Determining brain death in adults

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Overview. The Quality Standards Subcommittee of the American Academy of Neurology (AAN) is charged with developing guidelines for neurologists for diagnostic procedures, treatment modalities, and clinical disorders. The present document is intended to provide background for the report “Practice Parameters for Determining Brain Death in Adults” (in this issue), which has been produced by the Quality Standards Subcommittee of the AAN and approved by the AAN Executive Board. This document outlines diagnostic criteria for the clinical diagnosis of brain death in patients older than 18 years. The recommendations for diagnosis in neonates and children have been published as a position paper by the American Academy of Pediatrics; in addition, a review paper can be consulted. The sensitivity and specificity of laboratory tests that confirm the clinical diagnosis of brain death are discussed.

Justification. Brain death is seen frequently as a result of severe head injury, aneurysmal subarachnoid hemorrhage, and intracerebral hemorrhage. In medical and surgical intensive care units, large ischemic strokes associated with brain swelling and herniation, hypoxic-ischemic encephalopathy after prolonged cardiac resuscitation or asphyxia, and massive brain edema in patients with fulminating hepatic necrosis are the most common causes of brain death. In large referral hospitals, neurologists or neurosurgeons may diagnose brain death from 25 to 30 times a year.

The clinical diagnosis of brain death has never been easy for most physicians, including neurologists and neurosurgeons.

Brain death was selected as a topic for practice parameters because of a perceived need for standardized clinical examination criteria for the diagnosis of brain death in adults, large differences in practice in performing the apnea test, and controversies over appropriate utilization of confirmatory tests. In addition, government and third-party payers are demanding well-defined practice parameters in the clinical examination or confirmatory testing. New parameters are needed to add to the report of the medical consultants on the diagnosis of death submitted to the President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, published in 1981. The areas of need are as follows: 1. Unequivocal definition of clinical testing of brainstem function; 2. Description of conditions that may completely or partly mimic brain death; 3. Interpretation of clinical observations that are compatible with brain death but initially may suggest otherwise; 4. Clear description of apnea testing procedure; 5. Indications of confirmatory laboratory tests; 6. Validity and reproducibility of confirmatory laboratory tests; and 7. Initial practice guidelines for organ procurement.

Development of practice parameters. All literature pertaining to brain death was identified by MEDLINE for the years 1976 to 1994. Key words used were “brain death” and “apnea test” with the subheading “adult.” Peer-reviewed articles with original work were selected. Selection for this document was based on the quality of the original work. Current textbooks and handbooks of neurology, medicine, intensive care, pulmonology, and anesthesiology were reviewed for opinion. References were categorized as class I (well-designed clinical studies) or class III (case reports, uncontrolled studies, and expert opinion). (Class II or III studies are identified by a “II” or “III” in the list of references.) Class I studies (randomized clinical trials) were not available. The committee defined practice parameters as standards (generally accepted principles for patient management that reflect a high degree of clinical certainty); guidelines (recommendations for patient management that may identify a particular strategy and that reflect moderate clinical certainty); and options (strategies for patient management for which certainty is unclear). All suggestions in this document should be considered guidelines unless otherwise specified. Consensus was achieved by group discussion.

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Background. The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research\textsuperscript{15} defined “brain death” as irreversible cessation of all functions of the entire brain, including the brainstem. The clinical diagnosis of brain death is equivalent to irreversible loss of all brainstem function. Of particular importance in the clinical examination of patients who are brain-dead are (1) documentation of loss of consciousness, (2) no motor response to pain stimuli, (3) no brainstem reflexes, and (4) apnea. In the vast majority of patients, CT documents an abnormality that explains loss of brain and brainstem function. The clinical diagnosis of brain death should be in doubt in patients with normal CT or CSF findings. Nonetheless, occasional patients have an ischemic-anoxic insult to the brain that results in brain death without CT abnormality. In these patients, the clinical diagnosis of brain death should be made only if there is a high degree of certainty about the mechanism that led to brain death.

The diagnosis of brain death in patients with coma of undetermined origin is very complex. No studies have been reported that address this specific clinical dilemma. If a patient meets the clinical criteria, has a prolonged period of observation (>24 hours), and has no cerebral blood flow, and if confounding factors have been excluded, it is reasonable to make a diagnosis of brain death. Organ donation can be allowed if no transmittable disease (eg, rabies encephalitis) is present.

Confounding factors that mimic or partly mimic brain death should be excluded. First, hypothermia may blunt brainstem reflexes but only when rectal temperatures are below 32 °C. Brainstem reflexes have been absent in patients with rectal temperatures below 27 °C.\textsuperscript{16} It is not known whether patients with a major CNS catastrophe are susceptible at higher core temperatures. Second, drug intoxication should be excluded if the history is suggestive. In this situation, routine drug screens may be helpful but probably only when testing is requested for a specific drug or poison. The diagnosis of brain death most likely can be made when levels of barbiturates in the blood are subtherapeutic, although data in adults are sparse. In brain-dead children with therapeutic levels of barbiturates, no change in isoelectric EEGs was noted during decrease of barbiturates in the blood to subtherapeutic or undetectable levels.\textsuperscript{17} Third, the clinical diagnosis of brain death is probably not reliable in patients investigated at the time of an acute metabolic or endocrine derangement.\textsuperscript{15,19,20}

An important component of the clinical diagnosis of brain death is the demonstration of apnea. Misconceptions about the procedure are frequently encountered in clinical practice.\textsuperscript{11} Loss of brainstem function produces loss of breathing and vasomotor control that results in apnea and hypotension. Hypotension is frequently present at the time of the clinical diagnosis of brain death, but patients may have normal blood pressure despite fulfilling the clinical criteria of brain death.\textsuperscript{21}

The respiratory neurons are controlled by central chemoreceptors that sense changes in the P\textsubscript{CO\textsubscript{2}} and pH of the CSF, and these accurately reflect changes in plasma P\textsubscript{CO\textsubscript{2}}.\textsuperscript{22} There are many other mechanical and chemical stimuli and inhibitory influences on the respiratory neurons of the brainstem.

It is not known at what arterial P\textsubscript{CO\textsubscript{2}} level the chemoreceptors of the respiratory center are maximally stimulated in hyperoxegenated patients with brainstem destruction. Target arterial P\textsubscript{CO\textsubscript{2}} levels are derived from a small number of patients who had respiratory efforts after induction of hypercarbia but who otherwise fulfilled the criteria for the clinical diagnosis of brain death.\textsuperscript{21} The advisory guidelines for the determination of death submitted to the President’s Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research are based on these observations.\textsuperscript{16} That document recommends P\textsubscript{ACO\textsubscript{2}} levels greater than 60 mm Hg for maximal stimulation of the brainstem. Lower target levels have been suggested because four patients made effective normal breathing efforts at lower P\textsubscript{CO\textsubscript{2}} values (range, 30 to 37 mm Hg; mean, 34 mm Hg). At higher P\textsubscript{CO\textsubscript{2}} values (range, 41 to 51 mm Hg), respiratory-like movements have been observed.\textsuperscript{21} These movements are ineffective for ventilation and consist of shoulder elevation and adduction, back arching, and intercostal expansion. These respiratory-like efforts produce negligible tidal volumes and virtually no inspiratory force.\textsuperscript{21} Less reliable targets for P\textsubscript{CO\textsubscript{2}} may be obtained from anesthetized subjects (P\textsubscript{CO\textsubscript{2}} of 30 mm Hg)\textsuperscript{23,24} or in experiments with breath-holding (P\textsubscript{CO\textsubscript{2}} of 40 to 45 mm Hg).\textsuperscript{25,27}

The target P\textsubscript{CO\textsubscript{2}} levels of the apnea tests in brain death determination may be higher in patients with chronic hypercapnia. Typically, these patients have severe chronic obstructive pulmonary disease, bronchiectasis, sleep apnea, and morbid obesity.\textsuperscript{27,28} If metabolic acidosis is not present, chronic hypercarbia (“CO\textsubscript{2} retainers”) can be suspected in patients with high initial serum concentrations of bicarbonate. When initial arterial blood gas determination confirms chronic hypercarbia, additional noninvasive confirmatory tests are strongly encouraged.

Low arterial P\textsubscript{CO\textsubscript{2}} values can be expected in patients with acute catastrophic structural CNS damage. In many instances, hypocarbia is caused by high tidal volumes associated with mechanical ventilation, by hyperventilation instituted to decrease intracranial pressure, or by hypothermia. Hypocarbia can be corrected by changing the minute volume by decreasing either rate or tidal volume for several minutes. Correction of hypocarbia probably should not be done with CO\textsubscript{2} mixtures. Although administration of 5\% CO\textsubscript{2} in oxygen will elevate P\textsubscript{CO\textsubscript{2}} by 17.3 mm Hg in 1 to 2 minutes, this procedure may rapidly lead to severe hypercarbia and respiratory acidosis.\textsuperscript{24}
Apnea testing is easy with a starting arterial PCO₂ value of 40 mm Hg because the target level of 60 mm Hg is reached after 6 to 8 minutes of disconnection from the ventilator. The estimated PCO₂ increase is from 3 to 6 mm Hg per minute and varies with the rate of CO₂ production. Cardiac arrhythmias are side effects of hypercarbia and respiratory acidosis, occurring mostly in patients with hypoxia. The most common abnormalities are premature ventricular contractions and ventricular tachycardia. Severe hypotension (change in mean arterial blood pressure of more than 15%) has been observed in well-oxygenated patients in whom PCO₂ values reached very high levels (average, 90 mm Hg) from acidosis alone. Administration of 100% O₂ through a catheter placed at the level of the carina secures adequate oxygenation during apnea testing. A recent study of 70 apnea tests found no significant hypoxemia after previous oxygenation and placement of a catheter inside the endotracheal tube. Oxygenation may be inadequate, for example, in patients with severe pulmonary disease, acute respiratory distress syndrome, or neurogenic pulmonary edema.

The clinical diagnosis of brain death includes apnea with an arterial PCO₂ of 60 mm Hg. However, there have been only a few studies of the methods of testing, and the literature does not provide evidence to favor one method over the other.

**Clinical diagnosis of brain death.** Brain death is the absence of clinical brain function when the proximate cause is known and demonstrably irreversible. To overcome the possible pitfalls of making the diagnosis of brain death, the following prerequisites are proposed (figure 1): (1) there must be definite clinical or neuroimaging evidence of an acute CNS catastrophe that is compatible with brain death; (2) complicating medical conditions that may confound clinical assessment should be excluded (no severe electrolyte, severe acid-base, or severe endocrine disturbance); (3) drug intoxication or poisoning must be absent; and (4) core temperature must be at least 32 °C. Testing of brainstem function can proceed only after these precautions have been taken.

The three cardinal findings in brain death are coma or unresponsiveness, absence of brainstem reflexes, and apnea. The clinical examination of the brainstem includes testing of brainstem reflexes, determination of the patient's ability to breathe spontaneously, and evaluation of motor responses to pain.

**I. Coma or unresponsiveness**

A. Motor responses of the limbs

1. **Testing.** Motor responses of the limbs to painful stimuli should be absent after supraorbital pressure and nail-bed pressure stimulus.

2. **Pitfalls.** Motor responses ("Lazarus sign") may occur spontaneously during apnea testing, often during hypoxic or hypotensive episodes, and are of spinal origin. Neuromuscular blocking agents can produce prolonged weakness. If neuromuscular blocking agents have recently been administered, examination with a bedside peripheral nerve stimulator is needed. A train-of-four stimulus should result in four thumb twitches.

**II. Absence of brainstem reflexes**

A. Pupils

1. **Testing.** The response to bright light should be absent in both eyes. Round, oval, or irregularly shaped pupils are compatible with brain death. Most pupils in brain death are in middle position (4 to 6 mm), but the size of the pupils may vary from 4 to 9 mm. Dilated pupils are compatible with brain death because intact sympathetic cervical pathways connected with the radially arranged fibers of the dilator muscle may remain intact.

2. **Pitfalls.** Many drugs can influence pupil size, but light response remains intact. In conventional doses, atropine given intravenously has no marked influence on pupillary response. A report of fixed, dilated pupils after extremely high doses of dopamine has not been confirmed. Because nicotine receptors are absent in the iris, neuromuscular blocking drugs do not noticeably influence pupil size. Topical...
ocular instillation of drugs and trauma to the cornea or bulbous oculi may cause abnormalities in pupil size and can produce nonreactive pupils. Preexisting anatomic abnormalities of the iris or effects of previous surgery should be excluded.

B. Ocular movements

1. Testing. Ocular movements are absent after head-turning and caloric testing with ice water.4,5 (Testing is done only when no fracture or instability of the cervical spine is apparent, and in patients with head injury, the cervical spine must be imaged to exclude potential fractures or instability or both.) The oculocephalic reflex, elicited by fast and vigorous turning of the head from middle position to 90° on both sides, 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.

Caloric testing should be done with the head elevated to 30° during irrigation of the tympanum on each side with 50 ml of ice water. Tympanum irrigation can be best accomplished by inserting a small suction catheter into the external auditory canal and connecting it to a 50-ml syringe filled with ice water. Tonic deviation of the eyes directed to the cold caloric stimulus is absent. The investigator should allow up to 1 minute after injection, and the time between stimulation on each side should be at least 5 minutes.

2. Pitfalls. Drugs that can diminish or completely abolish the caloric response are sedatives, aminoglycosides, tricyclic antidepressants, anticholinergics, antiepileptic drugs, and chemotherapeutic agents.41,42 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.

C. Facial sensation and facial motor response

1. Testing. Corneal reflexes should be tested with a throat swab. Corneal reflex and jaw reflex should be absent. Grimacing to pain can be tested by applying deep pressure with a blunt object on the nail beds, pressure on the supraorbital ridge, or deep pressure on both condyles at the level of the temporomandibular joint.

2. Pitfall. Severe facial trauma may limit interpretation of all brainstem reflexes.

D. Pharyngeal and tracheal reflexes

1. Testing. The gag response, tested by stimulation of the posterior pharynx with a tongue blade, should be absent. Lack of cough response to bronchial suctioning should be demonstrated.

2. Pitfall. In orally intubated patients, the gag response may be difficult to interpret.

III. Apnea

A. Apnea test (guidelines for testing)

1. Prerequisites (figure 2). Important changes in vital signs (eg, marked hypotension, severe cardiac arrhythmias) during the apnea test may be related to lack of adequate precautions, although they may occur spontaneously during increasing acidosis. Therefore, the following prerequisites are suggested: (1) core temperature greater than or equal to 36.5 °C (4.5 °C higher than the required 32 °C for clinical diagnosis of brain death), (2) systolic blood pressure greater than or equal to 90 mm Hg, (3) euvolemia (option: preferably positive fluid balance in the previous 6 hours), (4) eucapnia (option: arterial Pco2 greater than or equal to 40 mm Hg), and (5) normoxemia (option: arterial Po2 greater than or equal to 200 mm Hg). A pulse oximeter is connected to the patient.

2. Testing (figure 3)

- Disconnect the ventilator.
- Deliver 100% O2, 6 l/min. Option: place a cannula at the level of the carina.
- Look closely for respiratory movements. Respiration is defined as abdominal or chest excursions that produce adequate tidal volumes. If present, respiration can be expected early in the apnea test. When respiratory-like movements occur, they can be expected at the end of the apnea test, when oxygenation may become marginal. When the result is in doubt, a spirometer can be connected to the patient to confirm that tidal volumes are absent.

Figure 2. Prerequisites for the apnea test in brain death. COPD = chronic obstructive pulmonary disease.
Figure 3. Procedure for the apnea test in brain death.

- Measure arterial $\text{PO}_2$, $\text{PCO}_2$, and pH after approximately 8 minutes and reconnect the ventilator.
- If respiratory movements are absent and arterial $\text{PCO}_2$ is equal to or greater than 60 mm Hg (option: 20 mm Hg increase in $\text{PCO}_2$ over a baseline normal $\text{PCO}_2$), the apnea test result is positive (ie, it supports the clinical diagnosis of brain death).
- If respiratory movements are observed, the apnea test result is negative (ie, it does not support the clinical diagnosis of brain death), and the test should be repeated.
- If, during apnea testing, the systolic blood pressure becomes ≤90 mm Hg, the pulse oximeter indicates marked desaturation, and cardiac arrhythmias occur, immediately draw a sample, connect the ventilator, and analyze arterial blood gas. The apnea test result is positive if arterial $\text{PCO}_2$ is greater than or equal to 60 mm Hg or $\text{PCO}_2$ increase is equal to or greater than 20 mm Hg above baseline normal $\text{PCO}_2$. If arterial $\text{PCO}_2$ is less than 60 mm Hg or $\text{PCO}_2$ increase is less than 20 mm Hg over baseline normal $\text{PCO}_2$, the result is indeterminate. In this situation of cardiovascular instability together with uncertainty about the upper limit of $\text{PCO}_2$ at which maximal stimulation of the respiratory center occurs, it is left to the discretion of the physician whether a confirmatory test is needed to finalize the clinical diagnosis of brain death.
- If no respiratory movements are observed, $\text{PCO}_2$ is less than 60 mm Hg, and no significant cardiac arrhythmia or hypotension is observed, the test may be repeated with 10 minutes of apnea.

Clinical observations compatible with the diagnosis of brain death. Respiratory acidosis, hypoxia, or brisk neck flexion may generate spinal cord responses. Conventional angiography.

Spontaneous movements of the limbs from spinal mechanisms can occasionally occur and are more frequent in young adults. These spinal reflexes include 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 of reaching the endotracheal tube. Respiratory-like movements may also occur and are typical agonal breathing patterns. They are characterized by shoulder elevation and adduction, back arching, and intercostal expansion without any significant tidal volume.

Other responses are profuse sweating, blushing, tachycardia, and sudden increases in blood pressure. Normal blood pressure and absence of diabetes insipidus without pharmacologic support are compatible with brain death. Muscle stretch reflexes, superficial abdominal reflexes, and Babinski reflexes are of spinal origin and do not invalidate a diagnosis of brain death. Patients may have 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 ("undulating toe flexion sign").

Confirmatory laboratory tests. Brain death is a clinical diagnosis. A repeat clinical evaluation 6 hours later is advised (option), but a firm recommendation cannot be given and the interval is arbitrary. A confirmatory test is not mandatory in most situations. All clinical tests are needed to declare brain death and are likely equally essential. Conventional angiography is limited. Many studies did not use blind assessment of the results, did not assess interobserver variation, and did not perform tests in control subjects. In addition, many tests need costly equipment and well-trained technicians. Conventional angiography tests that are generally accepted are conventional angiography and EEG. Consensus criteria are reported only for EEG and somatosensory evoked potentials. The Therapeutics and Technology Assessment Subcommittee of the AAN has accepted transcranial Doppler ultrasonography and conventional angiography as a reliable procedure for confirmation of brain death. Conventional angiography.

Technique. A selective four-vessel angiogram is done in the radiology suite. Iodinated contrast medium is injected under high pressure in both the anterior and the posterior circulations. The proce-
dure takes a few hours.

Result. Intracerebral filling is absent at the level of the carotid bifurcation or circle of Willis. The external carotid circulation is patent, and at times delayed filling of the superior longitudinal sinus is seen.

Validity. Interobserver studies have not been published. The procedure has the potential to yield conflicting results because no guidelines for interpretation have been developed.

Disadvantages. Repeated contrast injections may increase the risk of nephrotoxicity and decrease the acceptance rate in organ recipients, but in general do not result in refusal of kidney donation.

Electroencephalography. 47,55-62

Technique. Usually a 16- or 18-channel instrument is used with guidelines developed by the American Electroencephalographic Society for recording brain death.47,55

Result. No electrical activity occurs above 2 µV at a sensitivity of 2 µV/mm with filter setting at 0.1 or 0.3 second and 70 Hz. Recording should continue for at least 30 minutes.

Validity. Most patients meeting the clinical criteria for brain death have isoelectric EEGs. Nevertheless, in one consecutive series of patients fulfilling the clinical diagnosis of brain death, 20% of 56 patients had residual EEG activity that lasted up to 168 hours.50

Disadvantage. Considerable artifacts in the intensive care unit can limit interpretation.52

Isotope angiography. 83-65

Technique. Rapid intravenous injection of serum albumin labeled with technetium 99m is followed by bedside imaging with a portable gamma camera.

Result. Intracranial radioisotope activity is absent. Filling of sagittal and transverse sinuses may occur in delayed images from connections between the extracranial circulation and the venous system.

Validity. The sensitivity and specificity of lack of intracranial radioisotopes have not been defined in adults.

Disadvantage. The posterior cerebral circulation is not visualized.

Technetium-99m hexamethylpropyleneamine oxide (99mTc-HMPAO). 66-69

Technique. The procedure can be performed at the bedside and takes approximately 15 minutes. The isotope should be injected within 30 minutes of reconstitution. A portable gamma camera produces planar views within 5 to 10 minutes. Correct intravenous injection can be checked by taking additional chest and abdominal images.

Result. No uptake occurs in the brain parenchyma.

Validity. Experience with this technique is limited. Sensitivity of the brainstem has been reported to be as low as 94% with a specificity of 100%.66 Reproducibility has been tested in only a few patients. In one study, a correlation between cerebral an-
and absence of somatosensory evoked potentials beyond Erb's point were unique in patients with brain death and not found in comatose patients who still had preserved brainstem function. This study has not been confirmed or refuted.

**Miscellaneous tests.** Many of these tests have been done in small series of patients only and are not widely adopted as confirmatory tests. Contrast CT with a bolus of meglumine diatrizoate, 1 ml/kg of body weight, followed by drip infusion of 0.02 ml/kg per minute, does not visualize intracranial vessels.\(^{57-60}\) A good correlation with cerebral angiography has been demonstrated in a few anecdotal reports.\(^{69}\)

Many other confirmatory tests are variants or modifications. Experience is limited, or these tests produce similar results in patients with neurologic catastrophes who do not fulfill the clinical criteria for brain death.

**Recommendations after the diagnosis of brain death.** It is prudent to discuss organ donation with family members only after the clinical diagnosis of brain death. The following approach is suggested. The family should be told in unequivocal terms that the patient died. Mechanical ventilation, fluids, and blood pressure medication are administered only to procure organs in the event that permission for donation is given. Refusal by family members to harvest organs removes the rationale for supportive therapy, and mechanical ventilation is discontinued after the family has been allowed adequate time for consideration and visitation. When the family permits organ procurement, a local transplantation coordinator is notified.

Management of a brain-dead patient in preparation for donation is complicated, and advice from a neurologist specialized in neurologic critical care or from an anesthesiologist should be strongly considered.\(^{91,94}\)

Major immediate threats to organs are (1) pulmonary edema, requiring pulmonary artery catheter placement and treatment with positive end-expiratory pressure ventilation, (2) hypotension, requiring adequate fluid resuscitation and vasopressors (dopamine to 10 \( \mu \)g/kg per millimeter), (3) polyuria from diabetes insipidus,\(^{95}\) requiring 1-desamino-8-d-arginine vasopressin (1 to 4 \( \mu \)g) or desmopressin (0.5 to 2 \( \mu \)g) intravenously every 8 hours and guidance by urine output. Use of hormone substitution and prophylactic administration of antibiotics is controversial.\(^{91,94}\)

**Recommendation for future research.** Data on apnea testing are incomplete, and careful evaluation of respiratory efforts and the level of \( \text{PCO}_2 \) at which apnea occurs is necessary. Confirmatory test results need to be valid.

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