The totally artificial heart (TAH) is among the most prominent medical innovations of the 21st century, especially due to the increasing population with end-stage heart failure. The progressive course of the disease, its resistance to conventional therapy, and the scarcity of hearts available for transplantation were the prime impetus for developing a TAH, especially when other options of mechanical circulatory assist devices are exhausted. In this review, we narrate the history of TAH, give an overview of its technology, and address the pros and cons of the currently available TAH models in light of published clinical experience.
Background – Heart Failure, the Predicament

Heart failure (HF) continues to be a plight to modern-day humans, affecting almost 23 million people worldwide [1]. In 2004, HF claimed more lives in the U.S. than lung cancer, breast cancer, prostate cancer, and HIV/AIDS combined [2]. It is estimated that 1 in every 5 people will develop HF in their lifetime, a risk notoriously known to increases with age [3]. Furthermore, 5% of patients with HF are end-stage patients, or the so-called “stage D heart failure”, characterized by refractoriness to medical therapy [4]. Considering the progressive nature of the disease, more and more patients in the less severe stages will eventually end up in the D category. These are sobering facts considering the limited treatment options for such patients, for whom heart transplantation has long been considered the optimal salvation [5,6]. However, the paucity of available donors, much less the dysfunction of almost 60% of donated hearts, is a major hurdle impeding attempts to save the lives of these patients by means of transplantation [7,8]. Furthermore, waiting for a heart is a survival battle that almost 45% of patients lose [9]. Mechanically supporting the failing heart with ventricular pumps has emerged as an endeavor to preserve patients’ lives as long as possible until a donor heart is available, a term referred to as “bridge to transplantation” (BTT) [10].

Device for Heart or Devise a Heart

Ventricular assist devices (VAD) were sought and utilized as early as the mid-1960s, until they were FDA-approved in the mid-1990s [9]. Indeed, VAD did prolong life, and early studies have shown a doubling in the 1-year survival rate (from 25% to 51%) in end-stage HF patients [11]. With advances in VAD technology, by 2011, 85% of patients survived the first year with VAD as BTT [12,13]. Many models of VADs are available nowadays in the market, with either continuous or pulsatile flow. Continuous flow VADs are the most commonly used, those include HeartMate II, HeartWare, among others [9–12]. On the other hand pulsatile VADs with pneumatic pumps are more commonly employed for the pediatric populations e.g. Berlin Heart. However, a subset of patients require biventricular support, placing them in a critical state with narrow options, considering their aptness for biventricular pump implantations, which do not guarantee promising survival rates (56% for 6 months) [14]. Adding to the dilemma, late right heart failure was also shown to develop in a subset of patients on continuous-flow VAD, a phenomenon that severely compromise their survival even after transplantation [15,16]. Furthermore, those patients are added to another category of patients, for whom VAD is not even an option, including patients with severe ventricular anatomical damage, intractable arrhythmias, massive ventricular thrombus, or restrictive cardiomyopathy [17]. The only hope for such patients, until a donor heart is found, is the complete substitution of their ventricles with a fully functioning mechanical pump – a “totally artificial heart” (TAH).

Historical Beats

“Ancient Egyptian Mummy has Artificial Heart”, such an astonishing title was from an article published in March 17th, 1992 in Weekly World News, a Canadian newspaper. The article tells a surprising story from 1986 when a team of archeologists reported the discovery of a totally artificial heart in a 5000-year-old mummy of a little boy, which was carefully stitched into the chest and resembles to a great extent the ones available nowadays. As shocking as this might sound, it is, however, not the only such discovery. A second mummy was later discovered by a team of German, Belgian, and Egyptian archeologists excavating in the Valley of Kings. This time, it was of a 35–40-year-old woman, which had a nicely implanted artificial heart. According to pathologists who studied the mummy, it was implanted shortly before the woman’s death, and it had supported her circulation for several weeks, before a defective valve started to leak!

If we now go “back to the future”, the idea of creating a TAH has never stopped luring scientists and physicians. In 1975, Akutsu and Kolff implanted their first TAH in an animal model 10 years before the first human heart transplantation by Barnard in 1967 [18,19]. The first human TAH implantation usually refers to that of Barney Clark in 1982, who received the Jarvik 7, a TAH developed at Kolff’s lab and named after its designer, Dr. Robert Jarvik [20]. However, history has recorded 2 TAH implantation attempts that preceded the Jarvik 7 experiment, starting almost 13 years earlier [21,22]. The Argentinian Domingo Liotta, along with Denton Cooley, reported successful implantation of a Dacron, pneumatically-controlled, double-ventricle cardiac prosthesis that was prototyped earlier in 1961. The 47-year old recipient survived for 64 hours under TAH’s support until he received a donor heart [21–23]. However, the patient died shortly after transplantation from Pseudomonas pneumonia [22]. Twelve years later, in 1981, Dr. Cooley implanted his second TAH, this time using a pneumatic Akutsu TAH made of polyurethane, which supported the 36-year-old patient for 55 hours, of which the last 16 hours were under support of extracorporeal membrane oxygenation (ECMO), which was utilized along with TAH due to deteriorated blood gas values [24]. Nevertheless, bridging to transplantation was reached, and the patient survived for 7 days post-allograft before he died of multiple organ failure and infection [24].
Jarvik 7 – the Invention

The first human TAH to receive international conspicuity was the Jarvik 7, owing to its relatively longer post-implantation survival record and the initially claimed intention for destination therapy (DT), unlike the aforementioned attempts, aimed primarily at BTT [20]. The Jarvik 7 is a pneumatically-powered TAH, composed of 2 separate spherical polyurethane chambers, each representing a ventricle, with a 70-ml filling volume, and containing single-leaflet inflow (27 mm) and outflow (25 mm) valves, which are attached to the heart’s natural atria by Dacron cuffs. Inside each chamber is a 4-layered polyurethane diaphragmatic membrane attached to the interior of the chamber: 1 seamless blood-contacting diaphragm, 2 intermediate diaphragms, and an air diaphragm, which creates a cavity. Air is pulsed in this cavity, forcing the membranes into a disk-shaped volume displacement mechanism, which pushes the blood to the outlet valve, creating systole. Air is then sucked back leading to deflation of the air sac, which allows for passive filling of the blood-contacting compartment of the chamber, creating diastole. The air-driven system powers the pump through reinforced polyurethane drivelines that enter the TAH through the patient’s left side and are externally connected to a console, roughly the size of a household refrigerator, to which the patient is tethered. The console is connected to sources of compressed air, vacuum, and electricity, and is responsible for controlling the airflow, maintaining the heart rate (40–120 beats per minute), and monitoring the device function via pneumotachometers and a portable computer [19,25,26]. The Jarvik 7 can generate a cardiac output of 6–8 l/min [25].

Jarvik 7 – the Experiment

The first Jarvik 7 receiver, Barney Clark, suffered from end-stage HF secondary to a non-ischemic idiopathic cardiomyopathy and was deemed as unsuitable candidate for heart transplantation [25]. The 61-year old dentist, however, agreed to undergo the procedure out of his own wish to make a contribution to medical science, a generous intention that merits praise [26]. Implanted by Dr. William DeVries at the University of Utah, the Jarvik 7 functioned quiet well, achieving a decent cardiac output and relieving the congestion. Later on, however, Dr. Clark developed many complications, including pulmonary insufficiency, acute renal failure, a generalized seizure (of uncertain cause), and hemorrhagic complications of anticoagulation. On the 92nd postoperative day, the patient had diarrhea and vomiting, leading to aspiration pneumonia and sepsis. Progressive renal failure later ensued, and the patient died on the 112th day [20]. Interestingly, however, autopsy revealed that the device was intact and thrombus-free [20]. The outcome from this initial case was deemed promising and encouraged further implantations. Three more patients in the USA and 1 patient in Sweden were implanted with the Jarvik 7 as a permanent replacement to their hearts in 1984 and 1985. The second recipient survived 620 days, achieving the first survival record, although debilitated by a stroke [26]. Furthermore, the Jarvik 7 continued to show exceptional success in bridging patients to cardiac transplantation, after which some lived for up to 14 years of normal life [26].

CardioWest & SynCardia – the Descendants

The Jarvik 7 launched a new era of TAH implantation, and by 1991, a sum of 226 patients had received pneumatic TAHs at 39 centers worldwide, of which 5 patients were implanted for permanent support, and 4 patients even received a second TAH [27]. By that time, transfer of rights of the producing company had taken place, and the device was renamed and marketed as CardioWest [26]. The CardioWest heart is identical to the small size Jarvik 7 heart developed for use in women and smaller men in the mid-1980s, except for the smaller air driveline tubes, and an up-to-date laptop computer replacing the portable Compaq computer originally used [26]. To date, more than 1300 patients have used the Jarvik 7/CardioWest [28]. According to a 10-year clinical study by Copeland et al., CardioWest produced a 79% success rate for BTT with excellent overall survival, including post-transplantation (70% at 1 year, 50% at 5 years, and 45% at 8 years) [26,29]. In 2004, the FDA granted their approval, making CardioWest the first, and the only, fully approved TAH in the USA [26]. By that time, the company had changed its ownership again, and the device was later renamed and marketed under “Syncardia”. The prime upgrades associated with the introduction of Syncardia focus mainly on enhancing patient mobility. A portable pneumatic driver was introduced early on, allowing for patient discharge from the hospital after stabilization on the implanted TAH. The portable driver is the size of a briefcase, which can be dragged [26,30]. Syncardia broke the record again in a case reported in 2011, where it supported the patient for 2 years and 4 months of normal life as BTT, during which the patient was highly mobile by virtue of a modified version of the Berlin Heart Excor portable driver [32]. Furthermore, Syncardia recently introduced a wearable and even more flexible portable driver called Freedom®, which was FDA approved in 2014 [30].

TAH in the Pediatric Population

Cardiomyopathies in children are the leading reason for end-stage heart failure. In some cases children can respond to the conservative therapy; however, due to the aggressive course of the disease, the clinical state of many children can rapidly deteriorate, making circulatory support an inevitable option until a donor heart is found. Children on transplantation
The major surgical implantation steps can be summarized in the following [17,25]:

1. **The Device** is prepared by pre-clotting of arterial outflow connectors and trimming of atrial cuff connections;

2. **Patient** is anesthetized, central venous access is created and driveline exit sites are marked on the epigastrium;

3. **Median sternotomy** is performed, followed by heparinization and cannulation of the ascending aorta and the cavae, establishing cardiopulmonary bypass (CBP);

4. **Bilateral ventriculectomy** is performed; briefly starting with the right ventricle parallel to the ativoventricular groove, transecting the pulmonary trunk, entering the left ventricle and moving circumferentially around it. The ascending aorta is transected at the sinotubular junction, preserving the mitral-aortic curtain. Crucially, tricuspid and mitral valves anulii are to be preserved, as well as one to two cm of ventricle muscle around each ativoventricular valve plane;

5. **Anastomosis** is first prepared by excising the mitral and tricuspid valves, including all leaflet tissue, chordae and subvalvular apparatus and sewing the coronary sinuses. The quick atrial connectors are double sutured to the atrial cuffs, while care is taken not to bite deeply into the atria, so as to preserve as much healthy tissue as possible from scaring, especially near the left pulmonary veins. Ventricular outflow conduits are trimmed accordingly and sutured to the pulmonary and the aorta, the latter being a bit shorter;

6. **Implantation** of the artificial ventricles is done by first creating exit sites for the pneumatic drivelines and paving their pathway through the skin. The two drivelines are then tunneled under the skin. Ventricular chambers are then appropriately positioned and connected, starting with the left ventricle (Figure 2). Ventilation is resumed and deairing is performed by a needle vent;

7. **Weaning** is performed by first releasing the aortic and pulmonary cross clamping, and starting the pumping at a very slow rate, which is increased while patient is gradually weaned from CBP;

8. **Closure** is preceded by wrapping the device and adequately spacing the pericardium to prevent its contraction, which might complicate transplantation in the future (Figure 3). The use of expanded polytetrafluoroethylene (e-PTFE) membrane to wrap the device, separating the native atria from the pericardium was successfully reported to prevent peri-cardial adhesion and thickening, hence facilitating later explanation for transplantation [32]. Importantly, trans-esophageal echocardiography (TEE) is utilized, both pre- and post-CBP for assessment of function and ensure proper positioning of the TAH, respectively [25].

For further information on surgical implantation techniques for the pneumatic TAHs, as well as associated challenging scenarios, the reader is referred to the report by Torregrossa et al. [17].
Pneumatic TAHs – Pros and Cons

The revolutionary success achieved by SynCardia, CardioWest, and before them, the Jarvik 7, is mainly attributed to the following [25,26]:
1. The mere simplicity of the device; with no complicated electronics or batteries;
2. Biocompatibility of the device material, decreasing the risk of thrombosis;
3. Partial filling and complete ejection of the chambers, minimizing blood stasis;
4. Hemodynamic effectiveness; with high blood flow, allowing for organ recovery;
5. Independent pumping in left and right sides, permitting optimal filling and ejection;
6. Controllability of the right chamber allows for a lung-friendly hemodynamics, by preventing blood forcing into the lungs at an excessively high pressure;
7. Relatively small size and light weight (160 g), fitting in 90% of patients.

However, pneumatic TAHs bear some major drawbacks inherent to their design. First, the incessant noise generated by the pneumatic driver, which can be disturbing to the patient, as well as his companions. The second major disadvantage of the pneumatic TAHs is that they are not fully implanted within the body, and the patient is tethered to the powering console. Dragged, carried, or worn, the console accompanies the patient in every single activity, minimizing his mobility and comfort. Furthermore, the exit sites of the air tubes are a potential source of infection. Two recent studies reported driveline infections in up to 14% of patients [25]. Mediastinitis was reported in up to 5% of patients [25]. The risk of device infection increases with long-term support. A recent study by Torregrosa et al. in 2014 on 47 patients on SynCardia support for longer than 1 year has reported 27% driveline infections [33]. Lastly, the size and weight of the device is not expected to fit in smaller patients, mostly women and adolescents, and might create misfitting problems. Fitting criteria for the CardioWest-Implantation was set as the following [25]:
1. Body surface area (BSA) more than or equal to 1.7 m²;
2. Cardiothoracic ratio more than 0.5;
3. Left ventricular end diastolic linear diameter more than 66 mm;
4. Chest antero-posterior distance more than 10 cm;
5. Combined ventricular volume of more than 1500 ml.

The clinical experience with pneumatic TAHs has accumulated over the years and multiple studies were launched in different parts of the world, which were able to report the major complications upon TAH implantation (listed below) [25,33–35]:

1. Driveline infections;
2. Mediastinitis;
3. Device infection;
4. Fitting problems;
5. mobility and comfort.
1. Bleeding: In a 2012 study by Copeland et al. on 101 implanted TAHs, 24.7% were reported for hemorrhage [34];
2. Neurological complications: reported in 15.8% of patients; mainly embolic strokes [34];
3. Systemic infections: up to 53% of patients were reported after 1 year of support [33]. Urinary tract infections and pneumonia were mainly reported [34];
4. Multiple organ failure;
5. Device malfunctions and/or failure: up to 10% device failure was reported [33].

Abiocor

The unprecedented success accomplished by the Jarvik 7 progeny of pneumatic TAHs was probably satisfactory for BTT; much less if no other option is available for the critically ill patient, such as VAD. Although pneumatic TAHs have been, in a few cases, implanted with the intention for DT, one can clearly see they were not designed for this purpose. The need for a durable and totally implantable TAH is urgent, especially to overcome the paucity of donated hearts and the drawbacks of mechanical circulator support devices. Attempts to create a totally implantable electromechanical heart have been sought in late 1980s and early 1990s, utilizing an extra corporeally-controlled electrohydraulic system [35,36]. The AbioCor IRH (Abiomed, Danvers, MA, USA) is the culmination of these efforts. This TAH has implantable as well as external components [25,37].

Implantable components are:
1. Thoracic unit: a titanium-made case, with 2 blood-pumping compartments, each harboring a flexible blood-contacting polyether-urethane-made (Angioflex) sac with trileaflet inflow and outflow valves. Between the sacs is a miniaturized centrifugal pump (electrohydraulic unit), which agitates a low-viscosity hydraulic fluid between the 2 sacks alternatively, forcing 1 to contract in a systolic manner, while the other is being actively filled due to gradient difference, creating diastole. The direction of the fluid is controlled by an alternating rotary valve that shuttles the blood between the fluid chambers depending on the set heart rate. Due to the relatively smaller stroke volume of the device (55 mL), Abiocor has to beat at 110–140 beats/minute;
2. Internal Battery: a rechargeable battery made of lithium ion cells, serving as an energy source. Though being routine charged by an external source, if unattached to it, it can solely power the pump for 15 to 45 minutes, depending on its charged status. For example, this time frame can allow the patient to shower;
3. Controller: a microprocessor unit responsible for monitoring different parameters of the thoracic unit, which include the hydraulic chamber pressure, centrifugal pump speed (rpm), beating rate, and balance between the right and left atrial pressures.

Importantly, Abiocor utilizes an atrial hydraulic shunt, which functions to reduce the right side stroke volume upon increased left atrial pressure, obtaining the physiological difference between the 2 [38].

4. Internal transcutaneous energy transfer (TET) coil: a disc-shaped object, positioned in the subpectoral region, and responsible for energy transmission by inductive coupling with an external TET coil. By virtue of this, no wires or drivelines are needed to penetrate the body to transfer energy [39].

The external components include:
1. Console: a laptop displaying all monitored performance parameters, and allowing for their manual adjustment, as well as an alarm system and an internal battery;
2. Radiofrequency communication box: for transmitting information between the console and the thoracic unit;
3. External TET coil: responsible for conveying the magnetic waves through the skin to the internal TET, which converts it to electricity that powers the device.

Clinical Experience

In 2001, the FDA approved a human feasibility study of the Abiocor IRH [40]. Since Abiocor is intended as a permanent surrogate for the failing heart, candidacy criteria for recipients has to be met before they are considered for implantation. The selection criteria are governed by a prognostic model called AbioScore, which is a mortality prediction model to define patients with 30-day mortality risks greater than 70%. Various laboratory and clinical parameters are included in the AbioScore criteria [40]. Patients with more than 30% 1-month survival are excluded. Importantly, fitting of the device has to be tested prior to implantation decision. The Abiofit™ software, introduced by Abiomed, the developing company, utilizes computed tomography (CT) as well as magnetic resonance imaging (MRI) pictures to virtually implant the device in the chest of the potential candidate and ensure its proper fit [37].

Fourteen patients were implanted with Abiocor between 2001 and 2004 [25]. Two patients died at surgery due to bleeding or aprotinin reaction [40]. The 12 surviving patients lived up to 512 days on Abiocor support, of which 4 patients were ambulatory after the operation and 2 were discharged from the hospital [25,40]. However, multiple complications were reported, which later led to death of the surviving 12 patients. Nine recipients experienced cerebrovascular accidents (CVA), of which 3 had transient ischemic attacks [41]. CVA led to 6 deaths among the recipients. Furthermore, non-device-related infections were reported in 11 patients, and sepsis was reported in 2 patients, of which 1 followed a massive abdominal bleeding episode [41]. Additionally, 2 deaths were reported due to device malfunction; the first due to the membrane wearing out at 17 months, while the second was due to motor-bearing
failure at 4.8 months [25,41]. Moreover, there were 3 deaths due to multiple organ failure [40]. Importantly, device thrombosis was a major observation upon autopsy, with 4 patients bearing thrombus on atrial struts [25,40]. Nevertheless, humanitarian device exemption (HDE) approval was granted for Abiocor by the FDA in 2006 [41].

Abiocor – Pros and Cons

Abiocor’s major advantages over available pneumatic TAHs are:
1. The absence of trans-corporeal wires or tubes, significantly lowering the risk of infections and enhancing patient mobility;
2. Abiocor is much quieter than pneumatic TAHs.

However, Abiocor shows a number of drawbacks:
1. The bulkiness of the device, as well as its weight of almost 2 kg, requiring a recipient body surface area of almost 2 m² and, hence, limiting the number of suitable recipients;
2. Biocompatibility as well as durability of the device are questionable and entail great risks of thrombosis and death;
3. The TET system, though novel, wastes about 40% of the external battery power, requiring the patient to carry heavy portable batteries;
4. The short-lived internal battery, which needs to be replaced every 1–2 years, requiring major surgery;
5. The alternating, inseparable, and dependent pumping of both ventricles is not physiologically optimal and might lead to excessive pulmonary pressures.

Novel TAHs – Pending

Since thrombosis and hemocompatibility were major challenges in the previously developed TAHs, a new generation of bio-prosthetic TAHs has emerged. Carmat (Carmat, Velizy, France) is a recently developed electromechanical TAH, which incorporates bio-prosthetic valves as well as bio-membranes forming the ventricular cavities [42,43]. The ventricles are enclosed in a flexible external bag with silicon fluid that is pushed to the ventricular cavities [42,43]. The ventricles are enclosed in a flexible external bag with silicon fluid that is pushed to the ventricular cavities [42,43]. The ventricles are enclosed in a flexible external bag with silicon fluid that is pushed to the ventricular cavities [42,43].

In an attempt to simplify the device mechanics and reduce its size, a novel TAH was recently introduced [45]. RheinHeart is an electromechanical TAH developed in Aachen, and is undergoing pre-clinical validations. Two flexible blood chambers represent each ventricle and in between is a motorized linear drive which thrusts 2 pusher plates on the flexible membranes in an alternating pattern squeezing out the blood from 1 chamber while relaxing the other [45]. The device was tested both in vitro and in vivo in a calf animal model.

Conclusions

TAH is an emerging therapeutic tool for end-stage HF. Stuck in the dilemma of scarce hearts for transplantation, the progressive nature of the disease, and the refractoriness of some cases to other forms of mechanical support, TAH therapy is the last resort to prolong patient survival until a donor heart is found. However, some patients are not candidates for transplantation; therefore, TAH can be implanted as a DT. Modern attempts to create a TAH have been sought for almost half a century. TAH technology has since grown tremendously, improving implantation outcome. Promising results have been achieved with pneumatic TAHs as BTT, but they are not complication-free. On the other hand, totally implantable TAHs, intentionally designed for DT, have a long way to go if they are to permanently replace the natural heart. Issues such as size, powering energy, durability, biocompatibility, and anti-coagulation management remain challenging. Bioengineering and molecular research offer promising alternatives to optimize TAH’s hemodynamics and achieve a high degree of functional and physiological mimicry of the natural heart. Research on TAH remains an open avenue for creative minds, portending a bright future.

Conflicts of interest

The authors have no conflicts of interest to declare.

References:
1. Roger VL: Epidemiology of heart failure. Circ Res, 2013; 113(6): 646–59
2. Adler ED, Goldfinger JZ, Kalman J et al: Palliative care in the treatment of advanced heart failure. Circulation, 2009; 120(25): 2597–606
3. Bui AL, Horwich TB, Fonarow GC: Epidemiology and risk profile of heart failure. Nat Rev Cardiol, 2011; 8(1): 30–41
4. Costanzo MR, Mills RM, Wynne J: Characteristics of “stage D” heart failure: insights from the Acute Decompensated Heart Failure National Registry Longitudinal Module (ADHERE LM). Am Heart J, 2008; 155: 339–47
5. Gass AL, Emamian A, Lanier G et al: Cardiac Transplantation in the New Era. Cardiol Rev, 2015; 23(4): 182–88
6. Czyzewski I, Torba K, Jasińska M, Religa G: Comparative analysis of the quality of life for patients prior to and after heart transplantation. Ann Transplant, 2014; 19: 288–94

7. Rosenblum AM, Li AH, Roels S et al: Worldwide variability in deceased organ donation registries. Transplant, 2012; 25(8): 801–11

8. Yacoub M: Heart transplantation: the end of the beginning. Am J Transplant, 2008; 8(9): 1767–68

9. McClarty A: Mechanical Circulatory Support and the Role of LVADs in Heart Failure Therapy. Clin Med Insights Cardiol, 2015; 9(Suppl.2): 1–5

10. Holley CT, Harvey L, John R: Left ventricular assist devices as a bridge to cardiac transplantation. J Thorac Dis, 2014; 6(8): 1110–19

11. Oz MC, Gelins AC, Miller L et al: Left ventricular assist devices as permanent heart failure therapy: the price of progress. Ann Surg, 2003; 238(4): 577–83; discussion 583–85

12. Starling RC, Naka Y, Boyle A et al: Results of the post-U.S. Food and Drug Administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation: a prospective study using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). J Am CollCardiol, 2011; 57(19): 1890–98

13. Religa G, Jasińska M, Czyżewski Ł et al: The effect of the sequentialtherapy in end-stagehearth failure (ESHF) – from ECMQ, through the use of implantable pump for a pneumatic heart assist system, ReligaHeart EXT, as a bridge for orthotopic heart transplant (OHT). Case study. Ann Transplant, 2014; 19: 537–40

14. Cleveland JC Jr, Naftel DC et al: Survival after biventricular assist device implantation: an analysis of the Interagency Registry for Mechanically Assisted Circulatory Support database. J Heart Lung Transplant, 2011; 30(8): 862–69

15. Kormos RL, Teuteberg JJ, Pagani FD et al: Right ventricular failure in patients with the HeartMate II continuous-flow left ventricular assist device: incidence, risk factors, and effect on outcomes. J Thorac Cardiovasc Surg, 2010; 139(5): 1316–24

16. Takeda K, Takayama H, Colombo PC et al: Late right heart failure during support with continuous-flow left ventricular assist devices adversely affects post-transplant outcome. J Heart Lung Transplant, 2015; 34(5): 667–74

17. Torregrossa G, Anyanwu A, Zucchetta F, Gerosa G: Syncardia: the total artificial heart. Ann Cardiothorac Surg, 2014; 3(4): 612–20

18. Akutsu, Kolf WI: Permanent substitutes for valves and hearts. ASAIO Trans, 1958M; 230–235T

19. Barnard CN: The operation. A human cardiac transplant: an interim report of a successful operation performed at Groote Schuur Hospital, Cape Town. S Afr Med J, 1967; 41(48): 1271–74

20. DeVries WC, Anderson JL, Joyce LD et al: Clinical use of the total artificial heart. N Engl J Med, 1984; 310(5): 273–78

21. Cooley, Liotta D, Hallman GL et al: First human implantation of cardiac prosthesis for staged total replacement of the heart. Tr Am Soc Artif Int Organs, 1969, 252

22. Cooley DA, Liotta D, Hallman GL et al: Orthotopic cardiac prosthesis for two-staged cardiac replacement. Am J Cardiol, 1969; 24(5): 723–30

23. Liotta D, Taliani T, Giffoniello AH et al: Artificial heart in the chest: Preliminary report. Tr Am Soc Artif Int Organs (first American edition), 1961; 318

24. Cooley DA, Akutsu T, Norman IC et al: Total artificial heart in two-staged cardiac transplantation. Cardiovasc Dis, 1981; 8(3): 305–19

25. Sale SM, Smidika NG: Total artificial heart. Best Pract Res Clin Anaesthesiol, 2012; 26(2): 147–65

26. Robert Jarvik on the Jarvik 7. http://www.jarvikheart.com/basic.asp?id=69

27. Johnson KE, Liska MB et al: Registry report. Use of total artificial hearts: summary of world experience, 1969–1991. ASAIO J, 1992; 38(3): M486–92

28. Gerosa G, Sciri S, Iop L, Torregrossa G: Present and future perspectives on total artificial hearts. Ann Cardiothorac Surg, 2014; 3(6): 595–602

29. Copeland JG, Smith RG, Arabia FA et al: Cardiac replacement with a total artificial heart as a bridge to transplantation. N Engl J Med, 2004; 351(9): 859–67

30. Syncardia, http://www.syncardia.com

31. Park SS, Sanders DB, Smith BP et al: Total artificial heart in the pediatric patient with biventricular heart failure. Perfusion, 2014; 29(1): 82–88

32. Loforte A, Della Monica PL, Musemeci F: Two years and 4 months: a long-term bridge to transplantation with a total artificial heart. J Heart Lung Transplant, 2011; 30(12): 1419

33. Copeland JG, Arabia FA, Smith RG, Covington D: Synthetic membrane neo-pericardium facilitates total artificial heart explantation. J Heart Lung Transplant, 2001; 20(6): 654–56

34. Torregrossa G, Morshuis M, Varghese R: Results with Syncardia total artificial heart beyond 1 year. ASAIO J, 2014; 60(6): 626–34

35. Copeland JS, Copeland H, Gustafson M et al: Experience with more than 100 total artificial heart implants. J Thorac Cardiovasc Surg, 2012; 143(3): 727–34

36. Lioi AP, Orth JL, Crump KR et al: In vitro development of automatic control for the actively filled electrohydraulic heart. Artif Organs, 1988; 12(2): 152–62

37. Ahn JM, Kang DW, Kim HC, Min BG: In vivo performance evaluation of a transcatheteraneous energy and information transmission system for the total artificial heart. ASAIO J, 1993; 39(3): M208–12

38. Holmes EC. The AbioCor totally implantable replacement heart. J Cardiovasc Nurs, 2003; 18(1): 23–29

39. Kung RT, Yu LS, Ochs B et al: An atrial hydraulic shunt in a total artificial heart. A balance mechanism for the bronchial shunt. ASAIO J, 1993; 39(3): M213–17

40. Ahn JM, Kang DW, Kim HC, Min BG: In vivo performance evaluation of a transcatheteraneous energy and information transmission system for the total artificial heart. ASAIO J, 1993; 39(3): M208–12

41. Dowling RD, Gray LA Jr, Etoch SW et al: Initial experience with the AbioCor implantable replacement heart system. J Thorac Cardiovasc Surg, 2004; 127(1): 131–41

42. http://www.accessdata.fda.gov/cdrh_docs/pdf/H040006b.pdf

43. Jansen P, van Oeveren W, Capel A, Carpentier A: In vitro haemocompatibility of a novel bioprosthetic total artificial heart. Eur J Cardiothorac Surg, 2012; 41(6): e166–72

44. http://www.cardatsa.com/en/carmat-heart/heart-failure/pathology

45. Cigliano A, Gandaglia A, Lepedda AJ et al: Fine structure of glycosaminoglycans from fresh and decellularized porcine cardiac valves and pericardium. Biochem Res Int, 2012; 2012: 979351