

# Care of the Brain-Dead Organ Donor

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## Abstract

There remains a worldwide shortage of organs for transplantation. If not properly cared for, the organs of patients who are brainstem dead will deteriorate, making them either unsuitable for transplantation or reducing the success rate of transplants. The Medline database was searched with no time limit in January 2019 for English publications using keywords “brainstem death physiology” and “organ donor care.” Full texts of all publications related to care of deceased donors after brainstem death (DBD) were reviewed. Those that were not relevant were excluded. An online search for publications and guidelines produced by international organizations relating to organ donation and care of the organ donor was also preformed, and the results were reviewed.

Although there is a low level of evidence to support specific management strategies to optimize the care of potential DBD patients, there is reasonable consensus between different international guidelines on protocolized intensive care unit (ICU) management of potential DBD patients and donor resuscitation targets.

Key management concepts include (1) early recognition of brainstem DBD and referral to organ donation services, (2) ICU-led multidisciplinary team (MDT) approach to donor management, (3) shift in ICU teams thinking from management of raised intracranial pressure (ICP) to maintaining organ perfusion and function, (4) early active donor management to normalize donor physiology, and (5) prevention, recognition, and treatment of complications of brainstem death.

## Keywords

- brainstem death physiology
- organ donor care
- organ transplant

## Introduction

Since 2008 in the United Kingdom, there has been a reduction in the number of patients dying per year while waiting for an organ transplant. This is due to an increase in donor numbers following several national publicity campaigns.<sup>1</sup> However, the number of patients on the waiting list still outweighs the number of available donors (► **Fig. 1**). Between April 1, 2017 and March 31, 2018, there was a 15% increase in deceased donors after brainstem death (DBD).<sup>1</sup> With the continuing high demand for organs, there is a growing pressure on intensive care unit (ICU) services to provide care for potential DBD patients.

DBD, unlike deceased donors after circulatory death (DCD), donate more organs on average per donor (3.7 vs. 2.8 organs), act as the main source of thoracic organs, and provide the opportunity for the condition of the organs to be optimized prior to retrieval and transplantation.<sup>1</sup>

In 2008, the Organ Donation Taskforce and Academy of Medical Royal Colleges, both produced guidelines outlining the criteria for diagnosing and confirming death by neurological criteria, with the view to improve identification of potential donors. In the United Kingdom, brain death is defined as the irreversible cessation of brainstem function with the irreversible loss of the capacity for consciousness and the capacity to breathe. This is confirmed by (1) presence of known etiology of irreversible brain damage, (2) exclusion of reversible causes of coma and apnea, and (3) absence of brainstem reflexes, absence of movement to noxious stimuli, and presence of apnea on examination.<sup>2,3</sup>

The National Institute for Clinical Excellence (NICE) guidelines on organ donation for transplantation 2011 highlighted the importance of early donor identification of potential DBD patients to fulfill donor wishes and increase the number of organ donors.<sup>4</sup> Also with increasing demand for organs and waiting list deaths still occurring, the eligibility

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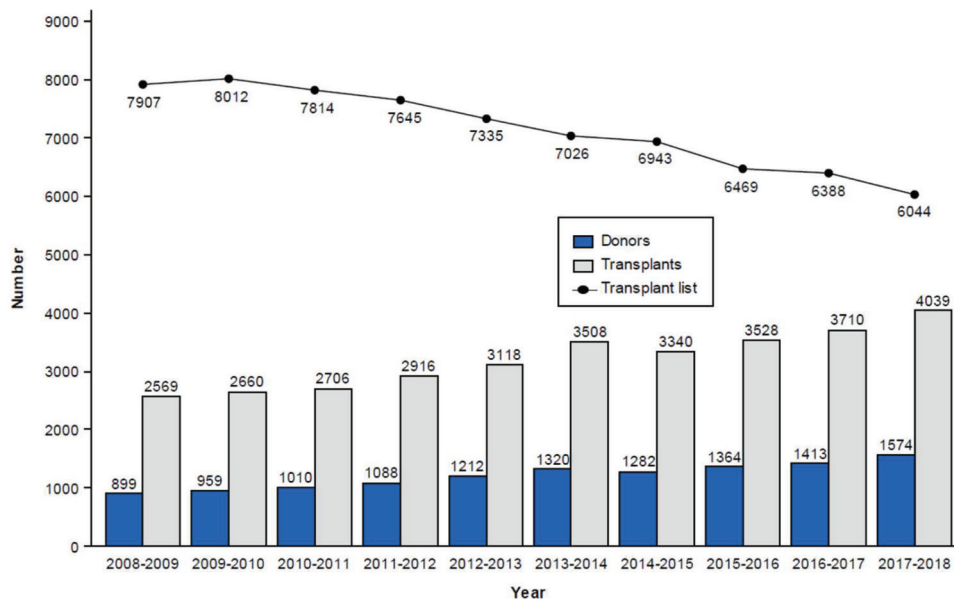
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**Fig. 1** Comparison of number of deceased donors and transplants in the United Kingdom between April 1, 2008 and March 31, 2018, and number of patients on the active transplant list on March 31 for each year from 2008 to 2018. (Reproduced with permission from Organ Donation and Transplantation Statistical Enquiries, NHS Blood and Transplant, NHS, UK.<sup>1</sup>)

of donors has been expanded to include extended criteria donors (ECDs). Unlike standard criteria donors (SCDs), ECDs are older and have one or more comorbidities.<sup>5</sup> Hence, those patients who were previously overlooked are now potential donors and may be more difficult to manage due to their physiological changes associated with advancing age and comorbidities. Furthermore, there are systemic pathophysiological changes that threaten the viability of the organs following brainstem death.<sup>6,7</sup> Hence, the challenges facing intensivists with the management of potential DBD patients include (1) early identification, (2) management of patients' underlying physiology, acute illness, and comorbidities, and (3) management of the systemic pathophysiological changes that occur following brainstem death.

It has been proposed that the quality of the active management of potential DBD patients, from diagnosis to organ retrieval, is fundamental to the outcome of DBD organs. A prospective multicenter epidemiological study showed that improved hemodynamic status of the donor was associated with less delayed renal graft function in recipients.<sup>8</sup> Also, early active potential DBD patient management has been shown to be associated with increased organ retrieval in a randomized control trial (RCT).<sup>9</sup> Another study has shown that the implementation of a structured donor management algorithm improved the number of organs retrieved and transplanted.<sup>10</sup> However, recent systematic reviews and meta-analyses suggest the level of evidence with regard to the management of potential DBD patients is low according to GRADE criteria and not consistent.<sup>11</sup>

This article reviews the pathophysiological changes associated with brainstem death and the current evidence with regard to the ICU management of potential DBD patients to optimize transplanted organ outcome.

## Methods

The Medline database was searched with no time limit in January 2019 for English publications using keywords: "brainstem death physiology" and "organ donor care." Full texts of all publications related to the care of potential DBD patients were reviewed. Those that were not relevant were excluded. An online search for publications and guidelines produced by international organizations relating to organ donation and care of the organ donor was also performed, and the results were reviewed.

## Pathophysiological Changes Associated with Brainstem Death

### Neurological Changes

Brainstem death is usually preceded by a variable degree and period of raised intracranial pressure (ICP). As ICP increases and compensatory mechanisms fail, brain-death ensues through two mechanisms: (1) reduced cerebral perfusion pressure (CPP), leading to global hypoxic-ischemic injury and (2) mass effect, leading to cerebellar tonsil foramen magnum herniation and compression of the brainstem, and in turn brainstem ischemia.<sup>12</sup>

Brainstem ischemia progresses in a cephalic to caudal manner. Midbrain ischemia is associated with the loss of consciousness and pupillary light reflexes. Subsequent ischemia of the pons leads to irregular respiration and loss of corneal reflex, cold caloric vestibulo-ocular reflex, and motor response of cranial nerves V and VII. Finally, ischemia of the medulla results in apnea and loss of gag and cough reflexes. With the irreversible loss of the capacity for consciousness and the capacity to breathe, the neurological criteria for brainstem death is fulfilled.<sup>2,3,13</sup>

### Cardiovascular Changes

Initially, midbrain ischemia results in parasympathetic nervous system (PNS) stimulation with a resultant period of sinus bradycardia and hypotension. Then pontine ischemia leads to the activation of the sympathetic nervous system (SNS) with an increase in the heart rate, cardiac output (CO), systemic vascular resistance (SVR), and redistribution of blood through peripheral vasoconstriction, resulting in a period of hypertension. Thus, in the face of raised ICP and ischemia, there is an attempt to maintain CPP through increasing the mean arterial pressure (MAP) as  $CPP = MAP - ICP$ .<sup>13,14</sup>

This systemic hypertension can be either superimposed onto the bradycardia related to midbrain ischemia or trigger a baroreceptor-mediated reflex bradycardia, which together with irregular respiration seen with brainstem ischemia, is known as Cushing's triad and signifies significant raised ICP.<sup>14</sup>

This period is followed by ischemia of the vagal cardio-motor nucleus in the medulla, which results in an unopposed hyperadrenergic state (catecholamine storm) characterized by intense systemic hypertension. With ischemia of the medulla, this catecholamine storm can coincide with the onset of brainstem death and can occur for a variable period post-brainstem death.<sup>2,13</sup>

Along with systemic hypertension, animal studies have shown significant pulmonary hypertension occurring post-brainstem death due to catecholamine-induced pulmonary vasoconstriction.<sup>15</sup> This systemic and pulmonary hypertension results in increased afterload on the left and right ventricles, which in turn increases the myocardial work and the oxygen demand, predisposing the heart to ischemia. This is further confounded by catecholamine-induced coronary vasoconstriction and limited increase in coronary blood flow. This results in an imbalance between supply and demand that has been shown in animal studies as the possible mechanism for early cardiac dysfunction post-brainstem death.<sup>16</sup> This acute myocardial injury seen at the time of brainstem death has been associated with left ventricular systolic dysfunction in approximately 42% of DBD patients.<sup>12</sup> The severity of this myocardial injury is linked to the rate of increase in ICP and inotropic dependence. An animal study showed that a rapid increase in ICP compared with a gradual increase was associated with an 800-fold greater increase in adrenaline levels post-brainstem death, and in turn a higher incidence of myocardial ischemia (93% vs. 23%).<sup>17</sup> A human study utilizing electromicroscopic examination showed up to 25% of DBD hearts are associated with moderate to severe myocardial injury, with a higher incidence seen in donors initially dependent on high inotropic support.<sup>18</sup> The catecholamine storm may also precipitate malignant arrhythmias, impairing CO and end-organ perfusion.<sup>19</sup> Furthermore, the catecholamine-induced increase in peripheral vascular resistance can impair end-organ perfusion.<sup>20</sup>

The catecholamine storm comes to an end with either depletion of catecholamine stores or through spinal cord ischemia and loss of SNS outflow. This results in vasodilation, reduced preload, and impaired CO. The resulting reduced afterload leads to reduced aortic diastolic pressure and in turn decreased myocardial perfusion.<sup>13</sup> The resulting

hypotension is seen in 81% of brainstem-dead patients and, if untreated, can result in hypoperfusion and end-organ ischemia.<sup>19</sup> Furthermore, end organs are susceptible to reperfusion injury when hemodynamic stability is restored, leading to a generalized inflammatory response.<sup>13</sup>

Thus, if unsupported during and post catecholamine storm, potential DBD patients are at high risk of end-organ damage and cardiac arrest.

### Respiratory Changes

The immobile DBD patient with no cough reflex is at high risk of basal atelectasis and pneumonia, leading to ventilation/perfusion (V/Q) mismatching and increased fraction of inspired oxygen (FiO<sub>2</sub>) requirements.<sup>13</sup> Neurogenic pulmonary edema can develop secondary to (1) raised pulmonary capillary hydrostatic pressure due to pulmonary vasoconstriction and increased systemic afterload and (2) increased capillary permeability due to endothelial damage from excess endogenous noradrenaline (NA) release during the catecholamine storm and proinflammatory mediators released from ischemic or necrotic brain tissue.<sup>21</sup> Hence, the pulmonary vasculature tolerates volume overload poorly, as can occur with cardiovascular (CV) fluid resuscitation. The loss of central respiratory centers would lead to ventilatory failure with irregular respiration and apnea if the patient was not mechanically ventilated.<sup>22</sup> Ultimately, if these issues are not managed appropriately, they would lead to hypoxic cardiac arrest.

### Endocrine Changes

Post-brainstem death, endocrine dysfunction is multifactorial and varies in severity and timing. Hypothalamus, anterior pituitary, and posterior pituitary function may be lost through ischemia. Also, critical illness stress response, systemic inflammatory response syndrome (SIRS), and high-dose steroids may drive endocrine dysfunction.<sup>20</sup>

Animal studies have revealed that after the catecholamine storm, endocrine changes manifest primarily due to anterior and posterior pituitary dysfunction.<sup>23</sup> Posterior pituitary function is more commonly lost than the anterior.<sup>19,24</sup> Animal models have shown that antidiuretic hormone (ADH) and adrenocorticotropic hormone (ACTH) levels start to decrease 15 and 45 minutes after brainstem death, respectively.<sup>25</sup> With a decrease in ADH, neurogenic diabetes insipidus (DI) ensues, with a 65 to 78% incidence of DI following brainstem death seen in human studies.<sup>19,24</sup> The associated hypernatremia, hypokalemia, hyperosmolality, and hypovolemia seen with DI may result in end-organ hypoperfusion, and thus compromise donor organ viability. The decrease in ACTH and in turn cortisol levels may impair stress response and in turn further impair hemodynamic stability. However, ACTH changes are less commonly seen, with some studies showing no change in ACTH levels despite reduced cortisol levels.<sup>24</sup> One study has shown that this may be in part due to a decreased cortisol reserve in DBD patients, with 76% of DBD patients revealed as nonresponders to ACTH stimulation.<sup>26</sup> Furthermore, adrenal suppression by high-dose steroids, used for the management of raised ICP prior to

brainstem death diagnosis, may be the underlying cause for the low cortisol levels.<sup>24</sup>

Several human studies have shown a euthyroid sick syndrome picture post-brainstem death with low levels of free triiodothyronine ( $fT_3$ ) and free tetraiodothyronine ( $fT_4$ ), normal or raised reverse  $T_3$ , and normal thyroid-stimulating hormone levels.<sup>23,24,27,28</sup> Controversy remains over the importance of thyroid dysfunction and replacement in potential DBD patients. Some studies have shown no link between low thyroid levels and hemodynamic instability or lactate levels in DBD patients.<sup>27,28</sup> However, others propose a link between reduced  $fT_3$  and reduced myocardial energy stores, leading to increased anaerobic metabolism, lactic acidosis, and impaired cardiac contractility.<sup>29-31</sup>

Post-brainstem death insulin level decreases and peripheral insulin resistance increases. This results in intracellular hypoglycemia and a shift toward anaerobic metabolism, and extracellular hyperglycemia and shift toward a hyperosmolar state with osmotic diuresis and hypovolemia.<sup>23,32</sup> This hyperglycemia may be worsened by the use of high-dose steroids and increased catecholamine levels.

Loss or impaired function of the hypothalamus leads to loss of central thermoregulation. During the catecholamine storm, there may be a period of hyperpyrexia. However, post-catecholamine storm, the patient is more susceptible to rapidly becoming hypothermic due to the loss of SNS outflow and resulting profound peripheral vasodilation. This is further confounded by the lack of skeletal muscle activity and reduced metabolic activity of the potential DBD patient. If untreated, hypothermia results in bradyarrhythmias, reduced CO, hypotension, impaired microcirculation, cold-induced diuresis, and leftward shift of the oxyhemoglobin dissociation curve, thus impairing end-organ perfusion and oxygenation.<sup>30</sup>

### Hematological Changes

Following brainstem death, coagulation may be impaired either through hypothermia, dilution of coagulation factors, or via precipitation of disseminated intravascular coagulation (DIC). In this context, DIC can be induced by plasminogen activator and thromboplastin released from ischemic or necrotic brain tissue in brainstem-dead patients, with an incidence of 28%.<sup>19</sup> Furthermore, plasminogen activator and excess catecholamines can impair platelet function.<sup>33</sup>

### Immunological Changes

A systemic inflammatory response is seen post-brainstem death due to release of proinflammatory mediators from ischemic or necrotic brain tissue and upregulation of peripheral inflammatory mediators, such as cytokines and adhesion molecules.<sup>23</sup> Furthermore, if brainstem death-associated CV changes are poorly managed, inflammatory mediators may be released from ischemic tissue and in response to subsequent ischemic-reperfusion injury.<sup>22</sup> These inflammatory mediators can worsen hemodynamic stability and neurogenic pulmonary edema. Furthermore, the presence of high levels of cytokines and adhesion molecules in donor organs have been associated with accelerated acute graft rejection.<sup>34</sup>

## Systematic Treatment Approach

The general aims of active potential DBD patient management protocols are to resuscitate the donor and maintain organ perfusion and function, maximizing the number and quality of transplantable organs, and thus improving recipient outcome. There is a reasonable consensus among international guidelines with regard to donor resuscitation targets (► **Table 1**) and management strategies (► **Table 2**).<sup>35-41</sup>

### Cardiovascular Support

Following brainstem death, the aim is to reduce the CV response to the catecholamine storm and support the CV system post-catecholamine storm, hence maintaining cardiac and end-organ perfusion.

### Cardiovascular Monitoring

Potential DBD patients are susceptible to desaturation, arrhythmia, myocardial ischemia, and hemodynamic instability. Hence, international guidelines promote the use of multiple measured variables to determine therapy. Along with standard ICU monitoring, CO monitoring may be required.<sup>13</sup> CO monitoring is indicated if left ventricular ejection fraction (LVEF) is  $\leq 40\%$  or if there is an escalation in inotropic or vasopressor support. The insertion of a pulmonary artery catheter (PAC) allows monitoring of mixed venous oxygen saturation and hemodynamic parameters. In addition, PAC is required for evaluation of the heart and lungs for donation.<sup>35</sup> This has been advocated by the Papworth hospital transplant program study that showed that utilization of PAC to guide CV resuscitation improved the function of 92% of organs that were initially considered unsuitable for transplantation.<sup>42</sup> Although the less invasive esophageal Doppler may be more desirable if the heart and lungs are not being considered for donation. Other minimally invasive hemodynamic monitors utilizing the pulse contour analysis technique, such as LiDCO Plus, have not been shown to be beneficial in the management of potential DBD patients in the recent Monitoring Organ donors to Improve Transplantation Results (MONITOR) trial.<sup>43</sup>

### Cardiovascular Investigations

Potential DBD patients considered for cardiac donation should have a base line 12-lead electrocardiogram (ECG) for arrhythmias and ischemia and a transthoracic echocardiogram (TTE) to identify any structural abnormalities that may preclude heart transplantation. However, it has been shown that 50% of functionally abnormal hearts on initial TTE can improve to meet hemodynamic transplant criteria following active DBD patient management.<sup>44</sup> Hence, a single TTE assessment should not be used to rule out donor suitability and repeat TTE should be considered if initial impaired function is shown.

A small study has suggested high donor levels of troponin correlates with high incidence of cardiac rejection.<sup>45</sup> However, the American consensus guidelines for management of cardiac donors concluded that high troponin levels can be present in donors without ventricular dysfunction and there is poor quality of evidence linking troponin levels

**Table 1** International donor resuscitation targets

Guidelines	UNOS (1999) <sup>38</sup>	American (2001) <sup>36,37</sup>	Canadian (2006) <sup>35</sup>	UK (2012) <sup>39,40</sup>	Eurotransplant (2015) <sup>41</sup>
Respiratory					
Saturations	≥ 95%	≥ 95%	≥ 95%	≥ 95%	≥ 95%
PaO <sub>2</sub>	≥ 12 kPa	≥ 10.7 kPa	≥ 10.7 kPa	≥ 10 kPa	> 13.3 kPa
PaCO <sub>2</sub>	4–4.7 kPa	4–4.7 kPa	4.7–6.0 kPa	5–6.5 kPa <sup>a</sup>	4.6–6.0 kPa
Tidal volume	10–15 mL/kg	8–10 mL/kg	8–10 mL/kg	4–8 mL/kg	6–8 mL/kg
PEEP	5 cm H <sub>2</sub> O	5 cm H <sub>2</sub> O	5 cm H <sub>2</sub> O	5–10 cm H <sub>2</sub> O	5–10 cm H <sub>2</sub> O
PIP	≤ 30 cm H <sub>2</sub> O	≤ 30 cm H <sub>2</sub> O	≤ 30 cm H <sub>2</sub> O	≤ 30 cm H <sub>2</sub> O	≤ 35 cm H <sub>2</sub> O
Cardiovascular					
Heart rate	70–120 beats/min	–	60–120 beats/min	60–100 beats/min	–
SBP	> 90 mm Hg	–	> 100 mm Hg	> 100 mm Hg	≥ 90 mm Hg
MAP	≥ 60 mm Hg	≥ 60 mm Hg	≥ 70 mm Hg	60–80 mm Hg	70–90 mm Hg
CVP	≤ 12 mm Hg	6–10 mm Hg	6–10 mm Hg	4–10 mm Hg	6–10 mm Hg
Urine output	1–3 mL/kg/h	≥ 1 mL/kg/h	0.5–3 mL/kg/h	0.5–2 mL/kg/h	1–2 mL/kg/h
PCWP	≤ 12 mm Hg	8–12 mm Hg	6–10 mm Hg	< 12 mm Hg	10–15 mm Hg
Cardiac index	> 2.5 L/min/m <sup>2</sup>	> 2.4 L/min/m <sup>2</sup>	> 2.4 L/min/m <sup>2</sup>	> 2.1 L/min/m <sup>2</sup>	–
SVR or SVRI	SVR 800–1,200 dyne.s/cm <sup>5</sup>	SVR 800–1,200 dyne.s/cm <sup>5</sup>	SVR 800–1,200 dyne.s/cm <sup>5</sup>	SVRI 1,800–2,400 dyne.s/cm <sup>5</sup> /m <sup>2</sup>	–
ScvO <sub>2</sub>	–	–	≥ 60%	> 60%	–
Metabolic and Endocrine					
pH	7.40–7.45	7.40–7.45	7.35–7.45	7.25–7.45	–
Blood glucose	6.7–10 mmol/L	4.4–10 mmol/L	4–8 mmol/L	4–10 mmol/L	6.6–9.9 mmol/L
Temperature	36.5–37.5°C	> 35°C	> 35°C	36–37.5°C	35–37°C
Sodium	< 150 mmol/L	< 150 mmol/L	130–150 mmol/L	< 150 mmol/L	134–150 mmol/L
Hematological					
Hb	≥ 10 g/L	≥ 10 g/L	≥ 70 g/L	≥ 70 g/L	> 96 g/L
HCT	≥ 30%	≥ 30%	–	–	> 20%

Abbreviations: CVP, central venous pressure; Hb, hemoglobin levels; HCT, hematocrit; MAP, mean arterial pressure; PaCO<sub>2</sub>, partial pressure of carbon dioxide; PaO<sub>2</sub>, partial pressure of oxygen; PEEP, positive end-expiratory pressure; PCWP, pulmonary capillary wedge pressure; PIP, peak inspiratory pressure; ScvO<sub>2</sub>, central or mixed venous saturation; SBP, systolic blood pressure; SVR or SVRI, systemic vascular resistance or systemic vascular resistance index; UNOS, united network for organ sharing.

<sup>a</sup>or higher as long as pH > 7.25.

with acute graft failure.<sup>36</sup> Canadian guidelines recommend serial troponin levels every 12 hours and recommend that one considers performing a coronary angiogram when the following donor factors are present: older heart donors, CV risk factors, history of coronary heart disease, ischemia on ECG, regional wall motion abnormalities, or LVEF ≤ 40%.<sup>35</sup>

### Management of Catecholamine Storm

The occurrence of the catecholamine storm in a brainstem-dead patient has been defined as the acute and sustained (> 10 minutes) increase in systolic blood pressure (SBP) > 200 mm Hg with a heart rate (HR) > 140 beats/min in the absence of any other cause.<sup>46</sup> A retrospective study showed this occurs in approximate 63% of brainstem-dead patients. This study also showed that active treatment of the catecholamine storm using short-acting antihypertensives improved LVEF and the success rate of cardiac transplantation.<sup>46</sup> Unfortunately, the power of the study did not allow comparison between

different antihypertensives to determine the most effective agent. Despite this, international guidelines recommend esmolol or sodium nitroprusside infusions as first-line agents to be started if MAP remains > 90 mm Hg or SBP remains ≥ 160/90 mm Hg.<sup>35,47</sup>

### Management Post-Catecholamine Storm

#### Fluid Management

Post-catecholamine storm-associated vasoplegia and hypotension need to be supported with adequate fluid resuscitation and vasopressor and/or inotropic support. Maintaining euvolemia is supported by a prospective observational study of DBD patients, which showed preload responsiveness (a pulse pressure variation [PPV] > 13%) was associated with higher cytokine levels and lower number of viable organs for transplantation.<sup>48</sup> Most advocate the use of balanced crystalloid solutions over colloids for fluid resuscitation in potential DBD patients,

**Table 2** Summary of donor management as per current literature<sup>22,35,36,40,41</sup>

Support	
Respiratory	<b>Lung-protective ventilation:</b> Tidal volume 4–8 mL/kg of IBW, PEEP 5–10 cm H <sub>2</sub> O, PIP ≤ 30 cm H <sub>2</sub> O, lowest possible FiO <sub>2</sub> to achieve PaO <sub>2</sub> ≥ 10 kPa (ideally < 0.4), and relative normocapnia with pH > 7.25. Conservative fluid management approach: If PaO <sub>2</sub> /FiO <sub>2</sub> ratio < 300, consider diuresis to normovolemia
Cardiovascular	<b>Management of catecholamine storm:</b> If SBP ≥ 160/90 mm Hg or MAP > 95 mm Hg wean inotropic/vasopressor support and consider <b>short-acting antihypertensives:</b> Esmolol: 100–500 µg/kg IV bolus followed by 100–300 µg/kg/min IVI Na nitroprusside: 0.5–5 µg/kg/min IVI <b>Management post catecholamine storm:</b> Use multiple measured variables, including cardiac output (if available), to guide resuscitation to achieve CV targets <b>Fluid resuscitate</b> with crystalloids to euolemia <b>Inotropes/vasopressors:</b> First line: vasopressin 0–4 U/h IVI and avoid catecholamines if possible If needed, avoid high-dose catecholamines (NA < 0.2 µg/kg/min or dopamine ≤ 10 µg/kg/min) <b>Consider T<sub>3</sub></b> IV bolus and IVI if CV unstable despite conventional therapy
Renal	<b>Avoid positive fluid balance and aim for 0.5-3 mL/kg/h</b> <b>Avoid nephrotoxic drugs</b> and minimize exposure to IV contrast <b>Correct electrolyte abnormalities</b>
Hepatic	<b>Maintain liver glycogen stores</b> with enteral feeding or glucose infusion. <b>Avoid hepatotoxic drugs</b>
Endocrine	<b>Consider combined HT</b> if LVEF ≤ 40% or hemodynamic instability remains despite conventional therapy: <ul style="list-style-type: none"> <li>• T<sub>3</sub>: 4 µg IV bolus followed by 3 µg/h IVI or T<sub>4</sub>: 20 µg IV bolus followed by 10 µg/h IVI</li> <li>• Vasopressin: 1 U IV bolus followed by 0–4 U/h IVI</li> <li>• Methylprednisolone 15 mg/kg (max. 1g) IV every 24 h</li> </ul> <b>Identify and correct DI:</b> Consider DI if: UO > 4 mL/kg/h with serum Na ≥ 145 mmol/L, and/or serum osmolarity ≥ 300 mOsmol/kg, and/or urine osmolarity ≤ 200 mOsmol/kg, or SG < 1.005. First-line vasopressin infusion to titrate against UO (aim ≤ 3 mL/kg/h) and Na < 150 mmol/L. If DI persists despite vasopressin, addition of DDAVP 1–4 µg IV boluses is indicated (titrate to effect). Enteral or IV hypotonic solutions may be required to maintain euolemia and normonatremia. <b>Tight glycaemic control</b> of 4–10 mmol/L with insulin IVI (min. 1 U/h ± glucose infusion to maintain blood sugar levels). Maintain normothermia using humidified warm inspired gases, warming blankets, and warm IV fluids
Immunological	<b>Methylprednisolone</b> 15 mg/kg (max. 1g) IV every 24 h
Hematological	<b>Correct coagulopathy</b> if bleeding with platelet and coagulation products to maintain international normalized ratio < 1.5 and platelet count of > 50,000 mm <sup>-3</sup> <b>Maintain Hb ≥ 70 g/L and hematocrit ≥ 30%</b> <b>Maintain venous thromboprophylaxis measures</b>
Other	<b>Review and stop all unnecessary medications</b> <b>Antibiotics for presumed or proven infection</b> following full septic screen

Abbreviations: CV, cardiovascular; DDAVP, 1-deamino-8-D-arginine vasopressin; DI, diabetes insipidus; FiO<sub>2</sub>, fraction of inspired oxygen; Hb, hemoglobin; HT, hormone therapy; IBW, ideal body weight; IV, intravenous; IVI, intravenous infusion; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; NA, noradrenaline; Na, sodium; PaO<sub>2</sub>, partial pressure of oxygen; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; SBP, systolic blood pressure; SG, specific gravity; T<sub>3</sub>, triiodothyronine; T<sub>4</sub>, tetraiodothyronine; UO, urine output.

with studies comparing their use in DBD patients reporting either no difference in early liver graft function or impaired immediate renal graft function with colloids.<sup>49,50</sup> However, recent studies suggest excessive crystalloids may increase the risk of delayed renal graft function, and hence advise the use of colloid boluses to minimize the volume of crystalloid.<sup>51</sup> The Eurotransplant manual promotes fluid resuscitation with a crystalloid-to-colloid fluid ratio of 2:1.<sup>41</sup> However, there is no evidence to support the use of colloids over crystalloids in the management of potential organ donors.

There is a balance that must be met between fluid replacement to maintain end-organ perfusion and function, especially in renal donors, versus fluid restriction to avoid organ edema, excessive lung water, and donor lung

impairment. Many centers advocate the use of PAC to guide fluid management.<sup>42</sup> The multicenter, randomized, MONITOR trial compared usual care to protocolized fluid therapy using LiDCO Plus to target cardiac index (CI), MAP, and PPV goals. This study showed that the protocolized fluid therapy group received more fluids with no difference in the use of vasoactive drugs. However, there was no difference in the number of organs transplanted from DBD patients and recipient mortality between the two groups.<sup>43</sup> This supports the conservative fluid management approach to maintain adequate intravascular volume, while preventing fluid overload from worsening neurogenic pulmonary edema. Several studies have shown that this conservative fluid approach increases the number of viable lungs for transplantation, while not

affecting the viability of other donor organs, and advocates a target CVP < 6 mm Hg.<sup>52-54</sup>

### *Inotropic and Vasopressor Support*

International guidelines promote vasopressin as the first-line agent when hypotension is fluid unresponsive and promote the avoidance of catecholamines.<sup>35,36,40,41</sup> Vasopressin has the added benefit of treating hypovolemia secondary to DI and decreasing inotropic requirements, without impairing short- or long-term renal graft function.<sup>35,37</sup> A study showed improved long-term control of CV stability in DBD patients with the use of a pressor dose of vasopressin (1–2 U/h).<sup>55</sup> However, a meta-analysis of two RCTs that reviewed the use of vasopressin and desmopressin in DBD patients showed no benefit on early renal graft function.<sup>11</sup> Despite this, the high incidence of DI in DBD patients means that vasopressin still has a clinically beneficial role in controlling the associated hypernatremia, hyperosmolality, and hypovolemia. This helps minimize the need for excessive fluid infusions and prevents end-organ hypoperfusion. Also, the use of vasopressin reduces inotropic requirements and in turn decreases the associated adverse effect of exogenous catecholamines on myocardial adenosine triphosphate (ATP) depletion, which can impair posttransplant cardiac function.<sup>7,56</sup> Also, low-dose vasopressin causes vasodilation of coronary and pulmonary arterial circulation, which improves coronary blood flow and reduces pulmonary hypertension. Thus, vasopressin is beneficial for both cardiac and lung donor organs.<sup>57</sup>

Prior to diagnosis of brainstem death, patients may already be on vasopressor/inotropic support to achieve a desired MAP and in turn CPP. This support is usually NA in most ICUs. However, the use of NA at doses > 0.05 µg/kg/min in DBD patients has been associated with increased right ventricular dysfunction and higher incidence of mortality in recipients.<sup>58</sup> Also excess exogenous β-agonists can lead to β-receptor downregulation, and an animal study has shown rapid desensitization of β-receptor function post-brainstem death.<sup>13,59</sup> Hence β-agonists should be used with caution in potential heart donors. Therefore, NA is considered a second-line agent as per international guidelines.<sup>35</sup>

Some centers advocate the use of dopamine as the first-line inotrope. Studies have shown improvement in initial renal graft function and reduced need for dialysis postrenal transplant with the use of dopamine in DBD patients, although there was no improvement in recipient survival.<sup>60,61</sup> However, a crossover, prospective, double-blind RCT showed that although low-dose dopamine infusions reduce renal vascular resistance in patients without acute kidney injury (AKI), dopamine actually worsens renal perfusion in the context of AKI and can induce AKI in normovolemic patients.<sup>62,63</sup> Also, dopamine may inhibit anterior pituitary hormone secretion, worsening brainstem death-associated endocrine dysfunction.<sup>63</sup> Furthermore, a meta-analysis comparing NA and dopamine in patients with septic shock showed a higher incidence of arrhythmias and mortality with dopamine.<sup>64</sup> Hence, dopamine should be used with caution. If the heart is considered for donation, international guidelines advise that dopamine at the rate of 10 µg/kg/min should not be exceeded.<sup>35,36</sup>

### *Antiarrhythmic Support*

During and post catecholamine storm, arrhythmias are common with an incidence of 25% in DBD patients, either due to a central cause, conduction system ischemia following catecholamine storm, or electrolyte disturbance.<sup>19</sup> Hence arrhythmias can be resistant to standard treatment. Initially, the underlying cause should be treated, if possible. The first-line management of tachyarrhythmias causing hemodynamic compromise in potential DBD patients is amiodarone. Anticholinergic drugs, such as atropine, are ineffective in the management of bradyarrhythmias that cause hemodynamic compromise. This is due to vagal nerve disruption at the level of the brainstem. Hence, adrenaline or isoprenaline is used as the first-line agent instead, and temporary pacing may be required.<sup>36</sup>

### *Respiratory Support*

All potential DBD patients require intubation and positive-pressure ventilation, which carries its own risks of barotrauma, volutrauma, and atelectotrauma. Canadian and American guidelines recommend high tidal volumes of 8 to 10 mL/kg and positive end-expiratory pressure (PEEP) of 5 cm H<sub>2</sub>O.<sup>35,37</sup> However, an RCT showed that adopting a lung-protective low tidal volume (6–8 mL/kg) and high PEEP (8–10 cm H<sub>2</sub>O) strategy reduces barotrauma and increases lung donor yield.<sup>65</sup> Although excessive PEEP should be avoided as it can impair preload and in turn CO. Also, excessive PEEP can promote vasoconstriction through the activation of the renin-angiotensin system, leading to impaired end-organ perfusion.<sup>7</sup>

The FiO<sub>2</sub> should be kept to a minimum to balance the need to provide adequate end-organ oxygenation and minimize the risk of potential oxygen toxicity and diffusion atelectasis. Furthermore, ventilation should be targeted to achieve normocapnia to avoid hypocapnia-associated peripheral vasoconstriction and leftward shift in the oxyhemoglobin dissociation curve, both of which may impair end-organ oxygen delivery.<sup>37</sup>

Hence, current literature promotes lung-protective ventilation strategy in potential DBD patients with (1) low tidal volume, (2) high PEEP, (3) recruitment maneuvers, (4) lowest possible FiO<sub>2</sub> to achieve a PaO<sub>2</sub> ≥ 10, and (5) relative normocapnia or hypercapnia as long as pH > 7.25 (–Table 2).<sup>22,40</sup>

All international guidelines promote good routine respiratory care bundles. Furthermore, if the partial pressure of arterial oxygenation/fraction of inspired oxygen (PaO<sub>2</sub>/FiO<sub>2</sub>) ratio is < 300, then it is recommended to perform chest physiotherapy, recruitment manoeuvres, and diurese to normovolemia.<sup>35</sup>

Potential DBD patients considered for lung donation require a baseline chest radiograph and arterial blood gas (ABG) test to assess suitability of the lungs for donation. Bronchoscopy may be considered to allow direct suctioning, bronchoalveolar lavage, and diagnosis of possible infection or suspicious lesions.<sup>35</sup>

### *Renal Support*

Renal donor hypotension has been associated with acute tubular necrosis, renal cortical necrosis, delayed graft function, and graft rejection. Thus, the main supportive

therapy for donor kidneys is to maintain an adequate MAP > 65 mm Hg for renal perfusion.<sup>30</sup> However, a retrospective review of the registry of the Eurotransplant International Foundation suggested that DBD patient treatment with catecholamines improved renal graft survival, despite no statistically significant difference in the MAP between donors receiving zero, single, and combined catecholamines.<sup>66</sup> This adds weight to the theory of the immunomodulatory effects of catecholamines improving renal graft survival.

Potential DBD patients considered for renal donation should have urinalysis and baseline creatine, urea, and creatine clearance rate measured.<sup>35</sup> Also, one should avoid nephrotoxic drugs and minimize exposure to intravenous contrast in these patients.

### Hepatic Support

Adequate nutrition to maintain liver glycogen stores has been shown to reduce liver graft loss; thus, nutritional support via continuous enteral feeding is required.<sup>13</sup>

DBD patient hypernatremia has been associated with increased liver recipient death and retransplantation. This is possibly due to osmotic shifts and cell lysis when a liver exposed to a hyperosmotic environment is transplanted into a normosmolar recipient.<sup>67</sup> However, a subsequent retrospective study found no correlation between DBD patient serum sodium (Na) levels and early liver graft function or 1-year graft survival.<sup>68</sup> Hence, it has been suggested that hypernatremia itself may not be the underlying cause of impaired liver graft outcome, but instead a marker of poor DBD patient management.<sup>22</sup> Nevertheless, international guidelines recommend maintaining a serum Na < 150 mmol/L with hypotonic intravenous solutions or nasogastric (NG) water.<sup>35,36</sup>

Literature recommends maintaining CVP < 10 mm Hg and PEEP < 10 cm H<sub>2</sub>O to help reduce hepatic congestion.<sup>47</sup> However, there is no study to suggest that these measures have any beneficial effect on liver transplant recipient outcomes.

Potential DBD patients considered for liver donation need liver function tests, coagulation screen, and hepatitis screen. Canadian guidelines recommend a liver biopsy prior to retrieval if the donor is obese or hepatitis C antibody positive to clarify transplantability.<sup>35</sup>

### Endocrine and Immunological Support Combined or Triple Hormonal Therapy

A retrospective study showed that 25% of potential DBD patients die prior to donating organs due to failure of physiological support despite maximal conventional therapy.<sup>69</sup>

Therefore, the concept of combined or triple hormonal therapy (HT) was introduced to help maintain hemodynamic stability. The traditional HT strategy, using hourly doses of triiodothyronine (T<sub>3</sub>) 2 µg, cortisol 100 mg, and insulin 20 units, has been shown to improve CV status, reduce inotropic requirements, and increase the number of organs transplanted per donor.<sup>29</sup> The current combined HT consists of methylprednisolone, vasopressin, and either T<sub>3</sub> or tetraiodothyronine (T<sub>4</sub>). A retrospective study of 10,292 DBD patients showed an increase in the number of organs transplanted per donor in those treated with combined HT compared with

non-HT-treated donors.<sup>70</sup> Similarly, a retrospective analysis of 18,726 DBD patients from the United Network for Organ Sharing database showed the use of combined HT was associated with more organ yield and increased renal graft and heart transplant recipient survival, but no change in liver transplant recipient survival.<sup>71</sup> However, currently there is no RCT to support routine use of combined HT. Hence, international guidelines recommend consideration of combined HT only if LVEF ≤ 40% or hemodynamic instability remains despite conventional therapy.<sup>35,36</sup>

### Thyroid Support

A prospective, non-RCT showed decreased vasopressor requirements with T<sub>3</sub> infusions in DBD patients who remained hemodynamically unstable despite fluid, inotropic, and vasopressor resuscitation.<sup>31</sup> In contrast, two separate meta-analyses of four prospective double-blind RCTs comparing intravenous T<sub>3</sub> with placebo in DBD patients showed no difference in CI.<sup>11,72</sup> However, one RCT not included in these meta-analyses has shown that using T<sub>3</sub> reduced inotropic requirements in terms of dose and duration.<sup>73</sup> Furthermore, a subsequent retrospective study showed that T<sub>3</sub> or T<sub>4</sub> therapy resulted in more transplantable organs per donor.<sup>74</sup> Thus, on the basis of current evidence, reduced T<sub>3</sub> does not seem to be a major contributor to CV instability in DBD patients, and there is a low level of evidence to support its routine use. Nevertheless, T<sub>3</sub> may still be a useful adjunct in the patients who remain CV unstable despite conventional therapy.

### Immunological Support

The systemic inflammatory state that occurs post-brainstem death may affect CV stability, worsen neurogenic pulmonary edema, and increase donor organ rejection.<sup>34</sup> In theory, the use of corticosteroids should suppress this inflammatory state and improve CV responsiveness to catecholamines and in turn have a catecholamine-sparing effect.

A retrospective study has suggested that the use of high-dose methylprednisolone in DBD patients is associated with improved oxygenation and resulted in more lungs transplanted.<sup>75</sup> However, an RCT showed DBD patient treatment with methylprednisolone decreased pulmonary water accumulation but did not increase donor lung yield.<sup>9</sup>

A prospective RCT showed reduced levels of cytokines and adhesion molecules in methylprednisolone-treated DBD patients compared with controls, resulting in reduced incidence of acute liver graft rejection.<sup>76</sup> However, a prospective, double-blind RCT comparing DBD patients pretreatment with methylprednisolone and no pretreatment prior to organ donation showed no difference in early renal graft function.<sup>77</sup>

A multicenter prospective study comparing hydrocortisone DBD patient therapy with controls concluded no difference in functional recovery of transplant grafts. However, steroid therapy was associated with improved CV stability, and hence the study supported steroid use in hemodynamically unstable potential DBD patients.<sup>78</sup>

In summary, although the current evidence is equivocal, international guidelines advocate the use of methylprednisolone 15 mg/kg to all potential DBD patients.<sup>35,36</sup>



### Management of Diabetes Insipid

Early recognition and appropriate management of DI are key to maintain hemodynamic stability. One should consider DI if urine output (UO) > 4 mL/kg/h with serum Na  $\geq$  145 mmol/L, and/or serum osmolality  $\geq$  300 mOsmol/kg, and/or urine osmolality  $\leq$  200 mOsmol/kg, or specific gravity < 1.005.<sup>35</sup> International guidelines promote management of DI with a continuous vasopressin infusion instead of intermittent desmopressin (DDAVP, 1-deamino-8-D-arginine vasopressin) boluses. This is because vasopressin has 1,500 times greater vasoconstrictor action and a shorter elimination half-life than DDAVP, even though vasopressin has 10 times less antidiuretic action than DDAVP. Hence, vasopressin has the added benefits of vasopressor activity and ease of titration against UO (aim  $\leq$  3 mL/kg/h) and Na target (< 150 mmol/L). However, if DI persists despite the administration of vasopressin, the addition of DDAVP 1 to 4  $\mu$ g intravenous boluses is indicated.<sup>35,79</sup> Furthermore, enteral or intravenous hypotonic solutions may be required to maintain euvolemia and normonatremia.<sup>47</sup>

### Glycemic Control

DBD patient hyperglycemia has been implicated as a risk factor for (1) pancreatic transplant failure due to direct pancreatic  $\beta$ -cell damage, (2) renal graft impairment, and (3) hypovolemia secondary to osmotic diuresis. Hence, many guidelines advocate tight glycaemic control of 4 to 10 mmol/L with an insulin infusion.<sup>35,36,40,80</sup>

### Thermoregulation

As described previously, hypothermia and associated adverse effects are common in DBD patients. However, an RCT found that maintenance of therapeutic hypothermia of 34 to 35°C in DBD patients was associated with reduced rate of delayed graft function.<sup>81</sup> Despite this, current guidelines promote maintenance of normothermia using humidified warm inspired gases, warming blankets, and warm intravenous fluids.<sup>7</sup> Thus, all potential donors should have invasive temperature monitoring.

### Hematological Support

Plasminogen activator and thromboplastin released from ischemic or necrotic brain tissue in brainstem-dead patients may stimulate DIC, leading to fibrin deposits within organs. These fibrin deposits may impair posttransplant organ function.<sup>33</sup> Hence early recognition and support of coagulopathy with clotting factors and platelet replacement are required to achieve international targets of an international normalized ratio < 1.5 and platelet count of > 50,000 mm<sup>-3</sup>.<sup>13</sup>

Blood transfusion is indicated if hemoglobin concentration falls < 70 g/L as per NICE 2015 guidelines.<sup>82</sup> International DBD patient management guidelines also recommend blood transfusion to maintain hematocrit  $\geq$  30% to optimize oxygen delivery.<sup>35,36</sup>

### Organizational Treatment Approach

Care of the organ donor requires a multidisciplinary team (MDT) approach involving communication and

collaborative work between ICU, retrieval, and Specialist Nurses–Organ Donation (SN-OD) teams to achieve the best outcome for the donor, donor's family, and the recipient. A retrospective analysis has shown that the implementation of an intensive care physician-led organ donor support team improved the number of transplantable organs from 66 (31%) out of 210 potential DBD organs to 113 (43%) out of 258 potential DBD organs.<sup>83</sup> Therefore, Eurotransplant guidelines advise that the ICU physician should act as the responsible clinician for donor management and the UK National Organ Donation Committee promote all trusts to appoint clinical leads for organ donation.<sup>19,41</sup>

Organs used to be recovered as soon as possible due to concerns over loss of unstable potential DBD patients. Now with improved potential DBD patient care, the timing of organ retrieval depends on which organs have been accepted for transplantation. One retrospective study showed that the longer the donor management time (brainstem death to retrieval time), the poorer the heart transplant recipient outcome.<sup>84</sup> However, another retrospective review showed that the quality and quantity of all types of transplantable solid organs do not decline with prolonged donor management time.<sup>85</sup> In fact, subsequent retrospective studies have shown reduced rate of delayed renal graft function and improved lung function associated with longer donor management time and advocated a relax and repair strategy.<sup>86,87</sup> Furthermore, early active potential DBD patient management has been shown in an RCT to be associated with increased lung yield.<sup>9</sup> Thus, these studies highlight the importance of early identification of brainstem death and early institution of active donor management, to maximize the time available to optimize organ function prior to planned organ retrieval.

The importance of an aggressive donor management protocol was highlighted by the Papworth hospital transplant program study, which showed that utilization of potential DBD patient management protocol improved the function of 92% of organs that were initially considered unsuitable for transplantation.<sup>42</sup> Similarly, a prospective study involving 88 ICUs in the United States has shown that the implementation of a structured potential DBD patient management algorithm improved the number of organs retrieved and transplanted without impairing the quality of the organs.<sup>10</sup> Furthermore, a retrospective study showed that the implementation of an aggressive donor management protocol decreased donors lost as a result of hemodynamic instability (by 87%), increasing the number of actual donors (by 82%) and organs retrieved (by 71%).<sup>88</sup> Another retrospective study showed that utilization of aggressive potential DBD patient management protocol could convert initially unsuitable donor lungs to transplantable ones, with no difference in 1-year graft survival.<sup>89</sup> Hence, the UK National Organ Donation Committee have endorsed a donor optimization care bundle and promotes its adoption by local donation committees' ICUs.<sup>19</sup>

### Conclusion

The incidence and the severity of the pathophysiological changes post-brainstem death depend on the etiology, speed

of onset, and duration of brainstem death. A good understanding of these pathophysiological changes allows effective active donor management strategies to be implemented to maintain the functional integrity of the organs.

Although there is a low level of evidence to support specific management strategies to optimize the care of potential DBD patients, there is reasonable consensus between different international guidelines on protocolized ICU management of potential DBD patients and donor resuscitation targets. Hence, we recommend that all ICUs develop local potential DBD patient protocolized management guidelines to optimize transplanted organ outcome.

Key management concepts include (1) early recognition of brainstem death and referral to organ donation services, (2) ICU-led MDT approach to donor management, (3) shift in ICU teams thinking from management of raised ICP to maintaining organ perfusion and function, (4) early active donor management to normalize donor physiology, and (5) prevention, recognition, and treatment of complications of brainstem death.

#### Conflict of Interest

None declared.

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