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Mini Review

It is time to abandon apneic-oxygenation testing for brain death

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Abstract

The apneic-oxygenation test is an integral part of clinical testing to determine brain death. The medical and legal criticisms of the test are presented together which make a strong argument that it should be abandoned. The requirement for hypercarbia to stimulate spontaneous respiration also causes intra-cranial hypertension and may exacerbate an existing brain injury and as such is a self-fulfilling test. Moreover in children, the onset of spontaneous respiration may commence at levels of blood carbon dioxide in excess of the minimum level used to define brain death. It is thus also unreliable. A number of legal cases in the United States have been adjudicated in favor of plaintiffs seeking to prevent performance of the test on the basis that it causes harm. Physicians have sought to perform the apneic-oxygenation test without consent of legal guardians but have failed. In lieu of the apneic-oxygenation test a brain scan using a lipophilic radionuclide is suggested. Demonstration of absent brain blood flow may be a more stringent test to determine brain death than apneic-oxygenation but is more reliable, less invasive, not harmful and not likely to reduce the rate of organ donation.

It is time to abandon apneic-oxygenation testing for brain death

For decades the apneic-oxygenation test has been used as a key component of clinical testing to determine if a potential organ donor has sustained irreversible loss of the ability to breathe spontaneously in the context of a hypercarbic challenge. When no respiratory effort is observed in association with irreversible unresponsive coma due to severe brain injury the victim is concluded to be "brain dead" and is an eligible organ donor. However, there is a growing clinical and legal opposition to performance of this test.

The apneic-oxygenation test is essential to satisfy the requirements of the second section of *Uniform Determination of Death Act* (UDDA), proposed in 1981, to define death in which:

An individual who has sustained either 1) irreversible cessation of circulatory and respiratory functions or 2) irreversible cessation of all functions of the entire brain, including the brainstem, is dead. A determination of death must be made in accordance with accepted medical standards."

The UDDA in this form or slight variations has been adopted by most States and has been adopted in other countries, again with slight variations such as that in section 41 of the *Human Tissue Act* 1982 in the State of Victoria in Australia:

"For the purposes of the law of Victoria, a person has died when there has occurred - (a) irreversible cessation of circulation of blood in the body of the person; or (b) irreversible cessation of all function of the brain of the person."

Such legislation does not stipulate how brain death should be determined but the apneic-oxygenation test is an integral part of death determination.

This test is conducted only when irreversible unresponsive coma is present and all confounding factors such as depressive medication, hypothermia, metabolic and electrolytic disturbances have been excluded. The test cannot be used if another injury such as high cervical cord damage prevents a neuromuscular response to hypercarbia, and is performed only when other brainstem reflexes are absent.

Medical opposition to the apneic-oxygenation test

Some organ procurement guidelines, for example those of the Australian and New Zealand Intensive Care Society [1] and

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of the New York State Department of Health [2] advise that the test is conducted only when all other brainstem reflexes have been extinguished, tacitly conceding that hypercarbia may depress brain function. Essentially the test is conducted by allowing the carbon dioxide content of arterial blood to increase, without hypoxemia, to a level which would be expected to generate a respiratory effort. In the United States, Canada, Australia and New Zealand, that level is a $PaCO_2$ of at least 60 mmHg (8 kPa), or 20 mmHg above resting level while in Britain the required minimum level is 50 mmHg (6.7 kPa).

The test is a diagnostic one, that is to determine if the patient's respiratory center is functional or not. The main argument against using the test is that it may cause brain death, if the patient's brain is not already dead. That is, it is a self-fulfilling test which by causing brain death yields a positive result [3-5]. It is well known in neuro-intensive care that any rise in blood carbon dioxide causes a rise in intracranial pressure, and that hyperventilation may acutely reduce intracranial pressure. These changes in intracranial pressure are the consequences of vasoconstriction and vasodilation. Of course, these effects are irrelevant if the patient is already dead, but since the test is a diagnostic one to determine if death is present or not, it is flawed, even when conducted without adverse events such as hypoxemia which are not uncommon [3-5].

Another problem with the test is that it may be unreliable and may yield a false positive result. The minimum limit of hypercarbia to stimulate respiration is scientifically unknown. Indeed, a number of case reports [6-10] in children, otherwise fulfilling the criteria for death, document the onset of spontaneous breathing at $PaCO_2$ levels well above the minimum required to diagnose death (60 mmHg). At this minimal $PaCO_2$ level these children could have been diagnosed dead when they were in fact alive.

That the conduct of the apneic-oxygenation test for brain death exacerbates intracranial hypertension and compromises brain perfusion was documented in a case series of adults with severe brain injury [11]. In 13 patients with severe brain injuries, testing with a range of $PaCO_2$ 60-81 mmHg caused mean intracranial pressure to rise from 87 +/- 23 to 95 +/- 28 mmHg which settled to 84 +/- 21 mmHg after the test. Simultaneously the mean arterial pressure increased from 95 +/- 22 to 109 +/- 21 mmHg during the test and settled to 86 +/- 16 mmHg after the test. Importantly, the cerebral perfusion pressure before the test was low (8 +/- 16 mmHg) but lower after the test (1 +/-16 mmHg) suggesting that if there was cerebral perfusion before the test, the conduct of the test caused a significant decrease (P=0.006). In jurisdictions where the test must be performed twice, it is likely that the outcome of a second test will be influenced by prior testing and yield a positive result.

Legal opposition to the apneic-oxygenation test

Recently, a number of high profile legal cases in the US have controversially challenged the use of the test, with plaintiffs (or their legal guardians) claiming that the test (with other tests) does not determine death, for example *Jahi McMath* [12-15] and *Israel Stinson* [16] in the US and *Ibrahim* [17] in Australia. However, Courts have ruled that the diagnosis of brain death does constitute death. Of more concern are several cases in which plaintiffs have claimed that performance of the apneic-oxygenation test has in fact caused harm. Another key issue is whether the performance of the test is a medical procedure which requires informed consent from legal guardians. These issues are illustrated by the following few selected legal cases.

Case of alex pierce

In 2016, Sabrina Pierce, petitioned the Superior Court of California for an order to prevent Loma Linda Medical Centre performing brain death deaths on her son, Alex, a minor who had nearly drowned at a school party. Paramedics gave cardiopulmonary resuscitation CPR with restoration of a pulse. He was subsequently transported with mechanical ventilation to Loma Linda Medical Center. He had spontaneous movement, eye opening and electroencephalographic (EEG) activity. However, onset of convulsions treated with anticonvulsant medication abolished spontaneous movement. Physicians planned to perform clinical brain death testing and a brain blood flow study but were refused consent by his mother who believed that the apneic-oxygenation test would cause further brain damage. Loma Linda maintained a right to conduct brain function tests without consent and to cease treatment if brain death was established. The Court issued a temporary restraining order [18] preventing Loma Linda performing an apnea test, removing mechanical ventilation, withholding nutrition and necessary medical care, utilizing medication which could influence neurological testing and ordered an independent assessment by a physician not affiliated with Loma Linda including a repeat EEG and brain blood flow study.

Case of allen calloway

Another case in 2016 concerned a child of almost 6 years who nearly drowned in a Montana Lake. He was rescued and with CPR regained spontaneous circulation and some respiratory effort but thereafter his neurological condition worsened. After 5 days, brain stem herniation was suspected. Clinical tests, including an apneic-oxygenation test were conducted with consent on the basis that they would determine brain function, not brain death. During the 10 minute apneic-oxygenation test, the $PaCO_2$ increased from 39 mmHg to 100 mmHg with no respiratory effort observed. The physicians believed the test confirmed their suspicion of brain death but Allen's guardian perceived that he had struggled to breathe and had experienced pain, distress and harm. A neurologist opined that because an EEG showed a brief burst of frontally dominant mixed alpha/beta activity and that the depressant effects of previously administered medications, Fentanyl and Dilantin had not been excluded, that the statutory requirements under UDDA to show that irreversible cessation of all functions of the entire brain had not been met. A second set of clinical examinations was proposed by the doctors but the guardian refused consent. A tracheostomy and gastrostomy were performed to facilitate ongoing mechanical ventilation and nutrition. The hospital sought a judicial declaration permitting it to conduct further brain death function tests. However, the Court ruled that the

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conduct of brain function tests was a medical procedure and as such a guardian had the right to autonomously choose or refuse treatment under privacy guarantees of Montana's constitution [19]. This includes the right to decide whether or not to conduct a brain death examination – a medical procedure with considerable repercussions. In addition, the Court ruled that it was unwilling to grant the medical profession the sole and exclusive authority to conduct brain death examinations, with the Judge remarking that such public policy was the role of legislature, not the Court.

Case of mirranda lawson

Also in 2016, a 2 year-old child choked on popcorn which led to prolonged cardiorespiratory arrest. Family members and then paramedics performed CPR. With mechanical ventilation she was conveyed to a pediatric intensive care unit in Richmond, Virginia. Since no neurological recovery was observed clinical tests for brain death were proposed. However, Mirranda's parents refused consent on the basis that the apneic-oxygenation test would cause harm by causing additional brain swelling and damage. They obtained a Court injunction against testing. In a District Court, the injunction was not extended leaving it open for the tests to be conducted, however her parents maintained opposition and appealed to the Supreme Court of Virginia which ruled that the hospital could not perform an apnea test [20]. It held that the hospital did not have authority to override the parents' statutory right to make decisions for their daughter and were not able to perform testing against the wishes of the parents. The Court ordered the hospital provide treatment requested by the parents pending transfer to another institution.

Alternative tests for brain death

Guidelines for organ donation make provision for ancillary testing if clinical tests cannot be performed or they are confounded [1,2], but they should be routine. The preferred test is scanning with lipophilic diffusible radionuclides including Technetium Tc^{99m} Exametazine or Technetium Tc^{99m}-ECD. Brain death testing by radioisotope scanning is more practical and more easily accomplished with one test [21] compared with clinical testing which must be performed twice before organ procurement [1,2]. In addition, scanning is much less invasive compared to apneic-oxygenation testing and not injurious to the brain or other organs and is not influenced by brain depressive medication, muscle relaxants, hypothermia, metabolic and endocrine derangements, electrolyte abnormalities, spinal cord injury and automatism which may be present in severe brain injury and confound clinical testing. Radioisotope brain scanning can be used in all ages [22]. It need not be deferred until medication, which may confound clinical test, to be metabolized or excreted [23]. The only clinical requirements are for adequate blood pressure to ensure delivery of the radionuclide to the brain and sufficient oxygenation and glucose supply to enable absorption of the radionuclide if any brain function is present. While absence of brain blood flow is considered to be the "gold-test" of brain death [24], scanning with lipophilic radionuclides are considered to be the "gold-tests" of blood flow [25-27] because they are taken up and metabolized by functioning brain tissue. Absence of intracranial radioactivity proves absence of brain blood flow. Other tests of brain blood flow such as scanning with non-lipophilic radioisotopes, angiography, and Doppler ultrasound are less suitable for assessing brain function because they yield once-only angiographic data and nothing about brain function.

A few logistical prerequisites exist to perform appropriate radionuclide scanning. Brain blood flow detection is within the capabilities of any institution with a nuclear medicine service. The cost of the radiopharmaceutical is minimal. Unless a portable gamma camera is available, transport of the patient from the critical care area is required but poses very little risk in hospitals already skilled in organ procurement. Single-photon emission computed tomography (SPECT) is superior to planar imaging for detecting brainstem blood flow and both anterior and lateral views are required, the latter to optimally detect cerebellar flow [28].

Possible impact of foregoing the apneic-oxygenation test

A test for absence of brain blood flow may be a more stringent test for brain death than the apneic-oxygenation test because some brain blood flow may still remain when brain stem reflexes are absent [29-31]. Consequently, the rate of organ donation as a percentage of deaths may decrease. However, this is only a theoretical risk. Scanning images showing complete absence of brain blood flow may be more convincing and less distressing for guardians to know that the patient is truly dead [32,33] and may contribute to the organ donation rate.

Proposals for legislative reform

Several authors have called for a reform of the UDDA [34,35]. If reform does occur, it may be opportune to specify that the absence of brain blood flow is a requirement to diagnose brain death. This could be accomplished by incorporating changes into medical guidelines or directly into legislation.

Lewis and colleagues [34] propose that the definition of brain death be modified to "irreversible cessation of functions of the entire brain, including the brainstem, leading to unresponsive coma with loss of capacity for consciousness, brainstem areflexia and the inability to breathe spontaneously". Secondly, they urge that all US States follow the example of Nevada which specifies that the determination of death by "accepted medical standards" be those of the American Academy of Neurology for adults and those of the Society of Critical Medicine, American Academy of Pediatrics and Child Neurology Society for children. Thirdly, these authors urge that the UDDA specify that ongoing hormonal function be exempted in requiring cessation of "all functions of the entire brain, including the brainstem". In addition, these authors urge that the UDDA specify that consent is not required from guardians for the performance of tests for brain death. However, abolition of informed consent is a retrogressive step in development of law and is most unlikely to be widely adopted. Of note is that the State of Nevada has adopted legislation to abolish the long-

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standing legal requirement of consent for testing [36,37]. While agreeing that the UDDA needs revision, Nguyen [35] maintains that the suggestions of Lewis and colleagues neither address the root cause of the litigations (harm caused by testing) nor the controversies about the neurological declaration of brain death. Instead, Nguyen advocated for informed consent for testing and proposed that reform of the UDDA accommodate personal religious, cultural or moral convictions, as exemplified in the *New Jersey Declaration of Death Act* 1991 [37] which provides for religious exemption to neurological declaration of death.

Conclusions

There is a need for legislative and policy reform in this contentious area. The apneic-oxygenation test should be abandoned because it is flawed, harmful and may exacerbate a brain injury if the patient is not already dead. Better tests, in particular radionuclide scanning with lipophilic radionuclides, are available. Brain scanning is reliable, not harmful, easily accomplished and may be more convincing and less distressing to loved ones that the patient is dead.

References

1. ANZICS Statement on Death and Organ Donation. Link: https://bit.ly/3hhCp9B
2. New York State Department of Health Guidelines for determining brain death. Link: https://on.ny.gov/33alpx6
3. Tibballs J (2010) A critique of the apneic-oxygenation test for the diagnosis for brain death. Pediatr Crit Care Med 11: 475-478. Link: https://bit.ly/3k3UGch
4. Joffe AR, Anton NR, Duff JP (2010) The apnea test: rationale, confounders, and criticism. J Child Neurol 25: 1435-1443. Link: https://bit.ly/3bH6Zse
5. Tibballs J, Joffe AR (2010) The impossibility of diagnosing brain death with clinical tests: apneic-oxygenation as a self-fulfilling diagnostic test. Functional Neurology and Clinical Ergonomics 1.
6. 6. Brilli RJ, Bigos D (1995) Altered apnea threshold in a child with suspected brain death. J Child Neurol 10: 245-246. Link: https://bit.ly/3k4upe6
7. Levin SD, Whyte RK (1988) Brain death sans frontières. N Eng J Med 318: 852-853. Link: https://bit.ly/2ZohA6m
8. Vardis R, Pollack MM (1998) Increased apnea threshold in a pediatric patient with suspected brain death. Crit Care Med 26: 1917-1919. Link: https://bit.ly/3k58bZc
9. Okamoto K, Sugimoto T (1995) Return of spontaneous respiration in an infant who fulfilled current criteria to determine brain death. Pediatrics 96: 518-520. Link: https://bit.ly/2Zr2D3p
10. Joffe AR, Kolski H, Duff J, de Caen AR (2009) A 10-month-old infant with reversible findings of brain death. Pediatr Neurol 41: 378-382. Link: https://bit.ly/33mdwoy
11. Roth C, Deinsberger W, Kleffmann J, Ferbert A (2015) Intracranial pressure and cerebral perfusion pressure during apnoea testing for the diagnosis of brain death – an observational study. Eur J Neurol 22: 1208-1214. Link: https://bit.ly/3ii4sHo
12. McMath v. California, Case No. 15-cv-06042-HSG (N.D. Cal. Dec. 12, 2016). Link: https://bit.ly/32gAvSD
13. Winkfield v. California, No. 4:15-06042 (N.D. Cal. Dec. 23, 2015). Link: https://bit.ly/33k0BDi
14. Truog RD (2018) Lessons from the case of Jahi McMath. Hastings Center Report 48: S70-S73. Link: https://bit.ly/3mbDRhk
15. Shewmon AD (2018) The case of Jahi McMath. Hastings Center Report 48: S74-S76. Link: https://bit.ly/2ZmEDi4
16. Fonseca v. Smith, No. 2:16-cv-00889-KJM-EFB (E.D. Cal. Mar. 27, 2017). Link: https://bit.ly/3bK1QPV
17. Ibrahim v South Eastern Sydney Local Health District [2018]. NSWSC 913. Link: https://bit.ly/35nY3XC
18. Pierce v. Loma Linda University Medical Center, No. CIV-DS-1608931 (San Bernardino County Sup. Ct., Cal. June 7, 2016). Link: https://bit.ly/3k2vkvu
19. In re: Allen Callaway, No. DG-16-08 (Pondera County Dist. Ct., Mont. Sept. 26, 2016)
20. In re: Mirranda Grace Lawson, No. CL16-2358 (City of Richmond Circuit Court, Va. June 10, 2016)
21. Conrad GR, Sinha P (2003) Scintigraphy as a confirmatory test of brain death. Seminars in Nuclear Medicine 33: 312-323. Link: https://bit.ly/32dTJlu
22. Okuyaz C, Gucuyener K, Karabacak NI, Aydin K, Serdarroglu A, et al. (2004) Tc-99m-HMPAO SPECT in the diagnosis of brain death in children. Ped Internat 46: 711-714. Link: https://bit.ly/3iiJLv1
23. Lopez-Navidad A, Caballero F, Domingo P, Marruecos L, Estorch M, et al. (2000) Early diagnosis of brain death in patients treated with central nervous system depressant drugs. Transplantation 70: 131-135. Link: https://bit.ly/3ma7T5m
24. Heran MK, Heran NS, Shemie SD (2008) A review of ancillary tests in evaluating brain death. Can J Neurolog Sc 35: 409-419. Link: https://bit.ly/3icT938
25. Wieler H, Marohl K, Kaiser KP, Klawki P, Frossler H (1993) Tc-99m HMPAO cerebral scintigraphy. A reliable noninvasive method for determination of brain death. Clin Nuc Med 18: 104-109. Link: https://bit.ly/33k24ti
26. Munari M, Zucchetta P, Carollo C, Gallo F, De Nardin M, et al. (2005) Confirmatory tests in the diagnosis of brain death: a comparison between SPECT and contrast angiography. Crit Care Med 33: 2068-2073. Link: https://bit.ly/3k2w5Vm
27. Banzo J, Razola P, Araiz JJ, Larraga J, Andrés A, et al. (2012) Cerebral perfusion scintigraphy study as confirmation test of brain death in the process or organ donation for transplant. Span J Nuc Med Moll Imaging 31: 278-285. Link: https://bit.ly/33i6Nf4
28. Joffe AR, Lequier L, Cave D (2010) Specificity of radionuclide brain blood flow testing in brain death : case report and review. J Intens Care Med 25: 53-64. Link: https://bit.ly/32fSE2B
29. Wijdicks EFM (2010) The case against confirmatory tests for determining brain death in adults. Neurology 75: 77-83. Link: https://bit.ly/3ik4E8Z
30. Wijdicks EFM (2013) Pitfalls and slip-ups in brain death determination. Neurol Res 35: 169-173. Link: https://bit.ly/2FjFoBB
31. Zuckier LS (2016) Radionuclide evaluation of brain death in the post-McMath era. J Nuc Med 57: 1560-1568. Link: https://bit.ly/2FeQPKE
32. Nakagawa TA, Ashwal S, Mathur M, Mysore M (2011) Clinical report – guidelines for the determination of brain death in infants and children: an update of the 1987 task force recommendations. Pediatrics 128: e720-e740. Link: https://bit.ly/2Zrwh8R
33. Palaniswamy V, Sadhasivam S, Selvakumaran C, Jayabal P, Ananth SR (2016) Single-photon emission computed tomography imaging for brain death donor counselling. Indian J Crit Care Med 20: 477-479. Link: https://bit.ly/3imxEwU
34. Lewis A, Bonnie RJ, Pope T (2020) It's time to revise the Uniform Determination of Death Act. Ann Int Med 172: 142-144. Link: https://bit.ly/3bJb8Mc

Citation: Tibballs J (2020) It is time to abandon apneic-oxygenation testing for brain death. Arch Organ Transplant 5(1): 006-0010.
DOI: https://dx.doi.org/10.17352/2640-7973.000015

35. Nguyen D (2020) Does the Uniform Determination of Death Act need to be revised? Linacre Q; 87: 317-333. Link: https://bit.ly/32dWhpQ

36. Nevada Revised Statutes (2019) Chapter 451 - Dead Bodies. NRS 451.007 - Requirements for determination. NV Rev Stat § 451.007. Link: https://bit.ly/3k2x5J6

37. Nevada Revised Statutes (2019) Chapter 451 - Dead Bodies. NRS 451.008 – Consent not required for determination; prohibition on withholding or withdrawal of organ-sustaining treatment in certain circumstances; notice. NV Rev Stat § 451.008. Link: https://bit.ly/2Zqv5T8

38. New Jersey Declaration of Death Act. 1991. Section 26:6A-5. Link: https://bit.ly/3k7brnc

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