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Management of the heartbeating brain-dead organ donor

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Editor's key points

- Brain stem death is frequently followed by a predictable pattern of complex multiple organ failure.
- Appropriate support before and after brain death can improve the number and quality of donor organs.
- Such support is intensive and time-consuming.
- Increasing numbers of marginal donors are now being accepted as potential donors.
- Organizational aspects of donor management (e.g. skilled retrieval teams) are important but have not been implemented fully.

Summary. The main factor limiting organ donation is the availability of suitable donors and organs. Currently, most transplants follow multiple organ retrieval from heartbeating brain-dead organ donors. However, brain death is often associated with marked physiological instability, which, if not managed, can lead to deterioration in organ function before retrieval. In some cases, this prevents successful donation. There is increasing evidence that moderation of these pathophysiological changes by active management in Intensive Care maintains organ function, thereby increasing the number and functional quality of organs available for transplantation. This strategy of active donor management requires an alteration of philosophy and therapy on the part of the intensive care unit clinicians and has significant resource implications if it is to be delivered reliably and safely. Despite increasing consensus over donor management protocols, many of their components have not yet been subjected to controlled evaluation. Hence the optimal combinations of treatment goals, monitoring, and specific therapies have not yet been fully defined. More research into the component techniques is needed.

Keywords: brain death; directed tissue donation; intensive care; organ donor; organ transplantation

Transplantation is totally dependent on the supply of viable organs for implantation. There is a marked imbalance between the numbers of available organs and potential recipients. In the UK, USA, and Eurotransplant areas, the number of potential transplant recipients has increased to more than 133 000, yet the number of donated organs from all sources is not increasing sufficiently to keep pace[1–3] (Fig. 1). Living donation contributes significantly, particularly for kidney transplantation. Although donation after circulatory death (DCD) is increasingly important, it is applied variably (6.1%, 10.6%, and 33% of deceased donors in Eurotransplant, USA, and UK in 2008).[1–3] DCD is discussed in detail elsewhere in this supplement.[4]

The majority of transplants use organs from heartbeating donors after brain death (DBD). DBD are more likely to donate multiple transplantable organs (mean 3.9 organs *vs* 2.5 for DCD in the UK),[3] and are currently the only reliable source for cardiac transplants. Unlike DCD, there is an opportunity to maintain the condition of organs before retrieval, both by ensuring donor management is optimal and retrieval warm ischaemic time is minimized. Identifying the potential DBD is essential. Progress in road safety legislation and management of conditions which can lead to brain death may now be limiting numbers of donors, and there will be pressures to increase live donation and optimize DCD.[5]

Increasing demand for transplantation has also led to expansion of the heartbeating donor pool by 'marginal' or 'extended criteria' organs, from older donors and those with comorbidities. The key to successful outcomes with these grafts is individually assessing donor risk indices,[6–9] and selecting appropriate recipients.[10] High-risk grafts are associated with increased mortality, primary non-function, and graft loss,[7 8 11] but deaths of recipients on the waiting list for thoracic organs and livers mean that they may still need to be used.

Outcomes are better with organs obtained from live donors compared with organs from brain-dead donors, as the widespread physiological changes that occur during brain death are avoided. In addition to acute changes, which if untreated lead to rapid deterioration and cardiac arrest (even if ventilation is continued),[12–14] there are ongoing generalized inflammatory[15] and hormonal changes associated with brain death which adversely affect donor organ function and propensity to rejection.[16–18] Analysis of the outcomes of kidney transplants to two recipients from the same donor,[19] or of dysfunction in multiple organ transplants from the same donor,[20] suggests that the quality of donor

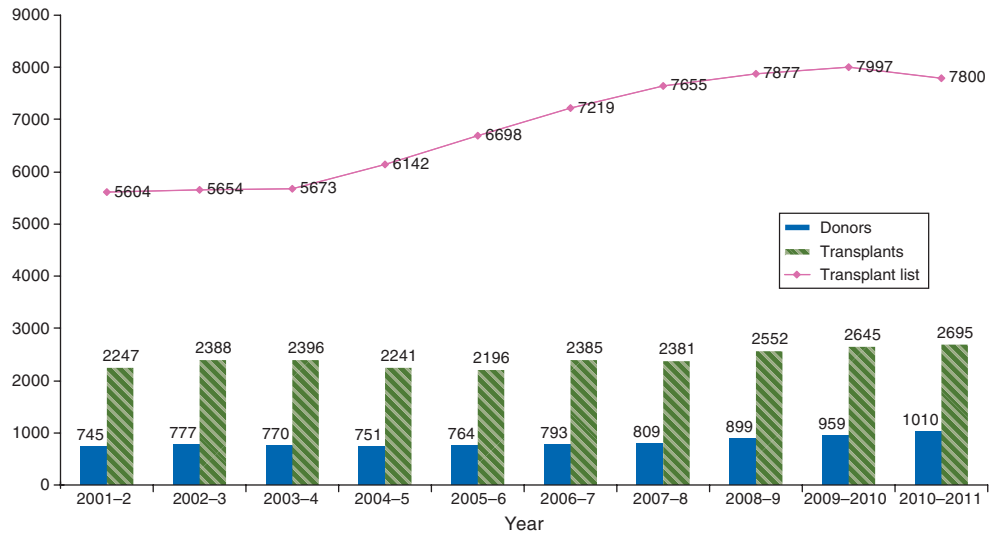

Fig 1 Numbers of deceased donors and donor organs transplanted in the UK. The number of patients waiting for an organ transplant continues to rise and the demand for organs exceeds supply. Redrawn from figures accessed at http://www.organdonation.nhs.uk/ukt/statistics/transplant_activity_report/transplant_activity_report.jsp (accessed September 20, 2011).

Table 1 Incidence of common physiological derangements in brain-dead donors

Derangement	Cause	Approximate incidence
Hypothermia	Hypothalamic damage; reduced metabolic rate; vasodilation and heat loss	Invariable if not prevented
Hypotension	Vasoplegia; hypovolaemia; reduced coronary blood flow; myocardial dysfunction	81[14]–97%[25]
Diabetes insipidus	Posterior pituitary damage	46[25]–78%[35]
Disseminated intravascular coagulation	Tissue factor release; coagulopathy	29[45]–55%[25]
Arrhythmias	'Catecholamine storm'; myocardial damage; reduced coronary blood flow	25[14]–32%[29]
Pulmonary oedema	Acute blood volume diversion; capillary damage	13[25]–18%[14]

management (active care of the donor from the time of diagnosis of brain death until retrieval and preservation of organs) is a major determinant of the outcome of DBD donation.

On rare occasion, brain-dead patients have been supported for prolonged periods because of coexisting pregnancy[21] or if relatives insisted on continued treatment.[22]

Pathophysiology of brainstem death

Brain death is usually preceded by a variable period of increasing intracranial pressure (ICP). Classic-associated physiological responses to this pressure increase were described by Cushing[23 24] in animal and human studies and can lead to effects on multiple organ systems (Table 1). These changes are superimposed on prior physiology, disease, and therapy. The resulting clinical presentation may be complex,[25] but the typical pathophysiological consequences of brain death are described below.

Cardiovascular

With increasing ICP, there is compensatory arterial hypertension, perhaps associated with bradycardia,[26] followed by marked sympathetic stimulation with intense vasoconstriction, raised systemic vascular resistance, and tachycardia (a 'catecholamine storm').[12 14 27] These are associated with central redistribution of blood volume, increased afterload, and visceral ischaemia. Acute myocardial injury occurring around the time of brain death has been demonstrated in animals and humans. The severity of changes depends in part on the speed of onset of brain death. In an experimental canine model, circulating epinephrine concentrations increased more than 1000-fold in association with an explosive increase in ICP. Slower increases in ICP resulted in lesser increases in catecholamine concentrations (200-fold) and a lower incidence of myocardial ischaemic damage (93% and 23% in the rapid ICP increase and slower ICP increase groups, respectively). In humans, myocardial injury occurs in 20–25% of DBD hearts[28] and echocardiographic evidence

of myocardial dysfunction is seen in ~40% of brain-dead donors being considered for heart donation.[29 30] After the catecholamine storm, there is a loss of sympathetic tone and peripheral vasodilatation. The resulting hypotension, if untreated, leads to hypoperfusion of all organs, including the heart, and may contribute to rapid donor loss.[31]

Respiratory

Raised pulmonary hydrostatic pressure causes pulmonary oedema which is aggravated and perpetuated by capillary endothelial damage triggered by endogenous norepinephrine.[16 32] If ventilation is not supported, respiratory arrhythmia progresses to apnoea and cardiac arrest.

Endocrine, metabolic, and stress responses

Endocrine changes in brain death are variable in timing and severity. In baboons with acute increases in ICP, posterior and anterior pituitary function is lost rapidly after brain death.[33] This is associated with a deterioration in cardiac function and a shift to anaerobic metabolism. In human donors, the profile is less consistent. Posterior pituitary function is very commonly lost, leading to diabetes insipidus with associated fluid and electrolyte changes. Anterior pituitary function may be preserved or only partially affected, perhaps because of preserved pituitary blood flow.[34] Thyroid hormonal changes may approximate to the 'euthyroid sick syndrome'[35–39] seen commonly in the critically ill patient without brain injury. Insulin concentrations decrease, insulin resistance develops, and hyperglycaemia is common.[12 14 40] Hypothalamic function and control of body temperature are lost. Although hyperpyrexia may occur at first, hypothermia follows. This is caused by a reduction in metabolic rate and muscle activity, in combination with peripheral vasodilatation.[14]

An active inflammatory response is common in brainstem-dead donors.[15] Trauma and critical illness are commonly associated with inflammation, but this might be particularly severe in brain death because of mediators released from damaged brain,[41 42] generalized ischaemia–reperfusion (IR) injury, metabolic changes at the time of the catecholamine storm, or failure to adequately restore the cardiovascular state.

Coagulopathy is present in up to 34% of isolated head injuries,[43] and release of tissue thromboplastin from necrotic brain[44] in brain death from other pathologies contributes to disseminated intravascular coagulation in donors.[45]

Assessment of suitability for organ donation and supportive intensive care unit care

In patients, brain death may be suspected following changes in clinical observations. Very active management may be required to achieve the physiological stability necessary to conduct brain death testing properly. Before the diagnosis of death, treatments are targeted to maximize the chances of patient survival rather than to support individual organs. After brain death, if donation is a possibility, an approach aimed at properly monitored balanced resuscitation of the donor and maintenance of all their organ systems ensures the greatest number of organs suitable for transplant.

In essence, donor management is a continuation of previous critical care management, but with a shift in goals.[46] It is as at least as rigorous as previous care, may even be more so, and should be delivered in an intensive care unit (ICU) by experienced staff. During the catecholamine storm, cardiovascular changes will be acute and transient, and active resuscitation, including cardiopulmonary resuscitation, may be required. This mandates invasive arterial monitoring. Central venous access allows administration of potent vasoactive drugs. Cardiac output measurement may already be in use, but if not, is helpful to guide therapy, particularly if cardiothoracic organ donation is contemplated. However, despite active standard support, the incidence of donor loss before retrieval may be up to 25%.[13] Alternative goals may be useful and 'Aggressive Donor Management' in one centre (including full support and pulmonary artery catheterization) reduced cardiovascular collapse in donors from 18% to 2%,[47] and in another centre from 13% to 0.[48]

The ideal organs are those from younger donors with no coexisting disease. In many countries, the number of trauma victims has decreased, stroke is a more common cause of brain death, and donors are older and more obese.[3 49] Although the donation of multiple organs is obviously preferable, the retrieval of even one transplantable organ is valuable. Transplant organizations provide 24 h advice, and every potential donor should be discussed with them. All will almost certainly be assessed formally. There are few absolute contraindications to donation other than certain malignancies and infectious processes. Age, comorbidity, systemic infection, transmissible viral diseases, and treated malignancy are relative, rather than absolute, contraindications.

Every donor must be meticulously reviewed. Retrieval of records, clarification of history, and interview of relatives will be time-consuming, but vital, as consequences can otherwise be devastating: four recipients from a single organ donor died after transmission of rabies virus infection in 2004.[50] Early involvement of an experienced transplant professional within the hospital or from the transplant organization can reduce delays.

The goals of organ donor management

Early in the history of DBD management, it was recognized in cardiac transplantation that donors were frequently unstable. Hypotension and hypothermia were common, and resuscitation with i.v. fluids and vasopressor drugs was often required.[51] Diabetes insipidus was not always actively managed, leading to hypernatraemia and dehydration. There was a wide variation in the choice of treatments, particularly in relation to cardiovascular support. In order to standardize management, donor goals were developed.

These aimed to maintain physiology close to normal values[52] and were based on measurements made routinely in ICU patients. They included goals to maintain body temperature, ensure adequate oxygenation, circulating volume, cardiovascular stability, and adequate urine output. An early, easily remembered series of goals was the 'rule of 100':[53] systolic arterial pressure >100 mm Hg, urine output >100 ml h^{-1}, Pa_{O_2}>100 mm Hg, haemoglobin concentration >100 g $litre^{-1}$. A later addition was 'blood sugar 100% normal' (Gelb AW, personal communication, 2011).

Steps to refine donor goals and management

Subsequent research into the physiology of brainstem death stimulated the introduction into clinical practice of new therapies, based on experimental laboratory data. Cardiac transplant centres formed teams to attend donor hospitals and institute advanced cardiovascular monitoring, including pulmonary artery catherization. With additional information and physiologically targeted treatment, they added a 'cocktail' of hormones and steroids to therapy.[36 54] Using such regimens, they were able to reduce catecholamine infusions and improve haemodynamics, and in one study, 92% of donors previously deemed unacceptable achieved target transplantation values.[54] This led to initiatives to standardize and then disseminate agreed therapies and physiological targets.

Standardization of goals and wider application

The United Network for Organ Sharing (UNOS) Critical Pathway for the Organ Donor was introduced in the USA in 1999.[55] This pathway recommended defined physiological goals and a consistent and active approach to donor management, including treatments and monitoring. In a pilot introduction of the pathway, the numbers of organs retrieved and transplanted per DBD increased by 10.3% and 11.3%, respectively. There was also a 19.5% increase in the hearts transplanted.[56] The pathway was subsequently modified to include a package of treatment comprising methylprednisolone, vasopressin, and triiodothyronine (T3) or L-thyroxine. This was termed 'hormonal resuscitation' (HR)[57] and the pathway was extended to a wider and different population. Retrieval rates after HR increased in comparison with historic controls, although those receiving HR were younger, less likely to have died from stroke, and had fewer comorbidities. More data are required.

Other therapeutic goals and treatment guidelines have been produced, based on expert opinion and current research. For example, the Crystal City Consensus Conference Cardiac Recommendations[58] suggested standardized cardiovascular management. The Canadian multidisciplinary forum on organ donor management has also recommended specific goals (Table 2) treatments, and areas for audit and research.[38]

There is still considerable variation in the application of management techniques, donor acceptance, and achievement of donor goals.[59 60] Those systems which reliably achieve management goals achieve higher numbers of transplantable organs.[2] The situation is similar to that which prompted recommendations of 'bundles' of care as per the Surviving Sepsis Campaign.[61] However, more work is needed as currently evidence-based ICU care is not always delivered reliably for patients[62] or donors.[63]

Table 2 Suggested cardiovascular goals for the active management of potential organ donors[38]

Parameter	Target
Heart rate	60–120 beats min^{-1}
Arterial pressure	Systolic pressure >100 mm Hg
	Mean pressure ≥70 mm Hg
Central venous pressure	6–10 mm Hg
Urine output	0.5–3 ml kg^{-1} h^{-1}
Electrolytes	Serum sodium 130–150 mmol $litre^{-1}$
	Normal potassium, calcium, magnesium, phosphate
	Glucose 4–8 mmol $litre^{-1}$
Blood gases	pH: 7.35–7.45
	Pa_{CO_2}: 4.7–6 kPa
	Pa_{O_2}: ≥10.7 kPa
	S_{O_2} saturation ≥95%
If pulmonary artery catheter inserted	
Pulmonary capillary wedge pressure	6–10 mm Hg
Cardiac index	2.4 litre min^{-1} m^{-2}
Systemic vascular resistance	800–1200 dyn s cm^{-5}

Practical aspects of organ donor management

The fundamental principles of organ donor management (Table 3) are based on monitoring and therapies used widely in ICU and include confirmation of therapeutic goals, regular review, and prompt change of therapy when required. The most common derangements requiring early attention are hypothermia, hypotension, and diabetes insipidus.

Temperature management

Current practice should include active warming to maintain temperature >35°C before and during the retrieval operation.[12 64 65] Cold preservation is integral to organ storage, however, and it has been hypothesized that active rapid cooling of organs before circulatory arrest might improve organ viability.[66]

Cardiovascular support and fluid management

Changing donor characteristics have reduced the numbers of organs available for cardiac transplantation. Hearts from older donors can have worse outcomes, particularly if there

Table 3 Summary of the principles of donor management

	Suggested approach
General care[12–14 38 39 46–48 64 135 137]	Manage in ICU. Facilitates required nursing and medical care, and support for relatives. Minimum invasive cardiovascular monitoring includes arterial and central venous pressure. Cardiac output monitoring preferred. Review ICU therapeutic goals and alter to donor goals. Stop unnecessary drugs, e.g. sedatives. Reduce heat loss and actively warm if necessary to maintain core temperature >35°C. Actively identify and treat any current infections. May require bronchoalveolar lavage (lung recruitment after)
Respiratory[7 38 72–76]	Use 'lung protective' ventilation. Tidal volume 6–8 ml kg^{-1} with optimal PEEP to allow minimum $F_{I_{O_2}}$. Recruitment manoeuvres initially, and repeated after apnoea testing or tracheal suction. Maintain tracheal cuff pressure at 25 cm H_2O and nurse with the head of the bed elevated to reduce the risk of aspiration. Avoid the administration of excessive i.v. fluids. Consider diuretics if marked fluid overload
Cardiovascular[30–33 37–39 53 58 67 90 91 99 100]	Review fluid balance and correct hypovolaemia; be aware that vascular tone may be impaired. Use cardiac output monitoring if possible to titrate fluids and inotropic or pressor drugs to intended goals as guided by retrieval team. If vasopressor drugs required, vasopressin 0–2.4 units h^{-1}* may reduce catecholamine requirements. High doses of catecholamines (e.g. norepinephrine >0.05 μg kg^{-1} min^{-1}) should be avoided if possible. Consider triiodothyronine bolus and infusion*
Fluids and nutrition[38 39 49 60 68 80 86 118–120]	Administer maintenance fluids (can use enteral route), but avoid positive balance and hypernatraemia. Monitor urine output and maintain at 0.5–2.5 ml kg^{-1} h^{-1}. If urine output is >4 ml kg^{-1} h^{-1}, consider diagnosis of diabetes insipidus and treat with vasopressin infusion or DDAVP. Insulin infusion (1 unit h^{-1} minimum). Maintain feeding or glucose source. Blood glucose target concentrations 4–8 mmol $litre^{-1}$. Correct electrolyte abnormalities to normal values
Blood and coagulation[38 43 44 55 60 138–140]	Correct coagulation if evidence of active bleeding; consider need for coagulation support during retrieval. Consider need for transfusion*. Maintain thromboprophylaxis as there is a high incidence of pulmonary emboli found at retrieval
Systemic effects[15–17 35 39–42 108]	Methylprednisolone 15 mg kg^{-1} bolus immediately after brain death confirmed. Triiodothyronine*
Investigations[29 30 50 58 67 75]	ECG, echocardiogram. Coronary angiogram may be indicated*. Bronchoscopy and lavage followed by lung recruitment manoeuvres. Chest X-ray after lung recruitment manoeuvres

*May be indicated or modified according to local policy or advice from retrieval team. DDAVP, 1-deamino-8-D-arginine-vasopressin.

is size mismatch between the donor and recipient. Therefore, it is vital that the number of transplantable organs from the small pool of donors is maximized. Furthermore, where target values suitable for the heart donation are achieved, the numbers of other donated organs are increased, even if the heart is not used. Cardiac function should be assessed using echocardiography. Functional abnormalities identified during early examination do not contraindicate heart transplantation as they respond to donor management in 50% of cases,[30] but structural abnormalities precluding transplantation may be identified. Coronary angiography may detect significant disease not appreciated by clinical inspection and may be considered for older donors.[58]

In clinical practice, it is often difficult to treat the cardiovascular changes associated with early acute brain death, but myocardial damage has been prevented in animals by reducing the cardiovascular response to the 'catecholamine storm'. Data from a small non-randomized study suggest that moderating the storm in donors improves subsequent cardiac function and the chances of successful transplant.[67]

The first priority when managing a patient with vasoplegia and hypotension is to maintain an adequate effective intravascular volume. Plasma cytokine concentrations are increased in donors who are inadequately resuscitated and 'preload-responsive' and organ yields are lower.[68] There is no evidence that any specific fluid has particular advantages for resuscitation in donors. If large volumes of crystalloid solution are given, balanced salt solutions may help avoid hyperchloraemic acidosis, and avoid confusion if base excess is being used as an index of the adequacy of resuscitation. Blood and blood products should be given if indicated by ICU protocols. Artificial colloids have few advantages in general ICU practice. Concerns that starch-based colloids are associated with delayed graft function[69] may have been related to older formulations,[70] but high doses of starch-based colloids should be avoided.[71] The choice of i.v. fluid and rate of administration should also account for previous therapy, polyuria from diabetes insipidus, and consideration of the effects of excessive fluid on the respiratory system.

Avoiding excessive fluid loading in donor management has now been consistently shown to increase the numbers of transplantable lungs.[72–76] The pulmonary artery catheter may be a useful monitor, but its use in general ICU has been declining[77] and this could impact on interpretation of results at the bedside. Central venous pressure measurement alone is a poor guide for directing resuscitation and alternative techniques can be used to assess effective fluid administration.[78 79] A multicentre clinical trial is underway to determine if protocolized fluid management of the DBD directed by pulse-pressure variation can increase the viability of lungs and other organs.[80] 'Restrictive' fluid regimens do not affect other donor organs adversely when monitored appropriately.[81]

Fluid administration is closely linked to cardiovascular function and vascular tone. Early workers used vasopressors such as metaraminol,[82] but dopamine and other catecholamines rapidly became popular,[83–85] and are commonly used for the first-line cardiovascular support. Catecholamines have anti-inflammatory and preservation effects,[86–88] and are liberally used by some transplant retrieval services, including for cardiac donation.[89] However, the use of high doses of norepinephrine (>0.05 μg kg^{-1} min^{-1}) in donors is associated with increased cardiac graft dysfunction, particularly right ventricular performance, and higher early and late mortality in recipients.[8 90]

The utility of low-dose vasopressin to treat diabetes insipidus, aid restoration of vascular tone, and reduce epinephrine requirement was first identified in brain-dead patients receiving long-term support.[91] When the loss of vascular tone is preventing achievement of donor goals, low-dose vasopressin may allow reduction or elimination of catecholamine use, as in other ICU patients.[92] In a study of 80 organ donors, Venkateswaran and colleagues were able to reduce (in 22) or eliminate (in 26) norepinephrine infusions by adding vasopressin. Terlipressin has been used[93 94] for similar purposes. Canadian guidelines recommend vasopressin as the first-choice vasopressor for donor resuscitation.[38]

Cardiac performance may also be affected by hormonal changes. Those who adopted thyroid hormone supplementation as part of an active donor management programme reported conflicting results. Positive studies where enthusiastic donor management included an 'HR' package often considered historic controls,[47 54 95 96] but randomized studies failed to demonstrate significant benefits.[97–99] Demonstrating additional benefit over effective donor management will require larger randomized studies and may be more obvious with longer treatment times. Some guidelines advocate thyroid hormone supplementation only if cardiac performance is documented as impaired despite good general management.[38 58] Thyroid hormone supplementation seems safe if overdosage is avoided,[96 100] although some observations from animal experiments indicate that thyroid hormone administration could be detrimental in some circumstances.[101] More and larger randomized studies of the individual roles of the components of HR are needed.

Ventilatory management

Lung damage from ventilator-induced lung injury is common in ICU patients.[102] Early donor guidelines recommended tidal volumes of 10–15 ml kg^{-1} body weight.[103] UNOS suggested tidal volumes of 10–12 ml kg^{-1} with a PEEP of 5 cm H_2O.[55] However, lower tidal volume ventilation has been associated with improved outcomes in acute lung injury and is now established practice in ICU. Its introduction to active donor management (using tidal volumes of 6–8 ml kg^{-1}, PEEP, and measures to prevent derecruitment) has been associated with increased numbers of transplantable lungs.[104] Avoiding high inspired oxygen concentrations may limit bronchiolitis obliterans syndrome in lung recipients.[7]

Therefore, the ventilator strategy for donors[75 105] is now similar to the modern management of patients with acute lung injury; focused on recruitment and retention of lung units while limiting tidal volumes and airway pressure; and avoiding fluid overload. Re-recruitment is particularly important after tracheal suction or after apnoea testing. It is also possible to continue management of the donor lung after the retrieval operation by the use of *ex vivo* perfusion, allowing transplantation of previously rejected organs.[106]

Management of liver function

The liver suffers from acute haemodynamic changes at the time of brainstem death,[107] but continues to be affected by the systemic response even after restoration of arterial pressure. Up-regulation of the production of, and response to, cytokines is present before and at the retrieval procedure. This is associated with experimental evidence of worse IR injury at reimplantation.[108 109] The administration of methylprednisolone reduces cytokine release both before retrieval and during surgery.[109]

The moderation of liver IR injury[110] by modification of preservation solutions and techniques has been extensively investigated in animal models. It has been suggested that ischaemic preconditioning of the liver in the heartbeating donor might reduce IR injury. One recent study found that 10 min of donor hepatic hilar occlusion at retrieval had no adverse clinical consequences, but also no clinical benefit.[111] Remote ischaemic preconditioning is currently being investigated in a randomized trial. Volatile anaesthetic drugs[112 113] and remifentanil[114] have potentially beneficial preconditioning effects in hepatic and cardiovascular surgery, and could be investigated in organ donation.

Renal and pancreatic function

Experimental animal and database evidence confirms that kidneys are vulnerable to catecholamine-induced ischaemia at the time of brain death, and subsequent hypoperfusion if donor management is inadequate.[17] Effective donor management aimed at multiple organ donation is associated with good renal graft function even if this avoids liberal fluid therapy. 1-deamino-8-D-arginine-vasopressin (DDAVP) does not seem to adversely affect graft function if blood volume is well maintained.

Cardiovascular support usually includes the administration of catecholamines, and dopamine is used in several countries. Dopamine has no significant renal protective effect on renal function in the critically ill[115] and can be deleterious in donors if fluid management is inadequate,[83] but might have beneficial effects in renal transplantation. The mechanism here could be related to moderation of preservation injury and inflammation, donor cardiovascular effects, or recipient treatment.[86 87]

Donor criteria for pancreatic graft retrieval are strict. Increasing obesity in the population is a significant factor reducing numbers of suitable organs.[49] Achievement of donor goals, low vasopressor use, and good glycaemic

control are all associated with increased numbers of retrieved grafts.[59]

Other organs

There are few specific recommendations for donor management for other organs other than that potential larynx/trachea donors should have short ventilation times.

Management of fluid and electrolyte disturbances

Untreated diabetes insipidus leads to marked hypernatraemia. A database review showed worse outcomes for livers transplanted from hypernatraemic (>155 mmol litre^{-1})[116 117] donors. This may reflect inadequate donor management at that time, and recent evidence suggests no difference in 1 yr survival for liver recipients even with marked donor hypernatraemia.[118] Analysis of heart donors in the Eurotransplant region from 1997 to 2005 showed increased recipient mortality where donor sodium concentrations were <130 or >170 mmol litre^{-1}. This may reflect donor management as risk seems related to the extremes of electrolyte disturbance.

Hyperglycaemia in the donor is common and is exacerbated by steroid administration. Insulin concentrations decline after brainstem death and insulin infusion with standard ICU protocols is required to maintain glucose control.[12 39 64] Poor glucose control adversely affects donor renal function[119] and normal blood glucose concentrations should be maintained.

Other electrolyte disturbances may be related to polyuria from diabetes insipidus, osmotic diuresis, or acute renal impairment. Expert opinion supports management using routine critical care techniques.[120]

Inflammatory response and steroids

The systemic inflammatory response associated with brainstem death leads to pulmonary infiltration of neutrophils. Elevated concentrations of interleukin (IL)-8 in bronchoalveolar fluid correlate with early graft failure.[41 121] Higher plasma donor IL-6 concentrations are associated with fewer transplanted organs and reduced recipient survival.[122] Active removal of cytokines by haemoadsorption is feasible,[123] and would be amenable to study in larger groups.

Methylprednisolone was a component of 'HR', but is more frequently given alone, usually in a dose of 15 mg kg^{-1}, to moderate the inflammatory response. The use of methylprednisolone is associated with improved oxygenation, reduced increases in extravascular lung water,[76] and increased lung yield. Inflammation in the liver,[109] heart,[124] and kidney[125] is also reduced. Steroid therapy with methylprednisolone to the donor reduces inflammation in the kidney after transplantation,[125] but does not reduce incidence or duration of primary graft failure. Methylprednisolone use is associated with increased organ retrieval[60] and it should be given as soon as possible.[126]

Duration of donor management

Donor instability and losses led early transplant programmes to retrieve organs as early as possible. If donors are adequately supported, however, timing of retrieval can be planned. The relationships between duration of brainstem death, organ retrieval, and utilization are complex. The time of brain death testing, rather than of brain death itself, is usually recorded. Unstable donors may prompt earlier retrieval operations or suffer cardiac arrest. Donors with longer recorded periods of active management may therefore have been more stable. There is variation between practice in the USA and Europe, with longer periods of donor management in the USA. A review of 20 773 single-kidney transplants[127] suggested that if high-quality donor management was available, delaying transplantation to improve donor condition would not always be deleterious. These authors emphasized a 'relax and repair' rather than a 'rush and retrieve' approach. The opposing view is that when the donor is stable, there may be little to gain and a risk of deterioration if retrieval is delayed.

Cardiothoracic teams have attended donors for varying periods before donor retrieval surgery. In one study, hearts previously defined as un-transplantable were improved by active resuscitation during retrieval surgery.[54] Instituting management earlier in ICU is also associated with increased numbers of transplantable hearts. Longer treatment times are associated with enhanced gas exchange, reduced lung water, and improved lung transplantation rates.[128] Prolonged management of the brain dead is not necessarily associated with reduction in organs retrieved[129] or worsening organ failure scores and no organ seems particularly vulnerable to loss.[130]

The actual timing of retrieval depends on which organs are likely to be retrieved, and whether other organs will be transplanted even if function improves. A prolonged cold ischaemic time certainly has an adverse effect on the function of all transplanted organs, particularly hearts.[131] Planning must limit cold ischaemic time and allow optimal timing for recipient operations.

Implementation and outcomes with changing donor acceptance criteria

Improving transplant outcomes, in the face of increasing demand for organs with a reduced supply, has led to campaigns which aim to produce change across systems. These include increasing public awareness and personal registration as a donor, early identification and notification of potential donors, avoidance of delay in diagnosing brain death, effective donor management, retrieval of organs, and preservation.[132] The use of these strategies has been associated with an increase in the number of donors and organs retrieved per donor.[133] However, these trends are difficult to interpret absolutely as donor characteristics have changed, acceptance criteria have broadened and more 'marginal' organs are now retrieved. This is discussed elsewhere in this supplement.[134]

Organizational aspects

In Germany in 2008, only 20% of smaller hospitals without neurosurgical departments had more than one heartbeating donor;[135] and in the UK, 25% of transplantable organs are retrieved from ICUs with two or fewer donors per year.[3] Barriers to increasing donor numbers include perceived difficulties with donor identification, communication with relatives, and the donation process. However, support from transplant units and specialist donor co-ordinators[136] is helpful. The close involvement of an experienced intensivist is associated with increased numbers of transplantable organs: a recent study reported an increase in organs from 66 out of 210 potentially available to 113 out of 258 when they were directly involved in the process.[137]

Other options include transport of donors to independent facilities[138] or critical care support travelling with the retrieval team.

Physiological support in the operating theatre

A multiple organ donation procedure involves midline laparotomy extended by sternotomy, even if thoracic organs are not to be retrieved. There is potential for significant blood loss and hypothermia. Surgical manipulations cause cardiovascular instability, and vasoactive infusions are likely to be in progress. Maintaining stability during the procedure allows unhurried removal of organs in optimum undamaged condition.[139] This can be demanding, and ideally donor support is provided by an appropriately experienced individual from anaesthesia or critical care.[140]

Spinal reflex movements are common and full neuromuscular block is required. Hypertension and increased plasma catecholamine concentrations have been observed during surgery and attributed to spinal reflexes. These can occur spontaneously or on surgical stimulus[141] and have prompted some to suggest that anaesthesia for organ donors is required. However, marked spinal reflexes have been observed in the brain dead with liquefied cortex[142] and cardiovascular changes are both generated and modifiable at spinal cord level alone.[143] Hypertension may be moderated with vasodilators, opiates, or volatile anaesthetic agents. In addition, volatile anaesthetics may induce ischaemic preconditioning in hepatic and cardiac surgery.[113 144] For this reason, some retrieval teams administer them during the last 30 min before aortic clamping.[12]

Future research

A defined active approach to achieve clear donor management goals is associated with increased numbers of donors and transplanted organs in comparison with historic controls. These improvements in organ supply may be related to specific changes in management, but organizational factors have also had major effects.[132] Nevertheless, the reliable application of interventions or attainment of goals continues to vary.[2 60 145 146]

Observational or randomized interventional studies can be performed best when an effective baseline donor management programme is in place. Several randomized donor intervention studies are now in progress in these settings.[147] Although research in these areas poses ethical and practical challenges, there is still significant room for improvement in outcomes for recipients.[148]

Conclusion

Donor management programmes with the best results stress the importance of high-quality ICU management of the potential heartbeating organ donor. They advocate the early use of advanced monitoring to guide the management of complex cardiovascular changes while avoiding fluid overload. In addition, they emphasize the importance of an experienced intensivist being directly involved in donor care.

Although there is considerable agreement on the appropriate physiological goals, there is significant variation in the therapies and techniques used to achieve these. This is in part because the optimal combinations of treatment goals, monitoring, and treatment techniques have not yet been fully defined. However, the key to future developments and research into the component techniques is to ensure that currently recommended therapies are delivered consistently and to a high standard.

Declaration of interests

D.W.McK. is a transplant anaesthetist and has assisted with the Clinical Leads for Organ Donation Professional Development Programme for NHSBT. R.S.B. is a cardiothoracic transplant surgeon and Chair of the Cardiothoracic Advisory Group of NHSBT. J.A.K. is an Intensivist and principal investigator of a clinical trial examining protocol-guided donor resuscitation (NCT00987714). All are actively involved in organ donor management including audit and research.

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