# Status on Heart Transplantation in China

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## Introduction

"End-stage heart disease" commonly refers to an irreversible stage of cardiac decompensation caused by a variety of pathologies that cannot be treated using conventional drugs or traditional surgical treatments. The life expectancy of patients with end-stage heart disease ranges from <6 months to 1 year. Therapeutic strategies for end-stage heart disease patients are primarily based on three approaches: Internal medicine therapy, surgical therapy (heart transplantation), and multiple organ protection therapy via the core method of mechanical circulation assistance. Among these approaches, heart transplantation has become recognized as the most effective treatment.

According to a report from the International Society of Heart and Lung Transplantation (ISHLT), the number of registered heart transplantations had reached 116,104 cases worldwide by June 2013. In the past 10 years, between 3500 and 5000 heart transplantations were performed each year. In 2013 specifically, 5036 heart transplantation procedures were performed across 416 heart transplant centers worldwide.[1] The effectiveness of heart transplantation has been quite satisfactory, with survival rates of 84.5% at 1 year, 78.0% at 3 years, 72.2% at 5 years, 66.8% at 7 years, and still 50% at 10 years after transplantation.[1]

Despite the delay in performing heart transplantation surgeries and the special medical environment in China, rapid progress is being made in terms of the quantity and quality of heart transplantations in China as well as in the related ethical considerations. According to a report by the Chinese Organ Transplantation Network in 2014, the number of registered heart transplantations performed in the mainland of China had reached 1291 by June 2014, and 232 of these cases were performed in 2013. However, fewer than five centers were able to perform more than 20 cases/year among 35 heart transplantation centers in China in 2013, and only two centers, Fuwai Hospital in Beijing and Union Hospital in Wuhan, completed more than 40 heart transplantations in 2013.

With improvements in surgical techniques, the development of new immunosuppressive drugs, and advances in perioperative management, the success rate and short to mid-term survival rates of heart transplantation in China have increased gradually. Taking Union Hospital in Wuhan as an example, from September 2008 to December 2014, 203 heart transplantations performed, with postoperative survival rates of 90.79% after 1 year, 86.20% after 3 years, and 91.67% after 5 years. The clinical status of heart transplantation in China is still associated with many challenges, though. For robust and sustainable development of this treatment strategy, several problems need to be solved, such as the optimization of donator–recipient selection, application of hearts from brain dead donors, clinical use of marginal donor hearts, heart transplantation in elderly and pediatric patients, and the development of routine mechanical circulatory

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support (MCS) therapy after heart transplantation that is suitable for the clinical situation in China. In the present review, we specifically discuss these four aspects of heart transplantation in China.

## Heart Transplantation with Donation after Brain Death

The shortage of donor organs is the major limitation for all forms of organ transplantation, for no transplantation can be carried out without a donated organ. In 2006, China initiated a citizen organ donation program with the goal of gradually eliminating its old, and to some extent, inappropriate organ procurement system.[2,3] By the end of 2014, China announced that it had finally achieved the goal of ceasing the use of organs from executed prisoners. This means all heart transplantations in China now rely on donation after brain death (DBD).[4] Hearts obtained via DBD exhibit specific pathophysiological changes; the catecholamine storm after brain death can cause tachycardia and hypertension, increase cardiac output and myocardial oxygen consumption, aggravate potential myocardial ischemia, and increase the incidence of postoperative primary graft failure (PGF).[5] The effects of brain death on donor hearts, the incidence of posttransplantation PGF, the transplant rejection rate, and the patient survival rate are hot areas of research and also controversial issues. The quality of donor hearts obtained through DBD is one of the most important factors that determine the perioperative success rate of heart transplantation and long-term survival of recipients. Therefore, proper assessment and selection of donor hearts are critical. Surgeons must gather as much information regarding donors as possible, such as the results of related laboratory tests, chest X-ray images, electrocardiograms, echocardiograms, and even coronary angiography results, if possible. To adequately assess the quality of DBD hearts, surgeons must consider all factors, including donor age, cause and time of brain death, hemodynamics of the donor, the usage of positive inotropic drugs, heart function, cold ischemia time, as well as characteristics of the recipient. Basically, the following criteria should be followed: (1) Although an upper limit for donor age has not yet been confirmed, if the donor's age is <45 years, the donor heart can endure a longer ischemia time or work well in a recipient presenting with complications or preoperative hemodynamic changes.[6] One research has shown that posttransplantation mortality and the possibility of graft dysfunction are greater with increasing heart donor age.[7] (2) The use of hearts from donors with coronary artery disease should be avoided based on the increased risk of postoperative graft vasculopathy; (3) A donor heart with a bicuspid aortic valve can be used in transplantation, if its cardiac function is normal. A donor heart with correctable mitral and aortic anatomic and hemodynamic abnormalities also can be used for heart transplantation after the abnormalities have been repaired or the abnormal structures replaced.[8,9] (4) Hearts from donors receiving treatment with a high concentration of positive inotropic drugs (dopamine ≥20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or similar doses of other adrenergic drugs) should not be used. (5) Based on safety concerns, it is believed that the donor's body weight should not be <70% of the recipient's body weight; when the donor is a woman, and the recipient is a men, the donor–recipient weight ratio should not be <90%.[10] However, recent studies and our own clinical experiences have shown that severely unmatched donor-recipient weight (between same-gender donors and recipients) does not affect outcomes after heart transplantation.[11,12] (6) No consensus has been reached regarding a cold ischemia time limit, but it is widely accepted that a longer cold ischemia time is associated with a higher incidence of graft failure or reduced long-term survival after heart transplantation.[13,14] The widely accepted standard for cold ischemia time is <4 h, but for hearts from young donors with normal cardiac function and no usage of positive inotropic drugs, the cold ischemia time can be prolonged beyond 4 h.[15] (7) Hearts from donors with infection or usage of some drugs can still be considered for use if the cardiac function remains good.

Not all DBD hearts are suitable for transplantation, and thus, the early identification of potential DBD donors and the application of effective interventions are vital. Interventions use to protect the function of donor hearts are the key to ensure the success of DBD heart transplantation, and such interventions include temperature management, hemodynamic management, ventilator management, and management of inflammation.[16]

## Clinical Usage of "Marginal Donor Hearts"

With the severe shortage of donor organs of all types, including hearts, more than 30% of patients die while on the waiting list for transplantation.[17] The "general standards" for donor hearts exclude some potential donors and thus worsen the imbalance of the donor–recipient ratio. The so-called "marginal donor heart" is a concept relative to the conventional standard donor heart.[17,18] It usually refers to donor hearts with characteristics extending beyond the standard criteria, such as donor age >50 years, cold ischemia time >6 h, donor/recipient weight ratio <0.7, unmatched donor/recipient ABO blood type, potential drug usage by donor; donor infection; donor with history of cardiopulmonary resuscitation; and structural abnormalities or mild to moderate coronary artery lesions in donor heart.[19,20] Along with technological developments in the areas of myocardial protection, immunosuppressive drugs, surgical techniques, perioperative management, and MCS, the criteria applied to "marginal donor hearts" continue to gradually expand as does the clinical application of these hearts.

Although satisfactory therapeutic effects have been observed in recipients of "marginal donor hearts,"[21] caution should still be used in the application of these hearts based on the lack of established standards for this novel concept. To ensure the rationality, safety, and effectiveness of their

use, "marginal donor hearts" should be transplanted into "marginal recipients," such as those of advanced age or with critical complications.[18] Appropriate countermeasures also should be taken simultaneously, including: Prolonging the assisted circulation time after transplantation of a donor heart exposed to a long cold ischemia time and providing effective anti-infection therapy after transplantation of a donor heart from an infected donor.[22] In addition, donor hearts obtained under the expanded criteria should be applied carefully in recipients with preoperative pulmonary hypertension. With the development of relevant techniques and the accumulation of clinical experience, transplantation of "marginal donor hearts" may become standard routine in the future, given that it affords more efficient use of donor hearts and improves the imbalance between the numbers of donors and recipients. The patients most likely affected are the so-called "marginal recipients" who are unlikely to receive a transplant under the use of present donor heart standards.

## Heart Transplantation for Elderly and Pediatric Patients

To maximize the utilization efficiency of donor hearts and the survival rates among elderly and pediatric heart transplant recipients, surgeons should strictly select appropriate recipients. Age is one of the most important selection criteria. According to the ISHLT report of 2014, recipients of heart transplants have mainly ranged in age from 40 to 59 years old, while the proportions of elderly and pediatric patients are increasing each year.[1] An age older than 60 years was once a contraindication for heart transplantation among end-stage heart failure patients due to their particular physiology and immunity status as well as the shortage of donor hearts. Advances in myocardial preservation and comprehensive treatment for end-stage heart failure as well as the extension of life expectancy in China have helped to alter the traditional contraindications for heart transplantation in recent years; older recipient age is no longer an absolute contraindication for heart transplantation. With comprehensive pre-operative examination and treatments to improve the function of a patient's heart, lungs, and other major organs, surgeons can exclude potential systemic disease in older recipients and still consider them the suitable candidates for transplantation. Studies have shown that there are no significant differences in long-term survival rates postheart transplantation between recipients older than 65 years and younger recipients.[23] In 2014, our department successfully transplanted a heart into a 76-year-old recipient with satisfactory outcomes, and to the best of our knowledge, this patient is the world's oldest heart transplant recipient.

Heart transplantations for pediatric recipients younger than 18 years old, especially those <1 year old, are extremely rare, with the number of operations accounting for <10% of those performed for adults.[24-26] By June 30, 2012, 11,134 pediatric heart transplantations had been completed worldwide.[1] The annual number of these operations worldwide has reached 500 per year, mainly concentrated in Europe and North America. The long-term survival rate of pediatric heart transplant recipients is quite satisfactory and is closely related to the recipient's status before transplantation. According to the latest report from ISHLT, the median survival time is 19.7 years for infant heart transplant recipients, 16.8 years for 1–5-year-old recipients, 14.5 years for 6–10-year-old recipients, and 12.4 years for 11–17-year-old recipients.[1] Dilated cardiomyopathy is still the main indication for pediatric heart transplantation. However, the proportion of patients with complex congenital heart disease as the primary etiology gradually increases with the increased age of recipients.[24-26] A total of 19 pediatric heart transplantations have been performed at the Union Hospital of Wuhan since September 2008, with an average age of recipients of 12.6 years (minimum age of 3 months). The etiologies of these recipients included 14 cases of cardiomyopathy, 3 of congenital heart disease, and 2 of a cardiac tumor. The perioperative success rate was 100%, and short-term follow-up of these patients has shown promising results (3-year survival rate of 94.7%).

## Mechanical Circulatory Support for Heart Transplantation Patients

Factors such as the shortage of donor hearts, the use of "marginal donor hearts," heart transplantation for elderly and pediatric recipients, and refractory heart failure require the clinical application of auxiliary mechanical circulation treatments. MCS can be subdivided into short-term MCS and long-term MCS. Short-term circulation support methods, such as the use of an intra-aortic balloon pump (IABP), extracorporeal membrane oxygenation (ECMO), and a centrifugal pump, among other strategies, can help transplanted hearts to overcome the acute and reversible lesion phase or low cardiac output syndrome early after the operation. These methods also can be applied as a bridge to heart transplantation. On the other hand, long-term support methods, such as the use of a left ventricular assist device (LVAD), double ventricular assist device, and total artificial heart, are suitable for patients who will wait for a very long time for a donor heart. These methods also can be used as ultimate alternative treatments for patients who are not suitable for heart transplantation based on the characteristics of their end-stage heart failure. Among the long-term support methods, use of the LVAD is most widely applied and best accepted in China.[27-29] It is clear that these mechanical circulation assist devices have specific effects in acute/chronic heart failure patients who are not eligible for internal medicine treatment and, therefore, can save these dying patients. To choose the proper type and timing of a mechanical circulation assist device, surgeons should comprehensively consider factors such as the recipient's age and heart function, presence of concomitant diseases, effectiveness of prior heart failure treatments, the recipient's status on the transplantation waiting list, and the possible recovery effects. For patients with illness believed to be treatable, surgeons can recommend short-term MCS, such

as IABP, ECMO, or ventricular assist device (VAD) use with percutaneous intubation or open chest intubation. If the patient's condition does not readily improve or the patient has indications for heart transplantation, it is reasonable to use embedded VADs or a totally artificial heart. Due to the limitations of economic conditions in China, high-cost VADs have not been widely applied, whereas the relatively inexpensive IABP and ECMO methods have become the preferable MCS methods for their specific curative effect and simple implantation process. Union Hospital in Wuhan has treated three patients with MCS by IABP or ECMO as a heart transplantation bridge for recipients preoperatively, and all cases survived for transplantation. In total, 17 cases were treated with posttransplantation MCS at the Union Hospital in Wuhan, including 8 cases of IABP, 5 cases of ECMO, and 4 cases of IABP combined with ECMO. Thirteen of these patients survived and were discharged from the hospital, whereas four cases died. The IABP method is the optimal choice for patients with left heart failure, and its use time can be properly extended according to each patient's situation. However, the ECMO technique has a better effect for patients with right heart failure or more whole heart failure. Also, ECMO can be used in combination with IABP. Therefore, the reasonable selection between IABP and ECMO for MCS can significantly influence the outcomes of heart transplantations based on their good therapeutic effects on perioperative cardiorespiratory failure.

In conclusion, over the past 5 years, nearly 200 heart transplantation procedures were completed per year at centers in the mainland of China. The overall perioperative success rates and mid-term survival rates have been satisfactory. Thus, many patients with end-stage heart disease were saved using this surgical treatment approach. With changes in the legislation regarding organ transplantation and the abandoning of organ harvesting from executed prisoners, China began to establish a new and more humanistic organ donation–transplantation system based on the usage of organs donated via DBD. These changes may bring some temporary difficulties for heart transplantation in China, but they surely represent a transition to an appropriate and healthy system. With the acceptance of DBD donation among the general public, the establishment and improvement of the donated organ sharing system as well as developments in the diagnosis and treatment of end-stage heart failure, heart transplantation in China offers a promising option for huge numbers of patients and also surgeons. However, the current situation calls for much more effort to be made toward future improvements, such as further establishing the system for the Chinese network of organ sharing, optimizing the management of donor hearts obtained via DBD, reducing the incidence of postoperative complications after heart transplantation, and improving long-term survival rates among all recipients.


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## Conflicts of interest

There are no conflicts of interest.

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