1964	Hardy (USA): heart xenotransplant (chimpanzees) Starzl (米): renal xenotransplant (chimpanzees and baboons)		March 20 Nakayama (Chiba University): heterotopic liver Tx from uncontrolled DCD donor March 27 Kimoto (Tokyo University): living RTx for chronic renal failure
1965	Lower (USA): long-term canine survival after HTx		June 25 Shinonoi (Tokyo Medical College): partial lobe lung Tx
1966		December 17 Lillihei (USA): pancreas Tx from uncontrolled DCD donor using CPB	
1967	Terasaki (USA): studies of HLA serotyping in RTx	December 3 Barnard (South Africa): HTx from uncontrolled DCD donor using CPB December 6 Kantrowitz (USA): HTx from an anencephalic baby	
1968	Cooley (USA): heart xenotransplant (sheep)	January 6 Shumway (USA): HTx from controlled DCD donor	August 8 Wada (Sapporo Medical College): first HTx
1969	Starzl (USA): liver xenotransplant (chimpanzees and baboons)		
1978		Calne (USA): use of cyclosporine in RTx	
1980	Reitz (USA): heart and lung Tx (primates)		
1981		March 9 Reitz (USA): heart and lung Tx	
1984	Bailey (USA): newborn heart xenotransplant (baboon)		September 25 Fukao (Tsukuba University): pancreas/kidney Tx from brain-dead donor
1988		Cooper (USA): bilateral lung transplantation December 8, 1988 Raia (Brazil): living liver Tx	January 19 Ohta (Tokyo Women Medical College): ABO-incompatible RTx
1989		Starzl, Todo (USA): use of tacrolimus in RTx and liver Tx	November 3 Nagasue (Shimane Medical College): living liver Tx
1990	Groth (Sweden): pancreas xenotransplant (pig)	Starnes (USA): living lobar lung Tx Grant (USA): simultaneous intestine/liver Tx Valero (Spain): RTx from uncontrolled DCD donors using PCPS	June 15 Ozawa (Kyoto University): living liver Tx

(continued)

Table 1.1 (continued)

	Animal experiment and xenotransplant	Clinical experiences in the world	Clinical experiences in Japan
1991	Czaplicki (Porland): heart xenotransplant (Pig)		
1992		Sollinger (USA): use of mycophenolate mofetil in RTx Starzl (USA): restart liver Tx from controlled DCD donors	
1993	Mokowka (USA): liver xenotransplant (Pig)	Love (USA): lung Tx from controlled DCD donor	October 22 Sugimachi (Kushu University): liver Tx from uncontrolled DCD donor
1994	Starzl (USA): liver xenotransplant (baboons)		
1995		Bunnapradist (USA): use of Neoral in RTX	
1996		Appel (Germany): use of everolimus in RTx	July 9 Tanaka (Kyoto University): living intestine Tx
1997			October 17 Japanese organ transplant act
1998			October 28 Shimizu, Date (Okayama University): living lobar lung Tx
1999		Shapiro (Canada): long-term graft after survival from pancreatic islet Tx	February 28 First heart, liver, and kidney Tx from a brain-dead donor: HTx (Osaka University), liver Tx (Shinshu University), RTx (Tohoku University, National Nagasaki Central Hospital) Tanaka (Kyoto University): living domino liver Tx
2000		October Steen (Sweden): lung Tx from uncontrolled DCD donor	March 29 Single lung Tx from a brain-dead donor (Osaka and Tohoku University) April 25 Pancreas/kidney Tx from a brain-dead donor (Osaka University)
2001		Budds (USA): use of FTY720 in RTx	March 19 Bilateral lung Tx from a brain-dead donor (Osaka University), intestine Tx from a brain-dead donor (Kyoto University)
2004			January 7 Living pancreas/kidney Tx (National Sakura University)
2009			January 17 Heart and lung Tx (Osaka University)

1.2 The Dawn of Organ Transplantation from DCD Donors

On April 3, 1963, Voronoy et al. [7] did the first allogeneic kidney transplantation in Ukraine. The recipient was a 25-year-old woman with acute renal failure by intake of mercuric chloride. The donor was a 60-year-old man who died of basilar fracture. His kidney was procured 6 h after cardiac arrest. Although she urinated soon after transplantation, urination stopped and she died on the second posttransplant day (POD).

In April 1962, Murray et al. [8] successfully performed DCD kidney transplantation in Boston. The recipient was a 23-year-old man. The donor was a 30-year-old man. As cardiopulmonary bypass could not be removed because of severe cardiac failure after open cardiac surgery, his body temperature was cooled down to 20 °C by CPB and his kidney was procured and transplanted. Total ischemic time (TIT) was 2 h. The graft started to function 5 days after transplantation and the recipient was given azathioprine (AZP) and survived for more than a year.

On March 1, 1963, Starzl et al. [1] did the first liver transplant in Denver. The recipient was a 3-year-old boy with biliary atresia. His thymus was excised on February 12 and he was given AZP for 14 days prior to transplantation. The donor was a 3-year-old boy whose heart arrested during the surgery of brain tumor. After cardiopulmonary resuscitation was tried for 45 min, he was pronounced dead. CPB was installed by putting the cannulae into the femoral artery and vein. After the body temperature was cooled down to 15 °C, his liver was procured. He died of massive bleeding. In the second and third case, CPB was started soon after cardiac arrest to shorten TIT. CPB time was 375, 98, and 126 min, respectively. TIT was 465, 152, and 192 min, respectively. The second case died of pneumonia on the 22nd POD and the third case died of gastrointestinal bleeding on the 7th POD. Starzl did the first successful liver transplantation from controlled DCD, as did Shumway's first heart transplantation.

On December 3, 1967, Barnard [2] did the first allogeneic heart transplantation from a DCD donor. After the donor was moved to the operating room with a coroner, she was extubated; 5 min after the heart stopped, she was pronounced dead by the coroner. Her chest was opened soon and CPB was installed. After the body was cooled down, her heart and kidneys were procured. The recipient died on the 18th POD.

On January 6, 1968, Shumway and Stinson et al. [9] did the first heart transplantation from a controlled DCD donor. After the donor was diagnosed as brain dead by neurologists and pronounced dead, he was extubated and the heart was procured.

The first brain-dead organ transplantation (kidney) was done by Alexandre et al. [10] in Belgium in 1963. As the concepts of brain death were not established yet then, brain-dead organ donation became the main current in the early 1970s after the Harvard criteria was published.

1.3 Marginal Donors in Brain-Dead Organ Donation

In the early 1970s when brain-dead organ donation was started, outcomes of cadaver organ transplantation were very poor, because the organ preservation technique was immature and the optimal organ donor criteria and the safe and efficient immunosuppressive regimen were not established. After good preservation solution, such as the UW solution, was developed and safe and efficient immunosuppressive regimen using cyclosporine and so on was established in the early 1980s, the outcomes of organ transplantation became satisfactory.

As the outcomes of organ transplantation were improved, organ donor criteria have been gradually modified. And then, the so-called standard criteria were established. As organ transplantation rapidly increased and donor shortage became severer, the criteria of organ donors were reevaluated and the extended criteria were made for each organ. As the extended criteria were different among organs and countries, please see details of the extended criteria in the chapter of each organ.

In order to save more patients who need organ transplantation, we need to increase organs transplanted per donor (OTPD) by intensively managing the donor. Antidiuretic hormone (ADH) and thyroid hormones have been used to stabilize hemodynamics of the donor in the developed countries since the late 1990s.

As donor shortage is extremely severe in Japan because of very strict Organ Transplantation Act, special strategies for maximizing organ transplant opportunities should be established. Since November in 2002, special transplant management doctors were sent to donor hospitals in order to assess donor's organ function and to identify which organ could be transplanted. They also intensively cared for the donor to stabilize hemodynamics and to improve cardiac and lung function by intravenously giving ADH and pulmonary toileting by bronchofiberscope. In Japan, OTPD has been 5.5 organs in consecutive 100 brain-dead organ procurement since February 1999 [11].

1.4 · Organ Transplantation from Controlled DCD Donors

In the late 1980s, organ shortage became more remarkable. DCD was paid attention again. As the outcomes of DCD organ transplantation in the dawn of organ transplantation in the late 1960s were very poor, many animal experiments were done in many institutes to establish DCD organ preservation technique. In the 1990s, DCD have been widely introduced in the clinical practice and the use of kidneys and livers from controlled DCD donors has been reported in multiple series [4].

However, in the Catholic countries, such as Spain, cessation of mechanical respiratory support means suicide and is not permitted, unless family consent for brain death is obtained. Therefore, controlled DCD is not permitted in such countries. The time after cardiac arrest for considering personal death is different among countries. In most countries, the time is about 5 min, but 15 min in Italy.

1.5 Organ Transplantation from Uncontrolled DCD Donors: Multiple Organ Transplantation from Uncontrolled DCD Donors in Spain

As PCPS was introduced in the clinical settings in the late 1980s, uncontrolled DCD using PCPS was initiated in Spain. Koyama et al. [12] did the first experiment of DCD using PCPS. Under PCPS, the body temperature of the donor animals was cooled down and the kidneys were procured and transplanted. The author of this chapter [13] also did several animal experiments of multiple organ transplantation (heart, lung, and kidneys) using PCPS.

In Spain, PCPS was first used in the clinical settings of uncontrolled DCD donors [5]. In the 1990s, they cooled donor body temperature from 15 to 20 °C, and normothermic recirculation trough CPB was used since 1997.

The donor criteria for multiple organ transplantation [14, 15] from uncontrolled DCD donors in Spain included, in addition to the general criteria for donor selection, an age under 65 and a warm ischemia time lower than 150 min with a period of warm ischemia without cardiopulmonary resuscitation maneuvers less than 30 min. Only I and IV Maastricht NHBD categories were considered. Currently kidneys, liver, and lungs were transplanted from uncontrolled DCD donors.

1.6 Lung Transplantation from Uncontrolled DCD Donors in Sweden

In 2000, Steen et al. [6] started uncontrolled DCD lung transplantation in Sweden. After cardiac arrest, the chest tubes were inserted and the body was topically cooled. Since then, uncontrolled DCD lung transplantation was started in Australia [16] and the outcomes became comparable to those of lung transplantation from brain-dead donors.

1.7 Increased Roles of "Normothermic" Perfusion Techniques on Organ Preservation [17]

Preservation injury is an important factor not only in the short-term but also in the long-term outcome of transplantation, and success rates are directly related to the duration of cold ischemia. In recent years, the increasing discrepancy between transplant waiting lists and the supply of cadaveric donor organs has led to the transplantation of increasingly marginal organs. This group is characterized by particularly poor tolerance of the various injuries that occur during the process of preservation and transplantation.

Although cooling reduces the metabolic rate of biological tissue, continued cellular processes lead to depletion of ATP and accumulation of metabolic products. When the organ is rewarmed and reperfused with oxygenated blood, the rapid metabolism of metabolic products within an organ depleted of energy stores leads to ischemia-reperfusion injuries. The use of marginal donor organs and, particularly, those from DCD donors exacerbates the problems of preservation and ischemia-reperfusion injury. This is a limiting factor in the use of such donor organs.

The use of hypothermic machine perfusion has been shown to improve the immediate function rate of stored kidneys, but does not enable normal cellular metabolic function or prevent depletion of energy stores or prevent all the deleterious direct effects of cooling. Cold preservation is now seen as an important limiting factor in the further expansion of transplantation.

The principle of normothermic perfusion is to recreate the physiological environment by maintaining normal temperature and providing the essential substrates for cellular metabolism, oxygen, and nutrition. In addition to a reduction in ischemia-reperfusion injury, a further potential advantage of normothermic perfusion is the assessment of viability, because the organ is metabolically active, and it is possible to measure function and to predict posttransplant outcome before subjecting the patient to surgery. This is an increasingly important issue as more marginal organs are used.

To date the only uses of normothermic perfusion in a clinical environment have been in heart and lung transplantation. As the utility and potential benefits of normothermic preservation are more recognized, we may expect to see further clinical trials in other areas of transplantation.

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Chapter 2
Management of Extended Criteria Donors

Norihide Fukushima

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 adenylcyclase. 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)], adrenocorticotropic 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 favorite 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/m^2 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 euvolemia, 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 H_2O (should be less than 30 cm H_2O) and a positive end-expiratory pressure of 15 cm H_2O 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 H_2O. 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 (PaO_2 and $PaCO_2$) are 70–10 mmHg and 30–35 mmHg, respectively. To protect the lungs, inspired fraction in oxygen (FiO_2) 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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Chapter 4
ECD for Heart Transplantation

Norihide Fukushima

4.1 Introduction

In October 1997, the Japanese Organ Transplant Act was issued and we needed to successfully start the first heart transplantation (HTx) in Japan. For this reason, very strict criteria for the donor heart were established by the task force committee for heart transplantation in the Ministry of Health, Labour and Welfare. These criteria were comparable to the so-called standard criteria for the donor heart in the world.

On February 28, 1999, the first HTx was successfully performed in Japan [1] and 127 HTx were done up to the end of August 2012. Although many efforts to shorten the transportation time of the heart were done, mean transportation and total ischemic time (TIT) were about 2 and 3 h, respectively. On the other hand, as the Japanese Organ Transplant Act was very strict, brain-dead organ donation was extremely limited in Japan and only 184 brain-dead donors were available for 13 years after the Act was issued. In order to respond to the will of the donor and donor families, we needed to transplant the heart as much as possible. For these reasons, more hearts should be transplanted from the extended criteria donor (ECD) in Japan than other developed countries.

Since brain-dead organ transplantation was started in 1999, every organ procurement team has taken their own skillful physicians to the procurement hospital [2]. They evaluated the condition of donor organs by echocardiography and flexible bronchofiberscopy (BFS) by themselves in the intensive care unit (ICU), before procurement operation [2].

Since November of 2002, special transplant management doctors (a medical consultant, MC) have been sent to the procurement hospital. They assessed donor organ function and identified which organs were useful for transplantation.

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They also intensively cared for the donor, stabilized the donor hemodynamics by giving antidiuretic hormone (ADH) and reducing the dose of intravenous catecholamine as much as possible, and improved donor cardiac and lung function by preventing and treating lung infection before procurement teams arrived at the donor hospital.

Out of 184 brain-dead donors, 136 heart, 1 heart–lung, 143 lung, 159 liver, 1,311 pancreas, and 12 small bowel transplants were performed. Organs transplanted per one donor (OTPD) increased to 5.5 organs after these strategies were applied.

Although 83 of 136 heart donors were ECD, no recipient died of primary graft dysfunction (PGD).

4.2 Definition

Extended donor criteria are shown in Table 4.1.

4.2.1 Heart Injury

Donor hearts are injured in great or lesser degree, by many causes, such as catecholamine storm at the completion of brain death, cardiac arrest, thoracic trauma, and maneuver of the cardiopulmonary resuscitation (CPR).

As the patients with brain injury are kept in dry condition to prevent brain edema, the heart looks hyperdynamic. To evaluate precise cardiac systolic function, central

Table 4.1 Extended criteria donor (ECD) for heart transplantation

Myocardial injury and/or underlying heart disease
Correctable valvular dysfunction or congenital heart anomaly by echocardiography (without history of open heart surgery)
Injury of the heart (history of chest trauma, open cardiac massage)
Cardiac arrest with cardiopulmonary resuscitation (>5 min)
High-dose catecholamine requirement (dopamine >15 μg/kg/min)
Left ventricular hypertrophy (wall thickness >15 mm)
Prolonged total ischemic time (>4 h)
Old age
>55 years(especially without coronary angiography)
Bypassable one- or two-vessel coronary arterial disease
Body and gender mismatch
Undersizing or oversizing by more than 20 % body weight
Female to male (especially undersized donor by more than 20 % body weight)
Infection
Local bacterial infection
Bacteremia