Brain Death & Organ Retrieval

Neurologically determined death *(NDD): the irreversible loss of the capacity for consciousness combined with the irreversible loss of all brain stem reflexes, including the capacity to breathe.*

ANESTHETIC CONSIDERATIONS:

- Confirm the diagnosis of brain death and confirm wishes of patient and family
  - NDD by physician (x2) not involved with transplant
  - Minimum clinical criteria for NDD (see guidelines)
- Physiologic Consequences of Brain death
  - Hemodynamic instability (myocardial dysfunction, vasomotor tone)
  - Hypoxemia (Neurogenic pulmonary edema, VAP, CHF etc)
  - Pulmonary dysfunction with ARDS
  - Neuro-endocrine dysfunction
    - DI (70%), hypernatremia / hypokalemia
    - Hypothyroid, hypocortisolemia
    - Hyperglycemia
  - Coagulopathy / DIC
  - Hypothermia secondary to hypothalamic dysfunction
- Etiology of Brain Death and secondary injuries
  - Trauma (potential for multi-organ involvement, pulmonary / cardiac contusions)
- Donation after cardio-circulatory death (DCD)
  - Canadian guidelines Oct 10 2006, CMAJ Vol. 175; No 8 (suppl)
  - Controlled vs. Uncontrolled DCD
  - Warm ischemic time

ANESTHETIC GOALS:

- Goal is to maintain end-organ perfusion with invasive hemodynamic monitoring, fluid resuscitation, vasopressor therapy & ventilatory support
  - Goals: rule of 100s + 2
    - SBP > 100 mmHg
    - pO_2 >100 mmHg
    - U/O 100 mL/h (1-1.5 ml/kg/h)
    - Hb > 100 g/L
    - CVP 5-10 mmHg
    - FiO_2 < 40% for lung retrieval
- Strategies for organ preservation using free radical scavengers including mannitol, superoxide dismutase, and the free radical synthesis blocker allopurinol
- Consider hormone replacement therapy (improve solid organ retrieval)
  - Methylprednisolone 15 mg/kg q24h
  - Tetra-iodothyronine (T4) IV: 20 mcg bolus followed by 10 mcg/h infusion
  - Vasopressin: 1 unit bolus followed by 2.4 units/h infusion

HISTORY

- Review history preceding NDD (etiology, e.g. trauma)
- Review for secondary injuries
- Review current meds / ventilation to maintain organ perfusion

PHYSICAL

- **GENERAL**
  - Vitals including temperature

INVESTIGATIONS

- Most investigations are preformed prior to NDD, if long time from NDD to harvest consider repeating
- **Labs**
  - CBC, Lytes, BUN, Cr, Group & Screen, ABG (looking for anemia, electrolyte abnormalities (DI) , renal insufficiency, acidosis)
- **Imaging**
  - CXR (line and tube placement, pulmonary edema, aspiration etc.)
  - ECG (rhythm, ischemia)
  - Echo (EF, wall motion abnormalities, contusions)

OPTIMIZATION

- Invasive monitoring, + large bore IV access
- Lung protection ventilatory strategy
  - (Vt 6-8, plateau < 30 mmHg, PEEP to minimize FiO_2, SaO_2 > 95%)
- Inotrope / vasopressor support
- Diagnosis and management of DI (fluid replacement, DDAVP vs. Vasopressin 1 U bolus + 2.4 U/h)
- Steroid and thyroid replacement (methylprednisolone 15 mg/kg/d; T4 20units + 10 U/h)
- Glycemic control (insulin infusion)
- Avoid hypothermia (use heating blanket as required)

ANESTHETIC OPTIONS

- Since patient is brain dead, no awareness or pain perception (therefore don't require anesthetic)
- NMB to facilitate surgical exposure and prevent spinal reflexes (can be distressing)
- Use of volatiles & narcotics is common to help control hemodynamic responses

- Coordination of surgical extraction teams

ANESTHETIC SETUP

- **Drugs**
  - Vasopressors (epinephrine, vasopressin) to support blood pressure
    - Dopamine and phenylephrine have been suggested for improvement of splanchnic perfusion.
  - Vasodilators (phentolamine, alprostadil [lung recovery]) to improve perfusion during cross-clamping
  - Direct chronotropes (isoproterenol, dopamine) to treat bradycardia as brain dead patient will not respond to vagolytics
- **Equipment**
  - CAS monitors + 5-lead ECG
  - Invasive lines (A-line, CVC)
  - Foley (urometer)
  - Temperature monitoring (+ fluid / body warmers PRN)
  - Be prepared to draw blood for pre-transplant tests as required

MANAGEMENT OF ANESTHESIA

- **Induction**
  - Ensure adequate resuscitation with fluid therapy (crystalloid, colloid or blood products)
  - Optimize ventilation with lung protective strategies (PEEP, low PAWP < 30 mmHg, low tidal volumes of 6-8 mL/kg, SpO_2 > 95%) with minimized FiO_2 (< 40%)
  - Some advocate Triple Hormone Therapy in donors whose EF < 40% on Echo or escalating hemodynamic support despite adequate fluid resuscitation
    - Vasopressin (1 U bolus followed by 2.4 U/h)
      - Vasopressin infusion (< 2.5 U/h) may be useful as it counteracts volume loss from DI and has been shown to reduce inotrope requirements
      - Excessive rates of infusion may lead to heart and kidney problems
    - Methylprednisolone IV (15 mg/kg q24h)
    - Tetra-iodothyronine / T4 (20 mcg bolus followed by infusion of 10 mcg/hour)
      - Tri-iodothyronine / T3 used as well
  - Large dose of NMB
- **Maintenance**
  - None required, but volatile, narcotics, inotropes / pressors titrated to hemodynamic responses
  - If lungs for transplant, consider colloid > crystalloid, minimize FiO_2
  - Heparin prior to aortic cross clamp
  - Once cross clamp applied and heart harvested, anesthesiologist no longer required
- **Emergence**
  - Treat body with dignity

DISPOSITION & MONITORING

- None

COMPLICATIONS

- Hypotension may be profound and is commonly associated with hemorrhage or hypovolemic effects of DI
  - Have pharmacologic adjuvants and infusions ready:
    - Vasopressors (epinephrine, vasopressin) to support blood pressure
      - Dopamine and phenylephrine have been suggested for improvement of splanchnic perfusion.
    - Vasodilators (phentolamine, alprostadil [lung recovery]) to improve perfusion during cross-clamping
    - Direct chronotropes (isoproterenol, dopamine) to treat bradycardia as brain dead patient will not respond to vagolytics

PATHOPHYSIOLOGY

- **Criteria For Brain Death** (Canadian Critical Care 2003 conference)
  - Established etiology capable of causing neurological death in the absence of reversible conditions capable of mimicking neurological death
  - Deep unresponsive coma
  - Absent brainstem reflexes as defined by absent gag and cough and the bilateral absence of:
    - Motor responses, excluding spinal reflexes
    - Corneal responses
    - Pupillary responses to light with pupils at mid-size or greater
    - Vestibulo-ocular responses
  - Absent respiratory effort based on the apnea test
    - Thresholds should be $PaCO_2$ > 60 mmHg and > 20 mmHg rise above the pre-apnea test level and with a pH < 7.28
  - Absent confounding factors
    - Unresuscitated shock
    - Hypothermia (Core Temp < 34°C)
    - Severe metabolic disorders capable of causing potentially reversible coma
    - Peripheral nerve or muscle dysfunction or neuromuscular blockade potentially accounting for unresponsiveness
    - Clinical significant drug intoxications (EtOH, barbiturates, sedatives, hypnotics)
  - Recommendations specific to children and adolescents
    - All children >1 year should have NDD as per standards with a second physician performing the NDD
  - Recommendations specific to infants
    - Minimum clinical criteria include the oculocardiac reflex, as this test may be more reliable that the vestibulo-ocular reflex in infants due to the unique anatomy of the external auditory canal

- Repeat exam at different time by another qualified physician, regardless of brain injury

Recommendation A.1: Minimum clinical criteria for NDD

We recommend use of the following minimum clinical criteria as a Canadian medical standard for NDD:

- Established etiology capable of causing neurological death in the absence of reversible conditions capable of mimicking neurological death
- Deep unresponsive coma with bilateral absence of motor responses, excluding spinal reflexes
- Absent brain stem reflexes as defined by absent gag and cough reflexes and the bilateral absence of
  - corneal responses
  - pupillary responses to light, with pupils at mid-size or greater
  - vestibulo-ocular responses
- Absent respiratory effort based on the apnea test
- Absent confounding factors

Recommendation A.2: Confounding factors

We recommend that, at the time of assessment for NDD, the following confounding factors preclude the clinical diagnosis:

- Unresuscitated shock
- Hypothermia (core temperature < 34°C)
- Severe metabolic disorders capable of causing a potentially reversible coma
- Severe metabolic abnormalities, including glucose, electrolytes (including phosphate, calcium and magnesium), inborn errors of metabolism, and liver and renal dysfunction may play a role in clinical presentation. If the primary etiology does not fully explain the clinical picture, and if in the treating physician's judgement the metabolic abnormality may play a role, it should be corrected.
- Peripheral nerve or muscle dysfunction or neuromuscular

Recommendation A.3: Minimum temperature

The core body temperature required to apply the minimum clinical criteria (Recommendation A.1) should be ≥ 34°C.

Recommendation A.4: Apnea testing

We recommend that the thresholds at the completion of the apnea test be $PaCO_2 \geq 60$ mm Hg (and ≥ 20 mm Hg above the pre-apnea test level) and pH ≤ 7.28. These thresholds must be documented by arterial blood gas measurement.

To interpret an apnea test correctly, the certifying physician must continuously observe the patient for respiratory effort throughout the administration of the test.

Recommendation A.5: Examination interval

We recommend that when a second determination is performed, there should be no fixed examination interval, regardless of the primary mechanism of the brain injury.

Recommendation A.6: Ancillary tests

We recommend that an ancillary test be performed when it is impossible to complete the minimum clinical criteria as defined in Recommendation A.1. At a minimum, 2 particular clinical criteria must be met before ancillary tests are performed:

- An established etiology capable of causing neurological death in the absence of reversible conditions capable of mimicking neurological death
- Deep unresponsive coma

We recommend that demonstration of the global absence of intracerebral blood flow be considered as the standard for NDD by ancillary testing.

- See **Miller's Table 79-1** below for slightly different American version (from Harvard)

Diagnostic criteria for the clinical diagnosis of brain death

A. Prerequisites. Brain death is the absence of clinical brain function when the proximate cause is known and demonstrably irreversible.
1. Clinical or neuroimaging evidence of an acute central nervous system catastrophe that is compatible with the clinical diagnosis of brain death
2. Exclusion of complicating medical conditions that may confound clinical assessment (no severe electrolyte, acid-base, or endocrine disturbance)
3. No drug intoxication or poisoning
4. Core temperature ≥32°C (90°F)
B. The three cardinal findings in brain death are coma or unresponsiveness, absence of brainstem reflexes, and apnea.
1. Coma or unresponsiveness—no cerebral motor response to pain in all extremities (nail-bed pressure and supraorbital pressure)
2. Absence of brainstem reflexes
a. Pupils
i. No response to bright light
ii. Size: midposition (4 mm) to dilated (9 mm)
b. Ocular movement
i. No oculocephalic reflex (testing only when no fracture or instability of the cervical spine is apparent)
ii. No deviation of eyes to irrigation in each ear with 50 mL of cold water (allow 1 minute after injection and at least 5 minutes between testing on each side)
c. Facial sensation and facial motor response
i. No corneal reflex to touch with a throat swab
ii. No jaw reflex
iii. No grimacing to deep pressure on nail bed, supraorbital ridge, or temporomandibular joint

d. Pharyngeal and tracheal reflexes
i. No response after stimulation of the posterior pharynx with tongue blade
ii. No cough response to bronchial suctioning
3. Apnea-testing performed as follows:
a. Prerequisites
i. Core temperature ≥36.5°C or 97°F
ii. Systolic blood pressure ≥90 mm Hg
iii. Euvolemia. *Option:* positive fluid balance in the previous 6 hours
iv. Normal $PaCO_2$. *Option:* arterial PCO_2 ≥40mm Hg
v. Normal PaO_2. *Option:* preoxygenation to obtain arterial PaO_2 ≥200 mm Hg
b. Connect a pulse oximeter and disconnect the ventilator.
c. Deliver 100% O_2, 6 L/min, into the trachea. *Option:* place a cannula at the level of the carina.
d. Look closely for respiratory movements (abdominal or chest excursions that produce adequate tidal volumes)
e. Measure arterial PaO_2, PCO_2, and pH after approximately 8 minutes, and reconnect the ventilator.
f. If respiratory movements are absent and arterial PCO_2 is ≥60 mm Hg (*option:* 20 mm Hg increase in PCO_2 over a baseline normal PCO_2), the apnea test result is positive (i.e., it supports the diagnosis of brain death).
g. If respiratory movements are observed, the apnea test result is negative (i.e., it does not support the clinical diagnosis of brain death), the test should be repeated.
h. Connect the ventilator if, during testing, the systolic blood pressure becomes ≤90 mm Hg or the pulse oximeter indicates significant oxygen desaturation and cardiac arrhythmias are present; immediately draw an arterial blood sample and analyze arterial blood gas. If PCO_2 is ≥60 mm Hg or PCO_2 increase is ≥20 mm Hg over baseline normal PCO_2, the apnea test result is positive (it supports the clinical diagnosis of brain death); if PCO_2 is <60 mm Hg or PCO_2 increase is <20 mm Hg over baseline normal PCO_2, the result is indeterminate, and an additional confirmatory test can be considered.

Adapted from Practice Parameters for Determining Brain Death in Adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 45:1012, 1995.

- **Neurological**
  - Usually the patient suffers brain stem death owing to a sudden or gradual rise in ICP after an acute intracranial hemorrhage or head injury
  - Pontine ischemia results in mixed vagal and sympathetic stimulation that gives rise to the **Cushing response** (bradycardia, hypertension, and an irregular breathing pattern)
    - As the ischemia progresses to the lower end of the medulla, the vagal and cardiomotor nuclei become ischemic, causing unopposed sympathetic stimulation
  - Hypothermia: Secondary to hypothalamic infarction or exposure
  - Management:
    - Keep patient warm
    - Eye care: the eyes should be kept closed and moist with the use of normal saline drops or artificial tears
- **Cardiovascular**
  - Physiology
    - Ischemic cerebrum → vagal activation (slow HR, low MAP, CO)
    - Progression to midbrain → vagal and sympathetic activation (Cushing phenomenon – slow HR, HTN)
    - Entire brainstem ischemic → no more vagal outflow, unopposed sympathetic → called autonomic storm → tachycardia, HTN (which may cause end organ ischemia)
    - Herniation of brain stem → sudden cessation of autonomic outflow with profound hypotension
      - After a few days of disconnection from supraspinal structures, spinal cord automaticity returns BP to normal
    - Development of heightened spinal cord reflexes → HTN with bladder distension and surgical stimulation (similar to autonomic hyperreflexia)
  - The initial period of intense autonomic activity is followed by loss of sympathetic tone and a massive reduction in SVR exacerbated by hemorrhage, massive diuresis from DI, or dehydration therapy for increased ICP
  - ECG abnormalities are common with brain stem death or secondary to increased ICP
    - ST segment and T wave changes
    - Atrial and ventricular arrhythmias
    - Conduction abnormalities
  - Bradycardia: resistant to atropine but responds to direct acting chronotropic agents (isoproterenol, dopamine)
  - Treatment:
    - Maintain multi-end organ perfusion while protecting heart
    - Esmolol for sympathetic over activity as it is usually short lived
    - Invasive cardiovascular monitoring
      - MAP of 60 mmHg with CVP of 5 to 10 mmHg
    - Restoration of intravascular volume with colloid and crystalloid
    - Vasopressin for DI and to maintain afterload, reduces inotrope requirements
    - Can also consider dopamine over phenylephrine for preserved splanchnic perfusion
- **Pulmonary**
  - Pulmonary dysfunction is common after brain stem death
    - Pneumonia (VAP), aspiration, neurogenic pulmonary edema, and pulmonary trauma, and secondary to over-zealous fluid resuscitation
  - Elevation of left atrial pressure, systemic hypertension, and pulmonary vasoconstriction cause increased pressure in the pulmonary capillary bed and endothelial damage
  - After brain stem death, high FiO_2 and PEEP are often required to maintain adequate oxygenation
  - Maintain oxygenation against risks of oxygen toxicity and pulmonary barotrauma in potentially transplantable lungs

- Management:
  - Use of Lung protective ventilation strategies:
    - Tidal volumes of 6 to 8 mL/kg
    - Optimize PEEP (limit to 10 cmH_2O if lungs are to be harvested)
    - If the lungs are to be considered for transplantation, FiO_2 should be as low as necessary to achieve a $PaO_2 > 60$ mmHg

- **Endocrine**
  - After brain stem death comes anterior and posterior pituitary failure
    - Early depletion of ADH and development of DI in almost 80% of brain stem dead organ donors
  - A rapid decline in free tri-iodothyronine (T3) is seen after brain stem death as a result of impaired TSH secretion and peripheral conversion of tetra-iodothyronine (T4)
  - Decreased insulin → anaerobic metabolism, acidosis, and hyperglycemia
  - The decrease in plasma cortisol may be associated with a decrease in the release of its stimulating factor adrenocorticotropic hormone (ACTH) from the anterior lobe of the pituitary gland
  - Temperature: after brain death the patient becomes poikilothermic (unable to alter temperature) and body temperature tends to be hypothermic
  - Management:
    - Triple therapy as above
    - In severe cases of DI, intermittent treatment with the synthetic analog 1-D-amino-8-D-arginine vasopressin (DDAVP) may also be required
    - Warming blanket
- **Hematological**
  - Ischemic or necrotic brain releases tissue thromboplastin that activates coagulation pathways in association with the disruption of endothelial surfaces
  - DIC occurs in up to 28% of brain stem dead organ donors
- **After Harvest**
  - Solid organ preservation is achieved using a wide variety of preservation fluids (Euro-Collins, University of Wisconsin / Belzer's) depending on the centre and the type of organ
  - Most are stored at 4°C without continuous perfusion after the initial flush
  - Cold preservation time varies between organ types → kidney can be kept for 1-2 days, heart only hours
  - Damage to organs may occur during one of three distinct periods:
    - During *ex vivo* cold storage and transport
    - During implantation and rewarming
    - After reperfusion and reintroduction of oxygen

REFERENCES

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- Smith, Physiologic Changes During Brain Stem Death—Lessons for Management of the Organ Donor, 2004 Journal of Heart and Lung Transplantation