Ancillary Ultrasound in Brain Death Confirmation in Neonates and Infants

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Disclosures

• No conflict of interest
Organ Donation

• The brain-dead patient is the source of viable organs for transplantation.

• Most hospital policies require contacting an organ procurement organization when clinical examination shows evidence of loss of all brain function, but also when rapid progressive loss of brain function is anticipated. These contacts are typically initiated by ICU nursing staff.
Brain death

• Is defined as the permanent complete loss of brain function or circulation

• Complete cessation of brain activity includes irreversible loss of:
  • Consciousness (GCS = 3)
  • All motor responses (excluding spinal reflexes): no posturing
  • All brainstem functions including absent gag and cough reflexes, absent corneal responses, absent pupillary responses to light (excluding pinpoint pupils in narcotic), absent vestibulo-ocular responses, absent respiratory effort (based on apnea test)

• To be permanent:
  • 1. The etiology of the coma has to be known and the alleged etiology causes neuronal death (eliminate reversible causes of Coma)
  • 2. There are no confounding factors that affect the neurologic exam
Etiologies of Brain Death

• Severe head trauma (50%)
• Asphyxial injury in septic shock, hemorrhagic shock, prolonged cardiac resuscitation, suffocation, strangulation, CO poisoning (30%), SIDS
• Severe cerebrovascular injury (12%)
• Severe brain tumor or acute hydrocephalus
Reversible etiologies of “coma dépassé”

• Toxic-metabolic coma
• Medication
• Hypothermia,
• Hypotension
• Surgically remediable causes
Apnea test (AT)

- T piece connected to endotracheal tube and insert a catheter or cannula into the endotracheal tube down to the level of the carina and provide pure oxygen at a rate of 4–10 l/min.
- CPAP mode

Apnea test: the goal is to achieve oxygenated apnea and produce an increased pCO2 to above 60 mm Hg or 20 mm Hg above the normal baseline (baseline should be at least > 40 mmHg)

Invalid AT: no elevation of PaCO₂ levels after 15 minutes AT or AT has to be stopped due to hypotension, arrhythmia, ....

No AT: hemodynamically instable, poor O₂ at baseline, significant pulmonary disorder or extensive thoracic chest injury, presence of abdominal spinal myoclonus interfering with assessment of diaphragmatic movements or confounding factors.
Confounding Factors Affecting the Neurologic Exam

- Resuscitated shock (systolic BP or MAP > 5th percentile of norm for age)
- Hypothermia (core temperature < 34°C) (should be > 35°C)
- Peripheral nerve or muscle dysfunction, neuromuscular blockade
- Trauma to face (eyes, ears, mouth) and high cervical cord
- Significant drug intoxication (Barbiturate, sedative, hypnotic, alcohol, opiates) (UDS negative)
- Severe metabolic disorders (hypoglycemia (glucose < 50 mg/dL), hyponatremia (Na < 130 mEq/L), hypokalemia, hypocalcemia, hypomagnesemia, acidosis (pH < 7.2), hyperammonemina (NH3 >100), hypothyroidism

CAVEAT

• Clinical assessment is the foundation of brain death determination
• Preserved neuroendocrine function is not inconsistent with the whole brain standard of death as it may be present despite irreversible injury to brainstem and hemispheres

• A clinical diagnosis of brain death should be allowed if drug levels (e.g., of barbiturates used to treat increased intracranial pressure) are below the therapeutic range. A reasonable approach is as follows: If it is known which drug or poison is present but the substance cannot be quantified, the patient should be observed for a period that is at least four times the elimination half-life of the substance, provided that the elimination of the drug is not interfered with by other drugs or organ dysfunction. Some drugs/toxins (e.g., cyanide, lithium, and fentanyl) may not be detected by routine screening tests.
Common spinal cord or peripheral movements in brain dead patients.

<table>
<thead>
<tr>
<th>Movement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Facial twitches</strong></td>
</tr>
<tr>
<td>Subtle, semi-rhythmic facial movements arising from the denervated facial nerve</td>
</tr>
<tr>
<td><strong>Finger twitching</strong></td>
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<tr>
<td>Finger flexor movements</td>
</tr>
<tr>
<td><strong>Arm pronation</strong></td>
</tr>
<tr>
<td>Upper limb pronation extension reflex</td>
</tr>
<tr>
<td><strong>Tonic neck reflexes “Lazarus sign”</strong></td>
</tr>
<tr>
<td>Passive neck displacements, especially flexion, maybe accompanied by complex truncal and extremity movements including adduction at the shoulders, flexion at the elbows, supination or pronation at the wrists, flexion of the trunk (“sitting up” type movements), and neck-abdominal muscle contraction or head turning to one side</td>
</tr>
<tr>
<td><strong>Truncal movements</strong></td>
</tr>
<tr>
<td>Asymmetrical opisthotonic posturing of the trunk and preservation of superficial and deep abdominal reflexes</td>
</tr>
<tr>
<td><strong>Abnormal Babinski</strong></td>
</tr>
<tr>
<td>Triple flexion response with flexion at the hip, knee, and ankle with foot stimulation</td>
</tr>
<tr>
<td><strong>Undulating toe sign</strong></td>
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<tr>
<td>Alternating flexion-extension of the toes with passive displacement of the foot</td>
</tr>
</tbody>
</table>
Role of Ancillary studies in Brain Death Diagnosis

• 1. Are not mandatory
• 2. Serve as a surrogate means of assessment when clinical diagnosis cannot be made
• 3. Decrease the risk of incorrect diagnosis
• 4. May reduce observation periods thus increasing potential for retrieving viable transplant tissue
Ancillary tests assessing brain function

• EEG: shows electrocerebral silence (no activity > 2 µV for 30 minutes) if **clinically brain death and no confounding factors**;
  • should be done using brain death protocol
    • A minimum of 8 scalp electrodes should be used.
    • Interelectrode impedance should be between 100 and 10,000 Ω.
    • The integrity of the entire recording system should be tested.
    • The distance between electrodes should be at least 10 cm.
    • The sensitivity should be increased to at least 2 µV for 30 minutes with inclusion of appropriate calibrations.
    • The high-frequency filter setting should not be set below 30 Hz, and the low-frequency setting should not be above 1 Hz.
  • Electroencephalography should demonstrate a lack of reactivity to intense somatosensory or audiovisual stimuli.
    • cannot always be performed
    • may be contaminated by artifacts
    • sensitive to hypothermia, drugs, or extreme hypotension; **electro-cerebral silence does not always mean brain death**

• Evoked potential: Though SSEP and BAEP are less susceptible to sedation than EEG, they are still influenced by hypothermia and by the presence of peripheral nerve disorders. **not used in our institution**
Ancillary Tests Assessing Lack of Brain Perfusion Require Neuroimaging

- All test have a 100% specificity and positive predictive value
- **False negative results**: preserved brain circulation does not exclude whole brain death
- There are several mechanisms causing a focal decrease in ICP resulting in preservation or restoration of residual blood flow while in the remaining parts of the brain cessation of flow is detected. This can be seen with:
  - Craniotomy,
  - Skull fracture,
  - Ventricular drainage
  - Open fontanelle
  - Unfused sutures
- **False positive results**: loss of brain circulation precedes the loss of function; basilar and posterior circulation have to be assessed
Positive Radionucleotide Brain Death Scan

• In the flow phase, no matter the tracer, the tracer should be seen in the carotid arteries. This confirms an adequate bolus was given (arrows image at 2 seconds).

In the delayed phase (15-20 min after tracer injection), the brain-specific tracer will be absent in brain tissue. The angiographic tracer will not be seen in the dural venous sinuses. This combination of findings is interpreted as positive for brain death (because of absent intracerebral perfusion).
flow to extracranial subcutaneous tissues can be seen, contrasting vividly with a total lack of intracranial signal. **In cerebral angiography scintigraphy with Tc99m HMPAO, only viable cells take up the tracer element**
‘empty lightbulb sign’ on isotopic perfusion exam

**FIGURE 3**
Case 6: Motor vehicle accident. A: Initial HM-PAO scan shows lack of supratentorial activity but flow persists to cerebellum. Patient was still breathing spontaneously. B: Follow-up HM-PAO study 24 hr later when patient required mechanical ventilation shows complete lack of intracranial flow.
Ancillary Tests Assessing Lack of Brain Perfusion require Neuroimaging

- **Cerebral angiography**
  - The contrast medium should be injected in the carotids and vertebral arteries/aortic arch under high pressure and reach both anterior and posterior circulations
  - No intracerebral filling should be detected at the level of entry of the carotid or vertebral artery to the skull.
  - Absence of contrast in deep veins (internal cerebral veins and vein of Galen)
  - The external carotid circulation should be patent.
  - The filling of the superior longitudinal sinus may be delayed.
Digital subtraction angiography remains the gold standard in adults

- It provides clear and unambiguous illustration of flow into the cerebral circulation. Cerebral circulatory arrest is consistent with a declaration of death by neurologic criteria.
CTA revealing the lack of blood flow in the brain. 3D-image reconstruction. *Fine arrows* point to the superficial temporal artery, a branch of the external carotid artery. *Thick arrow* indicates the site of craniectomy.
CT Angiography

- On the left: there is still delayed opacification on MCA
- On the right: no intracranial filling while superficial temporal arteries are visualized
- The earliest sign of cerebral circulatory arrest is lack of opacification of the deep veins (GCV, vein of Galen)

(Pol J Radiol 2014 : 79: 417-421)
CT Perfusion and CT Angiography in a clinically brain death patient with ECS

Fig. 5 CTA and CTP images for Patient 9. CTA shows the presence of both anterior and posterior intracranial blood flow. The image shows both carotid arteries, their intracranial branches, vertebral arteries, and basilar artery. The CTP scan indicates markedly reduced CBF with increased MTT at the level of the posterior circulation and right temporal lobe.
TCD in same patient

Fig. 6  TCD images for Patient 9.  a TCD shows the presence of CBF in the vertebral arteries, basilar artery, and the middle cerebral arteries insonated at different depths.  b TCD of the MCA performed 14 h later showing systolic spikes

Neurocrit Care 2009; 11: 261-271
Ancillary Tests Assessing lack of Brain Perfusion require Neuroimaging

- The use of transcranial Doppler (TCD) was only recommended in 42% of centers despite the AAN Therapeutics and Technology Assessment Subcommittee report, affirming that the TCD sensitivity and specificity for detecting circulatory arrest were 91–100 and 97–100%, respectively.
Increasing ICP will diminish and remove firstly diastolic cerebral perfusion followed by systolic perfusion – cerebral circulatory arrest is diagnosed from the point of oscillating blood flow i.e. no forward perfusion through to complete lack of signal.

Cerebral circulatory arrest is indicated by flow patterns without forward flow progress, progressing from decrease in diastolic flow to disappearance of diastolic flow to oscillating pattern with retrograde flow in diastole, short systolic spikes, and finally absence of Doppler signal.
Caveat with TCD

• 1) a requirement for skilled accredited sonographers

• 2) adequate acoustic ‘windows’: 10% of all patients will have too much bone density to provide adequate signals, and so the functional consequence is that death can only be declared when detecting some signal e.g oscillating flow or ‘systolic spikes’. Total lack of signal creates uncertainty as to the reason -and so other means of ancillary testing should be used.
Guidelines for the determination of brain death in children

1. Coma and apnea must co-exist. The patient must exhibit complete loss of consciousness, vocalization, and volitional activity.

2. Absence of brainstem function as defined by:
   a. Midposition or fully dilated pupils that do not respond to light
   b. Absence of spontaneous eye movement, those induced by oculocephalic and oculovestibular (caloric) testing
   c. Absence of movement of bulbar musculature including facial and oropharyngeal muscles (corneal, gag, cough, sucking, and rooting reflexes are absent)
   d. Respiratory movements are absent with patient off the respirator
   e. Apnea testing using standardized methods can be performed but is done after other criteria are met

3. The patient must not be significantly hypothermic or hypotensive for age

4. Flaccid muscle tone, absence of spontaneous or induced movements excluding spinal cord events such as reflex withdrawal or spinal myoclonus should exist

5. The examination results should remain consistent with brain death throughout the observation and testing period

6. Recommended observation periods according to age
   a. 7 days – 2 months: two examinations and EEG’s separated by 48 hours
   b. 2 months – 1 year: two examinations and EEG’s separated by 24 hours;
      A repeat examination and EEG are not necessary if concomitant cerebral radionuclide study demonstrates no visualization of cerebral arteries
   c. Older than 1 year: when an irreversible cause exists, laboratory testing is not required and an observation period of at least 12 hours is recommended. There are conditions, particularly hypoxic-ischemic encephalopathy, in which it is difficult to assess the extent and reversibility of brain damage. This is particularly true if the first examination is performed soon after the acute event. In this situation, a more prolonged period of at least 24 hours of observation is recommended. The observation period may be reduced if the EEG demonstrates electrocerebral silence or the cerebral radionuclide angiographic study does not visualize cerebral arteries.

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Brain death in the neonate

• The taskforce guidelines provide no recommendations for determining neurologic death in an infant < 7 days of age
  • No recommendations were made because of limited data in this age group
  • Misinterpretation of recommendations
    • They do not imply that testing should not be done
    • They do not imply that testing is unreliable
    • They do not state that brain death cannot be declared in infants under 7 days of age
Neurologic death in the neonate

“Brain death can be diagnosed in the term infant, even at less than 7 days of age. An observation period of 48 hours is recommended to confirm the diagnosis. If an EEG is isoelectric or if a CBF study shows no flow, then the observation period can be shortened to 24 hours.”

• Ashwal. Brain death in the newborn. Clinics in Perinatology 1997;24:859-879
Introduction: Brain death is accepted as an objective indicator of end of life with the aim of ending all brain functions. In this present statement, the Academy of Neurology related single-single transcranial Doppler (TCD) without imaging has been used as an indicator. We evaluated the reliability of the transcranial color and power Doppler Duplex imaging in infants.

Methods: Patients with hypotension (20% or lower), intracranial mass lesion, severe metabolic disturbance and hypothermia were excluded. Each patient was imaged through the temporal and anterior fontanelle using power or color Doppler Duplex imaging with purpose of optimization of the acoustic window. Attempt was made to identify all intracranial arteries in anterior and posterior circulation. Once identified arterial spectral pattern was evaluated. Brain circulatory arrest was declared if brief reverberating systolic signal lasting for a brief portion of the cardiac cycle was found and/or alternating flow (antegrade and retrograde) in diastole with mean flow velocities below zero was seen. In addition, special attention was paid to venous flow. All studies were performed for a total duration of 30 minutes.

Results: Six infants less than 12 months of age (mean age 105 days) were evaluated over the last 12 years. All infants had brain death diagnosed on EEG except case 5 (electrographic-deterred). TBI was cause of death in 1 who was 280 days old. Hypoxic ischemic encephalopathy was evident in 2 (4 days and 6 days respectively). Cardiac arrest was noted in 3 who were tested at mean age of 201 days. Acoustic window was adequate in all patients. Venous flow was seen in one infant with adequate central perfusion and did not fulfill diagnostic criteria of brain death. TCD Duplex showed a normal flow pattern of flow in all patients. In all 6 patients Doppler showed a monophasic wave pattern of flow in all patients. In all 6 patients Doppler showed a monophasic wave pattern of flow in all patients. In all 6 patients Doppler showed a monophasic wave pattern of flow in all patients.

Discussion: Clear standards for determination of pediatric brain death were established by the American Academy of Neurology and are supported by the American Academy of Pediatrics. Imaging such as CT angiography is indicated on TCD by flow patterns without forward flow progression, progressing from decrease in diastolic flow to disappearance of diastolic flow with retrograde flow in diastole, short systolic spikes, and finally absence of diastolic flow signal. In the absence of flow signal, alternative ancillary studies to TCD are frequently required. In patients with cervical spine injury examination of the basilar artery through the subclavian window may be contraindicated. In infants the oxygen anterior fontanelle always improves function of the basilar artery. In the absence of basilar artery evaluation, false positive results can occur. Meta-analysis of all TCD studies shows a sensitivity of 89% and a specificity of 99%. The prevalence of false positive and false negative results vary to be higher in infants. False positive TCD is thought to result from the time lag from cervical artery and total loss of function.

Abstract: Doppler ultrasound imaging appears suitable as an ancillary study in diagnosing brain death. If TCD absence of flow, a poor outcome can be predicted. Power Doppler imaging in case 2: blip in basilar; no central venous flow intra cranially. Patients with hypothermia (35°C or less), intoxication, intracranial mass lesion, severe metabolic disturbance and hypothermia were excluded. Each patient was imaged through the temporal and anterior fontanelle using power or color Doppler Duplex imaging with purpose of optimization of the acoustic window. Attempt made to identify all intracranial arteries in anterior and posterior circulation. Once identified arterial spectral pattern was evaluated. Brain circulatory arrest was declared if brief reverberating systolic signal lasting for a brief portion of the cardiac cycle was found and/or alternating flow (antegrade and retrograde) in diastole with mean flow velocities below zero was seen. In addition, special attention was paid to venous flow. All studies were performed for a total duration of 30 minutes.

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Study Inclusion Criteria and Study Protocol

• Patients less than 12 months of age who are deeply comatose (GSC = 3)
• Patients seen during last 5 years
• Patients with hypothermia (35°C or less), intoxication, neuromuscular blockade, severe metabolic disturbance and hypotension were excluded.
• EEG always obtained using brain death protocol
Brain Death Protocol in Infants

• Each patient was imaged through the temporal and anterior fontanelle using **power or color Doppler imaging** with the purpose of optimization of the acoustic window.

• **Attempt was made to identify all intracranial arteries** in anterior and posterior circulation. Once identified, arterial spectral pattern was evaluated.

• Brain circulatory arrest was declared if brief reverberating systolic flow signal lasting for a brief portion of the cardiac cycle was found and/or alternating flow (anterograde in systole and retrograde in diastole) with mean flow velocities below zero was seen. In addition, special attention was paid to venous flow.

• All studies were performed for a **total duration of 30 minutes**
# Population

<table>
<thead>
<tr>
<th>Case</th>
<th>Cause</th>
<th>Age (days)</th>
<th>Arteries</th>
<th>Central veins</th>
<th>EEG</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>cardiac arrest</td>
<td>250</td>
<td>Blip</td>
<td>None</td>
<td>ECS</td>
</tr>
<tr>
<td>2</td>
<td>cardiac arrest</td>
<td>225</td>
<td>TAMPV &lt;0</td>
<td>None</td>
<td>ECS</td>
</tr>
<tr>
<td>3</td>
<td>cardiac arrest</td>
<td>280</td>
<td>TAMPV &lt;0</td>
<td>None</td>
<td>ECS</td>
</tr>
<tr>
<td>4</td>
<td>TBI</td>
<td>238</td>
<td>Blip</td>
<td>None</td>
<td>ECS</td>
</tr>
<tr>
<td>5</td>
<td>HIE</td>
<td>6</td>
<td>TAMPV &lt; 10</td>
<td>Seen; N flow</td>
<td>No ECS</td>
</tr>
<tr>
<td>6</td>
<td>HIE/trauma</td>
<td>1</td>
<td>TAMPV &lt;0</td>
<td>None</td>
<td>ECS</td>
</tr>
</tbody>
</table>

TAMPV: Time Average Mean Peak Velocity in cm/sec
Arterial Power Doppler Imaging: Normal

Case 5
TAMPV < 10 cm/sec

Duret Hemorrhage in Case 5
Arterial Power Doppler Imaging: cases with Blip

Case 1

Case 4
Arterial Power Doppler Imaging: cases with TAMPV<0.

Case 2

Case 3
Arterial Power Doppler Imaging: cases with TAMPV<0

Case 6
Venous Flow in Case 5 (cerebral perfusion)

Flow in sagittal sinus
No flow in transverse sinus
Flow in deep veins
Case 4

No deep or superficial venous flow
Venous Flow in Patients with TAMPV <0

Case 2

No deep vein drainage
Preserved Sagittal sinus flow
Venous Flow in Patients with TAMPV <0

Case 3

Flow in sagittal sinus
No central venous flow
Venous Flow in Patients with TAMPV <0

Case 6

No deep venous flow
Flow in sagittal sinus
Power Doppler imaging and color Doppler imaging in Brain Death

• Power Doppler imaging and color Doppler imaging provide a clear and unambiguous illustration of venous flow. The earliest sign of cerebral circulation arrest is loss of flow in deep veins as demonstrated by CT angiography. ⁹
  • In cases 3, 4 and 6, arteries were visualized on power Doppler. TAMPV were negative or absent consistent early loss of cerebral perfusion. No venous flow was seen in deep veins.
  • In cases 1 and 4, only a blip of flow was seen in ICA and basilar. Venous flow was still seen in superficial sinus but not in deep venous sinuses.
  • In one of our patient deep venous flow was preserved. Adequate perfusion was seen in all vessel study and diagnosis of brain death was not be made. EEG was not showing ECS. Patient remained comatose.
Conclusion

• Power and color Doppler Imaging have not been previously investigated as a tool for brain death diagnosis in infants. All the vessels were insonated for a duration of 30 minutes in normothermic and hemodynamically stable infants potentially eligible for organ donation.

• Our study suggests that loss of deep venous circulation in normothermic and hemodynamically stable infants should be included as a criteria necessary for ancillary diagnosis of brain death.
Brain Death Determination (BDD)

- is primarily a clinical diagnosis
- ancillary tests are used primarily when confounding factors interfere with reliable completion of a clinical assessment, or physiologic instability precludes performance of an apnea test.
- The need to declare a person brain dead must be completely dissociated from the ever prevalence demand for organ donation.