

# Organ donor problems and their management

V. Shah, G. Bhosale

## Abstract

In recent years, transplantation has assumed an important role in the treatment of patients with end-stage organ failure. With the passage of Transplantation of Human Organ Act by the Indian parliament, transplantation of organs from brain dead donors has become a reality. Although there are many issues in success of cadaver programme, intensivists can play a crucial role by converting a potential donor into an actual donor. This article reviews the identification of potential organ donor and pathophysiological changes surrounding brain death, with particular emphasis on management of the organ donor in the intensive care unit. With an increased awareness of donor management issues and the application of a rational physiological approach, the number of functional organs for transplantation can be increased.

**Key words:** Transplantation, organ donor, selection, management.

Organ transplantation has achieved a state of preferred therapeutic option for patients with end-stage organ failure, in the western world. Cadaver donors form the largest pool of organs, approaching 95% and 70% in Europe and USA, respectively.<sup>[1]</sup> However, the predominant limitation to broader application of clinical transplantation is the inadequate number of donor organs available.<sup>[2]</sup>

In a developing country like ours, slow growth of organ transplantation is due to high costs involved, lack of facilities in government hospitals, non-availability of a suitable donor from the family and lack of well-developed cadaver programme. Since the passage of THO (Transplantation of Human Organ) Act by the Indian parliament in 1994, about 1000 cadaver organ transplants have been performed so far, with acceptable

results.<sup>[3]</sup> It is estimated that every year, 3500 kidney transplants are being performed in our country, out of which  $\leq 2\%$  are from cadaver donors<sup>[4]</sup> with sporadic reports of transplantation of other organs. There is a large pool of cadaver donors available in our country and if this is mobilized, there will not be any need to undertake living organ donation. This alone will stop unethical transplants involving commerce.<sup>[5]</sup>

## Successful Organ Donation Requires

- Identification of potential organ donor
- Determination and certification of brain death
- Consent to organ donation from the family
- Diagnosis and management of organ donor problems
- Organ retrieval and transplantation

Although we need a well-organized system and infrastructural support from government and non-government organizations to support the cadaver programme, the intensivist can play a very crucial role by converting a potential donor into an actual donor. It is the aim of this review to provide insight into problems of brain dead donors, their aetiology, pathophysiology and management.

### From:

Department of Anaesthesia and Critical Care, Institute of Kidney Diseases and Research Centre, Institute of Transplantation Sciences, Civil Hospital Campus, Ahmedabad, India

### Correspondence:

Dr. Veena Shah, Department of Anaesthesia and Critical Care, Institute of Kidney Diseases and Research Centre, Institute of Transplantation Sciences, Civil Hospital Campus, Ahmedabad - 380 016, India.  
E-mail: drveenarshah@yahoo.co.in

## Recognition of Potential Organ Donor

Any comatose patient with a known aetiology of irreversible cerebral damage who is likely to progress to brain death prior to terminal circulatory arrest, should be considered a potential organ donor. The absolute contraindications are:

- Uncontrolled sepsis
- Active viral infection - Hepatitis B and C, CMV, Herpes simplex
- HIV-positive serology
- Malignancy (except primary intracranial tumor, non-melanotic skin cancer and Ca-cervix in situ)

Ideally, the donor should be less than 60 years of age, without end organ damage from systemic disease, but these criteria have been liberalized, considering organ shortage.<sup>[6]</sup> Besides these general criteria, it is important to determine the intrinsic function of the organs to be transplanted and to ascertain that the illness has not impaired these organs irreversibly.

## Pathophysiology of Brain Death

Brain death is a catastrophic physiological event, associated with significant deterioration in the function of the organs distant from the brain. These changes occur due to the process of brain dying, as well as due to loss of integrated neurological function, with its central role in the coordination of autonomic and other basic organ functions. Even with maximal support, cardio-respiratory deterioration leading to somatic death will occur within days.<sup>[7,8]</sup>

In the early phase of the brain death process, massive sympathetic outflow produced as a result of cerebral ischemia (Cushing's reflex), exposes organs to extreme sympathetic stimulation. This is an adaptive response to maintain cerebral perfusion pressure. Organs suffer an ischaemic insult during this phase, the severity directly correlating with speed of herniation.<sup>[9]</sup> This early phase is followed by a profound reduction in sympathetic outflow, with loss of autonomic tone resulting in vasodilatation and hypotension. Coincident ischaemic damage to the hypothalamus and pituitary, results in temperature and endocrine dysfunction. During this period, circulation must be supported, respiration is artificially maintained and normal physiological sequelae of brain death should be anticipated and corrected.<sup>[10]</sup>

## Intensive Care Management

The most important goals in the management of brain dead organ donors are: hemodynamic stability and support of body homeostasis until the organs are retrieved. There is a shift in emphasis from cerebral protection with its usual accompaniment of intravascular volume depletion, to the optimization of organ perfusion and tissue oxygen delivery.

## Routine Care and Monitoring

Regular nursing care must be continued after brain death. Frequent turning of patient for decubitus ulcer prophylaxis, skin care, dressing changes, urinary and intravascular catheter care, must be meticulous to minimize the risk of infection. A nasogastric tube must be inserted for gastric decompression and prevention of aspiration. If necessary, arterial and central venous lines should be inserted into the upper extremities, because femoral line readings can become inaccurate during surgical procedure for organ procurement.<sup>[11]</sup>

Routine monitoring includes ECG, blood pressure, pulse oximetry, core temperature, U/O and central venous pressure. Use of a Swan-Ganz catheter for measurement of pulmonary capillary wedge pressure and pulmonary venous oxymetry, should be reserved for unstable donors, who have persistent acidosis with evidence of tissue hypoperfusion.<sup>[12]</sup>

Laboratory parameters like hemoglobin, hematocrit, complete blood count, blood glucose, urine analysis, blood urea nitrogen, serum creatinine, serum electrolytes, liver function tests, coagulation profile and microbiological screening for hepatitis B, C, HIV are necessary. Cultures of blood and urine may be required, if there is evidence of infection, or if the patient is hospitalized for more than 72 hours.<sup>[13]</sup> Some additional tests may be required for multiorgan donors e.g. echocardiography for heart and bronchoscopy for lung transplantation.

## Cardiovascular Support

Hypotension is the most common hemodynamic abnormality observed in upto 91% of brain-dead organ donors.<sup>[14]</sup> The contributing factors are multifactorial and include hypovolaemia, damage to vasomotor centre, left heart dysfunction and endocrine failure.

Fluid resuscitation is the cornerstone therapy for management of hypotension. Choice of fluid is guided by the patient's hematocrit and electrolyte status. It is suggested that hematocrit level of 25-30%, or hemoglobin level of 10 gm/dl should be targeted,<sup>[15]</sup> as the brain-dead patient's organs may have already suffered varying degrees of ischaemia-reperfusion injury and thus have compromised microcirculation. If haemodynamic goals are not achieved with volume replacement (CVP: 6-10 mm of Hg), vasoactive drugs are added.

There are widely divergent opinions over the best inotrope or pressor agents in these patients.<sup>[16]</sup> The first choice is usually dopamine, at a dose less than 10 µg/kg/min. Infusion rates >10 µg/kg/min have been associated with an increase in the incidence of acute tubular necrosis and decrease in the perfusion of other organs, due to splanchnic vasoconstriction.<sup>[17]</sup> Dobutamine (<10 µg/kg/min) and isoproterenol are considered second line agents, because of peripheral vasodilatation and poor tolerability.<sup>[18]</sup> If adequate B.P. (MAP > 70 mmHg) is not achieved, norepinephrine (0.5-2.5 µg/kg/min,) or epinephrine (2-4 µg/min), are added to treat severe systemic vasodilatation reducing dopamine to renal dose. If higher doses of catecholamines are required, addition of vasopressin (0.01-0.04 U/min) has been shown to enhance vascular catecholamine sensitivity, diminishing catecholamine requirements.<sup>[19,20]</sup> If hypotension persists despite fluid loading and optimum dose of vasopressors and inotropes, hormonal resuscitation with hydrocortisone, triiodothyronine and insulin, is worth considering.<sup>[21]</sup>

Hypertension, tachyarrhythmias and ischemic changes on ECG, may be seen around the time of brain stem coning, due to "autonomic storm", which is usually shortlived. In most of the cases, treatment is not required, however if lowering of BP or pulse rate is considered necessary, use of short acting vasodilator agents (e.g. nitroprusside), rapidly reversible β-adrenergic antagonists (e.g. esmolol), or antiarrhythmics (e.g. lidocaine), should be considered. Calcium channel blockers and long acting β-adrenergic antagonists should be avoided, because of negative inotropic effects and inability to titrate them precisely.<sup>[12]</sup>

Bradyarrhythmias during early phase of brain herniation are part of Cushing's reflex and do not require treatment. Haemodynamically significant bradyarrhythmias require use of either isoproterenol or epinephrine, because of lack of chronotropic effect of atropine after brain death.<sup>[22,23]</sup>

Cardiac arrest occurs in 25% of all donors during the maintenance phase<sup>[24]</sup> and should be treated with routine measures, with the exception that isoproterenol or epinephrine should be given during cardiopulmonary resuscitation, instead of atropine.

## Ventilatory Support

After brain death is declared, vigorous tracheobronchial toilet is important with frequent suctioning, using sterile precautions. The lungs must be inflated by manual inflation at regular intervals, to minimize the risk of atelectasis and infection. Standard management is aimed at maintaining PaO<sub>2</sub> between 70-100 mm Hg, using tidal volumes of 8-12 ml/kg, FiO<sub>2</sub><0.6, PEEP <5 cm H<sub>2</sub>O, keeping PaCO<sub>2</sub> within normal range.<sup>[25]</sup> If PaO<sub>2</sub> is <70 mm Hg, FiO<sub>2</sub> is increased to maintain SaO<sub>2</sub> >95% and PEEP is increased carefully, monitoring its effect on cardiac output and plateau pressure (<30 cm H<sub>2</sub>O), to reduce the risk of barotrauma.

Pulmonary edema in organ donors can be cardiogenic, neurogenic,<sup>[26]</sup> aspiration induced, or because of fluid overload. Treatment is supportive and excessive use of crystalloids should be avoided. If large amounts of crystalloids are required for resuscitation, addition of colloids or blood transfusions should be considered. All blood and blood products should be screened for HIV, HBsAg and HCV.

## Acid-Base Balance

Brain dead donors can develop respiratory alkalosis secondary to mechanical hyperventilation as a part of treatment protocol for elevated intracranial pressure, or lactic metabolic acidosis due to dehydration or tissue ischaemia. Both have deleterious effect on tissue oxygen delivery; hence, arterial pH should be adjusted to normal values. Treatment is first directed towards correcting cause, changing ventilatory parameters and finally pharmacological agents are administered to correct the calculated acid-base deficit.<sup>[27]</sup>

## Renal Support

Maintaining adequate systemic perfusion pressure and brisk urine output (>1-2 ml/kg/hr), while minimizing the use of vasopressors, contributes to good renal allograft function.<sup>[12]</sup> If urine output is less (<1 ml/kg/hr) after adequate volume loading, loop diuretics (furosemide), or osmotic diuretics (mannitol) should be used. Use of nephrotoxic drugs (aminoglycosides) and agents that adversely affect renal perfusion (e.g. NSAIDs), should be avoided.<sup>[12]</sup>

## Endocrine Dysfunction

Central Diabetes Insipidus (CDI) is present in over 70% of brain-dead donors,<sup>[28]</sup> resulting from insufficient blood levels of ADH from posterior pituitary. This should be suspected with the appearance of polyuria along with hypernatremia (S.Na  $\geq$ 150 mmol/L), hyperosmolality ( $\geq$ 310 mOsm/L) and inappropriately diluted urine (osmolality < 300 mOsm/L).

The management of CDI requires frequent monitoring of U/O, serum electrolytes, glucose and urinary electrolytes. Once U/O exceeds 300 ml/hr or 4 ml/kg/hr, desmopressin (1-4  $\mu$ g 8-12 hrly), a synthetic analogue of vasopressin is administered. It has enhanced antidiuretic potency, greatly diminished pressor activity and prolonged half-life as compared to Vasopressin.<sup>[29]</sup> If refractory hypotension is a problem, Desmopressin should be changed to Vasopressin (1 U bolus + infusion 0.5-4 U/hr).

Polyuria also causes obligatory loss of fluid and electrolytes, which should be aggressively managed to maintain haemodynamic and electrolyte stability. The common practice is to replace the previous hour's U/O with a hypotonic fluid (5% Dextrose in 0.45% NaCl), with close monitoring of electrolytes, as elevated serum sodium is a risk factor for delayed or primary nonfunction of grafted organs.<sup>[30]</sup>

Hyperglycemia in brain-dead donors may be due to stress, catecholamine-induced insulin resistance, steroid administration for treatment of cerebral edema, or infusion of large amounts of dextrose-containing IV fluids. There is no evidence of pancreatic endocrine failure.<sup>[31]</sup> As hyperglycemia leads to osmotic diuresis and electrolyte disturbances, it should be treated with insulin to keep blood glucose between 120-180 mg/dl.

There is a controversy regarding benefits of supplementation with hormones synthesized under anterior pituitary control (T3, T4, Corticosteroids), as variable blood levels of these hormones have been documented.<sup>[32-34]</sup> Although animal experiments have shown favorable outcome with administration of exogenous T3, findings in various human studies are inconsistent.<sup>[35-37]</sup> However, in patients with persistent hemodynamic instability, use of intravenous T3 (4  $\mu$ g bolus + infusion at 3  $\mu$ g/hr), Methylprednisolone (15 mg/kg/day) and Vasopressin have been associated with decrease in requirement of vasopressors, resumption of aerobic metabolism and more organs being available for transplantation.<sup>[38-40]</sup>

## Temperature Regulation

After brain death, the body becomes poikilothermic, because of loss of thalamic and hypothalamic central temperature control mechanisms. Systemic vasodilatation, administration of cold IV fluids and blood products, will further aggravate the problem. Hypothermia can lead to cardiac irritability, coagulopathy and reduce oxygen delivery to tissues. It also precludes the certification of brain death,<sup>[40]</sup> so donor core temperature must be maintained  $\geq$ 34<sup>o</sup> C. It is preferable to prevent hypothermia by using humidified, heated ventilator gases, warming IV fluids and forced air warming blankets.

## Coagulation System

Coagulopathy and disseminated intravascular coagulation are not uncommon findings in brain-dead donors, particularly in head injury patients, due to release of thromboplastin from the injured brain.<sup>[41,42]</sup> Other reasons are dilutional coagulopathy due to large volume resuscitation, massive blood transfusion for trauma, or hypothermia. If it results in clinically significant bleeding, treatment with appropriate blood components is required. Antifibrinolytic agents like Epsilon aminocaproic acid should not be used in organ donors, due to their potential of inducing microvascular thrombosis, thus rendering organs potentially unsuitable for transplantation.<sup>[12]</sup>

## Ischaemia-Reperfusion Injury

Brain death is also proposed to induce organ dysfunction via ischemia reperfusion injury, due to vasoconstriction and low flow associated with autonomic storm, followed by vasodilatation and reflow. Recent studies suggest that there is up-regulation of

inflammatory cytokines, increased expression of cell adhesion molecule/antigen and widespread microvascular and endothelial changes.<sup>[43,44]</sup> Use of cytoprotective strategies with high dose steroids, N-acetylcysteine and P-selectine inhibitors, have shown to improve short and long term recipient organ function.<sup>[45-47]</sup>

## Summary

Care of the brain-dead donor involves stepping in and reversing the normal sequelae of brain death, that ultimately results in somatic death. The aim is to support the body function with adequate oxygenation and tissue perfusion, till organs are retrieved, because the success of the transplant depends on quality of donor care during this critical period. The therapeutic end-points for adequate tissue perfusion are summarized by Gelb and Robertson,<sup>[48]</sup> as follows:

Rule of 100's: SBP >100 mm Hg  
 U/O >100 ml / hr  
 PaO<sub>2</sub> >100 mm Hg  
 Hb >100 gm / L

Avoiding lactic acidosis (pH = 7.35 – 7.45) and hypothermia (temperature > 34°C).

This finally results in a new life after successful organ transplantation.

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