

Mechanical circulatory support for destination therapy: why are we so late?

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During the time when cardiac centres almost everywhere worldwide were developing different and more daredevil surgical procedures to repair congenital and acquired diseases of the heart, several pioneers were already thinking to the future, which could lie with mechanical circulatory support of the heart when this organ was irreversibly damaged [1]. Two methods were started at almost the same time: human heart transplantation [2], and manufacture of cardiac assist devices and prosthetic hearts [3–4].

The explosion of space technology in the Kennedy years gave the wrong impression – that a totally implantable device would be rapidly developed. Kolff in the mid-1950s built the first total artificial heart, made of polyvinylchloride, with two ventricles encased in a common housing and driven pneumatically. After he incorporated a direct current (DC) motor with two polyurethane ventricles, he introduced the concept of nonpulsatile total artificial heart (TAH) pumping. Ultimately he proposed alternate compression of the ventricles and thus alternate pumping. Kolff became an inspiration for many disciples worldwide, who started their own chapels. New materials were introduced, selection of the best components was disputable, research for durable ventricles was not successful, and energy supply became a permanent nightmare for the scientists. On a top of that, one of the greatest misjudgements was to consider the heart as a fluid pump and all problems to be related to the multiple functions of the heart. The large number of technological and biological constraints was not considered to be a real problem. Early total artificial hearts mimicked the pumping action of the native heart.

In its turn, human heart transplantation faced a great number of problems related to immunology before becoming a safe surgical procedure [5–6]. But its success was counteracted by enormous limitations in its clinical application, making the use of mechanical circulatory systems indispensable. Since Harvey's famous treatise "De Moto Cordis" in 1628, the heart has been acknowledged to be the key organ for guaranteeing the blood supply to the different organs and for carrying the nutrients required everywhere in the body. We can understand that Carrel, in the late 1920s, was hindered in the development of cardiac transplantation because of the absence of immunosuppressive drugs, antibiotics and anticoagulants, but we have more difficulty in

realising that so much time elapsed between the development of the Carrel and Lindbergh machine for organ preservation in the 1930s and the devices that were first implanted in humans by Cooley and Liotta in Houston in 1969 and by De Vries and Jarvik in Salt Lake City in 1982. Why are we so late? Is it for technical reasons or a complete distortion of the medical philosophy?

In the case of cardiac weakness, the heart can no longer properly support the functions of its different tissues. Such weaknesses can be caused by organic deficiencies due to the recurring lesions arising from rheumatic illnesses, lesions to heart vessels, congenital lesions or functional weaknesses without any apparent lesion. The indications for transplantation from a donor or implantation of a device can be selected only if all medical and surgical possibilities are used up. They must be applied only in cases in which chronic failure is totally irreversible and will be responsible for the death of the patient in a short period of time. Should the deterioration of the heart function be accelerated for any reasons, producing fast and severe multiorgan failure, transplantation or implantation of a system that can provide complete circulatory support is fully justified. In the past, only transplantation was considered as permanent [7]. The assist devices likely to support the left heart and the artificial hearts were for too long considered to be bridges limited to temporary use, despite breath-taking achievements [8]. They are now designed as destination therapies and thus the concept of permanent implants is finally accepted. The implantation of a device as destination therapy requires very sophisticated team dedication that begins at the decision making process, and continues during the hospitalisation and after discharge [9–10]. Mechanical cardiac assistance has progressively come to be accepted as a destination therapy [11–13]. Emphasis should be given to the indication and time-point of implantation, selection of the device, and long-term outcomes and quality of life [14].

The gold standard therapy for chronic end-stage heart failure is transplantation [15–16]. According to the International Society for Heart and Lung Transplantation, the numbers of transplants (187 in 1982, 4939 in 1993, 3936 in 2005 and 4477 in 2013) look meagre as the prevalence of heart failure increases dramatically. The use of mechanical circulatory support can be considered as a permanent

therapy for patients in end-stage heart failure who are not transplant candidates [17–18]. The concept of xenotransplantation still looks very far away. The immunosuppression needed with homograft transplantation still requires a lot of attention [19]. In the early 1900s, organs from animals such as pigs, goats, monkeys or lambs were transplanted into humans to replace failing organs. In transplant recipients the immune system recognises donor tissues as foreign and attacks them, leading to acute transplant rejection. The first successful human transplant without any rejection was performed by Murray in 1954, who transplanted a kidney between identical twin brothers. However, immunosuppressive methods to prevent rejection were still not available.

A succession of animal to human transplants was attempted, but the success rates were low compared with human to human, even with immunosuppression. Since the 1990s, animals have been genetically modified to prevent organ rejection. The problem of donor species was addressed by researchers using pigs as donors [20–21]. The pigs are farmed and thus their health is kept under control. All xenotransplantation was banned worldwide in 1997 because of concerns about transmission to humans of a pig virus called porcine endogenous retrovirus (PERV). Some countries are now allowing xenotransplantation research on a case-by-case basis.

Because of the low number of potential donors and considering presently the xenotransplantation as a dead end, the most promising approach was to upgrade mechanical circulatory support from bridge-to-transplantation to destination therapy [22–23]. Collaborative effects in the fields of surgery, medicine and biomedical engineering supported by public and private funding have led to devices capable of providing reliable circulatory support. This therapy began in the USA with the National Heart, Lung and Blood Institute (NHLBI) artificial heart programme in the 1970s. Regrettably, the results of the first total artificial heart implantation were disappointing. In the meantime, the problem of death of patients on the heart transplant waiting list focused on the development of mechanical devices that could be used as bridges for patients awaiting donor hearts [24–25].

As the number of donors available did not increase, the concept of destination therapy was introduced in the early 2000s for the purpose of long-term, durable mechanical circulatory support. A plethora of devices were introduced into clinical trials [26]. The first generation of blood pumps refers to the pulsatile, positive displacement pumps available in the 1990s. The second generation includes: rotary pumps (Jarvik 2000), axial flow pump (HeartMate II) and the DeBakey Micromed pump. The third generation includes both axial flow and centrifugal flow devices. Thanks to databases such as INTERMACS (Registry for Mechanically Assisted Circulatory Support) funded by the NHLBI, annual reports of patient enrolment and outcomes bring the most clear-cut demonstration of the outstanding contribution of mechanical circulatory support for patients in the advanced stages of heart failure. For patients with biventricular failure who are not candidates for an isolated left ventricular assist device, the total artificial heart provides the most definitive option [27].

With continuous flow pumps, actual survival is 80% at 1 year and 70% at 2 years. Quality of life indicators are favourable and adverse events are on the decline. The issues of bleeding and thrombosis together with infection are now better controlled, but they require a multidisciplinary team approach. Device failures are becoming very rare.

We therefore applaud this publication of Tozzi [27], which is timely and brings hope for people suffering from chronic heart failure. The benefits for these patients are remarkable and undeniable. Further improvements in this area can be achieved by ensuring that the biofunctionality and the long-term durability are combined with true biocompatibility.

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