

Chapter 2

Management of Extended Criteria Donors

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2.1 Introduction

Only about 20 % of brain-dead donors in Japan have been fitted in a so-called standard criteria donor for all organs including the heart, lung, liver, pancreas, and kidney. Therefore, it is very important for us to maximize the number of transplantable organs in order to resolve severe donor shortage in Japan [1]. From these aspects, the purposes of donor management are not only to stabilize donor's hemodynamics until organ procurement surgery but also to maximize donor organ availability and to improve function of extended criteria donor organs. If organ availability is increased, more patients can be saved by organ transplantation. Maximizing donor organ availability is also the last wish of donors and donor families. However, if a transplant recipient died due to a very marginal donor organ, the donor family feels the loss of their loved one again. Therefore, the prevention of primary graft dysfunction (PGD) is essential for the donor family as well as for recipients.

Full-scale donor management begins after the patient is pronounced brain dead and his or her family agrees to donate the organ(s), especially in Japan. In general, donor management is based on the treatment of cardiac and respiratory dysfunction resulting in the improvement of hemodynamics, oxygen supply, and finally other organ function. The targets of hemodynamic parameters are systemic blood pressure >90 mmHg, central venous pressure (CVP) of 6–10 mmHg, urine output of 100 mL/h (0.5–3 mL/kg/h), and heart rate of 80–120 beats/min. As organ procurement surgery begins within 12 h after full-scale donor management is started, it is very different from the usual intensive care to stabilize hemodynamics and to maintain and improve organ function as much as possible in a short period. Moreover, it is important for the physicians who perform donor management to recognize the pathophysiology of brain death from the beginning to completion period.

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2.2 Pathophysiology of Brain Death

2.2.1 *Physiological Changes at Completion of Brain Death*

Novitzky et al. reported animal experiments of brain death in baboons, induced by placing a Foley catheter in the subdural space through a burr hole and instilling 20–30 mL of saline [2]. This resulted in acute intracranial hypertension leading to brain stem herniation and brain death. During and following the agonal period there was a short-lived, but devastating, catecholamine “storm” [2, 3], which was the result of endogenous catecholamine release from postganglionic sympathetic nerve endings. Novitzky et al. reported that serum concentration of noradrenaline (NAD), adrenaline (AD), and dopamine (DOA) elevated to approximately 1,600, 1,100, and 450 pg/mL, respectively, 5 min after balloon inflation in this baboon model. The hemodynamic response was a significant elevation of the systemic vascular resistance (SVR), resulting in systemic hypertension, acute left ventricular failure, fall in cardiac output, and acute transient mitral valve regurgitation, leading to a rise in left atrial pressure. These events led to blood volume displacement into the venous compartment, with pulmonary volume overloading. The electrocardiogram (ECG) showed multiple arrhythmias plus ischemic changes in all animals.

However, when the intracranial pressure is increased slowly, the animals underwent a lesser hyperdynamic response and experienced only approximately 25 % of the rise in epinephrine levels seen in animals undergoing sudden brain death. In the human clinical situation, there is a broad spectrum of adverse hemodynamic instability that is observed, which may, in part, reflect the speed at which brain death is induced.

After the initial outpouring of catecholamines following the onset of brain death, catecholamine levels rapidly returned to control levels and subsequently to levels below baseline, when endocrine changes, reflecting pituitary failure, developed.

In clinical settings, brain death is associated with a massive increase in catecholamine levels (the sympathetic/autonomic storm), sometimes resulting in increased heart rate, systemic blood pressure, cardiac output, and SVR. The consequences of autonomic storm are an imbalance between myocardial oxygen demand and supply, which triggers metabolic functional alterations and sometimes anatomical heart damage (myocytolysis and micronecrosis) [4]. Electrocardiographic signs of myocardial ischemia, conduction abnormalities, and arrhythmia are also common during this period.

Histological examination of cardiac tissue exposed to autonomic storm shows changes typical of widespread ischemic damage and necrosis, and profound end-organ vasoconstriction has been demonstrated in animal models [5]. However, this period of intense catecholamine release is short-lived (typically minutes) and self-limited and may require no treatment. Nevertheless, many experimental studies and recent clinical observations suggest that treatment of autonomic storm (short-acting β -blocker drugs or nitroprusside) is a viable strategy to attenuate myocardial dysfunction and increase the number and success rate of heart procurements and cardiac transplantation [6–8].

Regardless of whether the systemic arterial pressure is low or high, the donor is usually hypovolemic. Brain death-induced physiological changes lead to an increase in capillary permeability and create a functional intravascular hypovolemia. In addition, absolute or relative hypovolemia is commonly present in these patients because of increased fluid loss (i.e., mannitol, glycerol, other diuretic therapy, or diabetes insipidus). This hypovolemic state is difficult to assess without monitoring CVP or pulmonary capillary wedge pressure (PCWP).

Severely brain-injured patients develop acute lung injury (ALI) and/or adult respiratory distress syndrome (ARDS) in 15–20 % of cases. In addition, lung function can be impaired through different mechanisms including neurogenic pulmonary edema, aspiration, hemo-pneumothorax, atelectasis, and later on pneumonia. The presence of pulmonary dysfunction in acute brain injury is well known and has previously been attributed to hydrostatic phenomenon induced by a massive increase in sympathetic activity. However, an acute systemic inflammatory response also appears to play an integral role in the development of such injury by initiating infiltration of activated neutrophils into the lungs. Moreover, severe brain injury resulting in brain stem death is characterized by the release of proinflammatory mediators into the systemic circulation. This inflammatory response may determine the preclinical lung injury present in the potential lungs, which together with the ischemia-reperfusion injury may affect primary graft dysfunction. Indeed Follette et al. reported that the administration of high-dose steroids after brain death improved oxygenation and increased lung donor utilization by limiting the cytokine-mediated cellular injury [9].

2.2.2 Absent or Decreased Secretion of Antidiuretic Hormone After Brain Death

Antidiuretic hormone (ADH) is formed in the supraoptic and paraventricular nuclei of the hypothalamus by cleavages of a preprohormone of 168 amino acids and then a prohormone, vasopressin, is transported to the posterior lobe of the pituitary gland which stores it. Its release depends primarily on two factors, hyperosmolality and blood volume, and in addition on the effects of certain drugs.

The effects of vasopressin result from stimulation of V1 and V2 receptors, V1 mainly responsible for vasoconstriction, V2 for the antidiuretic effect.

V1 receptors are coupled by G protein to phospholipase C. Its activation elicits the hydrolysis of PIP2 in IP3 and DAG, which induces an increase of intracellular calcium concentration, responsible for the vasoconstriction. With doses higher than those which are necessary to induce water retention, ADH induces vasoconstriction. The plasma concentration of vasopressin can be sufficient to increase peripheral resistance and arterial pressure. The decrease in cutaneous blood flux seen in smokers could be the consequence of an increase in the secretion of vasopressin under the influence of nicotine.

V2 receptors are coupled by G protein to adenylyl cyclase. Its activation elicits an increase in cAMP which, via protein kinases, induces the activation of aqueous channels called aquaporins of type 2 or AQP2 mainly located in the renal collecting duct. Under the influence of vasopressin AQP2 migrate from the cytoplasm to the apical membrane. In nephrogenic diabetes insipidus there are AQP2 alterations. The ADH increases water permeability of collecting ducts in the cortical and medullary part of the kidney. It induces the incorporation of aquaporins in the apical membrane of collecting ducts and induces their opening, which allows water reabsorption.

The effects of brain death on the hypothalamic-hypophyseal axis are profound. The most frequent and almost immediate manifestation is diabetes insipidus due to loss of ADH secretion secondary to supraventricular and paraventricular hypothalamic nuclei ischemia. ADH was undetectable within 6 h. As ADH is secreted from the peripheral tissues, undetectable levels of ADH have been noted in 75 % of brain death. As antidiuretic action of ADH is decreased, the kidneys are unable to concentrate urine and excrete large amounts (4 mL/kg/h) of dilute urine (specific gravity <1.005 and urine osmolality <200 mOsm/L). Polyuria may lead to hypernatremia (>145 mEq/mL, which is common and sometimes severe and worsening), associated with rising serum osmolality and hypovolemia. As the vasoconstrictive effect of ADH is decreased, the vascular tone of systemic arteries is decreased, leading to hypovolemic shock. Therefore, absent or decreased secretion of ADH after brain death is associated with hemodynamic instability and compromised transplantable organ function.

Low-dose arginine vasopressin, in addition to treating diabetes insipidus, results in reduced inotropic requirements and has been associated with good kidney, liver, and heart graft function [2, 8, 10–12]. Pure vasopressors, like ADH, are less likely to cause metabolic acidosis or pulmonary hypertension and may be more appropriate than NAD for the vasoplegic shock phase.

2.2.3 Decrease in Anterior Pituitary Function After Brain Death

Anterior pituitary function (blood supply via hypophyseal extradural arteries) is usually preserved, but viable deficiency of hormones regulated by the anterior pituitary including thyroid hormone [triiodothyronine (T3) and free thyroxine (T4)], adrenocorticotrophic hormone, thyroid-stimulating hormone (TSH), and growth hormone has been described. This striking and acute hormonal depletion was very common and has been implicated in hemodynamic derangement seen after brain death in experimental animal models.

Cortisol levels were increased at 5 min and then declined progressively to sub-baseline levels [13]. Plasma levels of free T3 and T4 fell to 50 % of control levels within 1 h after brain death and became undetectable within 9 and 16 h, respectively, but TSH showed no significant change. Insulin levels declined to 50 %

within 3 h and to 20 % within 13 h [14]. Prompted by these results, the Cape Town group evaluated hormone replacement therapy, first in brain-dead animals [15] and then in brain-dead human organ donors [2].

However, this striking and acute hormonal depletion is not certain and questionable in clinical practice. Although a rapid decline in plasma levels of free T3 is seen after brain death as a result of impaired TSH secretion and peripheral conversion of T4, attempts to thyroid disturbances in organ donors have produced conflicting data [2]. Moreover, there has been inconsistent improvement or conflicting results in the assessed physiological parameters after replacement of these hormones in both animals and humans [16].

The studies by the Cape Town group on the benefits of hormonal therapy did not achieve rapid universal acceptance, in part because of published studies that failed to confirm low levels of T3, T4, cortisol, and insulin after brain death [17, 18] and/or published studies that failed to demonstrate any beneficial cardiac and circulatory effect of T3/T4 administration [19, 20]. This may have been for a number of reasons: not all brain-dead donors have total absence of anterior pituitary function (and therefore some have measurable T3 levels), some groups failed to measure free T3, not all donors are hemodynamically unstable [21–23] and the benefit from T3/T4 therapy might not be seen, and an inadequate dosage of T3/T4 may have been administered. However, in many countries, such as the USA, Canada, and Australia, hormone resuscitation strategies (ADH, T4, and methylprednisolone) are recommended to manage brain-dead donors [8].

The optimal dose of i.v. methylprednisolone for the brain-dead donor remains uncertain. High doses have been recommended [24, 25] and the UNOS study [8] indicated a beneficial effect on the heart when it was the sole hormone administered. Because the half-life of i.v. methylprednisolone is short [26], we believe that it is desirable to repeat the dosage when organ retrieval is delayed.

2.2.4 Cessation of Autonomic Nerve Regulations on Circulation

After brainstem ischemia and necrosis, the brain-heart connections are definitively disrupted. Brain death results in complete cessation of normal variations of the autonomic cardiovascular centers and a cessation of the baroreflex function [27]. Rapenne et al. [28] described that as soon as the diagnosis of brain death was clinically suggested, the heart rate variability (HRV) analysis demonstrated a lack of control of the sympathetic and parasympathetic components of the autonomic nerve system on cardiovascular regulation. A very small LF power spectrum could be found in these patients; free from regulation by the higher centers, the sympathetic nerves of the spinal cord continue to generate small autonomic impulses to control vasomotor tone.

Disrupted brain-heart connections, the so-called denervation, are also observed in heart transplant recipients. The authors described that transplanted hearts could

not augment cardiac performance rapidly in response to acute decrease in the preload due to loss of the brain-heart connection [29]. In normal hearts, if a preload of the heart rapidly decreases, autonomic sympathetic nerves are activated through vagal reflexes, resulting in an increase in heart rate and cardiac contractility. However, the transplanted hearts do not increase their rate or contractility by autonomic response to a rapid decrease in preload. The augmentation of cardiac performance of the transplanted hearts has been thought to depend mainly on an increase in AD secretion from the adrenal gland. Thus, the transplanted heart has been thought to be unable to rapidly enhance performance in response to a rapid decrease in the preload, such as sudden hemorrhage or occlusion of inferior vena cava.

As shown in heart transplant recipients, the hemodynamics of brain-dead persons is also unstable. For example, a decrease in blood return to the heart due to hemorrhage, putting pressure on the upper abdomen, or postural change may easily cause hypotension. After a few minutes of hypotension, AD is secreted from the adrenal glands due to spinal reflex and hypertension usually up to 150 mmHg and tachycardia may be observed. In uncontrolled brain-dead persons, systemic blood pressure and heart rate may rise and fall. This phenomenon is usually seen in a patient with hypovolemia due to diabetes insipidus. An increase in AD secretion may reduce a density of beta-adrenergic receptors (BAR) on the vessels and the myocardium.

2.2.5 Absent Cough Reflex

After brainstem ischemia and necrosis, the cough reflex is lost as seen in lung transplant recipients. This change probably influences susceptibility to respiratory infection and the consequences of atelectasis. As it is very difficult to aspirate deep sputa, bronchofiberscopy (BFS), by clearance of secretions and blood clots and correction of endotracheal tube malposition, may improve lung function.

2.2.6 Alteration of BAR Systems

Various changes in BAR systems occur during and after brain death. D'Amico et al. [30] reported a decrease in BAR density during brain death in adult and pediatric pigs. Deterioration of myocardial performance after brain death correlated temporally with desensitization of the myocardial BAR signal transduction pathway. Authors have previously reported that myocardial BAR may be depressed by the large doses of catecholamines (CAs) used to maintain donor hemodynamics after brain death [31]. The authors also revealed a significant inverse correlation between BAR density and serum AD level, but not between Bmax and serum NAD or DA levels [32]. Bmax values in patients treated with AD were significantly lower than

those in patients treated without AD; there was a significant inverse correlation between Bmax and the administered dose of AD. These data suggest that exogenous AD reduces BAR density in brain-dead patients and support the conventional criteria in which retrieval of cardiac grafts is restricted to donors who can be managed with minimal to moderate levels of inotropic support.

2.3 Donor Assessment and Management

In order to manage a donor properly, hemodynamics, respiratory function, infection, and other organ functions of the donor should be undertaken precisely. As there are no specific strategies for liver or renal dysfunction, cardiopulmonary management to improve organ perfusion and blood gas and metabolic management are the main therapeutic strategies for management of extended criteria donors.

2.3.1 *Role of Echocardiography and Circulatory Management*

The aggressive assessment and optimal management of donor left ventricular (LV) dysfunction offer a tremendous potential to increase cardiac donor utilization as a significant proportion of hearts are declined for reasons of “poor ventricular function.” However, strong evidence indicates that grafts from younger donors with left ventricular dysfunction can completely recover to normal function over time in the donor and following transplantation into a recipient [33]. Although echocardiography is very effective in screening for anatomical, especially valvular, anomalies of the heart, the use of a single echo examination in terms of a “snapshot assessment” of pump function to determine the physiological suitability of a donor graft is not well supported by evidence.

Instead, better physiological assessment and donor management of LV dysfunction are achieved by Swan-Ganz catheterization (SGC) investigations, which have led to favorable long-term outcomes [34]. By serial SGC investigations, specific physiological targets such as mean blood pressure >60 mmHg, CVP <12 mmHg, pulmonary capillary wedge pressure <12 mmHg, and left ventricular stroke work index >15 g m/m² while on only one single inotrope can be achieved, resulting in specified hemodynamic categories [34].

In the presence of LV underfilling, the LV seems to be hypertrophic or to have suitable LV systolic function. Therefore, circulatory blood should be estimated by CVP, PCWP, or the size and respiratory movement of the inferior vena cava (IVC) as well as doses of inotropes prior to undergoing echocardiography to assess cardiac function.

The goals of hemodynamic management are to achieve euvolesmia, to adjust vasoconstrictors and vasodilators to maintain a normal afterload, and to optimize cardiac output without relying on high doses of beta-agonists or other inotropes,

which increase myocardial oxygen demands, deplete the myocardium of high-energy phosphates, and decrease the density of BAR in the vessels and the myocardium. The target levels of hemodynamic parameter are as follows: systemic blood pressure >90 mmHg, CVP of 6–10 mmHg, urine output of 100 mL/h (or 0.5–3 mL/kg/h), and heart rate of 80–120 beats/min.

2.3.2 *Role of Bronchofiberscopy (BFS) and Respiratory Management*

A ventilatory strategy with high tidal volumes is potentially harmful and may exacerbate donor lung injury already triggered by the systemic inflammatory response. The use of low-tidal-volume ventilation was shown to be beneficial in a randomized controlled study for ALI and ARDS when compared to traditional tidal volumes. No such a trial has been performed to look if one ventilatory mode is superior to another in the care of the brain-dead organ donor. However, given similarities in the pathophysiological changes occurring in ARDS and lung injury after brain death, we might expect that beneficial management strategies can be extrapolated.

Recruitment maneuvers are an important component of donor optimization, especially when the oxygenation is subnormal and pulmonary abnormalities are visible on chest x-ray. Atelectasis is a common finding in the lung of cadaveric donors due to prolonged ventilation in the supine position. Prevention of atelectasis will reduce the development of atelectrauma by cyclic closing and reopening of the collapsed lung regions. Recruitment strategies include pressure-controlled ventilation with an inspiratory pressure of 25 cm H₂O (should be less than 30 cm H₂O) and a positive end-expiratory pressure of 15 cm H₂O for a short interval (2 h) before turning to conventional volume-controlled ventilation with a tidal volume of 10 mL/kg and positive end-expiratory pressure (PEEP) of 5 cm H₂O. To prevent loss of alveolar recruitment, higher levels of PEEP should be used immediately after these maneuvers. Bronchoscopy should be routinely (6–8 h interval) performed on all potential lung donors to assess for airway damage and visible signs of infection. Regular suctioning of retained secretions through a closed ventilator circuit may be beneficial to improve gas exchange. Target ranges of partial pressure of oxygen and carbon dioxide in arterial blood (PaO₂ and PaCO₂) are 70–10 mmHg and 30–35 mmHg, respectively. To protect the lungs, inspired fraction in oxygen (FiO₂) should be kept as low as possible.

Postural change and air tract aspiration may cause hypotension due to a decrease in blood return to the heart in brain-dead persons. From these aspects, it is very important to stabilize hemodynamics by using ADH. If one side of the lung was not suitable to be transplanted due to pneumonia, the other side of the thorax is held up to prevent purulent sputa coming into the healthy lung.

2.3.3 Administration of ADH

Low-dose arginine vasopressin, in addition to treating diabetes insipidus, results in reduced inotropic requirements and has been associated with good kidney, liver, and heart graft function as shown previously. As ADH is also effective to improve vascular tone and BAR system, ADH should be given even in patients with low urine output. ADH may improve hemodynamics and renal function resulting in an increase in urine output as shown in patients with postcardiotomy or septic shock [35].

Desmopressin is beneficial primarily for the treatment of diabetes insipidus in organ donors and is not usually associated with the reduction of inotrope requirements [36]. Furthermore, there is one report indicating that desmopressin may be associated with a higher incidence of human pancreatic graft thrombosis [37].

ADH should be given through CVP line with a continuous dose of 0.01–0.02 U/Kg/h or 0.5–1 U/h after an initial bolus dose of 0.5–1 U [1, 24, 25]. If hemodynamics improves, NAD and then AD should be tapered off rapidly in favor of DOA or DOB [1, 24, 25]. If internal and external adrenaline approaches a normal range, heart rate is usually in a range of 90–120 beats/min. ADH should be given until cannulation of all procured organs become ready and heparin is given to keep stable hemodynamics during procurement operation [1].

Diabetes insipidus may cause high urine output, high serum sodium, low serum potassium, high serum osmolality, reduced circulatory blood volume, and reduced intracellular fluid, resulting in liver or renal dysfunction and arrhythmia. To prevent or treat these consequences, ADH administration is also important for donor management [1].

Adjustments of serum sodium (135–150 mEq/L) [38] and potassium (3.8–4.5 mEq/L), hematocrit (>30 %), blood sugar (120–180 mg/dL), and body temperature (35.5–36.5 °C) are also important.

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Marginal Donors

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