Chapter

Donor Assessment and Management for Heart Transplantation

Norihide Fukushima

Abstract

For many years, heart transplantation has been an established procedure for patients with end-stage heart failure using the so-called "Standard Criteria" for an optimal heart donor. However, annually listed patients for heart transplantation greatly increased worldwide, and the use of extended criteria donor hearts has been utilized as many as possible in many countries. In this chapter, firstly, pathophysiology of brain death is explained. Secondly, donor assessment and issues of extended criteria donors are introduced. Then, donor management to maximize the heart graft availability, and the Japanese donor assessment and evaluation system and its outcome are reviewed.

Keywords: heart transplantation, donor assessment, donor management, anti-diuretic hormone (ADH), denervation, brain death

1. Introduction

Heart transplantation (HTx) has been established as the definitive therapeutic strategy in end-stage organ failure patients and results in satisfying long-term results. However, this surgical therapy is extremely limited by severe donor organ shortages worldwide, especially in Japan [1]. Therefore, adequate, and optimal assessment and management for deceased organ donors are mandatory to increase heart graft availability [2].

As the revised Japanese Transplant Act was issued on 17th July 2010 and organs can be donated after brain death (BD) with their family's consent if he or she does not deny organ donation since this revision [1], BD organ donation increased from 13 cases in 2009 to 97 cases in 2019. However, the number of HTx was still extremely smaller than in other developed countries. The extraordinarily severe organ shortage and long waiting time for HTx had made Japanese transplant programs consider using extended criteria donor (ECD) hearts.

The most troublesome issue facing HTx is primary allograft dysfunction (PGD) [3, 4]. This complication is the leading cause of early post-HTx death in the world. The use of ECD hearts may increase the PGF rate. Therefore, it is essential to establish a special donor evaluation and management system to maximize donor heart utilization. Maximizing donor heart availability is also the last wish of donors and donor families. However, if a transplant recipient dies soon after HTx due to PGD, the donor family feels the loss of their lover again. Therefore, donor management strategies to

improve heart graft function and reduce early post-HTx mortality are very important for the donor family as well as for recipients [2–4].

Disease-transmitted disease (DTD) is also an inherent risk of heart transplantation as well as other solid organ transplantation [5]. The Ad Hoc Disease Transmission Advisory Committee (DTAC) reported that unanticipated DTD occurred only in 0.18% of recipients, with 0.23% of proven or probable DTD to at least one recipient. DTD was related to significant morbidity and mortality with about 33% of graft loss or recipient death. The recipient death in malignancy occurred significantly higher than that in infection. Therefore, the procurement transplant coordinator (PTC) should carefully listen to the clinical course, data, and history of medical staff and family to rule out these absolute contraindications prior to obtaining informed consent for organ donation from the relatives.

Full-scale donor management begins after the potential donor is sentenced brain dead and his or her family's consent to organ donation is obtained [2–4]. Basic therapeutic strategies for donor management consist of interventions for impaired heart and lung function to optimize the patient's hemodynamics, increase oxygen delivery to peripheral tissue, and finally improve the function of other organs, such as the liver and kidney. The hemodynamic targets are arterial blood pressure greater than 90 mmHg, central venous pressure (CVP) between 6 and 10 mmHg, urine output around 100 ml/h (0.3 to 3 ml/kg/h), and heart rate between 80 and 120/minutes. As there are only about 15 to 20 hours between the start of full-scale interventions for donor assessment and management and the start of organ retrieval surgery in Japan, we need to establish specific therapeutic strategies to optimize patient's hemodynamics and restore the function of damaged organs as many as possible in such short period [2], which are extremely different from those in standard intensive that usually take several days to accomplish. Moreover, the donor management physicians need to understand the pathological and physiological mechanisms and characteristics of brain death from the initiation to the completion period.

2. Pathological and physiological mechanism and characteristics of brain death

2.1 Pathological and physiological changes from the initiation to completion of brain death

Many investigators [3, 4] have reported that a short-lived catecholamine (CA) storm derived from acute intracranial hypertension caused systemic hypertension, acute left ventricular (LV) failure, and acute transient mitral valve regurgitation, leading to a rise in left atrial pressure in animal experiments. These events led to ischemic myocardial damage of LV associated with pulmonary edema. Histological examination of myocardial tissue exposed to CA storm shows widespread ischemic damage and necrosis in animal experiments. However, in the human clinical situation, a broad spectrum of adverse hemodynamic instability is observed and may depend on the speed of development of BD.

Soon after the initial surge of the CA storm, CA levels decreased to levels below the baseline and pituitary failure developed [6, 7]. In addition, the lung is also impaired by an acute systemic inflammatory response, neurogenic pulmonary edema, aspiration, hemopneumothorax, atelectasis, and later pneumonia.

2.2 Absent or decreased secretion of anti-diuretic hormone (ADH) after brain death

The anti-diuretic hormone (ADH) is principally produced by neurosecretory cells that have their cell bodies in the supra-optic and paraventricular nuclei of the hypothalamus, and the ADH storage vesicles are transported down the axon via the hypothalamic-hypophysial tract, released into a portal system in the posterior pituitary and finally enter the body's systemic circulation (**Figure 1**).

ADH is the primary hormone to maintain tonicity homeostasis by promoting water reabsorption in the kidneys and causing vasoconstriction. Briefly, ADH binds to the V receptor on the renal principal cells within the late distal tubule and collecting ducts and promotes reabsorption of water guided by the osmotic gradient established by sodium chloride and urea in the kidney. This action makes concentrated, or hyperosmotic, urine, and keeps our body to conserve water in times of dehydration or blood volume loss [8]. ADH also binds to V receptors on vascular smooth muscle and activates the G protein signaling cascade, which leads to a contraction of vascular smooth muscle leading to increases in total peripheral resistance and thus maintaining sufficient arterial blood pressure and tissue perfusion [8].

BD causes profound supraventricular and paraventricular hypothalamic nuclei ischemia and secondary loss of ADH secretion into the posterior lobe of the pituitary gland, which results in diabetes insipidus. As ADH is also secreted from peripheral tissues, undetectable levels of ADH have been noted in 75% of BD. As water reabsorption action of ADH is decreased, the kidneys cannot concentrate urine and make large amounts of dilute urine, which leads to hyponatremia associated with high serum osmolality and hypovolemia. As the vasoconstrictive effect of ADH is decreased, the vascular tone of systemic arteries is decreased and leads to hypovolemia. Therefore, the absence or decreased secretion of ADH after BD causes hemodynamic instability and compromised transplanted organ function.

Administration of ADH [9–11], in addition to treating diabetes insipidus by volume supply, reduces inotropic requirements and has been associated with improved heart graft function. Pure vasopressors, such ADH, are less likely to cause reduced tissue perfusion, metabolic acidosis, or pulmonary hypertension and may be more appropriate medicine than noradrenaline for vasoplegic shock syndrome, especially after BD

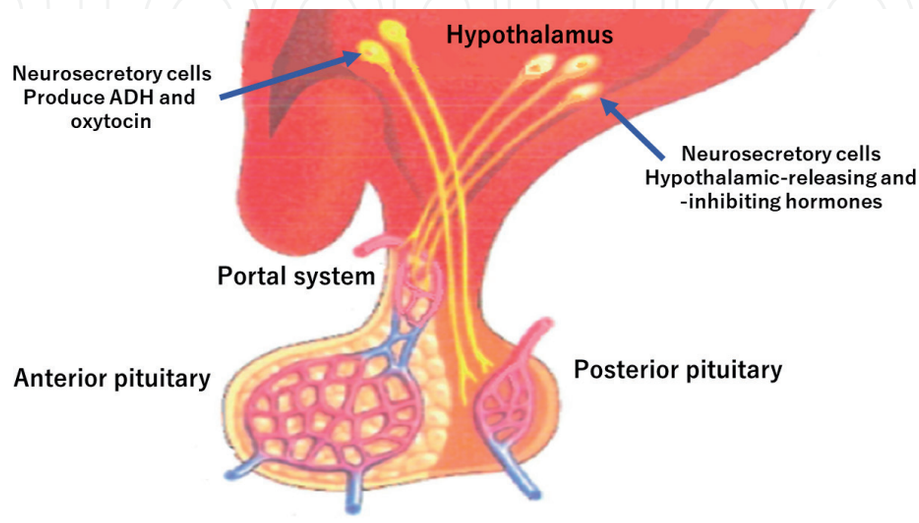

Figure 1.
Hypothalamo-hypophyseal portal system.

2.3 Cessation of autonomic nerve regulations on circulation

After BD, the brain-heart connections are definitively interrupted and autonomic cardiovascular regulation mainly thorough baroreflex is gone. Therefore, the hemodynamics of BD persons become unstable [4]. For example, a decrease in the blood return to the heart due to blood loss, hypovolemia, and putting pressure on the upper abdomen or postural change may rapidly cause low blood pressure in BD persons. After 20 to 30 seconds of the hypotension phase, the somatically induced adrenal sympathetic reflex responses result in an increase in adrenaline secretions from the adrenal medulla, which induces subsequent high blood pressure usually higher than 150 mmHg and tachycardia. In BD patients who are poorly controlled, arterial blood pressure and heart rate may go up and down. This phenomenon is often observed in hypovolemic patients derived from reduced ADH secretion due to BD. The subsequent increase in serum adrenaline decreases the myocardial density of beta-adrenergic receptors (BAR), which leads to PDG early post-HTx.

Disrupted brain-heart connections, so-called denervation, are also observed in HTx recipients. The authors [12] previously described that the heart graft could not augment cardiac performance rapidly in response to an acute decrease in the preload due to the cessation of autonomic nerve regulation on the graft. In normal individuals, if a preload of the heart rapidly decreases, autonomic sympathetic nerves are activated through vagal reflexes increasing heart rate and left ventricular contractility. Therefore, LV Emax after releasing occlusion of vena cava inferior (VCIO) is significantly higher than LV Emax during VCIO (**Figure 2A**). However, as the heart graft cannot autonomically increase heart rate or LV contractility soon after a rapid decrease in LV preload, LV Emax after releasing VCIO is not different from LV Emax during VCIO (**Figure 2B**). The heart graft performance may be augmented only after elevated serum adrenaline levels by secretion of adrenaline from the adrenal gland. Thus, the denervated heart, such as the heart graft as well as the heart of a BD person, cannot rapidly enhance its performance in response to a rapid decrease in the LV

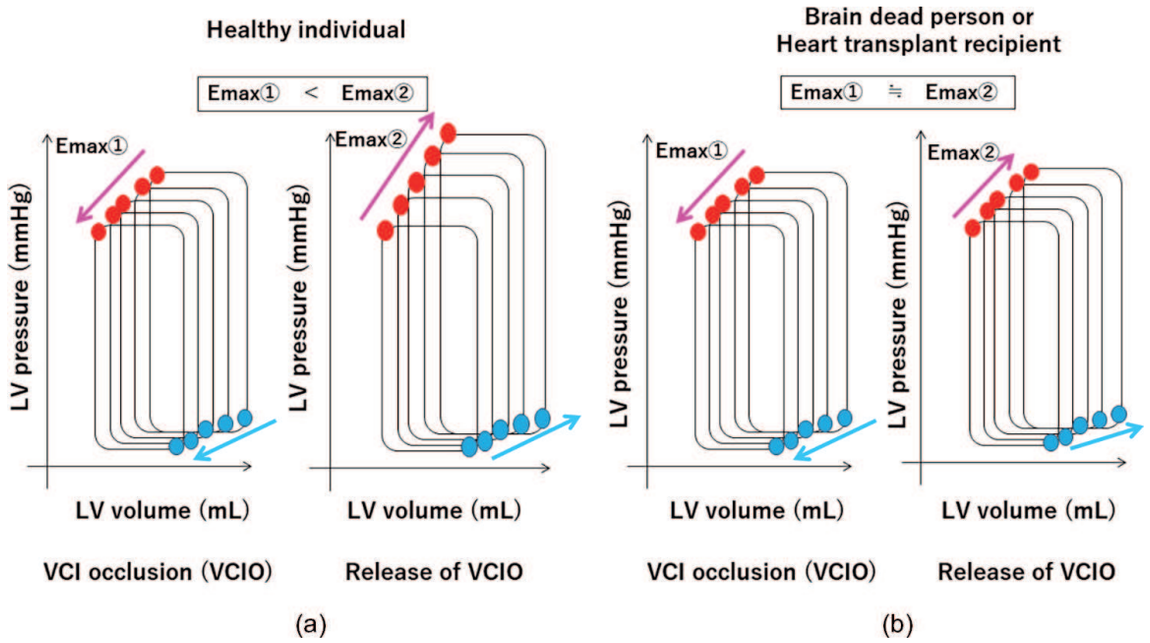

Figure 2.
Changes in left ventricular Emax during and after releasing vena cava inferior (VCI): A. Healthy individuals, B. Brain dead persons or heart transplant recipients.

preload, such as sudden blood loss or a sudden decrease in cardiac return. Therefore, denervation also causes hemodynamic instability in a BD person.

3. Donor assessment

3.1 Rule out of absolute contraindications for deceased donor eligibility

Although absolute contraindications for deceased donor eligibility depend on the organ procurement organization (OPO), most OPO provided a list of absolute contraindications for donor eligibility (**Table 1**).

As mentioned above, DTD is an inherent risk of heart transplantation [5]. Although DTAC reported that unanticipated DTD occurred only in 0.23% of proven or probable DTD to at least one recipient, DTD was related to significant graft loss or recipient death. It is important for PTC to carefully get information associated with DTD to rule out these absolute contraindications for heart transplantation.

3.1.1 Infection

3.1.1.1 Viral infection

Almost all OPOs determine that a positive test for human immunodeficiency virus infection and acquired immunodeficiency syndrome is an absolute contraindication, and most OPOs determined that hepatitis B virus (HBV) surface antigen (HBsAg), human T cell lymphotropic virus types I and II and determined or suspected prion-related disease are absolute contraindication.

Infection
Positive tests for
Anti-HIV-1 or anti-HIV-2
Hepatitis B or C* virus
Human T cell lymphotropic virus types I and II
History or evidence of HIV high-risk behaviors, even if HIV antibody negative
Prion-related disease
Creutzfeldt-Jakob disease (CJD)
family history of CJD
recipient of human-derived pituitary hormone or dura mater
Active systemic bacterial, viral, or fungal infections
Malignancies
Leukemias, lymphomas, and active malignancies

**Most organs from donors with a positive test for hepatitis C virus (HCV) can be transplanted to a recipient with a positive test for HCV.*
HIV: human immunodeficiency virus.

Table 1.
Absolute contraindications for donor heart eligibility.

Transplantation of donor hearts with anti-HBV core antibody (HBcAb) is associated with a small risk of virus transmission. In fact, Huprikar et al [13] reported that the risk of HBV transmission from HBcAb + HBsAg– donors are observed mainly in liver transplant recipients and that transmission is significantly lower in kidney transplant recipients and essentially negligible in thoracic transplant recipients. Even in liver transplantation, many investigators have reported that anti-hepatitis-B immunoglobulin (HBIg) or lamivudine can prevent HBV transmission by HBcAb + HBsAg– donors. In our institute, HBIg is routinely used in heart transplantation from anti-HBc + HBsAg– donors.

Most organs from donors with positive tests for hepatitis C virus (HCV) can be transplanted to a recipient with a positive test for HCV [5]. In the field of thoracic transplantation, transplantation of HCV + donor grafts to HCV + recipients is unacceptable, mainly because there are multiple strains of hepatitis C virus, and the presence of antiviral antibody in the recipient does not guarantee immediate immunity to HCV after heart transplantation.

3.1.1.2 Other pathogen infection

Regards bacterial or yeast infection, sepsis or infectious vegetation in the heart are contraindications for heart transplantation. Although the donor organ contamination (DOC) rate is high, infections due to DOC are rare after heart transplantation if adequate perioperative antibiotic prophylaxis and aseptic organ procurement are strictly performed [14]. The heart from a donor with positive blood culture without any signs of systemic infection can be transplanted if the proven bacteria are Gram-positive cocci and sensitive to common antibiotics.

3.1.2 Malignancies

Of the 335 donors who transmitted proven or probable disease to at least one recipient being reported to UNOS from 2008 to 2017, 70 transmitted malignancies and kidney, lung, and liver cancers were the most common malignancies, with 18, 10, and 10 donors, respectively, transmitting to at least one recipient. Fifteen donors with potential donor disease transmission events involving breast cancer and 28 involving thyroid cancer were reported by either transplant centers or OPOs with no proven/probable transmissions.

Regards to central nervous system (CNS) tumors, Hynes et al. [15] analyzed a cohort of 58,314 adult thoracic organ recipients from the UNOS database and reported none of 337 recipients who received organs from the donor documented CNS tumor, developed CNS tumors at a median follow-up of 72 months and that Kaplan-Meier curves indicate no significant difference in the time to death between patients with and without receiving from the donor with CNS tumor.

Donors with past histories of certain types of cancers may be considered as donors, including certain types of primary CNS tumors. Desai et al. [16] reported that the use of organs from selected donors with a history of cancer had a potential overall benefit in survival. But a small, yet real, risk of cancer transmission is present, of which the recipient should be informed. Although the transmitted risk can be reduced by sophisticated evaluation, it cannot be no risk.

3.2 Viability assessment of donor heart

The real goal of donor heart assessment is not to evaluate the donor heart function just prior to the heart procurement but rather to predict the transplanted heart graft

performance after weaning from the cardiopulmonary bypass in the operating room and through the postoperative period. One also should consider the preexisting myocardial damage as well as myocardial damage due to BD-related stress.

3.2.1 Assessment of Hemodynamics and Heart Function

To accomplish optimal donor management, we need to obtain clinical information, such as the cause of BD, pathophysiological mechanism and findings of BD, past and family history, underlying disease, therapeutic interventions, especially inotrope dosage, ADH, thyroid hormone, and antibiotics, water and blood valance, and parameters of preload and afterload on the heart, such as systemic and pulmonary arterial pressure, CVP and pulmonary capillary wedge pressure, cardiac output, and/or mixed-venous oxygen saturation [2, 4].

Multicenter analysis (1719 consecutive primary HTx) reported that donor hearts requiring inotropic support of up to 6 mcg/kg/min of dopamine or dobutamine had satisfactory results [17]. Even if the donor experiences cardiopulmonary resuscitation (CPR) > 5 minutes, the donor heart might be acceptable to transplant, if optimal donor management stabilizes the donor's hemodynamics, improve left ventricular wall motion, and restore ischemic myocardial changes in ECG [2].

3.2.2 Evaluation tools for donor heart viability

3.2.2.1 Chest X-ray

As in usual clinical settings. cardiomegaly, chest trauma, or pleural effusions are checked by chest X-ray.

3.2.2.2 Electrocardiogram (ECG)

As most BD donors have some degree of myocardial damage caused by combined pre-underlying heart disease and BD events, ECG usually shows some degree of abnormality in ST segments and QRS waves. Sustained abnormalities in ST segments and QRS and multifocal ventricular ectopic beats under optimal donor management are considered high risks.

Even in an elderly donor with a history of cardiac arrest, the heart was acceptable for transplantation if hemodynamics becomes stable with a minimum dosage of inotrope administration and ischemic ECG changes disappear after optimal donor treatment.

3.2.2.3 Echocardiography

Echocardiography is the most reliable assessment tool to determine donor heart suitability. Echocardiography can evaluate cardiac valve function and myocardial hypertrophy as well as the existence of congenital malformations. Even if global and even regional ventricular dysfunction may be induced by the BD event, these wall motion abnormalities can be reversible within hours. Therefore, serial echocardiography should be done before a heart graft is abandoned to use due to myocardial dysfunction

In the presence of LV underfilling, LV seems to be hypertrophic or to have suitable LV systolic function. Therefore, circulatory blood volume should be estimated by central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), or the

size and respiratory movement of inferior vena cava (IVC), as well as the required dosage of inotropes prior to undergoing echocardiography to assess heart function.

3.2.2.4 Coronary angiography

As asymptomatic coronary atherosclerosis is found even in children and young people, coronary angiography, at least in donors >45 years or according to the donor risk factors, is routinely performed in western countries. However, it has not been elucidated which type or level of donor coronary atherosclerosis really impairs the post-transplant outcome, which suggested that angiography in donors <60 years might not be necessary. Of course, recent myocardial infarction especially during the completion of BD and diffuse coronary sclerosis are absolute contraindications for heart transplantation, but single stenosis with good myocardial performance in the responsible region is acceptable, especially if it can be treated by percutaneous cardiac intervention or concomitant bypass surgery during transplantation [18, 19].

3.2.2.5 Chest computed tomography (CT)

For several social reasons in Japan, we do not routinely perform coronary angiogram before procurement. Therefore, we often check for coronary artery calcification (CAC) on conventional chest computed tomography (CT) to estimate the risk of pre-existing coronary artery disease in the donor heart. But we previously reported that the pre-existing CAC in a donor heart is significantly associated with the maximum intimal thickness of the coronary artery greater than 0.5 mm after transplantation, but that it was not a significant predictor for cardiac events in the future, probably due to the higher use of everolimus in the CAC group post-transplant [20].

In the future, contrast CT scan, especially cardiac CT scan, might be useful to rule out coronary arterial disease in the donor heart.

4. Extended donor criteria and how to decide the suitability of ECD hearts

To expand the cardiac donor pool, ECD hearts should be used. In this section, extended donor criteria are shown and how to select and deal with ECD hearts are discussed (**Table 2**).

4.1 Myocardial damage

The donor myocardium is damaged to a greater or less extent, for many reasons, such as massive CA secretion at the BD completion, heart arrest, chest trauma, and the CPR maneuver.

As the brain-damaged patients are often maintained on the dry side to reduce brain edema, the heart appears to move with vigor due to reduced preload on the heart. To evaluate the precise cardiac systolic function, central venous pressure at the time of evaluation should be 8–10 mmHg. It is also important to adjust hemoglobin concentration, electrolyte balance, and acid-base equilibrium at that time. As Swan-Gatz catheterization or coronary angiography are not routinely able to perform in the procurement hospital in Japan for several social reasons, myocardial damage and underlying heart diseases are determined by hemodynamics, requirement doses of

1. Myocardial damage
• Injury of the heart (history of chest trauma, maneuver of cardiopulmonary resuscitation, and open cardiac massage)
• Cardiac arrest with cardiopulmonary resuscitation (> 5 minutes)
2. High-dose requirement of inotrope administration (dopamine >15 mcg/kg/min)
3. Underlying heart disease defined by echocardiography (without a history of open-heart surgery)
• Correctable valvular dysfunction
• Correctable congenital heart anomaly
4. Left ventricular hypertrophy (wall thickness > 15 mm)
5. Prolonged total ischemic time(> 4 hours)
6. Elderly age
• 55 years (especially without coronary angiography)
• Bypassable one- or two-vessel coronary arterial disease
7. Body size and gender mismatch
• Undersizing or oversizing by more than 20% body weight
• Female to male (especially undersized donor by more than 20% body weight)

Table 2.
Extended criteria donor (ECD) for heart transplantation.

inotropes and ADH administration, the LV wall motion and morphology by echocardiogram, and electrocardiogram (ECG) findings.

It is very important to evaluate donor cardiac function after treating diabetes insipidus, adjusting the tone of peripheral vessels, and recovering the affinity of the β-adrenergic receptor for adrenaline in the myocardium by administrating ADH via the central venous line and optimizing circulating blood volume [2].

The heart with a history of cardiac arrest with cardiopulmonary resuscitation can be transplanted if the cardiac function is recovered and the heart has no significant underlying disease or ischemic ECG changes [2, 21]. Recently, the ISHLT registry report 2020 also reported that recipients of donors who died from anoxia or head trauma had the highest 1-year survival (89.9%), whereas the lowest 1-year survival (84.1%) was seen in recipients of donors who died from cerebrovascular accident/stroke [22].

4.2 High-dose requirement of inotrope administration

Even hemodynamics or cardiac systolic function are well maintained, the myocardium is considered damaged if a high dose of inotrope administration is required to stabilize hemodynamics. Therefore, an assessment of LV function should be done after reducing dosages of inotropes as less as possible.

As high serum adrenaline concentration, as well as a high dose of intravenous adrenaline administration, has a significant relationship with a decrease in the myocardial density of β-adrenergic receptors [23, 24], the use of adrenaline should be used as less as possible. Less than 0.05 mcg/kg/min of adrenaline is acceptable. Regards to the dose of dopamine and others, the donor heart requiring greater than 15 mcg/kg/min of dopamine is considered ECD heart, especially with abnormal ECG and echocardiographic findings. Mostly, less than 15 mcg/kg/min of dopamine is acceptable.

4.3 Underlying heart disease

The hearts with the most valvular and congenital cardiac abnormalities are not eligible for transplantation. Therefore, pre-existing heart diseases should be carefully assessed by the echocardiogram and the chest CT scan before procurement surgery.

In donors with acceptable heart function, however, a simultaneous repair can be done on a donor heart with simple congenital heart disease (e.g., atrial septal defect, ventricular septal defect, or patent ductus arteriosus), mild or moderate valvular regurgitation in the mitral and/or tricuspid valve or normally functioning bicuspid aortic valve.

4.4 LV hypertrophy

As the hypertrophic myocardium is susceptible to ischemia-reperfusion injury, the hypertrophic heart with left ventricular wall thickness greater than 13 mm should be decided carefully to use. The hypertrophic heart with ECG criteria for LVH and total ischemic time (TIT) longer than 4 hours is inadvisable to transplant.

4.5 Prolonged total ischemic time (TIT)

It has been reported that prolonged total ischemic time (TIT) was a significant correlation with the early post-transplant death after HTx. The acceptable safe preservation time limit for HTx might be less than 4 hours. In fact, the report of the International Society for Heart and Lung Transplantation (ISHLT) showed that the relative risk of 1-year mortality was affected by TIT for longer than 6 hours [23]. However, pediatric hearts with TIT longer than 8 hours were reported to be safely transplanted [21].

To prolong the safe limit of preservation period in immerse heart preservation method, many studies were carried out. The author of the chapter reported that the modification of preservation solution and the application of terminal leukocyte-depleted blood cardioplegia preserved good function of orthotopically transplanted cardiac grafts after 24-hour immersed preservation in the canines and goats [25].

4.6 Elderly age

As aging increases the risk to have the myocardial damage due to coronary arterial disease, left ventricular hypertrophy, and valvular disease, donors older than 50 years of age were generally considered to be ECD. In fact, older donor age is associated with decreased survival after heart transplantation, especially within the first month after transplantation [23]. Moreover, the relative risk of developing cardiac allograft vasculopathy within 8 years is also affected by donor age. Therefore, meticulous evaluation of coronary arteries with coronary angiography as well as left ventricular wall motion with echocardiography are essential to assess the heart of elderly persons.

Although coronary arterial interventions are applicable in the recipient after heart transplantation, several cases of simultaneous coronary arterial grafting have been reported to use the donor hearts with significant coronary artery disease [18, 19]. Overall graft patency at 2 years was reported to be 82%.

One may consider completion of BD as a certain kind of stress test on the myocardium such that if subsequent ECG or echocardiography is favorable, the chance of an elderly donor having significant CAD is probably low. This screening strategy

without the use of coronary angiography is thought to make an efficient selection of elderly donor hearts for transplantation with a good outcome. But if the donor has left ventricular hypertrophy and/or significant ECG changes, the heart is not eligible for transplantation [2].

4.7 Body size and gender

Although a small donor size relative to the recipient may increase a survival risk post-transplantation, a normal-sized adult male is suitable for most recipients. Russo et al. [26] demonstrated that transplanting a female donor heart into a male recipient is associated with a significantly higher risk of PGD. On the other hand, the risk of CAV universally increased with increasing donor age [22]. However, recipients of male allografts had an increased risk of CAV development, regardless of the recipient's gender [22].

5. Donor management

To manage a donor optimally, hemodynamics, cardiac and respiratory function, infection, and other organ functions of the donor should be assessed precisely. As there are no specialized therapeutic strategies for liver or renal dysfunction during a short period of donor management usually less than 20 hours, cardiopulmonary management to improve organ perfusion and blood gas supply, and metabolic management are the main therapeutic strategies for ECD management.

5.1 Circulatory management

The repeated 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, it has been reported that in younger donors, left ventricular dysfunction can completely recover to normal overtime prior to procurement in a donor and after transplantation in a recipient. Although echocardiography is a very effective tool to assess heart anatomy, especially valvular anomalies, the use of a single echo assessment of ventricular function is not recommended to decide the functional suitability of a donor heart graft.

The goals of hemodynamic management are to achieve normovolemia, minimize vasoconstrictors and vasodilators to keep a normal cardiac afterload and optimize cardiac output with minimal doses of inotropes, which increase myocardial oxygen demands, deplete high-energy phosphates and the density of BAR in the myocardium. The targets of hemodynamic parameters are systemic blood pressure > 90 mmHg, central venous pressure (CVP) 6 to 10 mmHg, urine output 100 ml/h (0.5 to 3 ml/kg/h), and heart rate 80 to 120/minutes with a minimum dosage of inotrope administration.

5.2 Respiratory management

The use of low-tidal-volume ventilation is recommended because a mechanical ventilator with high tidal volumes is potentially harmful and may exacerbate donor lung injury already damaged during the completion of BD. Recruitment maneuvers

are an important component of donor optimization, especially when the oxygenation is subnormal and pulmonary abnormalities are visible on the chest x-ray. Repeated bronchoscopy (6 to 8 hours interval) is also important to improve donor lungs.

5.3 Administration of ADH

Administration of low-dose arginine vasopressin in conjunction with correction of hypovolemia due to diabetes insipidus reduces inotropic requirements and improves kidney, liver, and heart graft function, as shown previously [2]. As ADH increases both vascular tone and the affinity of BAR, ADH is effective even in patients with reduced urine output. ADH may stabilize hemodynamics, increase renal blood flow, and finally increase urine output.

Although desmopressin is mostly beneficial for the primary treatment of diabetes insipidus, it does not usually reduce inotrope requirements in organ donors [2]. Furthermore, desmopressin is reported to increase the incidence of thrombotic events.

ADH should be continuously given through a central venous line with a dose of 10–2o microU/Kg/h or 0.5–1 U/h. In case of hypotension, a loading bolus dose of ADH 0.5 to 1U is effective. If hemodynamics is stabilized by ADH administration, noradrenaline, and then adrenaline can be discontinued. If serum adrenaline level comes within a normal range, the heart rate is converged to an intrinsic heart rate between individuals of the same age, usually into a range of 90 to 120/minutes which is higher than the resting heart rate, because the autonomic regulation on the heart is gone in a BD patient. To optimize hemodynamics throughout procurement surgery, ADH should be continuously infused until the insertion of perfusion cannulas for all procured organs become ready and heparin is given [2].

Reduced ADH secretion due to BD may increase urine output, serum sodium, and osmolality, as well as reduce serum potassium, which decreases circulatory blood volume and intracellular fluid and cause hepatic or renal dysfunction and arrhythmia. Therefore, ADH administration can restore these consequences and is considered a key medication for donor management. Adjusting serum sodium and potassium with 135–150 and 3.8–4.5 mEq/l, respectively, hematocrit greater than 30%, blood sugar with 120–180 mg/dl, and body temperature with 35.5–36.5°C, are also important for optimal donor management.

6. Japanese strategies for donor evaluation and management

6.1 Medical consultant system in Japan

Since BD organ transplantation was started on 28th February 1999 in Japan, every organ procurement team has taken its own staff physicians to the procurement hospital. They evaluated the donor heart function by performing echocardiography by themselves in ICU prior to procurement operation.

Since November 2002, special transplant management doctors (a medical consultant; MC), who used to be cardiac transplant surgeons and are currently cardiac transplant cardiologists, have been sent to the procurement hospital. They estimate donor heart function and determine whether the heart is useful for transplantation. They also intensively manage the donor by giving ADH as shown above, minimizing the dose of intravenous inotropes, and improving the donor organ function until the procurement heart team arrives at the procurement hospital.

Management strategy of lungs has been modified after the 50th organ procurement from a BD donor in December 2006. After then, in addition to routine bronchial toileting and posture change, repeated broncho fiberscope and frequent bronchial toileting were performed, if there were symptoms and/or signs of atelectasis or pneumonia in the chest x-ray and CT chest scan, After changing the lung management strategy, not only lung availability but also patient survival rate after lung transplantation significantly increased [27]. Then, since 2011, lung transplant surgeons played a role in evaluating and managing lungs as lung MC [28].

6.2 1st step donor evaluation

PTC of Japan Organ Tx Network (JOT) is sent to a hospital if there is a potential BD organ donor. They evaluate the patient clinical course and check clinical records to rule out the absolute contraindications, shown above. They obtain informed consent for BD organ donation from his or her relatives. After then, two times of legal examination for BD is carried out.

6.3 2nd step donor evaluation

After completion of 1st legal examination for BD determination, MCs come to the hospital. They and JOT PTC obtain the donor's clinical data such as past history, family history, clinical course during the completion of BD and after BD, such as the history of cardiopulmonary resuscitation and pulmonary aspiration, medication given, such as inotropes, ADH and antibiotics, transfusion, blood examination, blood gas examination, hemodynamic parameters, ECG findings, and data of image examination such as the chest x-ray and the abdominal and chest CT scan. MCs also perform ultrasound examinations for heart and abdominal organs and broncho fiberscope. Rule out malignancies by findings of the CT scan and ultrasound examination and support of making donor evaluation sheets by JOT PTCs are is also an important job of MC.

After 2nd legal examination for BD determination, the patient has declared dead and donor evaluation sheets and images of sequential ECGs, chest x-rays, echocardiography, and chest CT scans are sent to the heart transplant centers of potential recipients using a mobile system, called a donor data delivery system (DDDS) established by JOT. Then transplant center decides whether the recipient undergo heart transplantation from this BD donor and the procurement team is sent to the hospital

According to their assessment of donor hemodynamics and respiration, MCs proposed individualized donor management strategies to physicians taking care of the donor in the procurement hospital.

6.4 3rd step donor evaluation

After arriving at the donor hospital, the procurement team also evaluates the donor heart function with echocardiography by themselves in ICU and determines whether the heart can be transplanted to their recipient. They send this information to their transplant team.

6.5 Pre-procurement meeting and management of the procurement operation

Before starting the procurement operation, all procurement surgeons, anesthesiologists, and operating room nurses gathered in the meeting room. They negotiated

on the types of organs procured, the organ transportation method, the method of each organ procurement (e.g., organ dissection/perfusion technique, incision lines, blood drainage technique, etc), what kinds of samples (e.g., blood, lymph nodes, and spleen) were needed, and how to manage the donor during operation. A heart procurement surgeon also supports anesthesiologists to stabilize the patient's hemodynamics throughout the procurement operation.

Skillful staff surgeons, not resident surgeons, harvests the donor heart. As it was reported that increased intraoperative colloid infusion was significantly associated with poor allograft function post-lung transplantation, maintenance of circulating blood volume and blood osmolality by infusing packed red blood cells and albumin during procurement operation are very important to improve lung graft function posttransplant. To achieve good organ perfusion with preservation solution, the dosage of inotropes should be kept to the minimum to dilate the procured organ vessels and ADH is continuously given until heparin sulfate (400 U/Kg) is given.

6.6 Final donor evaluation

After opening the chest, the procurement team will evaluate the heart by inspection and palpation to decide to use the heart. They also look out for unexpected malignancies in the pleural and abdominal cavities.

7. Discussion

For many years, heart transplantation has been an established treatment strategy for end-stage heart failure patients using the so-called "Standard Criteria" donor heart. However, over the past three decades, the number of annually listed patients for heart transplantation greatly increased worldwide, and the strict use of the "Standard Criteria" hearts has enhanced severe donor heart shortage, significantly prolonged waiting times and increased the death rate of listed patients prior to heart transplantation. Therefore, the use of ECD hearts has increased worldwide. However, even in 2020, only 3,658 hearts of 9,364 BD donors (39.1%) were transplanted in the USA. As only 760 BD donors have been available in Japan for more than 20 years until the end of 2020 because of the very strict Japanese Organ Transplant Act, only 297 donor hearts would have been transplanted if the rate of heart utilization from the BD donors in Japan is same as in the USA. These extraordinary pressures of donor heart shortage had made Japanese heart transplant programs use a much greater number of ECD donor hearts than in developed countries. Therefore, an original and sophisticated donor evaluation and management system have been established in Japan, such as MC and pre-procurement meetings and so on.

To elucidate the role of this Japanese donor evaluation and management system, consecutive 775 BD donors since the Act was issued until the end of August 2021 in Japan, were reviewed. A total of 611 hearts (78.8%) were transplanted, and organ transplanted per donor was 5.1 (3,985 organs from 775 donors). The number of heart donor ≥ 60 years of age was 63 (10.3%). In the heart donors who had information about the cause of death, the cause of BD was subarachnoid hemorrhage in 160, hypoxic brain damage in 126, other cerebrovascular disorders in 120, head trauma in 100, post-cardiopulmonary resuscitation in 29, and asphyxias in 23. Overall survival rates of cardiac recipients at 1 year, 5, 10, and 20 years were 93.3, 88.3, 79.1, and 75.3%, respectively. Patient survival at 10 years with donor aged 10–19 years, 20–29 years, 30–39 years, 40–49 years, 50–59 years, and 60–69 years were 100, 61.6, 95.5,

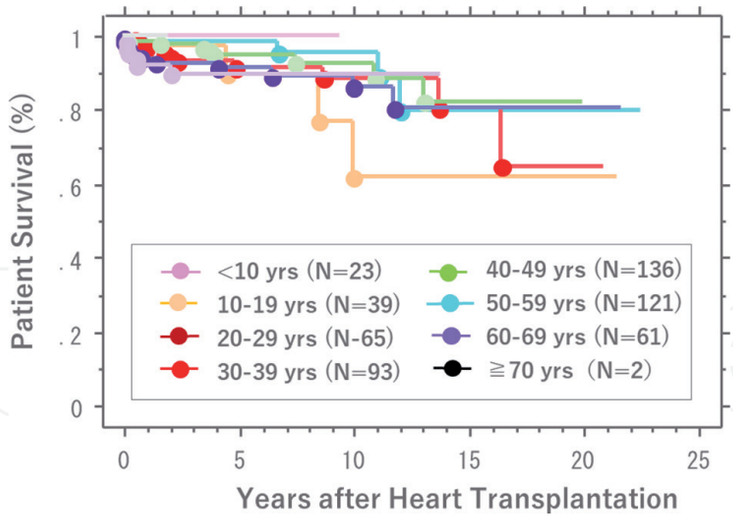

Figure 3.
Cumulative patient survival rate of heart transplant recipients by donor age group (up to August 31, 2021). yrs: years.

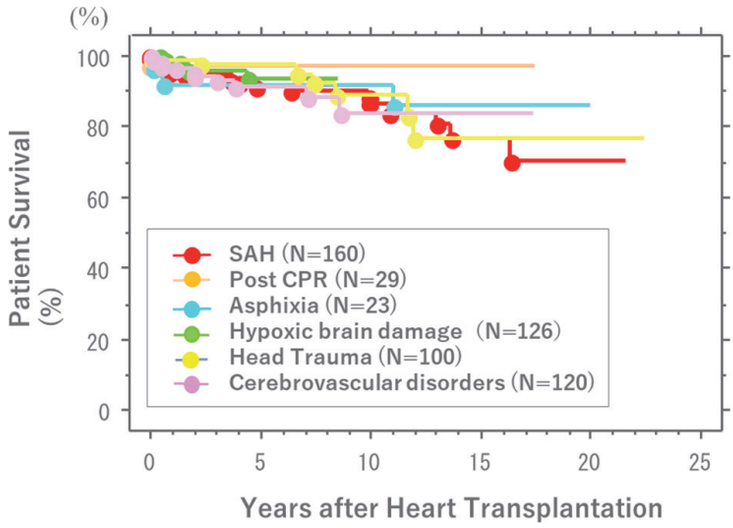

Figure 4.
Cumulative patient survival rate of heart transplant recipients by donor cause of death group (up to August 31, 2021). SAH: subarachnoid hemorrhage, Post-CPR: post-cardiopulmonary resuscitation.

88.4, 92.7, 85.9, and 89.3%, respectively (**Figure 3**). Patient survival at 10 years from a donor with subarachnoid hemorrhage, hypoxic brain damage, other cerebrovascular disorders, head trauma, post-cardiopulmonary resuscitation, and asphyxias were 87.7, 93,2 (at 8.6 years), 82.9, 88.3, 96.6, and 85.2%, respectively (**Figure 4**). These values were not significantly different.

8. Conclusion

As deceased organ donation has not increased compared to an increase in listed candidates for heart transplantation worldwide, extended criteria donor hearts have been used in many countries. However, in most countries, only 20–30% of donor hearts from BD donors have been used. Therefore, in Japan where donor shortage has been extremely sever than in other developed countries, special strategies for

maximizing heart availability should be established. By establishing the MC system in Japan, the availability of hearts has been very high (79%) and the patient survival rate at high (89% at 10 years). MC doctors may play a great role in increasing donor heart availability as well as in improving outcomes of cardiac recipients even from elderly donors or donors who died of post-resuscitation and anoxia in Japan. These strategies may be useful for maximizing heart transplant opportunities and improving post-transplant outcomes.

Author details

Norihide Fukushima
Department of Transplant Medicine, National Cerebral and Cardiovascular Center, Suita, Japan

*Address all correspondence to: nori@ncvc.go.jp

IntechOpen

References

[1] Fukushima N. Revised organ transplant act and transplant surgeons. Japan Medical Association Journal. 2011;**54**(6):387-391

[2] Fukushima N, Ono M, Nakatani T, et al. Strategies for maximizing heart and lung transplantation opportunities in Japan. Transplantation Proceedings. 2009;**41**(1):273-276

[3] Novitzky D, Cooper DK, Rosendale JD, Kauffman HM. Hormonal therapy of the brain-dead organ donor: Experimental and clinical studies. Transplantation. 2006;**82**(11):1396-1401

[4] Mascia L, Mastromauro I, Viverti S, et al. Management of optimize organ procurement in brain dead donors. Minerva Anesthesiol. 2009;**75**:125-133

[5] Kaul DR, Vece G, Blumberg E, et al. Ten years of donor-derived disease: A report of the disease transmission advisory committee. American Journal of Transplantation. 2021;**21**:689-702. DOI: 10.1111/ajt.16178

[6] Audibert G, Charpentier C, Sequim-Devaux C, et al. Improvement of donor myocardial function after treatment of autonomic strom during brain death. Transplantation. 2006;**82**:1031-1036

[7] Ryan JB, Hicks M, Cropper JR, et al. Functional evidence of reversible ischemic injury immediately after the sympathetic storm associated with experimental brain death. The Journal of Heart and Lung Trasnplantation. 2003;**22**:922-928

[8] Boone M, Deen PM. Physiology and pathophysiology of the vasopressin-regulated renal water reabsorption. Pflügers Archives. 2008 Sep;**456**(6):1005-1024

[9] Pennefether SH, Bullock RE, Mantle D, Dark JH. Use of low dose arginine vasopressin to support brain-dead organ donors. Transplantation. 1995;**59**:58

[10] Kinoshita Y, Okamoto K, Yahata K, et al. Clinical and pathological changes of the heart in brain death maintained with vasopressin and epinephrine. Pathology, Research and Practice. 1990;**186**(1):173-179

[11] Iwai A, Sakano T, Uenishi M, et al. Effects of vasopressin and catecholamines on the maintena,nce of circulatory stability in brain-dead patients. Transplantation. 1989;**48**(4):613-617

[12] Fukushima N, Shirakura R, Nakata S, et al. Failure of rapid autonomic augmentation of cardiac performance in transplanted hearts. Transplantation Proceedings. 1998;**30**(7):3344-3346

[13] Huprikar S, Danziger-Isakov L, Ahn J, et al. Solid organ transplantation from hepatitis B virus-positive donors: Consensus guidelines for recipient management. American Journal of Transplantation. 2015;**15**(5):1162-1172. DOI: 10.1111/ajt.13187

[14] Ruiz I, Gavaldà J, Monforte V, Len O, Román A, et al. Donor-to-host transmission of bacterial and fungal infections in lung transplantation. American Journal of Transplantation. 2006;**6**:178-182

[15] Hynes CF, Ramakrishnan K, Alfares FA, et al. Risk of tumor transmission after thoracic allograft transplantation from adult donors with central nervous system neoplasm–A

UNOS database study. Clinical Transplantation. 2017;**31**(4):e12919. DOI: 10.1111/ctr.12919

[16] Desai R, Collett D, Watson CJE, Johnson P, Evans T, Neuberger J. Estimated risk of cancer transmission from organ donor to graft recipient in a national transplantation registry. BJS. 2014;**101**:768-774. DOI: 10.1002/bjs.946

[17] Grauhan O. Screening and assessment of the donor heart cardiopulmonary. Pathophysiology. 2011;**15**:191-197

[18] Laks H, Gates RN, Ardehali A, et al. Orthotopic heart transplantation and concurrent coronary bypass. The Journal of Heart and Lung Transplantation. 1993;**12**:810-815

[19] Marelli D, Laks H, Bresson S, et al. Results after transplantation using donor hearts with preexisting coronary artery disease. The Journal of Thoracic and Cardiovascular Surgery. 2003;**126**:821

[20] Kimura Y, Seguchi O, Iwasaki K, et al. Impact of coronary artery calcification in the donor heart on transmitted coronary artery disease in heart trnsplant recipients. Circulation Journal. 2018;**82**:3021-3028. DOI: 10.1253/circj.CJ-18-0107

[21] Bailey LL, Razzouk AJ, Hasaniya NW, Chinnock RE. Pediatric transplantation using hearts refused on the basis of donor quality. The Annals of Thoracic Surgery. 2009;**87**(6):1902-1908

[22] Khush KK, Potena L, Cherikh WS, et al. The international thoracic organ transplant registry of the International Society for Heart and Lung Transplantation: 37th adult heart transplantation report—2020; focus on deceased donor characteristics. The Journal of Heart and Lung Transplantation. 2020;**39**(10):1003-1015

[23] Sakagoshi N, Shirakura R, Nakano S, et al. Serial changes in myocardial beta-adrenergic receptor after experimental brain death in dogs. The Journal of Heart and Lung Transplantation. 1992;**11**:1054-1058

[24] Fukushima N, Sakagoshi N, Ohtake S, et al. Effects of exogenous adrenaline on the number of the beta-adrenergic receptors after brain death in humans. Transplantation Proceedings. 2002;**34**:2571-2574

[25] Fukushima N, Shirakura R, Nakata S, et al. Study of efficacies of leukocyte-depleted terminal blood cardioplegia in 24-hour preserved hearts. The Annals of Thoracic Surgery. 1994;**58**(6):1651-1656

[26] Russo MJ, Iribarne A, Hong KN, et al. Factors associated with primary graft failure after heart transplantation. Transplantation. 2010;**90**(4):444-450

[27] Fukushima N, Ono M, Saito S, et al. Japanese strategies to maximize heart and lung availabilities: Experience from 100 consecutive brain-dead donors. Transplantation Proceedings. 2013;**45**:2871-2874

[28] Hoshikawa Y, Okada Y, Ashikari J, et al. Medical consultant system for improving lung transplantation opportunities and outcomes in Japan. Transplantation Proceedings. 2015;**47**:746-750