SUPPLEMENTARY MATERIAL

# Objective

To establish a protocol for the determination of brain death in adult patient population across University Hospital, in accordance with state and federal regulations. This protocol is based on the 2010 guidelines by the American Academy of Neurology (AAN) for determination of brain death.

# Background

The earliest accounts of brain death were published by European physicians with two major papers by Wertheimer (1959) and Mollaret (1959). The issue became of interest to U.S. physicians only after the publication of the “Harvard Criteria” by the Ad Hoc Committee of Harvard Medical School in 1968. Several years later there was a large-scale study supported by NINDS, which later became known as the US Collaborative Study. This study defined brain death as “cerebral death” in which death of the brain should involve all supratentorial structures with little emphasis on the brain stem. The study defined brain death by demonstration of irreversible coma and apnea, however, confirmatory tests such as electrophysiologic testing or cerebral blood flow testing were stressed for further confirmation. Although erroneous in a few ways, the Collaborative Study became a model for President’s commission report in 1981, which later led to the creation of the Uniform Death Determination Act (UDDA).

UDDA defines death as 1) irreversible cessation of circulatory and respiratory functions, or 2) irreversible cessation of all functions of the entire brain, including the brain stem. Most US states have adopted the UDDA with added amendments by some states. UDDA proposed only the “legal” definition of death but did not define “accepted medical standards.” The American Academy of Neurology (AAN) published a 1995 practice parameter to delineate the medical standards for the determination of brain death with further updates released in 2010.

Despite publication of practice parameters, significant practice variations have been observed in prerequisites, examination and ancillary testing from state to state and hospital to hospital. This document aims to create a more unified approach to brain death assessment and reduce deficiencies in documentation.

Prerequisites

* Establish an irreversible and proximate cause of coma
* The cause of coma should be established by history, examination, neuroimaging, and laboratory tests
* Neuroimaging should explain coma
* In the vast majority of patients, CT documents an abnormality that explains the loss of global cerebral function. The clinical diagnosis of brain death should be in doubt in patients with normal CT findings
* In patients with no CT abnormality, brain death assessment should proceed only if there is a high degree of certainty about the mechanism that led to brain death
* CNS depressant drug effect
* Exclude the presence of a CNS-depressant drug effect by:

1) History

2) Drug screen whenever possible

3) Calculation of clearance using 5 times the drug’s half-life (assuming normal hepatic and renal function)

4) If available, drug plasma levels below the therapeutic range (ie.. barbiturate level <10µg/ml)

* The legal alcohol limit for driving (blood alcohol content 0.08%) is a practical threshold below which an examination to determine brain death could reasonably proceed.
* Prior use of hypothermia (e.g., after cardiopulmonary resuscitation for cardiac arrest) may delay drug metabolism and patient should be off sedation for at least 72 hours
* There should be no recent administration or continued presence of neuromuscular blocking agents (this can be defined by the presence of a train of four, using the ulnar nerve)
* Effect of neuromuscular blockers is unlikely if the patient has deep tendon reflexes.
* Absence of severe acid-base, electrolyte, endocrine abnormality
* Recent metabolic panel, TSH level, other endocrine lab testing if indicated. There should be no severe electrolyte, acid-base, or endocrine disturbance
* What defines “severe abnormality” is left to the evaluating physician by referring to established norms
* Normothermia or mild hypothermia (core temperature >36°C)
* Systolic blood pressure ≥100 mm Hg.
* Hypotension from loss of peripheral vascular tone or hypovolemia (diabetes insipidus) is common.
* Vasopressors can be used if required
* No spontaneous respirations.
* **Assessment**
* Texas Health and Safety Code 671.001 gives the legal standard for the determination of brain death in the state of Texas
* Legally, all physicians are allowed to determine brain death
* One neurologic examination is sufficient to pronounce death after irreversibility of brain insult is ascertained

**Brainstem reflexes**:

### Pupillary reflex absent

* The pupils are not reactive to bright light
* The pupils are fixed in a mid or dilated position (4–9 mm)
  + - Constricted pupils suggest the possibility of drug intoxication
    - Anisocoria is acceptable
    - Pitfall: Preexisting anatomic abnormalities of the iris (trauma) or effects of previous surgery can cause abnormality in size and nonreactive pupils and should be excluded
  + Corneal reflex absent
    - Demonstrated by touching the cornea with a piece of tissue paper, a cotton swab, or drops of water.
    - No eyelid movement should be seen

### Oculocephalic reflex absent

### Only one ocular reflex test required for brain death determination, but must have oculocephalic and/or oculovestibular documented for complete exam

* + - Testing is done only when no fracture or instability of the cervical spine is apparent
    - Review imaging to ensure integrity of c-spine
    - The oculocephalic reflex is elicited by fast and vigorous turning ofthe head from middle position to 90" on both sides and normally results in eye deviation to the opposite side of the head-turning. Vertical eye movements should be tested with brisk neck flexion
    - Eyelid opening and vertical and horizontal eye movements must be absent in brain death

### Oculovestibular reflex absent

* + - Confirm the patency of the external auditory canal and presence of intact tympanic membranes
    - The head is elevated to 30 degrees
    - Each external auditory canal is irrigated (one ear at a time) with approximately 50 mL of ice water. The investigator should allow up to **1** minute after injection. Movement of the eyes should be absent during 1 minute of continued observation with eyelids held open
    - Time between stimulation on each side should be at least **5** minutes
    - Pitfalls:
    - There are multiple drugs that can diminish or completely abolish the caloric response including: sedatives, aminoglycosides, tricyclic antidepressants, anticholinergics, antiepileptic drugs, and chemotherapeutic agents
    - After closed head injury or facial trauma, lid edema and chemosis of the conjunctiva may restrict movement of the globes
    - Clotted blood or cerumen may diminish the caloric response, and repeat testing is required after direct inspection of the tympanum
    - Basal fracture of the petrous bone abolishes the caloric response only unilaterally and may be identified by an ecchymotic mastoid process

### Facial movement to noxious stimuli absent

* + - Deep pressure on the condyles at the level of the temporomandibular joints and deep pressure at the supraorbital ridge should produce no grimacing or facial muscle movement.

### Gag reflex absent

* + - The pharyngeal or gag reflex is tested after stimulation of the posterior pharynx with a tongue blade or suction device or simply by movement of the endotracheal tube

### Cough reflex absent

* + - The suction catheter should be inserted into the trachea and advanced to the level of the carina followed by 1 or 2 suctioning passes

**Lack of responsiveness**

### Absence of motor response to noxious stimuli in all four limbs

### **Spinally mediated reflexes** are spontaneous movements seen in brain death and are more frequent in young adults and can include:

* + - Muscle stretch reflexes, superficial abdominal reflexes, and Babinski reflexes
    - Undulating toe flexor sign: Initial plantar flexion of the great toe followed by sequential brief plantar flexion of the second, third, fourth, and fifth toes after snapping of one **of** the toes
    - Rapid flexion in arms, raising of all limbs off the bed, grasping movements, spontaneous jerking of one leg, walking-like movements, and movements of the arms up to the point ofreaching the endotracheal tube (“Lazarus sign”)
    - Respiratory-like movements characterized by shoulder elevation and adduction, back arching, and intercostal expansion without any significant tidal volume.
    - Respiratory acidosis, hypoxia, or brisk neck flexion may generate spinal cord responses. They are usually absent with supraorbital compression
    - Hemodynamic responses such as profuse sweating, blushing, tachycardia, and sudden increases in blood pressure can also sometimes be elicited by neck flexion

**Apnea testing**

The estimated PaCO2 increase is from **3** to **6** mm Hg per minute varying with the rate of CO2 production.

### Prerequisites:

1) Normotension: SBP ≥ 100 mm Hg

2) Normothermia: Temp > 360 C

* + - Normal or near-normal core temperature is preferred during the apnea test, to avoid delayed increase in PaCO2 by ensuring optimal body metabolic rate

3) Eucapnia: PaCO2 35–40 mm Hg,

* + - Hypocarbia is common and should be corrected by changing the minute volume by decreasing either rate or tidal volume for several minutes
    - Normalize PCO2 as best as possible. Patients with a history of CO2 retention (COPD) can have apnea test but will fall under requirement of PCO2 increase by 20mmHg

4) Absence of hypoxia:

* PaO2 of >200mmHg is recommended but lower levels are acceptable as long as oxygen saturation can be maintained

5) Euvolemia:

* Even fluid balance recommended to assist in improved pulmonary function
  + - Procedure:
      * Adjust vasopressors to maintain a systolic blood pressure ≥100 mm Hg
      * Preoxygenate for at least 10 minutes with 100% oxygen. AAN recommends a goal PaO2 ≥200 mm Hg but not all patients can achieve this
      * Ensure PaCO2 is within range as above
      * Reduce positive end-expiratory pressure (PEEP) to 5 cm H2O. Desaturation with decreasing PEEP may suggest difficulty with apnea testing
      * If pulse oximetry oxygen saturation remains ≥95%, obtain a baseline arterial blood gas and record values along with time drawn
      * Disconnect the patient from the ventilator. The ventilator can cause artifactual findings by indicating respiratory drive of the patient and this phenomenon – caused by minimal pressure or volume changes in the breathing circuit – is commonly not recognized
      * Preserve oxygenation by placing an insufflation catheter through the endotracheal tube and close to the level of the carina and deliver 100% O2 at 6 L/min
      * Look closely for respiratory movements for 8–10 minutes. Respiration is defined as abdominal or chest excursions and may include a brief gasp
      * Abort if systolic blood pressure decreases to <90 mm Hg
      * Abort if oxygen saturation measured by pulse oximetry is <85% for >30 seconds. Attempt to get blood draw for ABG immediately before reconnecting to ventilator without compromising patient safety
      * Retry procedure with T-piece, CPAP 10 cm H2O, and 100% O2 12 L/min
      * If no respiratory drive is observed, repeat blood gas (PaO2, PaCO2, pH, bicarbonate, base excess) after approximately 8 minutes.

### Apnea test aborted (without blood draw before reconnecting to ventilator)

* + - * Abort if systolic blood pressure decreases to <90 mm Hg
      * Abort if oxygen saturation measured by pulse oximetry is <85% for >30 seconds
      * Retry procedure with T-piece, CPAP 10 cm H2O, and 100% O2 12 L/min

### Results:

* + - * **Positive apnea test** (supports diagnosis of brain death): Respiratory movements are absent and arterial PaCO2 is ≥60 mm Hg (or 20 mmHg increase in arterial PaCO2 over a baseline
      * **Negative apnea test** (refutes diagnosis of brain death): Respiratory movements are observed. The test should be repeated after a period of time
      * **Inconclusive** **results**: If no spontaneous respirations observed and PaCO2 <60 mmHg and the patient is hemodynamically stable during the procedure, it may be repeated with 10-15 minutes of apnea, after the patient is again adequately preoxygenated
      * **Indeterminate** **results** – If the apnea test was aborted due to marked hypotension, desaturation or cardiac arrhythmia and ABG could not be performed, it is at the discretion ofthe physician whether to repeat the test or to perform ancillary test, to finalize the clinical diagnosis of brain death
* Inconclusive assessment

If any component of brain death assessment is inconclusive, the physician has 2 options:

* + Repeat assessment: A repeat clinical evaluation 6 hours later is advised, interval is, however, arbitrary

OR

* + Ancillary testing as explained below

If any component of the exam cannot be performed (c-spine not cleared AND tympanic membranes not intact), ancillary testing is performed

* Ancillary testing
* Ancillary test is not mandatory in most situations. It is needed for patients in whom specific components of clinical testing cannot be reliably evaluated or if apnea testing is inconclusive or indeterminate
* Only one ancillary test needs to be performed for diagnosis
* Interpretation of each of these tests require expert consultation of respective field
* The following tests are preferred as ancillary test given availability of stronger evidence for their use:

|  |  |
| --- | --- |
|  | Results |
| Cerebral angiogram | • 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. |
| Cerebral blood flow testing | • 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 |
| EEG | • No electrical activity occurs above 2 µV  at a sensitivity of 2 µV/mm, with at least 30 min of EEG recording |
| Transcranial doppler | • Absent diastolic or reverberating flow indicated flow only during systole or retrograde diastolic flow |

* Insufficient data exists to support the use of CT angiography, MRI, MR angiography, or somatosensory evoked potentials for brain death determination, thus these are not currently considered acceptable ancillary tests
* Declaration
* Document the time of death in note
* Time of death is the time the arterial PaCO2 reached the target value OR when the ancillary test has been officially interpreted
* Inform family and contact an organ procurement organization following determination of brain death