Review Article

Brain death and care of the organ donor

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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.

Key words: Brain death, organ donation, donor care

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 20th 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.

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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 (PaO_2 ≥200 mmHg after 100% oxygenation) and near normal $PaCO_2$ (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 $PaCO_2$ 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 $PaCO_2$ of 60 mmHg or 20 mmHg above baseline in those with an elevated $PaCO_2$.[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 $PaCO_2$ 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_2O and oxygen flow of 12.0 L/min. Reducing the positive end-expiratory pressure (PEEP) to 5 cm H_2O 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

5. Baseline $PaCO_2$ ≥40 mmHg or ≤35 mmHg: A rise of ≥20 mmHg above baseline can be considered a positive apnea test in patients with elevated baseline $PaCO_2$. Reducing the frequency of ventilation to allow a $PaCO_2$ in the recommended range should be considered prior to testing for apnea.

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.[15] However, the clinician will have to use his or her judgment on the use of these tests to support a brain stem death.[16]

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.[11] Computerized tomography (CT) angiography has emerged as a safer alternative that can accurately document CBF.[10,11,17]

Transcranial Doppler is recommended as an ancillary test and is used in Intensive Care Units (ICU) as it is simple, easily available and noninvasive.[18] 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 isolelectric 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.[19]

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.[1] 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.[1]

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.[20] 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.[21]

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.[22] 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.[23,24] However, in the last two decades, increased awareness of donor management has contributed to improved outcomes following transplant surgery.[25-28]

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.[29] Subsequent to this is a period of intense vasoconstriction and tachycardia associated with increased circulatory catecholamines, which can increase visceral and myocardial ischemia.[30] 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.[31] 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.[32,33] Subsequent to the catecholamine surge resulting in hypertension is the depletion accompanied by vasodilatation and hypotension, which contributes to

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_2 needed to maintain a PaO_2 >100 mmHg, SpO_2 >95%, $PaCO_2$ 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.

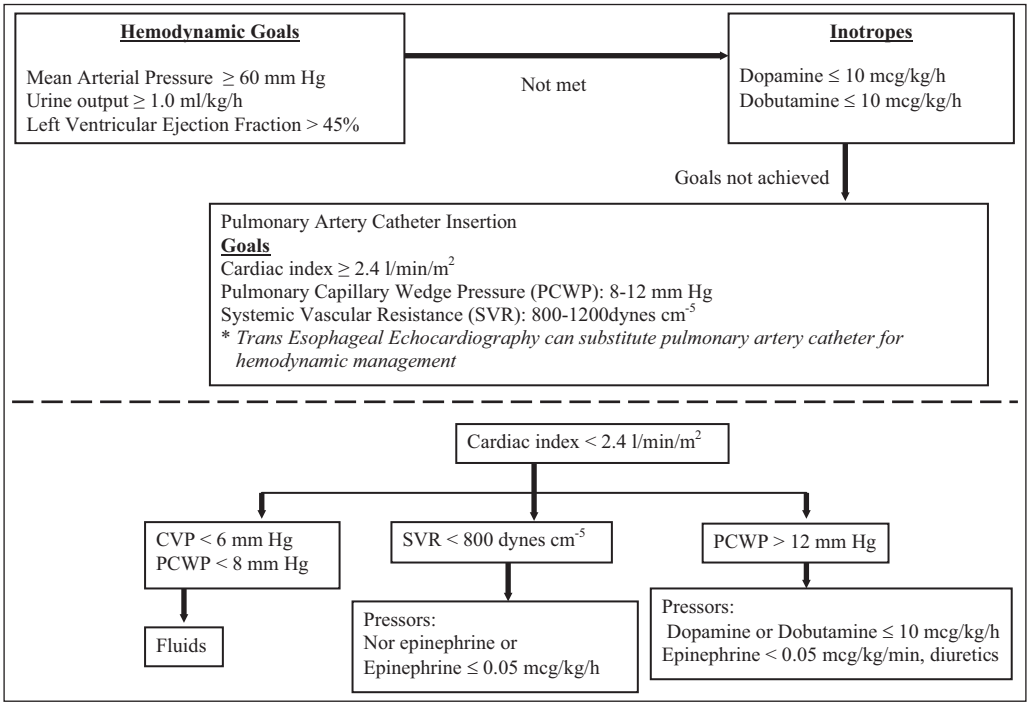

Figure 1: Hemodynamic management protocol

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 polyuric and dehydrated which is worsened by a vasoplegic 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.[30]
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.[20])
   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.[55] 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 resources to support the organ donor to improve the numbers and quality of donor organs will be the immediate goals in our country.

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References

1. Wijdicks EF, Varelas PN, Gronseth GS, Greer DM, American Academy of Neurology. Evidence-based guideline update: Determining brain death in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2010;74:1911-8.
2. Shroff S. Legal and ethical aspects of organ donation and transplantation. Indian J Urol 2009;25:348-55.
3. Wijdicks EF. Brain death worldwide: Accepted fact but no global consensus in diagnostic criteria. Neurology 2002;58:20-5.
4. Machado C, Perez J, Scherle C, Areu A, Pando A. Brain death diagnosis and apnea test safety. Ann Indian Acad Neurol 2009;12:197-200.
5. Amalorpavanathan J, Shroff S, Karunakaran CE, Castro R. Annual Report from Tamil Nadu Organ Sharing Registry for the year 2013-2014. Available from: http://www.tnos.org/pdf/report.pdf. [Last accessed on 2015 Feb 25].
6. Gómez MP, Arredondo E, Páez G, Manyalich M. International Registry in Organ Donation and Transplantation 2010. Transplant Proc 2012;44:1592-7.
7. Johnson RJ, Bradbury LL, Martin K, Neuberger J. UK transplant registry organ donation and transplantation in the UK-the last decade: A report from the UK national transplant registry. Transplantation 2014;97 Suppl 1:S1-27.
8. Sherrington A, Smith M. International perspectives in the diagnosis of brain death in adults. Trends Anaesth Crit Care 2012;2:48-52.
9. Dwyer R, Calreavy F, Phelan D. Diagnosis of Brain death and Medical management of the Organ Donor. Guidelines for Adult patients 2010. Intensive care Society of Ireland. Available from: https://www.anaesthesia.ie/archive/ICSI/ICSI%20Guidelines%20MAY10.pdf.[Last accessed on 2015 Mar 02].
10. Smith M. Brain death. In: Bersten AD, Soni M. editors. Oh's Intensive Care Manual. 7th ed., Ch. 53. Oxford: Butterworth Heinemann, Elsevier 2014; p. 591-6.
11. Mori K, Shingu K, Nakao S. Brain death. In: Miller RD, editor. Miller's Anaesthesia. 7th ed., Ch. 98. Philadelphia, PA: Churchill-Livingstone, Elsevier; 2010; p. 3007.
12. A code of practice for the diagnosis and confirmation of death. Academy of the Medical Royal Colleges. London, 2008. Available from: http://www.aomrc.org.uk/reports-guidance.html.[Last accessed on 2015 Mar 01].
13. Guidelines for determining brain-death-New York State department of health and New York State Task force on life and law. Available from: https://www.health.ny.gov/professionals/.../brain death guidelines.[Last accessed on 2014 Dec 30].
14. Saposnik G, Bueri JA, Mauriño J, Saizar R, Garretto NS. Spontaneous and reflex movements in brain death. Neurology 2000;54:221-3.
15. Young GB, Shemie SD, Doig CJ, Teitelbaum J. Brief review: The role of ancillary tests in the neurological determination of death. Can J Anaesth 2006;53:620-7.
16. Webb A, Samuels O. Brain death dilemmas and the use of ancillary testing. Continuum (Minneap Minn) 2012;18:659-68.
17. Welschehold S, Boor S, Reuland K, Thömke F, Kerz T, Reuland A, *et al.* Technical aids in the diagnosis of brain death: A comparison of SEP, AEP, EEG, TCD and CT angiography. Dtsch Arztebl Int 2012;109:624-30.
18. Sharma D, Souter MJ, Moore AE, Lam AM. Clinical experience with transcranial Doppler ultrasonography as a confirmatory test for brain death: A retrospective analysis. Neurocrit Care 2011;14:370-6.
19. Sinha P, Conrad GR. Scintigraphy in the confirmation of brain death: Indian context. Indian J Nucl Med 2012;27:1-4.
20. Wood KE, Becker BN, McCartney JG, D'Alessandro AM, Coursin DB. Care of the potential organ donor. N Engl J Med 2004;351:2730-9.
21. Truog RD. Consent for organ donation — balancing conflicting ethical obligations. N Engl J Med 2008;358:1209-11.
22. Nygaard CE, Townsend RN, Diamond DL. Organ donor management and organ outcome: A 6-year review from a Level I trauma center. J Trauma 1990;30:728-32.
23. Oto T, Excell L, Griffiths AP, Levvey BJ, Bailey M, Marasco S, *et al.* Association between primary graft dysfunction among lung, kidney and heart recipients from the same multiorgan donor. Am J Transplant 2008;8:2132-9.
24. Bos EM, Leuvenink HG, van Goor H, Ploeg RJ. Kidney grafts from brain dead donors: Inferior quality or opportunity for improvement? Kidney Int 2007;72:797-805.
25. Jenkins DH, Reilly PM, Schwab CW. Improving the approach to organ donation: A review. World J Surg 1999;23:644-9.
26. Lopez-Navidad A, Caballero F. For a rational approach to the critical points of the cadaveric donation process. Transplant Proc 2001;33:795-805.
27. Wheeldon DR, Potter CD, Oduro A, Wallwork J, Large SR. Transforming the "unacceptable" donor: Outcomes from the adoption of a standardized donor management technique. J Heart Lung Transplant 1995;14:734-42.
28. Rosendale JD, Chabalewski FL, McBride MA, Garrity ER, Rosengard BR, Delmonico FL, *et al.* Increased transplanted organs

from the use of a standardized donor management protocol. Am J Transplant 2002;2:761-8.
29. Agrawal A, Timothy J, Cincu R, Agarwal T, Waghmare LB. Bradycardia in neurosurgery. Clin Neurol Neurosurg 2008;110:321-7.
30. McKeown DW, Bonser RS, Kellum JA. Management of the heartbeating brain-dead organ donor. Br J Anaesth 2012;108 Suppl 1:i96-107.
31. Pinelli G, Mertes PM, Carteaux JP, Jaboin Y, Escanye JM, Brunotte F, *et al*. Myocardial effects of experimental acute brain death: Evaluation by hemodynamic and biological studies. Ann Thorac Surg 1995;60:1729-34.
32. Dujardin KS, McCully RB, Wijdicks EF, Tazelaar HD, Seward JB, McGregor CG, *et al*. Myocardial dysfunction associated with brain death: Clinical, echocardiographic, and pathologic features. J Heart Lung Transplant 2001;20:350-7.
33. Venkateswaran RV1, Townend JN, Wilson IC, Mascaro JG, Bonser RS, Steeds RP. Echocardiography in the potential heart donor. Transplantation 2010 15;89:894-901.
34. Novitzky D, Wicomb WN, Rose AG, Cooper DK, Reichart B. Pathophysiology of pulmonary edema following experimental brain death in the chacma baboon. Ann Thorac Surg 1987;43:288-94.
35. Mascia L, Pasero D, Slutsky AS, Arguis MJ, Berardino M, Grasso S, *et al*. Effect of a lung protective strategy for organ donors on eligibility and availability of lungs for transplantation: A randomized controlled trial. JAMA 2010;304:2620-7.
36. Sakuma T, Folkesson HG, Suzuki S, Okaniwa G, Fujimura S, Matthay MA. Beta-adrenergic agonist stimulated alveolar fluid clearance in *ex vivo* human and rat lungs. Am J Respir Crit Care Med 1997;155:506-12.
37. Blasi-Ibanez A, Hirose R, Feiner J, Freise C, Stock PG, Roberts JP, *et al*. Predictors associated with terminal renal function in deceased organ donors in the intensive care unit. Anesthesiology 2009;110:333-41.
38. Murugan R, Venkataraman R, Wahed AS, Elder M, Hergenroeder G, Carter M, *et al*. Increased plasma interleukin-6 in donors is associated with lower recipient hospital-free survival after cadaveric organ transplantation. Crit Care Med 2008;36:1810-6.
39. Gelb AW, Robertson KM. Anaesthetic management of the brain dead for organ donation. Can J Anaesth 1990;37:806-12.
40. Wood K, McCartney J. Management of the potential organ donor. Transplant Rev 2007;21:204-18.
41. Totsuka E, Fung JJ, Ishii T, Urakami A, Moras NP, Hakamada K, *et al*. Influence of donor condition on postoperative graft survival and function in human liver transplantation. Transplant Proc 2000;32:322-6.
42. Cittanova ML, Leblanc I, Legendre C, Mouquet C, Riou B, Coriat P. Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients. Lancet 1996;348:1620-2.
43. Angel LF, Levine DJ, Restrepo MI, Johnson S, Sako E, Carpenter A, *et al*. Impact of a lung transplantation donor-management protocol on lung donation and recipient outcomes. Am J Respir Crit Care Med 2006;174:710-6.
44. Pennefather SH, Bullock RE, Dark JH. The effect of fluid therapy on alveolar arterial oxygen gradient in brain-dead organ donors. Transplantation 1993;56:1418-22.
45. Venkateswaran RV, Patchell VB, Wilson IC, Mascaro JG, Thompson RD, Quinn DW, *et al*. Early donor management increases the retrieval rate of lungs for transplantation. Ann Thorac Surg 2008;85: 278-86.
46. Miñambres E, Rodrigo E, Ballesteros MA, Llorca J, Ruiz JC, Fernandez-Fresnedo G, *et al*. Impact of restrictive fluid balance focused to increase lung procurement on renal function after kidney transplantation. Nephrol Dial Transplant 2010; 25:2352-6.
47. Schnuelle P, Gottmann U, Hoeger S, Boesebeck D, Lauchart W, Weiss C, *et al*. Effects of donor pretreatment with dopamine on graft function after kidney transplantation: A randomized controlled trial. JAMA 2009;302:1067-75.
48. Schnuelle P, Yard BA, Braun C, Dominguez-Fernandez E, Schaub M, Birck R, *et al*. Impact of donor dopamine on immediate graft function after kidney transplantation. Am J Transplant 2004;4: 419-26.
49. Abdelnour T, Rieke S. Relationship of hormonal resuscitation therapy and central venous pressure on increasing organs for transplant. J Heart Lung Transplant 2009;28:480-5.
50. Salim A, Vassiliu P, Velmahos GC, Sava J, Murray JA, Belzberg H, *et al*. The role of thyroid hormone administration in potential organ donors. Arch Surg 2001;136:1377-80.
51. Mi Z, Novitzky D, Collins JF, Cooper DK. The optimal hormonal replacement modality selection for multiple organ procurement from brain-dead organ donors. Clin Epidemiol 2014;7:17-27.
52. Angelis M, Cooper JT, Freeman RB. Impact of donor infections on outcome of orthotopic liver transplantation. Liver Transpl 2003;9:451-62.
53. Shroff S, Navin S, Abraham G, Rajan PS, Suresh S, Rao S, *et al*. Cadaver organ donation and transplantation-an Indian perspective. Transplant Proc 2003;35:15-7.
54. Shroff S, Rao S, Kurian G, Suresh S. Organ donation and transplantation-the Chennai experience in India. Transplant Proc 2007;39:714-8.
55. Magnus DC, Wilfond BS, Caplan AL. Accepting brain death. N Engl J Med 2014;370:891-4.
56. Esmaeilzadeh M, Dictus C, Kayvanpour E, Sedaghat-Hamedani F, Eichbaum M, Hofer S, *et al*. One life ends, another begins: Management of a brain-dead pregnant mother-A systematic review-. BMC Med 2010;8:74.
57. Halpern SD, Shaked A, Hasz RD, Caplan AL. Informing candidates for solid-organ transplantation about donor risk factors. N Engl J Med 2008;358:2832-7.
58. Srinivasan A, Burton EC, Kuehnert MJ, Rupprecht C, Sutker WL, Ksiazek TG, *et al*. Transmission of rabies virus from an organ donor to four transplant recipients. N Engl J Med 2005;352: 1103-11.

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