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### Optimal Management of the Potential Organ Donor Following Catastrophic Brain Injury

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This article presents best practice in organ donation, aimed at maximising organs that can be retrieved and optimising graft function and survival. Failure to optimise organ function prior to assessment and retrieval should and can be avoided.

#### Introduction

Except in exceptional circumstances, cadaveric solid organ donation occurs following catastrophic brain injury (CBI). Cadaveric solid organ donation is highly successful and enjoys broad public and professional support. However, there is a significant, and worsening, supply-demand imbalance. In this context, it is appropriate, morally, ethically and economically, to ensure that no opportunities are missed. Common avoidable causes of missed opportunities include failures to:

- Consider organ donation, once the clinical decision has been made that continuing supportive care has no realistic prospect of achieving a meaningful functional recovery for the patient;
- Continue organ support until the patient's wishes with regard to organ donation can be established;
- Establish a diagnosis of brainstem death (BSD);
- Discuss with, and gain consent for, organ donation, with the patient's next of kin; and
- Optimise organ function prior to assessment and retrieval, especially of thoracic organs (Statistics and Clinical Audit).

The first four issues remain both challenging and controversial (Randall and Downie 2012; Neuberger 2012). However, there is emerging, and I believe, compelling evidence that should remove the fifth item from this list. In this article, I will attempt to present both the specific elements that constitute current best practice and the evidence that this package of care is effective in increasing the chances of successful donation, maximising the number of organs that can be retrieved and optimising both graft function and survival (Minambres et al. 2013; Hagan et al. 2009; Franklin et al. 2010; Malinoski et al. 2013; Malinoski et al. 2012).

This article is based upon practices and legislation in the United Kingdom. There are significant differences between these and those of other countries, a topic recently reviewed by Bilgel (Bilgel 2013).

#### A Clinical Scenario

A 45-year-old man suffers an isolated, severe traumatic brain injury. He has been intubated and ventilated, computed tomography scanning has been completed from vertex to mid thigh, immediate resuscitation has been completed together with a full secondary survey, following which he is transferred to ICU. Despite optimal care and minimisation of secondary brain injury, the intracranial pressure remains persistently elevated. The clinicians reach a consensus that there is no realistic prospect of achieving a meaningful functional recovery for the patient.

Three processes should now be simultaneously instituted:

1. Confirmation or refutation of the diagnosis of BSD. BSD should be suspected if there are fixed and dilated pupils, a Glasgow coma score of 3/15, an absence of triggering / patient interaction with the mechanical ventilator, and the absence of any potentially reversible cause for these

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clinical findings. In the UK, the reversible causes are detailed in *A code of practice for the diagnosis and confirmation of death* (Academy of Medical Royal Colleges, 2008) and listed in Table 1. Thus, the first steps may be cessation of all depressant and neuromuscular blocking drugs, and rewarming to ~35°C, if therapeutic hypothermia has been instituted. Of note, there is a small but significant incidence of complex-spontaneous motor movements and false-positive triggering / interaction with the ventilator in patients who are brain dead (Wijdicks et al. 2010). Examples of the latter usually occur due to the high sensitivity of modern ventilators and represent cardiovascular triggering (Arbour 2012; McGee and Mailloux 2011). Failure to be aware of these phenomena can result in significant delays in confirming brain death.

2. Physiological optimisation should be initiated / continued, both to enable BSD testing and maximise the potential for heart, lung, kidney, liver and other organ transplantation (for the suggested timeline see Figure 1, p.13). This is considered controversial by some, who argue that it is not in the patient's best interests. However, failing to do this may delay or prevent BSD testing and will result in worse outcomes, if organ donation proceeds, which can only occur if it is in accordance with the patient's wishes. If consent or other issues subsequently preclude organ donation then withdrawal of organ support should be undertaken at a time, and in a manner, that is consistent with best practice in end-of-life care. In addition, from a societal perspective, it can reasonably be argued that following the confirmation of BSD, you are no longer treating the donor but instead are treating multiple recipients.

3. Establish whether there are any absolute contra-indications to organ donation (medical and/or legal), and whether the wishes of the patient have been registered and/or are known to the next of kin.

### Physiological Optimisation Following CBI

Severe brain injury is commonly associated with a multiple organ dysfunction syndrome, characterised by a systemic proinflammatory state and endogenous catecholamine excess. Neuro-critical care practices may have added to this physiological derangement by inducing a state of relative hyperosmolar, hypovolaemia, with high systemic arterial pressures, hyperoxia, hyperventilation / hypocarbia and suboptimal positive end expiratory pressure (PEEP). If this progresses to BSD, a highly variable, autonomic and endocrine, failure syndrome occurs, which in the majority of cases, results in cardiovascular instability and a further deterioration in the function of all other organs (Bugge 2009). This multiple organ dysfunction syndrome often abates within a 6-24 hour period if actively managed. In this setting, physiological optimisation merely represents routine (best practice) critical care. A summary of targets, tests, drugs and procedures is shown in Table 2. Notes regarding specific elements of this care package are outlined below.

### Respiratory System

- Standard lung protective ventilation (Kilickaya and Gajic 2013) should be employed and is of proven benefit in this patient population (Van Raemdonck et al. 2009, Minambres et al. 2013, Mascia et al. 2010). This should include regular assessment of lung recruitability and PEEP optimisation (Minambres et al. 2013, Jauncey-Cooke et al. 2009).
- Airway pressure release ventilation may be beneficial, (Hanna et al. 2011) but only if the clinicians caring for the patient are familiar with its use.
- Apnoea testing should be conducted using continuous positive airway pressure (CPAP) (Mascia et al. 2010). This can easily be achieved without disconnection from the ventilator, either by disabling apnoea backup and/or switching to a non-invasive setting.
- Exposure to hyperoxic gas mixtures should be minimised (Kallet and Matthay, 2013).

### Cardiovascular System

- Cardiovascular instability may develop rapidly due to:
  - hypovolaemia secondary to diabetes insipidus;
  - myocardial depression due to catecholamine and cytokine toxicity;
  - the transition from hypertensive catecholamine excess into vasoplegic hypotension.

Hence, invasive blood pressure and cardiac output monitoring is essential. Management should employ standard methods for optimisation of the circulation. Recommended physiological targets are shown in Table 2. There are however, a few points worth emphasising.

- Fluid (and electrolyte) management can be especially challenging and benefits from senior review. The trade-off between euvoalaemia with adequate organ perfusion and organ oedema (especially lung) must be actively managed. Central venous pressure cannot be relied upon as a marker of preload (Durairaj and Schmidt 2008).
- Myocardial stunning is a common observation following BSD but may reverse with optimal supportive therapy, albeit over a 24-48 hour period (Casartelli et al. 2012, Christmas et al. 2012). - Low dose dobutamine (2.5µg/kg/min) may be beneficial in ameliorating ex vivo, cold ischaemic injury (Benito et al. 2004) but high doses may deplete high energy phosphates.
- Some cardiothoracic transplant units encourage the use of thyroid replacement therapy for all donors. Trial evidence (Macdonald et al. 2012) suggests it may add little to active donor management and is not necessary routinely. There is also anecdotal evidence of a small but significant incidence of cardiac toxicity if routinely used.

Thus, thyroid replacement therapy should be considered as a second line positive inotrope in patients with myocardial depression (Ranasinghe and Bonser, 2010).

- Vasopressin (or terlipressin) should be used as the first line vasopressor. The addition of norepinephrine may be required. Vasopressor resistance may be encountered and may respond to hydrocortisone, which should be given regardless of whether or not methylprednisolone has been given (see below). The rationale for this approach is based on the mineralocorticoid effects of hydrocortisone (Druce et al. 2008) (methylprednisolone has no mineralocorticoid action).
- Markers of global oxygen supply demand balance are valuable physiological targets, however the following should be noted.
  - Arterial / central venous lactate measurements may be elevated despite optimal oxygen delivery as high levels of catecholamines, endogenous or exogenous (especially  $\beta_2$  agonists) increase production beyond the elimination threshold. In addition, the injured brain may produce significant amounts of lactate.
  - ScvO<sub>2</sub> has a number of important pitfalls (Barbee et al. 2010). A low (<70%) central venous oxygen saturation (ScvO<sub>2</sub>) may be improved by packed red blood cell transfusion, but this has potentially negative consequences, in particular related to transfusion related immunomodulation. Hence it is best to discuss the pros and cons with the organ donation co-ordinator.
  - Central venous-to-arterial carbon dioxide difference (Pcv-aCO<sub>2</sub>) may be a useful additional target (Vallee et al. 2008).

#### **Endocrine Therapies and Donor Immunosuppression**

- The incidence and clinical impact of functional hypothyroidism and hypoadrenalism remain controversial. Universal use of blind therapy is at best of no benefit and may be harmful. However the use of tri-iodothyronine and / or hydrocortisone may be beneficial in some individuals (see above).
- Acute posterior pituitary failure is very common, results in diabetes insipidus (DI) and is a major contributor to vasoplegic shock. Hence, vasopressin (or terlipressin) are recommended as first line vasopressors whilst simultaneously treating DI.
- Insulin is recommended for all potential organ donors and has myriad potential beneficial effects, though evidence of these from well designed and conducted randomised control trials is lacking.
- Methylprednisolone at a dose of 15mg/kg is recommended as it may reduce extravascular lung water and leukocyte activation and transfer from donor to recipient.

#### **Duration of Physiological Optimisation**

Emerging data from the United States suggest that prolonged organ donor management (>20 hours (Christmas et al. 2012)) both increases the number of organs that are retrievable and improves early graft function. If further data confirm this finding, then continuing physiological optimisation for extended periods will need to become the standard of care. This clearly has resource implications, but may also benefit recipients.

#### **Future Innovations**

A number of other areas may add further improvements to the above care package in the near future. Remote ischaemic preconditioning, innovative organ preservation solutions and extracorporeal pulsatile perfusion are all currently under active investigation (Dikdan et al. 2012).

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