Brain Death

Last updated: May 8, 2019

Diagnosing brain death must never be rushed or take priority over the needs of the patient or the family

**Brain Death (BD)** - neither *cerebrum nor* brain stem is functioning.*

*single exception is osmolar control* - some patients develop diabetes insipidus only after clinical signs of brain death (i.e. diabetes insipidus is not required for BD diagnosis).

- the only spontaneous activity is cardiovascular (apnea persists in presence of hypercarbia sufficient for respiratory drive); pulse rate is invariant and unresponsive to atropine!
- the only reflexes present are spinal; muscles show generalized flaccidity and no movement (except spinal reflexes to pain).
  - N.B. presence of seizures is not compatible with BD diagnosis!
  - N.B. presence of any face / tongue movement is not compatible with BD diagnosis!
  - N.B. complex-spontaneous motor movements and false-positive triggering of ventilator may occur in patients who are brain dead!

- BD rarely lasts more than few days (always followed by circulatory collapse* even if ventilatory support is continued); mean = 4 days.
  - *progressive hypotension that becomes increasingly unresponsive to catecholamines
- recovery has never been reported!
- in USA, BD = legal death (i.e. death by brain criteria*)
  - vs. somatic criteria (irreversible cessation of cardiopulmonary function)

Somadic death precludes function of brain. The opposite is true as well, so death of organism can be determined on basis of brain death.

There is no explicit reason to make diagnosis of brain death except when organ transplantation or difficult resource-allocation (intensive care) issues are involved. ethical issues – see p. 4667 >>

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**CRITERIA FOR BRAIN DEATH**

although some details may be dictated by local law, standard criteria are established by President's Commission report of 1981.

Clinical examination is performed by two different physicians (for children - attending physicians)

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<td>1.</td>
<td>Coma, unresponsive to stimuli (incl. painful) above foramen magnum.</td>
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<td>2.</td>
<td>PERMISSIVE DIAGNOSIS - structural disease or irreversible metabolic disturbance</td>
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<td>1) Body temperature &gt; 34°C.</td>
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<td>2) Systemic circulation may be intact.</td>
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3) Serum **electrolytes** must be WNL + no known **endocrine** disturbances + **absence of drug intoxication** (incl. ethanol, sedatives, potentially anesthetizing or paralyzing drugs).

HYPOTENSION, HYPOTHERMIA, and METABOLIC DISTURBANCES should be corrected!

Pentobarbital level should be < 10

4. **ADULTS**
   - known **structural** cause – at least 6 hours observation (absent brain function)
   - others (incl. anoxic-ischemic brain damage) – at least 24 hours observation

**CHILDREN**
   - < 7 days of age or prematures – BD diagnosis inappropriate (i.e. wait until age 7 days)
   - 7 ÷ 30 days – observation at least 24 hours
   - older children – observation at least 12 hours (24 hours if anoxic-ischemic brain damage)

Child's brain is more resilient - more difficult determination of BD!

5. **Absence of cephalic reflexes**, incl. pupillary, corneal, oculocephalic, oculo-vestibular (caloric), gag, sucking, swallowing, cough, stereotyped posturing.

   Decorticate or decerebrate posturing is not compatible with BD diagnosis!

   Purely spinal reflexes may be present (incl. tendon reflexes, plantar responses, limb flexion to noxious stimuli, tonic neck reflexes).

6. **Apnea off ventilator** (with ongoing oxygenation) for duration sufficient to produce hypercarbic respiratory drive (usually 10-20 min to achieve $\text{Paco}_2 \geq 60 \text{ mmHg}$).

7. **Optional confirmatory studies**:
   1. EEG - isoelectric for 30 minutes at maximal gain.
   2. Absent brain stem **evoked responses**.
   3. Absent **cerebral circulation** demonstrated by radiographic / radioisotope / MR angiography.

- assessment of BD after **cardiopulmonary resuscitation** or other severe acute brain injuries must be deferred for 24 hours if there are concerns or inconsistencies in the examination.
  - when death results from criminal assault, or there is possibility of litigation regarding death, extra care must be taken and **legal counsel** may be advisable before making determination of brain death.

**First stage** - demonstrate **DEEP UNRESPONSIVE COMA** with apnea* and **no response to painful CENTRAL stimuli** (*PERIPHERAL stimuli* may elicit spinal reflex movements and may confuse family).

*always first check if patient is triggering the ventilator = “breathing over the vent” (i.e. real f > ventilator set f)

- **spinal cord mediated reflex movements** (flexor plantar reflexes, flexor withdrawal, muscle stretch reflexes, and even abdominal and cremasteric reflexes) can be compatible with brain death, and may occasionally consist of complex movements, including bringing one or both arms up to face, or sitting up (*"Lazarus" sign*) especially with hypoxemia (thought to be due to spinal cord ischemia stimulating surviving motor neurons in upper cervical cord).

  N.B. if complex integrated motor movements occur, it is recommended that confirmatory testing be performed prior to pronouncement of brain death

**Second stage** - demonstrate **PERMISSIVE DIAGNOSIS**; i.e. there must be **diagnosis adequate to explain death of brain** (including brain stem!).

- this **need not be ETIOLOGICAL diagnosis** (e.g. massive intracerebral hemorrhage qualifies as permissive diagnosis, even if etiology of hemorrhage is unknown).

- this **does not require demonstration of ANATOMICAL lesion** (e.g. history of prolonged anoxia would suffice).

- this **requires documentation of IRREVERSIBILITY**.
Exclusion criteria (irreversibility and BD cannot be determined): 1) sedative drugs, 2) hypothermia (< 32.2°C), 3) shock (MAP < 55 or SBP < 90), 4) neuromuscular blockade.

- below 32.2°C (90° F), pupils may be fixed and dilated, respirations may be difficult to detect, and recovery is possible!
- shock (SBP < 90 mmHg) and anoxia can produce lethargy.
- immediately post-resuscitation: shock or anoxia may cause fixed and dilated pupils; atropine may cause slight dilatation but not unreactivity
  N.B. neuromuscular blockage (e.g. for intubation) does not affect pupils because iris lacks nicotinic receptors
- should be no evidence of remediable exogenous or endogenous intoxication, including drug or metabolic (barbiturates, benzodiazepines, mempamabote, methaqualone, trichloroethylene, paralytics, hepatic encephalopathy, hyperosmolar coma ...).
  N.B. for patients coming out of pentobarbital coma, wait until level < 10 mcg/mL
- pseudocholinesterase deficiency (prevalence 1/3000) can cause succinylcholine to last up to 8 hours (instead of 5 mins); H: twitch monitor can rule-out NMB (place electrodes immediately behind eye or across zygomatic arch)

Third stage - demonstrate no detectable function above level foramen magnum:
midbrain – absent pupillary light reflex (most easily assessed by bright light of ophthamoscope); unreacitive pupils may be either at midposition (as they will be in death) or dilated (in setting of dopamine infusion); pupils should not be constricted!
pons:
  1) absent corneal reflex - eye closing to corneal (not scleral) stimulation
  2) no inducible eye movements:
     a) absent doll’s eyes (contraindicated if C-spine not cleared)
        OR
     b) absent oculovestibular reflex (cold water calorics): instill 60-100 ml ice water into one ear (do not do if TM perforated) with HOB at 30° - wait at least 1 minute for response, and 5 min before testing the opposite side.
        Brain death is excluded if any eye movement is noted!
medulla:
  1) absent oropharyngeal (gag) reflex to stimulation of posterior pharynx
  2) absent cough reflex, i.e. no cough response to bronchial suctioning
  3) apnea test (last test to perform! - elevating PaCO₂, increases ICP which could precipitate herniation and vasomotor instability)

Fourth stage - period of observation with sequential testing; recommended observation periods during which time the patient fulfills criteria of clinical brain death before the patient may be pronounced dead:
  N.B. there is insufficient evidence to determine minimally acceptable observation period to ensure that neurologic functions have ceased irreversibly!
  1) well established overwhelming brain damage from an irreversible condition (e.g. massive intracerebral hemorrhage), some experts will pronounce death following a single valid brain death exam in conjunction with a clinical confirmatory test.
  2) well established irreversible condition and clinical confirmatory tests are used: 6 hours.
  3) well established irreversible condition and no clinical confirmatory tests are used: 12 hours
  4) if diagnosis is uncertain and no clinical confirmatory tests: 12-24 hours
  5) if anoxic injury is cause of brain death: 24 hours (may be shortened if cessation of CBF is demonstrated)
• when BD criteria are met, it is legal time of death – *artificial ventilation* and *blood pressure support* are no longer an option (unless organ harvesting is intended).
  – if BD patient is maintained on mechanical ventilation, *brain gradually undergoes autolytic process*. 
  – removal of ventilator results in *terminal rhythms* (most often complete heart block without ventricular response, junctional rhythms, or ventricular tachycardia). 
  – *purely spinal motor movements* may occur in moments of terminal apnea: back arching, neck turning, leg stiffening, upper extremity flexion.

N.B. BD diagnosis is made primarily by clinical methods!

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**APNEA TEST (s. APNEA CHALLENGE)**

- observing *brain stem response to hypercapnia* without producing hypoxemia.

- although acidosis, rather than hypercapnia, is real afferent trigger for ventilation, \( \text{PaCO}_2 \geq 60 \text{ mmHg} \) (50 mmHg in United Kingdom) is usually endpoint for this test.
  
  Additional requirement for *children*, \( \text{PaCO}_2 \geq 20 \text{ mmHg above the baseline} \)

- in order to prevent hypoxemia (→ arrhythmias, MI):
  – *preapneic oxygenation* (15 minutes of 100% \( \text{O}_2 \) ventilation) is required before starting test; also adjust ventilator to bring \( \text{PaCO}_2 \) to 40 mmHg (to shorten test time and thus reduce risk of hypoxemia).
  – during the test - *supplemental oxygen by diffusion*:
    a) 100% \( \text{O}_2 \) flow administered at 6* L/min through either *pediatric oxygen cannula* or 14 F *tracheal suction catheter* (with side port covered with adhesive tape) passed to estimated level of carina
    *N.B. too high flow may wash out \( \text{CO}_2 \) and it might be difficult to achieve \( \text{PaCO}_2 \geq 60 \text{ mmHg} \)
    b) *continuous positive airway pressure* (CPAP) with 10 cmH\( \text{O}_2 \) pressure - does not provide ventilation, so it does not interfere with observation for spontaneous respirations.

N.B. some patients with cardiorespiratory dysfunction still may not tolerate \( \approx 10 \) minutes of apnea (necessary to raise \( \text{PaCO}_2 \) to 60 mmHg) without becoming hypoxemic & hypotensive → take blood gases sample and stop apnea test → perform **CONFIRMATORY TEST** (see below) instead.

- in absence of ventilation, \( \text{PaCO}_2 \) passively rises 3 mmHg/min;
  – although it may be possible to predict this point by following trend in end-tidal \( \text{CO}_2 \) (Pet\( \text{CO}_2 \)) measurements, there is enough discrepancy between arterial blood \( \text{PaCO}_2 \) and Pet\( \text{CO}_2 \) to indicate use of arterial measurement.
  – starting from normocapnia, average time to reach \( \text{Paco}_2 \) 60 mmHg is 6 minutes (sometimes as long as 12 minutes may be necessary)

- *visual observation* is standard method for detecting respiratory movement; this may be supplemented by airway pressure monitoring.

- **test is aborted prematurely if:**
  a) patient breathes - incompatible with brain death
  b) significant hypotension occurs
  c) if \( \text{O}_2 \) saturation drops below 80% (on pulse oximeter)
  d) significant cardiac arrhythmias occur

- if apnea test cannot be safely completed, ancillary study should be performed. *see below*

- \( \text{PaCO}_2 \) 60 mmHg will adequately stimulate ventilatory drive within 120 seconds in functioning brain;
- if patient remains **apneic ≥ 2 minutes despite PaCO₂ 60 mmHg**, diagnosis of apnea is confirmed.
- any respiratory movement negates diagnosis of apnea.
- not valid with severe COPD or CHF

### ANCILLARY STUDIES

**Indicated if:**

a) patient is *unable to tolerate apnea test*.
b) some *portion of examination cannot be performed* (e.g. face too swollen to examine eyes, slowly cleared barbiturates present in blood).

- usually indicated *only for potential organ donors*, because there is no requirement that death be diagnosed in order to withdraw supportive measures, but at times may be helpful for patient's family (it is commonly accepted that respirator can be disconnected from brain-dead patient, but problems may arise because of inadequate explanation and preparation of family by physician).

**EEG**

- **electrocerebral silence (ECS)**

example – EEG in brain-dead patient following attempted resuscitation after cardiopulmonary arrest:
N.B. EEG is prone to false-positive (e.g. artifacts that cannot be distinguished from cerebral activity with certainty) and false-negative (due to hypothermia, shock or hypnosedative drug intoxication) results.

- **residual EEG activity** (alpha coma-like activity, low-voltage fast waves, sleep-like slowing with spindle activity) may persist for some days following brain death.
- some guidelines require EEG confirmation of brain death in children < 1 yr of age.
- EEG does not detect brainstem activity.
- ECS does exclude reversible coma - at least 6 hours observation is recommended in conjunction with ECS.
- definition of ECS on EEG: no electrical activity > 2 µV with the following requirements:
  - recording from scalp or referential electrode pairs ≥ 10 cm apart
  - 8 scalp electrodes and ear lobe reference electrodes
  - inter-electrode resistance < 10,000 ohms (or impedance < 6,000 ohms) but over 100 ohms
  - sensitivity of 2 µV/mm
  - time constants 0.3-0.4 sec for part of recording
  - no response to stimuli (pain, noise, light)
  - record > 30 mins
  - repeat EEG in doubtful cases
  - qualified technologist and electroencephalographer with ICU EEG experience
  - telephone transmission not permissible

**EvoKed ResPonSeS**

1. **BAER** - absent (apart from wave I and early part of wave II, which are generated peripherally);
   - in many patients with suspected BD, however, all BAER components (incl. wave I) are absent
   - not possible to exclude other causes (such as technical factors of deafness) for absent response.

2. Bilateral absence of all **somatosensory evoked responses** later than N13-N14 is supportive of brain death.

**Tests of Cerebral Perfusion**
- most definitive confirmatory tests!!! (in some countries, used as indication for terminating life-support).
- **blood does not flow intracranially** above foramen magnum* (static column of contrast medium)
  * absence of intracranial flow at level of carotid bifurcation or circle of Willis; filling of superior sagittal sinus may occur in delayed fashion
- some conditions may mimic this pattern: arterial dissection, embolic / arteritic occlusion just beyond ophthalmic artery, severe catheter-induced spasm, subintimal injection.

1. **Conventional contrast four-vessel angiography**

2. **Cerebral Radionuclide Angiogram (CRAG)**
   - can be performed at the bedside with a general purpose scintillation camera with low energy collimator.
   - may not detect minimal blood flow to the brain, especially brainstem, therefore 6 hours observation in conjunction with CRAG is recommended unless there is a clear etiology of overwhelming brain injury (e.g. massive hemorrhage or GSW).
   - indications:
     1) where complicating conditions are present, e.g. hypothermia, hypotension (shock), drug intoxication, severe facial trauma where ocular findings may be difficult or confusing
2) severe COPD or CHF where apnea testing may not be valid
3) to shorten observation period, especially when organ donation is a possibility

- technique:
  o scintillation camera is positioned for an AP head and neck view
  o inject 20-30 mCi of 99mTc-labeled serum albumin or pertechnetate in a volume of 0.5-1.5 ml into a proximal IV port, or a central line, followed by a 30 ml NS flush
  o perform serial dynamic images at 2 second intervals for 60 seconds, then obtain static images with 400,000 counts in AP and then lateral views at 5, 15 & 30 minutes after injection
  o if a study needs to be repeated because of a previous non-diagnostic study or a previous exam incompatible with brain death, a period of 12 hours should lapse.

- findings:
  o no uptake in brain parenchyma = "hollow skull phenomenon":
    
    ![Image of brain scan]
    
    o termination of carotid circulation at skull base, and lack of uptake in ACA and MCA distributions (absent "candelabra effect").
    o there may be delayed or faint visualization of dural venous sinuses even with brain death due to connections between extracranial circulation and venous system.

3. In some areas, **transcranial Doppler** blood flow velocity measurements are considered adequate.
   - small peaks in early systole without diastolic flow or reverberating flow (indicative of significantly increased ICP).
   - initial absence of doppler signals cannot be used as criteria for brain death since 10% of patients do not have temporal insonation windows.

**ATROPINE**
- in brain death, *1 amp of atropine (1 mg) IV should not affect heart rate due to absence of vagal tone* (normal response to atropine of increased heart rate rules out brain death, but absence of response is not helpful since some conditions such as Guillain-Barre may blunt response).
- systemic atropine in usual doses causes slight pupillary dilatation, but does not eliminate reaction to light (therefore, to eliminate uncertainty, examine pupils before giving atropine).

**CARE OF ORGAN DONOR**
- once brain death occurs, cardiovascular instability eventually ensues, generally within 3-5 days - management with pressors is required.
- fluid and electrolyte imbalances from loss of hypothalamic regulation must be normalized.
- in some instances a beating-heart cadaver can be maintained for months
Hypotension and urinary output control:

1. Control hypotension through volume expansion whenever possible (after brain death, ADH production ceases, producing diabetes insipidus with high urine output, thus copious fluid administration is anticipated (> 250-500 ml/hr is common). Most centers prefer AVOIDING exogenous ADH (risk of renal shutdown)
   - start with D5 - 1/4 NS + 20 mEq KCl/L (replaces free water) “replace urine cc for cc plus 100 cc/hr maintenance”
   - use colloid (FFP, albumin) if unable to maintain BP by replacement.

2. Vasopressors if still hypotensive:
   - start with low dose dopamine, increase up to 10 µg/kg/min, add dobutamine if still hypotensive at this dosage

3. If UO is still > 300 ml/hr after above measures, use ADH analog
   N.B. aqueous vasopressin (Pitressin®) is preferred over DDAVP to avoid renal shutdown!

4. Thyroglobulin IV converts some cells from anaerobic to aerobic metabolism - may help stave off cardiovascular collapse.

### 13.3.1. Criteria for qualification for organ donation

**General exclusionary criteria for organ donation** (modified)

1. infection
   - A. untreated septicemia
   - B. the following infections or conditions: AIDS, viral hepatitis, viral encephalitis, Guillain-Barré syndrome
   - C. current IV drug abuse
   - D. active TB
2. malignancy; brain tumors represent possible exceptions (see below)
3. relative exclusions: chronic untreated HTN, hypotension (desired SBP > 100 with normal CVP)
4. disease of the organs considered for donation
5. anencephalic newborns: recent consensus is that the functioning brainstem in these infants (e.g. spontaneous respirations) disqualifies them from the diagnosis of brain death (furthermore, few such organs would likely benefit others)

**Guidelines for inclusion** (some recommendations from reference included)

These guidelines are constantly being revised, in part due to improved results with the use of cyclosporin in recipients. In general, consultation with a transplant coordinator is recommended to determine appropriateness of donation.

1. brain death or cardiac death
2. organs:
   - A. kidneys: age > 6 mos (because of size). Normal blood pressure, BUN, serum creatinine & UA. No SLE (because of possible lupus nephritis)
   - B. heart and heart/lung: age ideally < 40 years for males and < 45 for females (above these ages, a cardiac cath is usually performed) but up to 60 yrs may be used depending on condition of heart and potential recipients. Exam by cardiologist indicating no heart disease (cardiomyopathy, valve defect, reduced ejection fraction, severe ASHD, S/P CABG). No IDDM
   - C. liver: age > 1 mos. Normal hepatic function (normal or acceptable AST, ALT, LDH, bilirubin (direct, indirect & total) and normal clotting studies) with no history of liver disease
3. tissues:
   - A. corneas: age ≥ 1 yr. Neither cancer nor sepsis disqualifies (rabies and Creutzfeldt-Jakob disease are contraindications)
   - B. skin: age 15-65 yrs. Excluded if cancer
   - C. bone: age 15-65 yrs. Excluded if cancer
   - D. bone marrow: age ≤ 50 yrs
   - E. heart valves: age ≤ 55 yrs
13.3.2. Organ donation in patients with brain tumors

Among patients with a brain tumor:
1. those that are not candidates for organ donation:
   A. metastatic tumors to the brain
   B. brain tumors that have been manipulated (biopsied or excised)
   C. patients with brain tumors who have been shunted
2. those that might be candidates, but considered high-risk donors\(^A\) include unmanipulated:
   A. glioblastoma
   B. anaplastic astrocytoma
   C. medulloblastoma
3. unmanipulated tumors that might not be considered high risk
   A. hemangioblastoma
   B. meningioma

Optimally, if no metastases are seen on CT (chest, abdomen and pelvis) and no mets are found at time of organ procurement, a brain biopsy would be performed after the organs are procured at the same anesthetic and the organs would not be “released” until the biopsy proves which of the above categories applies.

LABORATORY EVALUATION \(^{37}\)

General initial labs
1. serology: VDRL or RPR, HBsAg, HIV, CMV, ABO blood group, HLA tissue type
2. chemistry: electrolytes, glucose, BUN, creatinine, calcium, phosphate, liver function tests, UA (urine analysis)
3. hematology: CBC, PT/PTT
4. microbiology: blood, urine and sputum cultures; sputum Gram stain

Kidney donor
1. in addition to general labs (see above), check BUN & creatinine \(= q\) day
2. check electrolytes \(= q 12\) hrs (modify as appropriate)

Liver donor
1. in addition to general labs (see above), check LDH, AST, ALT, bilirubin (direct, indirect, and total)

Heart donor
1. all require an echocardiogram prior to donation

ORGAN DONATION AFTER CARDIAC DEATH
13.3.4. **Organ donation after cardiac death**

**Key concepts:**
- candidates: ventilator dependent patients (typically with brain or spinal cord injury) who are so near death that further care is futile
- consent from legal next of kin for: organ donation, heparin, and femoral lines
- clearance from medical examiner when applicable (usually unnatural death)
- counsel the family that the procedure cannot be done in ~ 20%. They are to be notified immediately if this happens and end-of-life care resumes
- transplant team cannot participate in end-of-life care, declaration of death, and should not be in O.R. until after cardiac death is declared

Covered in this section because of relevance to organ donation.

Candidates for organ donation after cardiac death are typically ventilator dependent patients with brain or spinal cord injuries who are so near death that further treatment is futile, but who do not meet brain death criteria. Organs typically recovered in this manner: kidneys, liver, pancreas, lungs, and rarely the heart. Ethical concerns related to this practice have been raised. Cardiology consultation may help determine the likelihood that cardiac death will follow extubation in a timeframe consistent with organ procurement.

**Consent**

Consent for withdrawal of care and procurement of organs must be obtained from the legal next of kin (which may be a family member, designated health care representative or health care surrogate). Consent must also be obtained for any donation-related procedures prior to death (which typically includes heparin infusion to prolong organ viability and the possibility of femoral catheters).

Clearance from the medical examiner must be obtained in applicable cases (including deaths due to accident, homicide, suicide...).

**Procedure**

Life sustaining measures are then discontinued (typically consisting of extubation) usually in the operating room. Death is pronounced typically ~ 2 minutes after cardiac activity becomes insufficient to generate a pulse, because limited data indicates that circulation will not spontaneously return (NB: EKG activity does not need to cease). After declaration of death, cold perfusion of organs is performed and they are procured.

To avoid potential conflicts of interest, no member of the transplant team can participate in end-of-life care nor the declaration of death. About 20% of the time, the progression to cardiac death does not occur in a timeframe that permits organ retrieval. In these cases, organ donation is cancelled, the family must be immediately notified, and end-of-life care continues.

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**BIBLIOGRAPHY**


“Harrison’s Principles of Internal Medicine”, 1998, ch. 24

