Brain death has implications for organ donation with the potential for saving several lives. Awareness of maintenance of the brain dead has increased over the last decade with the progress in the field of transplant. The diagnosis of brain death is clinical and can be confirmed by apnea testing. Ancillary tests can be considered when the apnea test cannot be completed or is inconclusive. Reflexes of spinal origin may be present and should not be confused against the diagnosis of brain death. Adequate care for the donor targeting hemodynamic indices and lung protective ventilator strategies can improve graft quality for donation. Hormone supplementation using thyroxine, antidiuretic hormone, corticosteroid and insulin has shown to improve outcomes following transplant. India still ranks low compared to the rest of the world in deceased donation. The formation of organ sharing networks supported by state governments has shown a substantial increase in the numbers of deceased donors primarily by creating awareness and ensuring protocols in caring for the donor. This review describes the steps in the establishment of brain death and the management of the organ donor. Material for the review was collected through a Medline search, and the search terms included were brain death and organ donation.

**Key words:** Brain death, organ donation, donor care

### Abstract

Brain death has implications for organ donation with the potential for saving several lives. Awareness of maintenance of the brain dead has increased over the last decade with the progress in the field of transplant. The diagnosis of brain death is clinical and can be confirmed by apnea testing. Ancillary tests can be considered when the apnea test cannot be completed or is inconclusive. Reflexes of spinal origin may be present and should not be confused against the diagnosis of brain death. Adequate care for the donor targeting hemodynamic indices and lung protective ventilator strategies can improve graft quality for donation. Hormone supplementation using thyroxine, antidiuretic hormone, corticosteroid and insulin has shown to improve outcomes following transplant. India still ranks low compared to the rest of the world in deceased donation. The formation of organ sharing networks supported by state governments has shown a substantial increase in the numbers of deceased donors primarily by creating awareness and ensuring protocols in caring for the donor. This review describes the steps in the establishment of brain death and the management of the organ donor. Material for the review was collected through a Medline search, and the search terms included were brain death and organ donation.

### Introduction

Brain death is a state of cessation of cerebral function wherein the proximate cause is known and is considered irreversible. The American Association of Neurology (AAN) has defined brain death with three cardinal signs, cessation of the functions of the brain including the brainstem, coma or unresponsiveness and apnea.\(^1\)

In India, the Transplantation of Human Organ Bill was introduced in the Lok Sabha on 20\(^{th}\) August 1992 and became the Transplantation of Human Organ Act in 1994.\(^2\) The limited availability of organs amidst a growing demand emphasizes the need for optimal donor care. There is no global consensus in the criteria for establishing brain death, and significant differences exist in the tests used.\(^3\) In many countries, including India, the diagnosis of brain death is made after fulfilling the mandatory criteria and by the apnea testing which is a safe technique for documentation.\(^4\)

In India the deceased donor organ donation rate is only 0.26 per million\(^5\) while USA at 25.6 per million,\(^6\) UK at 18.3 per million\(^7\) and Spain at 32 per million\(^6\) are well ahead.

A checklist of requirements\(^8\) that need to be fulfilled before proceeding with tests for brain death is indicated in Table 1.

### Clinical testing for brain death

1. **Coma:** Absence of response to noxious stimulus (supraorbital pressure or pressure on the nail bed) with the exception of spinally mediated reflexes.
2. **Absent brain stem reflexes** (a formal evaluation of the brain stem reflexes is undertaken when the patient has had fixed dilated pupils and absent cranial nerve reflexes for more than 4 h).\(^9\) Table 2 lists the individual tests for brain stem reflexes.
3. **Apnea test:** The aim of this test is to check for the integrity of the brain stem respiratory center at high levels of blood carbon dioxide. Prerequisites include a patient who is normothermic (core temperature ≥36.5°C), hemodynamically stable (systolic pressure ≥100 mmHg), free from sedative and paralytic...
drugs, with normal oxygenation (\(\text{PaO}_2 \geq 200\ \text{mmHg}\) after 100% oxygenation) and near normal \(\text{PaCO}_2\) (35-45 mmHg).

Oxygen is insufflated through a catheter placed at the level of the carina at 6.0 L/min after disconnection from the ventilator. The observer looks for respiratory movements at 8-10 min after disconnection. Assuming a rate of rise in \(\text{PaCO}_2\) of 3 mmHg/min,\(^{[10]}\) this will result in an increase of 24 mmHg above baseline in 8-10 min. The test is considered positive if there are no respiratory movements at a \(\text{PaCO}_2\) of 60 mmHg or 20 mmHg above baseline in those with an elevated \(\text{PaCO}_2\).\(^{[9,11]}\) Certification of brain death is after a second apnea testing, the timing of which varies between countries. UK legislation states that the second test can be done at any time after the first when the blood gases have normalized.\(^{[12]}\) In the USA, amendments to the earlier guidelines suggest the performance of the apnea test after giving appropriate time for confirming absence of brain recovery and the use of only one apnea test.\(^{[13]}\) In India, the apnea test needs to be repeated after an interval of 6 h and certified by four physicians from a recommended panel, one of whom has to be a neurologist. The time of death is the time \(\text{PaCO}_2\) reaches the target value\(^{[1]}\) during the second apnea test.

The increase in intracranial pressure (ICP) that accompanies brain death spares the rostral portion beyond the second cervical spine and does not compromise blood supply to this area.\(^{[11]}\) This could be the explanation for complex motor movements at the spinal cord level even after diagnosing brain death.\(^{[1,9,14]}\)

**Troubleshooting during performance of apnea test**

1. Patient’s systolic blood pressure (SBP) ≤100 mmHg: Vasopressors, inotropes and fluid boluses need to be administered to keep the blood pressure (BP) above the target. The apnea test is aborted if systolic BP is ≤90 mmHg and the test needs to be repeated after stabilization.

2. Oxygen saturation not maintained during apnea testing: The apnea testing is terminated if the saturation is ≤85% for more than 30 s.\(^{[1]}\) The test can be retried with T-piece and continuous positive airway pressure of 10 cm H\(_2\)O and oxygen flow of 12.0 L/min. Reducing the positive end-expiratory pressure (PEEP) to 5 cm H\(_2\)O prior to disconnection from the ventilator for apnea testing can predict the tolerance to apnea.

3. Patient is hypothermic (<36.5°F): Guidelines for apnea testing are not valid and needs to be repeated after correction of hypothermia.

4. Patient repeatedly desaturates or becomes hypotensive during apnea testing: One should consider ancillary tests for confirming brain death (electroencephalography, cerebral angiography, transcranial Doppler and scintigraphy). In India, the laws are not clear about the use of ancillary tests.

**Table 1: Checklist prior to proceeding with tests for brain death**

| Prerequisite | Details |
|--------------|---------|
| Proximate cause for unresponsive state that is incompatible with survival | Major trauma, intracranial bleed with midline shift |
| Neurological imaging to confirm diagnosis | CT brain, MRI, angiography |
| Exclusion of associated medical conditions that could account for unresponsiveness | Exclusion of severe acid-base, metabolic or electrolyte abnormalities |
| Exclusion of drugs causing unresponsiveness | Sedatives, narcotics, muscle relaxants. In drug overdose allow time for 5 half-lives/measure drug levels |
| Normal temperature | Core temperature >32°C/90°F |

*CT = Computed tomography, MRI = Magnetic resonance imaging*

**Table 2: Clinical tests for brain death**

| Specific test | Nerves tested |
|---------------|---------------|
| Absent pupillary light reflex | Afferent II cranial nerve, efferent III nerve |
| Absent corneal reflex | Afferent V nerve, efferent VII nerve |
| Absent reflexes in the face and maxillary region | Area supplied by V cranial nerve (trigeminal) |
| Absent oculo-cephalic reflex (doll’s eye movement) | Afferent VIII, efferent III and VI. Lateral 90° movements of the neck result in deviation of the eyes in an opposite direction with an intact brain stem. Cervical spine injury must be ruled out prior to testing |
| Absent oculo-vestibular reflex | The afferent is the VIII and efferent III and VI cranial nerves. With the patient at a 30° head up position (lateral semicircular canal becomes vertical), 50 ml of ice-cold saline is injected into the ear. Nystagmus with a slow component toward the side of injection is seen with a functioning brain stem (confirm intact tympanic membrane. Allow 5 min to elapse prior to testing the other ear) |
| Absent pharyngeal (gag) and laryngeal (cough) reflex | Afferent IX and efferent X cranial nerves |
Care of the Potential Organ Donor

A brain-dead organ donor needs the same intensity of care with the focus of treatment directed toward organ perfusion and improved quality of grafts. Intensive care with the use of invasive lines is mandatory for improved quality of care and titration of inotropes and fluids.

A potential donor is one who is brain-dead or one with catastrophic brain injury with a clearly expressed intent from the physician and the family to withdraw life support. The organ procurement organization recently has adopted a “presumptive strategy” in counseling wherein grief counselors communicate with the family with the presumption that organ donation is the natural thing to be done and act both in the interests of the potential donor as well as the pool of recipients.

Pathophysiological changes following brain death and its relevance to organ preservation

The time from a diagnosis to declaration of brain death is complicated by fluctuating donor hemodynamics. The instability is greater when the time to organ retrieval from the diagnosis of brain death is longer. Even while ensuring optimum donor care, the inevitable hormonal and inflammatory changes accompanying brain death can result in graft dysfunction and increased chances of rejection. However, in the last two decades, increased awareness of donor management has contributed to improved outcomes following transplant surgery.

Cardiovascular system

In all patients with brain death, medullary ischemia associated with brain death causes a reflex hypertension and bradycardia (Cushing’s reflex). This is a reflex attempt by the body to maintain the CBF. Subsequent to this is a period of intense vasoconstriction and tachycardia associated with increased circulatory catecholamines, which can increase visceral and myocardial ischemia. The level of rise in catecholamines is dependent upon the rate of rise in ICP and could be as much as 1000 fold elevation from baseline if the rise in ICP is very rapid. The effects of the catecholamine surge on the myocardium are an altered metabolism associated with depletion of adenosine triphosphate in the cardiac myocyte. This can be documented by the fact that 20-25% brain-dead donors showed evidence of myocardial ischemia and 40% have echocardiographic evidence of myocardial dysfunction. Subsequent to the catecholamine surge resulting in hypertension is the depletion accompanied by vasodilatation and hypotension, which contributes to

Ancillary tests for establishing brain death

Ancillary tests can be used when uncertainty exists about the reliability of the neurologic evaluation or when the apnea test cannot be performed. However, the clinician will have to use his or her judgment on the use of these tests to support a brain stem death.

These tests are classified as tests that document cerebral blood flow (CBF) and those that evaluate the electrical activity of the brain. The conventional 4 vessel digital subtraction angiography is the gold standard for CBF documentation. Brain death is confirmed by demonstrating the absence of intracerebral filling at the level of the carotid bifurcation or vertebral arteries. Computerized tomography (CT) angiography has emerged as a safer alternative that can accurately document CBF.

Transcranial Doppler is recommended as an ancillary test and is used in Intensive Care Units (ICU) as it is simple, easily available and noninvasive. The presence of diastolic reverberation flow and little or no forward flow is diagnostic. The drawbacks include operator variability, inconsistent availability of an acoustic window, presence of a ventricular drain or concomitant surgery that could affect the interpretation.

Electroencephalography is widely used as an ancillary test for documentation of brain death. An isoelectric recording from 18 to 20 channels over a 30 min period is suggestive; however, electrical quiescence can occur from the use of sedative drugs and from hypothermia which must be excluded prior to interpretation.

Cerebral tissue perfusion techniques using technetium 99 m hexamethylpropylene amine oxime labeled brain perfusion study is being used in some centers as an ancillary test.

The AAN has discussed the role CT angiography, somatosensory evoked potentials, magnetic resonance angiography and have declared that there is insufficient evidence at this time to determine the accuracy of these tests in confirming cessation of function of the entire brain. The AAN recommends that the physician can decide against a declaration of brain death rather than ordering ancillary tests if the clinical findings are unreliable.

5. Baseline PaCO₂ ≥40 mmHg or ≤35 mmHg: A rise of ≥20 mmHg above baseline can be considered a positive apnea test in patients with elevated baseline PaCO₂. Reducing the frequency of ventilation to allow a PaCO₂ in the recommended range should be considered prior to testing for apnea.
the challenges in the maintenance of organ perfusion in brain death.

The goals in the management include maintenance of BP with minimal use of inotropes, optimizing the fluid management and maintenance of organ perfusion.[20] Figure 1.

An echocardiogram is indicated in all potential donors, and pulmonary artery catheterization (PAC) is indicated for donors with an ejection fraction (EF) <45%, more in the background of cardiac and lung transplants.

**Respiratory system**

A rise in pulmonary hydrostatic pressure causes damage to the pulmonary endothelium resulting in pulmonary edema that is perpetuated by endogenous epinephrine.[34] The goals of ventilatory management include minimal FiO\textsubscript{2} needed to maintain a PaO\textsubscript{2} >100 mmHg, SpO\textsubscript{2} >95%, PaCO\textsubscript{2} of 35-40 mmHg and pH 7.35-45. Earlier recommendations suggested liberal tidal volumes 8-15 ml/kg, but currently ventilation strategies similar to those used for acute lung injury (ALI) are recommended and have improved the use of lungs for transplant.[35]

Excessive fluid resuscitation to correct perfusion can result in pulmonary edema following an increase in extravascular lung water. The use of a PAC may restrict excessive fluid use. Albuterol has been used for reducing the pulmonary edema in human ex vivo studies[36] and can be considered along with diuretics in the treatment of pulmonary edema.

**Endocrine system, stress and metabolic responses**

The endocrine responses of the body are lost with brain death and form the rationale for hormone replacement therapy for brain-dead patients.

The posterior pituitary function is lost early in brain death with occurrence of diabetes insipidus with polyuria and hypernatremia. Arginine vasopressin and desmopressin can be given as replacements. The anterior pituitary functions are preserved for a slightly longer period. Thyroid hormone levels decrease and a state similar to the sick euthyroid state in critical illness can occur.

In addition to the decrease in insulin levels, hyperglycemia worsens with stress, alteration in carbohydrate metabolism and use of glucose solutions. Insulin levels normalize subsequently with an increase in C peptide levels. Hyperglycemia induced pancreatic cell damage may affect the pancreatic graft and measures aimed at strict euglycemia may minimize this risk. Hyperglycemia can also affect the outcomes after renal transplantation.[37]

Temperature regulation in the hypothalamus is affected, manifesting with initial hyperthermia followed by hypothermia. Hypothermia is worsened by lack of shivering, peripheral vasodilatation and a decrease in the metabolic rate. Hypothermia can worsen acidosis and coagulopathy, increase the risk for arrhythmias and cold-induced diuresis besides causing a leftward shift in the oxygen dissociation curve.

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**Hemodynamic Goals**

- Mean Arterial Pressure ≥ 60 mm Hg
- Urine output ≥ 1.0 ml/kg/h
- Left Ventricular Ejection Fraction > 45%

**Inotropes**

- Dopamine ≤ 10 mcg/kg/h
- Dobutamine ≤ 10 mcg/kg/h

**Pulmonary Artery Catheter Insertion**

**Goals**

- Cardiac index ≥ 2.4 l/min/m\textsuperscript{2}
- Pulmonary Capillary Wedge Pressure (PCWP): 8-12 mm Hg
- Systemic Vascular Resistance (SVR): 800-1200 dynes cm\textsuperscript{-5}

* Trans Esophageal Echocardiography can substitute pulmonary artery catheter for hemodynamic management

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**Figure 1: Hemodynamic management protocol**
**Systemic inflammatory response**

A systemic inflammatory response occurs and could be quite severe. This is mediated by inflammatory mediators from an ischemic brain, ischemic reperfusion injury, metabolic changes that occur during the catecholamine storm and an inadequately restored cardiovascular state. Increased plasma levels of interleukin-6 in the donor have translated to the poorer graft utilization and graft dysfunctions.\(^{38}\)

Disseminated intravascular coagulation occurs after brain death due to the release of tissue thromboplastin from necrotic brain tissue.

**Protocols for donor management**

The circulatory and biochemical variables are managed by the general principle of the “Rule of 100”\(^ {39}\) suggesting targets of SBP ≥100 mmHg, urine output ≥100 ml/h, hemoglobin of ≥100 g/L, PaO\(_2\) ≥100 mmHg and blood sugar targeted at 100% normal. Other elements of donor management are listed below:

1. **Temperature:** The aim is to keep the core temperature >35°C prior to organ donation. Circulating hot air blankets, warmed intravenous fluids and adjustments of ambient temperature may be needed to achieve this goal.

2. **Fluid management:** These patients are often polycyclic and dehydrated which is worsened by a vasoplegetic state resulting in central volume depletion. Crystalloids are the first choice and balanced salt solutions (Ringer’s lactate, Plasmalyte-A, Ringer’s acetate, half normal saline with sodium bicarbonate) may be superior to normal saline as they do not produce hyperchloremic acidosis.\(^ {40}\) Uncorrected hypernatremia could result in graft losses after liver transplant.\(^ {41}\) Hydroxyethylstarches are contraindicated in organ donors because they can damage renal epithelial cells and cause early graft dysfunction in the transplanted kidneys.\(^ {42}\) There is little evidence to date supporting the use of gelatins in donors. A restrictive strategy with monitoring of filling pressures with a PAC may be beneficial particularly in the context of lung transplant. Studies have documented the impact of fluid loading\(^ {43-45}\) on outcomes in lung transplantation. This does not affect the quality of the renal graft for transplantation.\(^ {46}\) Replacement of blood and blood products could follow guidelines for the care of the critically ill and a hemoglobin of 10 g/L could improve tissue oxygenation indices.

3. **Inotropes and cardiovascular system:** Dopamine is the first choice of inotrope in hypotension unresponsive to volume and has beneficial effects on the renal graft. Though it has no renal protective effect and may predispose to arrhythmias, the benefits are probably related to moderation of preservation injury and inflammation, donor cardiovascular effects, or recipient treatment.\(^ {47,48}\) Nor-adrenaline in doses >0.05 mcg/kg/min resulted in impaired cardiac contractility in transplanted hearts and in particular impairment of right ventricular performance.\(^ {50}\)

4. **Ventilatory management:** The principles are along the lines of management of ALI (low tidal volume 6-8 ml/kg, minimum plateau pressure, lung recruitment). The lowest FiO\(_2\) needed should be used, and optimal PEEP with a restrictive fluid strategy improves graft harvesting for lung transplants.

5. **Replacement of hormones after brain death:** Standardization of hormone therapy after brain death in combination with a central venous pressure <10 mmHg significantly improved utilization of the heart and lungs for transplant without affecting other organ systems.\(^ {49}\)

The recommended replacements are:

a. Vasopressin 1 U bolus followed by an infusion of 0.5-4.0 U/h (desmopressin intranasally has a selective action on the V2 receptors and a half-life varying from 6 to 20 h).\(^ {201}\)
b. Methylprednisolone 15 mg/kg immediately after diagnosis of brain death and 24th hourly thereafter.
c. Insulin 10 U in 50% dextrose followed by an infusion to maintain blood glucose between 80 and 150 mg.
d. Thyroxine (T4) 20 mcg bolus followed by infusions of 10 mcg/h. Tri-iodothyronine (T3) given as a 4-mcg bolus followed by an infusion of 3 mcg/h. T4 improves hemodynamics and prevents cardiovascular collapse in hemodynamically unstable organ donors.\(^ {50}\)

An analysis of 10 years data of several hormone replacement modalities in the United Network for Organ Sharing (UNOS) data showed that the combination of thyroid hormone, corticosteroid, insulin and antidiuretic hormone was the best for multiple organ procurement.\(^ {51}\)

**Other concerns and considerations**

Barring overwhelming sepsis, bacteremia or fungemia in the donor are not absolute contraindications to donations.\(^ {52}\)

However, infections with human immunodeficiency-virus, herpetic meningo-encephalitis and T-cell leukemia-lymphoma virus preclude organ donation.\(^ {33}\)

Registries supported by the state governments, Tamil Nadu Network of Organ Sharing and Kerala Network on Organ Sharing have substantially increased organ donation in south India.\(^ {53,54}\)

Concerns exist in some areas such as the role of ancillary testing and the accepted modality for certification that is safe
and confirmative. Continuation of organ support in a pregnant patient who is brain-dead has again been controversial.[53]
A systematic review of brain death during pregnancy has concluded that the mother should be supported until the delivery of the fetus and then can be considered for organ donation.[56]

In the background of growing enthusiasm to support organ donation and multiple organ transplants one must keep in mind that preoperative donor screening for viruses may be missed in the first 2 weeks of infection. Transmission of HIV and rabies from infected donors has been documented.[57,58]

**Conclusion**

“Care of the donor” is essentially “the simultaneous care of multiple recipients.” The barriers that exist in limited resource environments are the time to diagnosis and the costs involved in sustaining care for the brain-dead donor to the point when consent is obtained. The recognition and acceptance of brain death, awareness amongst public on the eventuality and consent is obtained. The diagnosis and apnea test safety. Ann Indian Acad Neurol 2002;58:20-5.

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