sweep gas flow rate.

We report a patient who met the neurological criteria for brain death but because of ECMO, an apnea test could not be performed in the typical manner. We describe the process we used to perform the apnea test and declare brain death and review the literature of brain death testing for patients on ECMO.

Case Report

A 39-year-old woman with systemic lupus erythematosus was found unresponsive at home following a brief febrile illness. She was found to be on cardiogenic shock suspected to be secondary to fulminant myocarditis. Shortly after admission, she had a pulseless electrical activity (PEA) cardiac arrest. An attempt at resuscitation followed for the next 40 min, which included sternotomy, open heart massage, and eventually VA ECMO support. Therapeutic hypothermia was begun. After 24 h, the patient was taken to the operating room for a cardiac washout and was found to have no evidence of cardiac activity even when electrically paced. She was rewarmed, sedation was stopped and the following day (48 h after the event), the

neurology service was consulted for evaluation and prognostication.

The initial examination found her to be normothermic (temperature of 36.5 °C) and normotensive (mean arterial pressure (MAP): 70 mm Hg). She was comatose. Brain stem examination revealed bilateral fixed and dilated pupils, absent cough and gag reflexes and absent corneal reflex. Eyes were midline and showed no reflexive movement to head turning (Doll's eyes maneuver) or to cold water irrigation into the ears (cold calorics or oculo-vestibular reflex). Motor examination showed no movement of the limbs to noxious stimulation. The physical examination was repeated the following day (72 h after the vent and 24 h off sedation). Her neurological examination was identical. Because she was being supported with VA ECMO, certain adjustments were required to perform an apnea test.

Her initial VA ECMO settings were blood flow rate 5 L/min, FiO₂ 70%, and gas sweep flow rate 4 L/min. Her MAP was 70 mm Hg. First, preoxygenation was done for 10 min by increasing the FiO₂ on the membrane oxygenator to 100%. A baseline arterial blood gas showed pH 7.33, PaCO₂ 47 mm Hg, and PaO₂ 535 mm Hg. Second, the gas sweep flow rate was reduced to 1 L/min and the mechanical ventilator was disconnected. The patient was observed for any evidence of spontaneous respirations. A repeat arterial blood gas at 5 min showed pH 7.30, PaCO₂ 50 mm Hg, and PaO₂ 185 mm Hg. Another arterial blood gas at 10 min showed pH 7.20, PaCO₂ 65 mm Hg, and PaO₂ 444 mm Hg. During the 10-min period disconnected from the ventilator, no spontaneous respiration was observed. After reaching the PaCO₂ target and with no evidence of respiratory drive, the patient was declared brain dead.

Discussion

Apnea testing in brain death

Apnea, the absence of spontaneous breathing, is an essential criterion for the diagnosis of brain death. Various methods of performing an apnea test have been recommended. In the original landmark Harvard report from Beecher and colleagues in 1968, apnea was defined as absent spontaneous breathing for 3 min after discontinuation of the mechanical ventilator. In the cerebral survival study done from 1970 to 1972, apnea was defined as a lack of respiratory effort to override the ventilator for 15 min. In 1978, Schafer and colleagues suggested for the first time a specific PaCO₂ threshold to determine apnea. That is, in order to definitively confirm apnea, the PaCO₂ level must be high enough to ensure supramaximal stimulation of the medullary respiratory centers. To determine what that threshold was, 10 patients who otherwise met the clinical criteria for brain death were disconnected from the ventilator and the PaCO₂ was serially measured. Spontaneous resumption of breathing occurred in three of the 10 patients. The authors wrote, "the highest respiratory threshold or apnea point we measured was a PaCO₂ of 56 mm Hg. Therefore it appears safe to conclude that apnea is absolute when a PaCO₂ of 60 mm Hg cannot stimulate spontaneous breathing." This forms the basis of

Table 2. Summary of ECMO Settings During Apnea Testing [21-25]

Report	Case	Initial ECMO settings	Oxygenation method	ECMO during testing	Ancillary testing
Jarrah et al [21]	#1	Blood flow rate 88 mL/kg/min Sweep flow rate 0.5 L/min FiO ₂ 100%	CPAP FiO ₂ 100%	Blood flow rate 88 mL/kg/min Sweep flow rate 0.1 L/min FiO ₂ 100%	None
	#2	Blood flow rate 38 mL/kg/min Sweep flow rate 5.5 L/min FiO ₂ 100%	CPAP FiO ₂ 100%	Blood flow rate 38 mL/kg/min Sweep flow rate 1.0 L/min FiO ₂ 100%	None
	#3	Blood flow rate 140 mL/kg/min Sweep flow rate 0.22 L/min FiO ₂ 100%	CPAP FiO ₂ 100%	Blood flow rate 140 mL/kg/min Sweep flow rate 0.1 L/min FiO ₂ 100%	EEG
Hoskote et al [24]		Blood flow rate 4.5 mL/kg/min Sweep flow rate 6 L/min FiO ₂ 100%	None	Blood flow rate 4.5 mL/kg/min Sweep flow rate 0.5 L/min FiO ₂ 100%	None
Smilevitch et al [22]		Blood flow rate 4.1 mL/kg/min Sweep flow rate 3 L/min FiO ₂ 40% increased to 100% during preoxygenation	T-piece 9 L/min	Blood flow rate 4.1 mL/kg/min Sweep flow rate 3 L/min FiO ₂ 100%	EEG
Goswami et al [25]	#1	Blood flow rate 5.0 mL/kg/min Sweep flow rate Not documented FiO ₂ 100%	Not specified	Blood flow rate 5.0 mL/kg/min Sweep flow rate 0.5 L/min FiO ₂ 100%	EEG
	#2	Blood flow rate 4.1 mL/kg/min Sweep flow rate 3 L/min FiO ₂ 40% increased to 100% during preoxygenation	Not specified	Blood flow rate 6.0 mL/kg/min Sweep flow rate 0.5 L/min FiO ₂ 100%	EEG
Iannuzzi et al [23]		Blood flow rate 4.0 mL/kg/min Sweep flow rate 8 L/min FiO ₂ 70%	CPAP FiO ₂ 100%	Blood flow rate 2.0 mL/kg/min Sweep flow rate 0.5 L/min FiO ₂ 100%	None

the current guidelines, which recommend discontinuing the ventilator for approximately 8 min after which the PaCO₂ is measured again. Because under normal circumstances, without respiration, the PaCO₂ rises on average 2.5 mm Hg per minute, beginning with a normal PaCO₂ of 40 mm Hg, after 8 min of no respiration, the PaCO₂ should be 60 mm Hg. If the apnea test cannot be performed, the guidelines recommend that an ancillary test be performed.

The apnea test with ECMO

Performing brain death testing in patients supported by ECMO is challenging because patients are not dependent on the mechanical ventilator for removal of CO₂, which is achieved through the membrane oxygenator. There have been few reports in the literature regarding the protocol of brain death testing in patients supported by ECMO. In one review of children who died on ECMO, brain death was determined in 29% of them but the protocol that was used was not described [18]. In another review of 87 patients on ECMO over an 8-year period, three met criteria for brain death but in two of them, apnea testing was deemed “too difficult to perform” and in the third, support was withdrawn before apnea testing could be done [19]. Hsieh and colleagues reported three patients supported by

ECMO who underwent brain death testing. In their protocol, however, the ECMO oxygenator was turned off and then the ventilator was disconnected. Apnea testing proceeded in the usual manner [20]. There are five additional case reports that described, in varying degrees of detail, protocols used to perform apnea testing in eight patients. All involve maintaining patients on ECMO but decreasing the sweep flow rate in order to cause the PaCO₂ to rise above the target of 60 mm Hg after which patients were declared brain dead (Table 2) [21-25].

Jarrah and colleagues for example reported three pediatric patients on VA ECMO [21]. After preoxygenating by increasing the ECMO circuit FiO₂ to 100%, all were placed on CPAP with FiO₂ 100% administered through a flow-inflating anesthesia bag connected to the endotracheal tube. The blood flow rate was left unchanged while the sweep gas flow rate was decreased. Specifically, the sweep gas flow rate in the first patient, a 2.5-year-old child, was titrated down from a baseline of 0.5 L/min to 0.25 - 0.1 L/min. No spontaneous respirations were observed and, after 48 min, the PaCO₂ reached the target and brain death was declared. In the second patient, a 14-year-old child, the baseline sweep gas flow rate was 5.5 L/min and was decreased to 1.0 L/min. The PaCO₂ reached the target after 60 min and no respiratory movements were observed. In the third, a 5-month-old infant, the baseline sweep gas flow rate was 0.2 L/min and was decreased to 0.1 L/min.

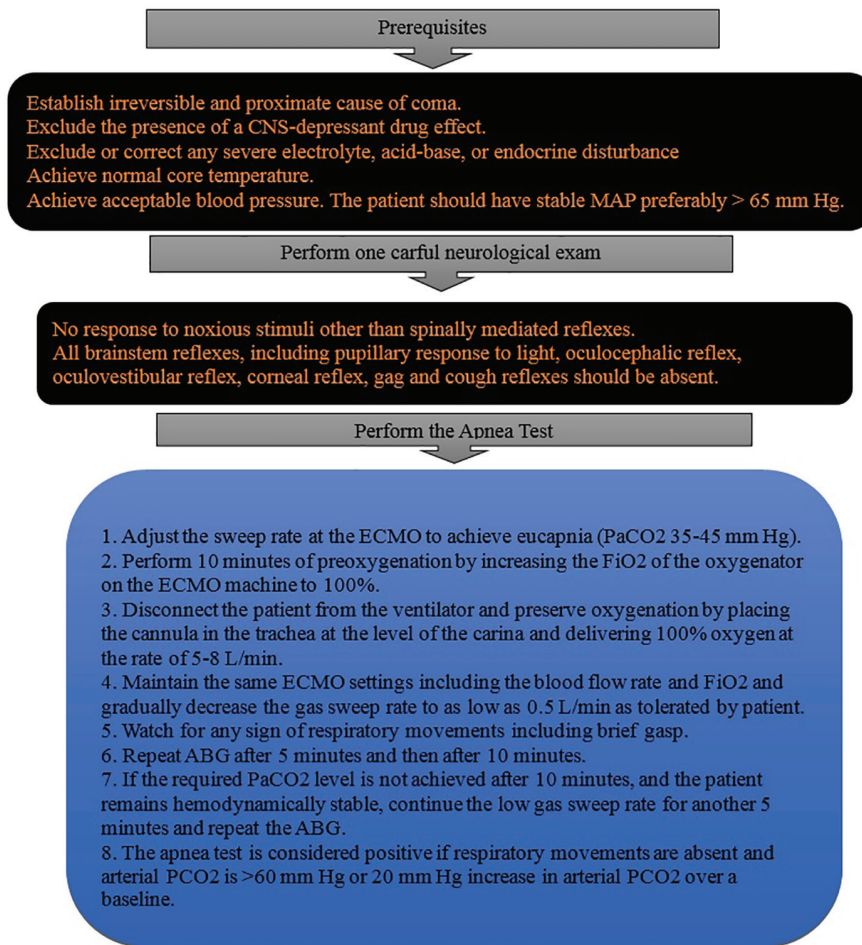


Figure 3. Steps of performing apnea test in patients on ECMO. Stepwise illustration of performing apnea test to confirm brain death in patients supported by ECMO.

The PaCO₂ reached the target after 11 min. In this third patient, EEG was done and showed no evidence of brain electrical activity. Smilevitch and colleagues described a similar approach in a 29-year-old patient on VA ECMO [22]. After preoxygenation by increasing the FiO₂ to 100%, the patient was placed on T-piece instead of CPAP and supplemental oxygen delivered at 9 L/min. The sweep flow rate was then decreased from 4.1 to 1.0 L/min. The PaCO₂ reached the target after 10 min. Two EEGs showed absence of brain electrical activity.

Iannuzzi and colleagues described apnea testing in a 40-year-old patient on a VV ECMO [23]. In their report, both the blood flow rate and the sweep flow rate were decreased. The baseline blood flow rate was 4.0 L/min and the sweep flow rate was 8.0 L/min. The FiO₂ was increased to 100% and the patient was placed on CPAP with FiO₂ of 100% administered through a T-piece. The blood flow rate was then decreased to 2.0 L/min and the sweep flow rate to 0.5 L/min. The PaCO₂ reached the target level after 6 min. Finally, in two other case reports, the protocol did not include preoxygenation. In the 58-year-old patient described by Hoskote and colleagues [24], the baseline sweep flow rate was 6.0 L/min. The ventilator was simply disconnected and the sweep flow rate decreased

to 0.5 L/min. The PaCO₂ reached the target level after 9 min. Goswami and colleagues described two patients on VA ECMO [25]. In both, there was no mentioning of the baseline sweep flow rate, but it is mentioned that it was decreased to 0.5 L/min during the apnea testing. The PaCO₂ reached the target level after 3 min in the first patient and after 10 min in the second.

While the rate of PaCO₂ rise on ECMO is proportional to the ECMO circuit blood flow and sweep gas flow, there are no clear guidelines in the literature to follow while performing the apnea test on these patients. Yang and colleagues [26] proposed decreasing the sweep gas flow rate to zero during apnea testing but that might make it hard to maintain adequate oxygenation at that level [19]. Thus most people have chosen 0.5 - 1.0 L/min of sweep gas flow during apnea testing as an estimation of the optimal level balance between providing oxygenation and CO₂ clearance.

Conclusion

With increasing use of ECMO to support critically ill patients, physicians should become familiar with the challenges this

technology has created when testing for apnea in the determination of brain death. Because CO₂ clearance is solely dependent on the rate of sweep gas flow through the oxygenator rather than the mechanical ventilator [13], the standard apnea testing protocol of disconnecting the ventilator, observing for spontaneous respirations and measuring the PaCO₂ after 8 - 10 min, does not apply. Ancillary tests have been suggested as a way to confirm brain death when performing the apnea test is not possible. In this case report, however, we showed that apnea testing can be done in patients on ECMO without the need for ancillary testing. The mainstay of performing apnea testing on these patients is decreasing the gas sweep rate to 0.5 - 1 L/min while maintaining the same blood flow rate (Fig. 3). Implementation of such a standardized approach for apnea testing in this patient population is helpful in making the timely diagnosis of brain death.

Conflict of Interest

The authors declare that they have no conflict of interest.

Abbreviations

ECMO: extracorporeal membrane oxygenation; VV: veno-venous; VA: veno-arterial

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