Brain Death

Mack Drake, DO[a,*], Andrew Bernard, MD[a], Eugene Hessel, MD[b,c]

KEYWORDS

• Brain death • Organ donor • Brain injury • Critical care • Confirmatory testing
• Ancillary testing • Clinical examination

KEY POINTS

- Critical care both improves outcome in survivors and improves organ graft function in those who do not survive but become brain dead organ donors.
- Brain death determination technique varies among hospitals and clinicians.
- Mimickers of brain death must be carefully considered and factors that confound the brain death examination must be absent.
- Published guidelines provide structure and process to the brain death determination process.
- Ethical controversies remain, therefore clinicians who care for neurologically injured patients should continue to engage in dialogue and research.

BRAIN DEATH IN CONTEXT

Critical care physicians are frequently called on to diagnose and manage brain death. Although the medical and legal concepts of brain death are generally accepted, establishing the diagnosis is not simple and must be performed accurately. The details of how to diagnose brain death have been codified in guidelines by panels of experts[1–4]; however, precision in the brain death examination varies, and skepticism has been expressed in the lay literature about the accuracy of brain death determination.[5] Thus, it is imperative that clinicians perform brain death determination accurately

Disclosure: Drs M. Drake, A. Bernard and E. Hessel receive stipends from Kentucky Organ Donor Affiliates to provide organ donor critical care. Dr A. Bernard receives salary support as institutional liaison for UK Healthcare to Kentucky Organ Donor Affiliates. Dr A. Bernard serves as a board member benefits for Kentucky Organ Donor Affiliates (includes travel, lodging, meals, continuing education).

[a] Section on Trauma and Acute Care Surgery, Division of General Surgery, Department of Surgery, University of Kentucky College of Medicine, C224, 800 Rose Street, Lexington, KY 40536-0298, USA; [b] Department of Anesthesiology, University of Kentucky College of Medicine, 800 Rose Street, Lexington, KY 40536-0298, USA; [c] Department of Surgery, University of Kentucky College of Medicine, 800 Rose Street, Lexington, KY 40536-0298, USA
* Corresponding author. Division of General Surgery, UKCOM, C224, 800 Rose Street, Lexington, KY 40536.
E-mail address: mack.drake@uky.edu

Surg Clin N Am 97 (2017) 1255–1273
http://dx.doi.org/10.1016/j.suc.2017.07.001 **surgical.theclinics.com**

and beyond reproach. In this article, we describe the critical components of brain death examination and briefly review the management of patients with impending and established brain death.

The most common causes of brain death in adults are traumatic brain injury and spontaneous subarachnoid hemorrhage. In children, the most common cause is nonaccidental trauma.[6] Surgeons are keenly aware of the prevalence of end-stage chronic organ failure and the importance of organ transplantation and therefore tend to be diligent and timely in brain death evaluations and support of potential organ donors.

In caring for patients with severe neurologic injury, clinicians must first remember that most will recover. Half of patients who present with a Glasgow Coma Scale score of 3 will survive.[7] Clinicians should not make hasty judgments but should provide optimal physiologic support and careful neurologic examination. Principles of optimal care for neurologic injury are the same as for the potential organ donor, so good critical care is always the first priority.

Today, the medical community is generally comfortable with the general concept of brain death, but testing for and determination of brain death still draws occasional uncertainty and disagreement among providers; there is significant variability across hospitals.[8] Guidelines are available and any clinician performing brain death examination or supervising intensive care units should review and implement practice standards accordingly. The American Academy of Neurology (AAN) is considered the authoritative body on brain death testing in the United States. The AAN first promulgated its guideline, the American Academy of Neurologic Practice Parameters (AANPP), for diagnosis of brain death in adults in 1995[1] and an updated version in 2010.[2] The update is more prescriptive and definitive. The Society of Critical Care Medicine, American Academy of Pediatrics, and the Child Neurology Society updated their guidelines for determination of brain death in infants and children in 2011.[3,4]

Brain death testing has become more consistent across major neurologic centers but still lacks uniformity across the United States.[8] Variability is greater in smaller hospitals in which specialized neurologic and critical care expertise may be lacking.[9] Two areas of major concordance today between the guidelines and actual practice that had not existed previously are the use of apnea testing and the use of ancillary tests. Major areas of continued practice variability are the exclusion of confounders of brain death determination and the precise components and technique of clinical examination. In a recent survey, only 56% of surveyed hospitals excluded hypotension and only 79% excluded hypothermia.[8] These confounders of the examination and others, like acid-base disorders, electrolyte abnormalities, and intoxication, could reduce the examination's diagnostic accuracy. Failure to fully implement the 2010 AANPP guidelines may be due to overconfidence by providers or institutions or a lack of regulatory oversight, such as by hospital policy or leadership.

HISTORY

Mollaret and Goulon[10] from the Hospital Claude Bernard in Paris first described irreversible coma ("le coma depasse") in 1959. In 1968, Harvard Medical School convened an ad hoc committee to examine the concept of brain death from a clinical and ethical perspective. Led by renowned ethicist Henry Beecher, the committee published what it felt to be its unbiased and relatively simple assessment in *JAMA* that same year.[11] Three years later, Mohandas and Chou[12] expanded on this work by emphasizing the role of the brainstem in brain damage in 1971. A 1976 Conference of Royal Medical Colleges in the United Kingdom described loss of brain stem function

as a part of brain death.[13] The Uniform Brain Death Act of 1978 attempted to clarify ambiguity regarding the definition of brain death and was then later replaced by the Uniform Determination of Death Act (UDDA) of 1980, which also included the definition of cardiorespiratory death. Most state laws governing brain death determination are now based on the UDDA legal standards. In 1981, a US President's Commission examined brain death determination, including confirmatory tests and waiting periods for anoxic deaths, and concluded that providers had in the past wrongly diagnosed brain death in some individuals who suffered from drug intoxication or other confounders. The AAN put forth the first evidence-based practice guidelines in its 1995 and 2010 publications.[2]

BRAIN DEATH POLICIES

Every hospital caring for patients with severe neurologic injury should have a policy for determining brain death. This policy should specify what specialties and professional roles (eg, attending, resident) might determine brain death, how they will be trained, whether credentialing for brain death determination will be required, and the precise criteria and parameters for the process. These should all be in accordance with or at least in consideration of the AAN guidelines.

A recent survey found that almost half of US hospitals require training for those determining brain death.[8] Forty-nine percent of those surveyed require that a neurologist or neurosurgeon be involved, but this is not a mandate in the AAN guideline. Although the AAN advocates the involvement of a neurologist, the guideline goes on to say, "neurosurgeons and intensive care specialists may have specialized expertise. It seems reasonable to require that all physicians making a determination of brain death be intimately familiar with brain death criteria and have demonstrated competence in this complex examination."[2]

Professional credentials, training, and even components and thresholds of the examination itself differ among countries, states, and individual hospitals. Intensivists and hospital leaders should maintain a high standard for who may perform brain death determination. Not all provider groups will maintain the same knowledge, experience, and skill set. Few hospitals require credentialing to perform brain death testing but such a practice merits consideration.

There is little evidence showing that 2 clinical examinations are superior to 1, although many hospitals and state statutes require 2.[9] A second test can delay the process of brain death determination and complicate the organ donation process.[14] Mandatory waiting periods and multiple examinations are very important for some clinical scenarios, such as in very young children and after cardiac arrest.

Many hospital brain death policies lack sufficient detail with regard to parameters necessary for allowing the clinical determination of brain death. Examples include thresholds for temperature, blood pressure, serum levels for confounding drugs, and details surrounding the performance of apnea testing.[8] Specificity is most lacking outside major neurologic specialty centers. Variability in hospital policy with regard to determining brain death should be considered avoidable risk.

NEUROIMAGING IN BRAIN DEATH

Determination of brain death begins with identifying a cause. Cause is determined by history, clinical examination, and neuroimaging studies. Clinicians should take pause when the circumstances are unclear or when imaging appears normal. Computerized tomography (CT) findings after neurologic injury include hemorrhage, edema, mass lesions, or ischemia, but imaging may be normal in the first 24 to 48 hours

or longer in situations of hypoxic injury and central nervous system (CNS) infection. In the case of hypoxic injury, as seen with hanging or following severe shock and cardiac arrest, a waiting period of up to 24 hours followed by an interval clinical examination is necessary. Therapeutic hypothermia following cardiac arrest should be considered a confounder preventing clinical diagnosis of brain death until normothermia is restored.

Even when circumstances of the neurologic injury are clear and imaging is abnormal, a regimented, detailed and precise clinical examination is fundamental. Some neurologic findings are reversible. For example, numerous cases have been reported of transtentorial herniation being reversed with aggressive critical care maneuvers, even to favorable outcomes.[15,16] So the clinician must approach severe neurologic injury without bias or supposition. Abnormal imaging supports the brain death diagnosis but is only one part of a complete evaluation.

CLINICAL CRITERIA

After establishment of cause, review of neuroimaging and assurance that other prerequisites have been met, brain death determination may proceed. The process involves neurologic tests, consideration of confounders, resolution of any misleading or conflicting evidence, and if necessary, performance of confirmatory tests. Normothermia, hemodynamic stability, correction of extreme electrolyte disturbances, and confirmation of absence of neuromuscular blockade are essential before examination (**Box 1**). Neurologic testing is based on 3 fundamental findings: (1) coma, (2) absence of brainstem reflexes, and (3) apnea. Assess coma by inducing a pain stimulus to all 4 extremities (eg, nail beds), trunk (eg, sternum), and head (eg, supraorbital nerve or temporomandibular joint). The latter is important to avoid a false-positive test in the event of occult spinal cord injury. Seven brainstem reflexes must be assessed (**Box 2**). (1) Pupils should be fixed at "mid-position"; that is, between constricted and dilated, usually approximately 4 mm, and nonreactive to bright light. Pupillary dilation alone is not a sign of brain death and this examination finding should not withhold resuscitation of what may be a salvageable patient.[17] (2) Oculocephalic reflexes (doll's

Box 1
Prerequisites for brain death examination

1. Cause of irreversible brain death established
2. Supported by neuroimaging
3. Observed for at least 4 hours
   a. In cases of anoxic brain injury or following cardiac arrest observed for 24 hours
   b. If treated with hypothermia observe for 24 hours after resumed to normothermia
4. Normothermic. Adults $\geq$36°C; children (<15 years old) $\geq$35°C
5. Adequate systolic arterial pressure (with or without vasopressor support). Adults $\geq$100 mm Hg; children (<15 years old) above 2 SD below norm for age
6. No evidence of neuromuscular blockade (normal twitch to peripheral nerve stimulation)
7. Confounding factors ruled out
   a. Shock or severe hypotension
   b. Significant levels of central nervous system depressants (pentobarbital >10 μg/mL)
   c. Hyperosmolar coma, hepatic encephalopathy
   d. Extreme abnormalities of glucose, sodium, and pH

Box 2
Steps in the determination of death by neurologic criteria

1. Meets all prerequisites (see Box 1)
2. The clinical neurologic examination
   a. Establishment of irreversible coma
      Lack of motor responses to noxious stimuli including those applied above the neck (Glasgow Coma Score = 3)
   b. Absence of brainstem reflexes
      i. Absent pupillary response to light
      ii. Absent oculocephalic reflex (dolls eyes)
      iii. Absent of oculovestibular reflex (cold calorics)
      iv. Absence of corneal reflex
      v. Absence of facial muscle movement to noxious stimulus
      vi. Absence of pharyngeal reflex (gag)
      vii. Absence of tracheal reflex (cough)
   c. Apnea (Box 3)
3. In certain circumstances, ancillary testing (Boxes 4 and 5)

eyes) are tested by rapidly turning the head but this can be difficult to perform after injury and is prohibited in patients with spinal cord injury. (3) Vestibulo-ocular reflex (cold caloric responses) should be absent when irrigating the auditory canal with cold water with the head turned at 30°. Occlusion of the meatus or auditory canal can confound this test. (4) Corneal reflexes should be absent when stimulated with a swab. (5) A gag reflex should be absent on stimulation of the posterior pharynx. (6) A cough reflex should be absent with endotracheal suctioning. Cough reflex should not be tested with manipulation of the endotracheal tube alone. (7) Facial muscle movement should be absent in response to deep pressure on the temporomandibular condyles and supraorbital ridges.

APNEA TESTING

After establishing coma and absence of the 7 brainstem reflexes, confirmation of apnea is the third and final step in determining brain death. Various methods exist but all of them rely on a period of observing the patient during cessation of mechanical ventilation.[18] Essential steps are shown in **Box 3**. Before apnea testing, the patient must be preoxygenated for at least 10 minutes with 5 or more cm H_2O of positive end-expiratory pressure (PEEP) to wash out respiratory nitrogen and facilitate oxygen transport. This critical step reduces the risk of hypoxemia during testing, which is a common reason for arrhythmias and hypotension during apnea testing.[19] Minute ventilation is also adjusted, usually decreased, before commencing the period of apnea testing so that the examination begins with $Paco_2$ in the normal range. An arterial blood gas (ABG) is obtained after preoxygenation and before commencement of apnea testing to document baseline $Paco_2$ and pH. Mechanical ventilation is then discontinued. The traditional technique is to disconnect the ventilator circuit, pass oxygen tubing down the endotracheal tube to the carina, and instill 5 to 10 L/min oxygen. Alternatively, a T-piece may be used through which oxygen is insufflated at 5 to 10 L/min and on which the exhaust end is covered with a PEEP valve set at 5 to 10 cm H_2O. Addition of the PEEP valve may reduce hypoxia during apnea.[20,21] The patient is observed for any respiratory effort for at least 8 to 10 minutes and until the $Paco_2$ is expected to rise to $\geq$60 mm Hg. Carbon dioxide rises at a rate of about

Box 3
Apnea testing

1. Prerequisites
   a. Patient must have met all of the prerequisites for preforming a clinical examination for brain death
   b. First 2 components of the clinical examination (deep coma and absence of brain stem reflexes) must be compatible with diagnosis of brain death
2. Conduct
   a. Place on 100% Fio_2 and a low rate (~6 BPM) and 5 cm positive end-expiratory pressure (PEEP) for at least 10 minutes
   b. Then obtain baseline arterial blood gas (ABG) and ensure satisfactory parameters:
      i. Pao_2 >200
      ii. $Paco_2$ ~40
      iii. Treat severe base deficit (>6) with bicarbonate
   c. Take patient off ventilator and
      i. Insufflate oxygen at 10 L/min via a small catheter (small compared with ID of ETT) threaded into the trachea through the ETT, or better,
      ii. Attach a T-piece supplied with oxygen at 5 to 10 L/min to the ETT with a PEEP valve set at 5 to 10 cm H_2O at end of exhaust tube of T-piece
   d. Observe chest and abdomen for any respiratory activity for $\geq$10 minutes
   e. Must maintain SpO_2 >85%, mean arterial pressure >60, and systolic arterial pressure >90 (otherwise MUST abort and perform ancillary test)
   f. Obtain ABG after 10 minutes (to ensure that $Paco_2 \geq 60$)
   g. Resume ventilation
3. Abort if become hypoxic (SpO_2 <85) or hypotensive (systolic pressure <90) and obtain an ancillary test
4. Interpretation
   a. Confirms brain death
      i. Considered a positive test if no respiratory activity despite a $Paco_2$ of $\geq$60 mm Hg
   b. Uninterpretable if test aborted. Must be followed with ancillary test
   c. May be unreliable if positive in presence of (and hence an ancillary test may be indicated):
      i. High levels central nervous system (CNS) depressants
      ii. Severe neuromuscular disease
      iii. High spinal cord injury
      iv. Preexisting carbon dioxide retainer
         1. If known, require $Paco_2$ 20 mm above usual premorbid baseline
         2. If unknown but suspected obtain ancillary test

3 mm Hg per minute. An ABG is then drawn and ventilation is resumed. Absence of respiratory effort while $Paco_2$ has risen to the target threshold constitutes a positive apnea test that is consistent with brain death. The apnea test must be aborted if the patient becomes hypoxic or hemodynamically unstable. If the $Paco_2$ did not reach 60 mm Hg at the completion of the test, it must be repeated with a longer period of apnea to produce the desired level of CO_2. Variations in apnea testing include how the test is performed (continuous positive airway pressure, oxygen tubing blow-by, T-piece) and how the results are interpreted. For example, patients who are CO_2 retainers have a higher baseline $Paco_2$ so in these patients, apnea testing should be based on a rise in $Paco_2$ of 20 mm Hg above their normal premorbid baseline. If a patient's baseline value is not known but the patient has severe chronic obstructive pulmonary disease and is suspected of being a CO_2 retainer, the apnea test must be interpreted with some skepticism and consideration given to performance of an ancillary test.

Box 4
Indications for ancillary testing

- Portions of clinical examination cannot be performed because of anatomic limitations or injuries
- Apnea test had to be aborted due to hypotension or hypoxia
- Limitations to interpreting a positive apnea test because of high levels of CNS depressants, severe neuromuscular disease, high spinal cord injury, or suspected preexisting carbon dioxide retainer
- Possible high levels of CNS depressants, for example, barbiturates
- Less than 24 hours since cardiac arrest, hypoxic brain damage or recovery from hypothermia therapy
- Disturbing residual movements/possible spinal reflexes
- Physician or family discomfort with diagnosis of brain death

MISLEADING MOTOR MOVEMENTS

Muscle movements in brain dead patients can confuse and cause uncertainty among clinicians, staff, and families. The exact physiologic basis for such movements is not known.[18] These movements arise from the spinal cord and include spontaneous twitches, movements of the limbs, including arm raises, head turning, toe twitching, positive Babinski, triple flexion response (hip and leg flexion and foot dorsiflexion), respiratorylike movements that can trigger the ventilator and confuse apnea testing, and even contraction of the abdominal muscles during organ retrieval or appearance of a brief attempt to sit up in the bed.[18] Saposnik and colleagues[22] observed 107 brain dead patients over a 5-year study period and almost half had spontaneous and reflexive movements, most commonly "undulating toe reflex" and the "triple flexion response." A follow-up review of 131 published reports concluded that such movements are present in 40% to 50% of brain dead patients and that these phenomena should not preclude diagnosis of death or eligibility for organ donation.[23] Any question regarding the relevance of such movements by the examining clinician should be

Box 5
Ancillary testing

1. Whole brain blood flow
   - 4-vessel contrast intra-arterial cerebral angiogram
   - Nuclear perfusion scan (single-photon emission computed tomography with Technetium 99m hexamethylpropyleneamine oxime)
   - Computed tomography angiography
   - Magnetic resonance angiography
   - Transcranial Doppler
2. Electrical activity in brain
   - Electroencephalogram
   - BIS
   - SSEP
3. Other imaging
   - MRI
   - PET

allayed by a complete clinical examination that is consistent with brain death followed by an ancillary test.[22–24] Proper terminology and careful explanation is important for both families and staff. Jain and Degeorgia[25] suggest referring to movements provoked by stimulus and brain death–associated reflexes and spontaneous movements as "brain death–associated automatisms." This nomenclature does not address specific pathophysiology of each movement, but does help ensure that they are categorized according to inciting action and avoids usage of the term "spontaneous motor movements."

CONDITIONS THAT MIMIC BRAIN DEATH

Three conditions may mimic brain death: locked-in syndrome, hypothermia, and drug intoxication. Locked-in syndrome results from an injury at the level of the pons with preservation of portions of the midbrain. The patient cannot move his or her limbs, grimace, or swallow but consciousness is preserved, as are blinking and vertical gaze. Locked-in syndrome most commonly results from basilar artery embolic stroke.[26] A similar clinical picture can occur with Guillan-Barre in which cranial and peripheral nerves are lost. In this specific syndrome, recovery is quite possible, which raises the alarming notion that these patients could be mistaken as brain dead.[27] The locked-in and Guillan-Barre syndromes are examples of cases in which the involvement of a consultant in the field of neuroscience with specific expertise in these disorders would be valuable to avoid errors in diagnosis. Hypothermia is a well-known mimicker of brain death. Cranial nerve reflexes disappear at approximately 28° Celsius but can then be recovered with rewarming.[28]

Drug intoxication can mimic brain death. Brain stem reflexes are normally preserved with intoxication so a complete examination is essential. Autopsy reports of brain death determined clinically in the context of sedative or toxic levels of pentobarbital raise the frightening specter of this error in clinical practice.[29] Critically ill or injured patients have altered drug clearance and may require more than 72 hours for pentobarbital or other drugs to be eliminated. Pentobarbital's lower limit of therapeutic range is 10 mg/L but there is no clinical consensus on the minimum concentration threshold for pentobarbital or any other barbiturates when determining brain death.[30] It is prudent to obtain a quantitative drug level before determining brain death in cases of drug intoxication. No specific waiting period has been reported in drug-intoxicated patients but the investigators recommend waiting 4 half-lives of whatever drug is present.

Urine drug screens cannot be considered inclusive of the effects of all drugs because not every drug or metabolite is routinely measured with standard screening assays. Particularly elusive are lithium, fentanyl, and cyanide. Drug ingestion should be particularly considered in cases in which neuroimaging is inconsistent with clinical examination.[31] Unless there is irrefutable evidence that drug effects have subsided, clinicians are wise to either prolong the period of delay in performing clinical brain death examination or proceed with ancillary testing.[18] At the time of this writing, there exists significant controversy regarding the management of clinically brain dead patients who also have drug/substance intoxication. Mandatory ancillary testing in intoxication situations is being debated. Even at the US federal level there is ongoing discussion regarding regulation over clinical criteria for brain death and specifics regarding these controversial circumstances.

ANCILLARY TESTING

Brain death is primarily a clinical diagnosis. After clinical confirmation of brain death as described previously, including confirmation of apnea, death may be declared. In

adults, ancillary tests are not required except when the examination is not reliable or when mandated by institutional guidelines. Some advocate routine use of ancillary tests in conjunction with the clinical examination for the determination of brain death,[32] whereas others argue that confirmatory tests are unnecessary and if determination of brain death cannot be made based on clinical examination, then brain death should not be determined at all.[2,4] Ancillary tests may be indicated when elements of the clinical examination cannot be performed (eg, facial trauma, preexisting cranial nerve deficits), motor movements are present, or when the apnea testing cannot be completed due to hypoxia or hypotension or when confounding factors are present (see **Box 4**). Ancillary testing has been used to assist families with understanding the finality of brain death, but this practice should be avoided.[33]

Ancillary testing must not replace a thorough clinical examination. Ancillary tests should not be performed until all prerequisites for the clinical examination have been met and all evaluable components of the clinical examination including the apnea test are consistent with brain death. At many centers, ancillary tests are routinely used when declaring brain death in children, although they are not required in all infants and children by the most recent pediatric guidelines.[3] When ancillary testing is used, the time of death is best recorded as the time the testing results are finalized or reported. In clinical cases, time of death is reported as the time the $Paco_2$ reaches its maximum value, thus representing an apnea test confirmatory of brain death.

MECHANISTIC BASIS FOR ANCILLARY TESTING

Ancillary tests are based on either absence of cerebral blood flow or lack of electrical activity (see **Box 5**). To understand the mechanism by which confirmatory tests determine brain death, one must consider brain death physiology. Palmer and Bader[34] suggest hypothetical mechanisms for brain death. First, intracranial pressure exceeds mean arterial pressure (ICP > MAP) resulting in brain and brainstem death due to lack of blood flow. This first hypothesis is the one on which most ancillary tests are based. Second, ICP does not exceed MAP, therefore the cerebral blood flow is preserved but intrinsic pathology is present that causes neuronal and axonal injury, ultimately resulting in brain death. This second mechanistic hypothesis would make any confirmatory test based on blood flow falsely negative.[35–37] In the final and least common mechanistic hypothesis, direct catastrophic brainstem or cerebral pathology may exist.[34]

TYPES OF ANCILLARY TESTING

The 3 most commonly performed ancillary tests are cerebral scintigraphy (hexamethylpropyleneamine oxime [HMPAO]), cerebral angiography, and electroencephalogram (EEG). Other potential confirmatory tests include transcranial Doppler study (TCD), CT angiography, and magnetic resonance angiography (MRA). Conventional MRI and CT lack the sensitivity and specificity required to act as an ancillary test for brain death. The Canadian Guidelines[38] and the Australian-New Zealand Intensive Care Society (ANZICS) Guideline[39] do not include EEG or TCD. The American pediatric guidelines[3] do not include TCD. However, the American adult guidelines[2] accept all 4 studies but prefer EEG, cerebral angiography, and nuclear scan. The Canadian Forum on Determining Brain Death[38] recommends that demonstration of absence of intracerebral flow be the standard ancillary test.[40] Ancillary tests based on assessing blood flow are based on the hypothesis that if blood flow to the entire brain is absent for a substantial period, there can be no brain function. Therefore, the absence of flow is compatible with the clinical diagnosis of brain death. On the other hand,

some persistent blood flow does not rule out clinical brain death. Tests of electrical activity (eg, EEG) assume that the absence of electrical activity indicates absence of brain function. Each ancillary test carries its own potential pitfalls (see **Box 4**) and each its own reportable rates of specificity and sensitivity. Most require transport of the critically ill patient out of the care area.

CEREBRAL ANGIOGRAPHY

Cerebral angiography is the test by which most other ancillary tests are referenced. However, angiography is invasive, requires prolonged travel to the angiography suite, is not readily available and interpretable at many centers, and is relatively expensive. Proper technique for cerebral angiography is specified in the AANPP guideline and includes high-pressure injection into the aortic arch, contrast medium should reach both anterior and posterior circulations, no intracerebral filling at the level of entry of the carotid or vertebral artery to the skull. The external carotid circulation should be visualized as a positive control. Filling of the superior longitudinal sinus may be delayed and does not affect accuracy.[2] No false-positive cases have been reported in the literature using cerebral angiography. False negatives (cerebral flow in the face of apparent brain death) have been reported, usually when ICP was not elevated.[40]

CEREBRAL SCINTIGRAPHY

Scintigraphy, often called nuclear flow testing or SPECT (single-photon emission CT), uses a gamma-emitting radioactive tracer instilled into the venous system and detected by a radio counter in nuclear medicine. Reliability is comparable to cerebral angiography.[41] The tracer is technetium 99m-HMPAO (Tc99-HMPAO). Nuclear scintigraphy requires instrumentation, a radiologist with expertise to interpret the test, and the relatively expensive radioisotope that must be reconstituted by a specialty pharmacy. Technical specifics include injecting the isotope within 30 minutes of reconstitution, collection of images from anterior and both lateral planar views immediately, between 30 to 60 minutes later, and at 2 hours after injection, liver uptake as a positive control, no radionuclide localization in the middle cerebral artery, anterior cerebral artery, or basilar artery territories of the cerebral hemispheres (hollow skull phenomenon), and no tracer in superior sagittal sinus. Minimal tracer can come from the scalp.[2,42,43]

If perfusion is identified on HMPAO SPECT, brain death cannot be determined. If a repeat test is planned, most radiologists recommend waiting 24 to 48 hours.[40] Proposed explanations for blood flow on scintigraphy in the circumstance of clinical brain death include the temporal relationship between actual cessation of flow and clinical diagnosis, as well as a potential rostrocaudal necrosis of neuraxial tissue that makes lower brain blood flow the last to dissipate.[40]

ELECTROENCEPHALOGRAPHY

EEG in brain dead patients seeks to establish a lack of reactivity to intense somatosensory or audiovisual stimuli. Techniques for reliable testing are demanding and specific and include a minimum of 8 scalp electrodes, a check of the entire recording system, a distance between electrodes of least 10 cm, and sensitivity increased to at least 2 μV for 30 minutes.[2] EEG is the most technically cumbersome to perform and interpret, time-consuming, and least often used ancillary test.

TRANSCRANIAL DOPPLER ULTRASONOGRAPHY

Transcranial doppler ultrasonography (TCD) is noninvasive, bedside, and relatively quick to perform and interpret, but there is little consensus on the usefulness of TCD as an ancillary test, as it does not necessarily quantify cerebral blood flow. TCD is very technician and interpreter-dependent. It requires visualization of each hemisphere (both internal carotid arteries and the basilar artery) and demonstration of an abnormal flow pattern. TCD is useful only if a reliable signal is found. Up to 20% of patients are poor candidates for TCD secondary to increased thickness of cranial vaults or other technical limitations.[44]

Abnormalities consistent with brain death include either reverberating flow or small systolic peaks in early systole. Complete absence of flow is not reliable, as it may result from inadequate transtemporal windows. Reliability is augmented if the patient has had prior TCD studies by the same TCD team with the previous studies noting normal flow in all 3 vessels. Technical details are critically important. Many reports in the literature of both false positives and negatives make the utility of TCD as an ancillary test in brain death questionable.[2,45]

COMPUTED TOMOGRAPHY ANGIOGRAPHY

Computed tomography angiography (CTA) was first reported as an ancillary test in the diagnosis of brain death in 1998 as having 100% specificity.[46] It is used widely in Europe as an ancillary test to determine cessation of cerebral blood flow but has not yet been adopted in the United States.[47] CTA is readily available, relatively inexpensive, easy to acquire, minimally invasive, and fast, but requires precision performance. Diagnostic criteria are lack of intracranial arterial contrast opacification, defined as vertebrobasilar circulation within the dura and within the internal carotids above the clinoid. Some investigators suggest interpretation should specifically reference lack of filling of the cortical middle cerebral artery branches and cerebral veins.[48,49] CTA was compared with nuclear perfusion study in 2010 among 25 clinically brain dead patients with no false negatives, but the investigators found 3 patients without flow on nuclear perfusion who showed minimal flow on CTA, all of whom had open skull defects, suggesting that CTA is even more sensitive than HMPAO SPECT for detecting blood flow just above the skull base.[50]

Nonangiographic CT perfusion scans, such as Xenon CT, are more difficult to interpret and less available. Critics cite incomplete quantitative measurement of cerebral blood flow. Xenon CT shows some promise, but at this point is limited to large academic centers and should not be considered the standard of care.

MAGNETIC RESONANCE ANGIOGRAPHY

Determination of brain death by MRA should be based on the same criteria as CTA. Although likely a reliable test for cerebral blood flow, MRA has not yet been proven as an ancillary test in brain death. Like any MRI, the patient must be transported to the radiology suite, examination time is longer than CT or HMAO-SPECT, and the patient and monitors must be MRI-compatible.[2]

Regardless of the test used, radiologists and others who interpret the tests hold a precarious position in brain death determination. They rarely perform clinical examination of the patient, but the radiologic study is often used as the final examination determining brain death. The time of death is often recorded as the time the report is finalized. It is recommended that radiologists refer strictly to brain blood flow testing and avoid the terminology “consistent with brain death” when referencing their

assessment that cerebral blood flow is absent.[51] This practice will allow the radiologist to maintain the appropriate relationship with respect to the process of brain death determination.

DOCUMENTATION OF BRAIN DEATH

The authors endorse the use of the checklists provided in both adult and pediatric published guidelines.[2,3] We include these in the documentation of brain death examination in the electronic health record at our institution and believe it serves to remind the examiner to perform a complete examination and documents the examination accurately in the medical record. If all requirements are not met, the electronic record should not accept the note.

CRITICAL CARE OF THE BRAIN DEAD PATIENT

Cerebral ischemia progresses from rostral to caudal as brain death ensues and physiologic changes occur simultaneously. First, cerebral ischemia results in vagal activation with bradycardia and possibly hypotension. Next, the pons becomes ischemic, stimulating the Cushing response of sympathetic stimulation with parasympathetic modulation resulting in moderate hypertension and bradycardia. With uncal herniation, the upper medulla becomes ischemic. A "sympathetic storm" is caused by sympathetic stimulation without parasympathetic modulation. Severe hypertension and tachycardia occur, which may in turn be responsible for the myocardial dysfunction often encountered in brain death as well as neurogenic pulmonary edema.

Finally, herniation of the cerebellar tonsils, also called coning, compresses and causes ischemia of the lower medulla and C1 level of the spinal cord, resulting in autonomic paresis. This final insult is associated hypotension due to vasodilation from sympathectomy and vasopressin deficiency combined with left ventricular dysfunction as well as hypovolemia from diabetes insipidus. Much individual variability exists in these hemodynamic abnormalities, but in all cases, deterioration of cardiovascular status to cardiac arrest is likely if aggressive management is not proactively instituted. Evidence suggests that preventing or ameliorating the sympathetic storm may decrease cardiac and pulmonary injury associated with brain death.[52,53] When deterioration occurs, the authors' policy is to resuscitate aggressively, even including advanced cardiac life support and blood transfusion. It is our policy to maximally support every potential organ donor until and unless the family indicates the patient would not want to donate.

Physiologic abnormalities in brain death that require critical care are listed in **Box 6**. Management of brain dead patients and organ donors has been reviewed with established guidelines and innovative therapies offered.[38,54–57] Salim and colleagues[58] found that vasopressors were required in 97.1% of their series of brain dead patients and that coagulopathy, thrombocytopenia, and diabetes insipidus occurred in half. Hypovolemia is extremely common and requires aggressive treatment. Optimization of donor management goals yields a larger number of organs transplanted for each donor.[59,60] Aggressive management of potential organ donors may include steroids, thyroid hormone, peritoneal resuscitation, and even extracorporeal membrane oxygenation.[61–70]

We recommend early implementation of institutional catastrophic brain injury guidelines (CBIGs) before herniation. CBIGs provide an algorithm by which hemodynamic and hormonal support and management of other complications associated with brain death may be addressed. Donor management protocols are often provided by regional organ procurement organizations and can even be used before brain death. Most protocols are based on empiric guidelines, consensus statements or conferences, and case series from the literature.[59,71] A simplified algorithm for managing

Box 6
Common problems/complications in subjects who are brain dead that may need to be managed

1. Hemodynamic complications
   a. Bradycardia
   b. Hypotension
   c. Low cardiac output/stress cardiomyopathy
2. Arrhythmias
3. Diabetes insipidus
   a. Hypovolemia
   b. Hypernatremia
4. Pulmonary dysfunction and complications
   a. Pulmonary edema
   b. Traumatic lung injury
   c. Aspiration
   d. Infection
5. Endocrine deficiency
6. Hypothermia (rarely hyperthermia)
7. Hyperglycemia
8. Coagulopathy
9. Cyto- and endothelial dysfunction
10. Hypernatremia (adverse effect on liver allograft)

brain dead or dying patients is the "Rule of 100s." Maintain a systolic blood pressure greater than 100 mm Hg using vasoactive drugs, intravenous fluids, and blood products. Maintain Pa_{O_2} greater than 100 mm Hg. Maintain urine output of approximately 100 mL/h by aggressively monitoring for and treating hypervolemia, hypovolemia, and diabetes insipidus. Equally important is monitoring for and aggressively treating coagulopathy and anemia.

The Society of Critical Care Medicine recommends a goal urine output of 1 mL/kg per minute and a MAP 60 mm Hg, ideally without high-dose vasopressors.[57] Invasive hemodynamic monitoring is used for goal-directed care of patients who are brain dead at our institution. Enteral nutrition should be considered, as it may diminish inflammatory effects of brain death on organ dysfunction.[72]

VARIABILITY IN BRAIN DEATH DETERMINATION AMONG NATIONS

In the United States, the UDDA makes the regulatory definition of death clear; however, in other countries such regulatory consistency is not always present. Although most European nations rely primarily on clinical examination and view brain death similar to the United States, in several European countries, ancillary testing is mandatory.[73] Cultural and religious differences between nations coincide with differences in the concept of the meaning of death. For this reason, an international consensus for declaration of brain death is unlikely.

BRAIN DEATH AND THE LAW

In 1978, as definitions regarding determinations of death were being increasingly scrutinized in criminal and civil litigation, the Uniform Law Commissioners created the

Uniform Brain Death Act. This Act was modified to become the UDDA in 1980. The UDDA sought to clarify terminology and added "irreversible cessation of circulatory and respiratory functions" as an alternative to the standards. The act is designed to address minimum reasonable standards and is intentionally vague. By recognizing cardiopulmonary and brain death as separate entities, it lends discretion on interpretation to the medical profession.

Each US state has formal criteria for determination of death, but the legal language provides woefully little specificity with regard to clinical brain death testing. State and federal law can provide guidance in unique situations, such as a pregnant mother who has suffered catastrophic brain injury or brain death but maintains a viable intrauterine pregnancy. Current US law requires and ethical and clinical practice guidelines advocate support of the intrauterine pregnancy until maturation of the fetus to the point at which delivery can be safely induced.[74–76]

BRAIN DEATH AND RELIGION

Early scholars of brain death asserted that its concept and practice were compatible with the beliefs of the world's principal religions.[77] Most Christians accept brain death without serious exception.[78] Before an International Transplant Society meeting in 2000, Pope John Paul II affirmed brain death to be compatible with Catholic beliefs.[79] A rabbinic debate persists in Judaism. Reform and Conservative rabbis accept brain death almost without exception but this is not the case within more traditional arms of Judaism. In contrast to a rather long history of opposition to the concept of brain death, religious authorities in several Islamic countries, including conservative Saudi Arabia, permit brain death and organ transplantation.[80] Hindu culture in India endorses brain death.[81] Following a lengthy social battle, Shinto-Confucian religious authorities in Japan also acknowledge the occurrence of brain death.[82] All states in the United States have enacted statutes or written administrative regulations permitting physicians to declare death by brain death determination[83] with only New Jersey and New York in the 1990s enacting escape clauses for those who may have religious or personal convictions against the concept.[83,84]

ETHICAL CHALLENGES

Ethical controversy exists among medical practitioners of the same specialty regarding the real meaning and definition of brain death. Even neurologists lack a consistent teleologic definition of brain death and argue about the optimal diagnostic tests for brain death. Almost half of neurologists accept brain death fundamentally as a state of permanent unconsciousness, but many do not consider brain death as equivalent to circulatory death.[85–87] Wijdicks writes "confirmatory tests do not confirm anything [because brain death] is synonymous with a certain clinical state [from which] there are no recoveries on record." These sentiments imply that our conceptual framework of brain death is, at least to a certain degree, based in theory rather than clear scientific basis, as we might think. For example, one would presume that cessation of brain flow would lead to significant cerebral tissue necrosis following arterial inflow occlusion but varying degrees of tissue necrosis have been reported in pathologic examination after brain death. Most recently, Wijdicks and Pfeifer[88] reported varying degrees of necrosis on microscopic examination and concluded that neuropathologic examination may not be diagnostic of brain death.

A wide range of specialists performing brain death testing with different policies and different techniques illustrates the broad ethical and contextual variability in brain death determination.[89] Similar variability regarding the determination of brain death

can be found worldwide.[2] We must not accept our current understanding of brain death as the end-all. We must continuously challenge our scientific understanding of brain death through further research and ethical discussion.

SUMMARY

Brain death determination is a fundamental part of surgical critical care. It has an interesting history and continuing ethical implications. Statutory guidance is minimal. Practice guidelines exist but are not widely implemented. Significant policy and practice variation exists, putting the ill-informed or inexperienced intensivist at risk. The gravity of brain death determination is arguably the greatest of any clinical assessment we perform. We should feel confident in following our own guidelines but we should never be afraid to ask ourselves if we are making the correct decisions. We should remain open-minded and not be afraid to question our practice or compare our practices with those of others to ensure that our standards are most impeccable. Brain death testing should be performed rigorously, with attention to detail in clinical examination and with knowledgeable, deliberate application of ancillary tests where necessary. In all cases, we should aggressively deliver high-quality neuro-critical care. The outcome of our efforts is the very determination of life or death, for both our own patient and the potential organ donor recipient.

REFERENCES

1. Wijdicks EF. Determining brain death in adults. Neurology 1995;45(5):1003–11.
2. Wijdicks EF, Varelas PN, Gronseth GS, et al. Evidence-based guideline update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2010;74:1911–8.
3. Nakagawa TA, Ashwal S, Mathur M, et al. Guidelines for the determination of brain death in infants and children: an update of the 1987 Task Force recommendations. Crit Care Med 2011;39:2139–55.
4. Wijdicks EFM. Brain death. 3rd edition. New York: Oxford University Press; 2017.
5. Teresi D. The undead. New York: Penguin Random House; 2012.
6. Practice parameters for determining brain death in adults (summary statement). The Quality Standards Subcommittee of the American Academy of Neurology. Neurology 1995;45(5):1012–4.
7. Chamoun RB, Robertson CS, Gopinath SP. Outcome in patients with blunt head trauma and a Glasgow Coma Scale score of 3 at presentation. J Neurosurg 2009; 111(4):683–7.
8. Wang HH, Varelas PN, Henderson GV, et al. Improving uniformity in brain death determination policies over time. Neurology 2017;88(6):562–8.
9. Greer DM, Wang HH, Robinson JD, et al. Variability of brain death policies in the United States. JAMA Neurol 2016;73(2):213–8.
10. Mollaret P, Goulon M. Le coma depassse. Rev Neurol (Paris) 1959;101:3–15.
11. Beecher H. A definition of irreversible coma: report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death. JAMA 1968; 205:337–40.
12. Mohandas A, Chou SN. Brain death: a clinical and pathological study. J Neurosurg 1971;35:211–8.
13. Diagnosis of brain death. Statement issued by the honorary secretary of the Conference of Medical Royal Colleges and their Faculties in the United Kingdom on 11 October 1976. Br Med J 1976;2:1187–8.

14. Lustbader D, O'Hara D, Wijdicks E, et al. Second brain death examination may negatively affect organ donation. Neurology 2011;76:119–24.
15. Koenig MA, Bryan M, Lewin JL, et al. Reversal of transtentorial herniation with hypertonic saline. Neurology 2008;70(13):1023–9.
16. Skoglund TS, Nellgard B. Long-time outcome after transient transtentorial herniation in patients with traumatic brain injury. Acta Anaesthesiol Scand 2005;49(3):337–40.
17. Mauritz W, Leitgeb J, Wilbacher I, et al. Outcome of brain trauma patients who have Glasgow Coma Scale score of 3 and bilateral fixed and dilated pupils in the field. Eur J Emerg Med 2009;16(3):153–8.
18. Busl KM, Greer DM. Pitfalls in the diagnosis of brain death. Neurocrit Care 2009;11(2):276–87.
19. Goudreau JL, Wijdicks EF, Emery SF. Complications during apnea testing in the determination of brain death: predisposing factors. Neurology 2000;55(7):1045–8.
20. Levesque S, Lessard MR, Nicole PC, et al. Efficacy of a T-piece system and a continuous positive airway pressure system for apnea testing in the diagnosis of brain death. Crit Care Med 2006;34(8):2213–6.
21. Kramer AH, Couillard P, Bader R, et al. Prevention of hypoxemia during apnea testing: a comparison of oxygen insufflation and continuous positive airway pressure. Neurocrit Care 2017;27(1):60–7.
22. Saposnik G, Maurino J, Saizar R, et al. Spontaneous and reflex movements in 107 patients with brain death. Am J Med 2005;118(3):311–4.
23. Saposnik G, Basile VS, Young GB. Movements in brain death: a systematic review. Can J Neurol Sci 2009;36(2):154–60.
24. Wijdicks EF. The diagnosis of brain death. N Engl J Med 2001;344:1215–21.
25. Jain S, Degeorgia M. Brain death-associated reflexes and automatisms. Neurocrit Care 2005;3(2):122–6.
26. Patterson JR, Grabois M. Locked-in syndrome: a review of 139 cases. Stroke 1986;17:758–64.
27. Kotsoris H, Schleifer L, Menken M, et al. Total locked-in state resembling brain death in polyneuropathy. Ann Neurol 1984;16:150.
28. Danzl DF, Pozos RS. Accidental hypothermia. N Engl J Med 1994;331:1756–60.
29. Molina DK, McCutcheon JR, Rulon JJ. Head injuries, pentobarbital, and the determination of death. Am J Forensic Med Pathol 2009;30(1):75–7.
30. Hallbach JL, von Meyer L, Maurer HH. Recommendations from the Clinical Toxicology Committee of the Society for Toxicological and Forensic Chemistry (GTFCh) for toxicological analysis in the context of determining brain death. TIAFT Bulletin 2004;34:14–5. Available at: https://www.gtfch.org/cms/images/stories/RichtlinienBDeath.pdf. Accessed July 2, 2017.
31. Yang KL, Dantzker DR. Reversible brain death: a manifestation of amitriptyline overdose. Chest 1991;99:1037–8.
32. Roberts DJ, MacCulloch KA, Versnik EJ, et al. Should ancillary brain blood flow analyses play a larger role in the neurological determination of death? Can J Anaesth 2010;57(10):927–35.
33. Palaniswamy V, Sadhasivam S, Selvakumaran C, et al. Single-photon emission computed tomography imaging for brain death donor counseling. Indian J Crit Care Med 2016;20(8):477–9.
34. Palmer S, Bader MK. Brain tissue oxygenation in brain death. Neurocrit Care 2005;2(1):17–22.

35. DeCampo MP. Imaging of brain death in neonates and young infants. J Paediatr Child Health 1993;29:255–8.
36. Flowers WM, Patel BR. Persistence of cerebral blood flow after brain death. South Med J 2000;93(4):364–70.
37. Kurtek RW, Lai KK, Taue WN, et al. Tc-99m hexamethylpropylene amine oxime scintigraphy in the diagnosis of brain death and its implications for the harvesting of organs used for transplantation. Clin Nucl Med 2000;25(1):7.
38. Shemie SD, Ross H, Pagliarello J, et al. Organ donor management in Canada: recommendations of the forum on medical management to optimize donor organ potential. CMAJ 2006;174:S13–30.
39. Australian and New Zealand Intensive Care Society. The ANZICS statement on death and organ donation. Edition 3.2. Melbourne: ANZICS; 2013.
40. Heran M, Heran N, Shemie S. A review of ancillary tests in evaluating brain death. Can J Neurol Sci 2008;35:409–19.
41. Munari M, Zucchetta P, Carollo C, et al. Confirmatory tests in the diagnosis of brain death: comparison between SPECT and contrast angiography. Crit Care Med 2005;33(9):2068–73.
42. Donohoe KH, Agrawal G, Frey KA, et al. SNM practice guideline for brain death scintigraphy 2.0. J Nucl Med Technol 2012;40(3):198–203.
43. Conrad GR, Sinha P. Scintigraphy as a confirmatory test of brain death. Semin Nucl Med 2003;33(4):312–23.
44. Young GB, Lee D. A critique of ancillary tests for brain death. Neurocrit Care 2004;1(4):499–508.
45. Sharma D, Souter MJ, Moore AE, et al. Clinical experience with transcranial Doppler ultrasonography as a confirmatory test for brain death: a retrospective analysis. Neurocrit Care 2011;14:370–6.
46. Dupas B, Gayet-Delacroix M, Villers D, et al. Diagnosis of brain death using two-phase spiral CT. AJNR Am J Neuroradiol 1998;19(4):641–7.
47. Wijdicks EF. Brain death worldwide: accepted fact but no global consensus in diagnostic criteria. Neurology 2002;58(1):20–5.
48. Leclerc X, Taschner CA, Vidal A, et al. The role of spiral CT for the assessment of the intracranial circulation in suspected brain-death. J Neuroradiol 2006;33(2):90–5.
49. Frampas E, Videcoq E, deKerviler F, et al. CT angiography for brain death diagnosis. AJNR Am J Neuroradiol 2009;30(8):1566–70.
50. Berengeur CM, Davis FE, Howington JU. Brain death confirmation: comparison of computed tomographic angiography with nuclear medicine perfusion scan. J Trauma 2010;68(3):553–9.
51. ACR 2017 guideline updated 2016. Available at: www.acr.org/Quality-Safety/Standards-Guidelines/Practice-Guidelines-by-Modality.
52. Yeh T, Wechsler AS, Graham L, et al. Central sympathetic blockade ameliorates brain death-induced cardiotoxicity and associated changes in myocardial gene expression. J Thorac Cardiovasc Surg 2002;124(6):1087–98.
53. Audibert G, Charpentier C, Segin-Devaux C, et al. Improvement of donor myocardiac function after treatment of autonomic storm during brain death. Transplantation 2006;82(8):1031–6.
54. Smith M. Physiologic changes during brain stem death—lessons for management of the organ donor. J Heart Lung Transplant 2004;23(9s):S217–22.
55. Frontera JA, Kalb T. How I manage the adult potential organ donor: donation after neurological death. Neurocrit Care 2010;12(1):103–10, 111-116.

56. McKeown DW, Bonser RS, Kellum JA. Management of the heartbeating brain-dead organ donor. Br J Anaesth 2012;108(S1):i96–107.
57. Kotloff RM, Blosser S, Fulda GJ, et al. Management of the potential organ donor in the ICU: Society of Critical Care Medicine/American College of Chest Physicians/Association of Organ Procurement organizations consensus statement. Crit Care Med 2015;43(6):1291–325.
58. Salim A, Martin M, Brown C, et al. Complications of brain death: frequency and impact on organ retrieval. Am Surg 2006;72(5):377–81.
59. Franklin GA, Santos AP, Smith JW, et al. Optimization of donor management goals yields increased organ use. Am Surg 2010;76(6):587–94.
60. Malinoski DJ, Daly MC, Patel MS, et al. Achieving donor management goals before deceased donor procurement is associated with more organs transplanted per donor. J Trauma 2011;71(4):990–6.
61. Guglin M. How to increase the utilization of donor hearts? Heart Fail Rev 2015; 20(1):95–105.
62. Krishnamoorthy V, Borbely X, Rowhani-Rahbar A, et al. Cardiac dysfunction following brain death in children: prevalence, normalization, and transplantation. Pediatr Crit Care Med 2015;16(4):e107–12.
63. Mohamedali B, Bhat G, Tatooles A, et al. Neurogenic stress cardiomyopathy in heart donors. J Card Fail 2014;20(3):207–11.
64. Mohamedali B, Bhat G, Zelinger A. Frequency and pattern of left ventricular dysfunction in potential heart donors: implications regarding use of dysfunctional hearts for successful transplantation. J Am Coll Cardiol 2012;60(3):235–6.
65. Casartelli M, Bombardini T, Simion D, et al. Wait, treat and see: echocardiographic monitoring of brain-dead potential donors with stunned heart. Cardiovasc Ultrasound 2012;10:25.
66. Venkateswaran RV, Townend JN, Wilson IC, et al. Echocardiography in the potential heart donor. Transplantation 2010;89(7):894–901.
67. Berman M, Ali A, Ashley E, et al. Is stress cardiomyopathy the underlying cause of ventricular dysfunction associated with brain death? J Heart Lung Transplant 2010;29:957–65.
68. Dujardin KS, McCully RB, Wijdicks EF, et al. Myocardial dysfunction associated with brain death: clinical, echocardiographic, and pathologic features. J Heart Lung Transplant 2001;20(3):350–7.
69. Smith JW, Matheson P, Morgan G, et al. Addition of direct peritoneal lavage to human cadaver organ donor resuscitation improves organ procurement. J Am Coll Surg 2017;220(4):539–47.
70. Fan X, Chen Z, Nasralla D, et al. The organ preservation and enhancement of donation success ratio effect of extracorporeal membrane oxygenation in circulatory unstable brain death donor. Clin Transplant 2016;30(10):1306–13.
71. Salim A, Velmahos GC, Brown C, et al. Aggressive organ donor management significantly increases the number of organs available for transplantation. J Trauma 2005;58(5):991–4.
72. Singer P, Shapiro H, Cohen J. Brain death and organ damage: the modulating effects of nutrition. Transplantation 2005;80(10):1363–8.
73. Guignard NG, Gardner AI, Baker S, et al. Brain death determination in Australia and New Zealand: a survey of intensive care units. Crit Care Resusc 2011;13: 271–3.
74. Hussein I, Govenden V, Grant J, et al. Prolongation of pregnancy in a woman who sustained brain death at 26 weeks of gestation. BJOG 2006;113:120–2.

75. Powner DJ, Bernstein IM. Extended somatic support for pregnant women after brain death. Crit Care Med 2003;31(4):1241–9.
76. Esmaeilzadeh M, Dictus C, Kayvanpour E, et al. One life ends, another begins: management of a brain-dead pregnant mother—a systematic review. BMC Med 2010;8:74.
77. Veith FJ, Fein JM, Tendler MD, et al. Brain death—a status report of medical and ethical considerations. JAMA 1977;238:1651–5.
78. Campbell CS. Fundamentals of life and death: Christian fundamentalism and medical science. In: Youngner SJ, et al, editors. The definition of death: contemporary controversies. Baltimore (MD): Johns Hopkins University Press; 1999. p. 194–209.
79. Furton EJ. Brain death, the soul, and organic life. Natl Cathol Bioeth Q 2002;2(3):455–70.
80. Yaqub BA, Al-Deeb SM. Brain death: current status in Saudi Arabia. Saudi Med J 1996;17:5–10.
81. Bernat JL, Beresford R. 1st Edition. Ethical and legal issues in neurology, vol. 118. New York: Elsevier; 2013.
82. Lock M. Contesting the natural in Japan: moral dilemmas and technologies of dying. Cult Med Psychiatry 1995;19(1):1–38.
83. Beresford HR. Brain death. Neurol Clin 1999;17(2):295.
84. Olick RS. Brain death, religious freedom, and public policy: New Jersey's landmark legislative initiative. Kennedy Inst Ethics J 1991;1(2):275–92.
85. Joffe AR, Anton NR, Duff JP, et al. A survey of American neurologists about brain death: understanding the conceptual basis and diagnostic tests for brain death. Ann Intensive Care 2012;2:4.
86. Souter M, van Norman G. Ethical controversies at end of life after traumatic brain injury: defining death and organ donation. Crit Care Med 2010;38(9Suppl):S502–9.
87. Controversies in the determination of Death. A white paper of the President's Council on Bioethics. Washing DC, 2008. Available at: https://bioethicsarchive.georgetown.edu/pcbe/reports/death/. Accessed July 2, 2017.
88. Wijdicks EF, Pfeifer EA. Neuropathology of brain death in the modern transplant era. Neurology 2008;70(15):1234–7.
89. Greer DM, Varelas PN, Haque S, et al. Variability of brain death determination guidelines in leading US neurologic institutions. Neurology 2008;70(4):284–9.