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3. THE EVOLUTION OF THE LEFT VENTRICULAR ASSIST DEVICE AS A TREATMENT FOR HEART FAILURE

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1. Introduction

This chapter is about the origin, development, and growing use of a device used to help heart failure patients, the Left Ventricular Assist Device, or LVAD for short. These devices are implanted in the body to assist failing hearts do their pumping. Early versions of the LVAD began to be used in the late 1960s and since that time approximately 20,000 LVADS have been implanted around the world. As one would expect, today's LVADs are very different from the early versions. They are much less prone to malfunction, more effective in enabling patients to live longer, and easier for them to live with in reasonable comfort. The implantation procedure has become simpler, more routine, and less dangerous for the patient.

The initial chapter of this book discussed advance in medical practice more broadly and proposed that there were three different pathways associated with progress: the advance of scientific understanding of the human body and disease, the development of new technologies that could be used directly or indirectly to advance practice, and learning by experience in practice. The importance of these different routes to progress obviously differs depending on the type of advance. A large percentage of the cases analyzed in this book involve the development of new

devices that often enabled (and required) new techniques to be used by physicians. The LVAD is of this genre. (The book also includes studies of the development and employment of the artificial lens, angioplasty, artificial hips, and disks). In the case of LVAD, and also the other new devices considered in this book, the prior emergence of new technological capabilities that made the development of the device feasible was of critical importance. So too was learning in actual practice about what worked well and what didn't, with resulting changes in the procedures used, and also feedback to the engineers involved in design of the device. In the LVAD case advance in basic biomedical understanding was more something that came from experience with LVADS than something that motivated and oriented the development of the device.

The historical case of the evolution of the LVAD from its origins in the 1960s to today presented in this chapter is mainly based on archival materials and sources. The structure of the rest of this chapter is as follows. Sections 2 and 3 are the basic history of the evolution of LVAD as treatment for heart failure, with 2 giving a brief overview, and 3 filling in the details. In section 4 we summarise what can be learned from the case of LVAD about advances in medical practice more broadly.

2. Contextual Background

Advanced heart failure is a clinical syndrome that presents a collection of symptoms – fatigue, shortness of breadth, and congestion – that hits a person when her heart can not pump enough blood to satisfy her body's needs (Jessup, 2001). In industrialized countries the improved management of coronary heart diseases short

of heart failure and the improved longevity of the population more generally resulted in a growing number of patients with heart failure[1]. The evolution of treatments options for advanced heart failure patients over the last few decades has been impressive and includes now medical treatment based on drugs, heart transplantation and most recently mechanical circulatory device support therapies. The therapeutic innovation discussed in this paper is a device-based treatment for patients with advanced heart failure who are end-stage, i.e. they do not respond anymore to medical treatment and their only options are either heart transplantation or a mechanical circulatory device like the total artificial heart or the left ventricle assist device.

The treatment for failing hearts or heart failure in the 1950s would be considered primitive by today's medical standards. It was based on a combination of general measures - including dieting, limiting exercise and resting in bed for days or weeks - and a mix of drugs such as digitalis and injected mercurial diuretics, both known for their substantial toxicity. It was only at the end of the decade that new diuretics with more limited side effects became available. These diuretics are one of the many advances in treatment and technology for heart failure and other cardiac diseases that have been introduced since the 1950s (Silverman, 1999). The 1950s have seen also development of the heart-lung-machine which made possible a new path of open heart surgery, including not only repairing vessels, valves, and hearts but also replacing them. In 1953 the first successful open-heart surgical procedure

[1] In the US and in Europe, with over 700 million inhabitants the estimated incidence of heart failure is around 7 millions, and the prevalence of advanced heart failure is estimated to total between 70.000 and 700.000 patients (Deng and Naka, 2007).

demonstrated that the function of the heart and lungs could be replaced temporarily by mechanical means (Le Fanu, 1999). Individuals have long dreamed about the possibility of replacing hearts and other organs of the human body that were beyond repair. Two alternative conceptions of what could be used to replace the failing heart of the patient have co-evolved. The first was heart transplantation, replacing the failing heart with a healthy natural organ provided by a deceased donor. The second was replacing it with a man-made or artificial heart. The natural heart of a donor was viewed as the best alternative, but both solutions were pursued in parallel.

In the early 1960s the dream of developing an artificial heart became a national priority in the US. Lobbied by the medical establishment the US Congress created the Artificial Heart Program in 1964. Modeled on the program to land a man on the moon, it was based on the assumption that the artificial heart device could be brought into existence by using existing component technologies and that it would be developed in a few years (Hogness and Van Antwerp, 1991).

"At the time, everyone believed that there was nothing we could not achieve utilizing modern scientific technologies. This was strongly influenced by the enthusiasm and the dream projected by former President John F. Kennedy. We were convinced that it was possible to develop a totally implantable cardiac prosthesis in the next 20 years."[2]

The initial plan presented by National Institute of Health (here after NIH) to

[2]Pierce quoted in Berkowitz (1990).

Congress in their 1966 budgetary request called for both the development of cardiac replacement pumps or artificial hearts, and also for the development of other circulatory support devices to be used in emergency or acute situations as well as supporting failing hearts until transplantation.

The development of these mechanical circulatory devices occurred in parallel with the initial era of the heart transplants which began with the first successful heart transplant procedure performed in December 1967. However, the hopes that heart transplantation could be the ultimate solution for patients with failing hearts were shattered quite quickly by the limited supply of donors, immunological problems that caused rejection of the received organs and severe complications in the few patients who received the heart transplants. Some of these problems were reduced by but not solved by the introduction of immunosuppressives in the 1980s which reduced the problem of organ rejection (Frazier and Kirklin, 2006) and by the creation of heart transplant lists and organ donors' networks that facilitate the allocation of hearts among transplant centers. Nonetheless, the problems encountered with developing heart transplantation to the point that it could be used more commonly in clinical practice, especially the limited number of donor' hearts and the need to keep patients with failing hearts alive until transplantation, reinforced the demand and the expectations, for the artificial heart (Fox and Swazey, 1992).

However, the high hopes for the artificial heart soon were damped. Initial tinkering, using existing technologies, revealed the complexity of this undertaking.

"'We thought the problem wasn't going to be complicated as it turned out to be' he [William Pierce] says candidly, referring to the 'problem' of devising a safe and effective permanent artificial heart to replace ailing natural hearts. As we've solved some problems, we've uncovered others. That's why it remained a wonderful challenge"[3].

It became evident that two big 'technical' problems existed: the lack of materials that could be accepted by the body, and an appropriate source of energy. Another major limitation of the use of existing technologies to develop an artificial heart was the size of the overall device and its components that constrained the possibility to totally implant the device in patients' bodies. Patients were bedridden, and confined to live with those devices in hospitals. Moreover, the first patient who received an artificial heart, and the few others who followed, died of complications. Continuous media scrutiny exposed their misery. This early experience of using the artificial heart in human volunteers turned the public and some key opinion leaders in the medical community against the full blown artificial heart technology as a solution to failing hearts. In the mid 1980s, the hopes for rapid fulfillments of the dreams of greatly expanded use of heart transplantation and the development of an effective total artificial heart lay in tatters. The involved medical community largely refocused their attention and expectations instead on LVADs. The development of an LVAD increasingly came to be seen as much less demanding technically and thus a more quickly achievable solution for the problem of replacing and supporting

[3]Pierce quoted in Berkowitz (1990).

failing hearts.

The LVAD is now viewed as a treatment option for patients with advanced heart failure who are not responding to medical therapy. This humble technology has come a long way and, in the following section, we consider the more detailed history of the evolution of the LVAD, fleshing out its developments after 1964, when the Artificial Heart Program was started by NIH in the US. Our history will be mostly about the US, although we will also recount events in Europe and in other parts of the world that are relevant to understanding US developments.

3. A Detailed History of the Origin and Evolution of the Left Ventricular Assist Device (LVAD)

In this section we examine more deeply the history of LVAD that we sketched in Section 2. We treat in order the evolution of the device itself, advances over time of the clinical use of the LVAD as treatment for heart failure, and finally the gains in scientific understanding of what is involved in heart failure and prognosis for recovery that have accompanied the advances of the device and the associated therapy.

3.1 The Evolution of the Device

Over the years LVAD devices have become more durable and reliable, smaller, simpler, easier to implant and more comfortable. The major developments that have enabled these improvements include: the development of materials compatible with

the human body; technologies for components such as energy sources, storages, transmissions and converters; new instrumentation and improved methods to design and to test new devices. These developments were not independent and occurred over a number of decades. Many were made possible by exogenous advances drawn from broad technological areas, particularly electronics, computing and biomaterials, advances which enabled the design of improved component technologies for LVAD devices. In addition, there were, over the same period of time, improvements in surgical procedures and techniques to implant devices within the human body. In this sub-section we focus on the evolution of the LVAD devices.

3.1.1 LVAD as a device therapy for heart failure

To understand the origins and evolution of the LVAD device as treatment for heart failure it should be recognized that in the 1950s and 1960s the human body was viewed as a machine which had parts that could be repaired and replaced. The heart was seen as a pulsatile pump supporting the circulation of the blood within the human body and heart disease was understood to be caused by a diminished ability of the heart to pump blood. Broken or failing hearts were repaired by plumbing the heart through open heart surgery which was made possible, as we have seen in the previous section, by the development of the heart-lung machine. It was believed that the only solutions for failing hearts that could not be mended through surgery and could not be replaced through heart transplants were mechanical blood pumps that could assist or replace these sick hearts. People

believed that, because they knew how to build pumps, the goal of building mechanical blood pumps could be easily achieved in a short period of time and the problem of assisting or replacing broken or failing hearts could be readily solved. The common view was that two types of mechanical blood pumps could be developed as spare parts for broken or failing hearts: a 'total artificial heart (TAH)', a mechanical replacement of the whole natural heart, which would be removed; and a 'ventricular assist device (VAD)' that was a mechanical circulatory support device which would assist the heart in doing its work (i.e. the natural heart itself would remain in place). The latter was in many cases a left ventricle assist device (LVAD) because the majority of the pumping work of the heart is done by the left ventricle.

The conceptualization of the LVAD as a mechanical blood pump shaped the initial designs of the LVAD artifacts. Two families of designs started to appear from an early stage. First, temporary LVADs, i.e. blood pumps that could be used for a few hours or up to several days to bypass or augment the flow of the left ventricle in patients after cardiac damage, where all the components of the LVAD system, including the pump in some cases, were to be located outside the body, making the installation procedure much easier and safer, and enabling the pump to be easily removed when it was no longer needed (DeBakey, 1971). Second, permanent LVADs, involving blood pumps where as many components as possible of the LVAD system (pump, energy converter, back-up battery, energy transmission receiver) were to be surgically inserted within the patient's body in order to take over most, if not all of the work of the left ventricle for longer periods than several weeks

(Kantrovitz, 1990). A device of the first family of temporary blood pumps, the intraortic balloon pump (IABP), which was developed in the 1960s, quickly gained broad clinical acceptance and it is still used in clinical practice as temporary cardiac support. We focus in this paper on the second family of devices, permanent LVADs, most of whose components were designed to be implanted and to remain in the body for an indefinite time in support of failing hearts.

3.1.2 Pioneering cardiac surgeons and engineers started to build mechanical replicas of the heart (1950s-1960s)

In the 1950s and early 1960s, people exploring the feasibility of an effective LVAD were mostly cardiac surgeons and engineers. A number of research groups led by pioneering cardiac surgeons started designing, experimenting in animals and testing in a limited number of patients permanent and implanted LVAD devices that were very primitive. They were prototypes patched together and fabricated with existing components by surgeons and their technicians and trialed out in clinical practice through implantations in patients who were desperate cases. Different device configurations were explored and redesigned based on learning accumulated through animal studies and these initial implantations. Moreover, these devices were a mechanical copy of the human heart (at least in the part of the device that was implanted within the body). They were pulsatile pumps, implanted in the body and connected directly to the heart in order to enable blood flow to

bypass the left ventricle[4]. The main components of the device were the pump itself, the energy source and the control or drive unit, plus other additional components depending on the specific design of each device[5].

These research groups were based mainly in medical centers with open heart surgery programs. The developmental activities were conducted within experimental surgery and engineering laboratories, where electrical engineers were employed to solve the problems identified by surgeons in the process of translating different ideas of LVAD designs into physical artifacts that were to be implanted in the body (Bronzino, 2005). In some cases where this engineering expertise was not available in house or the problems encountered were beyond it, the help of outside specialized engineers based in commercial companies was sought to solve the problems encountered in the fabrication and redesign of these devices. These ad-hoc collaborations resulted in the development of close and personal relationships between a number of surgeons and engineers, based both inside and outside medical centers (Kantrovitz, 1990).

Moreover, significant cooperative work took place between different heart centers. Many surgeons knew each other since their medical school training or research fellowships under the mentorship of leading pioneers in the new and emerging field of open heart surgery. Informal and cooperative relationships were also created by frequent and face to face interactions. It was a common practice to meet and argue

[4]The device was removing blood through the ventricular apex and returning it to the abdominal or thoracic aorta.
[5]For instance internal batteries, inflow and outflow grafts to connect the pump to the heart, air drive lines, etc.

about new ideas and practices at medical conferences and in committees of professional associations and federal agencies and for surgeons and researchers to visit each other laboratories when word of mouth spread about new surgical techniques and/or new devices developed by an investigator. Publications in the literature were used to share ideas but also to gain peer recognition and visibility in the medical field. Although competitive behaviors and the desire to be the first in successfully attempting new surgical innovations and make a name in the community was typical among cardiac surgeons, it was considered in the interest of the innovator to allow other physicians to use and evaluate the new technique independently in their own patients in order to gain clinical acceptance of the new practice. One way to do this was to organize cooperative studies across a number of centers and funded through NIH grants (Kantrovitz, 1990).

A limited number of research groups quickly became the hubs of this informal network among leading cardiac centres. In the early 1960s new artificial heart research programs were formed at Pennsylvania State University, University of Utah, Baylor College and the Cleveland Clinic. In these institutions research on artificial heart technologies were conducted by large multidisciplinary groups of surgeons, cardiologists, physiologists, engineers, veterinarians and other medical and technical individuals. Their work included the design of devices, fabrication of prototypes and small batches of devices, bench evaluation, animal evaluation and clinical use. External collaborations with other academic institutions and commercial companies were established on specific investigator-initiated projects,

funded in many cases by the NIH. Other medical centers such as the Children's Hospital in Boston, Stanford, and the Massachusetts General Hospital were engaged in validating and testing the functionality of the devices, and were developing techniques for implanting them, providing also feedbacks on possible adaptations of the artifacts.

Due to problems encountered in clinical applications such as the inadequacy of the materials to support patients beyond several days or weeks, the need for a major surgical procedure and the almost prohibitive cost of using the device clinically early pulsatile devices were considered only investigative procedures (DeBakey, 1971). However, the possibility to further develop these early prototypes with the ambitious goal of using them in the clinical treatment of heart failure patients was becoming clear to an increasing number of people involved in the LVAD field.

3.1.3 More resources are needed: the creation of the Artificial Heart Program (mid 1960s)

The surgical investigators who were early entrants to the field played a pivotal role as the main advocates for securing federal support for their research and lobbied for the establishment of the Artificial Heart Program, which the US Congress established in 1964 and started funding in 1966. The National Heart, Lung and Blood Institute (NHLBI), through its Device Branch, was the NIH institute in charge of the Artificial Heart Program, with the task of directing and guiding the targeted effort to develop a family of mechanical circulatory devices for temporary and permanent applications to solve the national cardiac problems. In contrast to

the majority of research funded by NIH, the mission-oriented and targeted research activities supported under the Artificial Heart Program both on the total artificial heart and the left ventricular assist device were financed through contracts awarded from targeted requests for proposal, and not through grants to fund investigator-initiated projects (Altieri et al., 1986).

The continuity of funding in the late 1960s based on contracts for the development of artificial heart technologies stimulated the formation of new industrial research and development groups working in this area both within existing commercial companies and in newly established laboratories. For instance, companies working in the defense, space and instrumentation sectors like Aerojet and Thermo Electron Corporation started internal 'medical R&D groups' that were working mainly on NIH contracts. At the same time industrial scientists and engineers started new small ventures like Avco Everett Research Laboratories, Andros Loboratories and Thoratec Laboratories to work on research and development of the artificial heart devices. Both the work in commercial companies and in these new laboratories was conducted in collaboration with surgeons and engineers based in medical centers and funded by federal contracts.

An annual conference was started since the beginning of the artificial heart program by the NHLBI Device Branch for all investigators and contractors, based in medical centers, commercial companies and laboratories which were funded by its contracts. The event was considered an effective and essential way to facilitate the sharing and dissemination of knowledge among the medical and engineering

people working on developing a device treatment for heart failure.

3.1.4 A system approach to search for new component technologies (1970s)

By the early 1970s the hopes that a full blown artificial heart would be quickly developed were seriously compromised by the lack of progress on the problems of biocompatibility of materials and availability of appropriate energy sources encountered in the first decade of the artificial heart program. It was believed that these problems would be less severe for the LVAD, so the NHLBI Device Branch decided to concentrate its limited resources on the development of this family of devices. This new direction in the development of a LVAD device came out from a broader consultation in the community involved which NHLBI finalized in 1972. The Device Branch sponsored a conference, where many people involved in the field of mechanical circulatory devices were invited. The discussions during the conference emphasized the need for the development of long term and permanent LVADs and a shared view was that 'technology development for implantable assist devices would have application to all other forms of circulatory support' including the artificial heart (Altieri et al., 1986: 108). As a direct outcome of the conference a separated LVAD program was created within NHLBI in 1974. The targeted effort of NHLBI was not only directed to the development of component technologies but also to the improvement of instruments and methods used in the testing off line of new devices. Testing of a device starts with in vitro or bench test, followed by animal studies and then by use in humans. These systems are in vitro tests, which simulate the body's environment, allowing the reliability and durability of devices

to be evaluated[6]. For instance, the introduction of 'mock or artificial circulatory systems' in the early 1970s was a fundamental step in the development of the LVAD device due to its role in improving bench testing of devices.

The overall research and development effort of the field steered by the NHLBI Device Branch resulted in a number of LVAD devices designed and tested in the 1970s. These devices were the result of new collaborations between research groups based in commercial laboratories or companies and in academic medical centers that responded to NHLBI targeted requests for proposals and were awarded contracts to develop further the existing projects in their pipelines and to undertake new ones within the remit of the requests of proposals. In all of these pulsatile LVAD devices the blood pumps were made of polyurethane and implanted in the abdominal cavity (so the devices were called Abdominal LVADs or ALVADs) and connected to the heart by surgically opening the chest, with the connected console unit and energy sources left outside the body, with patients tethered to them and confined in beds.

The first group of devices to be tested in the 1970s were the ones originally developed in the late 1960s using existing component technologies. First results of the in vitro testing of the abdominal LVADs were reported in the literature, followed immediately by the results of tests in animals in early 1970s. The testing work in the lab with in vitro and in vivo on animal was fundamental for surgical innovators in order to develop experimental implantation techniques. Initial clinical

[6]The mock circulatory system that became de facto the NIH standard for LVAD testing was developed at Penn State in 1972 based on research funded by NHLBI.

trials in humans to evaluate the devices as a bridge to transplant or a device used to keep a patient alive in the period before a heart for transplant became available started in 1976[7]. The NHLBI sponsored a multi-centre trial at the Texas Heart Institute and the Children's Hospital Medical Center in Boston, to evaluate the devices. These LVADs, built with old component technologies, were not very durable and reliable. However, the multi-center trial and the cumulated clinical experience with these devices in other hospitals from 1960s through the early 1970s confirmed the clinical usefulness of LVADs in supporting the circulation of patients for longer periods than was possible with temporary blood pumps which could be used for only a few hours or up to several days.

Better implantation techniques, along with the need for better energy systems and biomaterials, were the main research challenges of LVAD programs in the 1970s for the development of durable and reliable devices (Norman, 1974). NHLBI supported the research activities of surgical innovators engaged in improving the implantation techniques of LVAD devices. These innovators were experienced and talented cardiac surgeons mainly located in medical centers with high volumes of heart procedures. An example of these medical centers is the Texas Heart Institute (THI), which was established in the early 1970s, and that quickly became a central hub in the development and testing of new LVAD devices, due to its cutting edge research

[7]It is important to notice that the Medical Device Amendment Act in 1976 changed the existing practices to develop and test LVAD devices. The use of implantable medical devices like LVADs in patients both for research and clinical use became regulated by the Food and Drug Agency (FDA). Whereas before the passage of this act the use of experimental devices in humans was monitored by local advisory committees, after 1976 these decisions were centralized and supervised by the regulatory federal agency.

on surgical procedures and the high volume of patients treated. Cardiac surgeons in medical centers like the THI were focusing their research activities on improving surgical techniques for the implantation of the devices but also on testing and evaluating their performances in animals and in patients, providing valuable feedbacks – in some cases only in pointing out problems encountered implanting the LVADs but in other cases also in terms of ideas on how to fix them - to commercial companies and laboratories that were designing and manufacturing these devices.

3.1.5 The LVAD becomes a temporary device for patients waiting for a heart transplant (1980s)

The NHLBI Device Branch continued in the 1980s to play an active role in guiding the efforts of the LVAD community to solve existing problems of durability and reliability of the devices which centered on energy sources and materials technologies. Different technological solutions were systematically explored and the most promising ones were selected out and incorporated as constraints in subsequent requests for proposals. An example of this approach is provided by the choice of electrical energy as standard sources for LVAD devices in the 1980s. In this case, the Device Branch initiated a program to develop implantable integrated electrically-actuated LVADs with two-year reliability. Contracts were awarded to the proposals for the development of pulsatile electrically-actuated devices or so called 'first generation devices' presented by four commercial research groups[8]. In order to solve existing technological problems such as durability, reliability,

[8]These groups were: Andros / Novacor, Thermedics / TCI, Thoratec, Avco-Everett / Abiomed.

complications caused by biomaterials such as bleeding and clotting, and improving the location for implanting the device, each group pursued different pulsatile designs of electrically-actuated LVADs. All these pulsatile blood pumps were big and heavy devices, requiring lot of space to be implanted in the body, with two of the different devices still implanted in the abdomen and the other two implanted in the chest[9]. In addition to the devices developed under the four contracts awarded by NHLBI other devices were in the pipeline of other commercial groups.

The design of these electrically-actuated pulsatile devices was conceived in mid 1980s with technologies and ideas inspired by the abdominal devices of the 1970s. Between 1975 and 1985 the devices 'underwent considerable development work to arrive to the design we are currently using' (Poirier, 1997). The development and testing work by engineers over the bench and in the lab with animals performed well in in-vitro evaluation with mock circulatory systems, but it encountered unexpected problems when the devices started to be used in patients during clinical studies, which were initiated in mid 1980s. For example, one of these devices was highly reliable but introduced complications such as clotting that were not foreseen during its development and required further modifications. Other devices lacked reliability or were difficult to implant and required continuous modifications in response of feedback from surgeons that were putting these pumps in patients. New protocols were designed to manage the complications of each pump in addition to fix some of the technological problems encountered in using these devices in clinical

[9]The Abiomed was the largest at 1210cc in implanted volume and 2.2 Kg of components weight and the Thermedics the smallest respectively at 760cc and 1.3 Kg.

trials. The problems were only partially due to technological choices embedded in the artifact. Additional factors that played a role in the outcomes of LVAD procedures, included the reaction of each patient's body to the procedure, which in turn depend on a number of personal circumstances, and the quality of the implantation procedure, which surgeons were still in the process to developing and standardizing for each device.

Notwithstanding the complexity involved in LVAD procedures, a number of first generation pulsatile electrically-actuated devices were successfully implanted in patients who were waiting for a heart transplant during the mid-1980s. To evaluate the progress of these pulsatile electrically-actuated devices, the NHLBI decided to sponsor an audited testing program of the in-vitro readiness of these devices between 1986 and 1988. Altogether, the durability and reliability of four devices were evaluated. Because the LVAD devices were intended as bridge to transplant, they needed to reliably support the heart for longer periods then a few days or weeks, so the Device Branch determined a two year period testing period. When one device successfully completed the evaluation, the NHLBI decided to sponsor the clinical trial of this device as bridge to transplant, which started in 1991.

3.1.6 Pulsatile LVADs were the Model T of the industry (1990s)

All LVAD manufacturers used the learning generated by the 2-years in vitro test funded by NIH to modify their devices and to improve them in terms of durability and reliability through continuing clinical studies, sponsored by NIH or by partnership between manufacturers and hospitals. In 1994 the FDA approved the

first LVAD device as a bridge to transplant device[10]. Although this was an important moment in the evolution of the device, there was a high level of consensus in the field that major problems in the existing pumps remained. The devices were in average more durable and reliable, and their complications could be managed with different strategies such as drugs for blood clot prevention and the use of better biomaterials for the coating on the wires that penetrated the patient's skin, but they were still bulky and patients remained hospitalized.

In the mid 1990s, a lot of development work went into reducing the size of the LVAD devices. Electrically-actuated pulsatile devices were smaller than earlier abdominal LVADs. It was only with the introduction of rechargeable electrical batteries as primary energy source, located outside the patient' body[11], that the average dimension of the LVAD device became comparable to a large format paperbound book. The devices became 'implantable', i.e. the devices changed from being mostly outside the body, to being mostly implanted leaving outside only the controller and the batteries and 'portable' or un-tethered, i.e. the patients could leave the hospital to wait for transplantation. In 1997 the first LVAD patient could be discharged from the hospital and wait at home for its heart transplant. Overall, the lives of patients with end stage of heart failure were extended and made relatively better by LVAD devices, although not yet very comfortable due to the invasive surgical procedure necessary to implant the device, and after the implantation the need to follow a drug therapy to manage complications, the noise

[10]The first device approved was the Heartmate by Thermedics.
[11]The external batteries were connected via a lead going through the patient's skin to the inside pump.

produced by the device and the need to regularly charge the electrical batteries. In 1998, the FDA approved two pulsatile LVAD devices to be used as bridge to transplant[12], which were fully implantable electrically-powered, wearable LVAD devices. The regulatory approval for their use in clinical practice and commercialization was given based on the provision of evidence of safety and effectiveness by the two manufacturers of the devices. This evidence was produced through multi-centres clinical trials conducted both in Europe and in the US in large-volume cardiac institutions.

For many people in the LVAD field, the two pulsatile devices were the Model T of the industry. They widely believed that more effective devices were getting ready to move from research and development pipelines of academic laboratories and commercial companies to clinical trials in medical centres (Goldstein and Oz, 2000). Moreover, some people came to the somewhat new view that LVAD could be a bridging technology but also a permanent treatment for end-stage heart failure. Surprisingly some of these people were cardiologists involved in the diagnosis and treatment of heart failure patients for whom the approval of the first fully implantable and wearable devices caused a dramatic shift in view about this therapeutic innovation. Since the beginning for many cardiologists, even the ones involved directly with heart transplant centers, mechanical devices – both the artificial heart and the LVAD - were not real therapeutic options for patients with late stage heart failure due to the poor quality of life that these pumps were

[12]The Thermedics device called HeartMate I and the Novacor device.

offering. With the limited number of heart transplants due to the shortage of organs available, the only medical therapy they would consider for their heart failure patients was the one based on drugs. However, in the late 1990s with the availability of new approved pumps some of them changed their view and started to consider LVAD as a therapeutic option.

In order to overcome problems of the first generation pulsatile devices including the size of the devices and implantation complications, alternative technological trajectories for the development of new pumps started to be explored from the 1980s onwards. In the early 1990s, new innovative designs for non pulsatile LVAD were developed and tested by different groups involved in the LVAD field. The development of these non pulsatile designs, but also continued work on pulsatile LVADs, was once again steered in part by the NHLBI. In 1994 the Device Branch issued a request for proposals for the development of 'Innovative Ventricular Assist Systems (IVAS)' to encourage innovation in the development of totally implantable ventricular assist devices. NHLBI decided to fund proposals based on several different technological paths. Additional development for some of these devices was supported from mid 1990s also by the NIH - Small Business Innovation Research (SBIR), a new federal funding scheme addressed in particular to small firms. An increasing level of commercial and financial interest in the LVAD market created a new wave of start-ups companies which was partially funded by the SBIR program. Now that the proof of concept of the LVAD technology had been obtained and the LVAD therapy was increasingly accepted for patients with heart failure, much of

the development work for the design of new LVAD devices was taking place in commercial companies. The IVAS program and other schemes like the SBIR, and the entry of new commercial companies in the LVAD field contributed to bring the new LVAD devices to a good stage of development and ready to be introduced in clinical studies. A very limited number of new non-pulsatile pumps started to be evaluated in medical centers in Europe and in Australia, where many LVAD manufacturers began to conduct their initial clinical trials in the early 1990s. In 1998 the first clinical application of continuous-flow assist devices as bridge to transplant was done in the US. Clinical trials for many of rotary LVADs in the research and development pipelines of different manufacturers really started in the US only in the early 2000s.

3.1.7 'The LVAD devices are quite effective, but there are too many of them!' (2000s)

Over the last 10 years the views of some heart failure cardiologists and of many other actors within and outside the LVAD community of these devices started to change, since LVAD pumps are becoming more effective medical devices, e.g. reliable, smaller, simpler comfortable to live with, and easier to implant. We have now a number of different LVAD devices with several ones still being in development and in clinical trials, with a minority approved for clinical use[13]. The smaller sizes of rotary pumps opened up also the possibility to develop devices for children, women and in general for people with small body size to whom the larger

[13]In 2007 there were 7 or more LVADs in different stages of clinical trials in the US.

pulsatile devices could not be implanted[14].

It is the opinion of some people within the LVAD community that there are presently too many devices with similar technical characteristics both in the market and in the pipelines of companies. This suggests a need to compare their real effectiveness through head to head clinical studies. Furthermore the major problem that now needs to be tackled is not building another pump but reducing the complications or adverse events caused by LVAD implantation in the human body (Hunt, 2007; Mussivant, 2008), which can not be eliminated only by developing more effective devices. And this leads us to the discussion of the advances in the LVAD application procedures that have emerged and are currently employed.

3.2 Advances in the Clinical Procedures of LVAD

In the previous part of this section we described how LVAD moved from being an idea in the minds of a few surgeons and engineers to an effective device at the centre of a thriving community populated by medical centers, federal agencies, manufacturers, patients and other actors. We illustrated the interaction between the design and modification of the device and its use initially as investigational or experimental procedure and then as an approved treatment for heart failure patients. We will now discuss the advances that occurred and made the LVAD an increasingly adopted life saving therapy for the treatment of heart failure patients, starting with the improvements in the implantation procedure. At the present time this procedure remains a major cardiac surgical operation, and this is likely to

[14]In 2004 NHLBI funded five contracts for five years to develop pediatric LVADs.

continue be the case for some time. It requires the skills of an experienced cardiac surgeon and a supporting surgical team, an appropriate infrastructure to conduct the operation and the pre- and post-operative care. Furthermore, it carries all the risks of complications and the recovery problems of a major cardiac surgical procedure[15].

3.2.1 The improvement of the LVAD implantation

When the LVAD pumps started to be implanted substantial experimentation was devoted to finding better ways to put them in human bodies and connecting to the heart. In the 1960s and 1970s, the work to develop surgical innovations and new implantation techniques was left to experienced and talented surgeons who needed to figure out how to put inside patients pumps of the size of a large format paperbound book or even bigger. Procedures were first tried it out in animals in order to minimize the amount of experimentation in patients. Over time a number of different implantation techniques have been developed, refined and chosen over alternatives. For instance, the first generation pulsatile devices, which were large pumps, were placed in the abdomen of the patient. The new rotary devices, now in clinical trials, due to their smaller sizes, are implanted near or within the heart (i.e. in the left ventricle) and they do not require the total opening the chest. The reduced size makes the implanting procedure easier and faster to perform, but also less invasive, so reducing the rate of surgical complications, making the recovery of the patient shorter and less painful. A further reduction in the size of the devices,

[15]For instance limited risks of death and of neurological damages when the cardiopulmonary bypass is used plus pain to the chest and time to recover after the surgery.

which are now in development and offer a partial support of the heart, allows envisaging the implementation of some of these devices through minimally invasive or interventional techniques instead of major cardiac surgery.

Currently, the implantation techniques of different pulsatile and rotary LVAD devices involved in clinical trials are almost standardized procedures. Many cardiac surgeons involved in heart transplants are also the ones doing the LVAD implantations in patients who ultimately receive transplants as well as other patients. A cardiac surgeon can perform an implantation with the skills acquired during surgical residency, complemented by further training with surgeons with LVAD experience and with specific knowledge of the device, which is normally supplied by the manufacturers. The basic steps required are the creation of a device pocket, the connection of the pump to the heart, the placement of the driveline and the actuation of the device. As in the case of other major surgical procedures, each surgeon has preferences over alternative ways to conduct some of these steps (e.g. choosing to do the implantation with or without the use of cardiopulmonary bypass) (Morris, 2007).

3.2.2 The development of pre- and post-operation procedures, LVAD teams and centres

The competence and experience of the heart surgeons who implant LVADs is a necessary, but not sufficient condition for successful outcomes from the procedure. A team of professionals needs to support the surgeon during the operation, but also in the pre-operation and post-operation care stages. This support includes explaining

the risks and benefits involved to possible patients and their families of the LVAD as therapeutic option and managing the complications of the implantation and the management of the devices. The core LVAD group normally includes, besides the cardiac surgeon, a bioengineer in charge of monitoring the LVAD device, a coordinator to take care of protocols and hospital logistics and a physician who could follow up and manage the patient's daily conditions, including nutrition, exercise, medications and various tests (Oz, 1998). In many centers this physician, the 'transplant or LVAD doctor' or the heart failure cardiologist, refers the patient to the surgeon for a LVAD procedure and follows it up afterwards. Additional members of these normally multidisciplinary LVAD teams include nurses, social workers, physical therapists, physician assistants and psychologists.

In early 1990s with the first generation devices approved as bridge to transplant for end stage heart failure patients a number of LVAD programs were created in existing heart transplant centers with significant volumes of patients treated. The management of the patients undergoing LVAD implantation and heart transplant has some similarities, in addition to the fact that the same patients were implanted with an assisted device in order to be transplanted later on. Additional new programs were set up subsequently by many hospitals with existing heart programs[16]. Leading LVAD programs manage a small sub-set of the devices currently available (both under experimentation/trials or for approved clinical use) because there is continuous learning derived from the use of each of these devices

[16]In some cases these centers do not have a transplant program.

and the development of the LVAD therapy is still on ongoing process. Furthermore, new procedures are currently being developed in order to refer and screen patients who are good LVAD candidates, but also to design and to manage outpatient programs, i.e. services for implanted patients who leave the hospital to return at home. Nutrition, exercise and complementary drug therapy are examples of additional factors in the pre-op and post –operative care stages that contribute to better outcomes in the overall LVAD therapy.

3.2.3 Improving outcomes, expanding indications and proving effectiveness

A significant step in establishing a therapy for heart failure patients based on the LVAD was demonstrating its effectiveness in comparison to existing treatment modalities. The REMATCH trial (1998 – 2001)[17] involving first-generation LVADs implanted in end-stage heart failure patients was a major step forward in the investigation of LVAD as therapy for heart failure and it showed that early survival of patients on LVADs doubled compared to those on medical therapy at one year. It generated solid and robust evidence about the safety and effectiveness of LVAD in very sick patients – the therapy supports functional survival of patients - establishing LVAD as 'destination' or permanent therapy for these patients, i.e. the last hope for dying patients with 'one foot in the grave').

Since Rematch trial, the indications for LVAD therapy have changed and expanded, although the progress of establishing LVAD as therapy for other than heart failure

[17]The clinical trial started in 1998 and results were published by the main investigators for the first time in 2001 on the highly prestigious New England Journal of Medicine (see Rose et al., 2001).

patients at extreme end stage proceeded at slow pace. The availability of smaller devices less prone to technological failures, i.e. more reliable, and the improved experience with implanting procedures contributed to this progress. The key problem is now to characterize the target population that can benefit from LVAD beyond end-stage heart failure. The expansion of the inclusion criteria for mechanical support in recent years towards less sick patients has been important[18]. Several reports have sought to identify significant pre-operative variables that may predict risk and impact outcomes (e.g. in terms of reducing of mortality and/or complications). For example, the timing of intervention has proven to be an important determinant of clinical outcomes. Risks and complications can also be viewed as the result of treating patients who are too sick to be treated. "If we could operate on these patients earlier, our results would be better". It is a vicious circle that is difficult to break: patients who are treated are too sick, so putting LVAD in them carries additional risks and complications compared to the ones associated with the device and the characteristics of patients (i.e. who receive the implantation after their nutritional status and end-organ function have declined too much). Cardiologists who are treating heart failure patients view the LVAD as a last resort and refer patients when they are too sick for other treatments.

The NHLBI Device Branch in cooperation with the FDA and the Center for Medicare and Medicaid Services is trying to monitor changing effectiveness and

[18]LVAD is now used for a larger population of patients with heart failure, generated by both acute and chronic cardiovascular disease. The devices can be used as a bridge to transplantation and as destination therapy in patients with end stage heart failure, but also as a bridge to recovery as described in more detail in the next sub-section.

safety outcomes. The three federal institutions have supported the creation of a clinical data registry – called Intermacs (Interagency Registry of Mechanically Assisted Circulatory Support) – to cumulate outcomes and other data on LVAD patients across different centers implanted with different devices. Initially, this register was built by professional medical societies, which were trying to encourage manufacturers to share data about devices and patients, initially cumulated in proprietary registries only available to their investigators. The formation of a registry was not welcomed by manufacturers who viewed this as an effort to harm competition among different devices and companies. At the beginning the participation to the Intermacs registry was left at the discretion of manufacturers and investigators, whereas it is now enforced through a cooperation where FDA and CMS link the approval and reimbursement processes of new devices to the participation in the registry. This serves to stimulate learning at the level of the field across devices, for example, in the selection and management of patients. The significant improvement in the quality of the clinical outcomes of use of LVADs, as evidenced by the Rematch study, certainly provides an argument for its more general use. However, the cost of treatment using LVAD continues to be very high, which certainly is and should be a deterrent to the diffusion. While the experience cumulated by some LVAD programs with a significant volume of patients shows that further reductions in the cost of LVAD therapy are possible, this hasn't happened yet. At present, both because of its high cost and because many cardiologists are not yet persuaded of its benefits to heart failure patients, the

LVAD therapy is still not widely adopted as treatment for eligible patients by the wider medical community involved in the treatment of heart failure. Although the LVAD was included as a therapy for end stage heart failure patients in the medical guidelines published in 2005 by the American College of Cardiology (Hunt et al., 2005), the clinical implementation of guidelines in the LVAD case, like in other medical therapies, is still limited and eligible patients are not referred to this therapy, showing that a number of barriers still need to be overcome.

In the next sub-section we discuss how the use of LVAD treatment in clinical practice was instrumental in advancing the understanding of heart failure and the diseases that produce it. Perhaps this more recent development in the LVAD story could lead to a larger adoption of this therapy, based on the legitimacy provided by relating its advancement to scientific understanding of the heart failure disease.

3.2.3 Advances in the Scientific Understanding of Heart Failure

'Despite repeated attempts to develop a unifying hypothesis that explains the clinical syndrome of heart failure, no single conceptual paradigm for heart failure has withstood the test of time.'(Mann, 1999)

Over the last century we have developed a much better scientific understanding of the heart, which in some cases has been instrumental in developing treatments for some of its diseases. For instance, understanding of the anatomy and physiology of the heart was important for the development of surgical treatments of vascular diseases. Heart failure in clinical practice is diagnosed based on a number of

measures of the cardiac output or capacity of the heart to pump blood and treated with a combination of approaches, which includes drugs, surgery, devices, nutrition, exercise and rest. But these treatments for heart failure, like in the cases of other heart diseases, have been developed since the 1950s without a deep scientific understanding of the causes and mechanisms of this disease.

A scientific model of the causes and mechanisms of heart failure largely accepted by the medical community is the hemodynamic model, where the disease is thought to arise as a result of abnormalities of the pumping capacity of the heart or excessive peripheral vasoconstriction as in obstructed arteries. However, we do not know what causes these abnormalities in the first instance. Furthermore this hemodynamic model for example does not explain the progression of heart failure in patients treated with current medical therapy (Mann and Bristow, 2005). 'Heart failure has a worse prognosis than most cancer, but heart failure lags far behind cancer in the robust staging of patient profiles and prognosis' (Warner Stevenson and Couper, 2007: 750), because we do not have a detailed understanding of the factors behind the risk, mechanisms and progression of heart failure in patients. Like in the case of other treatments for heart failure the LVAD therapy has been developed without a detailed scientific understanding of the causes and mechanisms of this disease. On the contrary, a lot was learned about the heart relevant to LVADs and beyond in the course of developing and using LVADs. This is the case of the recovery of the heart: we now know that heart failure can be reversed by providing prolonged LVAD support to the heart that can in this way

temporarily download its pumping function and recover. Cardiac clinicians and researchers did not think that the heart could recover from heart failure, although this idea was initially proposed in the 1960s by Burch who stated that 'the heart, like any other diseased organ, improves with rest'. The possibility of cardiac recovery during ventricular assist device support was reported anecdotally in the literature in 1994 by Frazier and later on observed by other researchers.

'While end-stage heart failure was once thought to be irreversible, research now suggests that LVAD support may lead to both cellular and functional recovery. Ultimately, patients with advanced cardiac disease might be managed with temporary mechanical support combined with pharmacological and cellular therapies, in place of cardiac transplantation or long term LVAD support.'

It has now been demonstrated with sufficient evidence that the heart can recover in some cases even completely when supported for a prolonged period of time by a LVAD and in the last ten years a major focus of investigation in the field of advanced heart failure research became the temporary use of LVADs as bridge to recovery of the patient own heart. Both basic and clinical heart failure scientists are now working to understand and explain the cumulated clinical evidence and the underlying cellular and structural mechanisms for cardiac recovery seen in patients with prolonged LVAD support (Torre-Amione and Loebe, 2006). Moreover, the combination of LVAD implantation with new pharmacological therapy and stem cells that can increase the chances to succeed in promoting the recovery of the heart in a larger number of patients is now investigated (Birks et al. 2006). The

contribution played by the LVAD treatment of heart failure in improving the scientific understanding of the heart disease could be lead to its widespread dissemination as adopted medical practice.

4. The Evolution of the LVAD as a Treatment for Heart Failure

Overall, for some people the LVAD is now ready for the 'prime time' in the clinical treatment for heart failure after a 50-years journey (McCarthy and Smith, 2004): the device is quite effective, especially the new devices that are now in the pipeline and are reaching clinical trial stage; the LVAD practice is clinically used, although not widely diffused to treat heart failure; and new scientific understanding about heart failure disease is coming out from the development of the device and its clinical use in patients. As LVADs have improved, they increasingly have been implanted as a treatment for heart failure in their own right, rather than as a bridge to transplant. Whereas there was a considerable period when knowledgeable people could argue that an LVAD implantation did not generally improve the conditions of life of a patient, the most recent evaluations indicate that the current LVADs (or more accurately the earlier LVAD implantations that were evaluated) do on average extend the life of the patient, and that living with an LVAD, while still not easy, is more comfortable than it used to be. There are strong indications that in the coming years LVADs will become more reliable, be much smaller, easier to implant, and to live with, maybe even cheaper or cost effective, although we are more skeptical about the latter.

The LVAD case shows vividly the fabric and the dynamics of the three mutually constituting, interdependent and evolving pathways involved in the advance of medical therapy when a medical artifact is involved: enhanced ability to design and develop effective medical artifacts like new drugs and medical devices of various sorts, improvements in the medical procedures employed by physicians and healthcare organizations themselves, and advances in scientific understanding of disease and body function. The efforts that led to today's LVADs were not induced by any advance in understanding of heart disease. Rather, the efforts started in the 1960s because of the general view that the basic technology was then available for the development of an artificial heart, an effort that gradually shifted over to the development of heart assist devices. Nor, over the course of these efforts to date, has there been any major advance in basic biomedical understanding that has helped to guide the effort. On the other hand, experience with patients who have had LVADs implanted has led to an enhanced ability to design and develop new medical technologies and a new understanding that a damaged heart can at least partially heal itself if relieved of some of the pumping burden needed to sustain life. While not from basic scientific research, a lot has been learned over the history of LVAD that has helped the evolution of this new medical therapy.

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