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.

As Swan–Ganz catheterization or coronary angiography is not performed in procurement hospitals in Japan, heart injury and underlying heart diseases are determined by evaluating hemodynamics and the dose of catecholamine and ADH injection and the wall motion and morphology by echocardiography and electrocardiogram (ECG).

As the detail was shown in the chapter "Management of Extended Criteria Donors," it is very important to evaluate donor heart function after treating diabetes insipidus, adjusting the tone of peripheral vessels and recovering the affinity of β-adrenergic receptor for adrenaline (AD) in the heart by continuously intravenous infusion of ADH [2].

As serum adrenaline reduces the density of β-adrenergic receptor [2], adrenaline should be pused as less as possible. With regard to the dose of catecholamine, less than 15 mcg/kg/min of dopamine (DOA) is acceptable.

The heart with a history of cardiac arrest with CPR can be transplanted if the cardiac function is recovered and the heart has no significant underlying disease [2, 3].

4.2.2 Underlying Heart Disease

The presence of most valvular and congenital cardiac abnormalities is a contraindication to transplantation. Therefore, the underlying heart diseases should be carefully evaluated by the echocardiogram before harvesting.

In some cases, however, "bench" repair can be performed on a donor heart with simple congenital heart disease, such as atrial septal defect, ventricular septal defect, or patent ductus arteriosus, mild or moderate mitral or tricuspid regurgitation, or other mild valvular abnormalities, such as a normally functioning bicuspid aortic valve, if the heart function is acceptable by the echocardiogram.

As the hypertrophic left ventricle (ventricular wall thickness >15 mm) is susceptible to ischemia, the use of the heart should be decided carefully. Transplantation is inadvisable if echocardiographic (>15 mm) and ECG criteria for LVH are present and TIT is longer than 4 h.

4.2.3 Total Ischemic Time

There was reported to be a significant correlation between the TIT and the early posttransplant death after HTx. The acceptable safe preservation time for HTx has been considered to be 4 h. 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 longer than 6 h [4] (Fig. 4.1). However, pediatric hearts with TIT longer than 8 h were reported to be safely transplanted [3].

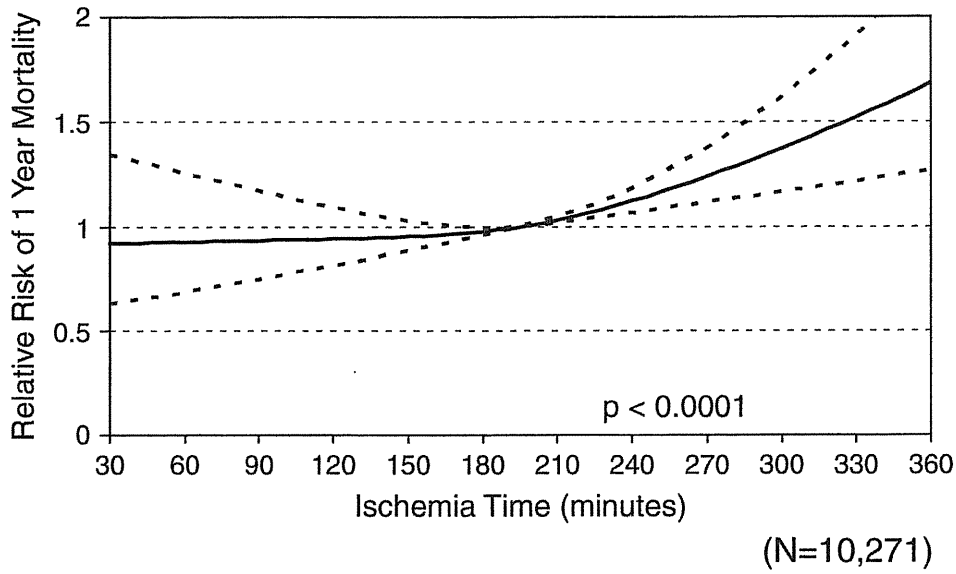

Fig. 4.1 Adult heart transplants (1/2004–6/2009). Relative risk of 1 year mortality with 95 % confidence limits with respect to ischemia time

In order to prolong safe ischemic time, many investigations were done. The author of this chapter reported that the modification of preservation solution and the application of terminal leukocyte-depleted blood cardioplegia enabled 24 h heart transplantation in large animals [5].

4.2.4 Old Age

As older persons have more risks of having damaged myocardium by coronary atherosclerosis, cardiac hypertrophy, and valvular disease than younger ones, older donors were generally considered to be ECD. In fact, mortalities at 1 and 5 years are affected to a great degree by donor age (Fig. 4.2) [4]. Moreover, the relative risk of developing cardiac allograft vasculopathy (CAV) within 8 years is also affected by donor age (Fig. 4.3) [4]. Therefore, in an older donor, coronary angiography and careful echocardiography are essential.

Although coronary arterial revascularization procedures can be performed in the recipient subsequently [6], little has been reported so far on the systematic use of donor hearts with significant coronary artery disease (CAD). In 59 % of those recipients [7], simultaneous bypass grafting of donor vessels was performed backtable at the time of heart transplantation using recipient conduits, mostly saphenous vein, but rarely the left anterior descending artery. Besides the reported favorable intermediate-term results with regard to survival, overall graft patency at 2 years was 82 %. One may consider brain death as a stress test such that if subsequent ECG or echocardiography is favorable, the chance of an older donor having CAD is probably low. This screening strategy without the use of coronary angiography is thought

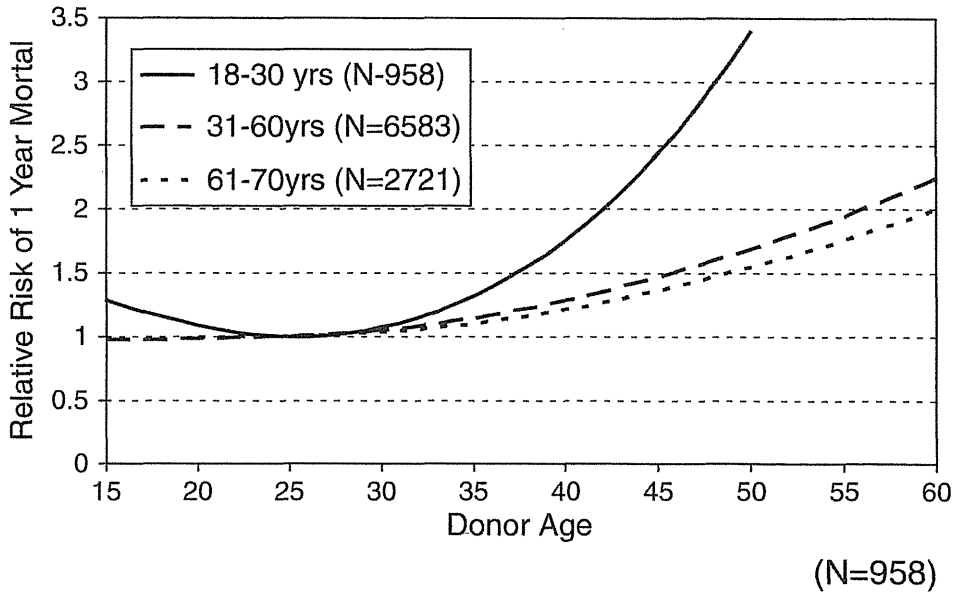

Fig. 4.2 Adult heart transplants (1/2004–6/2009). Relative risk of 1 year mortality with 95 % confidence limits with respect to donor age

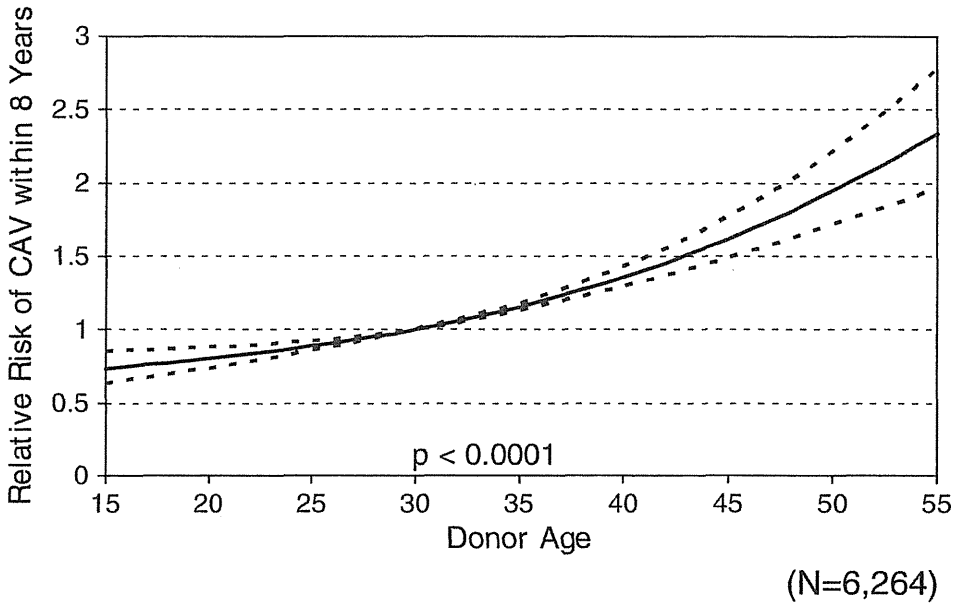

Fig. 4.3 Adult heart transplants (1/1998–6/2002). Relative risk of developing cardiac allograft vasculopathy within 8 years conditional on survival to transplant discharge with respect to donor age

to enable efficient selection of older donors for hearts [7] with the understanding that the additional presence of LVH including ECG changes generally precludes the use of such donor hearts.

4.2.5 Body Size and Gender

Despite an increased risk associated with small donor size relative to the recipient, a normal-sized adult male is considered to be suitable for most recipients. In the specific case of a small donor, size matching with body mass index or height is more

accurate than weight matching, but generally undersized hearts have been used successfully with excellent long-term outcomes. Although recipient obesity is known to have an adverse effect on survival, extended donor weight above 90 kg represents also an independent risk factor for the recipient's late death. A recipient-oriented and much individualized assessment process is very important when accepting organ offers, especially from marginal donors.

Consistent with previous studies, we demonstrate that transplanting a female donor heart into a male recipient is associated with significantly higher risk of PGD [8]. On the other hand, the risk of CAV universally increased with increasing donor age (Fig. 4.3). However, recipients of male allografts had an increased risk of CAV development, regardless of the recipient's gender.

4.2.6 Infection

With regard to bacterial or yeast infection, sepsis and infectious vegetations in the heart are contraindications for the heart donor. It was reported that despite high donor organ contamination (DOC) rates, posttransplant infections due to DOC were rare under the condition of adequate preoperative antibiotic prophylaxis and aseptic organ retrievement [9]. The heart from a donor with positive blood culture without any signs of sepsis can be transplanted, if the bacteria are proved to be Gram-positive cocci and sensitive to common antibiotics.

With regard to virus infection, seropositivity against HIV, HTLV-1, and HBV surface antigen is contraindication for the heart donor. The transplantation of donor hearts with HBV core antibody is associated with a small risk of virus transmission. The use of these hearts has the potential to safely expand the current donor pool [10].

As nearly all recipients of kidney transplants from HCV-positive donors became infected with the virus, many thoracic transplant centers do not accept HCV-positive donors as seroconversion also occurs following HTx of infected organs. The transplantation of HCV-positive grafts to HCV-positive recipients is undesirable for two specific reasons: firstly, there is more than one strain of hepatitis C virus, and, secondly, the prevalence of antiviral antibody does not guarantee immediate immunity.

4.3 Viability Assay

The real goal of donor heart assessment is not to estimate the functional status of the heart just before 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 "brain-death-related stress."

4.3.1 Hemodynamic Assessment Before and After Brain Death

For the hemodynamic assessment as well as for the appropriate management of the donor with regard to the cause of brain death, the clinical course and pathophysiology of brain death, past history of heart disease, treatment of the patients, especially doses of inotropes [DOA, dobutamine (DOB), AD, and noradrenaline (NAD)], ADH, other pituitary hormones, and antibiotics, fluid intake and transfusion, urine output, and 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, are required.

Multicenter analysis (1,719 consecutive primary HTx) reported that donor hearts requiring inotropic support of up to 6 μg/kg/min of DOA or DOB can be accepted as the so-called marginal grafts had acceptable outcome [11]. Even if the donor has a history of cardiopulmonary resuscitation longer than 5 min, the heart might be eligible for transplantation, if hemodynamics, cardiac function, wall motion of left ventricle, and ischemic changes in ECG are restored under optimal donor management [12].

4.3.2 Chest X-Ray

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

4.3.3 Electrocardiogram

As most BD donors have some degree of myocardial insufficiency caused by combined preexisting and brain-death-induced damage, ECG usually shows abnormality in ST segments and QRS wave. Sustained abnormalities in ST segments and QRS and multifocal ventricular ectopic beats under optimal donor management are considerably high risks.

4.3.4 Echocardiography

Echocardiography allows reliable assessment of cardiac valve function and myocardial hypertrophy as well as the verification/exclusion of congenital malformations. As global and even regional ventricular dysfunction may be brain death induced and these wall motion abnormalities may be reversible within hours, serial echocardiography is required before a graft is rejected because of myocardial dysfunction.

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

4.3.5 Coronary Angiography

As asymptomatic coronary atherosclerosis is common even in children and young people, coronary angiography, at least in donors older than 40 years or according to the anamnesis and/or risk factors, should be performed in Western countries. However, up until now there is no evidence which kind or degree of transmitted coronary atherosclerosis really impairs the posttransplant outcome since angiography in donors younger than 60 years has been regarded as unnecessary. Of course, 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 [13], especially if it is treated interventionally during donor angiography or by concomitant bypass surgery during transplantation [14].

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

4.4 Outcome

Outcomes of HTx from ECDs in the world were already presented in each category.

Here, outcomes of HTx from all 200 consecutive brain-dead donors since the Japanese Organ Transplantation Act was issued on October 17, 1997 until November 25, 2012 were reviewed. Seventy donors were male. The mean age of the donors was 45.1 years. The cause of brain death was 119 in cerebral stroke (91 in subarachnoid hemorrhage, 7 in cerebral infarction, and 21 in cerebral bleeding), 37 in head trauma, 27 in asphyxia, and 17 in brain injury after cardiopulmonary resuscitation.

From these BD donors, 146 HTx and 1 heart–lung Tx (HLTx) were performed (heart transplanted rate was 73.5 %). One hundred and eight recipients were male. The age at HTx was 37.5 ± 12.9 years. The underlying disease of HTx was dilated cardiomyopathy in 100 patients, dilated phase hypertrophic cardiomyopathy in 14, restrictive cardiomyopathy in 3, secondary cardiomyopathy in 14, ischemic cardiomyopathy in 14, and congenital heart disease in 1 and that of HLTx was Eisenmenger syndrome with double outlet right ventricle. One hundred and thirty-one patients were implanted left ventricular assist device (LVAD) for bridge to HTx. The waiting time for HTx was 182–2,872 days (a mean of 956 days), and support days with LVAD were 29–1,607 days (a mean of 864 days). With regard to donors for HTx, age at donation was 42.3 ± 12.9 years and 86 were male. The cause of brain death

was 84 in cerebral stroke (67 in subarachnoid hemorrhage, 4 in cerebral infarction, and 13 in cerebral bleeding), 31 in head trauma, 22 in asphyxia, and 10 in brain injury after cardiopulmonary resuscitation. Twenty-seven donors were older than 55 years old. Fifty-seven had a history of cardiopulmonary resuscitation longer than 5 min. Sixty-three required inotropic support of up to 10 μg/kg/min of DOA or DOB or AD/NAD.

None of the 146 heart Tx recipients died of PGD. Patient survival rate after heart Tx was 92.3 % at 10 years.

4.5 Basic Research

4.5.1 Preharvest Management of the Donor

Nilsson et al. [15] showed that glycogen stores in the hearts of brain-dead pigs could be boosted by administration of a glucose–insulin–potassium (GIK) infusion. Wheeldon et al. [16] have shown that replacement of thyroid hormone, adrenal corticosteroids, and insulin significantly improves the state and function of donor organs including the heart. The use of this aggressive treatment of marginal donors can increase the number of acceptable donor organs. A recent consensus meeting has recommended the use of a uniform and aggressive donor management procedure [17].

4.5.2 Interfering with NF-κB Signalling Pathways

Many drugs familiar to clinicians act on the NF-κB pathway. For instance, cyclosporine inhibits the enzymes involved in the early activation of NF-κB, its final cytoplasmic activation step, and its action within the nucleus. Aspirin and sulfasalazine also act at several levels to inhibit NF-κB [18]. Although these simple drugs have additional actions, they, or more selective derivatives, have a real potential to play a crucial role in future treatment of the donor and the donor organs by diminishing the inflammatory response initiated by NF-κB signalling. Sakaguchi et al. showed that gene transfection of the NF-κB decoy attenuated ischemia–reperfusion injury after prolonged heart preservation in a rat model [19].

4.5.3 Preservation Solutions

Preservation solutions are formulated to counteract the effects of perturbation of ion homeostasis. Table 4.2 shows the composition of the commonly used preservation

Table 4.2 Standard preservation solutions

Component	UW	EC	HTK	Celsior	Stanford	STHS
Ionic composition						
Na^+ (mmol/L)	30	10	10	100	25	120
K^+ (mmol/L)	120	115	10	15	30	16
Cl^- (mmol/L)	0	15	50	41.5	30	203
Mg^{2+} (mmol/L)	5	0	4	13	0	16
Ca^{2+} (mmol/L)	0	0	0.015	0.25	0	1.2
pH	7.4	7.45	7.2	7.3	8.1–8.4	7.8
Osm (mOsm/L)	320	406	310	360	440	324
Impermeants						
Lactobionate (mmol/L)	100	0	0	80	0	0
Raffinose (mmol/L)	30	0	0	0	0	0
Hydroxyethyl starch (g/L)	50	0	0	0	0	0
Mannitol (mmol/L)	0	0	30	60	12.5	0
Metabolic agents						
Glucose (mmol/L)	0	198	0	0	50	0
Adenosine (mmol/L)	5	0	0	0	0	0
Glutamate (mmol/L)	0	0	0	20	0	0
Ketoglutarate (mmol/L)	0	0	1	0	0	0
Tryptophan (mmol/L)	0	0	2	0	0	0
Buffers						
Phosphate buffer (mmol/L)	25	100	0	0	0	0
Bicarbonate buffer (mmol/L)	0	10	0	0	25	10
Histidine buffer (mmol/L)	0	0	180	30	0	0
Antioxidants						
Glutathione (mmol/L)	2	0	0	3	0	0
Allopurinol (mmol/L)	1	0	0	0	0	0

UWS University of Wisconsin solution, *EC* Eurocollins solution, *HTK* Brettschneider's histidine–tryptophan–ketoglutarate solution, *STHS* St. Thomas' Hospital solution, *Osm* osmolarity

solutions. "Extracellular" and "intracellular" solutions differ in their concentrations of Na^+ and K^+ ions. "Intracellular" solutions abolish the ionic gradients responsible for passive exchanger activity. However, several studies have shown that high potassium levels in cardioplegic solutions used during standard cardiac surgery have damaging effects on the endothelium.

Impermeants and oncotic agents play a key role in preservation solutions that include them. Molecules that are able to escape from the vascular bed but are unable to enter the cell will counteract intracellular edema and are known as impermeants. Edema places stress upon the cytoskeleton and makes the cell vulnerable to structural failure at reperfusion. Impermeants include raffinose (a trisaccharide) and lactobionate. The omission of lactobionate from University of Wisconsin solution (UWS) results in significant deterioration in stored organs and poor recovery after reperfusion. Celsior solution contains lactobionate on the basis of this observation. Mannitol is an effective oncotic agent that is a potent free radical scavenger. HTK, Celsior, and Stanford solutions contain mannitol.

The inclusion of antioxidants in preservation solutions is a useful protective strategy that can introduce free radical damage. Allopurinol is an inhibitor of the xanthine oxidase enzyme and has been incorporated into UWS. Histidine, a component of Celsior and HTK solutions, reacts with hydrogen peroxide and reduces the formation of hydroxyl radicals produced by the Fenton reaction. UWS and Celsior contain glutathione that may benefit antioxidant capacity; however, with shelf storage glutathione may become oxidized, ineffective, and potentially harmful.

4.5.4 Continuous Perfusion of the Explanted Donor Heart

Continuous perfusion has been employed in donor kidneys since the 1960s. Similar techniques have been employed in experimental heart transplantation. Experimentally, normothermic perfusion has been studied in heart as well as many organs. Normothermic perfusion enables successful transplantation of organs after ischemic damage that would be incompatible with cold preservation at 120 min warm ischemia of the canine kidney, 60 min warm ischemia of the porcine liver, and 65 min warm ischemia in porcine lung transplantation.

To date the only uses of normothermic perfusion in a clinical environment have been in the heart and lung transplantation. Approximately 80 clinical heart transplants have been carried out worldwide using the "Organ Care System" developed by the TransMedics company [20], which has been shown to be safe and effective; it also permits ex vivo donor heart assessment including identification of occult pathologic condition such as donor coronary disease.

4.5.5 Reperfusion Conditions

The ischemic conditions prevailing during the preservation phase of donor heart retrieval predispose the heart to significant injury by white blood cells when the heart receives blood during reperfusion. Therefore, the removal of the white cells responsible for causing this damage may reduce the severity of reperfusion injury. Short ischemic times seem to result in less benefit from leukocyte depletion [21]. Pearl et al. [22] have demonstrated in a clinical trial in heart transplant patients reductions in coronary sinus levels of markers of myocardial cell damage (CK-MB, lactate), mediators of reperfusion injury (thromboxane B2), and a reduction in histological signs of reperfusion injury.

Recent studies of cardiac injury have measured levels of cytokines as an index of leukocyte-induced inflammation within the heart. Several studies carried out on standard cardiac surgery patients have revealed a clinical benefit of leukocyte depletion in terminal blood cardioplegia [23]. A reduced period on ventilators in ICU and reduced length of hospital stay have been reported [23], suggesting a reduced incidence of graft injury, better performance, and reduced damage downstream

from the heart, especially in the lungs. In animal experiments, leukocyte-depleted terminal blood cardioplegia (LDTC) prolonged the safe preservation period up to 24 h [5, 24]. In the clinical setting, we started HTx program using LDTC for reperfusion of the donor heart resulting in successful outcomes [25].

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Chapter 7
ECD for Lung Transplantation

Yasushi Hoshikawa, Yoshinori Okada, Tatsuaki Watanabe, and Takashi Kondo

7.1 Introduction

The short supply of donor organs has been one of the most critical problems in the area of lung transplantation (LTx), and this is especially serious in Japan. One approach to attempt to address this limitation is the use of extended criteria donor (ECD) lungs. The currently accepted criteria for suitable donor lungs (Table 7.1) were instituted in the mid-1980s during the early development of clinical LTx [1]. These criteria were chosen by early transplant physicians and surgeons based on prevailing knowledge of pulmonary physiology, but were not based upon strict scientific evidence [2]. Afterward the ever-increasing number of recipients on waiting lists compelled lung transplant doctors to consider the use of ECD lungs. Liberalization of the donor selection criteria has been gradually accepted worldwide since the mid-1990s [2]. A recent large registry study of more than ten thousand LTxs performed in the USA from 1999 to 2008 revealed that at least one variance from the criteria occurred in more than a half of transplants [3]. Although results have varied among studies, outcomes of LTx using ECD lungs have generally been acceptable [4–18]. However, proper judgment is still difficult if multiple factors are defined extended and if ECD lungs are used in high-risk recipients especially who are rapidly deteriorating on the waiting list. To properly assess and optimize ECD lungs in such circumstances, a new strategy utilizing normothermic ex vivo lung perfusion (EVLP) system has been developed, and the impact of the system on LTx has been explored in several high-flow transplant centers [19, 20].

In Japan, 124 LTxs from deceased donors have been successfully performed as of the end of 2012 [21]. These transplantations achieved a 5-year patient survival rate of 72.0 % and a 10-year survival of 57.3 % [21]. To maximize the lung

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Table 7.1 Current donor lung guidelines

Age <55 years
ABO compatibility
Clear chest radiograph
PaO_2 >300 torr on FiO_2 = 1.0, PEEP 5 cm H_2O
Smoking history <20 pack-years
Absence of chest trauma
No evidence of aspiration/sepsis
No prior cardiothoracic surgery
No organisms on endotracheal aspirate gram stain
No purulent secretions on bronchoscopy

PaO_2 arterial difference in partial pressure of oxygen, FiO_2 fraction of inspired oxygen, *PEEP* positive end-expiratory pressure. Adapted from [23]

utilization rate in multiorgan donors, Japan Organ Transplant Network has operated a system involving the partnership of well-trained transplant consultant doctors and local doctors in assessing donor lungs and providing intensive care to donors since 2002 [22]. These consultant doctors tirelessly performed bronchial toileting for donors and provided advice on respiratory therapy, mechanical ventilation, infection controls, and circulatory management of donors. Since such sustained efforts by the consultant doctors in cooperation with local doctors have been made to effectively utilize ECD lungs, the lungs were used for transplantation in more than 60 % of brain-dead donors [22].

This chapter reviews definition and assessment methods of ECD lungs, studies showing outcomes of LTx using ECDs, and progress in recent research regarding ECD lungs.

7.2 Definition

The extended donor criteria are defined according to the standard criteria [23], which are as follows: age <55 years, ABO compatibility, clear chest radiograph, arterial difference in partial pressure of oxygen (PaO_2) >300 mmHg at 100 % fraction of inspired oxygen (FiO_2) and positive end-expiratory pressure (PEEP) of 5 cm H_2O, a cumulative smoking history of <20 pack-years, absence of chest trauma, no evidence of aspiration/sepsis, no prior cardiothoracic surgery, no organisms on endotracheal aspirate gram stain, and no purulent secretions on bronchoscopy (Table 7.1).

7.3 Viability Assay

To assess the viability of donor lungs, all donor criteria listed on Table 7.1 must be carefully evaluated. The most difficult judgment decisions pertain to the chest radiograph, the bronchoscopic findings, and the intraoperative assessment of the

donor lung by means of hands-on inspection and palpation [24]. These assessments cannot be performed in quantitative form and critically depend on the experience of the retrieval surgeon. We believe that the donor bronchoscopic examination is of most importance and that the findings of copious purulent secretions, which cannot be suctioned clear, and of edematous and/or reddened bronchial mucosa coincident with chest radiograph infiltrates indicating pneumonia represent strong contraindications to the use of that lung. In Japan, a transplant consultant doctors sent from one of seven lung transplant centers assesses bronchoscopic findings and chest radiograph infiltrates at several time points to evaluate if the ECD recovers from pneumonia after suitable management.

In addition to the careful evaluation of all donor criteria, consideration must also be given to the recipient's underlying disease and the severity of illness when using an ECD lung [6]. Usually, care is taken not to place organs from truly extended donors into high-risk recipients especially with pulmonary hypertension or pulmonary fibrosis with secondary pulmonary hypertension, or into other complex cases [24].

Normothermic EVLP is currently being explored to evaluate the viability of ECD lungs. This system allows the lungs after procurement to be perfused under normothermic conditions for approximately 4 h so that the lungs can be optimized as well as continually reassessed. Steen et al. were the first to create a successful EVLP evaluation system for donating after cardiac death [19] by means of Steen solution, a hyperoncotic fluid with 15 % hematocrit [25]. Cypel et al. applied this system to the clinical trial where they evaluated early post-LTx outcomes of ECD lungs which were physiologically stable during 4 h of normothermic EVLP and compared them with those of the conventionally selected lungs [20]. ECD lungs were defined by specific criteria, including pulmonary edema and a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/FiO_2) less than 300 mmHg. Twenty out of 26 ECD lungs were transplanted after EVLP and demonstrated comparable incidence of primary graft dysfunction (PGD), 30-day mortality, bronchial complications, duration of mechanical ventilation, and length of stay in intensive care unit (ICU) and hospital, to 116 conventionally selected lungs. However, the clinical use of normothermic EVLP system for assessing ECD lungs has not yet been spread worldwide since Steen solution is not yet approved by the Food and Drug Administration (FDA) for use in the USA and also has not been approved for use based on pharmaceutical affairs law in most countries including Japan as of the end of 2012.

The use of biomarkers in bronchoalveolar lavage (BAL) fluids also has been explored to assess the viability of ECD lungs. Fisher and associates found that high IL-8 levels in the donor BAL were associated with poor outcomes after LTx, especially with development of severe PGD and with early recipient mortality [26]. Similarly, Kaneda and associates found that IL-6, IL-8, TNF-α, and IL-1β were risk factors for 30-day mortality, while IL-10 and IFN-γ were protective [27]. However, none of such biomarkers have yet been generally utilized in clinical transplantation.

7.4 Outcomes

First, several studies demonstrating the effects of the clinical use of ECDs in LTx are listed in chronological order. Kron et al. reported the efficacy of the use of 10 ECDs in LTx performed at a single center in the USA to expand the donor pool in 1993 [4]. It was the first report showing the possibility to utilize ECD lungs without an increased risk of mortality. Sundaresan et al. reported the first retrospective study comparing 44 ECDs and 89 standard donors (SDs) [5]. No differences were found between recipients of the lungs from ECDs and SDs with respect to duration of postoperative mechanical ventilation, gas exchange, and 30-day mortality. However, cardiopulmonary bypass was required more often in the ECDs than in the SDs. Gabbay et al. published their experiences in Australia with 64 ECDs and 48 SDs [2], showing no significant differences in length of ICU stay, postoperative gas exchange, 30-day mortality, and 1-, 2-, and 3-year survival between recipients of the lungs from ECDs and SDs. They found graft ischemic time was predictive of recipient gas exchange after transplantation. Bhorade et al. performed the retrospective evaluation comparing patients receiving the lungs from 52 ECDs and 61 SDs at a single center in the USA [6]. To define ECDs, the authors were the first to use following criteria: donor ventilator time >5 days and donor use of inhaled drugs (cocaine or marijuana) in addition to the previously accepted standard criteria, such as donor age, tobacco history, and abnormal chest radiograph. There were no differences in operative and early-term complications and hospital survival. Moreover, this is the first report to suggest that no alteration in lung function or 1-year survival occurs with the use of ECDs. Since the authors observed a trend toward slightly decreased pulmonary function at 1 year in single-ECD-lung recipients, they advocated to be cautious against the use of single lungs from ECDs. Pierre et al. reported the retrospective review of 128 consecutive lung or heart-lung transplants performed in Toronto comparing 63 ECDs and 65SDs [24]. This is the first to find a higher early mortality at both 30 (17.5 vs. 6.2 %, $p=0.047$) and 90 days (22.2 % vs. 7.7 %, $p=0.0391$) after transplantation using ECDs. The authors warned against using ECDs in higher-risk recipients, especially ones with pulmonary hypertension (PH), pulmonary fibrosis with PH, and cystic fibrosis with *Burkholderia cepacia* colonization. Oto et al. retrospectively reviewed 173 heart-lung and bilateral single-lung transplant recipients of whom 77 were ever smokers and 64 out of those were current smokers [7]. The authors found more than 20 pack-years was associated with impaired early oxygenation and longer ventilation time and ICU stay, but no differences in 3-year survival and incidence of death due to bronchiolitis obliterans syndrome (BOS) which is one of the major factors affecting long-term survival after LTx. Thabut et al. investigated the effect of donor characteristics on short- and long-term outcomes of a total of 785 adult patients undergoing LTx at seven centers in France [8]. The authors found donor gas exchange before harvest was significantly associated with recipient early gas exchange, duration of mechanical ventilation, and long-term survival. A nonlinear model showed a steep increase in the relative risk of death when donor PaO_2/FiO_2 before harvest was below 350 (hazard ratio 1.43; 95 % confidence interval 1.10–1.85; $p=0.01$). Lardinois et al. evaluated an

impact of ECDs, especially low PaO_2 (<250 torr) before harvesting and multiple extended criteria, on early outcomes and medium-term survival of 148 consecutive recipients at a single center in Switzerland [9]. The authors did not find any difference in early and intermediate results when they analyzed survival among the number of extended criteria. Moreover, this is the first report showing that the use of ECD lungs with a PaO_2 <250 mmHg in selected cases is not associated with an unfavorable outcome. However, the authors cautioned against the use of ECD lungs with an association of PaO_2 <300 mmHg and purulent secretions. Aigner et al. retrospectively analyzed 98 consecutive lung transplantations performed at a single center in Austria during a 2-year period of time with the lungs from 26 ECDs and 72 SDs [10]. The analysis of major outcomes in the short and the medium term did not show any differences between ECDs and SDs. Kawut et al. performed a retrospective cohort study of 51 patients undergoing LTx at a single center in the USA for 2 years [11]. This study included comprehensive data reflecting the condition of the recipient at the time of transplantation. Significant differences between recipients of 27 ECD and 24 SD lungs in several primary endpoints were shown. Recipients of ECD lungs had fewer ICU-free days, a longer time to hospital discharge, and lower spirometry at 1 year than did SD lung recipients. Donor age 55 years or older and smoking were associated with fewer ICU-free days than younger donors and nonsmokers, respectively. No differences were observed in 30-day and longer-term survival between ECDs and SDs. Luckraz et al. analyzed 362 double-lung and heart-lung transplantations performed at a single center in the UK from 50 donors with low levels of PaO_2 (<300 mmHg) and 312 donors with normal PaO_2 [12]. They observed, in the low PaO_2 group, a compromised 30-day mortality rate (22 % vs. 13 %, odds ratio = 1.92) and comparable 1- and 5-year survival when compared with the normal PaO_2 group. Botha et al. retrospectively reviewed 201 patients undergoing lung or heart-lung transplantation at a single center in the UK of whom 83 received ECD lungs [13]. Recipients of ECD lungs had a higher incidence of severe PGD (43.9 % vs. 27.4 %) and 90-day organ-specific (respiratory failure or multiorgan failure with severe PGD) mortality (15.7 % vs. 5.1 %) when compared with recipients of SD lungs. They found significantly high 30-day mortality (17 %) with ECD lungs for bilateral lung transplantation with the use of cardiopulmonary bypass. Moreover, the authors advocated current heavy smoking as a risk factor for impaired oxygenation and longer ICU stay after transplantation. De Perrot et al. compared the outcome of 60 LTxs of the lungs from donors aged 60 years or more with 407 LTxs of the lungs from younger donors, all of which were performed at a single center in Toronto for 11 years [14]. The authors found the increased age is associated with borderline risk for increased 10-year mortality (39 % vs. 16 % in the younger donor group, $p = 0.07$) and increased risk of BOS (65 % vs. 34 % in the younger donor group, $p = 0.01$). Meers et al. analyzed 50 LTxs with the lungs from 27 ECDs and 23 SDs performed at a single center in Belgium and observed a negative impact of ECDs in terms of ICU stay and the PGD rate [15]. The study of Berman et al. [16] was based on smoking donors (n = 184) and their impact on LTx performed at a single center in the UK. Over a period of 13 years, 454 patients were included. The authors found a significant association between smoking history and

lower 3-month survival (21 % vs. 13 % in the nonsmoking donor group, $n=240$, odds ratio 1.9, $p=0.04$) and also ICU stay for >2 days. No differences were observed in long-term survival and infection between recipients of the lungs from smoking and nonsmoking donors. Reyes et al. utilized multivariable survival methods to determine several donor factors, adjusted for recipient risk factors on 10,333 LTxs performed during a 10-year period of time in the USA [3]. Increasing number of variances was not associated with worse survival after LTx. Of donor guideline variables, a smoking history of greater than 20 pack-years appeared to be a small but statistically significant risk factor for mortality. Mortality did not significantly increase despite the use of donor lungs with an abnormal chest radiograph, age greater than 55 years, or a lower donor PaO_2 (as low as 230 mmHg). Recently, Zafar et al. retrospectively analyzed 12,045 LTxs performed over a 9-year period of time to assess the effect of donor PaO_2 at the time of procurement on graft survival [17]. Kaplan-Meier survival analysis on LTxs from 12,045 donors who had a PaO_2 of greater than 300 mmHg ($n=9,593$), of 201 to 300 ($n=582$), and of less than 200 ($n=1,830$) showed no difference in graft survival, irrespective of whether recipients had a single or double LTx. A Cox multivariable analysis of 21 donor characteristics also demonstrated that donor PaO_2 had no association with graft survival [17]. The study limitation is they did not look at the short-term or the acute events, such as development of PGD, sepsis, and 30-day mortality in these patients. Recently, Bonser et al. [18] retrospectively analyzed 1,295 LTxs performed during a 12-year period of time in the UK to assess the impact of donor smoking history on recipient early outcomes and survival. In this study, the authors estimated the effects of non-acceptance of the lungs from donors with positive smoking histories. This study showed increased 3-year mortality after adjustment for other independent factors such as recipient's age, cytomegalovirus mismatch, and increasing ischemic time (67.2 % vs. 55.7 %, $p=0.0002$, adjusted hazard ratio 1.36, 1.11–1.67) and an increased incidence of BOS associated with 510 smoking donors compared with 712 nonsmoking donors. Furthermore, recipients of the lungs from smoking donors were likely to spend longer in ICU and hospital and could derive less functional benefit from transplantation than recipients of the lungs from donors with negative smoking histories. The stratified Cox regression model revealed recipients receiving the lungs from donors with positive smoking histories had a significantly lower unadjusted hazard of death after registration than did those remaining on the list for a potential transplant from a donor with negative smoking history (HR 0.79, 95 % CI 0.70–0.91; $p=0.0004$).

In summary, although results have varied, outcomes of LTx using ECD lungs have generally been acceptable. Next, considerations regarding each extended criteria (age, P/F ratio, and smoking history) are listed below.

7.4.1 Age

Although the current guidelines for upper age limit suggest 55 years as maximum age, small-size studies with some dozens of donors have not shown a survival

disadvantage with the use of older donors [11, 28, 29]. A larger study with hundreds of LTxs has shown that increased age (of 60 years or more) is associated with borderline risk for increased 5-year mortality, increased 10-year mortality, and increased risk of BOS [14]. A recent larger registry study with more than ten thousand LTxs has demonstrated no significant increase in mortality despite the use of donor lungs with an age greater than 55 years [3].

7.4.2 Low Ratio of Pulmonary Arterial Oxygen to Fraction of Inspired Oxygen (P/F Ratio)

Although small studies demonstrated an impact with the use of donors presenting low P/F ratio on 30-day mortality (P/F ratio <300) [12] and long-term mortality (P/F ratio <350) [8], recent larger registry studies have shown no significant increase in long-term mortality despite the use of donor lungs with a lower P/F ratio [3, 17]. In the future more and more centers will utilize EVLP to assess the viability of borderline grafts with P/F ratio of 300 mmHg or lower.

7.4.3 Smoking History

Although no study has evaluated the number of pack-years of smoking history that would preclude the lungs from being transplanted, a retrospective study by Oto et al. showed more than 20 pack-years was associated with impaired early oxygenation and longer ventilation time and ICU stay, but no differences in 3-year survival and incidence of death due to BOS [7]. The study of Berman demonstrated a significant association between smoking history and lower 3-month survival and longer ICU stay, but no differences in long-term survival and infection [16]. Recent larger studies have shown increased long-term mortality (3, 18) and an increased incidence of BOS associated with smoking donors. It is of interest that a study by Bonser revealed recipients receiving the lungs from donors with positive smoking histories had a significantly lower hazard of death after registration than did those remaining on the list for a potential transplant from a donor with negative smoking history [18].

7.5 Research

Recently, approaches for an effective reconditioning of ECD lungs by means of EVLP system have been explored. Several studies have demonstrated a high incidence of thrombi in donor lungs which cause rejection of the lungs for LTx or PGD after LTx [30–33]. Motoyama et al. reported the effect of the fibrinolytic agent plasmin administered in an EVLP model of cardiac arrest rats on pulmonary vascular resistance,

dynamic compliance, and lung weight gain [34]. Plasmin administration dissolved thrombi in the rat lungs, resulting in reconditioning of the lungs as assessed by significantly decreased pulmonary vascular resistance, stable dynamic compliance, and less lung weight gain when compared with non-plasmin rats.

Although cold flush and static cold storage is the accepted standard for preservation of donor lungs in clinical transplantation, deterioration of the donated lungs still occurs. Usually, the longer the lung is kept cold and ischemic, the greater the extent of injury. To minimize this cold ischemia injury and to assess and improve ECD lungs, organ care system (OCS), a portable normothermic EVLP system, has been developed [35]. The OCS provides immediate and sustained lung recruitment starting at the donor site and substantially reduces cold ischemic time [35]. An international randomized trial is ongoing in which the impact of portable ex vivo perfusion and ventilation of donor lungs by means of the OCS on post-LTx outcomes as compared to current cold storage technique is evaluated. Interim results from this trial were presented at the International Society for Heart and Lung Transplantation (ISHLT) 33rd Annual Meeting in Montreal (http://www.transmedics.com/wt/page/pr_1366904571). The donor lungs preserved using the OCS had significantly lower incidence of severe PGD after LTx as compared to the lungs that were preserved using cold storage. In addition, other important clinical parameters like in-hospital mortality, six-month survival, rate of lung-related complications, time on mechanical ventilation, and ICU time were better in the OCS group as compared to cold storage.

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