Fifty years of heart transplantation

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Heart transplantation has made tremendous progress since its first clinical use in 1968 and has enabled survival of many patients with intractable heart failure. A pioneer of the Swiss heart transplant programme looks back.

Recently we witnessed a world-wide celebration of a breakthrough in treatment of terminal heart failure: the onset of heart transplantation. On 3 December 1967, Christiaan Neethling Barnard successfully implanted the heart of a young traffic accident victim, declared to be brain dead, into a 54-year-old patient suffering from terminal heart failure [1]. Although the operation itself was successful, the patient died after 18 days from immunosuppression-related pneumonia. The operation received unprecedented world-wide attention, and was shortly followed by Barnard’s second heart transplantation, which showed much improved survival.

Many details about this first transplantation are not so well known. Groote Schuur authorities made very simple, politically astute rules in the politically charged, apartheid atmosphere of South Africa:

- The donor must be of white race
- The recipient must be also of white race
- Nobody photographed or filmed the operation (and the media were later known to be offering millions...).

This pioneering procedure encouraged many renowned heart surgeons to begin heart transplantation in their own centres, but first results were disappointing. Review of the first worldwide experience with human heart transplantation shows that only 3 out of 19 patients survived 30 days [2]. Disappointment with clinical results, which was probably due to lack of proper preparation and limited immunosuppression, led to a sharp drop in number of heart transplants worldwide (fig. 1).

Because of the disappointing survival of patients after initially successful transplantation, the operation was practically abandoned, and was continued only in Cape Town and in Stanford, under imaginative leadership of Norman Shumway. The original operative technique was retained, but several innovations in immunosuppression were explored. Originally, standard therapy with azathioprine (1–3 mg/kg), prednisone (1 mg/kg) and polyclonal rabbit antithymocyte globulin (RATG) was used, later with the addition of ciclosporin and monoclonal antibody RATG, and later still the monoclonal antibody
OKT3. Improved results led Christian Cabrol at La Pitié-Salpêtrière in Paris to resume heart transplantation in France, following sustained efforts at Groote Schuur and the University of Richmond.

In Switzerland, the first two heart transplants were performed in Zurich by Åke Senning in 1969, both patients surviving only few weeks. The programme was restarted by the author in 1985 and it quickly developed into the largest Swiss heart transplantation programme (fig. 3). Several important scientific contributions emerged from Zurich programme: first experience with heart transplantation in congenital anomalies [5], detailed analysis of the advantages of bicaval anastomosis for orthotopic transplantation versus the standard Shumway-Lower technique or right atrial anastomosis [6], and a rare case of re-transplantation of the already transplanted heart because of the sudden brain death of the first recipient [7], resulting in one heart having functioned in three different persons.

In the nineties the number of Swiss heart transplants was reduced owing to the lack of donors, so that the waiting period for a transplant became seriously extended. Today, only 27% of patients on the waiting list receive a heart (fig. 4). Today, various methods are being explored to alleviate the scarcity of donors. One of them is the donation after circulatory death:

- The DCD method (donation after circulatory death) is increasingly used instead of DBD (donation after brain death), as it is more acceptable to the relatives of the deceased. Organs are removed from a dead, not from a living donor.

- After circulatory standstill and an appropriate waiting period (3–5 minutes), the heart and other organs are resuscitated using a pump oxygenator and sometimes by cooling, the same technique Barnard used in his first heart transplantation.

When using DCD methods, transplant surgeons must adhere to Maastricht donor criteria [8]:

- Dead on arrival
- Unsuccessful attempts at resuscitation
- Anticipated cardiac arrest
- Cardiac arrest after brain death.
- Unexpected arrest in intensive care unit (ICU) patients

Although less common with heart donors, this method of organ retrieval is widely used in many countries. In Switzerland in 2017, DCD donors accounted for 27% of all organ retrievals.

Another method which has been explored experimentally for more than 50 years is xenotransplantation: use of an animal heart to be implanted in a sick human. Incidentally, the first heart transplantation in humans was not the one performed by Barnard, but was a xenotransplantation performed in 1964 by James Hardy in Jackson, Mississippi. He used a chimpanzee heart, which functioned only couple of hours. Major immunological problems emerge when this method is tested. A recent review [9] describes nine cases of human xenotransplantation, two of them performed by Barnard as heterotopic transplants. Results are disappointing: most transplanted hearts failed within minutes or a few hours after transplantation, with the exception of Barnard’s heterotopic cases, which functioned for several days. The best described case was that of Bailey at Loma Linda University, who implanted a baboon heart into a newborn with hypoplastic left heart syndrome. In spit of optimal monitoring and
maximal immnosuppression, the heart failed after 20 days. This method is still being actively explored experimentally; although some progress is being reported [10], most experts doubt if xenotransplantation will be available in near future.

Although the scarcity of donors remains, long-term survival of heart transplant patients in Zurich remains well above the average survival data published by the Society of Heart and Lung Transplants. Survival after heart transplantation is now up to 60% after 10 years, but serious late problems remain: chronic rejection, graft vasculopathy and malignancies. And a crucial problem is emerging with the longer life span observed in all First World countries: the age limit for heart transplantation. It is generally accepted that the recipient’s age should be less than 70 years: both early and late mortality are thought to be higher in older patients, although newer literature questions this assumption [11]. But intractable heart failure is common in older age, reaching 10% at age >75 years. For these patients, only mechanical circulatory assistance seems to offer a reasonable hope of improved survival. Previous experience with total artificial hearts was predominantly negative, due to a high complication rate (thrombosis, embolism) and mechanical unreliability of the pumping system. Recent advances in small left ventricular assist devices (LVADs), especially with continuous flow pumps and magnetically levitated devices, have shown encouraging results. The latest trials with newer devices in elderly patients show a 2-year survival of close to 80%, like the survival after a heart transplant [12].

To summarise, heart transplantation has made tremendous progress since its first clinical use in 1968 and has enabled survival of many patients with intractable heart failure. The major remaining problems are scarcity of donors and late complications, such as chronic rejection and increase of malignancies. For elderly patients not qualifying for heart transplantation, a new generation of circulatory assist devices is opening exciting new prospects for treatment of chronic heart failure.

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References
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