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Diagnosis of death using neurological criteria in adult patients on extracorporeal membrane oxygenation: Development of UK guidance

CIS Meadows[1], M Toolan[1], A Slack[1], S Newman[1,2], M Ostermann[1], L Camporota[1], D Gardiner[2], S Webb[3,4], J Barker[5], A Vuylsteke[3], C Harvey[6], S Ledot[7], I Scott[8] and NA Barrett[1]; on behalf of the NHS England "ECMO in adults with severe respiratory failure" commissioned service

Abstract

The diagnosis of death using neurological criteria is an important legal method of establishing death in the UK. The safety of the diagnosis lies in the exclusion of conditions which may mask the diagnosis and the testing of the fundamental reflexes of the brainstem including the apnoea reflex. Extracorporeal membrane oxygenation for cardiac or respiratory support can impact upon these tests, both through drug sequestration in the circuit and also through the ability to undertake the apnoea test. Until recently, there has been no nationally accepted guidance regarding the conduct of the tests to undertake the diagnosis of death using neurological criteria for a patient on extracorporeal membrane oxygenation. This article considers both the background to and the process of guideline development.

Keywords

Death by neurological criteria, extracorporeal membrane oxygenation

Introduction

The diagnosis of death using neurological criteria, also known as brainstem death, is an important and accepted method of establishing death in the UK. Adherence to national guidance is key, including the demonstration of apnoea during brainstem exposure to an elevated arterial pCO_2. The provision of extracorporeal membrane oxygenation (ECMO) for both severe respiratory and cardiac failure has been expanding in the UK, and specific additional guidance to securely diagnose death by neurological criteria is required. NHS England (NHSE)-commissioned severe respiratory failure centres sought to produce a consensus guideline for use in adults. This article explains the background rationale as well as the process of development. The guideline itself follows as a supplement. Please note that organ preservation through post-mortem application of ECMO to facilitate donation is an entirely separate process and is not considered here.

[1]Department of Critical Care Medicine, Guy's and St Thomas' NHS Foundation Trust, London, UK
[2]NHS Blood and Transplant, Nottingham University Hospitals NHS Trust, Nottingham, UK
[3]Department of Critical Care Medicine, Royal Papworth NHS Foundation Trust, Cambridge, UK
[4]Joint Standards Committee of the Intensive Care Society & Faculty of Intensive Care Medicine, London, UK
[5]Department of Critical Care Medicine, Manchester University Hospitals, Manchester, UK
[6]Department of Critical Care Medicine, University Hospital of Leicester, Leicester, UK
[7]Department of Critical Care Medicine, Royal Brompton and Harefield NHS Foundation Trust, London, UK
[8]Department of Critical Care Medicine, Aberdeen Royal Infirmary, Aberdeen, UK

Corresponding author:
NA Barrett, Guy's and St Thomas' NHS Foundation Trust, Westminster Bridge Road, London SE1 7EH, UK.
Email: nicholas.barrett@gstt.nhs.uk

The diagnosis of death using neurological criteria in the UK

In the UK, the accurate diagnosis of brainstem death is an essential responsibility of intensive care doctors. The declaration of death using neurological criteria was developed in the 1960s in recognition of the inadequacy of the declaration of death using circulatory criteria for patients receiving mechanical ventilation, to provide criteria for stopping futile treatment to patients on intensive care and to facilitate organ donation for the purposes of transplantation, particularly heart and lung.[1,2] In the UK, the criteria was established by statements issued by the Conferences of Royal Medical Colleges[3,4] and this criteria has been accepted by the courts. The justification of the use of death by neurological criteria equating to human death is summed up by the US President's Council on Bioethics: "there is a fundamental vital work of a living organism – the work of self-preservation, achieved through the organism's need-driven commerce with the surrounding world."[5,6] Current UK guidance for the declaration of death using neurological criteria is drawn from the UK Academy of Royal Medical Colleges,[7] with practical guidelines published by the Faculty of Intensive Care Medicine and the Intensive Care Society.[8] National endorsed forms to assist with making this diagnosis are commonly used in the UK (https://www.ficm.ac.uk/standards-guidelines-resources/access-ficm-guidelines-resources). Although these guidelines cover both the clinical and ancillary testing processes to legally declare death by neurological criteria, they have not, until now, covered the circumstances where patients are supported by ECMO due to either absent or extremely limited respiratory and/or cardiac function. The lack of accepted guidance in this clinical setting has led to concern the declaration of death using neurological criteria is insecure in this population. Key requirements for the declaration of death using neurological criteria, following fulfilment of preconditions, include the demonstrable absence of brainstem reflexes, including an apnoea response to a respiratory acidosis.

Why is ECMO a special circumstance?

In England, the provision of ECMO for respiratory failure is provided through the NHSE-commissioned service, ECMO for adults with severe respiratory failure.[9] Using standardised criteria for acceptance based on the CESAR inclusion model,[10] mobile ECMO services deployed from specialised centres are able to achieve outcomes comparable with other large international centres.[11,12] In practice, veno-venous (VV), veno-arterial (VA) and veno-arterio-venous (VAV) ECMO are applied to achieve physiological stability dependent on the degree of cardiorespiratory organ dysfunction and the underlying pathological mechanisms.[13] There is, as yet, no formally commissioned service specifically for cardiac (VA) ECMO. However, any cardiac surgery centre can utilise ECMO and the highest patient volumes are reported from cardiothoracic transplant centres. An emerging indication is refractory cardiac arrest where extracorporeal cardio-pulmonary resuscitation (E-CPR) may be used. Although not commissioned, E-CPR is increasingly being provided in an *ad hoc* manner in some UK hospitals. It is essential to be able to secure a diagnosis of death using neurological criteria[14] in the setting of ECMO, because of the increased prevalence of intracranial haemorrhage, risk of anoxic or ischaemic neurological injury associated with severe cardiac or respiratory failure, particularly following cardiac arrest.

The application of ECMO involves the placement of large diameter cannulae into the great veins or arteries using a peripheral or central approach.[15] Blood is passed through the extracorporeal circuit, using centrifugal pumps, at high flow rates (3–6 L/min). A gas exchange membrane both oxygenates and de-carboxylates by sweeping oxygen or an oxygen/air gas mixture over blood. Oxygenation is dependent on blood flow through the membrane, while decarboxylation is determined by the sweep gas flow. At a sweep gas flow of 0 L/min, both oxygen provision and carbon dioxide removal cease.

ECMO can impact upon the testing of brainstem and apnoea reflexes in two ways. Firstly, pharmacokinetic alterations can occur, due to membrane sequestration and leaching of drugs; and secondly, de-carboxylation may affect the performance of the apnoea test.

ECMO patients, like all critically ill patients, can have significant hepatic and renal impairment as well as significant alterations in total body water, all affecting the clearance and distribution of drugs. The additional impact of ECMO on pharmacokinetics is not completely understood.[16] However, it is known that ECMO circuits sequester drugs, both by adsorption and absorption. Lipophilic drugs, including the sedatives and opiates commonly used in critical care, are particularly well absorbed by the circuit. It is possible that they return to the circulation after cessation of systemic administration giving them a longer than expected context-sensitive half-life.[17] This may make it difficult to reliably exclude reversible causes of coma and apnoea. It is possible to either measure levels of drugs, commence reversal agents or provide additional time to be more certain about the impact of altered pharmacokinetics. Should it not be possible to exclude the effect of drugs then ancillary testing, with the exception of MRI, can be undertaken. Ultimately, should the impact of drugs not be excluded, the attempt to certify death by neurological criteria should be abandoned.

The different ECMO circuit configurations have implications for both oxygen and carbon dioxide

levels to which the brainstem is potentially exposed. This impacts on the performance of the apnoea test.

VV ECMO takes blood from either or both of the great veins and returns it to the right atrium.[18] In the right heart, the blood mixes with native venous return, passes through the lungs where it may have additional oxygen added or carbon dioxide removed, and then enters the systemic circulation via the left ventricle. On VV ECMO, the arterial blood gas tensions are identical in all patent systemic arteries. Consequently, the change in CO_2 partial pressure measured at any arterial site is an accurate reflection of the CO_2 to which the brainstem is exposed and makes this element of the apnoea test reliable.

VA ECMO takes blood from the great veins and either returns it to the aorta (central VA ECMO) or peripheral arterial tree (peripheral VA ECMO), most commonly the femoral or subclavian vessels are used.[18] If the heart is ejecting, but the lungs are poorly functioning then it is possible, in peripheral VA ECMO, to have varying arterial blood gas tensions and pH in different parts of the body. This is because the native left ventricular output may not be well oxygenated if pulmonary gas exchange is compromised. Therefore, the brainstem may be exposed to a different pCO_2 level depending on whether the native output, or extracorporeal circuit output is perfusing the cerebral circulation. It is essential that the arterial blood gas samples should come from a number of arterial sites, and that all samples, including the one most distal to the return arterial flow should show the minimum rise in pCO_2 of at least 0.5 kPa in order to guarantee the safety of the diagnosis. Hypoxaemia can be a significant problem in the setting of co-existing respiratory failure.[19] If hypoxaemia is severe enough to preclude apnoea testing, it should be considered whether it is in the patient's overall benefit to convert to VV ECMO or to a hybrid VAV ECMO configuration. Importantly, it has been reported some ancillary testing techniques may also be impaired on VA ECMO. For example, transcranial Doppler relies to a degree on pulsatile cerebral blood flow which may not be present in severe cardiac failure,[20] and CT angiography may be difficult to time in a hybrid circulation.

A further issue with the apnoea test is that achieving the required increment in pCO_2 may be difficult. Cases reported in the literature describe increasing pCO_2 by removing all extracorporeal sweep gas support, or reducing it to a prescribed minimum value, or even adding exogenous CO_2 to the circuit.[21–26] In these circumstances, either oxygenation may be impaired, or the pCO_2 may rise unpredictably with potential adverse neurological effects. As CO_2 clearance is non-linear, it is important to make small changes to sweep gas flow rates and ventilator minute ventilation to prevent rapid and large CO_2 swings. Both may need to be manipulated carefully, depending on the relative CO_2 clearance via the membrane and the native lungs. In addition, lungs that are completely consolidated with virtually no dynamic compliance will result in no measurable end-tidal CO_2 ($ETCO_2$) or any visible chest wall movement. These elements make the clinical component of the apnoea test more difficult to perform. Thoraco-abdominal dysynchrony may be the only sign of respiratory effort and this must be actively examined for, although in the presence of significant abdominal pathology this too may be difficult to assess. By using a careful stepwise approach to downward titration of the sweep gas flow, coupled with repeated arterial blood gas analysis, and direct clinical observation of chest and abdominal excursion, $ETCO_2$ and movement of a Mapleson C bag, we believe many of these challenges can be overcome. However, it is important to state that testing should be abandoned should hypoxaemia occur, or an adequate rise in pCO_2 not be achieved and if apnoea cannot be convincingly demonstrated.

Haemodynamic instability can be encountered with neurological injury and brainstem death testing. ECMO support can be used to mitigate this instability by increasing extracorporeal support such that it accounts for a greater fraction of the overall cardiac output.[27,28] However, this may not be possible with limitations of circuit flow and adequate drainage from the right atrium. If so, testing should again be abandoned.

What was the process of guideline development?

Recognition of the requirement for formal guidance arose following identification of potential organ donors on both VV and VA ECMO at Guy's and St Thomas' NHS Foundation Trust. Without clear accepted processes and lines of accountability, the legality of organ recovery from donors on ECMO was in doubt. Interrogation of the literature revealed little more than retrospective case series, but no nationally endorsed guidance. The initial protocols for reliable and reassuring physiological testing were then drawn up, considering both VV and VA ECMO states. Following this, an approach was made to other NHS England-commissioned ECMO centres and NHS Blood and Transplant for their support in the development of national guidance. In November 2017, at the National ECMO Centres meeting, all five centres agreed to an outline guidance which was authored with contributions from the group over the ensuing months. In May 2018, the final wording of the document was agreed. To the authors' knowledge, the guideline has not yet been used for the declaration of death. The guideline has now been approved by the Faculty of Intensive Care Medicine at the Royal College of Anaesthetists, the Intensive Care Society and the National Organ Donation Committee as supplementary guidance for the diagnosis of death using neurological criteria. The supplementary guidance

should be used in conjunction with, the Academy of Medical Royal Colleges *A Code of Practice for the Diagnosis and Confirmation of Death* and the forms for the Diagnosis of Death using Neurological Criteria endorsed by the Faculty of Intensive Care Medicine and the Intensive Care Society. This new supplement is available alongside the endorsed testing forms at: https://www.ficm.ac.uk/standards-guidelines-resources/access-ficm-guidelines-resources.

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ORCID iD

I Scott http://orcid.org/0000-0002-9732-5922

References

1. A definition of irreversible coma. Report of the Ad Hoc Committee of the Harvard Medical School to examine the definition of brain death. *J Am Med Assoc* 1968; 205: 337–340.
2. Machado C, Korein J, Ferrer Y, et al. The declaration of Sydney on human death. *J Med Ethics* 2007; 33: 699–703.
3. Diagnosis of brain death. Statement issued by the honorary secretary of the conference of medical royal colleges and their faculties in the United Kingdom on 11 October 1976. *Br Med J* 1976; 6045: 1187–1188.
4. Diagnosis of death. Memorandum issued by the honorary secretary of the conference of Medical Royal Colleges and their Faculties in the United Kingdom on 15 January 1979. *Br Med J* 1979; 6159: 332.
5. President's Commission. Defining death: a report on the medical, legal and ethical issues in the determination of death. Washington: President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, http://bioethics.georgetown.edu/pcbe/reports/past_commissions/defining_death.pdf (1981, accessed 3rd September 2018).
6. Aramesh K, Arima H, Gardiner D, et al. An international legal review of the relationship between brain death and organ transplantation. *J Clin Ethics* 2018; 29: 31–42.
7. Academy of Medical Royal Colleges. A Code of Practice for the Diagnosis and Confirmation of Death, www.aomrc.org.uk/wp-content/uploads/2016/04/Code_Practice_Confirmation_Diagnosis_Death_1008-4.pdf (2008, accessed 3rd September 2018).
8. Intensive Care Society. Diagnosing death using neurological criteria, www.ics.ac.uk/ICS/Guidelines___Standards/ICS/guidelines-and-standards.aspx?hkey=4ed20a1c-1ff8-46e0-b48e-732f1f4a90e2 (2008, accessed 3rd September 2018).
9. Barrett NA, Camporota L, Langrish CJ, et al. Severe respiratory failure in the UK. *J Intensive Care Soc* 2013; 14: 114–119.
10. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009; 374: 1351–1363.
11. Sherren PB, Shepherd S, Daly K, et al. Intensivist delivered severe respiratory failure service with mobile extracorporeal membrane oxygenation (ECMO) capabilities. *Anaesthesia* 2015; 70: 707–714.
12. Gillon SA, Rowland K, Shankar-Hari M, et al. Acceptance and transfer to a regional severe respiratory failure and veno-venous extracorporeal membrane oxygenation (ECMO) service: predictors and outcomes. *Anaesthesia* 2017; 73: 177–186.
13. Vogel DJ, Murray J, Czapran AZ, et al. Veno-arterio-venous ECMO for septic cardiomyopathy: a single-centre experience. *Perfusion* 2018; 33(1_suppl): 57–64.
14. Lockie CJA, Taylor D, Daly K, et al. Intracranial Haemorrhage in patients with severe respiratory failure managed with and without extracorporeal membrane oxygenation. *Crit Care Med* 2017; 45: 1642–1649.
15. Burns J, Cooper E, Salt G, et al. A retrospective observational review of percutaneous cannulation for extracorporeal membrane oxygenation. *ASAIO J* 2016; 62: 325–328.
16. Dzierba AL, Abrams D, and Brodie D. Medicating patients during extracorporeal membrane oxygenation: the evidence is building. *Crit Care* 2017; 21: 66.
17. Cheng V, Abdul-Aziz M-H, Roberts JA, et al. Optimising drug dosing in patients receiving extracorporeal membrane oxygenation. *J Thorac Dis* 2018; 10(Suppl 5): S629–S641.
18. Squiers JJ, Lima B, and DiMaio JM. Contemporary extracorporeal membrane oxygenation therapy in adults: fundamental principles and systematic review of the evidence. *J Thorac Cardiovasc Surg* 2016; 152: 20–32.
19. 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.
20. Cestari M, Gobatto ALN, and Hoshino M. Role and limitations of transcranial Doppler and brain death of patients on veno-arterial extracorporeal membrane oxygenation. *ASAIO J* 2018; 64: e78.
21. 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: 423–426.
22. Yang HY, Lin CY, Tsai YT, et al. Experience of heart transplantation from hemodynamically unstable brain-dead donors with extracorporeal support. *Clin Transplant* 2012; 26: 792–796.
23. Goswami S, Evans A, Das B, et al. Determination of brain death by apnea test adapted to extracorporeal cardiopulmonary resuscitation. *J Cardiothorac Vasc Anesth* 2012; 27: e6–e7.
24. Smilevitch P, Lonjaret L, Fourcade O, et al. Apnea test for brain death determination in a patient on extracorporeal membrane oxygenation. *Neurocrit Care* 2013; 19: 215–217.

25. Pirat A, KömürcüÖ, Yener G, et al. Apnea testing for diagnosing brain death during extracorporeal membrane oxygenation. *J Cardiothorac Vasc Anesth* 2014; 28: e8–e9.
26. Shah V, and Lazaridis C. Apnea testing on extracorporeal membrane oxygenation: case report and literature review. *J Crit Care* 2015; 30: 784–786.
27. 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–e43.
28. Hoskote SS, Fugate JE, and Wijdicks EF. Performance of an apnea test for brain death determination in a patient receiving venoarterial extracorporeal membrane oxygenation. *J Cardiothorac Vasc Anesth* 2014; 28: 1027–1029.