Assessment of Brain Death in the Neurocritical Care Unit

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KEYWORDS

• Brain death • Intensive care unit • Organ donation • Ethics • Communication

KEY POINTS

- The concept of brain death developed in conjunction with the use of mechanical ventilators in modern intensive care units, and the guidelines for determining brain death have evolved over time.
- The most current American Academy of Neurology Practice Parameters for brain death determination emphasize 3 necessary clinical findings: coma (with a known irreversible cause), absence of brainstem reflexes, and apnea.
- Despite the availability of standardized guidelines, a large degree of practice variability exists, including the role of ancillary testing.
- Issues such as the relationship of brain death determination to organ donation and whether brain death represents "true death" have been debated in ethical, legal, and religious contexts, and special care should be taken when advising families of patients who may fulfill brain death criteria.

INTRODUCTION

The concept of brain death was born with the rise of modern intensive care medicine. When a lack of brain function precipitously leads to apnea, mechanical ventilation is the means by which patients can artificially maintain circulation and other bodily functions. Unfortunately, brain death is not a uniformly defined entity among institutions, states, countries, or religions. In addition, there is neither a universally accepted standard nor a consistently applied algorithm for its determination. It has been said, "if one subject in health and bioethics can said to be at once well settled and persistently unresolved, it is how to determine that death has occurred."[1]

HISTORICAL CONTEXT

The historical evolution of brain death as a concept has been reviewed in detail in the literature.[2–4] Although Rabbi Moses Maimonides, in the Middle Ages, was among the first to suggest that the brain was of primary importance in life,[2] general medical opinion before the 1800s focused on the heart as the residence for a person's central and controlling "life force."[5] The advent of resuscitative measures in the mid-1970s, such as electroshock and artificial ventilation, forced the medical community to reconsider the location of "vital principles" as residing in a divine cardiac organ.[4]

As summarized by Machado and colleagues,[3] a number of experiments in the late 1800s demonstrated situations in which patients with high intracranial pressure ceased to have respirations but continued to have beating hearts shortly thereafter. Horsley,[6] Duckworth[7] and Cushing[8] noted in sequential and separate articles that patients with disease states such as intracerebral hemorrhage and brain tumors that increase intracranial pressure tended to pass away first from respiratory failure rather than circulatory arrest. These

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reports include descriptions of patients who now fit widely accepted criteria for brain death; however, because they preceded the introduction of mechanical ventilation, the authors did not attempt to define death by neurologic criteria at that time.[3]

Leading up to the development and use of mechanical ventilators in intensive care units (ICUs) in the 1950s were important observations made regarding the use of ancillary testing in brain-injured patients.[3,4] Shortly after the first electroencephalogram was recorded by Berger[9] in 1929, Sugar and Gerard[10] were able to show in cats that an occlusion of a carotid artery resulted in the complete abolition of electric potentials in the brain—a real-time physiologic demonstration of cerebral blood flow, ischemia, and brain function. Another important report came in the 1950s, when Löfstedt and von Reis[11] described 6 patients with apnea and absent brainstem reflexes who showed no intracranial blood flow during cerebral angiography but who did not have subsequent cardiac arrest until 2 to 26 days afterward. Although autopsies showed advanced cerebral necrosis, no obstructions of the cerebral arteries were seen, a finding which led the investigators to conclude that increased intracranial pressure was the most probable explanation for the radiographic findings.[3,4,11]

One of the most seminal works with regard to the concept of brain death before the development of formal guidelines was authored by Mollaret and Goulon in 1959.[12] The authors coined the term "coma dépassé," meaning "a state beyond coma," to describe 23 ventilated patients in which loss of consciousness, brain stem reflexes, and spontaneous respirations were associated with absent encephalographic activity.[2] They argued that the patients' conditions were irreversible and that continuation of care in these cases was futile. This report coincided with a description of "death of the nervous system" by Wertheimer and colleagues[13] and Jouvet,[14] who proposed similar criteria to Mollaret and Goulon for stopping the ventilator in such cases.

CLINICAL DIAGNOSIS OF BRAIN DEATH

Guidelines Before American Academy of Neurology

In 1968, the Harvard Criteria, driven by the advances in critical care medicine, the advent of mechanical ventilation, and issues surrounding organ donation, were introduced in a landmark publication examining the definition of irreversible coma as a new criterion for death.[15] Coma in an individual with no discernible central nervous system activity was characterized by the following 4 features: unreceptivity and unresponsiveness, absent movements or breathing, absent reflexes, and a flat electroencephalogram.[15]

More than a decade later, the President's Commission put forth the Uniform Determination of Death Act (UDDA), which stated "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 brain stem, is dead. The determination of death must be made in accordance with accepted medical standards."[16] However, no definite criteria or algorithmic approach were delineated, thus allowing for continued variation in interpretation and practice.

It was not until 1995, when the American Academy of Neurology (AAN) set forth practice parameters on the determination of brain death, that there came a standard by which brain death could be algorithmically assessed.[17] Using principles from the definition provided by the UDDA, the AAN proposed "accepted medical standards" for the determination of brain death. Brain death was defined as "the irreversible loss of function of the brain, including the brainstem."[17] This was the first publication to not only give precise definitions but actually recommend a methodical approach to the clinical diagnosis of brain death, apnea testing, the use of ancillary tests, and the documentation of brain death in the medical record. The prerequisites for proceeding with the clinical diagnosis consisted of clinical and/or neuroimaging evidence of an acute central nervous system catastrophe compatible with the clinical diagnosis of brain death, the exclusion of complicating medical conditions (electrolyte, acid-base, or endocrine derangements), absence of drug intoxication or poisoning, and a core temperature of at least 32°C. This publication is the foundation for the current practice of declaring brain death in neurologically devastated patients.[17] See **Table 1** for a summary of the guidelines leading up to the AAN's practice parameter.

Current AAN Guidelines

In 2010, the AAN published an update to the 1995 guideline focusing on several clinical questions regarding the potential for misdiagnosis when using the criteria, adequate observation times, the implications of complex motor movements, and new ancillary tests.[18] The guidelines incorporated new evidence to date since the prior guidelines and provided a step-by-step approach to brain death determination (**Box 1**) that emphasized the 3 clinical findings necessary to declare brain death: coma (with a known irreversible cause), absence of brainstem reflexes, and apnea. The

Table 1
Summary of brain death determination leading up to the AAN practice parameter

Harvard Criteria (1968)	Minnesota Criteria (1971)	United Kingdom Criteria (1976)	President's Commission Criteria (1981)
• Unreceptivity and unresponsivity • No movements or breathing • No reflexes • Flat electroencephalogram • Exclusion of hypothermia (below 90°F or 32.2°C) and central nervous system depressants. *All the above tests shall be repeated at least 24 hours with no change.*	• No spontaneous movement • No spontaneous respirations when tested for a period of 4 min at a time • Absence of brain stem reflexes • A status in which all the findings above remain unchanged for at least 12 h • Electroencephalogram is not mandatory • Spinal reflexes have no bearing on the diagnosis of brain death *Brain death can be pronounced only if the pathologic process for the above are deemed irreparable with presently artificial means.*	• Establish etiology • Exclude mimicking conditions • Absent motor response • Absent brainstem reflexes • Apnea with a P_{CO_2} target of $\geq$50 mm Hg • Prolonged observation in anoxic-ischemic injury • Temperature should be $\geq$35°C	• Unreceptive and unresponsive coma • Absent papillary, corneal, oculocephalic, oculovestibular, oropharyngeal reflexes • Apnea with P_{CO_2} greater than 60 mm Hg • Absence of posturing or seizures • Irreversibility demonstrated by establishing cause and excluding reversible conditions (sedation, hypothermia, shock, and neuro muscular blockade) • Period of observation determined by clinical judgment • Use of cerebral flow tests when brainstem reflexes are not testable, sufficient cause cannot be established, or to shorten period of observation

Data from Wijdicks EF. Brain death. New York: Oxford University Press; 2011.

Box 1
Checklist for determination of brain death

Prerequisites (all must be checked)

- Coma, irreversible and cause known
- Neuroimaging explains coma
- Central nervous system (CNS) depressant drug effect absent (if indicated toxicology screen; if barbiturates given, serum level <10 g/mL)
- No evidence of residual paralytics (electrical stimulation if paralytics used)
- Absence of severe acid-base, electrolyte, endocrine abnormality
- Normothermia or mild hypothermia (core temperature $\geq$36°C)
- Systolic blood pressure $\geq$100 mm Hg
- No spontaneous respirations

Examination (all must be checked)

- Pupils nonreactive to bright light
- Corneal reflex absent
- Oculocephalic reflex absent (tested only if C-spine integrity ensured)
- Oculovestibular reflex absent
- No facial movement to noxious stimuli at supraorbital nerve, temporomandibular joint
- Gag reflex absent
- Cough reflex absent to tracheal suctioning
- Absence of motor response to noxious stimuli in all 4 limbs (spinally mediated reflexes are permissible)

Apnea testing (all must be checked)

- Patient is hemodynamically stable (even with the use of vasopressors)
- Ventilator adjusted to provide normocarbia ($Paco_2$ 34–45 mm Hg)
- Patient preoxygenated with 100% Fio_2 for $\geq$10 minutes to Pao_2 $\geq$200 mm Hg
- Patient well-oxygenated with a positive end-expiratory pressure (PEEP) of 5 cm of water
- Provide oxygen via a suction catheter to the level of the carina at 6 L/min or attach T-piece with continuous positive airway pressure (CPAP) at 10 cm H2O
- Disconnect ventilator
- Spontaneous respirations absent
- Arterial blood gas drawn at 8–10 minutes, patient reconnected to ventilator
- Pco_2 $\geq$60 mm Hg, or 20 mm Hg rise from normal baseline value

OR:

- Apnea test aborted

Ancillary testing (only 1 needs to be performed; to be ordered only if clinical examination cannot be fully performed because of patient factors, or if apnea testing inconclusive or aborted)

- Cerebral angiogram
- HMPAO single-photon emission computed tomography (SPECT)
- Electroencephalogram (EEG)
- Transcranial Doppler (TCD)

From Wijdicks EF, Varelas PN, Gronseth GS, et al. American Academy of Neurology. Evidence-based guideline update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2010;74:1917; with permission.

AAN guidelines do not differentiate between a primary brainstem lesion ("brainstem" death) and a lesion of the cerebrum and brainstem ("whole brain" death) as long as the examination is consistent with brain death.[18] Guidelines in other countries vary in how they deal with patients with primary brainstem lesions (**Table 2**).

Variability Among Institutions

Because state law drives brain death policies on an institutional level, there remains significant practice variation despite the new detailed AAN Practice Parameter. Although most US state laws have adopted the UDDA and reference the AAN Practice Parameter, many have amendments addressing physician qualifications and the need for a second examination, as well as religious exemptions. Practice inconsistencies are evidenced both anecdotally through the personal experiences of providers who perform such declarations and systematically in relatively recent reviews of policies at esteemed institutions of neurology and neurosurgery across the country.[19] The disparity is widespread, ranging from which prerequisites should be met, what the lowest acceptable core temperature should be, how the apnea test should be performed, how many examiners should be required, and what and under which circumstances an ancillary test should be used.

The absence of federal or national standards and the vague policies adopted on a state and institutional level allow for tremendous liberty in interpretation, which contributes to the confusion for providers and mistrust among the public. There is room for misinterpretation and a grave potential for mistakes, of which the media never hesitates to take full advantage.[20] Most recently, a *New York Post* article highlighted several cases in which the motives of declaring brain death were called into question.[21] It is the variation in practice as well as on a state law level that in many ways adds further fuel to the fire. For example, New York State law requires that physicians consider accommodating families who, on religious or moral grounds, desire the maintenance of mechanical ventilation once a patient has been declared dead by neurologic criteria.[22] However, it is up to individual hospitals to establish written procedures on what constitutes reasonable accommodations in such circumstances. Because objections to the brain death standard based solely on psychological denial that death has occurred or on an alleged inadequacy of the brain death determination are not based on the individual's moral or religious beliefs, "reasonable accommodation" is not required in such circumstances.[22] Unfortunately, such accommodations can send mixed messages to the public, particularly when there are publications of brain dead patients "surviving" for more than 14 years.[8] The ethical and legal controversies surrounding brain death will be touched on later in the article, but a comprehensive discussion is beyond the scope of this article.

With brain death guidelines falling under the jurisdiction of individual states' legislatures and ultimately at the discretion of institutions to formalize and implement, it will be difficult to reach conformity. This has led to an outcry from experts in the field to push for a national standard for the declaration of brain death, as well as advocate for a certification process, akin to Advanced Cardiac or Trauma Life Support (ACLS) training, for providers involved in the sensitive assessment of these patients.

Guidelines in Other Countries

Just as there is great variability across North America, there is great variability across the world with regard to the diagnosis of brain death. Until Wijdicks[23] published on the subject in 2002, the degree to which countries differed had not been formally characterized. Wijdicks[23] reviewed original brain death documents for 80 countries throughout the world; the differences were astounding. Although brainstem reflexes were consistently evaluated, there are marked differences in apnea test performance. A Pa_{CO_2} target value for the confirmation of apnea was used in only 59% of the guidelines, whereas 28% felt disconnecting a patient from the ventilator for 10 minutes after preoxygenation with 100% oxygen was sufficient. Additionally, the number of physicians required to diagnose brain death varied, with 44% of countries requiring 1 physician, 34% requiring 2 physicians, and 16% requiring more than 2 physicians. Forty percent of countries required ancillary testing, although the type varied considerably and appeared arbitrary. In one country surveyed, a cerebral angiogram was performed twice, separated by an "adequate" observation period to document the absence of cerebral blood flow. Half of countries surveyed require 2 or more physicians to confirm brain death. Most of Africa not only did not have legal provisions for organ transplantation but also could not perform brain death criteria testing simply because it was too difficult. In the Middle East, very few countries have official guidelines for determining brain death. Conceptually, brain death by neurologic criteria has not been accepted in Asia. China has no legal criteria for the determination of brain death. In countries that do have guidelines, there are often

Table 2
Differences in recommendations regarding clinical determination of brain death in Canada, the United Kingdom, and Germany

	Canada	United Kingdom	Germany
Definition of Neurologic determination of death (NDD)	The irreversible loss of the capacity for consciousness combined with the irreversible loss of all brainstem functions including the capacity to breathe.	The irreversible loss of the capacity for consciousness combined with the irreversible loss of the capacity to breathe due to the irreversible cessation of brainstem function. Does not entail the cessation of all neurologic activities in the brain.	Clinical determination of coma and loss of brainstem reflexes and apnea. Irreversibility established by repeat examination after 24 h.
Primary brainstem lesions	Death determined by neurologic criteria may be a consequence of intracranial hypertension or primary direct brainstem injury or both. No satisfactory ancillary tests for the confirmation of NDD in instances of isolated primary brainstem injury.	Primary brainstem lesions are sufficient to meet definition of NDD and ancillary testing is not required.	Must fulfill clinical criteria based on examination and in addition requires ancillary testing with electroencephalogram, evoked potentials, or absent cerebral blood flow in patients with primary brainstem lesions.
Global hypoxic-ischemic injury	Neurologic assessments unreliable in acute postresuscitation phase after cardiorespiratory arrest. Clinical evaluation for NDD should be delayed for 24 h after cardiorespiratory arrest or an ancillary test could be performed demonstrating absence of intracranial blood flow.	Acknowledges that in brain injury due to hypoxic-ischemic brain injury it may take longer to establish irreversibility of injury, although no specific observation period is stated.	Must wait at least 12 h to start brain death testing. Repeat examination after 24 h and requires ancillary testing to establish irreversibility.
Drug intoxications, including sedative and analgesic medications	Clinically significant drug intoxications may confound clinical NDD; however, therapeutic levels or therapeutic dosing of sedatives and analgesics do not preclude NDD. Under these circumstances, if patients fulfill minimal clinical criteria, NDD can be established by demonstration of absence of intracranial blood flow.	Acknowledges that actions of sedative and analgesic medications may confound NDD and that hypothermia may further prolong effects. Advises that length of time from discontinuation to exclude drug effects depends on multiple factors and should be based on pharmacokinetic principles. Recommends use of opioid and benzodiazepine antagonists and monitoring of specific drug levels with a threshold stated for thiopentone (95 mg/L) and midazolam (910 2 g/L). Acknowledges that ancillary tests may be required if drug effects cannot be completely excluded.	Must exclude potential confounders explaining clinical condition, including metabolic factors and sedative medications, but no specific recommendations regarding duration or drug levels.

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panels of doctors who corroborate in order for the declaration of death to be made. Canada published criteria in 1999 that were quite similar to the AAN guidelines, differing only in that they did not require oculocephalic reflex testing, permitted hypothermia (Temperature $\geq$32.2°C) during apnea testing, as well as a variable interval between examinations depending on the etiology.[24]

Countries vary not only in their neurologic criteria for brain death but also in the way they approach primary brainstem lesions, global hypoxic-ischemic injury, and drug intoxications, including sedatives and analgesics. See **Table 2** for a comparison of the approach in Canada, the United Kingdom, and Germany to common clinical situations surrounding brain death.

Common Pitfalls

To our knowledge, there are no peer-reviewed reports in medical journals of conditions mimicking brain death that have detailed a complete brain death examination. The most-cited potential mimics are fulminant Guillain-Barre syndrome,[25–27] baclofen overdose,[28] barbiturate overdose,[29] delayed vecoronium clearance,[30] and hypothermia.[31] However, when the criteria for brain death are used correctly and corroborated with ancillary testing when necessary, there should be no concern for the misdiagnosis of brain death in such conditions.

On the other hand, there are several clinical signs or "red flags" that should caution one from moving forward with the assessment of brain death. These include, but are not limited to, a normal computed tomography (CT) scan, unsupported blood pressure, absence of diabetes insipidus, marked heart rate variations, fever or shock, marked metabolic acidosis, hypothermia lower than 32°C as this is often accidental and reversible, marked miosis (opiate or organophosphate toxicity), myoclonus (lithium or selective serotonin reuptake inhibitor [SSRI] toxicity), rigidity (SSRI or haloperidol toxicity), profuse diaphoresis, and positive urine or serum toxicology.[32]

The AAN guidelines recognize that "because there are deficiencies in the evidence base, clinicians must exercise considerable judgment when applying the criteria in specific circumstances" and that "ancillary tests can be used when uncertainty exists about the reliability of parts of the neurologic examination or when the apnea test cannot be performed."[18] There are conditions in which the diagnosis of brain death cannot be made on clinical grounds alone and confirmatory testing may be required. These include severe facial trauma preventing complete brain stem reflex testing, preexisting pupillary abnormalities, and sleep apnea or severe pulmonary disease resulting in chronic retention of carbon dioxide.[18]

Patients who meet criteria for brain death are by definition motionless. However, there are a host of reflexes and movements that can cast doubt on the diagnosis and be alarming for the inexperienced examiner. Fortunately, many of these observations are well described phenomena in the literature and are entirely consistent with brain death.[33–35] In brain death, several functions, including temperature regulation, hypothalamic-pituitary-adrenal axis function, as well as spinal reflexes can be maintained for up to several hours/days. The presence of spinal reflexes is not surprising, given early twentieth century work showing retained forward location in cats and dogs with transected spinal cords.[36] It has been postulated that it is the absence of cortical inhibitory and modulatory afferents to spinal cord centers that allows for the activation of basic spinal cord sequences, causing the reflex movements commonly seen in brain death.[37] In addition to spinal reflexes,[38,39] movements after death have been described during apnea testing and during organ procurement, as well as in the morgue.[35,40,41] Movements can manifest in the head, neck, upper and lower extremities, and the trunk, and have been named "Lazarus signs" for their biblical connotation.[33,39,42] These movements range from neck, limb, and trunk flexion to facial twitches and finger jerks.[32]

In a recent publication describing a "new" spinal reflex observed in brain death, Mittal and colleagues[43] outline the following 5 aspects of the movements after brain death that may assist the clinician in differentiating spinal from postural responses:

1. There is no resemblance of a spinal response to the classic postural motor responses. These responses are recognized by synchronized decorticate (thumb folded under flexed fingers in a fist, pronated forearm, flexed elbow, and extended lower extremity with inverted foot) or decerebrate responses (pronated and extended upper and lower extremity).

2. Most often, the spinal responses are slow and short in duration. However, there can be some exceptions as follows: finger flexion can be seen as quick jerks with minimal excursions, and lower extremity responses are often more complex and can be wavy or shocklike.

3. The most common spinal response is triple flexion response (flexion in foot, knee, and hip) which may have variations, such as undulating toe sign or a Babinski sign.

4. Most movements are provoked and not spontaneous. The provocation can be movement during nursing care procedures of the patient, such as turning in bed or transfer from bed to a transport cart.

5. In some patients, spinal responses can be elicited by forceful neck flexion and by noxious stimuli below cervicomedullary junction. They are not seen with pressure at the supraorbital ridge or temporomandibular joint.

ANCILLARY BRAIN DEATH TESTING

Apnea testing is the final component in the clinical diagnosis of brain death. If for any reason apnea testing cannot be performed as discussed previously, then an ancillary test must be completed. It is not uncommon for providers to have concern about the safety of apnea testing. Some ICUs have published their experiences, but risks of reported complications are quite variable.[44–46] See **Box 1** for the prerequisites for proceeding with apnea testing. Identified factors associated with the early termination of apnea testing include insufficient preoxygenation, T-piece oxygen administration, high intratracheal flow of oxygen (>10 L/min), high A-a gradient (>300), hypotension (systolic blood pressure <90 mm Hg), mild acidosis (arterial pH <7.30), chest tube for pneumothorax, polytrauma, and younger age.[32]

In the United States, if apnea testing is performed and consistent with brain death, ancillary testing is not required. However, this is not the case worldwide. In 40% of 80 countries surveyed in 2002, an ancillary test was legally required.[23] When apnea testing cannot be performed or is aborted, there are several ancillary tests that can be used for the determination of brain death when an expert clinical neurologic examination is consistent with brain death. Ancillary tests measure a clinical state (cerebral circulatory arrest) that is closely related to the clinical determination of brain death.[47] Ancillary tests should never supersede the clinical examination and should never be performed on patients who do not meet neurologic criteria for brain death. Ancillary tests are divided into tests that assess the brain's electrical function and those that test the brain's blood flow.

The ancillary tests available often depend on institutional policies and resources. Validated tests include digital subtraction cerebral angiography, transcranial Doppler (TCD), electroencephalography (EEG), and nuclear cerebral blood flow scanning. Unfortunately, such tests are only as good as the technician performing them and the practitioner interpreting them. False-positive and false-negative ancillary tests are not uncommon.[47]

Digital subtraction cerebral angiography is the most invasive way of documenting cerebral circulatory arrest. Cerebral circulatory arrest is defined by a lack of opacification of the internal carotid arteries above the level of the petrous portion or of the vertebral arteries above the level of the atlanto-occipital junction. Some venous filling of the superior sagittal sinus may result from connections with the external carotid artery circulation. Specific criteria for confirmation of brain death by cerebral angiography have not been developed by neuroradiologic societies.[32] Another way to assess cerebral blood flow is with the use of TCDs. Unfortunately, TCDs are limited by one's ability to obtain a reliable signal, which is both operator and patient dependent. Approximately 10% to 20% of patients will not have an adequate bone window for ultrasound transmission.[18] However, when obtained, TCDs have a specificity of 98% to 100% and a sensitivity ranging from 88% to 99%.[32,48] Although EEG is quite simple to perform and provides insight into the cortical activity of the brain; it is often difficult to interpret secondary to artifact in either a positive or negative direction.[49] Electromyographic signal may produce a false-negative result, whereas sedation and hypothermia may produce a false-positive result. Cerebral scintigraphy, or nuclear cerebral blood flow scanning, is a frequently used method of determining cerebral circulatory arrest. After the intravenous administration of a tracer isotope, both dynamic and static images are taken with a gamma camera to detect cerebral blood flow. When uptake into the cerebral circulation is absent, the ''hollow skull'' or ''empty light bulb'' sign is present.[32] The Society of Nuclear Medicine has published detailed guidelines for scintigraphy for brain death determination.[50] See **Box 2** for the AAN's summary of ancillary tests.

At this time, magnetic resonance angiography, CT angiography, somatosensory evoked potentials and the bispectral index are not accepted ancillary tests because of insufficient evidence to support their use as part of a brain death evaluation.

ORGAN DONATION

Although it is important that both the medical community and the lay public recognize that the concept of irreversible brain death did not evolve solely to benefit organ transplants but rather inevitably developed out of the advancement of critical care,[3,51] donation after brain death is currently a principal source of transplant organs in Western countries.[52] If a patient in the ICU who has been declared brain dead has also been identified as a potential organ donor, the goals of care for the

Box 2
Methods of ancillary testing for the determination of brain death

Cerebral angiography

- The contrast medium should be injected in the aortic arch under high pressure and reach both anterior and posterior circulations.
- No intracerebral filling should be detected at the level of entry of the carotid or vertebral artery to the skull.
- The external carotid circulation should be patent.
- The filling of the superior longitudinal sinus may be delayed.

Electroencephalography

- A minimum of 8 scalp electrodes should be used.
- Interelectrode impedance should be between 100 and 10,000 Ω.
- The integrity of the entire recording system should be tested.
- The distance between electrodes should be at least 10 cm.
- The sensitivity should be increased to at least 2 μV for 30 minutes with inclusion of appropriate calibrations.
- The high-frequency filter setting should not be set below 30 Hz, and the low-frequency setting should not be above 1 Hz.
- Electroencephalography should demonstrate a lack of reactivity to intense somatosensory or audiovisual stimuli.

Transcranial Doppler ultrasonography

- TCD is useful only if a reliable signal is found. The abnormalities should include either reverberating flow or small systolic peaks in early systole. A finding of a complete absence of flow may not be reliable owing to inadequate transtemporal windows for insonation. There should be bilateral insonation and anterior and posterior insonation. The probe should be placed at the temporal bone, above the zygomatic arch and the vertebrobasilar arteries, through the suboccipital transcranial window.
- Insonation through the orbital window can be considered to obtain a reliable signal. TCD may be less reliable in patients with a prior craniotomy.

Cerebral scintigraphy (technetium Tc 99m exametazime [HMPAO])

- The isotope should be injected within 30 minutes after its reconstitution.
- Anterior and both lateral planar image counts (500,000) of the head should be obtained at several time points: immediately, between 30 and 60 minutes later, and at 2 hours.
- A correct intravenous injection may be confirmed with additional images of the liver demonstrating uptake (optional).
- No radionuclide localization in the middle cerebral artery, anterior cerebral artery, or basilar artery territories of the cerebral hemispheres (hollow skull phenomenon).
- No tracer in superior sagittal sinus (minimal tracer can come from the scalp).

From Wijdicks EF, Varelas PN, Gronseth GS, et al. American Academy of Neurology. Evidence-based guideline update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2010;74:1917; with permission.

patient should transition toward optimal preservation of as many organs as possible. Although hospital systems may have dedicated organ bank teams who can help dictate the care plans for brain-dead patients who are donors, it is important for all involved physicians and staff to be aware of special considerations that these patients warrant, especially with regard to widespread physiologic changes that regularly occur during brain death.[53] The presence of an intensivist comanaging these patients with an organ bank team has been shown to improve organ recovery for transplantation.[54]

The most common physiologic dysfunctions that are associated with brain-dead patients have been the subject of multiple recent reviews.[52,53,55] A predictable pattern of hemodynamic compromise begins with systemic hypertension induced by an attempt to maintain cerebral perfusion, followed by a transient "autonomic storm" with massive catecholamine release from brainstem dysfunction. A subsequent catecholamine insufficiency then results in marked vasodilation and hypotension, which may require treatment with a combination of vasopressin and catecholamines, such as dopamine.[56,57] The initial rise in systemic vascular resistance and rise in cardiac afterload may also increase hydrostatic pressure across the capillary membranes of the lungs, a phenomenon resulting in "neurogenic pulmonary edema."[58] Maintenance of adequate of oxygenation and avoidance of barotrauma with low tidal volume ventilation apply to the potential organ donor as they do to other patients in the ICU.[59]

Posterior pituitary dysfunction is seen in up to 90% of patients after brain death, which leads to central diabetes insipidus and requires hypotonic volume replacement and exogenous replacement of antidiuretic hormone, usually with vasopressin or desmopressin.[60] Dysfunction of the anterior pituitary hormones is more variable, but may involve the "sick euthyroid" syndrome, insulin resistance, and adrenal insufficiency.[52] Hypothalamic damage may manifest itself as hypothermia.[53] Generalized tissue factor release may cause disseminated intravascular coagulation and/or coagulopathy.[53]

A wide variation in the treatment of brain-dead organ donors has led to the development of some goal-driven protocols for standardized management in the literature,[61,62] most notably with the introduction of the United Network for Organ Sharing (UNOS) Critical Pathway for the Organ Donor.[63] These protocols are essentially geared toward keeping physiologic parameters as close to normal as possible. However, it is important to note that much of the data for developing such protocols are from retrospective studies, and the field of medical management of brain-dead patients currently has few randomized control trials as guides.[64] Care of the potential multi-organ donor often involves prioritization of salvageable organs, which may complicate management.[52] Special situations, such as pregnant brain-dead women who are identified as organ donors, require further strategies to achieve a balance of competing outcome goals.[65]

It is important to be aware as well that controversy exists over the timing between brain death determination and organ retrieval, given that the physiologic changes of brain death may promote ongoing donor organ injury. Various reports have been geared toward demonstrating this effect, notably in the cardiac literature,[66] as heart transplants are not available by any other means aside from donation after brain death. A number of recent studies from the neurology literature have argued that requiring a second brain death examination for formal declaration—no longer mandated by the American Academy of Neurology[18] —is not only redundant but also negatively affects the recovery of donor organs.[67,68] Conversely, other studies have argued that the length of time from the declaration of brain death to the procurement of organs is less important than the optimization of critical care for these patients.[69–71]

ETHICAL AND RELIGIOUS CONCERNS

Following the publication of the 1968 Harvard Committee report and other more recent criteria, neurologic determination of death has largely become accepted in societies around the world, with widespread consensus among medical professionals and lawmakers.[23,72] Understandably, the logic and coherence of "brain death" as a concept, in and of itself, has nonetheless generated controversy over the past half-century, not only seen in books intended for laypeople[46,73] but also throughout formal bioethical circles.

Arguments regarding the incoherence of defining death by neurologic criteria have been repeatedly reviewed and debated in academic forums over decades.[74–77] Recently, these arguments have been advocated ardently by Truog in multiple articles,[78–80] among others. Among the major points made are that patients determined to be brain "dead" but who remain on life support maintain a variety of integrative bodily functions, such as "circulating blood, maintaining respiration and body temperature, regulating salt and water homeostasis, digesting food, healing wounds, fighting infections… even gestating fetuses successfully."[81] It is possible that a patient who fulfills all criteria for brain death may in fact survive with mechanical ventilation for extended periods of time.[82] Miller and Truog write, "All neurologic conceptions of death… fail to capture a critical feature of what we mean by 'death'—that is, a dead human body is a corpse."[80] This viewpoint—the so-called "circulatory formulation"[83] —has in part been tied to the idea that perhaps it may be ethically sound for donors to not necessarily be "dead" at the time of organ procurement for transplantation, but that this "dead donor rule" should instead be abandoned and that patients who have suffered severe and irreversible brain damage should simply be allowed to donate organs despite the fact that are not yet dead.[84]

Bernat[83] has written extensively in defense of the ethics regarding current conceptions of brain death, stating that whereas many of these arguments against death by neurologic criteria have logical merit, a purely circulatory formulation of death is "unnecessarily conservative." Championing a "whole-brain formulation" of death, Bernat states that "the cessation of the organism as a whole requires only that all clinical brain functions cease."[83] This formulation makes "intuitive and practical sense" and, perhaps most importantly, "can be translated into successful public policy that is… acceptable and maintains… the integrity of the organ procurement enterprise."[85] The ethics of brain death determination were officially reviewed by the US President's Council on Bioethics, and, in a subsequent white paper,[86] the status quo of medical and public policy was upheld. However, in an effort to address ongoing controversies, the Council suggested "total brain failure" as an alternative to the phrase "brain death," while maintaining that, regardless of the name attached to the process, fulfilling the associated criteria does in fact mean that a given patient fulfills the criteria for "death."[86]

It should be noted that whereas the debate over the legitimacy of brain death has also continued among religious communities, the concept has mostly been accepted by the world's major belief systems.[87,88] Protestantism,[89] Catholicism,[90] and Reform and Conservative Judaism[91] have for the most part accepted brain death as a concept.[83] Notably, divergent views on whether death by neurologic criteria does in fact represent death exist within Orthodox Judaism[91] and Islam.[92] Brain death determination is practiced in Hindi societies[93] and in Confucian-Shinto Japan,[85] although the latter of which has had a protracted nationwide debate for decades and has instituted a law where a patient's family can veto a diagnosis of brain death if it is not consistent with their beliefs.[94]

DISCUSSION WITH PATIENTS' FAMILIES

Discussing brain death with the families of patients who may fulfill the neurologic criteria has the understandable potential to raise questions: "What is death? When does it happen? And does life linger on after a diagnosis of brain death?"[95] Multiple studies, reviewed by Long and colleagues,[95] have demonstrated that many family members of (1) patients who have been declared brain dead and (2) living patients who are potential future organ donors are unable to describe the medicolegal definition of brain death accurately. Of note, in a single survey study of 403 family members of brain-dead patients who either did or did not donate organs, Siminoff and colleagues[96] found that whereas the 95% of respondents were at least able to give a partially correct definition of brain death, only 15.8% of these respondents equated brain death with actual death. Furthermore, almost one-third of the participants in the study agreed with the statement that a person is dead only when the heart has stopped beating,[96] reflecting the aforementioned academic debate in the literature.[95]

Various strategies for helping families best understand and cope with the determination of brain death for a loved one have been proposed. Giving a family adequate time to process and accept the meaning of brain death is important,[97] especially because in most situations the associated neurologic catastrophe was unexpected.[98] In certain situations, families may find it useful to review neuroimaging with the physician team.[99] It is also generally accepted as appropriate that families be given a choice as to whether to observe the brain death testing process.[100] Some families may find that, given that their loved one may appear to be breathing on a ventilator, witnessing brain death testing may help them rationalize emotional and cognitive conflict.[100,101] To remove distrust on the part of the family that a patient's physician may have vested interest in organ donation, multiple studies have now advocated that the topic of organ donation be first brought up by a nonphysician health care worker, followed by a more detailed discussion with an organ bank coordinator. "Decoupling" of the news of brain death from the request for organ donation has been shown to increase consent rates for organ donation.[102,103]

SUMMARY

Defining death by neurologic criteria is not without controversy, but having a consensus for what criteria constitute brain death and how best to evaluate for those criteria is a necessity in our current era of intensive care medicine and organ donation. Future directions for this field must include efforts to decrease practice variability among institutions in North America and worldwide, so as to decrease confusion, avoid pitfalls, and further solidify the conceptual and ethical legitimacy of brain death.

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