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► **To cite this version:**

Karl Bounader, Erwan Flécher. End-stage heart failure: The future of heart transplant and artificial heart. *La Presse Médicale*, 2024, 53 (1), pp.104191. 10.1016/j.lpm.2023.104191 . hal-04467355

HAL Id: hal-04467355

<https://univ-rennes.hal.science/hal-04467355v1>

Submitted on 4 Apr 2024

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End-stage heart failure: the future of heart transplant and artificial heart

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Abbreviations

DBD: Donation after Brain Death

DCD: Donation after circulatory death

ECMO: Extracorporeal membrane oxygenation

HF: Heart failure

HTx: Heart transplantation

LVAD: Left ventricular assist device

MCS: Mechanical circulatory support

RVAD: Right ventricular assist device

TAH: Total Artificial Heart

XTx: Xenotransplantation

Abstract

In the last decades, outcomes significantly improved for both heart transplantation and LVAD. Heart transplantation remains the gold standard for the treatment of end stage heart failure and will remain for many years to come. The most relevant limitations are the lack of grafts and the effects of long-term immunosuppressive therapy that involve infectious, cancerous and metabolic complications despite advances in immunosuppression management. Mechanical circulatory support has an irreplaceable role in the treatment of end-staged heart failure, as bridge to transplant or as definitive implantation in non-transplant candidates. Although clinical results do not overcome those of HTx, improvement in the new generation of devices may help to reach the equipoise between the two therapies.

This review will go through the evolution, current status and perspectives of both therapeutics.

1. Introduction

1.1. End-stage heart failure

End-stage or advanced heart failure (HF) is characterized by persistent HF symptoms that interfere with daily life's activities and with recurrent hospitalizations despite a maximal medical therapy. In France, HF (whatever the stage) affects 2 % of the French adult population, and 10% of people over 60 years old. Its incidence remains however underestimated and increases of 25% every 4 years due to the aging population. It is the cause of over 150,000 hospitalizations per year and 70,000 deaths which represent 1 death every 7 minutes (1). The overall mortality of patients with HF is estimated at 20% at the age 55 years old and 50% at the age of 85 years old after a first hospitalization (2). Patients with end-stage HF have a worse prognosis, their overall survival is estimated at 70% at one year and 50% at two years (3).

1.2. Heart Transplantation and mechanical circulatory support

According to the American and European guidelines (4,5), three therapeutic options are possible for patients with end-stage heart failure. The first one is heart transplantation (HTx) which is the gold standard treatment providing the best survival rate and life quality scores (6). Its main limitations are the lack of heart grafts and the heaviness of the immunosuppressive therapy. The latter may contraindicate transplantation for a number of candidates, as those with a recent history of malignant tumors for example. The second option is the implantation of a long term mechanical circulatory support (MCS) device, which can be a partial artificial heart assisting only the left ventricle (left ventricle assisted

device or LVAD), or a total artificial heart (TAH) which replaces both right and left ventricles (Figure 1). These two therapeutic options will be discussed in depth further in this article. Implantation of simultaneous right and left current ventricular assist devices for biventricular support has also been reported but remains rare with very few publications, mainly as case reports, and will not be discussed herein. The third option is palliative care when HTx and MCS are not judged reasonable/feasible, which is the case mostly in elderly patients. In those patients, a fourth therapeutic option may develop with time and would consist in less invasive techniques such as the emerging electric cardiac neuromodulation techniques or long term percutaneous and intravascular support pumps (7-8).

2. Heart transplantation

2.1 A quick history

On December 3rd 1967, south African surgeon Christiaan Barnard performed the first human heart transplant at the Groote Schuur Hospital in Cape Town, South Africa. The donor was Denise Darvall, a 25-year-old woman in a state of brain death after being hit by a car with her mother on December 2nd; the recipient was Louis Washkansky, a 53-year-old diabetic man in terminal heart failure due to an ischemic heart disease. He died 18 days later of pneumonia (9).

Three challenges had to be resolved in order to achieve this feat. First of all the surgical technique. The first experimental work on heart transplantation was carried out by a Russian surgeon Vladimir Demikhov on canine models. His first orthotopic transplant was performed on December 25th, 1951, in circulatory arrest and deep hypothermia (10). The advent of

extracorporeal circulation led to the development of technical aspects on humans, notably with the work of Richard Lower and Norman Shumway at Stanford (11). The second challenge was immunosuppression. Advances in this field were first made by Sir Peter Medawar with his work on the immune system and the mechanisms of acceptance or rejection of skin grafts in burn victims which made him win the Nobel Prize for Medicine in 1960. In 1962, at the University of Colorado, Thomas Starzl demonstrated the benefits of combining azathioprine and corticoids to prevent graft rejection and performed the first human liver transplant in 1963. The corticosteroid/Azathioprine protocol was the immunosuppressive treatment of choice for two decades, including in HTx, despite its association with a high incidence of infection and rejection. It was not until the introduction of cyclosporin A in 1983 that overall survival significantly improved by the mean of a more efficient immunosuppressive therapy (12).

Finally, the third challenge was legislative. In the absence of clear legislation on brain death, harvesting organs from donors with beating hearts was subject to public criticism. Therefore, Christian Barnard performed his first HTx after circulatory determined death today known as Maastricht 3. It was not until 1968 that the precise definition of brain death was published by Harvard University, and subsequently recognized by legislators (13).

2.2 Today's outcomes

Over 150 000 HTx has been registered by the international society for heart and lung transplantation (ISHLT) since 1982. Over time, the number of HTx per year has been increasing and reaches since 2016 more than 5500 cases worldwide. Post-transplant survival has also continuously improved over time. The median survival after an adult heart transplantation was 12.5 years if performed between 2002 and 2009. Today's overall median

survival of a HTx patient exceeds 15 years (14). These results vary according to recipients and donors' characteristics. A young recipient with no history of cardiac surgery who is transplanted with a young donor's heart will have the best possible outcomes (15).

Recipients and donors' characteristics differ significantly according to countries which mostly explains outcomes differences. For example, the average age of donors in Europe is 44 years old vs 35 years old in the USA. Also, in France, 20 % of patients are transplanted while on extracorporeal membrane oxygenation (ECMO) support vs 1 % according to the ISHLT registry (15-16).

Temporary ECMO support emerged in the early 2000s and has played an important role in increasing the number of candidates for HTx since it allowed acute heart failure patients' survival until receiving a matching graft (the so called "bridge to transplant" strategy). Most of all, ECMO allows also temporary support after HTx until the graft recovers in cases of severe primary graft dysfunction, which has an incidence of approximately 30 % in France (16-17). ECMO support is now widely accepted and used in all heart transplant centers, as bridge to transplant in most severe HF patients awaiting a cardiac graft and as bridge to recovery after HTx when severe graft dysfunction occurs.

2.3 Today challenges

The surgical technique has little evolved since the first HTx. Future improvements in outcomes and major developments will not pass by the pure technical aspects of HTx since little can be improved at this level. However, one should keep in mind that the surgeons involved in this field did not confine themselves to the technical aspects of their surgical profession, but also improvised themselves as researchers, physician-immunologists, legislators, and visionaries allowing evolution of HTx. Today challenges of HTx differ from

its first days. The first one, which would be a game changer if resolved, is the lack of available grafts.

In 2020, we reached 15,000 heart transplants in France since 1968. The number of heart transplants performed per year varies between 400 and 480, with over 800 patients on the waiting list, which mean that only one graft is available for two patients. As a result, about a 100 patients per year (10 to 15%) die because of the lack of grafts without counting those derived for long term MCS as an alternative therapeutic option (16).

These numbers are even more relevant in other countries with more restrictive legislation concerning organ donation. In France, anyone who has not expressed opposition to organ donation during his living is considered a donor by law. In opposition, in Germany or the USA, only the organs of those who registered as donors during their living can be harvested. This means that an individual will not be an organ donor unless he or she explicitly states otherwise. This is the reason why in France, there are time folds 2 donors than in Germany, (20,1 donors per million of citizens vs 10,1) and also why the mean delay for heart transplantation is much shorter in France than in Eurotransplant countries where Germany is the largest country (3 months vs 18 months) (18).

To resume, the two main challenges of HTx in our decade are to improve even more the survival rates and to fill the lack of available grafts by expanding the donor's pool. In order to achieve this, several solutions exist and are being applied or explored.

2.3.1 Expanded criteria grafts

In France, over 80 heart grafts proposed yearly by the national agency of biomedicine are rejected by transplantation teams and hence not harvested. The approval or rejection of grafts is in many cases subjective and can differ from one team to another. With time and with experience, an increasing number of expanded criteria grafts are being accepted with good results. Indeed, mean age of donors is increasing with time, and donors with medium to high doses of catecholamines or with relevant medical history such as diabetes, smoking or drug use are being increasingly harvested (15-16). New objective algorithms predicting correct size matching between the recipient and the donor are being used such as the calculated predicted heart mass, allowing an improved size matching and higher rate of graft acceptance that could reach 30 % (19-20). Moreover, improved immunological evaluation and matching by the mean of new techniques in antibody detection and histocompatibility testing have allowed an expansion of the donor pool for some sensitized patients using techniques that help to distinguish pathogenic from nonpathogenic antibodies. Also, traditional desensitization protocols as well as emerging therapies for desensitization in the appropriate patient are increasingly used to decrease the number and level of preformed antibodies and increase transplant eligibility (21-22). All these procedures allowed to increase with time the number of harvested grafts although more efforts still remain to be done.

2.3.2 Graft conditioning and preservation

The classical preservation technique for a harvested heart is a simple re-usable icebox with no active control on temperature (Figure 2). The optimal temperature for a heart graft preservation has to be between 4 and 8 °C (23). In recent years, a true revolution has begun in preservation and storage of the donor organs. New technologies have been developed and

are increasingly used for improved graft conditioning, with encouraging results and a reduction in the rate of primary graft dysfunction, allowing increasing harvesting of expanded criteria grafts. Currently, active organ perfusion before transplantation is routinely performed in many centers for kidneys, lungs and livers. Three new techniques for heart preservation are currently being used and/or investigated. The first and most expensive one is the normothermic perfusion technique (Organ care system, OCS, Transmedics ®) (Figure 3). The heart is implanted in a Langendorff model box that allow continuous perfusion of the heart in the beating state. This method would allow a better ex vivo evaluation of the graft and most of all an extended preservation time of it when needed. This procedure is particularly interesting in large countries with great distances between the donor and the recipient centers. It's also of a great help in cases of complex redo recipient who would require extended dissection time before graft transplantation (24-25). The OCS device allowed the longest ex vivo allograft perfusion time for a successful human cardiac transplant reaching 16 hours (26). The con of this technique is its logistic complexity since the harvesting team has to travel with bulky material and requiring several professionals (3 or 4 people including most often two surgeons, a perfusionist and/or an anesthesiologist) (Figure 3). The second procedure is a hypothermic perfusion technique (Xvivo Perfusion, AB®) (Figure 2). The heart is implanted in a smaller and more transportable Langendorff model box that continuously perfuse the heart with cold cardioplegia solution and in a rest state. No cardiac evaluation is possible outside of the donors in this case, but this system may allow to keep the protective effects of cold against ischemia. A non-randomized study has already proven its superiority comparing to traditional heart preservation in terms of recipient survival and a randomized study is currently being achieved with promising results specially in high-risk donors and recipients (27). The third technique is the less expensive and the simplest one since a single surgeon can travel alone with the material to harvest the

heart. It's an improved icebox allowing a better passive control of the heart's temperature by the mean of specific icepacks and a heart entirely suspended in the cardioplegia solution that maintain the grafts temperature homogeneously at an optimal temperature 6°C (Sherpapack, Paragonix®) (Figure 1 and 2). A propensity matched study has proved the superiority of Sherpapack compared to traditional cold storage with a reduction of severe primary graft dysfunction from 12.1% to 3.4% and increased one year survival of 8 % (28).

2.3.3 Maastricht 3

Solid organ procurement has historically undergone on brain death patients (DCB) excepted for living kidney donors. However, during last years, using short term mechanical circulation support and ECMO development, it has been possible to harvest organs in circulatory determined death patients (Maastricht 3 patients according to the Maastricht classification). Donation after circulatory death (DCD) refers to the use of a donor who has irreversible brain injury and may be near death but does not meet formal brain death criteria. This specific population allows an increase of donor pools. In these patients, abortion of medical support, which is mainly withdrawal of respiratory assistance and vasoactive drugs, is achieved. If the death occurs within an acceptable lap of time (which is 3 hours in France) and after circulation arrest, a regional normothermic circulation (ECMO like support) is rapidly implanted at the bedside in order to restore organ perfusion, expected for the brain that is excluded from recirculation by the mean of an intra-aortic thoracic balloon occlusion.

In France, the first case of Maastricht 3 organ procurement took place in 2016 for the kidneys. To date, about 400 kidneys are yearly harvested using this procedure which represents about 20% of all kidney transplantations in France (16).

Heart procurement after circulatory determined death is more complicated technically and legislatively. The first cases of HTx using Maastricht 3 donors have been described in Australia in 2015 (29). Several surgical techniques exist for the heart's retrieval according to each country legislation and each centers experience. The largest series of heart procurement on DCD heart have been reported from the Royal Papworth hospital using a direct procurement and reperfusion technique by specialist retrieval teams trained in ex-situ normothermic machine perfusion (30). A recent randomized study proved that survival at 6 months after transplantation with a DCD heart using normothermic perfusion preservation is not inferior to standard-care transplantation with a donor heart that had been preserved with cold storage after brain death (31). Other techniques include in situ recovery and evaluation of the heart after cardiac arrest before harvesting.

DCD donors increased overall heart transplantation in the UK by 28% (31). Many other European countries began DCD heart procurement such as Spain, Netherlands or Belgium. However, legislation remains a consequent barrier in other countries such as in France where a protocol adapted to French legislation is being developed.

2.3.4 Public awareness and legislation

Beyond medical considerations, legislators and public figures have an important role to promote organ donation. Law can be restrictive in countries operating under a model of expressed consent. Moreover, public awareness and education for organ donation might be a game changer. In France, about 45 % of possible DCB are not harvested because of opposition from donor or his legal representative. This percentage represents about 1000 donors that would theoretically significantly ameliorate the issue of lacking grafts.

2.3.5 Xenotransplantation

Xenotransplantation (XTx) is not a new concept and existed even before the first case of human heart donation. Indeed, James Hardy realized the very first XTx on humans in 1964 using a chimpanzee heart (32). Xenotransplantation could not only allow to overcome limited supply of allografts but also improve heart transplantation outcomes by offering to recipients a rapidly available graft before deterioration while on waiting list. Overcoming hyperacute, acute humoral, and acute cellular xenograft rejection is central to the success of cardiac XTx but is not the only challenge researchers have to overcome. Zoonotic spillover (transmission of pathogens from wild animals to humans) as well as ethical consideration concerning treatment of animal source represent other barriers (33). However, in January 2022, the first heart transplant from a pig to a human being was performed by a team headed by Bartley Griffith at the University of Maryland, Baltimore using a genetically modified swine (34). The patient survived 2 months before decision was made to withdraw medical care. The cause of death remains complex and unclear, combining viral and undefined immunological reactions. Therefore, there is a need to remain vigilant for unknown types of immunologic, infectious, and physiological barriers as well as important social, ethical, and economic challenges to address for the acceptance and application of XTx. New clinical studies may start in the United States in that field for patients that are not eligible for standard transplantation nor long term mechanical circulatory support.

3 Mechanical Circulatory Support

3.1 Definition

One has to distinguish between partial artificial heart which consist of a single conduit assisting the left ventricle (LVAD) or more rarely the right ventricle (RVAD) alone and the total artificial heart which replace entirely both left and right ventricles. An LVAD is a less invasive device connecting the apex of the left ventricle to the ascending aorta. Therefore, the main condition for a successful implantation of an LVAD is a right ventricle that would be able to absorb the increase in volume sent by the device to the systemic circulation. LVADs represents about 95 % of all implanted long term MCS and TAH 5% (35). An LVAD is an electrical intrathoracic device alimented by an external driveline. It can be used until a heart graft is available (as bridge to transplantation) or until death occurs (so called destination therapy). In cases of heart failure with severe right ventricle dysfunction or if the ventricles cannot be preserved such as in cardiac tumors, a TAH is required which is a more complicated intervention in more severe patients with consequent decreased survival rates. TAH can only be used as a bridge to transplantation strategy because of it less favorable long term outcomes and quality of life mainly due to bulky external commands.

3.2 History of MCS

3.2.1 LVAD

The first LVAD was implanted in 1963 by Liotta at Baylor College of Medicine in Houston, in a patient with a cardiogenic shock after an aortic valve surgery. With the development of transplantation programs, assist devices were first envisioned as a tool to support patients until a donor heart could be obtained. In 1967, the pneumatic Liotta-DeBakey Paracorporeal LVAD was successfully implanted as a bridge to transplantation strategy for

the first time (36). In 1975, authorization was given to start clinical trials of LVADs for temporary use in patients with postcardiotomy cardiac shock. The first generation of LVADs used pneumatic energy with extracorporeal ventricles that could remain in place only for a short term period. As TAH, they suffered from faulty control mechanisms, inadequate power supplies, and traumatic blood-pump interfaces, which produced hemolysis, bleeding and thrombosis (37). Quality of life was poor with these noisy devices and complications occurred promptly after implantation in most cases. In 1983, the use of cyclosporine for cardiac transplantation led to a sharp decline in allograft rejection and large improvements in patient survival encouraging proliferation of heart transplant programs worldwide, growing the cohort of patients with end-stage HF awaiting a donor. At that time, pneumatically activated devices could not be sufficiently miniaturized to provide a suitable quality of life. Researchers aimed to design simpler pumps to be implanted within the failing left ventricle. Therefore, clinical and technological advances worked for the development of miniaturized non-pulsatile electrically powered pumps that allow patients to leave the hospital and resume an independent existence. Both Jarvik 2000 (CE Mark in 2005) and Heartmate 2 (FDA approval in 2008) axial pumps LVADs were the first intrapericardial devices, followed by Heartware (FDA approval in 2012) which is a centrifugal designed pump that was also approved for less-invasive techniques (FDA approval in 2017). Miniaturization of these devices allowed the emergence of minimally invasive technique (38). However, LVAD devices are still not fully implantable and require external drivelines that are persistent gateways of infection and lower quality of life scores (Figure 4).

3.2.2 TAH

The most implanted TAH in the world is the one developed by SynCardia Systems® (Tucson, AZ) and is the direct descendent of the world's first TAH designed by Dr Liotta

and implanted by Dr Cooley at the Texas heart institute in 1969 as a bridge to transplantation device (39). Its design has little changed since. It is a fully implantable pneumatically driven pulsatile system and consists of two 70 cc independent artificial ventricles. Each ventricle is divided by a multi-layer flexible polyurethane diaphragm that separates the blood chamber from the air chamber. The direction of blood flow is controlled by four mechanical tilting disc valves. Each artificial ventricle has a conduit for air (driveline) from the external driver that allows the movement of the diaphragm for filling and ejecting the blood from the blood chamber. Each driveline is tunneled through the chest wall and connected to a bulky and noisy external pneumatic driver that limit considerably the mobility of the patients. In order to improve outcomes and quality of life new TAH devices are emerging offering improved blood compatibility and better mobility for patients by dint of lighter controllers and longer lasting batteries. As for new LVADs, the future of TAHs might be in using non pulsatile flow technology that will allow to decrease very significantly their size and power consumption allowing fully implantable devices with no external drivelines (40). Moreover the absence of pneumatic energy would significantly decreases the induced noise and improve quality of life. However, such devices are still at their early stages of animal experimentation and many years are needed until their commercial use in humans.

3.3 Today's outcomes of MCS

3.3.1 LVAD

According to the latest INTERMACS Report, the one-year survival rate is now equal to HTx, median survival of LVADs have recently outlined 5 years due to improved devices technology and better medical management (41). To date, the only commercially available

LVAD is the Heartmate 3 (Abbott, USA) which is a third generation centrifugal, continuous-flow pump, with a friction-free fully magnetically levitated rotor and wide blood flow pathways to decrease destruction of red blood cells. New technologies improved devices hemocompatibility and drastically decreased the rate of common adverse events in mechanical devices including pump thrombosis, stroke, and bleeding (42). There is significant improvements on functional capacity and quality of life after implantation of an LVAD compared to optimal medical treatment alone (43). Despite these major improvements, quality of life of an LVAD patient remains lower than HTx patients. The LVAD remain currently an unphysiological device with an external driveline and a laminar flow that do not vary between rest or effort (44). Therefore, driveline infection and functional limitations still exist compared to HTx. LVAD-related complications remain frequent and impact quality of life with potential psychological distress. Suicide rate in LVAD recipients are higher than in the general population or those with other chronic diseases (45). This emphasizes the need to develop, in addition to technological improved devices, multidimensional approach that considers patients' psychological characteristics to enhance LVAD acceptance and outcomes.

3.3.2 TAH

TAH outcomes are less satisfactory than LVAD mostly because of the initial state of illness of the candidates but also because of the device itself. According to the last INTERMACS report on the TAH, overall 3 and 12-month actuarial survival rates are 73%, and 53% taking account that most of TAH implanted patients are INTERMACS Profile 1 or 2 (80%) (46). The most common causes of death are multi system organ failure (40%), and

neurologic injury due to stroke (20%). The rate of patients discharged home with device in place is 25%.

A new TAH recently received FDA and CE approval. The french CARMAT® device has the particularity of being a completely biocompatible device with biologic valves therefore associated with lower anticoagulation targets and less hemorrhagic and thrombotic complications. It also allows a better freedom of movement patients with external batteries of only 5kg of weight and longer autonomy. However, CARMAT® TAH is available in only one size that is not suitable for small size patients. Preliminary results are encouraging but further studies should determine its exact role in advanced heart failure in the future. In smaller patients other TAH can be considered such as the 50 cc version of Syncardia (pneumatic TAH with 2 orthotopic polyurethane ventricles and 4 mechanical valves), a Berlin heart Excor® (extracorporeal pneumatic biventricular support mostly used in pediatric patients), or the use of two Hearmate 3 in a biventricular support configuration as an RVAD and an LVAD as recently described with excellent outcomes (47).

3.3.3 Medical and surgical innovations

Since the firsts MCS implantations, consequent medical and surgical innovations have been made allowing improved outcomes. Although the majority of patients implanted in France with an MCS are not ambulatory patients and are particularly severe (more than 20 % under ECMO support at the time of LVAD implantation), medical enhanced pre-operative management with better timing for implantation and optimization of hemodynamics using selected drugs allowed better preparation of patient and significantly improved outcomes (48). This includes preoperative aggressive management with control of diuresis and preparing the right ventricle with phosphodiesterase-5 inhibitors, levosimodan infusion and

extubating and mobilization when possible. Also, per operative anesthesia management is of major importance by using nitric oxide or inhaled epoprostenol and early epinephrine for systemic blood pressure and contractile sufficiency. At the surgical level, implanting the device on a beating heart without cardiac arrest, controlled bleeding and pericardial sac opening avoidance by using minimally invasive techniques allows to spare the right ventricle function and reduce transfusion requirement resulting in better outcomes (49).

Moreover, a dedicated medical organization with an advanced heart failure team is mandatory to take care of these very severe and specific patients. Trained and specialized cardiac surgeons, anesthesiologists, heart failure cardiologists and VAD nurses coordinators should be part of such advanced heart failure programs. Referral centers specialized in heart transplantation and all kind of mechanical support should be identified with a minimal activity and volume in that field. Regional organization is essential to optimize better care and outcomes in such rare and most severe patients (50).

3.4 Tomorrow challenges of MCS

3.4.1 Biocompatibility

Major advances have been made since the first generation of LVAD and TAH regarding biocompatibility of these devices with much lower rates of thrombo-embolic and hemorrhagic complications. However, the rates of gastrointestinal bleeding due to angiodysplasia and the loss of physiologic pulsatility with current LVADs (acquired Von Willebrand syndrom) remain as high than in other devices. In order to be even more physiologic, the next generation of LVADs will have the capacity of generating a pulsatile

flow that would eventually adapt to the activity of the patient. This might be the case of the French company Corwave® technology which can mimic the native heart blood flow pattern (low shear stress and pulsatile), reduces energy-requirements and gives opportunities to downsize LVADs further. Moreover, better biocompatibility may allow to significantly decrease the level of anticoagulation.

3.4.2 Fully implantable LVADs

Driveline and device infection remain a constant complication of TAH and LVADs. While new devices have reduced the rates of blood related complications, driveline infection is still the number one device related complication. Indeed, with time, almost all drivelines get infected. Local dress wound must be done at least twice a week, daily if infected, impacting greatly the quality of life and reducing mobility and freedom of movement. Driveline infection can also be a cause of chronic pain or unintentional incidents of the cable. New technologies are emerging allowing fully intracorporeal LVAD implantation, with a device being percutaneously charged via a subcutaneous battery. Initial limitations were skin burns due to the heat of the battery and energy transmission. However, new generation of LVAD will have the particularity of being less energy consuming hence increasing the possibility of manufacturing fully implantable devices. This is the case of the Corvion® LVAD device not yet commercialized but designed with a wireless recharging implanted power source.

4 Conclusions

In the last decades, outcomes significantly improved for both heart transplantation and LVAD. Heart transplantation remains the gold standard for the treatment of end stage heart failure and will remain for many years to come. The most relevant limitations are the lack of grafts and the effects of long term immunosuppressive therapy that involve infectious, cancerous and metabolic complications despite advances in immunosuppression management. Mechanical circulatory support have an irreplaceable role in the treatment of end-staged heart failure, as bridge to transplant or as definitive implantation in non-transplant candidates. Although clinical results do not overcome those of HTx, improvement in the new generation of devices may help to reach the equipoise between the two therapies.

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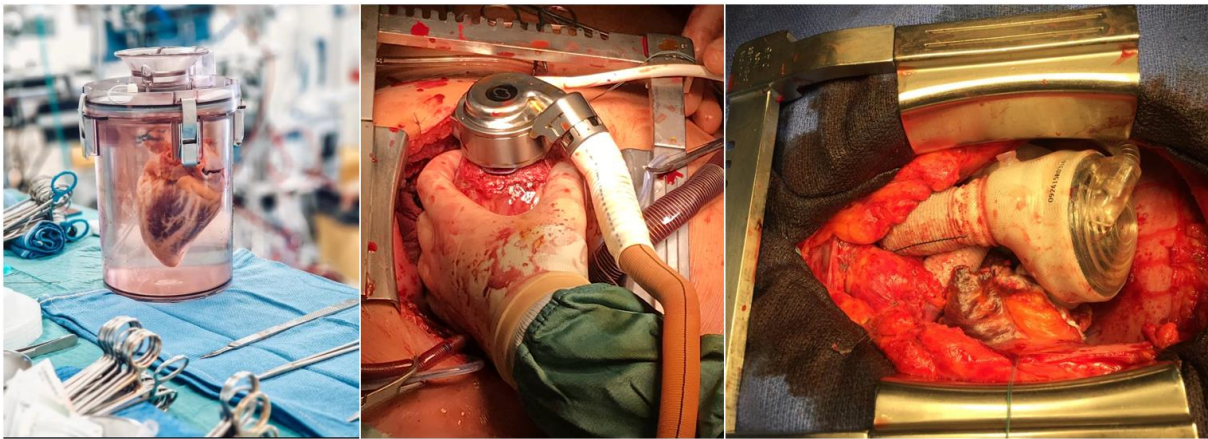


Figure 1. On the left. A heart harvested from a brain-dead deceased donor suspended in the cardioplegia solution and waiting on the back table for transplantation while the recipient is being prepared.

In the middle. An LVAD implanted into the apex of the left ventricle. The outflow which is laying on the surgeon's forearm will be anastomosed to the ascending aorta. The thin white cable above is the driveline.

On the right. An implanted TAH, the ventricle on the top represents the artificial right ventricle connecting the right atrium to the pulmonary artery, below hidden by it is the artificial left ventricle connecting the left atrium to the ascending aorta.



Figure 2. On the left the re-usable vitalpack[®] icebox
In the middle the Sherpapack, Paragonix[®] icebox
On the right the hypothermic perfusion machine Xvivo Perfusion, AB[®]



Figure 3. The normothermic perfusion machine Organ care system, OCS, Transmedics[®]

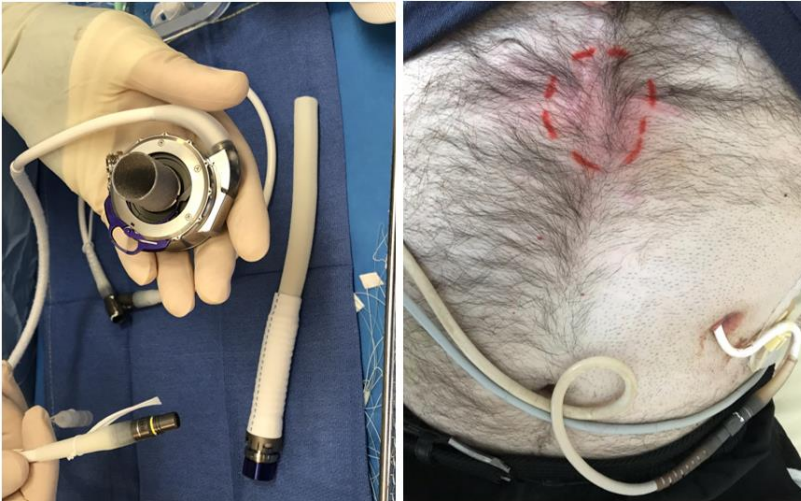


Figure 4. On the left a LVAD before implantation. The driveline cable is hold by the surgeon's right hand. On the right a driveline and wound infection.