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Chapter 2

Donor Assessment and Management for Maximizing Organ Availability

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Abstract

As donor shortage is extremely severe in Japan because of the 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 anti-diuretic hormone and pulmonary toileting by broncho-fiberscope. Out of a consecutive 180 brain dead donors, 5.5 organs were transplanted per one donor and patient/graft survival of all organs, including the heart, lung, liver, pancreas and kidney were acceptable. I would like to describe pathophysiology of brain death, organ evaluation technique and donor management in detail. These techniques may increase the organs transplanted per donor in the world.

Abbreviations

- transplantation (Tx)
- brain dead or death (BD)
- primary allograft dysfunction (PGD)
- central venous pressure (CVP)
- noradrenaline (NAD)

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- adrenaline (AD)
- dopamine (DOA)
- systemic vascular resistance (SVR)
- electrocardiogram (ECG)
- pulmonary artery wedge pressure (PCWP).
- acute lung injury (ALI)
- adult respiratory distress syndrome (ARDS)
- anti-diuretic hormone (ADH)
- triiodothyronine (T3)
- free thyroxine (T4)
- thyroid stimulating hormone (TSH)
- heart rate variability (HRV)
- occlusion of inferior vena cava (VCIO)
- releasing VCI (VCIR)
- heart transplantation (HTx)
- cardioplegic arrest (CPA)
- beta-adrenergic receptors (BAR)
- bronchofiberscopy (BFS)
- catecholamine (CAs)
- organ procurement organization (OPO)
- mean arterial pressure (MAP)
- pulmonary arterial pressure (PA)
- left atrial pressure (LAP)
- inferior vena cava (IVC)
- intensive care unit (ICU)
- computed tomography (CT)
- procurement transplant coordinators (PTC)
- Japan Organ Transplantation Network (JOT)
- left ventricle (LV)
- Swan-Ganz catheterization (SGC)
- peak end-expiratory pressure (PEEP)
- partial pressure of oxygen and carbon dioxide in arterial blood (PaO_2 and $PaCO_2$)
- inspired fraction in oxygen (FiO_2)

1. Introduction

Organ transplantation (Tx) represents established procedures in end-stage organ failure patients and result in satisfying long-term results. However, these surgical therapies are continuously limited by severe donor organ shortage in the last years. Therefore, adequate and optimal utilization of all suitable donor organs is mandatory to increase graft availability.

The Japanese Organ Transplantation Act for brain dead (BD) organ donation (the former Act) was issued in October 1997. [1] The Act required a living written consent for BD and organ donation and did not allow BD donation from children younger than 15 years. From

these reasons, only 81 BD organ donations have been performed in Japan for 13 years since the former Act was issued. The cardiac donation rate per million populations in Japan is only 0.08, while it is 7.3 in USA, 5.3 in Spain and 0.97 even in South Korea in 2007. A mean waiting time for HTx and LTx was extraordinary long in Japan, which was 1,026 days and 1,673 days in 2010, respectively.

Finally the Act was revised on 17th July in 2010. [1] By renewal of the Act, organs can be donated after BD with consent from their family, if he or she did not deny organ donation. Although the Act was revised in 2010 and BD organ donation increased from 13 to 44 cases in a year, the number was still extremely smaller than other developed countries. These great pressures of organ shortage and long waiting time had made Japanese transplant programs consider the use of donor organs that would be considered marginal.

The most troublesome issue facing Tx is the phenomenon of primary allograft dysfunction (PGD). This complication is the leading cause of death in the first 30 days and in the first year post-transplant in both organs in the world. The use of marginal donor organs may increase the rate of PGF. From this point of view, it is necessary to establish special donor evaluation and management system to maximize donor organ utilization.

Only about twenty percent of BD donors in Japan have been fitted in a so-called standard criteria donor for all organs including heart, lung, liver, pancreas, and kidney. Therefore, it is very important for us to maximize the number of transplantable organs in order to resolve the severe donor shortage in Japan. [2] 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 Tx. Maximizing donor organ availability is also the last wish of donors and donor families. However, if a transplant recipient died due to to a marginal donor organ, the donor family feels the loss of their lover again. Therefore, prevention of PGD is essential for the donor family as well as for recipients.

Full-scale donor management begins after the patient is sentenced BD and his or her family agrees to do so, especially in Japan. In general, donor management is based on treatment of cardiac and respiratory dysfunction resulting in 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) 6 to 10 mmHg, urine output 100 ml/hr (0.5 to 3 ml/kg/hr) and heart rate 80 to 120 /minutes. As organ procurement surgery begins within 12 hours after full-scale donor management is started, it is very different from usual intensive care to stabilize hemodynamics and to maintain and improve organ function as many as possible in the short period. Moreover, it is important for the physicians who perform donor management to recognize the pathophysiology of BD from the beginning to completion period.

2. Pathophysiology of Brain Death

1.) Physiological Changes at Completion of Brain Death

Novitzky et al. reported animal experiments of BD in baboons, induced by placing a Foley catheter in the subdural space through a burr hole and instilling 20–30 mL of saline. [3]

This resulted in acute intracranial hypertension leading to brain stem herniation and BD. During and following the agonal period there was a short-lived, but devastating, catecholamine (CA) "storm" [3,4], which was the result of endogenous CA release from postganglionic sympathetic nerve endings. Novitky et al reported that serum concentration of noradrenaline (NAD), adrenaline (AD) and dopamine (DOA) elevated to approximately 1600, 1100 and 450 pg/ml, respectively, 5 minutes 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, 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 edema. 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 AD levels seen in animals undergoing sudden BD. 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 BD is developed. After the initial surge of CA following the onset of BD, CA levels rapidly returned to control levels and subsequently to levels below baseline, subsequently when endocrine changes and pituitary failure developed.

In clinical settings, BA is associated with a massive increase in CA levels 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 heart damage (myocytolysis and necrosis). [5] Electrocardiographic sings of myocardial ischemia, conduction abnormalities, and arrhythmia are also common during this period.

Histological examination of cardiac tissue exposed to an autonomic storm shows changes typical of widespread ischemic damage and necrosis, and profound end-organ vasoconstriction has been demonstrated in animal models.[6] However, this period of intense CA 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 Tx. [7-9]

Regardless of whether the systemic arterial pressure is low or high, the donor is usually hypovolemic. BD-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 monitor without monitoring CVP or pulmonary artery 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 mechanism 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 release of proinflammatory mediators into the systemic circulation. This inflammatory response may determine the preclinical lung injury present in potential lungs, which together with the ischemia-reperfusion injury may cause PGD. Indeed Follettee et al. reported that the administration of high dose steroids after BD improved oxygenation and increased lung donor utilization by limiting the cytokine-mediated cellular injury. [10]

2.) Abscent or Decreased Secretion of Anti-Diuretic Hormone (ADH) After Brain Death

The anti-diuretic hormone (ADH) is formed in the supra-optic and paraventricular nuclei of the hypothalamus by cleavages of a preprohormone of 168 amino acids and then a prohormone; ADH is transported to the posterior lobe of the pituitary gland which stores it (Figure 1). Its release depends primarily on two factors: hyperosmolality and blood volume and in addition on the effects of certain drugs.

The effects of ADH 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 phosphatidylinositol 4,5-bisphosphate in inositol triphosphate and diacylglycerol, 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 ADH 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 ADH under the influence of nicotine.

V2 receptors are coupled by G protein to adenylcyclase. Its activation elicits an increase in cyclic adenosine monophosphate 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 ADH 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. This induces the incorporation of aquaporins in the apical membrane of collecting ducts and causes their opening, which allows water reabsorption.

The effects of BD 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 sepraventricular and paraventricular hypothalamic nuclei ischemia. ADH was undetectable within six hours. As ADH is secreted from peripheral tissues, undetectable levels of ADH have been noted in 75% of BD. 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: <200mOsm/L). Polyuria may lead hypernatraemia (>145 mEq/mL), which is common and sometimes severe and worsening and associated with rising serum osmolality and hypovolemia. As vasoconstrictive effect of ADH is decreased, vascular tone of systemic arteries are decreased to lead hypovolemic shock. Therefore, abscence or decreased secretion of ADH after BD is associated with hemodynamic instability and compromised transplanted organ function.

Low-dose arginine vasopressin, in addition to treating diabetes insipidus, results in reduced inotropic requirements and has been associated with improved kidney, liver, and heart graft function. [3, 9, 11-13] 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.

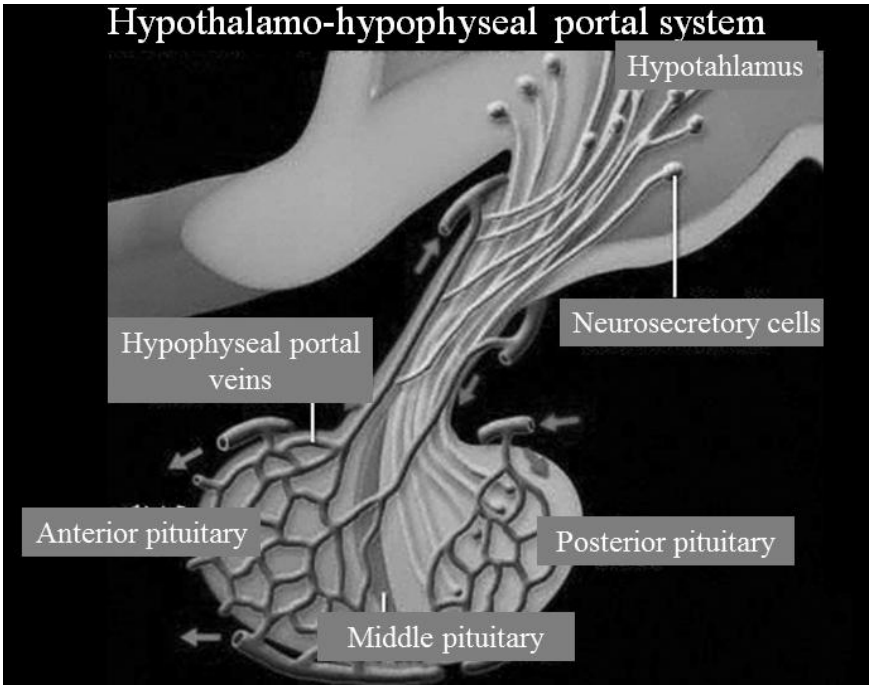

Figure 1. Hypothalamo-hypophesal portal system.

3.) Decrease in Anterior Pituitary Function after Brain Death

Anterior pituitary function (blood supply via hypophysical extradural arteries) is usually preserved in BD setting, but viable deficiency of hormones regulated by anterior pituitary including thyroid hormone [triiodothyronine (T3) and free thyroxin (T4)], adrenocorticotropic hormone, thyroid stimulating hormone (TSH), and growth hormone have been described (Figure 1). This striking and acute hormonal depletion was very common and has been implicated in hemodynamic derangement seen after BD in experimental animal models.

Cortisol levels were increased at five minutes and then declined progressively to below baseline levels. [14-16] Plasma levels of free T3 and T4 fell to 50% of control levels within one hour after BD and became undetectable within 9 and 16 hours, respectively. However, TSH showed no significant change. Insulin levels declined to 50% within three hours and to 20% within 13 hr.[15, 16] Prompted by these results, the Cape Town group studied hormone replacement therapy, first in BD animals and then in BD human organ donors. [3, 16]

Although a rapid decline in plasma levels of free T3 is seen after BD as a result of impaired TSH secretion and peripheral conversion of T4, attempts to thyroid disturbances in

organ donors have produced conflicting data [3]. Moreover, there has been inconsistent improvement or conflicting results in the assessed physiological parameters after replacement of these hormones in both animals and humans. [17]

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 have failed to confirm low levels of T3, T4, cortisol, and insulin after BD. [19, 20] Other published studies that failed to demonstrate any beneficial cardiac and circulatory effect of T3/T4 administration. [20, 21] This may have been for a number of reasons: 1) not all BD donors have total absence of anterior pituitary function (and therefore some have measurable T3 levels), 2) some groups failed to measure free T3, 3) not all donors are hemodynamically unstable [22-24] and the benefit from T3/T4 therapy might not be seen, and 4) an inadequate dosage of T3/T4 may have been administered. However, in many countries, such as USA, Canada and Australia, hormone resuscitation strategies (ADH, T4 and methylprednisolone) are recommended to manage BD donors. [9]

The optimal dose of i.v. methylprednisolone for the BD donor remains uncertain. High doses have been recommended [25, 26] and the United Network for Organ Sharing study [9] indicated a beneficial effect on the heart when it was the sole hormone administered. Because the half-life of methylprednisolone is short, we believe that it is desirable to repeat the dosage when organ retrieval is delayed. [27]

4.) Cessation of Autonomic Nerve Regulations on Circulation

After brainstem ischemia and necrosis, the brain-heart connections are definitively disrupted. BD results in complete cessation of normal variations of the autonomic cardiovascular centers and a cessation of the baroreflex function. [28] Rapenne et al. [29] described that as soon as the diagnosis of BD 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, so called denervation are also observed in heart transplant recipients. Transplanted hearts could not augment cardiac performance rapidly in response to acute decrease in the preload due to loss of the brain-heart connection [30]. In normal hearts, if a preload of the heart rapidly decreases, autonomic sympathetic nerves are activated thorough 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 (Figure 2). The augmentation of cardiac performance of the transplanted hearts depends 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.

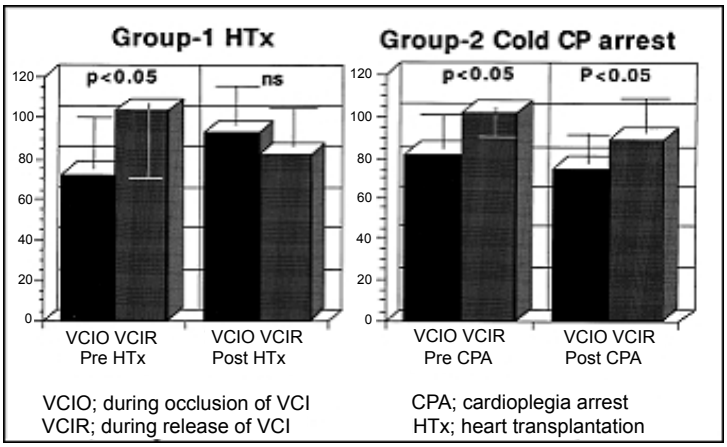

Figure 2. Preload recruitable stroke work during occlusion of inferior vena cava (VCIO) and releasing VCI (VCIR) before and after heart transplantation (HTx) in Group-1 and before and after cardiac arrest (CPA) [30].

As shown in heart transplant recipients, hemodynamics of BD persons is also unstable. For example, a decrease in blood return to the heart due to hemorrhage, putting pressure of the upper abdomen or postural change may easily cause hypotension. After a few minutes of hypotension, AD is secreted from adrenal glands due to spinal reflex and hypertension usually up to 150 mmHg and tachycardia may be observed. In uncontrolled BD 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.

5.) Abscence of Cough Reflex

After BD, 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 sputum, bronchofiberoscopy (BFS), by clearance of secretions and blood clots and correction of endotracheal tube malposition, may improve lung function.

6.) Alteration of BAR Systems

Various changes in BAR systems occur during and after BD. D'Amico et al. [31] reported a decrease in BAR density during BD in adult and pediatric pigs. Deterioration of myocardial performance after BD 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 CAs used to maintain donor hemodynamics after BD. [32] The authors also revealed a significant inverse correlation between Bmax which meant BAR density and serum AD level (Figure 3), but not between Bmax and serum NAD or DA levels. [33] 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 (Figure 4). These data suggest that exogenous AD reduces BAR density in BD 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.

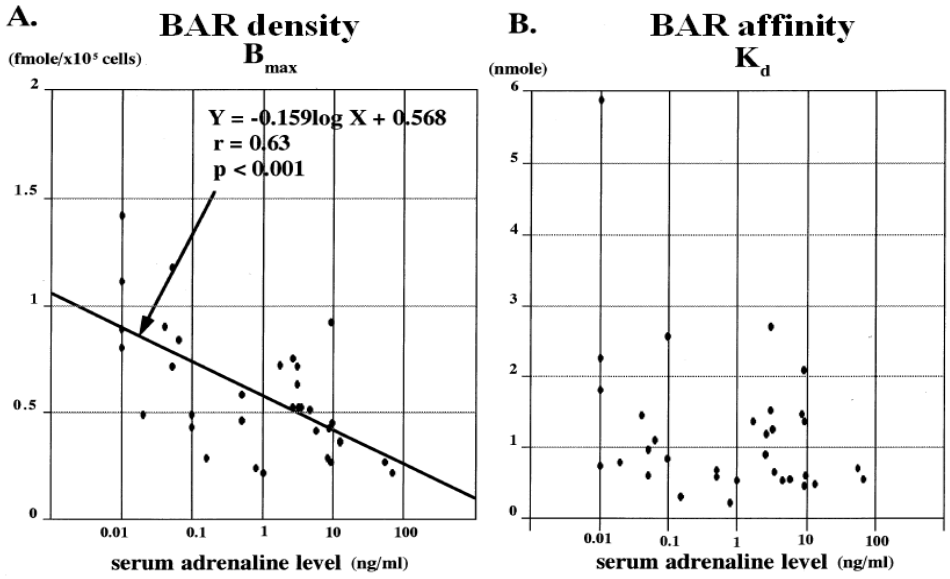

Figure 3. The relationship between Bmax (A) or Kd (B) and serum adrenaline. (A) There was a significant inverse correlation between Bmax and serum adrenaline level ($r = 0.63$, $P < 0.001$), (B) There was no correlation between Kd and serum adrenaline level [33].

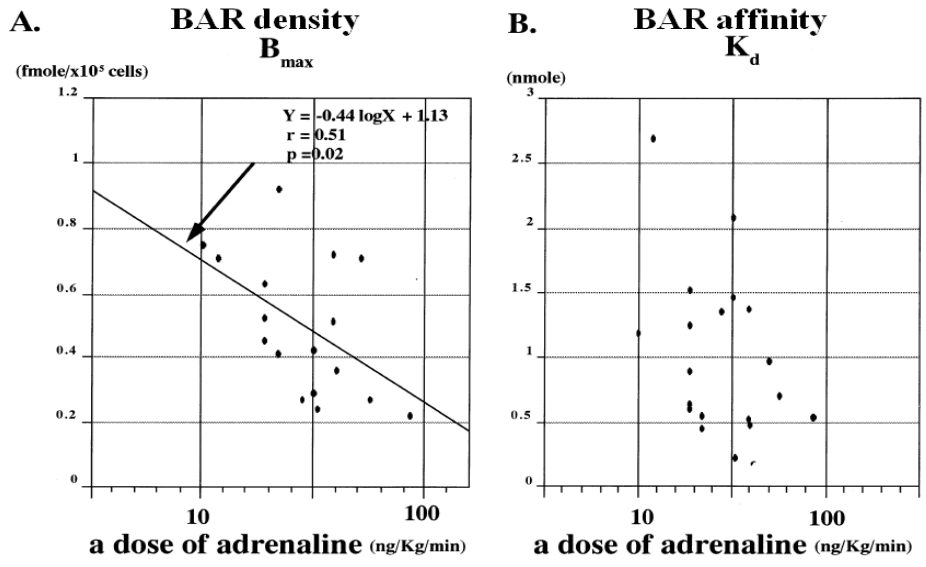

Figure 4. The relationship between Bmax (A) or Kd (B) and a dose of adrenaline given. (A) There was a significant inverse correlation between Bmax and a dose of adrenaline given in patients ($r = 0.63$, $P < 0.001$), (B) There was no correlation between Kd and a dose of adrenaline given [33].

3. Donor Assessment

Before obtaining informed consent for organ donation from relatives, we should rule out legal and medical absolute contraindications for donor eligibility. Then, anatomy and function of each organ are evaluated to determine which organ is eligible to be transplanted. In the same time, hemodynamic, respiratory status and other clinical data are assessed to define how to manage donor for maximizing organ availability and improving post transplant organ function.

1) Rule Out of Absolute Contraindications for Donor Eligibility

Although absolute contraindications for donor eligibility depend on organ procurement organization (OPO), almost all OPO determined that positive test for HIV/AIDS is contraindication for donation. Most OPO provided a list of absolute contraindications (Table 1).

Table 1. Absolute contraindications for donor eligibility

Positive tests for
Anti-HIV-1 or anti-HIV-2
Hepatitis B or C*
Human T cell lymphotropic viruses types I and II
History or evidence of HIV high-risk behaviors, even if HIV antibody negative
Prion-related disease (i.e., CJD, family history of CJD, recipient of human-derived pituitary hormone or durra mater)
Active systemic bacterial, viral or fungal infections
Leukemia, lymphoma and active malignancies

Transmission of donor malignancies is rare with 18 cases from 34,933 cadaver donors and 3 cases from 32,052 living donors being reported to United Network for Organ Sharing from 1994-2001. [34] Donors with past histories of certain types of cancers may be considered as donors including certain types of primary central nervous system tumors. Tumors that pose a high transmission risk include choriocarcinoma, melanoma, lymphoma, and carcinoma of the lung, breast, kidney and thyroid. High risk donors include glioblastoma multi forme, high grade astrocytoma, meduloblastoma, and any brain tumor donors who have undergo ventriculo-peritoneal shunting.

2) Assessment for Donor Heart Eligibility

The real goal of donor heart assessment is not to estimate the functional status of the heart just before the organ harvesting but rather to predict the performance of the transplanted graft after weaning from the extracorporeal circulation and in the postoperative period. One also has to take into account the cumulative injury by “preexisting damage” of the donor heart

and "BD-related stress". This cumulative damage/stress may still be functionally inert but become evident after subsequent damage by ischemic time and reperfusion.

Hemodynamic Assessment Before and After Brain Death

For the hemodynamic assessment as well as for the appropriate management of the donor following information are important; cause of BD, clinical course and pathophysiology of BD, past history of heart disease, treatment of the patients, especially doses of inotropes [DOA/dobutamine (DOB).AD and NAD], ADH, other pituitary hormones, and antibiotics, fluid intake and transfusion, urine output, hemodynamic parameters, such as mean arterial pressure (MAP), preload and afterload [CVP, PCWP/LAP, pulmonary arterial pressure (PA)], cardiac output and/or mixed-venous oxygen saturation, i.e. from arterial and venous lines as well as a pulmonary artery catheter. Mainly, the hemodynamic assessment has to differentiate between the three most common cardiovascular problems after BD: 1) hypovolemia due to diabetes insipidus because of BD related hypophyseal insufficiency 2) BD related peripheral vasoplegia and 3) myocardial insufficiency as a result of combined pre-existing and BD induced damage.

As shown by an analysis in 1719 consecutive primary heart Txs performed at 27 institutions, donor hearts requiring inotropic support of up to 6μg/kg/min of DOB or DOA can be accepted as so-called "marginal grafts" with acceptable outcome. [35]

Even if the donor has a history of cardiopulmonary resuscitation longer than 5 minutes, the heart might be eligible for Tx, if hemodynamics, cardiac function, wall motion of left ventricle and ischemic changes in ECG are restored under optimal donor management. [36]

Chest X-Ray

Cardiomegaly, chest trauma or pleural effusions are checked by chest x-ray.

Electrocardiogram (ECG)

Most BD donors have some degree of myocardial insufficiency caused by combined pre-existing and BD induced damage, ECG usually shows abnormality in ST segments and QRS wave. Subendocardial ischemia and necrosis occur accompanied by ST-elevation, Q-waves, multifocal ventricular ectopic beats and runs of ventricular tachycardia in ECG as well as transient ischemic mitral valve incompetence with an increase of left atrial pressure (LAP). These circumstances are regarded as responsible for the reversible wall motion abnormalities mentioned above.

Sustained abnormalities in ST segments and QRS and multifocal ventricular ectopic beats under optimal donor management are considerably high risks for heart Tx.

Echocardiography

Echocardiography allows a reliable assessment of cardiac valve function and myocardial hypertrophy as well as evaluation of congenital malformations. However, the assessment of myocardial performance is problematic since global and even regional ventricular dysfunction may be BD induced and these wall motion abnormalities may be reversible within hours after optimized donor management and recovery these marginal organs can be transplanted with excellent results. Therefore, serial echocardiography is required before a graft is rejected because of myocardial dysfunction.

In the presence of LV unveiling, 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 inferior vena cava (IVC) as well as doses of inotrope prior to undergo echocardiography to assess cardiac function.

Table 2. Parameter list for assessment of donor hearts

	Risk normal	Risk increased	Risk considerably increased	Validity
Donor age	<50 years	50 - 65 years	>65 years	evidence
Ischemic time	<240 min	>240 min		evidence
Circulation parameter				
Dobutamine/dopamine	<6µg/kg BW	6-10µg/kg BW	>10µg/kg BW	evidence
Adrenaline/noradrenaline	0	>0		evidence
Eletrocardiogram (ECG)				
Infarct (QRS)	No	yes		experts
ST-segment	No	yes		evidence
Ectopic ventricular beat	Single	unifocal	Multifocal	experts
Echocardiography				
Ventricular septum	<12 mm	12-16 mm	>16 mm	experts
Shortening fraction	>30%	20-30%	<20%	evidence
Regional hypokinesia	No	yes	Yes	evidence
Valve stenosis	No	yes		experts
Valve insufficiency	1st degree	> or = 2nd degree		experts
Coronary angiogram	no lesion	single lesion	diffuse sclerosis	experts
Chemistry				
Troponin T	Normal	elevated	Elevated	evidence
Resuscitation		at time of brain death/injury	during later course under optimal donor management	experts

Coronary Angiography

In the western countries asymptomatic coronary atherosclerosis is common even in children and young people. The prevalence of significant coronary atherosclerosis – defined as a 50% stenosis of at least one main coronary artery – is found in about 20% (including 3% coronary occlusions) in a "healthy" population with a mean age of 20 to 25 years. Therefore, coronary angiography, at least in donors older than 40 years or according to the anamnesis and/or risk factors – is a "sine qua non" for the adequate evaluation. However, up until now there is no evidence which kind or degree of transmitted coronary atherosclerosis really impairs the post-transplant outcome since angiography in donors younger than 60 years has been regarded as unnecessary. On the other hand, although there are individual patients with excellent long-term outcome despite significant and (postoperatively) well documented transmitted coronary atherosclerosis, probably many of those Txs end in so-called "early graft failure". [37]

Recent infarction and diffuse coronary sclerosis are contraindications without any doubt, but a single stenosis with good performance of the dependent myocardial area seems to be acceptable, especially if it is treated interventionally during donor angiography or by concomitant bypass surgery during Tx. [35-38]

In the future, contrast computed tomography (CT) scan, especially cardiac CT scan might be useful to rule out of coronary artery disease in the donor heart.

3) Assessment for Donor Lung Eligibility

Successful lung procurement is challenging because of the association of BD with neurogenic pulmonary edema, pneumonia, and intense inflammatory responses. One also has to take into account the cumulative injury by "preexisting damage" of the donor lung and "BD-related stress". This cumulative damage/stress may still be functionally inert but become evident after subsequent damage by ischemia and reperfusion injury.

The ideal lung donor is one with $PaO_2/FiO_2 > 300$, positive end expiratory pressure requirement of <5 cmH_2O, clear chest-x-ray, age < 55 years, smoking history of <20 packs/year, no evidence of trauma, surgery, aspiration, malignancy, and purulent secretions. Pathological studies of lungs deemed unsuitable for donation have indicated that bronchopneumonia, diffuse alveolar damage, and lung consolidation are the most common reasons for rejecting lung allografts.

The major concern for utilizing donors with a history of cigarette smoking is the potential for poor lung function due to the obstructive pulmonary disease, the risk of transplanting an undetected primary or metastatic cancer, or for developing a malignancy in the donor lung in the years after the Tx. Careful examination of the chest-x-ray and chest CT scan whenever available, as well as meticulous examination of the lung and biopsy of any suspicious lesions in the operating room at the time of organ retrieval are of prime importance to limit the risk of lung cancer transmission.

The recipients of lungs of donors with asthma were reported to have asthma attacks; donor history of asthma is a risk for lung Tx. Donors who became BD due to asphyxia from an asthma attack is a relative contraindication for lung donation.

For the assessment of donor lungs as well as for the appropriate management of the donor with regard to the cause of BD, clinical course and pathophysiology of BD, how, the condition of intra-tracheal intubation, history of pulmonary aspiration, past history of lung disease, treatment of the patients, especially mechanical ventilatory strategies and antibiotics, fluid intake and transfusion, urine output, hemodynamic parameters are important.

Radiographic Findings

Serial standard portable chest x-rays are usually taken as part of the evaluation of a potential lung donor. However, it is important to recognize that plain chest x-rays taken at the bedside are far less sensitive than computed tomographic scanning and may underestimate structural abnormalities such as minor contusions or small infiltrates. The predictive value in accepting or rejecting the lung based on chest x-ray was low and the inter-observer variability was high in a retrospective study from Johns Hopkins. [39]

There is a paucity of data to establish firm guidelines regarding chest x-ray findings. Donors with strong unilateral abnormalities on chest x-ray should not be excluded for donation of the contralateral lung. Even if a ratio of arterial oxygen tension to inspired oxygen *fraction (PaO_2/FiO_2* ratio) was lower than 300, the contralateral lung was transplanted if *PaO_2/FiO_2* ratio of the pulmonary venous blood of that side sampled at procurement operation was more than 400. McGowin and co-workers have shown that 37% of donors have infiltrates on the initial film of which 51% resolved completely after proper donor management. [40] Diffuse bilateral lung infiltrates are highly suspicious for a developing pneumonia, especially in a patient with high temperature and purulent secretions. These lungs should not be utilized if heavy, pneumonic infiltrates are confirmed during organ retrieval. In

conclusion, evaluation of donor chest-x-ray is a highly subjective process and as an isolated criterion has a limited role in the determination of organ suitability.

Gram Stains and Bronchoscopy Findings

Sputum gram stains and cultures are usually obtained on all lung donors either by suction catheter or BFS. Studies have shown that a positive donor gram stain did not predict post transplant pneumonia, oxygenation or duration of post transplant mechanical ventilation. The incidence of donor infection was reported to be 52% and transmission to the recipient occurred in 8.1% despite appropriate antibiotic prophylaxis. [41] However, the impact of microbial colonization or subclinical infection in assessing the donor lung is not clear. Successful lung Tx is possible with frequent postoperative microbial airway sampling and adequate antibiotic treatment.

Gas Exchange

Good oxygenation is believed to be the most important indicator for the functional quality of the lung. Arterial blood gas analysis in a donor with an indwelling arterial catheter can be easily repeated to follow the evolution in gas exchange in the interval between BD and organ retrieval. The PaO_2/FiO_2 ratio can be easily affected by reversible processes such as retained secretions, pulmonary edema, and atelectasis. Aggressive donor management is important. The initial poor gas exchange values should not immediately exclude any donor. It remains unclear how low the PaO_2/FiO_2 ratio can be without affecting transplant outcome. In a French multicenter study, donor gas exchange before harvest was significantly associated with early and long-term outcome. Moreover, there was a steep increase in the relative risk of death when the PaO_2/FiO_2 ratio was below 350 mm Hg. Luckraz and coworkers found higher 30-day mortality but similar overall mortality in a group of recipients with a donor PaO_2/FiO_2 between 225 and 300. Successful transplants with donor lungs with ratios < 300 have been reported. In donors with unilateral abnormalities on chest-x-ray, initially low arterial blood gases may significantly improve after exclusion of the unacceptable lung intraoperatively. Direct left and right pulmonary vein blood gas sampling may also be helpful in (re)assessing the lungs individually immediately prior to pulmonary flush. $PpvO_2$ was reported to correlate much more reliably with outcome in the recipient than PaO_2. Much higher oxygen values are then often measured compared to samples taken from the radial artery catheter with the donor still in the intensive care unit. Therefore, a low PaO_2/FiO_2 ratio alone is not good criteria to exdclude lungs for transplant suitability.

Bronchofiberscope (BFS)

Bronchopneumonia, diffuse alveolar damage, and lung consolidation are the most common reasons for rejecting lungs for Tx. Given these findings, it is recommended that every lung donor undergo BFS for therapeutic bronchial toilet, and to isolate potential pathogens to guide antibiotic therapy in both the donor and the recipient.

4) Assessment for Donor Liver Eligibility

The liver appears to tolerate long periods of hypoperfusion because of large physiological reserves. The liver is a tolerogenic organ. Initially poor functioning of the liver allografts

results from factors like inflammatory processes of BD and preservation reperfusion injury. Long cold ischemia time leads to edema and detachment of sinusoidal lining cells of the liver leaving hepatocytic microvilli exposed to the sinusoidal lumen resulting in cell death. High donor serum sodium concentration is a significant risk factor for primary hepatic nonfunction as it may promote the accumulation of idiogenic osmoles within hepatocytes. Subsequent Tx of these livers into recipients with relatively normal sodium levels may promote intracellular water accumulation, cell lysis, and death. Correcting donor serum sodium levels < 155 mmol/L, keeping CVP between 8 and 10 mm Hg, using low PEEP to prevent hepatic congestion, and restoring liver glycogen stores with adequate nutrition have been shown to decrease the incidence of liver allograft dysfunction.

Donor characteristics associated with a higher risk of delayed graft function or primary nonfunction include: age > 65 years, macrovesicular steatosis >40%, donation after cardiac death donor, serum sodium >155 mEq/dL, split-liver Tx, and cold ischemia time exceeding 12 hours. Donors with an increased risk of disease transmission include positive serologic data (hepatitis C or B, HBV core antibody, human T-cell lymphotrophic virus), carcinoma outside of the liver, and Centers for Disease Control and Prevention (CDC) high-risk behavior.

Abnormal echography and CT scan are useful to diagnose fatty liver, hepatitis, malignancies and bile duct diseases.

5) Assessment for Donor Kidney Eligibility

BD is associated with histologic evidence of both immunological and nonimmunological renal injuries, which can increase the rate of delayed allograft function and also the risk of acute as well as chronic rejection The incidences of acute tubular necrosis and allograft failure increase when high doses of DOA are used (>10 mcg/kg/min) to support the donor and if donor systolic blood pressure is consistently <80 to 90 mm Hg as autoregulation of renal blood flow and glomerular filtration rates decline below this threshold. Consequently, timely hemodynamic management of the organ donor is important. If urine output remains <1 mL/kg/h after optimal hemodynamic management, diuretics should be used. Nephrotoxic drugs should be avoided and corticosteroids are recommended to decrease immunological damage. Abnormal ultrasound and CT scan are useful to measure the size of kidneys, evaluate renal circulation, diagnosis of renal cysts, malignancies and urinary duct diseases.

6) Japanese Strategies for Donor Evaluation

Medical Consultant System in Japan

Since BD organ Tx was started in 28th February 1999, every organ procurement team has taken their own staff physicians to the procurement hospital. They evaluated the condition of donor organs by ultrasound examinations for the heart and abdominal organs and BFS by themselves in ICU, before procurement operation. [2]

Since November in 2002, special transplant management doctors (a medical consultant; MC) who were usually cardiac Tx surgeons have been sent to the procurement hospital. They assessed donor organ function and identified which organs were useful for Tx. They also

intensively manage the donor by giving ADH (a bolus infusion in a dose of 0.01 U/kg followed by a drip infusion in a dose of 0.01 U/Kg/hr), reducing the dose of intravenous inotrpes as much as possible, and improving the donor organ function by preventing and treating lung infection before procurement teams arrived at the donor hospital.

Since the 50th BD donor in December 2006, management of lungs has been modified. In all donors, regular toileting and turning of the donor were done as previously. If there were symptoms and/or signs of atelectasis or pneumonia in chest x-ray and CT chest scan, repeated BFS and frequent toileting were performed. Since 2011, lung transplant surgeons played a role in evaluation and managing lungs.

Currently MCs consists of about 20 cardiac Tx surgeons, about 30 lung Tx surgeons and 3 liver Tx surgeons.

1st Step Donor Evaluation

Procurement Tx coordinators (PTC) of Japan Organ Tx Network (JOT) were called to a donor hospital if there was a potential BD donor. They access patient clinical course and check clinical records in order to find out whether the patient is suitable for organ donation such as no absolute contraindications for organ donation, such as untreated malignancy and severe viral infections. They get informed consent for BD organ donation from his or her family. Then legal examination for BD is carried out.

2nd Step Donor Evaluation

After completion of 1st clinical examination for determining BD, MCs were sent to the hospital. They and JOT PTC check clinical records such as clinical course before and after BD, medication given, blood examination, ECG, chest x-ray and abdominal and chest CT scan. The ultrasound examination for heart, liver, pancreas and kidneys and BFS is performed. MCs also rule out malignancies from findings of CT scan and ultrasound examination. JOT PTCs make donor evaluation sheets which is sent to Tx centers later.

After 2nd clinical examination for determining BD is completed and the patient is declared death. Donor information such as donor evaluation sheets and images of ECG, chest x-ray, ultrasound examinations, BFS and CT scans is sent to transplant centers using a mobile system. Then transplant centers can decide whether their recipient undergo Tx from that BD donor and their procurement team is sent to the hospital

3rd Step Donor Evaluation

After arriving at the donor hospital, the procurement team also evaluates the condition of donor organs by ultrasound examinations for the heart and abdominal organs and BFS by themselves in ICU, before procurement operation. [6] They will assess organ function and determined whether the organ could be transplanted to their recipient.

Final Donor Evaluation

After opening the chest and abdomen, the procurement team will evaluate organs by inspection and palpation. Liver biopsy is performed to rule out fatty liver and malignancies. They also look out for unexpected malignancies in the pleural and abdominal cavities.

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