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REVIEW ARTICLE/BRIEF REVIEW

Organ donation in patients on extracorporeal membrane oxygenation: considerations for determination of death and withdrawal of life support

Le don d'organes chez les patients sous oxygénation extracorporelle (ECMO) : considérations pour la détermination du décès et l'interruption des mesures de maintien des fonctions vitales

Shaurya Taran, MD · Andrew Steel, MBBS · Andrew Healey, MD · Eddy Fan, MD, PhD · Jeffrey M. Singh, MD, MSc

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Abstract *The use of extracorporeal membrane oxygenation (ECMO) is increasing globally, although mortality in this setting remains high. Patients on ECMO may be potential organ donors in the context of withdrawal of life-sustaining measures (WLSM) or neurologic determination of death (NDD). Nevertheless, there are currently no Canadian standards to guide clinicians on NDD or WLSM for the purposes of organ donation in this patient population. Apnea testing remains fundamental to determining NDD and is an area where ECMO may alter routine procedures. In this review, we outline protocols for the performance of apnea testing and WLSM for patients supported with ECMO, highlighting important technical and physiologic considerations that may affect the determination of death. In addition, we review important considerations for NDD in ECMO, including management of potential confounders, strategies for controlling oxygen and carbon dioxide levels during apnea testing, and the appropriate use of ancillary tests to support NDD. In the*

S. Taran, MD (✉)
Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada
e-mail: Shaurya.taran@mail.utoronto.ca

Interdepartmental Division of Critical Care, Li Ka Shing Knowledge Institute, University of Toronto, 204 Victoria Street, 4th Floor, Room 411, Toronto, ON M5B 1T8, Canada

A. Steel, MBBS
Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada

Department of Anaesthesiology, University Health Network, Toronto, ON, Canada

Trillium Gift of Life Network, Toronto, ON, Canada

A. Healey, MD
Department of Medicine, McMaster University, Hamilton, ON, Canada

Trillium Gift of Life Network, Toronto, ON, Canada

E. Fan, MD, PhD
Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada

Department of Medicine, University Health Network, Toronto, ON, Canada

Institute for Health Policy, Management, and Evaluation, University of Toronto, Toronto, ON, Canada

J. M. Singh, MD, MSc
Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada

Department of Medicine, University Health Network, Toronto, ON, Canada

Trillium Gift of Life Network, Toronto, ON, Canada

context of ECMO support, there is limited evidence to guide NDD and WLSM for the purposes of organ donation. Drawing upon extensive clinical experience, we provide protocols for these processes and review other important considerations in an effort to maximize donor potential in this growing patient population.

Résumé *L'utilisation de l'oxygénation extracorporelle (ECMO) augmente dans le monde, malgré le fait que la mortalité associée demeure élevée. Les patients sous ECMO pourraient être des donneurs d'organes potentiels dans le cadre d'une interruption des mesures de maintien des fonctions vitales ou d'un diagnostic de décès neurologique (DDN). À l'heure actuelle il n'existe cependant aucune norme canadienne pour guider les cliniciens en matière de DDN ou d'interruption des mesures de maintien des fonctions vitales aux fins de dons d'organes dans cette population de patients. Le test d'apnée demeure fondamental pour poser un DDN mais il s'agit d'un domaine dans lequel l'ECMO pourrait modifier les interventions de routine. Dans ce compte rendu, nous décrivons des protocoles pour la réalisation d'un test d'apnée et l'interruption des mesures de maintien des fonctions vitales chez des patients sous ECMO. Nous soulignons certaines considérations techniques et physiologiques importantes qui pourraient avoir un impact sur le diagnostic de décès. En outre, nous passons en revue certaines considérations importantes pour le DDN sous ECMO, notamment la prise en charge de facteurs confondants potentiels, les stratégies pour contrôler les niveaux d'oxygène et de dioxyde de carbone pendant le test d'apnée, et l'utilisation adaptée de tests complémentaires pour appuyer le DDN. Dans le cadre d'un maintien des fonctions vitales sous ECMO, il n'existe que peu de données probantes pour guider le DDN et l'interruption des mesures de maintien des fonctions vitales aux fins d'un don d'organes. En nous fondant sur notre vaste expérience clinique, nous proposons des protocoles pour ces processus et passons en revue d'autres considérations importantes afin de maximiser le potentiel de dons dans cette population de patients grandissante.*

Over the last decade the use of extracorporeal membrane oxygenation (ECMO) has increased by more than 400% worldwide.[1] Greater clinical experience, technological improvements, and better patient selection have been cited as factors leading to its enhanced uptake.[2] Patients supported with ECMO can be provided with stable cardiac, pulmonary, or combined cardiopulmonary support for periods of days to months. Nevertheless, mortality in this patient population remains high, and more than 30% of patients receiving ECMO for pulmonary failure currently do not survive to be weaned from the extracorporeal circuit.[1]

Patients on ECMO are considered eligible for organ donation following neurologic determination of death (NDD) or withdrawal of life-sustaining measures (WLSM) leading to circulatory determination of death. Nevertheless, the process of death determination in the setting of ECMO may require special adaptation of accepted protocols. While there have been recent efforts to standardize these processes for ECMO patients,[3] there are scarce resources in the published literature focusing on determining death in this population in the context of organ donation. Therefore, in Canada, physicians are without standards or clinical guidelines for important aspects of the procedure, including how to perform the apnea test, how to exclude potential confounders (e.g., hypothermia, sedative agents, neuromuscular blockers), and when extubation should be performed in relation to extracorporeal circuit disconnection. These challenges all have serious implications for organ donation.

In this narrative review article, we highlight important considerations for NDD or WLSM for the purposes of organ donation in the setting of ECMO. We review how WLSM, NDD, and apnea testing are normally performed, and examine key differences for patients supported on ECMO. Finally, we propose actionable protocols for the initiation of apnea testing and WLSM from a Canadian perspective. These recommendations are informed, wherever possible, by the limited available literature.

Organ donation and death determination in Canada: background

Successful organ transplantation was one of the medical triumphs of the 20th century. Despite increases in the rates of organ donation in Canada following the implementation of donation after circulatory death (DCD), there remains a significant shortage of organs available for transplantation.[4,5] In 2017, 4,333 Canadians were waiting for a solid organ transplant, with 242 patients on the waitlist dying.[4] Given the immeasurable impact of transplantation on the recipients, it is imperative that the altruistic wish to donate is realized in every potential donor, and that donation potential is maximized in every consented organ donor.

Deceased donation in Canada occurs through two distinct routes with practice set by two guideline statements.[6,7] In Canada, approximately 70% of deceased donation occurs after NDD.[4] Organs are recovered following demonstration of the permanent loss of the capacity for consciousness, and the irreversible loss of

brainstem function, including the capacity to breathe.[6] The apnea test—which assesses the capacity for respiration after a maximal stimulus to breathe generated by respiratory acidosis—is a crucial component of this assessment. When the clinical NDD assessment may be precluded by craniofacial injuries, or confounded by medications or physiology (e.g., chronic carbon dioxide [CO_2] retention with respiratory acidosis), ancillary testing may be ordered to support the available clinical assessment. Demonstration of absent intracranial blood flow (with radionuclide angiography, computed tomography angiography [CTA], traditional four-vessel angiography, or magnetic resonance angiography) is regarded as consistent with NDD and allows determination of death with an incomplete or confounded clinical exam.[8]

The alternate route for deceased donation is DCD, in which organ recovery occurs after determination of death following WLSM. Following WLSM and provision of palliative care, the patient is observed and death is declared after five minutes of circulatory arrest.[7] The first priority during WLSM is to optimize patient comfort and family experience, but it is also important to recognise that the total warm ischemic time of potential donor organs spans from withdrawal to the time of *in situ* cold perfusion. Care plans of consented, potential organ donors should limit any avoidable prolongation of the dying process, ischemia, and organ injury.

The processes of death determination and subsequent organ recovery in Canada are guided by established protocols.[6,7] Nevertheless, for patients on ECMO, modifications may be needed because of the unique nature of the extracorporeal circuit. Understanding these issues is important in NDD and WLSM as it will impact organ availability in consented organ donors.

Extracorporeal membrane oxygenation: background and specific challenges for death determination

Extracorporeal membrane oxygenation is a form of extracorporeal life support that provides temporary respiratory, cardiac, or cardiorespiratory support for patients in whom native lung or cardiac functions are insufficient to meet the metabolic demands of the body.[9] Extracorporeal membrane oxygenation may allow time for improvement of the patient's underlying pathology or serve as a bridge to definitive interventions when improvement is not anticipated or remains incomplete.

Extracorporeal membrane oxygenation exists in two primary configurations: venovenous (VV) and venoarterial (VA). In both configurations, deoxygenated blood is removed from the patient through a venous drainage cannula placed in a large central vein. A centrifugal pump moves blood through a circuit containing an oxygenator (i.e., "membrane lung") which is the primary site of oxygen and CO_2 exchange between the patient and the circuit. Oxygenation of blood in ECMO is determined by pump flow, degree of recirculation within the circuit, native cardiac output, "sweep gas" oxygen concentration (FsO_2), and venous oxygen saturation.[10] Carbon dioxide clearance is controlled primarily with adjustments to the sweep gas, which is a measure of gas flow in litres per minute across the oxygenator.[11] Following gas exchange, blood from the membrane lung is returned to the patient's circulation through a return cannula. The major anatomical distinction between VV and VA ECMO is the location of the return cannula. In VV ECMO, the return cannula is positioned in a central vein (e.g., the superior vena cava via the internal jugular vein). In VA ECMO, the site of blood return is an artery (e.g., descending aorta via the femoral artery), which allows for circulatory support in addition to gas exchange capabilities.

The fundamental tenets of NDD are constant in ECMO and non-ECMO patients. Requirements include an irreversible and proximate etiology for death, a lack of motor and brainstem responses, and a permanent loss of the capacity to breathe. Confounders of the clinical assessment such metabolic disorders, hypothermia, un-resuscitated shock, and peripheral nerve or muscle dysfunction must be ruled out.[6] Nevertheless, ECMO may create various challenges for the clinical processes of NDD and WLSM, which clinicians should understand before determining death. For example, drug pharmacokinetics are substantially altered in patients on ECMO,[12,13] leading to potential confounding by pharmacologic agents (e.g., sedatives and paralytics) that may require additional time to clear. Mechanisms of altered drug pharmacokinetics in ECMO include increased volume of distribution, and decreased drug metabolism and excretion secondary to concomitant organ failure.[13,14] These factors may lead to residual drug effect and potential confounding if insufficient time or interventions (e.g., dialysis) are provided for clearance. Common sedative and analgesic drugs are listed in the Table along with important pharmacokinetic and dosing considerations.

Second, the apnea test on ECMO is subject to several important considerations. The apnea test seeks to assess respiratory efforts from a maximal central stimulus (provided by an acute respiratory acidosis with partial pressure of carbon dioxide [$PaCO_2$] > 60 mmHg, an acute $PaCO_2$ rise > 20 mmHg above baseline levels, and a pH < 7.28). Nevertheless, ECMO rapidly and efficiently clears CO_2, and in most cases, adjusting the ECMO settings will be necessary to ensure an adequate accumulation of CO_2 while maintaining normoxia.[15] The usual practice is to decrease the sweep gas flow rate; however, at very low

Table Pharmacokinetic considerations of common sedatives in the setting of ECMO

Drug	Pharmacokinetic considerations
Midazolam	- Increased sequestration in circuit[37]
	- Dose may need to be increased by 10% greater than usual to achieve deep sedation[38]
Propofol	- Significant sequestration in the circuit[39]
	- Higher doses than usual likely needed to achieve drug effect although the adjustment factor is unclear[12]
Morphine	- Conflicting findings have been shown, with some studies indicating increased concentrations[40] and others showing preserved concentrations[37]
Fentanyl	- Irreversibly binds to circuit[37]
	- Fentanyl requirements likely increased, although limited data indicates otherwise[12,13]
Remifentanil	- Increased volume of distribution and clearance[41]
	- Possibly higher doses needed to achieve sedative effect
Dexmedetomidine	- May adsorb to ECMO circuit[12]
	- Nevertheless, pharmacokinetic alterations remain unknown
	- Higher starting doses and infusions may possibly be needed to maintain sedation[42]
Thiopental	- Highly sequestered in the circuit[43]
	- Nevertheless, limited *in vivo* data to guide dosing considerations

ECMO = extracorporeal membrane oxygenation

sweep gas flow rates, patients may become hypoxemic and hypercarbic without sufficient acidemia if the baseline pH is not normalized early in the process.

Third, apnea testing in VA ECMO requires particular attention to the location of arterial blood gas (ABG) sampling, since not all vascular sites will necessarily reflect cerebral blood composition.[16] This problem is unique to VA ECMO, in which the circuit return blood will mix with native blood pumped from the heart.[16] If there is concomitant lung pathology, blood from the native cardiac output will be poorly oxygenated, and the brain and upper limbs may be perfused with relatively deoxygenated blood. This complication of VA ECMO, called *Harlequin syndrome*, may contribute to neurologic morbidity through brain ischemia resulting from regional hypoxemia.[17-19] Moreover, arterial blood sampling from the ECMO circuit, radial artery, and femoral artery may reveal different regional $PaCO_2$ and acid/base states. Arterial blood gases in VV ECMO are not subject to this phenomenon because of the return cannulation on the venous side of the circulation. In addition, arterial blood samples should approximate cerebral arterial blood regardless of where samples are drawn.

Neurologic determination of death donation in ECMO: considerations

Management of potential clinical confounders

If confounding by pharmacologic agents (e.g., sedatives or paralytics) is suspected, sufficient time must be allowed to pass before NDD. Assays to monitor drug levels are available for some agents, and may be ordered to exclude drug effects. In cases where therapeutic drug levels cannot be monitored, the empiric use of antagonizing agents such as naloxone and flumazenil (for opioids and benzodiazepines, respectively) could be considered. Commonly used non-depolarizing neuromuscular blocking drugs (e.g., rocuronium and cisatracurium) may also confound the clinical exam. Neuromuscular blockade monitoring is widely available and its train-of-four (TOF) testing has been suggested to show adequate neuromuscular junction transmission prior to clinical assessment.[20] Nevertheless, its interpretation requires experience, and TOF without fade can be present despite clinically significant residual paralysis. Rocuronium is metabolised by the liver and cisatracurium is metabolised by Hoffmann elimination, and 25–35% of both are excreted unchanged into the urine.[21] If there is doubt about persistent drug effects, then sugammadex could be administered as an antagonist for rocuronium. Ongoing suspicion of confounding precludes use of clinical criteria alone to confirm death, and ancillary testing must be performed in addition to the clinical exam.[6]

Maintaining adequate oxygenation during apnea testing

During apnea testing, hypoxemia should be avoided. Oxygenation should be supported by maximizing sweep gas oxygen concentration across the oxygenator and optimizing ECMO flow. Passive oxygenation via the endotracheal tube can also occur as per usual techniques.[22,23]

Apnea testing

Carbon dioxide removal parameters often need modifying for the apnea test in ECMO. The most common suggested approach is to stop or reduce the sweep gas flow rate to 0.5–1 L·min^{-1} while serial ABGs are performed.[24] Carbon dioxide buildup is documented on successive ABGs while the patient is observed for respiratory efforts. Another described strategy is to add CO_2 directly to the sweep gas flow in a controlled fashion while maintaining the total sweep flow setting (or reducing it only slightly).[15,25] This approach is preferred in situations where the requisite CO_2 cannot be achieved by reducing sweep gas alone (e.g., where hypoxemia antecedes hypercarbia).

Measurement of ABGs is central to ensuring an adequate respiratory stimulus during the apnea test. The site of CO_2 sampling in VA ECMO is critical since there may be regional differences in CO_2 content due to incomplete intermixing of the native and circuit blood flow.[16] To ensure blood gas measurements reflect the cerebral $PaCO_2$, multiple sites (including post-membrane and systemic arterial sites furthest from the ECMO return flow) must be sampled and all blood samples should achieve target levels.[26,27]

The clinical assessment of respiratory effort may be more difficult in a patient with severe hypoxemic respiratory failure and severely reduced lung compliance, including those who receive ECMO. The complete consolidation of lung parenchyma or other intrathoracic disease may attenuate the usual chest wall rise observed during respiration. Care should be taken to observe abdominal muscles and accessory muscles of respiration. The apnea test may also be conducted on a ventilator circuit to allow continual monitoring of airway pressure, flow, and end-tidal CO_2.

Ancillary testing

There is limited evidence to guide selection of ancillary testing modalities in patients on ECMO. Possible choices included CTA, digital subtraction angiography, or other nuclear imaging. The use of CTA has become popular as an ancillary test because of its widespread availability. The timing of the arterial phase contrast bolus in CTA may be challenging because of low cardiac output, competitive flow of contrast through the ECMO, or competing native and circuit circulations in VA ECMO. These issues make acquiring and interpreting images difficult, especially when competitive aortic flow in VA ECMO produces asymmetry in opacification of the great arteries.[28] Nuclear perfusion scanning (technetium-99 hexamethylpropylene amine oxime single-photon emission computed tomography [Tc-99-HMPAO SPECT]) may be a more suitable imaging modality because the radiopharmaceutical kinetics are not substantially affected by the ECMO circuit. Nuclear perfusion scans have been used successfully in patients on ECMO, although some patients may not tolerate the long total scan time including radiopharmaceutical injection and subsequent delayed scanning.[29] The specific indication and choice of investigation should be discussed with the reporting radiologist. Irrespective of the modality chosen, an adequate perfusion pressure is required, and the logistics of coordinating safe intra-facility transport of ECMO patients require an experienced team.

Suggested protocol for apnea testing on ECMO

The following protocol provides a step-by-step approach to apnea testing in ECMO, incorporating the principles discussed in earlier sections. A visual summary is provided in Fig. 1.

1. Obtain baseline ABG. Ensure pH is 7.35–7.45.
   For VV ECMO, blood gases can be drawn post-membrane *OR* from peripheral arterial cannula. For VA ECMO, blood gas measurements should be made from both peripheral and post-membrane samples, with both samples meeting criteria to ensure that the cerebral $PaCO_2$ and pH is in range.
2. Expose patient's lower chest and abdomen (with appropriate draping) so respiratory effort can be observed.
3. Set sweep gas FsO_2 at 1.0 (i.e., 100% O_2 through ECMO circuit).
4. Adjust ECMO circuit blood flow to adequate oxygenation ($SpO_2 > 92\%$) during apnea testing. Note that the ECMO flow rate may need to be increased above previously established baseline rate to prevent hypoxemia.
5. Reduce sweep gas to 0.5–1 L·min^{-1} so CO_2 can accumulate. If this does not achieve the requisite CO_2, consider adding CO_2 to the sweep gas circuit to provide 8–9% gaseous CO_2 concentration. (This can be delivered using a Y-connector in the sweep gas line.)
6. Disconnect patient from ventilator, place ventilator on standby, or continuous positive airway pressure of 5 cmH_2O.
7. Continuously observe for respiratory efforts. Any respiratory efforts preclude neurologic death and terminate the apnea test.
8. Obtain an ABG after five minutes to ensure CO_2 is rising. If the CO_2 is rising very slowly consider reducing the sweep gas flow to 0.5 L·min^{-1} (or increasing the amount of exogenous CO_2

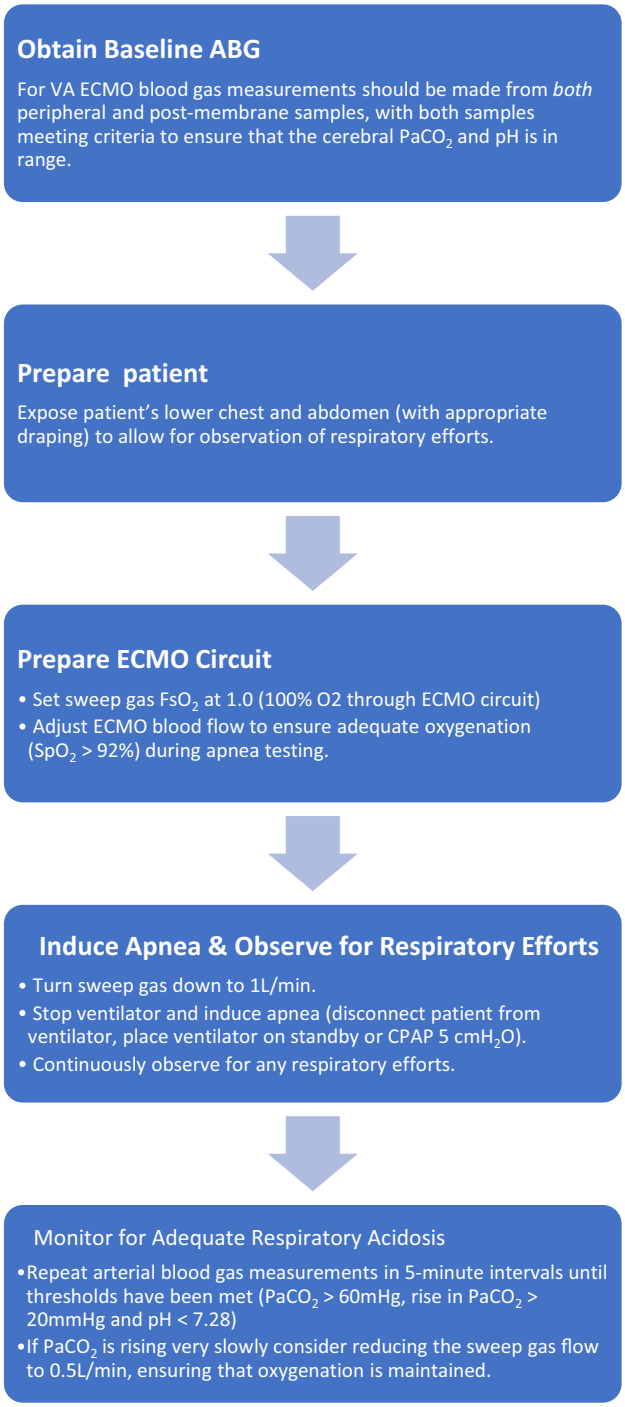

Fig. 1 Suggested protocol for apnea test in ECMO. ABG = arterial blood gas, CO_2 = carbon dioxide, CPAP = continuous positive airway pressure, ECMO = extracorporeal membrane oxygenation, FsO_2 = sweep gas oxygen fraction, $PaCO_2$ = partial pressure of carbon dioxide, VA ECMO = venoarterial extracorporeal membrane oxygenation

administration), ensuring that oxygenation is maintained.

9. Repeat ABG measurements in five-minute intervals until thresholds have been met ($PaCO_2 > 60$ mmHg, rise in $PaCO_2 > 20$ mmHg, and pH < 7.28). We have suggested a shorter interval than traditional NDD monitoring because 1) centres performing ECMO usually have easy and rapid access to ABGs, and 2) without tracheal gas insufflation (which is commonly used in conventional NDD in mechanically ventilated patients) $PaCO_2$ may climb more rapidly and a shorter initial observation period may be warranted.
10. Once observation period is completed and apnea testing is terminated, correct sweep gas to baseline, reconnect patient to ventilator at original settings, and ensure ABGs are corrected to baseline.

Donation after circulatory death after withdrawal of ECMO: considerations

Once the decision to withdraw life-sustaining measures has been made, there is an opportunity for a trained coordinator to approach the patient's family regarding organ donation. The WLSM prior to DCD in ECMO is comparatively straightforward, but still requires careful attention and a structured approach. Priorities during WLSM include minimizing patient discomfort and attending to family members if present, and reducing potential injury to organs prior to recovery. Mechanisms to achieve this are not different in ECMO and include administration of analgesics to reduce pain and dyspnea; use of anticholinergic agents (e.g., hyoscine or glycopyrrolate) to decrease oral secretions; and initiation of sedatives/anxiolytics to minimize agitation, anxiety, and discomfort.[30] Medications are titrated to the appropriate clinical endpoints under careful observation and with frequent re-evaluations. The patient's family should be encouraged to be present during this time if they wish.

We recommend rapid staged WLSM (Fig. 2). Patients should be extubated to room air, the ECMO circuit flow discontinued, and any inotropes or vasopressors turned off in quick succession while ensuring that the patient is comfortable at each step. In patients who have consented to donate organs, we advise against gradual weaning of invasive and mechanical support, unless driven by symptom management, because this practice prolongs warm ischemic time and decreases the likelihood of

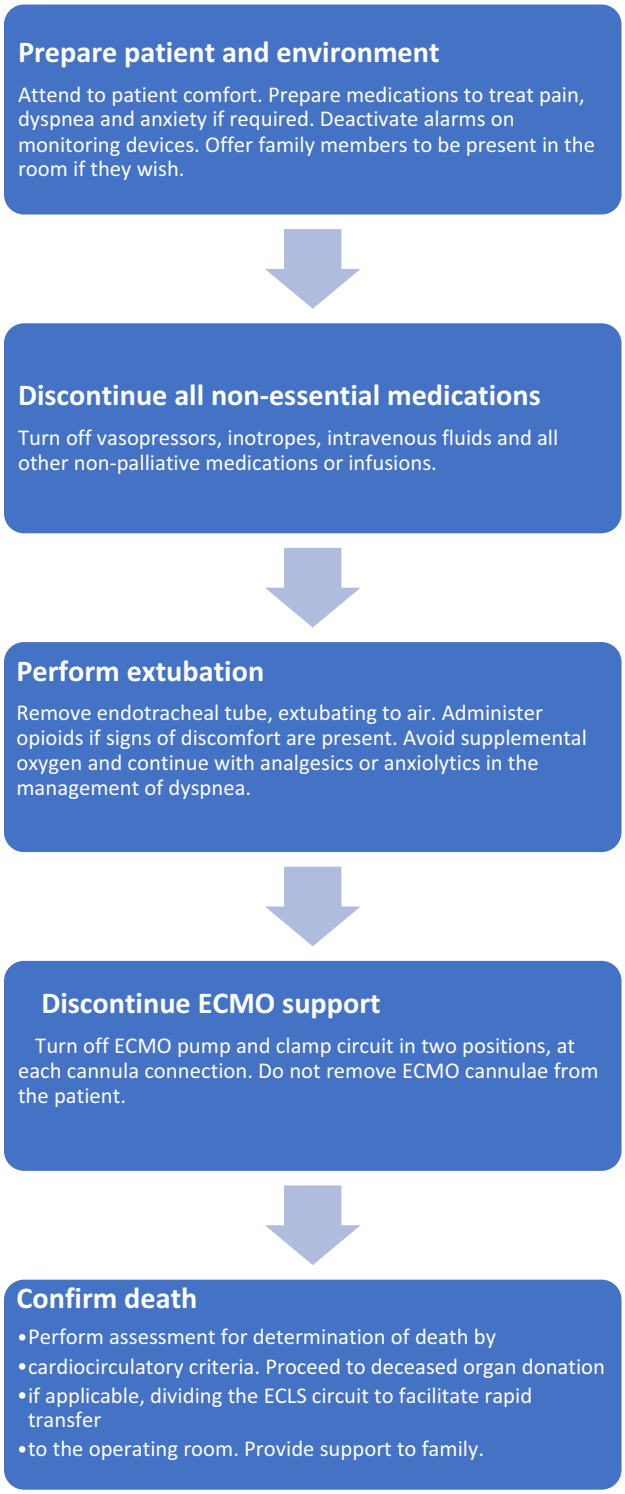

Fig. 2 Suggested protocol for WLSM in ECMO. ECMO = extracorporeal membrane oxygenation, WLSM = withdrawal of life-sustaining measures

honoring the patient's wish to donate. Clinical examination for determination of death by cardiocirculatory criteria on ECMO is the same as in other settings. Death is determined after five minutes of continuous circulatory arrest (defined by the loss of arterial pulse pressure) and apnea must be confirmed by two physicians.[7] If the patient is on VA ECMO, death will likely follow shortly after discontinuation of circuit flow, and family members should be appropriately and sensitively briefed to this fact. In VV ECMO, circuit flow should also be discontinued, but native cardiac contractility will be present so death may take longer. Once the circuit flow is discontinued, we do not suggest removing the ECMO cannulae. Organ viability for donation is affected by the duration of warm ischemia, and most organ donation will be ruled out if death has not occurred within one to two hours following WLSM.[7] Palliative care should proceed as usual if consideration of organ donation concludes.[7]

Extracorporeal interval support for organ retrieval (EISOR), also known as normothermic regional perfusion, is a recently described application of VA ECMO in which extracorporeal support is used to re-perfuse visceral organs after death as a bridge to organ retrieval.[31] Following determination of death, aortic interruption (with either balloon or surgical ligation) is obtained to prevent cerebral and cardiac re-perfusion from the ECMO circuit and ensure permanence of native circulatory arrest and death.[32] Venoarterial ECMO is then initiated to reperfuse abdominal organs with oxygenated blood while organ retrieval is organized. In one single-centre study, kidneys obtained from EISOR showed less delayed graft function compared with those obtained following standard DCD.[33] Nevertheless, use of EISOR is not without controversy,[34] and currently no organ donation organization in Canada is utilizing this method of organ recovery.

Conclusion

In Canada, organ donation rates have steadily improved since the adoption of DCD donation.[7] Nevertheless, while the 2018 rate of 20.6 deceased donors per million population represents a 46% increase from 2008 levels, the demand for transplantation continues to far exceed donation supply.[4] Hundreds of Canadians die on the transplant waiting list each year, and many of them are children. Seeking to identify strategies for improvement, a 2014 report by the Canadian Institute for Health Information cited limiting missed donation opportunities as an important way to enhance transplantation.[35]

In the setting of ECMO, lack of familiarity with the processes of NDD and WLSM may represent potential barriers to optimizing donor recruitment. Patients on ECMO present unique challenges to NDD and WLSM,

and previous reports suggest that there may be hesitation to perform important aspects of death declaration in this population.[36] Nevertheless, ECMO may also represent a unique opportunity for donation, given the stability it affords to the dying process (e.g., by minimizing total warm ischemic time to organs). In this review, we provide guidance for WLSM and apnea testing from a Canadian perspective, synthesizing elements of current strategies available in the literature. We also highlight important considerations that clinicians should be aware of when declaring death for the purposes of organ donation in ECMO.

Author contributions *Shaurya Taran* contributed to all aspects of this manuscript, including article conception and design, preliminary literature review, manuscript drafting, and critical revisions. *Andrew Steel* contributed to the conception and design of the manuscript, critical revisions, and preliminary literature review. *Andrew Healey* contributed to article conception and design, data acquisition, and critical revisions. *Eddy Fan* contributed to article conception and design and critical revisions. *Jeffrey Singh* contributed to all aspects of the manuscript, including article conception and design, manuscript drafting, and critical revisions.

Conflicts of interest Dr. Steel, Dr. Healey, and Dr. Singh are affiliated with Trillium Gift of Life Network (TGLN), a non-profit agency of the Government of Ontario responsible for the province's organ and tissue donation strategy, promotion, and supply.

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