Chapter

Heart Transplantation and Mechanical Circulatory Support in Japan; Past, Current and Future Aspects

Norihide Fukushima

Abstract

The first heart transplantation (HTx) done by Dr. Wada in 1968 misled the general public not to allow to do brain-dead organ transplantation in Japan. It took almost 30 years to issue the Organ Transplantation Act to allow us to perform HTx in Japan. However, this Act required living written consent for brain death and organ donation. Therefore, children younger than 15 years could not donate their organs under brain-dead condition. After 6 years of struggle to revise this Act, the revised Act was issued in 2010 and brain-dead organ donation as well as HTx increased then. But the number in a year has been still extremely less than other developed countries in Japan. Then, we established a special donor management and assessment system to maximize donor organ availability as well as to improve post-transplant outcomes. During these periods, many types of mechanical circulatory supporting (MCS) have been introduced in Japan. Moreover, there have been many developments in immunosuppressive regimens and monitoring to improve outcomes after LVAD implantation and HTx. The chapter will summarize the past, current status, and future aspects of HTx as well as MCS in Japan.

Keywords: heart transplantation, mechanical circulatory support, donor assessment and management, immunosuppressive regimen, organ transplantation network system

1. Introduction

At the beginning of the twenteeth century, when organ transplantation began, the concept of brain death was not widely recognized. Therefore, both the world's first liver transplantation [1] and heart transplantation [2] were performed after cardiac arrest. However, the graft was damaged by ischemia and rejection, and the results were disastrous. On the other hand, the determination of brain death has been discussed since 1957. Then, brain death was proposed as human death, so on June 25, 1968, when the Harvard group announced the definition of brain death, organ transplantation from brain death began in the world.

On August 8 of that year, Japan's first heart transplant was performed at Sapporo Medical University, which caused various controversies. Immediately after the transplant, Professor Juro Wada was hyped up in the mass media for his successful heart transplant. He was started to be accused by the media and public soon after the recipient died 83 days after transplantation. This heart transplant questioned the adequacy of the recipient's indications and the determination of the donor's death. He was indicted in December of the same year but was dismissed after an expert's evaluation was conducted. However, it has caused distrust in transplant medicine based on organ donation after brain death. There were problems with the reaction of the mass media and public opinion, but there were various problems with the Wada heart transplant. It is believed that the fact that these facts were not properly verified has spurred distrust in medical care and has been the reason why organ transplants from brain deaths have become impossible in Japan for many years.

The issues of Dr. Wada's heart transplantation are: (1) whether the recipient was suitable for heart transplantation, (2) whether the donor was truly brain dead, and (3) whether informed consent (IC) had been obtained from the recipient, donor, and their families etc. However, it took more than a decade for the movement to tackle this problem head-on. In 1981, the International Society for Heart Transplantation (ISHT) was established, and in 1982, the Japanese Society for Heart Transplantation was established. Many heart transplants have been performed worldwide, and brain-dead organ transplantation in Japan has come to be actively discussed. In December 1986, the Japan Society for Transplantation published a guideline, "When performing organ transplantation," as a basic provision that should be observed by brain-dead organ transplant recipients in Japan. In October 1987, the Special Committee on Medical Technology and Human Life of the Science Council of Japan announced the "View on Brain Death". In January 1988, the final report of the Japan Medical Association's Bioethics Roundtable was presented and approved by the board of directors, but there were objections from some doctors, and the medical community did not reach a consensus. In 1989, the Japanese Society of Thoracic Surgery established a special committee on organ transplantation to examine problems and solutions in Wada's heart transplantation and published the 1st edition of "Heart and Lung Transplantation - Summary Report on Technical Evaluation and Bioethics" (1991) and the second edition (1992).

As a result of these discussions, it was found that under the current system in Japan, regarding the issue of Wada's heart transplantation (1), to register brain-dead organ transplant patients, the approval of the central indication review committee is required, and strict determination of recipient eligibility is required. This is done so that patients who are not eligible for organ transplantation do not undergo transplant surgery. As for (2), the most stringent legal standards for determining brain death in the world have been established, and brain death is determined by specialists who are neither attending physicians nor transplant doctors. As for (3), IC for recipients and families is maintained at each facility, and IC for donor families belongs to the Japan Organ Transplantation Network, which is independent of donor facilities and transplant facilities, or has received a transplant. The donor coordinator is doing it.

2. Enactment and revision of the "organ transplantation act" in Japan

Since its establishment in 1985, the Legislative Council for Bioethics Research has been researching this issue. In March 1988, when it had reached an extremely

important social stage, the Liberal Democratic Party's Policy Research Committee launched the "Research Committee on Brain Death, Bioethics, and Organ Transplant Issues," based on the belief that it was important for the legislature to deliberate comprehensively and carefully. In 1990, the Ad Hoc Brain Death and Organ Transplant Research Committee was established within the Prime Minister's Office. In January 1992, a report entitled "Important Matters Concerning Brain Death and Organ Transplantation" was submitted, stating that brain death should be medically, socially, and legally defined as human death. Said, "It is not something that cannot be implemented without a law, but it is desirable to develop legislation such as the Organ Transplant Act (provisional name)." It has been submitted. When this law was enacted, the House of Councilors made amendments such as "Brain death is considered human death only in the case of organ donation," and "It is necessary for the person to indicate in writing their intention to accept the determination of brain death." In June 1997, the Organ Transplantation Act was passed.

During this period, the Joint Committee of Transplantation-Related Academic Societies was established to certify transplant facilities and to consider recipients, donor eligibility criteria, and recipient selection criteria. Furthermore, it is necessary to conduct a two-stage review because it is necessary to strictly select recipients, and in addition to the hospital review of transplant applicants, a committee has been set up in the Japanese Circulation Society to review indications for heart transplantation, and it is essential to determine the indications there. The Joint Committee of Transplantation-Related Academic Societies approved the Osaka University-National Cerebral and Cardiovascular Center joint team and Tokyo Women's Medical University as initial heart transplant facilities.

The Organ Transplant Act was enforced on October 16, 2009. At the same time, the Japan Kidney Transplantation Network was reorganized as the Japan Organ Transplantation Network, and registration of applicants for heart, liver, and lung transplants began. Under this organ transplantation law, the donor needed to express his/her intention to donate in writing. In addition, according to civil law, the age at which a will can be made is valid for people aged 15 and over, and people under the age of 15 cannot donate, and heart transplants for younger children cannot be performed.

The first heart transplantation [3] based on the Organ Transplant Act was performed at Osaka University on February 28, 1999, and the second [4] was performed at the National Cerebral and Cardiovascular Center on May 12, 1999. Since then, the number of cases has gradually increased from a few to more than 10 per year, but in 2003, not a single heart transplant was performed. On the other hand, the number of people who wanted a transplant was increasing, and the waiting period had been getting longer. Many adults as well as children went abroad and had a heart transplant in the U.S.A and Germany.

At that time, a movement to revise the law began to be seen in the Diet in 2003, led by Diet member Taro Kono, who had donated his liver to his father. On February 25, 2004, the Bioethics and Organ Transplantation Committee approved that "if the patient's intention is unknown, brain-dead organ donation is possible with the consent of the family." On the other hand, in addition to the Japan Society for Transplantation, various academic societies that are responsible for patients with severe organ failure established the Council of Organ Transplantation-Related Academic Societies as a community in November 2003, and patient groups are also actively involved in organ transplantation. Activities for revision have been

started. As a member of the Future Planning Committee of the Japanese Society for Transplantation, the author of this chapter was going to make petitions to Diet members one by one with members of patients' organizations related to transplantation. We created pamphlets and videos for petitions and distributed them to councilors of transplant-related academic societies.

In March 2005, the investigative committee stated three items as the skeleton of the revised Organ Transplantation Act, such as (1) organ donation is possible with the consent of family members regardless of age if the individual did not express a refusal to donate before death, and (2) if a donation will be expressed in writing before death, he/she can preferentially donate organs to his/her spouse or relatives within the second degree of kinship, and (3) an organ donation column on driver's licenses and insurance cards will be set up. It was decided that the discussion would be entrusted to the "Organ Transplant Study Group" consisting of volunteers from the Liberal Democratic Party and New Komeito. From March to April of the same year, hearings were held with experts from various fields. At that time, there was an opinion that the chairman of the Japan Pediatric Society Yoshikatsu Eto, and the Japanese Nursing Association had not agreed to regard brain death as human death. On April 28 of the same year, "if he/she has not indicated a refusal to donate, he/she can donate organs with the consent of his/her family regardless of age." was added (commonly known as Plan A) [5].

Although the details after that were omitted in the chapter, every country in the world has a shortage of organ donors, and the pros and cons of traveling overseas for transplantation have become a problem. In May 2010, the World Health Organization issued a new guideline on organ transplantation, putting pressure on legislation. However, what moved the members of the Diet the most was the fact that the parents of three boys who died while preparing to receive heart transplants abroad or after they had traveled abroad went to the Diet, saying, "Parents who lose their beloved children no more." I do not want you to make it."

As a result, the Revised Organ Transplant ACT was enacted in July 2009 and enforced in July 2010. With this revision, it is now possible to donate organs with the family's consent if the person's intention is unknown, and it is now possible to donate organs from children under the age of 15 who have been determined to be brain dead. In addition, as a criterion for selecting recipients, if an organ donation is received from a person under the age of 18, priority will be given to applicants who have registered under the age of 18 for heart transplantation. In February 2014, the recommended age for heart transplantation was raised from under 60 to under 65.

3. Development of mechanical circulatory support for advanced heart failure in Japan

Artificial heart development research was carried out in 1957 by Akutsu and Kolff at the Cleveland Clinic [6], and ventricular assist device (VAD) was carried out by Kusserow [7].

Atsumi et al. of the University of Tokyo started research and development of an extracorporeal pulsatile VAD in Japan at about the same time and in 1980 it was clinically applied at Mitsui Memorial Hospital. Subsequently, Takano et al. of the National Cerebral and Cardiovascular Center (NCVC) also developed the other extracorporeal pulsatile Nipro VAD (Nipro Co. Ltd., Osaka, Japan) and it was clinically applied at NCVC in 1982 [8]. Both VADs began clinical trials in 1986 as bridges

to recovery (BTR) for acute heart failure or cardiogenic shock, and both were covered by insurance in 1990. In 1992, when this VAD was applied to a 16-year-old boy with dilated cardiomyopathy, VAD for the purpose of a bridge to a heart transplant (BTT) was not covered by insurance. The patient later traveled to the United States and underwent a heart transplant, who is still alive today. A pulsatile flow implantable VAD, the Novacor (World Heart Corp., Oakland, CA) was the first to be reimbursed for BTT purposes in Japan (2004). It took a long time to get approval after the clinical trial, and it was no longer produced in the United States. In 2006, we withdrew from the Japanese market. However, it must not be forgotten that the fact that the implantable VAD was reimbursed by insurance at this time the home management fee was approved, and although the amount was small, the medical fee of this implantable VAD implantation was approved. It was the cornerstone of the current implantable VAD treatment. Moreover, the first heart transplantation under the Japanese Organ Transplant Act was performed on a 47-year-old man supported by a Novacor VAD for more than 4 months [3]. Meanwhile, another implantable VAD, the HeartMate XVE (Thoratec Corp., Pleasanton, CA) has completed clinical trials but has not been reimbursed. Following the reimbursement of this implantable VAD, the Nipro VAD has also been approved for use for BTT purposes.

Around this time, the mainstream changed from pulsatile flow VAD to non-pulsatile flow VAD in Europe and the United States. and was launched in 2008 and was reimbursed in April 2011 in Japan. As a result, the mainstream of VAD in Japan has become non-pulsatile flow implantable VAD [9]. After that, Jarvik 2000(Jarvik Heart, Inc.; New York, NY), HeartMate-II (Thoratec Corp., Pleasanton, CA), and HVAD (HeartWare Inc., Framingham, MA) were reimbursed one after another. As a result, it can be said that implantable VAD treatment can be performed according to the patient's physique, pathology, etc. After introducing the HeartMate 3 (Thoratec Corp.; Pleasanton, CA) for BTT use, HeartMate 3 became the most popularly used VAD for BTT purposes as well as destination therapy (DT) purposes which were reimbursed by insurance in April 2021.

For children, Nipro VAD, HVAD, or Jarvik 2000 can be fitted depending on their physique. Reimbursed, but currently out of production). In April 2015, Berlin Heart EXCOR VAD (Berlin Heart, The Woodland, TX) was reimbursed by insurance, which can be implanted in infants. The implementation of the revised Organ Transplant Act in 2010 made it possible to donate brain-dead organs from children under 15 years of age [5]. Then infantile heart transplantation has started since 2012 and 27 children supported with EXCOR LVAD and one with Biventricular ECOR VAD had transplantation at the end of 2022.

4. Social and medical system of heart transplant medicine

4.1 Heart transplant facility

Heart transplantation facilities are deliberated by the Council of Heart Transplant/Cardiopulmonary Simultaneous Transplantation Associations, which consists of the Japanese Circulation Society, etc., and the facilities deemed appropriate as heart transplantation facilities are recommended by the Joint Committee of Transplantation Associations and certified. be.

As of the end of 2022, there are 11 certified facilities. Five can perform transplants for all ages: the National Cerebral and Cardiovascular Center, Osaka University, the

University of Tokyo, Tokyo Women's Medical University, and Kyushu University. The other 5 can perform transplants for patients 11 years old and over, Hokkaido University, Tohoku University, Chiba University, Nagoya University, and Saitama Medical University International Medical Center. The last one can perform transplants for children who are listed under the age of 11: National Center for Child Health and Development There are a total of 11 facilities.

4.2 Indications for heart transplantation and registration with the Japan organ transplantation network

With the introduction of β-blockers and ACE inhibitors, the prognosis of severe heart failure has remarkably improved, and the eligibility criteria for heart transplantation have been reexamined. In Japan, the system is such that a patient is registered in the Japan Organ Transplantation Network after it has been approved through a two-step review by the transplant institution's adaptation review committee and the Japanese Circulation Society Heart Transplantation Adaptation Review Subcommittee.

4.2.1 Indications for heart transplantation

Severe heart disease that cannot be expected to save or prolong life with conventional treatment methods such as dilated cardiomyopathy (DCM), dilated phase hypertrophic cardiomyopathy (dHCM), ischemic myocardial disease, restrictive cardiomyopathy, secondary cardiomyopathy (post myocarditis, drug-induced and postpartum), and congenital heart disease that cannot be surgically repaired, etc.

The indicated diseases in Europe and the U.S.A are divided into cardiomyopathy and ischemic heart disease, which is different from cardiomyopathy accounting for more than 90% of registered cases in Japan. According to various statistics, the number of patients eligible for heart transplantation in Japan is estimated to be 228-670 per year, and the prognosis of these patients is poor, with a 1-year survival rate of around 50%.

4.2.2 Eligible conditions for heart transplantation

Eligible conditions include (a) heart failure requiring long-term or repeated hospitalization for incurable terminal conditions; (b) NYHA grade III-IV heart failure that does not improve with conventional therapy including beta-blockers and ACE inhibitors; (c) patients with fatal severe arrhythmia who are ineffective against any existing treatment. The patient should be under the age of 60 at listing.

4.2.3 Exclusion criteria for heart transplantation

(a) Severe disease other than the heart (hepatorenal dysfunction, chronic obstructive pulmonary disease, malignant tumor, severe autoimmune disease, etc.), (b) Active peptic ulcer or infection, severe diabetes, severe obesity, and severe osteoporosis (c) alcoholism, drug addiction, neuropsychiatric disease, and (d) severe pulmonary hypertension (recent pulmonary infarction, severe irreversible pulmonary vascular disease, etc., drug (prostaglandin, nitroprusside)), a pulmonary vascular resistance coefficient of 6 units or more, or a transpulmonary artery pressure gradient of 15 mmHg or more, even if oxygen or nitric oxide is used) are not indicated.

5. Organ transplant network

a. *Role of the Japan Organ Transplant Network (JOT)*

Regarding brain-dead organ donation, a network system that distributes them fairly and equitably is necessary. In response to this, it plays the role of an organ placement agency. More than 30 donor coordinators belong to JOT, and one to several prefectural organ transplant coordinators are appointed in each prefecture to handle donor information from organ donation facilities and identify donor candidates. Explain heart donation to the family and obtain consent for heart donation. Other tasks include updating the registration of transplant applicants, searching for recipients, following up on transplant recipients, establishing hospital systems at organ donation facilities, and raising awareness among the general public.

b. *Renewal of registration for transplant applicants*

Transplant applicants are registered after evaluating the suitability of each organ, but in particular, for the heart, the transplant facility applies for transplant request registration to JOT after the suitability study of the Japanese Circulation Society's transplant suitability review system. In other words, registration is done when the receipt of the transplant applicant registration form and the payment of the transplant applicant registration fee of 30,000 yen are confirmed.

Also, after registration, renewal procedures are required once a year. In other words, once the transplant request registration renewal form has been received and the payment of the renewal fee of 5000 yen has been confirmed, it will be renewed, and you will be a candidate for the next year. If it is not renewed for 2 consecutive years, it will be canceled. In addition, there is a system of exemption from registration fees and renewal fees for households on public assistance or households exempt from residence tax by submitting the prescribed documents.

c. *Selection of recipient*

Recipients are selected according to recipient selection criteria for each organ stipulated by the Ministry of Health, Labor, and Welfare. Heart transplant recipient selection criteria were established when the Organ Transplantation Act was enacted in October 1997, and after several revisions, were finally revised in November 2012.

First, as matching conditions, ABO blood group identity (identical) and compatibility (compatible) are targeted, and matching is given priority over matching. In addition, a weight difference (donor/recipient) of −20 to +30% is desirable, but the actual selection does not exclude cases outside that range and is a case-by-case decision. In adults, transplantation from a 20% smaller female to a larger male has been identified as a risk factor for premature graft failure. On the other hand, in the case of children, even if there is a large weight difference, the decision is made on a case-by-case basis. If the donor's heart is large, the number of days until chest closure and the length of stay in the ICU tends to increase, but it is said that there is no effect on the survival rate.

In addition, a lymphocyte direct cross-match test (direct cross-match) is carried out at the transplant testing center using the donor's T-cell lymphocytes and the recipient's T-cell lymphocytes, which are blood-collected and cryopreserved in advance. The recipients whose test is positive are excluded from the recipient list. In addition, if there is a blood transfusion within the last 4 weeks, it is necessary to conduct a new direct lymphocyte crossover test using fresh blood. If the panel test (PRA) test is negative, the lymphocyte direct crossover test can be omitted, but currently, all cases are not omitted and the lymphocyte direct crossover test is performed.

Since it is desirable that the permissible ischemic time is within 4 hours, transportation means will be arranged with a goal of 2 to 3 hours for transportation from the donor facility to the transplant facility.

The recipient's medical urgency is divided into three, Status 1 is the state of wearing a ventricular assist device, an intra-aortic balloon pumping, and extracorporeal membrane oxygenation, the state of being under mechanical ventilation management, or the state of requirement of intensive care receiving continuous administration of inotropic drugs in the intensive care unit. For registrants under the age of 18, even if they are receiving continuous administration of inotropic drugs but are not in the critical care unit, they will be registered as Status 1 (however, if they reach the age of 18 in this condition, they will be registered as Status 2). Status 3 is a state in which the registrant of Status 1 or 2 is temporarily removed from the list due to an exclusion condition such as an infectious disease. Status 3 returns to the original Status when the exclusion condition is resolved. Regarding age, heart donations from donors under the age of 18 will be given priority over applicants under the age of 18 at the time of enrollment. In addition, heart donations from donors aged 18 and over are given priority to applicants under the age of 60 at the time of registration. If medical urgency, age, and blood type are the same, the order of the list of Status 1 registrants is defined by the Status 1 waiting period and that of Status 2 registrants is defined by the total number of days from the date of registration.

6. Donor evaluation and management to maximizing heart availability

6.1 Medical consultant system

Among brain-dead donors, only 20% meet the standard donor criteria for all medical conditions. Therefore, to solve the shortage of donors, it is important to make it possible to transplant marginal donor organs. In other words, the purpose of donor management is not simply to stabilize the hemodynamics of the donor until the surgical resection, but to enable the donation of as many organs as possible, improve the organ function of the marginal organs, and improve the organ function after transplantation. This allows many transplant recipients to benefit from organ transplantation. At the same time, it fulfills the wishes of donors and their families, who want to donate as many organs as possible. However, if the recipient dies early after the transplant by forcing the transplant, the donor family feels that they have lost their family once again. Do not forget that the donor family will feel guilty if the recipient dies soon after transplantation. In other words, eliminating primary graft failure (PGF) is important not only for the recipient but also for the donor and their family.

In Japan, since November 2002, medical consultants (MCs) have introduced the system [10] and have been conducting meticulous evaluation and management of donors. After the first determination of brain death, the MCs are dispatched to the

donor hospital, evaluate the donor, and manage the donor from the second determination of brain death. Since the basics of donor management are respiratory and circulatory management, donor management is performed by heart and lung transplant doctors, but organ evaluation may be requested by the MC of each organ as necessary. At the beginning of 2002, the number of MCs was small, but now JOT entrusts MCs to 2 persons from each heart transplant facility, 3 persons from each lung transplant facility, and several transplant doctors for other organ transplants.

After obtaining the consent of the donor family to donate brain-dead organs, the MCs received the first call before the first brain-death determination began and arrived at the donor hospital. If the donor's hemodynamics are unstable, JOT coordinators consult with the MCs to stabilize it, and if requested by the donor hospital, MCs attend an apnea test and support hemodynamics management.

6.2 Donor management

6.2.1 Management of hemodynamics

There is no drug therapy that restores the organ viability and function in a short period of time, and it is extremely difficult to restore function after the organ has been removed. Improving organ function and restoring organ function are the mainstays of donor management. Again, why the hemodynamic/respiratory condition is poor should be evaluated first, and the treatment should be determined based on the evaluation results. Drugs that increase peripheral vascular resistance, especially noradrenaline, reduce blood flow in abdominal organs and worsen perfusion of organ preservation solutions, so the dose should be reduced as much as possible. Preservation of cardiac function is achieved by adjusting preload and afterload, administering anti-diuretic hormone (ADH) (details described later), and keeping the dose of catecholamine at the minimum maintenance dose (DOA 10 μg/Kg/min or less as much as possible).

The target values for hemodynamics are (1) systolic blood pressure of 90 mmHg or more, (2) central venous pressure (CVP) of 6–10 mmHg, and (3) hourly urine output of 100 ml/hr. (or 0.5–3 ml/kg/hr).) above, (4) Heart rate 80-120 beats/minute.

6.2.2 ADH replacement therapy

When the ADH blood concentration decreases, (1) diabetes insipidus, (2) a decrease in vascular tone, and (3) a decrease in the affinity of myocardial β-adrenergic receptors, resulting in unstable hemodynamics. Although there are reports that ADH is supplemented only in patients with diabetes insipidus, ADH should be administered even in cases of low urine volume in order to improve (2) and (3). Similar to the administration of ADH after open-heart surgery or in shock during sepsis, the administration of ADH improves hemodynamics, which in turn improves renal function, which often results in an increase in urine output.

Regards to the administration method of ADH, there are reports that it is administered to the bolus by intranasal administration or intramuscular injection, hemodynamics are well stabilized by initial intravenous administration of 0.02 U/Kg (or 1 U) as a bolus followed by continuous intravenous administration (0.01-0.2 U/Kg/hr. or 0.5-1 U/hr). If hemodynamics is stabilized after administration of ADH while maintaining systemic blood pressure of 90 mmHg or more and urine output of approximately 1-2 ml/Kg.hr., r catecholamines are tapered in the order

of noradrenaline and adrenaline. As endogenous and exogenous adrenaline levels decrease, the heart rate stabilizes at around 90-120 beats/minute. If the urine output drops sharply after starting ADH, the dose of ADH is reduced. There are many reports of discontinuing ADH before surgical resection, but discontinuation of ADH may lead to a sudden increase in urine output or decreased adrenaline sensitivity in the myocardium and blood vessels, resulting in intraoperative hemodynamic instability. Therefore, ADH administration is discontinued just before heparinization.

6.2.3 Respiratory management

Acute lung injury (ALI) and adult respiratory distress syndrome (ARDS) occur due to the occurrence of various systemic inflammatory reactions before and after brain death, and the sympathetic nervous system is overexcited (sympathetic/autonomic storm) in 15. -20% of brain-dead persons. In addition, due to the denervation, atelectasis easily develops, and pneumonia is likely to occur unless endotracheal suction is carefully performed. In addition, diabetes insipidus can lead to pulmonary edema when excessive hydration leads to a decrease in serum oncotic pressure.

Ventilator settings were made to maintain partial pressure of arterial oxygen (PaO2) of 100 mmHg or more by setting a low fraction of inspiratory oxygen (FiO2) and positive end-expiratory pressure (PEEP) of 5 cmH_2O or to maintain PaO2 of 70-100 mmHg or more, SaO2 of 95% or more, PaCO2 at 30-35 mmHg and pH of 7.35-7.45 by setting tidal volume of 10-12 ml/Kg and maximum airway pressure of 30 mmHg or less. Keeping oxygen concentration, tidal volume, and PEEP as low as possible reduces the inflammatory response in the lung and is thought to improve lung function after transplantation.

Because airway neural reflexes (cough reflex, etc.) are lost, regular repositioning and airway suctioning are important in preventing pulmonary infections and atelectasis. Atelectasis is especially likely to occur in the back of the body. However, in brain death, the cardiac and vascular reflexes are lost, so postural changes and endotracheal suctioning (fluctuations in airway pressure and blood return to the lungs) can easily cause blood pressure to fluctuate, making airway management difficult. Hemodynamic instability is even more difficult to manage, so replenishing ADH and stabilizing hemodynamics are also important in terms of respiratory management.

If the cough reflex is lost, deep sputum aspiration becomes insufficient, so bronchoscopic tracheal/endobronchial aspiration is important. Taking regular chest X-rays (generally every 6-8 hours), observing the progress of atelectasis and pneumonia, and repeating endotracheal aspiration not only improves the condition of the transplanted lung but also reduces the size of the lung. Increased availability.

6.2.4 Correction of electrolytes, hematocrit, and blood sugar

It is well known that hypernatremia adversely affects liver and pancreatic function. In the heart, Hoefer et al. [11] reported that the 1-year survival rate of heart transplant recipients from donors with Na < 130 mEq/l and ≥ 170 mEq/l was significantly lower than those from donors within the normal range. and normalizing Na is important. Na-free (or low-Na) transfusion is often performed to correct hypernatremia, but this alone is not sufficient, and it is important to achieve natriuresis by correcting ADH. Correct the serum Na level to a target of 135-150 mEq/l.

When diabetes insipidus occurs and the circulating blood volume decreases, a large amount of transfusion is required, the blood is diluted, and hypokalemia and anemia are likely to occur. First, while treating diabetes insipidus with ADH, it is important to periodically measure the serum K level and replenish K through the central route. Correct the serum K value to about 3.8-4.5 mEq/l. If short-term correction is unavoidable, it may be necessary to administer KCl in a double dilution (0.2 mEq/kg/hr) with a syringe, but this should be administered with careful monitoring. Generally, as diabetes insipidus improves, the serum K value often normalizes. Since anemia impairs organ function, blood transfusion should be performed so that the hematocrit is 30% or higher.

When brain death occurs, the adrenaline concentration in the blood increases, and various inflammatory reactions occur, making it easy to develop hyperglycemia. Suspect hyperglycemia if urine output does not optimize even after correcting ADH. Treatment is first with non-glucose transfusions, and if the condition is still not optimized, continuous intravenous administration of insulin (regular insulin 0.5-1.0 IU/hr). Blood glucose is corrected to target 120-180 mg/dl.

6.2.5 Body temperature control

When brain death occurs, body temperature cannot be regulated, so it is easy to fall into hypothermia. This is particularly noticeable after hypothermia of the brain or when a large amount of fluid is infused due to diabetes insipidus. Compensate for 35.5-36.5°C.

6.2.6 Control of infectious diseases

Long-term brain death can easily lead to pneumonia from atelectasis and infections from bedsores and various catheters. Therefore, in addition to endotracheal suctioning, postural changes to prevent bedsores and care for various catheters, wounds, and bedsores are important. If infection is suspected, ask for bacteriological examination (preferably culture) and administer sensitive antibiotics. Cultivation takes time, so smear examination (a Gram stain is sufficient) is helpful. Antibiotics are started 1 hour before leaving the ward to increase blood levels of antibiotics immediately before skin incision for excisional surgery.

As a result of such careful donor evaluation and management, the average number of organs donated from one donor is 5, which is more than in Europe and the United States (average of 3_4 organs). It seems that the wish of the donor family is also fulfilled.

7. Heart procurement surgery

Although it is a system unique to Japan, after each organ procurement team has completed the evaluation of the transplanted organ at the intensive care unit of the donor hospital, the donor hospital administrator/attending physician, operating department nurse, anesthesiologist (respiratory and cardiological management doctor), each organ procurement team, JOT Cos, et al. have gathered together to hold a meeting on organ procurement surgery. After self-introduction, the procedure for procurement of each organ, line of resection (pulmonary artery and vein, aorta, and superior and inferior vena cava), drainage method, dosage and timing of drugs (antibiotics, heparin, and steroid), organ transport method and scheduled hospital

departure time are confirmed. As a result, a very smooth procurement operation is performed. As a result of this meeting, the procurement surgery start time is determined, which in turn determines the recipient's surgery start time. At the same time, we are reaffirming our respect for the donor and her family. A cardiologist assists with cardiorespiratory management during the surgical excision.

In Europe and the United States, surgeons perform surgery in the order of arrival at the donor hospital, but in that case, the heart extraction is often started later, which sometimes makes the donor's hemodynamics unstable and results in giving up heart extraction. In Japan, all procurement teams perform surgery together after arrival. When the surgery start time is decided, consent for organ donation is obtained from the donor's family again, and the donor is transported to the operating room. At this time, it is customary for the entire procurement team to greet the donor and his/her family at the entrance of the operation department to show the utmost respect to the donor and his/her family. After a JOT Co finally confirms that the donor's family has agreed to the donation, all members observe a moment of silence before starting the operation. After all the organs have been removed, the chest and abdomen are closed in the clinically usual way, and the operation is discontinued after a moment of silence. Doctors accustomed to organ donation in Europe and the United States may think that it is not necessary to go that far, but the author thinks that it will continue as a custom that was born from the unique culture of Japan that respects the "heart". As the author mentioned to Co in the U.S.A., Southern California recently observed a moment of silence at the beginning of an operation. When transporting the heart, a cooler box is used to ensure that the heart functions better, and the cooler box is wrapped in a cloth and transported as if it was the donor's remains. This might be not enough to convey our gratitude to the donors and their families who donated their hearts, but we hope to convey our gratitude. Sometimes, for families who want to say goodbye to their hearts in the box for the last time, we arrange a moment of farewell to their hearts just before the heart board an emergency vehicle or helicopter. Because the heart has a short safe tolerance time, it is often airlifted by helicopter or airplane, arriving at the transplant hospital within 3 hours, within 4 hours the donor's heart is beating again, and within 1 hour the heart pulsation becomes stronger and the recipient can be weaned from the heart-lung machine. At that point, in most cases, the donor's family is still staying at the donor hospital, so the recipient Co at the transplant hospital will inform the JOT of the withdrawal from cardiopulmonary bypass so that the information will be available to the donor family. After knowing that the loved one's heart was beating strong in the recipient's body and knowing that the recipient's family was grateful, the donor family made their way home. We believe that it will reduce the grief of the family.

8. Care of heart transplant recipients

In principle, a heart transplant is a brain-dead organ donation, and it is a necessary condition for the recipient to cherish the heart that has been received. Although it depends on the progress after the transplant, the recipient should not forget to convey his/her gratitude to the donor's family with a thank-you letter. In order to take good care of the heart that has been given to the recipient, it is essential to take care of complicated oral treatment, various periodic examinations (including myocardial biopsy), meticulous self-management (consideration of diet and infectious diseases), and smoking cessation. By being grateful to the donor/donor family, the recipient will

be able to thoroughly manage his/herself, and as a result, the recipient will be able to live a long and healthy life.

Young children often do not decide to have a transplant by themselves and are prone to non-compliance and anxiety during puberty, so it is important to provide support that matches their mental development. Transplant patients are susceptible to infectious diseases, so it is important to take preventative measures against infectious diseases. However, if infectious diseases become prevalent at schools, they will be forced to take long-term absences from school, so cooperation with schools is important. As appropriate, we meet with staff at the educational institution (including school nurses, nurses, etc.) to ensure that the child is not excluded from class. The fact that the recipient takes good care of the heart that was given to them and, as a result, lives a long and healthy life, is a great way to show gratitude to the donor and the family, and to be happy for the donor's family as well.

9. Outcome of heart transplantation

9.1 Outline

In February 1999, the first heart transplant was performed by the Organ Transplant Act, but the number of organ donations was small, remaining at around 10 per year. In July 2010, the Revised Organ Transplantation Act was enacted, and with the increase in the number of brain-dead organ donations (**Figure 1**), the number of heart transplants increased, reaching 84 in 2019, and decreased to 54 cases in 2020 and 59 cases in 2021 (**Figure 2**). On the other hand, since April 2011, a

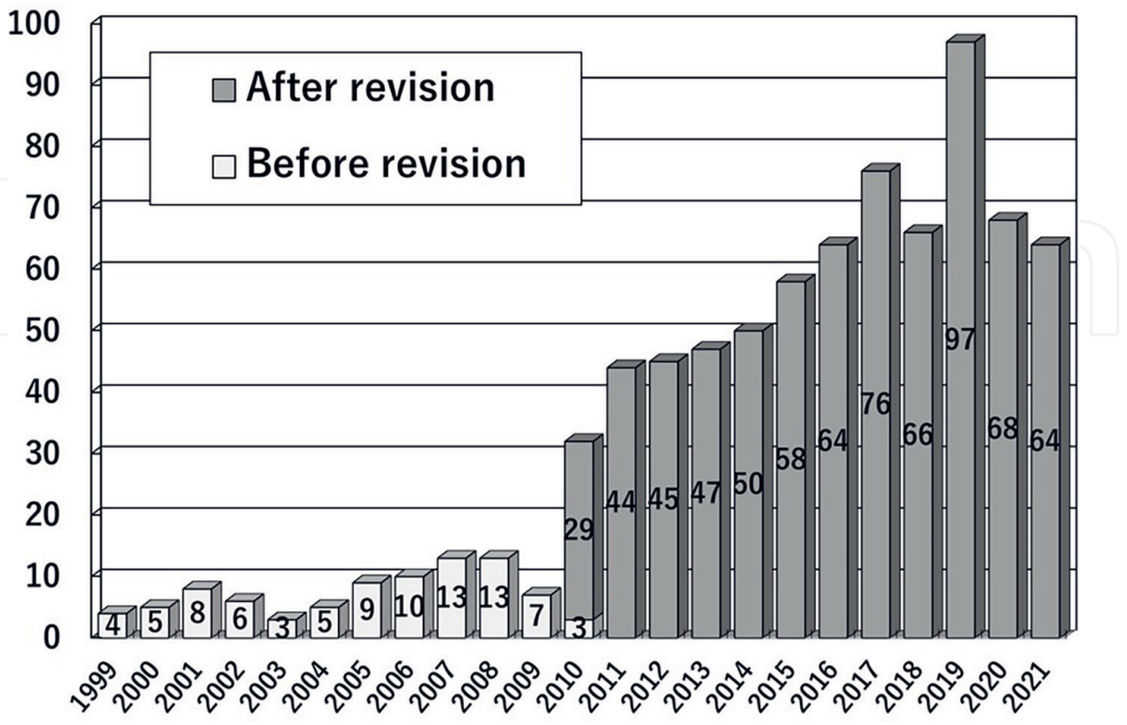

Figure 1.
Brain-dead organ donation performed in Japan by year (up to December 31, 2021) before and after implementation of the revised organ transplant act.

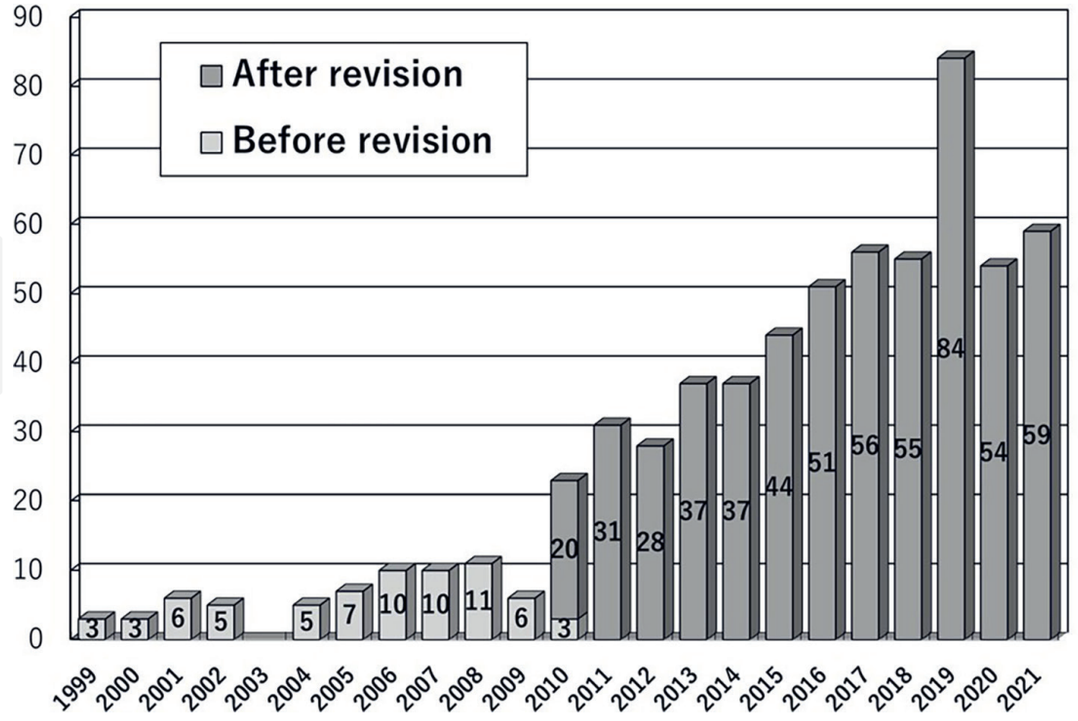

Figure 2.
Heart transplantation performed in Japan by year (up to December 31, 2021) before and after implementation of the revised organ transplant act.

relatively small non-pulsatile implantable VAD that can be treated at home has been reimbursed by insurance as a BTT. Since the increase in the number greatly exceeds the number of transplants, the waiting period for transplantation is increasing. At the end of August 2022, excluding 3 children after the enforcement of the revised Organ Transplantation Act, the cases are limited to Status 1 cases with high medical urgency, regardless of whether they are children or adults. Heart transplant request registration to the JOT began in October 1997, and by the end of June 2022, 2218 cases had been registered, of which 659 had undergone heart transplantation, 71 had undergone overseas transplantation, and 50 had undergone overseas transplantation. 517 cases have died, with cases being deregistered due to worsening conditions.

With the implementation of the revised law, it became possible to donate brain-dead organs from children under the age of 15, and heart transplants from children under the age of 6 began to be performed in 2012 and Berlin Heart EXCOR was reimbursed in 2015. As pediatric brain death organ donations gradually increased, 17 pediatric heart transplants were performed in 2019 and the number of pediatric cases (under 18 years old) reached 60 in total at the end of 2021 (**Figure 3**). The waiting period for transplantation was also shorter than that for adults.

9.2 Changes in the number of heart transplants

9.2.1 Enforcement case

The first heart transplantation based on the Organ Transplant Law was performed in February 1999 [3], and 3 cases were performed in the same year [4]. Since then, the number of heart transplants has increased from around 5 to around 10 per year,

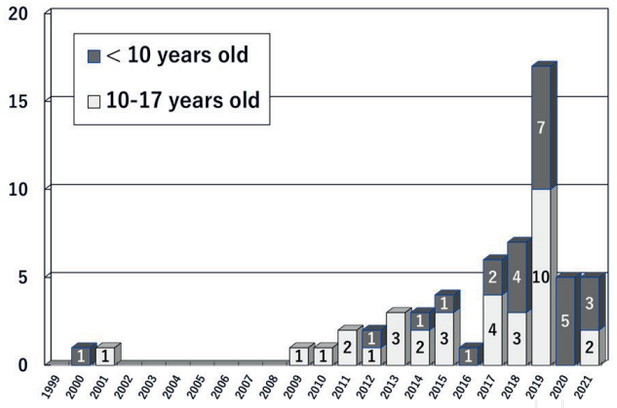

Figure 3.
Pediatric heart transplantation performed in Japan by year (up to December 31, 2021) (by recipient age).

and the amended Organ Transplant Act was enacted in July 2010, resulting in a marked increase in organ donations from brain-deceased patients [9], and 84 heart transplants in 2019. Of these, 17 children were performed, but the number decreased to 59 due to the impact of the new coronavirus infection (**Figure 2**). By December 31, 2021, 625 heart transplants had been performed, including 446 males (71%) and 179 females (29%), with ages ranging from 1 to 70 years (average 39.1). there were. <10 years: 26 cases, 10-19 years: 48 cases, 20-29 years: 88 cases, 30-39 years: 118 cases, 40-49 years: 160 cases, 50-59 years: 133 cases, 60-69 years Age: 51 cases, age 70 or older: 1 case. Currently, patients under 65 years of age are registered for heart transplantation, but due to the long waiting period, there were 4 patients aged 65 years or older (the oldest was 70 years old) who were transplanted.

9.2.2 Medical condition during waiting heart transplantation

Most of the heart transplant cases in Japan are BTT cases, and initially, the Nipro VAD was mainly used. After introducing implantable non-pulsatile VAD in 2011, non-pulsatile flow implantable VADs that can be treated at home, such as HeartMate 3, HVAD, EVAHEART, and Jarvik 2000, are mainly used. Therefore, of the 625 cases at the time of heart transplantation, only 3 were children with status 2, 35 were on inotropic agents, and 587 (94%) were BTT cases (including 46 children). BTT cases now account for 71% (444 cases). On the other hand, the number of pediatric cases transplanted from EXCOR Pediatric gradually increased to 6 cases in 2019 and 3 cases in 2021. The survival rate after installation of a non-pulsatile flow implantable VAD is high (3-year survival rate of 87%), and the number of waiting patients is increasing year by year. Of the 56 patients who underwent heart transplantation in 2015, 18 had been supported with a VAD for 4 to <5 years, 21 for 5 to <6 years, and 8 for 6 years or longer prior to heart transplantation (**Figure 4**).

9.2.3 Cardioplegia and transplant surgery

Modified Collins solution, St. Thomas solution, Bredshneider solution, UW solution, and Celsior solution have been used as cardioplegic solutions, but since 2006, Celsior solution has been used at all facilities other than Kyushu University. Lower-Shamway method, bicaval method, modified-bicaval method, etc. are used as surgical methods. The modified-bicaval method, which was developed in Japan [12], has been used, including in pediatric cases, except where the method is being used.

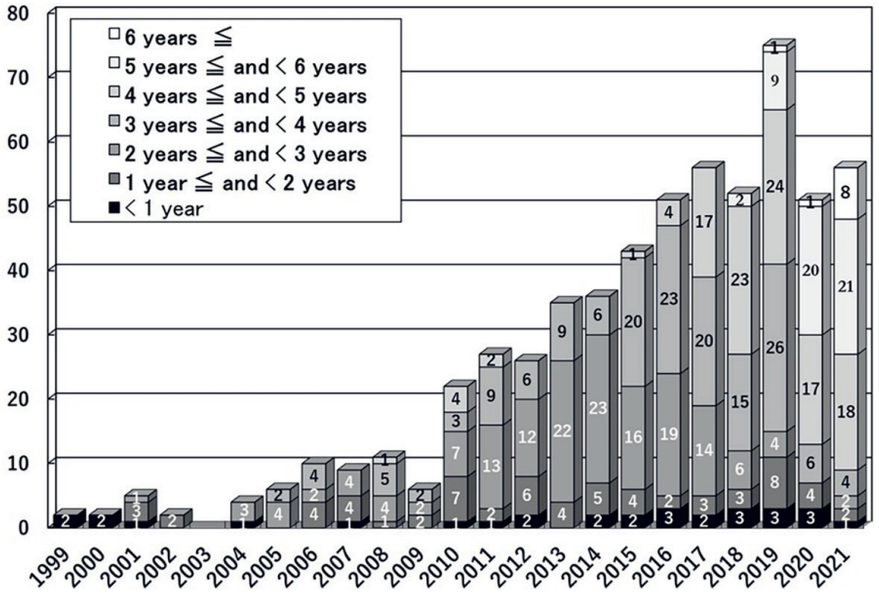

Figure 4.
Heart transplantation in patients supported with left ventricular assist device (LVAD) performed in Japan by year (up to December 31, 2021) (by support year of LVAD).

9.2.4 Immunosuppressive regimen

For induction therapy (including children), anti-CD3 antibody (monoclonal anti-CD3 antibody: OKT3), anti-lymphocyte globulin (ALG), and basiliximab have been used. Although 230 of 625 cases (37%) have been treated with basiliximab, insurance coverage as induction therapy for renal dysfunction cases and pediatric cases described later is awaited.

Initial immunosuppressive therapy was a triple therapy using a calcineurin inhibitor (CNI), cyclosporin (CyA) or tacrolimus (Tac), an antimetabolite [azathioprine or mycophenolate mofetil (MMF)], and a steroid in all patients. Currently, triple therapy with Tac, MMF, and steroids is the mainstream [507 out of 625 patients (81%)]. Everolimus has not been used from the early stage and has been used instead

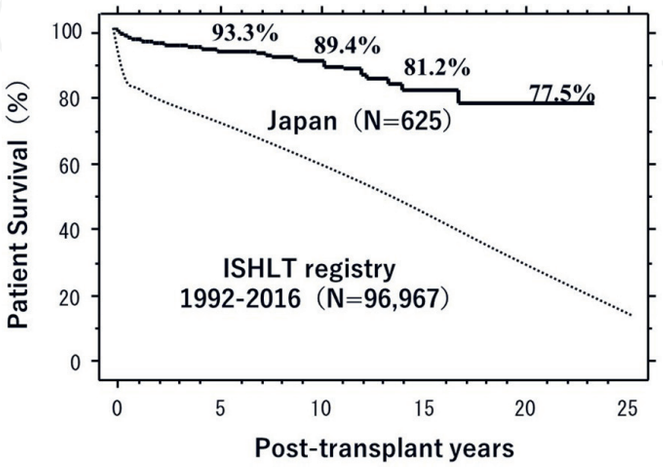

Figure 5.
Cumulative survival rate of heart transplant recipients (up to December 31, 2021). ISHLT, International Society for Heart and Lung Transplantation.

of MMF for post-transplantation coronary artery lesions, renal dysfunction, malignant tumors, and MMF-intolerant patients.

9.2.5 Recipient survival rate and social reintegration

The survival rates of 625 cases at 10, 15, and 20 years after transplantation are 93.5, 89.3, and 77.4%, which are better than those in the International Society for Heart and Lung Transplant (ISHLT) Registry (**Figure 5**). During the follow-up period of up to 23 years, 50 cases died, 13 cases of infectious diseases, 9 cases of malignant tumors (including PTLD and 1 case of brain tumor), 6 cases of multiple organ failure, 3 cases of fatal arrhythmia, and transplant coronary artery. 2 cases of sclerosis, 2 cases of transplant heart failure, 3 cases of sudden death, 1 case of renal failure, 1 case of traffic accident, 1 case of cerebral infarction, 1 case of hypoxemia, 1 case of right heart failure, 1 case of acute pancreatitis, acute respiratory failure 1 case, 1 case of heart failure, and 4 cases of unknown. As of the end of April 2022, 551 (96%) of the 575 survivors are outpatients.

Author details

Norihide Fukushima
Senri Kinran University, Japan

*Address all correspondence to: n-fukushima@cs.kinran.ac.jp

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