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History of Heart Transplant: Setting the Stage

REVIEW

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ABSTRACT

Heart transplantation is a marvel of modern medicine for patients with end-stage heart failure. Decades of research and surgical innovation have overcome challenges in immunology, organ preservation, and patient care. From the earliest heart transplants on canines and primates, the field evolved through immunosuppressive therapies, development of the bioptome for endomyocardial biopsy and, recently, the use of cell free DNA and molecular microscopy for assessing rejection. Newer developments in organ preservation systems and transport systems bring remarkable increases in the availability of donors.

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INTRODUCTION

Heart transplantation is a marvel of modern medicine. It prolongs survival and provides a better quality of life in patients with end-stage heart failure. The result of decades of research and surgical innovation, it has overcome many challenges in immunology, organ preservation, and patient care.

The early days of heart transplantation started with experiments in canines and primates. The field then evolved through many milestones, including immunosuppressive therapies, development of the bioptome for endomyocardial biopsy, and more recently use of cell free DNA and molecular microscopy in the assessment of rejection. Newer developments in organ preservation systems and organ transport systems such as Paragonix and Transmedics OCS have brought remarkable increases in the availability of donors (Figure 1).[1-38]

PRECLINICAL RESEARCH

The path to the first human heart transplantation began with mammalian transplants. Much of the early research was accomplished in dogs,[39-45] which helped develop surgical techniques and addressed immunological challenges associated with heart transplantation. These efforts laid the foundation for the future success of human heart transplantation. Insights also were gained from primate research involving other organs.[46]

Dr. James Hardy performed a transplant of a chimpanzee heart to a human recipient on January 4, 1964. Once implanted, the heart was defibrillated and restored a heartbeat for a couple of hours. Although the chimpanzee heart was too small to support human circulation, it was a tremendous milestone in proving the viability of human heart transplantation.[46,47] Hardy's work underscored the importance of developing techniques for vascular anastomosis, intraoperative management, and immunosuppression. It yielded essential insights into the mechanical obstacles of heart transplantation—for example, response of a transplanted heart to the circulatory needs of its recipient. It also suggested strategies for alleviating circulatory mismatch stemming from size discrepancies between the donor and recipient.[48]

FIRST HUMAN HEART TRANSPLANTS

The first human-to-human heart transplant was performed by Dr. Christiaan Barnard on December 3, 1967, in Cape Town, South Africa.[49,50] This groundbreaking surgery demonstrated the technical and logistical feasibility of transplanting a human heart, inspiring a wave of innovation and experimentation worldwide.

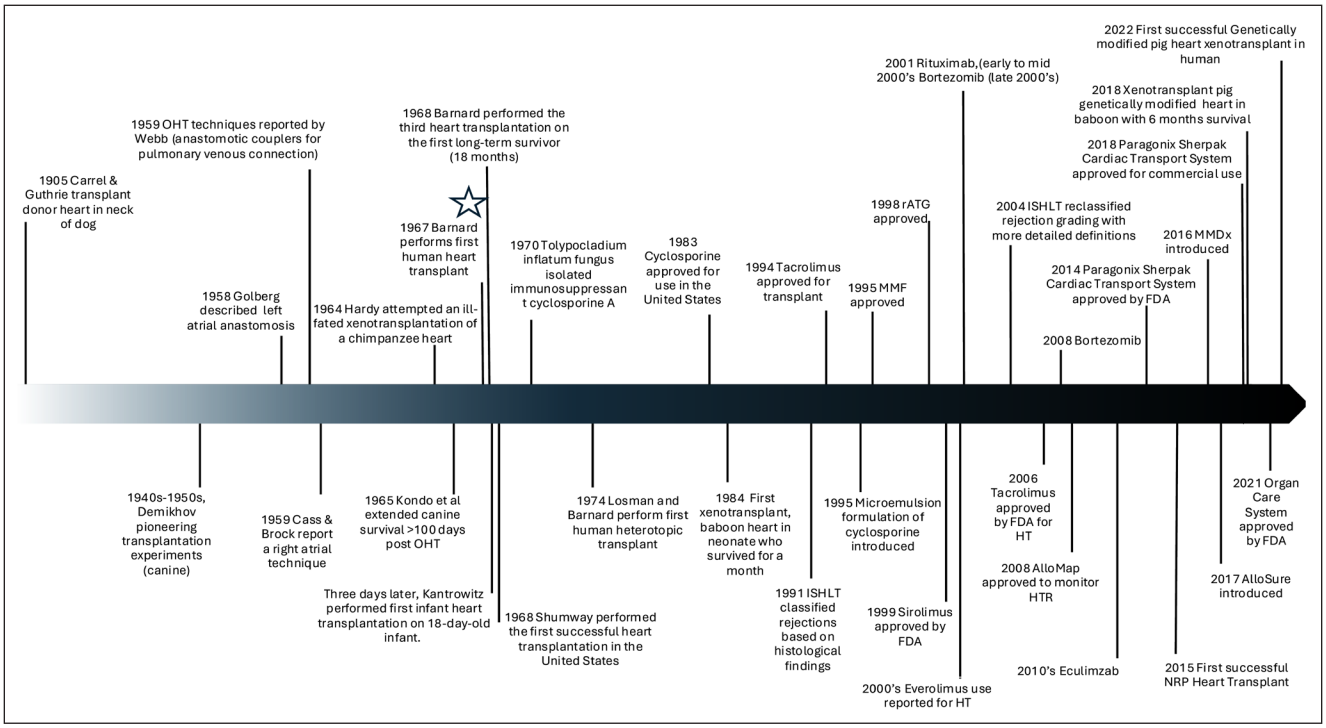

Figure 1 Timeline of the history of transplantation.

The donor was a 25-year-old woman who had suffered a fatal brain injury in a motor vehicle accident; the recipient was a 53-year-old man with end-stage heart failure. During the operation, Barnard also performed the first deceased circulatory heart donation by waiting until the donor heart stopped beating with no electrical activity. Upon sternotomy, the donor was connected to a heart-lung machine that continued to perfuse the donor heart with cold oxygenated blood while being moved to the recipient operating room. The surgery, which lasted nearly 5 hours, was a technical success, with the donor heart functioning effectively in the recipient.[49]

To prevent rejection, the recipient was given a combination of local irradiation, azathioprine, prednisone, and actinomycin. Nevertheless, the patient developed severe pneumonia and septicemia, expiring 18 days after transplantation.[51] The operation was hailed as a major achievement despite the limited survival time because it demonstrated that human heart transplantation was possible, opening the door to further advancements.[49]

Three days later, Adrian Kantrowitz performed the world's first infant heart transplantation using the heart of an anencephalic infant in an 18-day-old infant with Ebstein anomaly. The recipient died of acute cardiac failure shortly after the transplantation.[52]

Barnard performed the third heart transplantation a few days later, resulting in the first long-term survivor (18 months). Norman Shumway performed the fourth heart transplantation 4 days later, which is generally credited to be the first successful adult heart transplant in the United States. The recipient survived 18 days, identical to Barnard's first transplant patient.[52]

The initial success in heart transplantation sparked global interest and debate, raising critical ethical questions about organ donation, the definition of brain death, and the rights of donors and recipients. Within months, several transplant programs were established worldwide. While many of these early efforts resulted in high mortality rates, they provided invaluable data that informed the development of surgical and medical protocols critical to the field's progress.

IMMUNOSUPPRESSION DEVELOPMENT

Although the surgical challenges of heart transplantation were resolved in the 1960s, interest in the procedure quickly decreased because recipients had a high rate of early rejection and subsequent mortality. In the very early era (1968-1970), a total of 166 heart transplants were performed by 64 surgical teams in 24 countries. One-year survival was 18%, and 2-year survival was 11%.[51] The American Medical Association recommended a moratorium on heart transplantation in 1970 as a result of poor outcomes,[51,53] which led to most major medical centers abandoning transplantation.

The immune system, specifically the adaptive immune system comprised of T and B lymphocytes, posed the most significant challenge to successful heart transplantation. Lack of adequate immunosuppression led to allorecognition and, subsequently, organ rejection. As a few centers persisted, they gradually refined immunosuppression protocols.[52] The initial immunosuppressive regimens largely consisted of a combination of azathioprine, corticosteroids, and often systemic lympho-reductive radiation therapy, which could have dose-limiting side effects.

The discovery of cyclosporine in the 1970s revolutionized transplant medicine. It was derived from the soil fungus Tolypocladium inflatum and it selectively inhibited T-cell activation, which is a critical step in the immune response to foreign tissue.[54,55] This targeted mechanism allowed for more effective prevention of rejection with fewer systemic side effects compared to earlier treatments. Clinical trials in the late 1970s and early 1980s demonstrated cyclosporine's efficacy in reducing episodes of acute rejection, improving graft survival. In 1983, the US Food and Drug Administration (FDA) approved cyclosporine for clinical use, marking a new era in transplantation. One-year survival rates for heart transplant recipients improved dramatically, from less than 50% to over 80%.[56] The introduction of cyclosporine also allowed for the broader adoption of heart transplantation as a standard treatment for end-stage heart failure.

During the second half of the 1990s, the advent of the microemulsion formulation of cyclosporine was introduced and gave superior and predictable drug absorption profiles.[57,58] Since then, another calcineurin inhibitor, Tacrolimus, has been developed and has proven to improve survival and decrease rejection compared to cyclosporine in clinical trials.[59-61] T-cell selective therapies such as Thymoglobulin, an anti-human thymocyte immunoglobulin (ATG) formulation made of purified polyclonal antibodies, have been adopted in transplant medication regimens in the immediate post-transplant period and also to treat severe acute rejection.

The primary mechanism of ATGs involves T lymphocyte depletion and is associated with an increased risk of infection, malignancy, and cytokine release syndrome, which has led to a shift toward less lymphocyte-depleting approaches. With the advent of monoclonal antibodies, basiliximab (monoclonal antibody against IL-2 receptor of T cell) has become increasingly favored for induction therapy over Thymoglobulin, except in patients with higher rejection risk. Rituximab (anti B-cell) and daratumumab (anti plasma-cell) have been increasingly favored for treatment of sensitized patients.[62,63]

DETECTION AND MONITORING FOR REJECTION

The advent of the bioptome transformed the care of heart transplant patients by providing a dependable technique for rejection detection.[64] Before its invention, clinicians depended on indirect clinical and physiological indicators of myocardial limitation and considered electrocardiography the most effective approach for diagnosing rejection. Nevertheless, clinical signs due to cardiac dysfunction often manifested only after significant myocardial damage from lymphocytes, making them less sensitive.

Dr. Philip Caves, a Scottish surgeon practicing in the United States, innovated the use of the bioptome for endomyocardial biopsy during the 1970s. This forceps-like instrument was designed to obtain tissue specimens from the endocardium using the minimally invasive percutaneous technique. This led to the establishment of pathological grading as the diagnostic gold standard for diagnosis, classification, and treatment of rejection. Further, it provided an easier method for surveillance of rejection, leading to better management of immunosuppression.

Initial enthusiasm for invasive monitoring of the transplanted heart with endomyocardial biopsies was dampened by significant variation in pathological grading, tricuspid regurgitation due to valvular injury from bioptome, and patient dissatisfaction due to multiple biopsies. In the early 2000s, peripheral gene expression profiling (GEP) for circulating lymphocytes was developed and was shown to have excellent negative predictive value for ruling out rejections. This was tested in multiple studies including CARGO[65] and IMAGE,[66] leading to widespread adoption and eventual decrease in surveillance biopsies across many centers. Recently, donor-derived cell-free deoxyribonucleic acid (dd-cfDNA) has been shown to have better negative predictive value (NPV) compared with GEP. Currently, two dd-cfDNA tests are being offered by CareDx and Natera, both of which have comparable NPVs.

In order to address the issue of variation in pathological grading, MMDx (Molecular Microscope Diagnostic System) has been developed to describe the graft state based on mRNA expression in the transplanted heart. While this is currently not FDA approved, it is increasingly used to make treatment decisions in certain patients facing a discrepancy between the clinical suspicion of rejection and pathological grading.[67]

Although contemporary, noninvasive techniques like sophisticated imaging, biomarker analysis, and gene expression profiling are becoming more favored,[68-70] the bioptome continues to be an essential instrument in several transplant facilities globally. Furthermore, it is utilized and essential in obtaining a sample for MMDx analysis.[67]

DONATION AFTER CIRCULATORY DEATH

The shortage of donor hearts continues, as demand is ever-growing. Novel methods of organ procurement, including transfusion and storage, have also improved the preservation of donor hearts. Donation after circulatory death (DCD) refers to the process of harvesting organs from a deceased donor whose circulation system has permanently stopped functioning. Innovation in technology and techniques has permitted successful use of DCD hearts, which has increased the number of available donor hearts. These donors are patients who have been declared dead by a physician independent of the transplant team, based on cessation of circulation and cardiac activity. The number of DCD donor hearts has been steadily increasing since the 2010s and, as of 2021, over 20% of organs donated in the United States were from DCD donors.[71] In 2024, approximately 17.3% of heart transplants were from a DCD donor.

Normothermic regional perfusion is a method that provides oxygen repletion to organs (in-situ) after a period of prolonged warm ischemia. It uses extracorporeal membrane oxygenation or similar systems to perfuse the organs within the donor's body after the heart has stopped beating and before removal. This is done while simultaneously ceasing blood flow to the brain. The organs are then monitored and optimized prior to removal. The advantage of this system is that it can preserve multiple organs simultaneously.[72] Some ethical issues about restarting circulation in a donor postmortem have limited its widespread adoption.

DONOR STORAGE AND TRANSPORTATION

Until recently, the gold standard of donor heart preservation has been static cold storage.[73] However, newer advents in organ transportation and storage have increased donor heart viability and optimized heart transplantation. The organ care system, OCS Heart (TransMedics), is a medical device that preserves and transports donor hearts in a near-physiological functioning state. It involves taking the organ out of the body and perfusing it in a special nutrient-rich solution in a machine (ex-vivo perfusion), improving the organ's viability and out-of-body time. Additionally, it expands the geographical range for transplantation. OCS Heart was approved by the FDA in the United States in 2021.

The SherpaPak Cardiac Transport System (CTS) from Paragonix Technologies is an organ preservation technology for donor heart transportation and storage that uses a novel nested canister system in conjunction with thermal cooling to provide protection from cold injury in an ice-free environment with real-time monitoring. The organ is suspended in a preservation solution in a pressure-

controlled nested canister system[74] that is designed to maintain donor heart temperatures continuously between 4°C and 8°C, and it has led to improved outcomes by decreasing primary graft failure rates.

CONCLUSION

From early experiments on animal models to the present moment, the field of heart transplantation has evolved exponentially, offering a lifeline to terminal stage heart transplant recipients. Advances in knowledge and understanding of hemodynamics, surgical techniques, immunology, organ procurement, storage, and transportation have laid the foundation of heart transplant and led to significant milestones. Application and advent of new technologies and techniques in the future may yield even more promising outcomes, advancing heart transplantation to new milestones.

KEY POINTS

- The history of heart transplantation began with early experiments in animals and landmark surgeries, including the first human transplant by Dr. Christiaan Barnard, setting the stage for global progress.
- Breakthroughs in immunosuppressive therapies have dramatically improved graft survival and expanded the viability of heart transplantation.
- Innovations such as the bioptome, gene expression profiling, donor-derived cell-free DNA, and molecular microscopy have significantly enhanced rejection surveillance and patient management.
- Developments in organ preservation and transport, along with adoption of donation after circulatory death, have increased the availability and viability of donor hearts.

COMPETING INTERESTS

The authors have no competing interests to declare.

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