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# Neuroanesthesia and Intensive Care

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## Brain death: resolving inconsistencies in the ethical declaration of death

*[La mort cérébrale : résoudre les contradictions de la déclaration éthique de la mort]*

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**Purpose:** The first criteria for the determination of brain death were developed in 1968 in part to address concerns that had arisen with the retrieval of organs for transplantation. Despite over 30 years of application, some professional and public doubt persists over the validity of the theoretical construct underlying this method of determining death. Our review will address historical perspectives on the development of brain death criteria, and inconsistencies in current clinical criteria.

**Method:** Narrative review from selected MEDLINE references and other published sources.

**Principal findings:** The primary construct of the determination of death is that either cardiopulmonary or neurological function irreversibly ceases. However, there is inconsistency in the neurological criteria for death between jurisdictions, between patient populations, and in the use of confirmatory tests. These inconsistencies may cause concern in the public or profession about the validity of the determination of death by neurological criteria.

**Conclusions:** Organ transplantation is premised on professional and public acceptance that the donor is dead. Given that the criteria for brain death or their application remain variable, we suggest that it is reasonable to consider a national consensus to address these inconsistencies. Alternatively, the standard use of confirmatory radiographic testing prior to the retrieval of organs from donors who meet clinical brain death criteria should be considered to provide conclusive evidence of permanent and irreversible loss of brain function.

**Objectif:** Les premiers critères de mort cérébrale ont été formulés en 1968 pour répondre, en partie, aux inquiétudes soulevées par la recherche d'organes pour les greffes. Malgré 30 ans d'application, un certain doute subsiste chez les professionnels et le public sur la validité de la notion théorique à l'origine de cette façon de déterminer la mort. Notre revue aborde les perspectives historiques de la formulation des critères de mort cérébrale et des contradictions des critères cliniques actuels.

**Méthode :** La revue descriptive provient de la consultation de références dans MEDLINE et d'autres sources publiées.

**Constatations principales :** Le principal concept de la détermination de la mort est l'arrêt irréversible de la fonction cardio-pulmonaire ou neurologique. Cependant, il y a des contradictions dans les critères neurologiques de la mort entre les pays, entre les populations de patients et dans l'usage des tests de confirmation. Ces contradictions peuvent inquiéter le public et la profession médicale sur la validité de la détermination de la mort par des critères neurologiques.

**Conclusion:** La greffe d'organes est fondée sur l'acceptation publique et professionnelle du fait que le donneur soit décédé. Étant donné que les critères de mort cérébrale, ou de leur application, demeurent variables, nous croyons qu'il est raisonnable d'envisager la formation d'un consensus visant à traiter de ces contradictions. Autrement, l'utilisation standard des tests radiographiques confirmatifs, qui précèdent le prélèvement d'organes de donneurs répondant aux critères cliniques de mort cérébrale, devrait être considérée pour fournir la preuve concluante de la perte permanente et irréversible de la fonction cérébrale.

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*If one subject in health law and bioethics can be said to be at once well settled and persistently unresolved, it is how to determine that death has occurred.*<sup>1</sup>

**T**HE retrieval of organs for transplantation obtained from anonymous 'cadaveric' (brain dead, or non-heart beating) donors is based on the moral acceptance of the 'dead donor rule': that these patients are dead.<sup>2,3</sup> The retrieval of organs from individuals who are brain dead is based on the premise that permanent cessation of (whole) brain function equates with death and can be identified by simple bedside clinical criteria.<sup>4,5</sup> In the Uniform Determination of Death Act (UDDA), there are two distinct definitions for death: "an individual who has sustained either 1) irreversible cessation of circulatory and respiratory function, and 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."<sup>6</sup> Below, we address inconsistencies in the clinical criteria for brain death, and present an opinion that a reconsideration of a national medical standard is necessary.

### Historical perspectives

In 1959, Mollaret and Goullon used the term coma dépassé, "a state beyond coma", to describe a condition from which they believed recovery was not possible.<sup>7</sup> In 1965, 'brain dead' was used to describe a patient with a heart beat from whom a kidney was procured for transplant into a non-related recipient.<sup>8</sup> In 1968, the Harvard criteria for brain death were developed as the conclusions of the Ad Hoc Committee of the Harvard Medical School.<sup>9</sup> All subsequent criteria for brain death have been founded on this seminal work. To quote from their original communiqué, "Our primary purpose is to define irreversible coma as a new criterion for death. There are two reasons why there is need for a definition: 1) improvements in resuscitative and supportive measures have led to increased efforts to save those who are desperately injured. Sometimes these efforts have only partial success so that the result is an individual whose heart continues to beat but whose brain is irreversibly damaged. The burden is great on patients who suffer permanent loss of intellect, on their families, on the hospitals, and those in need of hospital beds already occupied by those comatose patients. 2) Obsolete criteria for the definition of death can lead to

controversy in obtaining organs for transplantation." The ad hoc committee's criteria were not based on a physiologic or philosophical understanding that the brain, and therefore the person, was dead. Rather, the committee's recommendations were premised on the understanding that the coma was irreversible and care was futile "we are concerned here only with those comatose individuals who have no discernible central nervous system activity... [and where it is possible to determine] the characteristics of a permanently non-functioning brain." The committee identified that function in the cerebrum including subcortical function (specific examples presented were thalamic and basal ganglionic mechanisms), and brainstem must be lost to be consistent with brain death.

The medical consultants to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research subsequently detailed a comprehensive set of clinical circumstances and a battery of tests to identify brain death.<sup>6</sup> "1) Cessation [of brain function] is recognized when evaluation discloses findings of (a) and (b): (a) cerebral functions are absent, (b) brain stem functions are absent. 2) Irreversibility is recognized when evaluation discloses findings of (a), (b), and (c): (a) the cause of coma is established and is sufficient to account for the loss of brain functions, (b) the possibility of any recovery of any brain function is excluded, (c) cessation of all brain functions persists for an appropriate period of observation and/or trial of therapy." The Uniform Determination of Death Act (UDDA - the United States Federal Legislation adopted by most State Legislatures which legally defines death) used the recommendation of the President's Commission as the basis for the statute. Though the Commission's report does provide detailed criteria on how to diagnose brain death, the authors did not attempt to provide a conceptual understanding of why these clinical findings equate with death, or provide evidence that these tests in fact assess the integrity of whole brain function.

Bernat provided a structural framework for the conceptual understanding of the diagnosis of brain death.<sup>10</sup> He argues that the formal acceptance of 'brain death' is dependent on three conditions: 1) the "permanent cessation and functioning of the whole brain"; 2) that future changes in clinical understanding of brain function and assessment including the use of technology will only slightly alter the criterion of death, and 3) that the "explicit formulation" must be consistent with "society's traditional" understanding of death. As will be discussed *vide infra*, the UDDA criteria (similar to Canadian criteria) for brain death

and the accepted standards of whole brain death enumerated in the policy do not meet these reasonable criteria of Bernat.

### Limitations in the clinical diagnosis of brain death

#### *Assessing permanent cessation of function*

The UDDA criteria for brain death, and guidelines from other jurisdictions such as current Canadian standards<sup>11</sup> do not test function of the "entire brain", and there is sound evidence that many individuals who meet the clinical criteria of brain death continue to have some cortical, subcortical, or brain stem function. The current clinical tests for brain death do not assess subcortical function of structures such as the hypothalamus-pituitary axis. Many patients diagnosed as brain dead have intact neurohumoral control of hypothalamic-pituitary function, demonstrate normal hypothalamic mediated thermoregulatory control, and have intact autonomic function: they do not have hemodynamic collapse, they have physical findings such as bowel sounds, and are reported to have autonomic reflexes (tachycardia and hypertension) at the time of organ retrieval.<sup>12</sup> Thermoregulatory control, maintenance of normal hypothalamus and pituitary gland function, and intact autonomic function represent normal subcortical functions inconsistent with the understanding of 'permanent cessation of functioning of the entire brain'. Given that current clinical testing does not assess subcortical brain function, 'whole brain death' cannot be conclusively identified at the bedside by using clinical criteria.

One of the enduring arguments in support of the consistency of the clinical confirmation of brain death equating with death is that loss of integrative functions of the cortex and brainstem will rapidly result in failure of other systems and death of the person - the so called somatic disintegration hypothesis.<sup>13</sup> "That structural disintegration follows brain death is not a contingent matter; it is a necessary consequence of the death of the critical system. The death of the brain is the point beyond which other systems cannot survive with, or without, mechanical support."<sup>14</sup> Shewmon reviewed 12,200 sources to identify 175 cases of individuals with brain death reported to have cardiac function persist for a minimum of one week; 56 cases are reported in detail.<sup>15</sup> In approximately 60% of the 56 cases, cardiac function persisted to one month. Of the individuals whose cardiac function ceased in this one month interval, half had cardiac arrest as a result of withdrawal of ventilatory support. Shewmon's publication has questioned the construct of the somatic integration hypothesis. His work was subject to much criticism in subsequent correspondence,<sup>16-19</sup> but the

importance of his work cannot be overlooked given that many lawmakers and judges have viewed the somatic integration hypothesis as a cornerstone to the legal basis for brain death equating with death.<sup>13</sup>

#### *Consistent standards*

It would be reasonable to assume that the criteria for the clinical diagnosis of brain death have remained relatively static over the past three decades since no new relevant physical examination maneuvers have been described during this time. This assumption is incorrect. In 1977, Walker published on behalf of a collaborative group from the National Institute of Neurological Diseases and Strokes, a study reviewing the then current criteria for cerebral death.<sup>20</sup> The criteria included coma, apnea, dilated pupils, absent motor responses, and electrocerebral silence on electroencephalogram (EEG). Four years later, the President's Commission criteria expanded the required number of brain stem reflexes that needed to be absent, and removed the criterion of electrocerebral silence. However, the Commission still recommended EEG as desirable when objective documentation was required to confirm clinical findings... "electrocerebral silence verifies irreversible loss of cortical functions, except in patients with drug intoxication or hypothermia... when joined with the clinical findings of absent brainstem functions, electrocerebral silence confirms the diagnosis." The Commission's decision to remove electrocerebral silence as a necessary confirmatory test remains puzzling given its subsequent recommendation for its use. Subsequent to the President's Commission report there are studies that document the presence of electrocerebral activity following the declaration of brain death.<sup>21,22</sup> Grigg and colleagues from Loyola University Medical Centre reported on EEG activity in a consecutive case series of 56 patients with confirmed clinical 'brain death'.<sup>21</sup> These authors reported that in 11 patients, electrocerebral silence was not present following the diagnosis of brain death. These authors used appropriate measures to avoid external interference (room noises, internal machine noise, muscle activity, or movement artifact), as a source of observed EEG activity. As well, EEG interpretations were conservative assuming any observed activity as artifact unless the observer was without doubt. EEG activity observed was categorized into low voltage theta or beta activity, alpha like activity, or sleep-like activity. In one of two patients EEG activity resembling physiologic sleep persisted at repeat EEG testing 168 hr following 'declaration' of 'brain death'. The finding of coordinated EEG activity, such as sleep, is inconsistent with the presumption of loss of coordinated and integrating whole brain func-

tion and raises doubt about the accuracy of the clinical diagnosis of brain death.

There remains considerable international inconsistency in the application of clinical criteria for the diagnosis of brain death.<sup>23</sup> In North America, the recently published guidelines prepared by expert opinion of the Canadian Neurocritical Care group differ from the 'evidence based approach' of the American Academy of Neurology.<sup>11,24</sup> A recent article reviews the American criteria.<sup>25</sup> For example, the Canadian guidelines do not require the testing of the oculocephalic reflex, permit a core temperature as low as 32.2°C during the apnea test, and allow an interval between examinations as short as two hours, or as long as 24 hr if due to anoxic-ischemic insult. The American criteria do not specify a necessary interval between assessments but recommend as reasonable an arbitrary six-hour interval, require a core temperature of 36.5°C during the apnea test, and do require testing of the oculocephalic reflex. The criteria used for the diagnosis of brain death in infants less than one year of age are also different than the criteria for the diagnosis in adults. In England, this definition of death has been adopted: "irreversible loss of the capacity for consciousness, combined with irreversible loss of the capacity to breathe should be regarded as the definition of death." The nomenclature in the United Kingdom has been changed from 'brain death' to 'brain stem death'.<sup>26</sup> Takeuchi has published on other inconsistencies.<sup>27</sup> There has been no coherent cogent pathophysiologic or philosophical explanation to explain these differences in diagnostic criteria. Perhaps, as discussed by Wijdicks in the only 'evidence based' synthesis of brain death criteria, the diagnosis of brain death has been established largely on class III data defined as "evidence provided by expert opinion, nonrandomized historical controls, or one or more case reports."<sup>24,28</sup> These inconsistencies, changes in the criteria for 'brain death' over time, and lack of specificity in tests of cortical and subcortical brain function exemplify the inadequacy and inconsistency of clinical criteria for confirming "complete cessation of brain function" and therefore brain death. This raises concern over whether these criteria are satisfactory.

#### *Society's and the medical profession's understanding of brain death*

There is a misunderstanding of the concept, definition, and clinical criteria for the diagnosis of brain death among the health care professions. Youngner and colleagues performed a multicentre survey of staff caring for organ donors including physicians responsible for determining brain death, and medical and

nursing staff involved in the care of the potential donor/their family.<sup>29</sup> Only 64% of physicians and 28% of other staff accurately identified the clinical criteria for brain death, and/or in case scenarios correctly categorized patients as dead or alive. Even physicians actively involved in the identification of brain death were unable to identify the requisite diagnostic components of brain death, and/or were unable to apply the criteria correctly.

In a recent editorial in the Journal *Anaesthesia*, Young and Matta advocate for the use of anesthetics during the harvesting of organs from brain dead organ donors.<sup>30</sup> They provided three reasons, of which two are particularly relevant: 1) the surgical retrieval of organs from brain dead donors is often associated with hypertension and tachycardia and this is distressing for operating room personnel to witness (ostensibly because these findings during operative procedures are usually an indication of awareness and/or pain); and 2) that the concept of brain death is not well understood and given the arbitrary nature of the clinical criteria for brain death, caution is required before assuming anesthesia is not necessary. In subsequent commentaries,<sup>31,32</sup> these authors were chided in part because "by urging the use of anaesthetic agents, they have accepted that there are doubts over the state of consciousness in the brainstem dead individual. It would have been far more appropriate to suggest reappraisal of the UK brainstem criteria, public debate, or even more openness and honesty in our discussions with bereaved relatives. We cannot hope to maintain public confidence merely by following their ill thought out suggestions."

Although two physicians with experience and expertise must be responsible for the declaration of brain death, and a neurologic condition capable of causing brain death is a mandatory prerequisite to the diagnosis of brain death, there are reports in the literature of conditions that mimic brain death or that provide examples of the mistaken diagnosis of brain death.<sup>33-40</sup>

Van Norman<sup>41</sup> describes three cases (two of which she has apparent immediate knowledge) involving the determination of brain death. In these three cases, the patients did not meet the clinical criteria for brain death, yet were referred for organ retrieval. In two of the cases, the patient's had suffered devastating brain injuries, but were breathing spontaneously. Despite spontaneous respiratory effort, these patients were certified as brain dead, and proceeded to organ retrieval. In the second of these two cases, organ retrieval occurred against the protests of the anesthesiologist who questioned the diagnosis of brain death, and despite the patient demon-

strating hypertension and movement during organ retrieval necessitating the use of muscle relaxants and general anesthesia. In the third case, a young woman postvaginal delivery with concomitant pregnancy induced hypertension suffered generalized seizures, and had clinical and radiographic evidence (computed tomography findings of coning, diffuse edema, and occipital lobe infarcts) of a "catastrophic neurological event". The patient was determined to be brain dead, and prepared for organ retrieval. One physician subsequently identified intact brainstem reflexes. A review of this case determined that the clinical diagnosis of brain death had occurred after the patient had received *in vivo* muscle relaxants, and had a serum magnesium level of 5.2 mEq·L<sup>-1</sup>. In the third case, the mother regained consciousness, and was discharged home alert and oriented, but with unspecified neurological deficits.

Brain death is a concept often misunderstood by the general public. Sanner performed a survey about attitudes toward autopsy and organ donation in a sample size of 1,950 randomly selected individuals.<sup>42</sup> Of respondents, only 62% would donate their organs, and only 39% would assent to the donation of their relative's organs. The two predominant reasons for refusal were the fear of not being dead at the time of organ retrieval and the uncertainty of the concept of brain death. Because families misunderstand brain death, many organ retrieval programs stress the necessity of stating that the patient is 'dead' and not 'brain dead', thereby potentially obviating any family concerns about the status of their loved one.

In summary, the current clinical criteria for brain death are not consistent with the stated objective of the outcome "to identify the permanent cessation of entire brain function". Nor are the clinical criteria for brain death either universally understood, and/or correctly applied, and at least in one report, two cases were presented where the criteria were deliberately misrepresented in an attempt to retrieve an organ for transplantation. Finally, brain death is not a concept that is coherent and clearly understood in the general public.

#### *Reconsidering the criteria for brain death*

Is this simply a pedantic and pedagogical discourse, or is there relevance in discussing these inconsistencies? As was identified in the seminal Harvard report, there are two reasons to determine that brain death has occurred: 1) to support withdrawal of treatment as further interventions are futile, or 2) for the purposes of solid organ donation which is now the most common practical reason.

A premature death from end-stage organ dysfunction is potentially preventable with an organ transplant.

Unfortunately, the scarcity of available organs for transplantation is a barrier to saving more lives. The ethical approach to organ donation dictates that the need of those requiring organs should not supercede the ethical management of potential donors.

Society's acceptance of organ transplantation, and the willingness to donate organs is dependent on absolute trust in the process, a process that starts with the diagnosis of brain death. Therefore, it would seem a reasonable proposal for a broad based coalition to re-examine the Canadian criteria to address issues such as the evidence that justifies the clinical criteria as proposed, the differences between published criteria and the current application of criteria in Canadian hospitals including professional training and standards. Such a forum is planned, and this approach should help ensure public confidence in the validity of the medical standard, and also address mechanisms to avoid conflict of interest when organ donation is considered.<sup>43</sup>

There is an alternative approach. A lack of blood flow to an organ causes an organ to die. The brain is considered the organ most sensitive to necrosis from cessation of blood flow. Lack of blood flow to the entire brain is an anatomic equivalent to the cessation of brain function. In the setting of normal arterial pressures, technetium 99 hexamethylpropyleneamineoxime (Tc99-HMPAO) perfusion scanning, or four-vessel selective cerebral contrast dye angiography can accurately assess anterior and posterior cerebral circulation (that is 'whole brain' blood flow).<sup>44,45</sup> Tc99-HMPAO scanning is usually performed with dynamic and static imaging. The dynamic imaging can quickly assess the presence or absence of intracranial perfusion, whereas static imaging detects any uptake of the tracer by functioning neurons. Both of these tests provide irrefutable proof of absent blood flow to the brain, and therefore permanent and irreversible cessation of brain function. If we cannot resolve the inconsistencies in the use of current clinical criteria, it may be reasonable to consider them as a mandatory component of determining 'whole' brain death.

#### **Conclusion**

Increasing organ donation is an important and laudable objective. To do so at the expense of exploiting society's most vulnerable cannot be supported despite the best of intentions. We share the opinion of Dossetor who states: "ethics dictates the following: organs should not be procured from bodies where there is life... no measures should be carried out on the dying person even with family consent, that are not directed at serving the best interests of the dying person... Our faith in the supposedly objective diagnosis of brain death leads us to

remove organs from the dead body where the heart is still beating. We now need to take seriously the question of whether the criteria to establish brain death are as reliable as we claim them to be. If they are not as satisfactory as we once thought, the whole matter should be brought into debate."<sup>46</sup>

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