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Cardiac transplantation: since the first case report

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Abstract

Heart transplantation was and is still recognised as a medical milestone. Its ability to offer a second chance of life to people with end-stage cardiac disease is its major triumph. Dr Christiaan Barnard's work was instrumental in realising the actual possibility of conducting a human transplant, and provided the framework for further advances in this field. He deserves due credit for conducting the first successful human heart transplant.

Keywords

Cardiac transplantation.

Introduction

Heart transplantation is one of the most widely publicised medical advances in the last century. Dr Christiaan Barnard accomplished this historic medical feat on December 3, 1967. The potentially life-saving operation immediately captured worldwide attention, lauding him with much deserved praise for his outstanding work in this field.

Heart transplants

Earlier experiments in heart transplantation were carried out in laboratories using canine models. As early as 1905, Alexis Carrel and Charles Guthrie[1,2] first attempted transplanting the heart of a puppy into the neck of an adult dog. The heterotopic heart immediately resumed cardiac contractions lasting approximately 2 h. Dr Norman Shumway and Dr Richard Lower of Stanford University performed the first orthotopic heart transplant in 1960 applying principles of topical hypothermia for graft preservation and immunosuppression in order to prolong graft survival times. They achieved a graft ischaemic time of 1 h and a recipient survival time ranging from 6 to 21 days.

Dr Christiaan Barnard initially trained under Dr David Hume and Dr Richard Lower in renal transplantation, learning about the techniques and the immunosuppression protocols used in the surgery. However, his aim was ultimately to conduct the first human heart transplant. He pursued his ambition resolutely and carried out 48 heart transplants in dogs, applying the techniques he had learnt during his training.

He chose his recipient for the first clinical cardiac transplant to be 53-year-old Louis Washkansky whose heart had been irreparably damaged by multiple myocardial infarctions leading to end-stage cardiomyopathy[3]. 24-year old Denise Darvall, who had suffered irreversible brain injury following a road traffic accident, served as a donor. The blood groups of both the donor and recipient were matched for compatibility. As soon as the donor was pronounced brain dead and her cardiac contractions had completely stopped, her chest was opened surgically and cardiopulmonary bypass

was initiated[4]. Hypothermia was used to bring down the myocardial temperature to 16 °C. The recipient's heart was surgically excised and the donor heart was soon placed inside the thoracic cavity of the recipient. Arterial anastomosis was established. Cardiopulmonary bypass was restarted and electrical cardioversion applied to the heart ensuring effective and co-ordinated ventricular contractions. The graft ischaemic time was 21 min. The immunosuppressive regime post-transplant consisted of local irradiation to the transplanted heart, azathioprine and prednisolone to counter possible immunologic rejection. Prophylactic actinomycin C was administered for 3 days[5].

Despite utmost sterile precautions observed during and after the transplant, the recipient contracted *Pseudomonas* and *Klebsiella* pneumonia. The success of the procedure appeared to be short-lived with the recipient expiring 18 days following the transplant despite the use of the appropriate antibiotics.

Soon afterwards, Adrian Kantrowitz conducted the second human heart transplant on an 18-day old infant with Ebstein's malformation[6]. The baby died 5 h later from cardiac failure and respiratory acidosis. Dr Christian Barnard attempted his second cardiac transplant early in 1968 on Dr Philip Blaibert, a 46-year-old man diagnosed with refractory congestive cardiac failure, severe coronary artery disease and large left ventricular aneurysm. This operation assumed importance in terms of the longest recipient survival time achieved thus far. The recipient survived for nearly 18 months post transplant. Duly acclaimed as a potentially life-saving measure for end-stage cardiac disease, heart transplants had enormous impact worldwide, but were financially and ethically controversial; at the end of the day it is an operation which can only help 50% of the population at best. Nevertheless by the end of 1968 an unprecedented number of nearly 100 such procedures had been performed.

However, the success story of cardiac transplants was curbed by the apparent short-term recipient survival outcomes. The picture was grim in this respect with a 1 year survival rate of only 20%. This was attributed to poor matching between donor and recipient, combined with an equally poor understanding of immunosuppression. Invariably, its popularity soon dwindled with the result that only a handful of cardiac transplants were conducted in the 1970s.

But they continued to be performed at a steady pace under Dr Shumway at Stanford University. During this time, new methods of early diagnosis of allograft rejection using endomyocardial biopsies of the heart, and its subsequent treatment, contributed to vastly improving the 1 year and 5 year post-operative survival rates to 63% and 39% respectively. However, it was the discovery of cyclosporin A, a new immunosuppressive agent, which brought about dramatic increments in recipient survival times. The 1 year and 5 year survival rates post transplant jumped to over 80% and 60% respectively. This sparked a resurgence of interest in cardiac transplantation in the 1980s. The introduction of cyclosporin A offered the distinct advantage in being able to reduce risk of acute rejection and infection during the early months following transplant. The use of OKT3 monoclonal antibodies and rabbit-derived anti-thymocyte globulin also played an important role in decreasing early rejection rates.

Since then, phenomenal advances have been made, particularly relating to immunosuppression. Current immunosuppressive strategy post transplant consists of cyclosporin A, azathioprine and steroids. Some groups have advocated weaning patients off steroids altogether, or maintenance on alternate low-dose therapy to offset the side effects. Tacrolimus, a potent immunosuppressive agent, has now replaced cyclosporin A in many protocols especially in patients with persistent rejection after renal, lung and heart transplant who were initially treated with cyclosporin A. Mycophenolate mofetil (MMF), another relatively new agent, has been used instead of azathioprine in cases of recurrent allograft rejection. Antilymphocyte serum or monoclonal anti-T cell antibodies are presently used for treatment of steroid resistant rejection or an induction therapy.

Statistics regarding heart transplants have been recorded by the International Society for Heart and Lung Transplantation (ISHLT), which was founded in 1981. It has been responsible for maintaining a transplant registry since 1983. Quarterly reports are published by the ISHLT based on data collected from transplant centres worldwide. These data show that average recipient survival 1 year and 3 years post orthotopic heart transplants performed between 1998 and 2002 stand at 83.9% and 77.4% respectively. In North America they are 85.1% and 78.1%[7], while in Europe they are documented at 81.2% and 75.6% respectively[8]. Analysis of the data also shows graft ischaemic time to be a

major determinant of survival outcomes. The shorter the duration of ischaemia, the better the survival rates. For example, with a graft ischaemic time less than 2 h, the average survival rate 1 year post transplant is 88.3% whereas it is 79.1% for graft ischaemic time of more than 8 h. Thus, improved surgical techniques, better ABO histocompatibility, blood group matching between donor and recipient, newer methods of organ preservation using special electrolyte solutions, combined with better immunosuppressive management have been vital contributing factors in achieving current survival rates.

Modern research is presently looking into xenotransplantation and the possibility of heart transplants using mechanical devices.

Finally, the introduction of an operation which insists on the clear definition of death in the donor has raised a number of ethical issues which have recently been discussed in an article in the British Medical Journal by Raymond Hoffenberg.

Conclusion

Heart transplantation was and is still recognised as a medical milestone. Its ability to offer a second chance of life to people with end-stage cardiac disease is its major triumph. Dr Christiaan Barnard's work was instrumental in realising the actual possibility of conducting a human transplant, and provided the framework for further advances in this field. He deserves due credit for conducting the first successful human heart transplant.

Barnard died on 2nd September 2001; you can read his obituary in the *British Medical Journal*.

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