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Chapter 1

Introductory Chapter: Dedicated Initial Giants Breaking the Barriers to Successful Cardiac Transplantation Therapy

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1. Introduction

> *'Just before 6 a.m. on Sunday 3 December 1967, at Groote Schuur Hospital in CapeTown, a new heart in the chest of Dr. Louis Washkansky was electrically shocked into action'* [1–3].

Despite previous studies and efforts in animal labs, this sentence represents the 'official' beginning of one of the most challenging scientific steps of the modern era, which has been the ability to replace functionally or anatomically the failing heart [1–5]. To understand the real need of such a radical therapy, as being now widely well-accepted, we have to face briefly with its 'recent' history since it was the dedicated initial giants of the field, who broke the barriers to successful cardiac transplantation therapy.

Between 1902 and 1909, in France, Dr. Carrel 'already' performed successful transplants of different organs in dogs. In 1938, a Russian biology student, Vladimir Demikhov 'already' tested an implantable total artificial heart (TAH) in a dog that survived for 2.5 hours. However, these attempts resulted to be only strictly experimental [4, 5].

In 1964, Dr. DeBakey 'finally' convinced the United States of America (USA) National Institutes of Health to fund the development of a workable TAH [4, 5]. Thus, Baylor researchers in Houston began a series of calf experiments led by the Argentinian physician Domingo Liotta. However, the results were not encouraging and long-lasting. DeBakey decided that the TAH was not ready clinically for 'human being' and Houston MCS program shifted to the 'partial artificial heart,' which was defined as left ventricular assist device (LVAD). In 1966, DeBakey performed the first successful clinical implantation of a postcardiotomy LVAD [4, 5]. The 37-year-old woman patient was supported by the device for 10 days, gaining full myocardial

function recovery and successful pump removal. By the late 1960s, the Baylor team had used the LVAD in several patients; thus, stimulating the new era of the 'mechanically supported failing heart' [4, 5].

But, it was Barnard's brave and pioneering event that really stunned the world and surprised all medical and scientific community [1–3]. Consequently, on December 2017, we celebrated the 50th anniversary of the world's first human heart transplant performed.

It was the dream of many surgeons in the mid-20th century to transplant a healthy heart into a patient dying of end-stage heart disease. This was greatly pushed by Dr. Shumway and Dr. Lower at Stanford, who perfected the surgical procedure and demonstrated normal physiologic function by the resulting denervated heart [1–3]. Additionally, under the leadership of Dr. Starzl, they had demonstrated that the combination of corticosteroids and azathioprine would permit survival of solid organs transplanted across a human leukocyte antigen mismatch [1–3].

After the first human case in Cape Town, 3 days later Dr. Kantrowitz in New York transplanted a 2-day-old donor heart in a 17-day-old baby and on January 6, 1968, Drs. Shumway and Stinson performed the first adult Htx in USA being parallel to the first case of Dr. Cooley and the second case of Dr. Barnard on Philip Blaiberg, a 58-year-old dentist, who lived for 20 months, 'finally and impressively' encouraging both clinical and scientific community [1–3].

The initial results were so promising that the procedure was soon adopted by many other surgeons throughout the world. But the application of this therapy was severely limited by the scarcity of donor hearts even according to the 'no proper' definiment, at that time, of brain death, timing for organ procurement with the need of heart electrical activity cessation, and absence of a 'correct' cold organ storage not allowing a long distance transport [1–5].

This resulted in research efforts to develop implantable mid- to long-term mechanical assist and replacement devices for the failing heart in terms of two stage cardiac replacement approach as being cardiac allografting dependent on two not synchronized events, which are the 'salvaging the life of a recipient' and 'the death of a donor' as mentioned by Dr. Cooley [5].

It was Dr. Cooley himself, who performed the first bridge-to-transplant operation with a mechanical TAH at the Texas Heart Institute (THI) in April 1969, even due to the cooperation of Dr. Liotta [4, 5]. The next interface of this technology with transplant occurred in 1978, again at the THI, when an intra-abdominal left ventricular assist device (LVAD) to treat a postcardiotomy syndrome and thereafter a simultaneous heart and kidney transplant was performed [4, 5]. In 1981, a total heart replacement with an Akutsu TAH was implanted after a failed heart surgery. The patient was supported for almost 3 days, and then underwent heart transplantation (Htx) [4, 5].

However, despite its promise, the early epoch (1967–1972) of Htx soon ended in disappointment: as of March 1971, of 167 recipients in 20 countries, 143 had died due to infection or organ rejection [1–3]. For this reason, Htx was almost universally abandoned for at least a decade. The USA and non-USA governments redirected their research funds toward the development of an implantable LVAD, not as a bridge to transplantation but as a permanently implantable device [4–8]. It was the introduction of cyclosporine, which dramatically expanded the use of heart transplantation and made bridging patients to transplant feasible [1–3].

The first really successful total heart replacement with subsequent heart transplantation was performed by Dr. Copeland in Arizona in 1985 [4, 5]. After this demonstration of feasibility, the world got the Food and Drug Administration (FDA) approval of the first pulsatile MCS devices as a bridge to transplant first in 1994 and then in 1998 [4, 5].

As of early 2012, more than 10,000 pneumatic LVADs had been implanted worldwide. However, they were too large to fit in smaller patients, including many women and children. Perhaps even more important, the durability of these pumps was limited [4–6].

Infact, the success was limited to 2-year pump since according to the REMATCH era, the long-term survival would only be possible if device implantation was followed by Htx. The result was simply adding patients to the transplant list as complained by Dr. Shumway at Stanford [4, 5].

Thus, dedicated researchers began to further explore the use of implantable continuous-flow (CF) blood pumps, whose better 'human fitting' due to miniaturization and better durability since the absence of 'flexing membranes and other pulsatile components' was expected to be more likely reliable.

In the early 80s, the concept of a small, high-speed (25,000 rpm) blood screw-type pump (by Wampler with the Hemopump) and of a blood-washed bearings (by Jarvik with the Jarvik heart) pump became the basis for initial clinical progress in this field [4–6].

The first clinical implantation of the axial National Aeronautics and Space Administration (NASA) heart in human being at the Deutsches Herzzentrum Berlin (DHZB) by Dr. Hetzer and Dr. DeBakey in 1998 and then of the Jarvik heart in 2000 followed by the HeartMate II in 2003 at THI by Dr. Frazier [4–6], ultimately resulted in thousands of pumps implanted and lives saved by several dedicated centers [4].

So far, over 60,000 continuous-flow pumps have been implanted worldwide with the aim of bridge to recovery, Htx or even as permanent support (destination therapy) covering the infant age in pediatrics and the 'very' old age in adults with good outcomes, excellent clinical/surgical versatility, and acceptable durability [4, 7, 8]. This is even due to the recent and still active research on implantable centrifugal-force pumps as being the HeartWare HVAD (Medtronic) and the HeartMate 3 (Abbott) mostly implanted, currently [4, 7, 8].

All the abovementioned is stimulating more and more the adoption of CF pumps to focus on the need of long-term biventricular support even if historically all efforts were oriented to develop a physiologically pneumatic TAH [4, 5, 9–13].

However, despite all encouraging results of technology evolution and the current knowledge/management of induced MCS physiology, as abovementioned, the Achilles' heel of implantable MCS still remains the absence of a satisfactory biocompatibility with consequent related thromboembolic events and the presence of a percutaneous driveline, which leads to high risk of infective disorders and represents a real barrier to the long-term application of VADs and TAHs in terms of definitive therapies [4–13]. Additionally and unfortunately, the regenerative medicine is still far from resulting a reliable and suitable strategy as treatment of refractory advanced heart failure [14–16].

This is why heart transplantation remains the 'gold standard' solution to be reached through whatever encouraging long-term implantable MCS in terms of 'bridge' therapy to support the current lack of donors and avoid recurrent acute decompensation events; thus, clinically optimizing the transplant candidates and contributing to the improvement of transplant results.

2. Conclusions

The dramatic nature of the first heart transplant operation and the charismatic personality of the surgeon had enormous impact on the public throughout the world.

The early research of Shumway and Lower, the first human case by Barnard, the development of successful cold organ storage allowing long distance transport, and the refinement of immunosuppressant protocols, all culminated in the institution of the formal disciplines of cardiac transplant surgery and transplant cardiology and the formation of dedicated societies, which have truly pioneered the rapid expansion in this field.

These collective worldwide efforts achieved a better understanding of all heart transplant clinical details, which provided by time better and better outcomes. We do all have to profit of such lessons in order to offer 'success' to all our transplant patients particularly in terms of 'teamwork' strategy and clinical development as we have seen even historically.

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