Physiological changes after brain stem death and management of the heart-beating donor

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Key points

Despite the increasing importance of organ transplantation, the number of organs from brain-dead donors is decreasing.

Brain stem death causes adverse cardiovascular, respiratory, endocrine, and metabolic changes.

Optimization of donor physiology increases the number of transplantable organs.

The use of a protocol helps guide a target-driven therapy.

For the financial year ending March 2011, 7797 people were registered for a solid organ transplant in the UK,[1] with 2686 cadaveric organs transplanted during this period. Between April 2009 and March 2010, 978 lives were saved through transplantation of lungs and non-paired organs, and it is now recognized that, where once deemed to be 'life-improving' and cost-effective, kidney transplants also prolong life expectancy. The number of people requiring organ transplantation continues to increase as a result of an ageing population and expanding indications for transplantation (e.g. hepatocellular carcinoma).[2] Despite the increasing importance of organ donation, the numbers of organ donations after a neurological diagnosis of death (i.e. brain dead donors) are decreasing.[1] Organ donation after neurological death represents the only source of thoracic organs suitable for transplantation. It is, therefore, increasingly important to actively manage brain-dead donors. Suboptimal donor management reduces the number and quality of organs for transplantation with 10–20% of potential donors lost due to progression from brain death to cardiac arrest.[3]

Pathophysiological changes of brain stem death[4]

Increased intracranial pressure (ICP) initially causes an increase in arterial pressure to maintain cerebral perfusion pressure. If ICP continues to increase, then brain herniation ensues with pontine ischaemia and a hyper-adrenergic state. Pulmonary hypertension occurs. There is increased afterload to both the left and right ventricles causing myocardial ischaemia. The classic Cushing's reflex (hypertension with bradycardia) may occur in about one-third of patients, secondary to reflex baroreceptor activation and/or central midbrain activation of the parasympathetic nervous system.

After foramen magnum herniation, loss of spinal cord sympathetic activity reduces vasomotor tone, resulting in vasodilatation and impaired cardiac output. Reduced preload and afterload reduces aortic diastolic pressure, decreasing myocardial perfusion. Pituitary ischaemia leads to diabetes insipidus (DI) creating further fluid loss and electrolyte disturbance. Only a minority of brain stem-dead donors remain haemodynamically stable without critical care intervention. The factors influencing cardiovascular instability are summarized in Figure 1.

Hypothalamic dysfunction leads to the loss of thermoregulation which is exacerbated by the donor's reduced metabolic rate, functional hypothyroidism, and vasodilatation. Coagulation abnormalities can occur, secondary to the effects of catecholamines on platelet function, hypothermia, and the release of plasminogen activator and thromboplastin in response to damaged brain tissue.

Optimization of organ function in a potential brain-dead donor

General measures

Potential donors are most appropriately managed in a critical care setting. In most cases, the donor will require similar, if not more intensive, levels of nursing once a decision for organ donation has been made. Invasive monitoring is required to target haemodynamic parameters. Once the diagnosis of brain stem death is made, the patient is legally dead. (Completion of the first set of tests marks the official time of death, subject to the second set of tests confirming apnoea and brain stem areflexia.) Therefore, the focus of management moves away from a patient-focused approach to an organ management approach. This differs from the management of the potential heart-beating donor where until asystole, the patient is still alive, and

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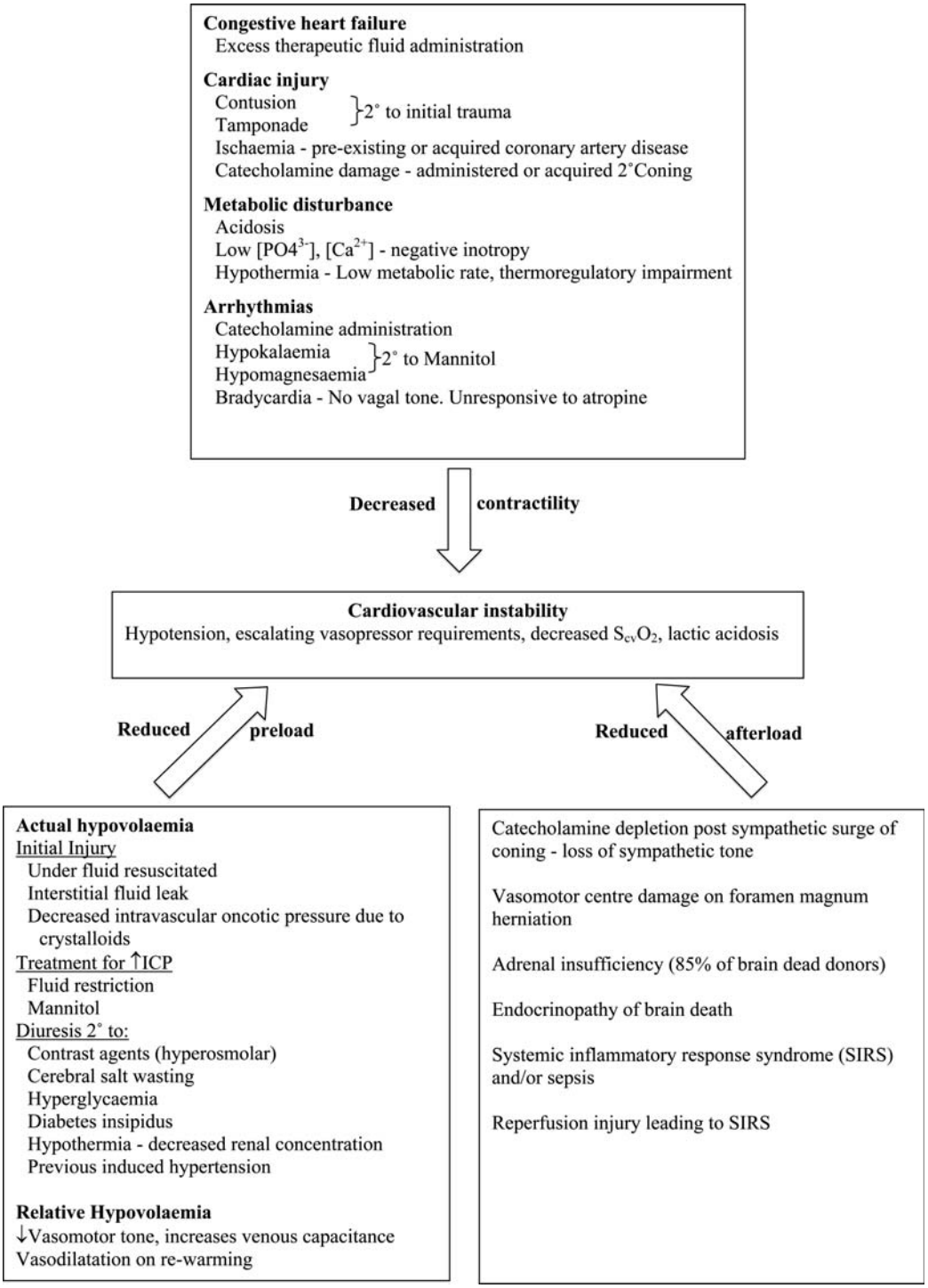

Fig 1 Factors causing cardiovascular instability in the potential organ donor.

management is guided by the principle of 'best interest'.[5] Therefore, in the brain-dead donor, if indicated for organ optimization, insertion of new invasive monitoring is appropriate. Owing to the sequence of ligation of the great vessels during organ retrieval, newly placed arterial cannulae should be inserted into the left brachial or radial artery. Similarly, the right internal jugular or subclavian vein should be used for new central venous access or pulmonary artery (PA) catheter monitoring.

I.V. methylprednisolone (15 mg kg^{-1}) should be administered early as this has been shown to attenuate the increase in the

extravascular lung water index.[6] A review of the drug chart should take place and unnecessary medication stopped. Any microbiologically indicated antibiotics should continue along with enteral feeding, ensuring a 30° head-up tilt to prevent aspiration. Catecholamine release, the use of i.v. dextrose to replace water in DI, and corticosteroids all cause hyperglycaemia. Insulin, by infusion, is used to prevent pancreatic damage and osmotic diuresis. Other electrolyte disturbances are also corrected. Active warming is often needed to prevent hypothermia, although this is likely to have been commenced earlier to ensure that the patient's temperature is >34°C in order to perform brain stem testing.

Blood transfusion and correction of coagulopathies may be necessary in patients with ongoing bleeding. Brain stem death itself is associated with clotting abnormalities and the incidence of disseminated intravascular coagulation increases with the duration of brain stem death. The surgical retrieval process can involve significant haemorrhage and pragmatically, blood products are transfused to maintain an international normalized ratio <1.5, a platelet count >50 000 mm^{-3}, and a haemoglobin >7 g dl^{-1}.

Cardiovascular management

Maintaining haemodynamic stability in brain-dead organ donors can pose a major challenge (Fig. 1). During cerebral herniation, hypertension occurs, but this is usually self-limiting. If the mean arterial pressure (MAP) remains persistently >95 mm Hg, vasoactive infusions should be weaned or stopped and short-acting agents used to control hypertension (esmolol, glyceryl trinitrate, and sodium nitroprusside infusions).

Hypotension will occur in most donors secondary to relative hypovolaemia exacerbated by reduced systemic vascular resistance. Crystalloid or colloid infusions should be titrated to achieve euvolaemia. Hydroxyethyl starch appears to be safe, with respect to renal graft function,[7] and might limit the accumulation of extravascular lung water.

Early restoration of vascular tone aids haemodynamic stability and helps reduce the risk of excessive fluid administration. Vasopressin is considered as the first-line agent where hypotension is resistant to fluid therapy. It restores vascular tone, treats DI, minimizes catecholamine requirements, and is less likely than norepinephrine to cause metabolic acidosis or pulmonary hypertension. Frequently, patients will receive norepinephrine as part of previous ICP-directed management. In this case, the addition of vasopressin often results in rapid weaning of catecholamine infusions. This is beneficial since even modest catecholamine doses (e.g. norepinephrine, 4 mg in 50 ml, infused at a rate in excess of 10 ml h^{-1}) are regarded as damaging to the myocardium and are a contraindication to heart donation.

Additional investigations to guide fluid, inotrope, or vasopressor use include transthoracic echocardiography (TTE) and bedside flow monitoring (e.g. oesophageal Doppler, calibrated or non-calibrated pulse contour analysis, PA catheterization). TTE will identify significant valve pathology or left ventricular hypertrophy, either of which may preclude heart donation. Where a potential donor has contraindications to heart donation, there is less restriction on using higher catecholamine doses, potentially improving the chance of successful donation of other organs. The initial assessment of ventricular function by TTE can be unreliable as a predictor for donation potential as active management can improve contractility significantly. However, a left ventricular ejection fraction of ≤45% should prompt flow monitoring, as should increasing requirement for fluids, inotropes, or vasopressors.

Thyroid hormone replacement can improve cardiac function in the haemodynamically unstable donor[8] and graft function in the recipient of the transplanted heart. There is deficiency of triiodothyronine (T_3) in some patients. Since this subgroup can be difficult to identify, many transplant units administer T_3 irrespective of cardiac function.

Arrhythmias can be difficult to treat as there is a loss of vagal control, and bradyarrhythmias are resistant to anticholinergic drugs prompting management with epinephrine or isoprenaline. Amiodarone is appropriate for tachyarrhythmias caused by brain stem ischaemia and myocardial damage secondary to the autonomic storm.

Several international consensus groups have agreed on haemodynamic targets.[9] These are summarized in Table 1.

Table 1 Cardiovascular targets for potential organ donors

Cardiovascular parameter	Target range
Heart rate	60–120 beats min^{-1}
Systolic arterial pressure	>100 mm Hg
Mean arterial pressure	>70 mm Hg but <95 mm Hg
Central venous pressure	6–10 mm Hg
Pulmonary artery occlusion pressure	10–15 mm Hg
Stroke volume variation	<10%
FTc (flow time corrected) on oesophageal Doppler	330–360 ms
Cardiac index	>2.1 litre min^{-1} m^{-2}
Mixed venous saturation	>60%

Pulmonary management

Donors may have specific pulmonary damage, including aspiration, contusion, or infection. Neurogenic pulmonary oedema may occur during cerebral coning, so a recent plain chest radiograph is required and frequently requested by the transplant surgeons considering suitability for lung donation. Chest radiographs should be clear, but minor degrees of infiltrates may be accepted. Post brain stem death, there is an active inflammatory process which renders the lungs vulnerable to damage. As with other intensive care unit patients, a lung protective strategy should be used with targets for mechanical ventilation (Table 2). Routine critical care respiratory management should continue, including aseptic tracheal tube suctioning and regular rotation to the lateral position to reduce atelectasis together with recruitment manoeuvres to improve oxygenation.

Extravascular lung water can be minimized by the early use of methylprednisolone[6] and avoiding a positive fluid balance.

Table 2 Mechanical ventilation targets

Ventilation parameter	Target range
Tidal volume	6–8 ml kg^{-1}
PEEP	>5 cm H_2O
Peak inspiratory pressure	<25 cm H_2O
pH	7.35–7.45
Pa_{CO_2}	4.5–6.0 kPa
Pa_{O_2}	≥10 kPa
Sp_{O_2}	≥95% for the lowest F_{IO_2}, ideally <0.4

Table 3 Hormonal therapy

Hormone	Dose
Methylprednisolone	15 mg kg^{-1} i.v. every 24 h
T_3	4 μg i.v. bolus. Infusion 3 μg h^{-1} i.v.
Vasopressin	1 IU slow i.v. bolus. Infusion up to 2.4 IU h^{-1} i.v. titrated to arterial pressure
Desmopressin	1–4 μg i.v. bolus. 1–2 μg i.v. 6 hourly
Insulin	Titrate infusion to maintain serum glucose 4.0–8.0 mmol $litre^{-1}$

Restricting fluids may however be detrimental to renal and cardiovascular resuscitation.

Additional tests include bronchoscopy and arterial blood gas sampling. Bronchoscopy allows directed suction, can obtain broncho-alveolar lavage (BAL) specimens to guide antibiotic therapy, can achieve pulmonary re-recruitment, and may identify contraindications for donation. Transplant centres may request arterial blood gas samples on 100% oxygen to help determine suitability for donation. The duration of ventilation at high F_{IO_2} should be minimized and recruitment manoeuvres post-exposure reduces absorption atelectasis, including after the apnoea test for the determination of brain stem death.

Renal management

The fluid status of the donor is assessed carefully on a regular basis to avoid hypovolaemia with spiralling doses of vasopressors which results in poor organ perfusion. Hydroxyethyl starch can be used for fluid resuscitation, nephrotoxic drugs should be stopped, diuretics might be indicated, and adequate renal perfusion maintained (systolic arterial pressure of 80–90 mm Hg). Vasopressin is not thought to have deleterious effects on renal graft function in the recipient.[10]

Hepatic management

Minimizing cold ischaemia time, avoiding large platelet transfusions, restoring liver glycogen, and maintaining serum sodium levels <155 mmol $litre^{-1}$ are thought to reduce transplantation failure rates.[11] [12] Donor hypernatraemia is believed to cause osmosis from the recipient's cells into the donor hepatocytes, resulting in cell lysis and death. Maintaining a central venous pressure of 6–10 mm Hg and avoiding high PEEP reduce hepatic congestion and adequate nutrition restores liver glycogen, decreasing the rate of liver allograft loss.[13]

Endocrine abnormalities

DI is characterized by a urine output >4 ml kg^{-1} h^{-1} with a high serum sodium >145 mmol $litre^{-1}$, an increased serum osmolality >300 mosmol kg^{-1}, and a low urine osmolality <200 mosmol kg^{-1}. It occurs in up to 65% of potential donors. Fluid replacement with enteral or i.v. solutions containing minimal sodium needs to treat both fluid deficit and ongoing losses. Early use of vasopressin may prevent the need for additional treatment, but if DI persists, desmopressin is indicated. All anterior pituitary hormones can decrease and hypothyroidism can occur, contributing to multi-organ failure. Transplant centre protocols vary, but T_3 replacement is frequently given to all brain stem-dead donors. Suggested hormonal therapies are summarized in Table 3.

Protocol use

Clinical management of brain-dead potential organ donors before organ retrieval is complex. From the time of brain injury to organ retrieval, the hospital team must overcome significant organizational, ethical, and clinical challenges. The use of protocols has been shown to increase the number of organs recovered by 71% and decrease the number of donors lost due to instability by 87%.[14] Protocols help guide the clinical team by reinforcing the importance of aggressive donor management, reminding staff of general measures and specific drug therapies and detailing physiological targets. Protocols should also help guide the management of social aspects of organ donation. A comprehensive map of management of the brain stem dead donor can be found on the National Health Service Map of Medicine website.[15] Alongside government-led initiatives to raise awareness of organ donation, more widespread use of donor management protocols may help alleviate the growing shortage of transplantable organs.

Critical care support during organ retrieval[16]

The multi-organ retrieval procedure is a laparotomy extended by a median sternotomy. Steps taken on the intensive care unit to optimize organ function should continue. It is important to maintain cardiovascular stability.

Although there is no need to provide anaesthesia, low concentrations of volatile anaesthetic agents are frequently used to treat hypertension and may have beneficial pre-conditioning effects. Full paralysis is required, as spinal reflexes will persist, but histamine release after atracurium administration can cause unexpected hypotension. Other drugs administered are antibiotics and heparin (as guided by the retrieving surgical teams).

Good communication between theatre team members is essential. The visiting retrieval teams (there are separate surgical teams for cardiothoracic and abdominal retrieval) will request blood

sampling for pre-transplantation renal function and to exclude coagulation abnormalities. If lung retrieval is involved, a catheter mount with a bronchoscopic port is required. Bronchoscopy helps exclude malignancy and aberrant endobronchial anatomy. Frank pus in the airway is a definite contraindication to donation but mucopurulent secretions are not and BAL helps guide antibiotic choice. Differential arterial blood gases from bilateral superior and inferior pulmonary veins help inform decisions about the suitability for single-lung transplantation. The Pa_{CO_2} should be >300 mm Hg on 100% oxygen with a PEEP of 5 cm H_2O. If heart donation is contemplated, PA catheterization is often requested by the cardiothoracic retrieval team. Since PA catheters are infrequently used outside of cardiothoracic centres, most retrieval teams requesting these will provide both the equipment and expertise to insert the device themselves.

Conclusion

Brain stem death causes widespread cardiovascular, respiratory, endocrine, metabolic, and haematological changes. Where organ donation is a possibility careful management of these disturbances is important to increase rates of successful transplantation. Target-driven therapy helps guide treatment and the use of protocols to ensure the optimal management of any potential heart-beating organ donors is recommended.

Declaration of interest

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Please see multiple choice questions 1–4.