Management of the potential heart-beating organ donor

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Key points

There is a severe shortage of organs for donation from brainstem-dead heart-beating donors.

Diagnosing brainstem death is good intensive care practice and should be performed irrespective of any possibility of organ donation.

All potential organ donors should be discussed with transplant services; the organ donor register should always be checked.

Pathophysiological changes during and after brainstem death lead to organ damage.

Optimal medical management of the organ donor increases the number of potential organs suitable for transplantation and may also improve outcome.

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Although St Cosmas and St Damian are said to have miraculously performed a leg transplant in the third century, the first documented organ transplant took place in France in 1906, when Jaboulay grafted a pig kidney into the antecubital fossa of a woman dying of renal failure. Voronoy in Russia performed the first human to human kidney transplant in 1933 using a donor kidney from a woman who had died 6 h before. Unsurprisingly, all of these procedures failed. It was only in the 1940s that the role of the immune system in rejection of transplanted organs was recognized and over the next two decades work began on the immunosuppressive therapy which would make transplantation possible.

The advent of artificial ventilation and Intensive Care in the 1950s resulted in the first brainstem-dead heart-beating patients. Diagnostic criteria for brainstem death were subsequently developed and, in 1968, after a complex ethical and philosophical debate, brainstem death was accepted as being equivalent to somatic death by the World Medical Association. This was accepted in 1976 in a memorandum from the Conference of the Medical Royal Colleges and their Faculties which allowed discontinuation of ventilation of such patients in the UK.

The development of the concept of brainstem death also made organ transplantation from heart-beating donors possible. This review summarizes the management of potential heart-beating organ donors.

Shortage of organ donors

Throughout the last decade, the demand for organs has risen inexorably and waiting lists continue to grow (Fig. 1). There were 7072 patients on the transplant waiting list in the UK at the end of 2002 (increase of 1% compared with 2001); 368 patients died in the preceding year without an organ becoming available. There were 773 cadaveric donors in the year ending March 2003, donating 2402 organs for transplantation; this compares with only 376 organs donated from living donors. A cadaveric organ donor can provide several transplants.

Identification of the potential organ donor

Although the diagnosis of brainstem death allows consideration of potential organ donation, it is vital the issues are considered separately. Diagnosing brainstem death is simply good intensive care practice; it allows discontinuation of intensive care treatment in a patient with no chance of recovery and allows the family to understand that the patient has died. The timing of death occurs at completion of the first set of brainstem death tests, before which no treatment in respect of organ donation should be administered as it is not of direct benefit to the patient.

Donors should usually be <75 yr of age with no medical or social risk factors for HIV or hepatitis B/C infection. There must be no evidence of untreated sepsis or malignancy (apart from primary tumours of the central nervous system). In fact, these contraindications are often relative and much depends on recipient characteristics—for example an organ from a hepatitis C positive donor may be suitable for transplant if the proposed recipient is also hepatitis C positive. It is therefore good practice to refer all potential organ donors to the transplant team for discussion, regardless of any apparent contraindications to transplantation. The Potential Donor Audit is currently assessing the true potential for organ donation for all deaths in more than 150 ICUs in the UK.

Brainstem death

The UK criteria for the diagnosis of brainstem death are well known and described in detail in a recent edition of this journal (see key references). The time of the first set of tests is legally regarded as the time of death, and it is usually after this that the relatives are approached to discuss organ donation. It is only after brainstem death has been diagnosed that the

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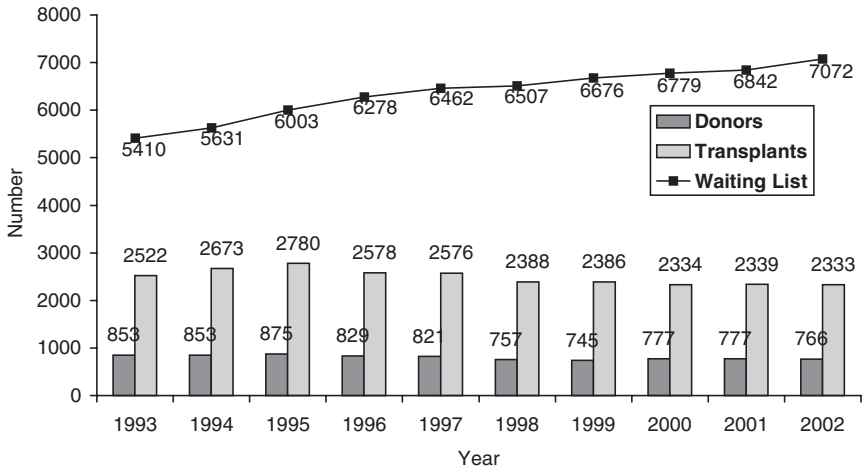

Fig. 1 Number of cadaveric donors and transplants in the UK, 1993–2002 and patients on the active and suspended waiting lists as of December 31, 2002 (reproduced courtesy of United Kingdom Transplant).

emphasis of care can shift to the preservation and optimization of organ function. The general standards of intensive care treatment provided for the patient before brainstem death must continue after this diagnosis to maintain the organs in optimum condition.

Approach to the donor's family

The family should be fully informed of progress at every stage; they will usually be facing a sudden, catastrophic loss and a thoughtful and compassionate manner is essential. It is important to discuss the meaning of brainstem death and its implications in appropriate detail. The concept of brainstem death may be difficult for many families to understand and this may require time and careful explanation. Families themselves may raise the subject of organ donation, otherwise the timing and manner of such a request is a matter for the individual clinician. It is wise to discuss any potential donors with the local transplant coordinators before approaching the family in case donation is not appropriate. The organ donor register currently stands at 10.3 million people and should be checked (Tel: 01179 75 75 75) before raising the subject of organ donation with the family, usually after the first set of brainstem tests. This allows time for discussion and questions before the second set of tests when a more formal request is made. Occasionally, relatives may wish to be present during brainstem testing and this may be beneficial, providing appropriate support and explanation is available. Permission for donation may be required from the coroner or procurator fiscal; it is rare for them to refuse.

The subject of organ donation should be raised with the families of all potential organ donors. The request may come from a transplant coordinator, senior doctor or nurse. The wishes of the patient whilst alive are paramount and families gain great comfort from following their relative's wishes after death, as well as knowing that some good has come from their tragedy.

Table 1 Incidence of pathophysiological changes after brain stem death

Hypotension	81%
Diabetes insipidus	65%
Disseminated intravascular coagulation	28%
Cardiac arrhythmias	27%
Pulmonary oedema	18%
Metabolic acidosis	11%

Physiological changes associated with brainstem death

The pathophysiological effects of brainstem death are summarized in Table 1. Subsequent organ damage associated with cardiovascular derangement is well documented but it is increasingly clear that hormonal derangement following failure of the hypothalamic–pituitary axis and immune changes also affect donated organs adversely. Not all features are seen in every case; it depends on the aetiology and time course of brainstem death.

The 'sympathetic storm'

Hypertension and bradycardia are often seen initially in these patients as intracranial pressure rises and the brainstem is rendered ischaemic. Critical ischaemia and subsequent infarction of the brainstem is associated with intense autonomic activity and massive catecholamine release leading to dramatic increases in heart rate, blood pressure, cardiac output and peripheral vascular resistance. Electrocardiographic evidence of myocardial ischaemia, conduction abnormalities and arrhythmias are also common during this phase. Unsurprisingly, histological examination of hearts exposed to this phenomenon show changes typical of widespread ischaemic damage and necrosis, most commonly in the left ventricle. Profound end-organ vasoconstriction has also been demonstrated in animal models. The catecholamine surge is also associated with large increases in cytoplasmic calcium, leading indirectly to impaired ATP production and increased free radical

formation, both of which further exacerbate cellular damage. Later, as brain stem infarction causes death of the vasomotor centres, endogenous sympathetic activity is lost and the patient develops a relative vasodilatory hypovolaemia which, if left untreated, will progress to asystole, usually within 72 h. Impaired oxidative metabolism secondary to endocrine failure after brainstem death may also worsen cardiac function.

The lungs

Neurogenic pulmonary oedema is common and is related to a combination of elevated pulmonary capillary hydrostatic pressure caused by acute left ventricular dysfunction and increased capillary permeability, as part of a more generalized inflammatory response. This patient population may also have concomitant pulmonary aspiration, contusion, pneumonia, atelectasis and fluid overload as part of the underlying illness.

Endocrine system

Progressive failure of the hypothalamic–pituitary axis leads to a gradual but inexorable decline in plasma hormone concentrations, in particular antidiuretic hormone (ADH), thyroid hormones, cortisol and insulin (indirectly). Lack of ADH produces diabetes insipidus (large volumes of dilute urine). If untreated, it leads to dehydration, metabolic derangement (hypernatraemia, increased serum osmolality, hypomagnesaemia, hypocalcaemia) and relative hypovolaemia. Blood thyroid hormone concentrations (particularly free T3) fall as a result of impaired TSH secretion and peripheral conversion of T4. Reduced T3 has been implicated in the progressive loss of cardiac contractility associated with depletion of high-energy phosphates, increased anaerobic metabolism and accumulation of lactate. It also contributes to metabolic acidosis, together with poor peripheral perfusion. Blood cortisol concentrations are reduced causing hypoadrenalism which impairs the donor stress response and, together with hypothyroidism, contributes to cardiovascular collapse. Finally, insulin secretion is usually impaired, secondary to a decreased stress response; hyperglycaemia is common.

Temperature regulation

Hypothalamic temperature regulation is lost and hypothermia is common unless temperature is actively corrected.

Haematology

Coagulopathy may also occur because of thromboplastin and other mediator release from ischaemic brain tissue.

Immunological effects

Transplanted organs are immediately vulnerable to attack by the recipient's immune system, and the extent of early rejection is crucial in determining the long-term survival of any transplant. It is increasingly clear that the process of brainstem death itself increases the immunogenicity of solid organs by a variety of mechanisms that are still not understood. Animal models of brainstem death have demonstrated elevated pro-inflammatory cytokine concentrations in solid organs, as well as increased expression of leucocyte adhesion molecules that may have a role once transplantation has occurred. Comparisons of outcomes from organ transplantation consistently show more frequent and more severe acute rejection episodes in organs from brain dead donors compared with those from living donors. Future therapy may be targeted at modulating this immune response in the donor before organ retrieval. Steroids may help to ameliorate this process.

Management of the potential organ donor

Much of the management strategy is not specific to the organ donor and should reflect optimum ICU care, which should be continued beyond brainstem death testing, for example strict asepsis, aggressive treatment of arrhythmias and infection, chest physiotherapy. It is reasonable to assume that interventions recently associated with improved outcome in the general intensive care population, such as maintenance of normoglycaemia, might be equally applicable to the donor population.

However, there are several aspects of management that are specific to the potential organ donor which have been shown to increase the number of transplantable organs (~60% in one study). In particular, there is a renewal of interest in more aggressive hormone 'resuscitation' of brainstem dead organ donors, which may result in more successful transplants and better long-term function. However, optimum management of different organ systems can be in conflict. For example, whilst fluid loading optimizes organ perfusion, it may worsen pulmonary oedema; the use of inotropes may optimize organ perfusion but it may prevent the heart being suitable for transplantation. Management depends on compromises and should reflect which organs are being considered for transplantation. It is first necessary to consider the lungs.

Ventilation

The donor lung is particularly vulnerable to insults from several sources. As a crude measure of function pre-transplantation, the donor lungs must be able to achieve a PaO_2 of ~50 kPa with an FIO_2 of 1.0 and a PEEP of 5 cm H_2O. The use of physiotherapy, regular tracheal suctioning, strict asepsis, bronchoscopic lavage and regular sputum culture represents good intensive care practice. Suggested ventilatory strategies aim to protect the lung whilst optimizing oxygenation. These include tidal volumes of 6–8 ml kg^{-1} and the use of ideal PEEP. Higher tidal volumes (12–15 ml kg^{-1}) are associated with volutrauma, with increased alveolar cytokine release and presumed alveolar damage. PEEP of 5–10 cm H_2O may be particularly useful in the treatment of pulmonary oedema as well as preventing alveolar collapse. PEEP >10 cm H_2O may be associated with lung damage or induce hypotension.

If the lungs are considered for transplantation, FIO_2 should be as low as necessary to achieve a PaO_2 >10 kPa and PEEP

should be limited to 5–10 cm H_2O. The donor lung is particularly susceptible to developing pulmonary oedema, as the left ventricle is often significantly impaired in comparison with the right and the central venous pressure (CVP) may not be an accurate reflection of left ventricular filling. Fluid loading to a CVP greater than 6 mm Hg (in absence of PEEP) may worsen alveolar arterial oxygen gradient in brainstem dead donors. If the lungs are considered for transplantation, fluid should be given cautiously and measurement of left sided filling pressures should be considered.

The role of Swan–Ganz catheterization in cardiovascular manipulation in the critically ill remains controversial and may be clarified after publication of the PAC-MAN trial. If the lungs are not being considered, fluids may be administered more freely with the intention of optimizing cardiac function and organ perfusion.

Circulation

The aim of treatment is to protect the heart itself from ischaemic or other damage while maximizing its ability to perfuse other organs. Absolute or relative hypovolaemia is commonly present in these patients because of either increased losses (mannitol, other diuretic therapy or diabetes insipidus) or profound vasodilatation. Fluid resuscitation is usually necessary (mean 4.3 litre in one series) but fluid overload should be avoided by utilization of invasive haemodynamic monitoring. CVP monitoring is mandatory and cardiac output measurement may be required. Suggested targets are conservative: CVP or pulmonary artery occlusion pressure (PAOP) 10–12 mm Hg (if the lungs are not being considered for transplantation); cardiac index 2.2–2.5 litre min^{-1} m^{-2}; mean arterial pressure 70 mm Hg.

If the heart is being considered for transplantation, a mean arterial pressure of 70 mm Hg (in the absence of hypovolaemia) is a reasonable compromise providing there is good organ perfusion in a vasodilated circulation and 'offloaded' left ventricle. Aiming for greater systemic blood pressures may require greater inotropic requirements making the heart less suitable for transplantation. Transoesophageal echocardiography or PAOP measurement may be required by the cardiac transplant team to further assess the suitability of the heart and, in combination with 'hormone resuscitation', this increased the number of organs retrieved in one study. If the heart is not considered, systemic pressures may be driven higher, particularly in older donors, where organs may have been used to higher perfusion pressures.

If hypotension remains a problem despite correction of hypovolaemia, low dose vasopressin replacement is increasingly seen as first line inotropic therapy. Both sepsis and brainstem death are associated with low vasopressin concentrations and vasopressin is seen as restoring 'physiological' vasomotor tone. However, the dose may be crucial. Guidelines suggest 0.5–4 U h^{-1} in diabetes insipidus but, in septic patients, doses <2.5 U h^{-1} are associated with increased blood pressure and urine output. Doses >2.5 U h^{-1} are associated with adverse effects, such as cardiac arrest.

Table 2 Standard 'hormone resuscitation' (Adapted from United Network for Organ Sharing)

Vasopressin	1 unit bolus, infusion at 0.5–2.5 U h^{-1}, titrated to SVR 800–1200 dyne s^{-1} cm^{-5}
Triiodothyronine (T3)	4 mcg bolus, infusion at 3 mcg h^{-1}
Methylprednisolone	15 mg kg^{-1} bolus
Insulin	1 U h^{-1} minimum, titrated $\propto$ glucose

If hypotension persists, dopamine should be commenced at inotropic doses; there is no evidence that 'low dose dopamine' improves renal function. The addition of low dose norepinephrine should then be considered if dopamine and low dose vasopressin fail to deliver an adequate perfusion pressure. Hormone replacement should also be started (see below). The use of high dose inotropes, particularly epinephrine and norepinephrine, should be guided by measurement of cardiac output, PAOP and systemic vascular resistance, particularly if cardiac transplantation is considered, as myocardial ATP is rapidly depleted by exogenous catecholamine administration.

Arrhythmias are common and should be treated together with any associated biochemical disturbance, such as hypokalaemia or hypomagnesaemia.

Endocrine replacement

The deterioration in endocrine function after brain stem death has led to renewed interest in the replacement of those hormones essential for maintenance of homeostasis and organ function (Table 2).

If polyuria occurs despite vasopressin, urine and serum osmolalities should be measured to confirm diabetes insipidus; treatment with intermittent DDAVP may be required.

Although the evidence that i.v. triiodothyronine (T3) improves cardiovascular stability in the donor is controversial, it has been shown to improve function of the donor heart in the recipient. I.V. T4, which is significantly cheaper, does not appear to undergo peripheral conversion to T3 in the brainstem dead patient and may therefore be of less benefit. High dose methylprednisolone has been advocated to attenuate the effects of pro-inflammatory cytokines, improving oxygenation and increasing lung donor recovery; it may be indicated if lung transplantation is planned or 'hormone resuscitation' considered. Hyperglycaemia is common and should be treated with insulin.

Three-drug 'hormone resuscitation' is included in the standardized management protocol of the United Network for Organ Sharing (UNOS), which led to a 22% increase in numbers of organs recovered. In the UK at the present time, each regional transplant team has their own donor management protocol.

Temperature control

Normothermia is achieved by using fluid warmers, forced air warming blankets and active inspired gas humidification.

Haematology

Coagulopathy should be managed with clotting factors and platelets, as necessary. Blood transfusion may be required; however, previous strategies targeting a haemoglobin of 10 g dl^{-1} and haematocrit of 30% may be excessive, as lower target haemoglobin concentrations are associated with an improved outcome in the intensive care population. Four units of blood should be available before organ procurement in theatre, as surgery may involve significant blood loss.

Tissue donation

It is important to remember that, even if organ donation cannot be performed, tissue donation may be a possibility. In particular, corneas and heart valves may be taken up to 24 h and 72 h after asystole, respectively.

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See multiple choice questions 61–65.