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Abstract

Many patients with end-stage heart disease die because of the scarcity of donor hearts.
A total artificial heart (TAH), an implantable machine that replaces the heart, has so far been successfully used in over 1,700 patients as a temporary life-saving technology for bridging to heart transplantation. However, after more than six decades of research on TAHs, a TAH that is suitable for destination therapy is not yet available. High complication rates, bulky devices, poor durability, poor biocompatibility and low patient quality of life are some of the major drawbacks of current TAH devices that must be addressed before TAHs can be used as a destination therapy. Quickly emerging innovations in battery technology, wireless energy transmission, biocompatible materials and soft robotics are providing a promising opportunity for TAH development and might help to solve the drawbacks of current TAHs. In this Review, we describe the milestones in the history of TAH research and reflect on lessons learned during TAH development. We summarize the differences in the working mechanisms of these devices, discuss the next generation of TAHs and highlight emerging technologies that will promote TAH development in the coming decade. Finally, we present current challenges and future perspectives for the field.

Introduction

Cardiovascular disease is the leading cause of death globally, and heart failure, one of the end points of cardiovascular disease, affects approximately 2% of the adult population worldwide[1]. The estimated prevalence of heart failure will increase markedly owing to the ageing global population. It is predicted that by 2030, more than 8 million people in the USA (1 in every 33) will have heart failure[2]. Heart transplantation is currently considered the gold standard treatment for end-stage heart failure. However, a tremendous shortage of donor hearts exists worldwide. In 2018, more than 2,500 patients were actively awaiting heart transplantation in the USA alone[3]. To compensate for this shortage, mechanical devices to support the failing heart, such as left ventricular assist devices (LVADs), have been widely implanted over the past two decades as an alternative therapy for end-stage heart failure. At present, over 3,000 LVADs are implanted in North America every year, either as a bridge to heart transplantation or as destination therapy[4]. LVADs are a treatment option for patients with left ventricular failure but are not suitable for patients with severe biventricular failure or other conditions that preclude the use of LVADs5. Furthermore, LVAD support is associated with poor quality of life and a risk of complications, such as thromboembolic events, bleeding and driveline infections[6,7,8,9]. A total artificial heart (TAH) is a surgically

implanted pump that provides blood circulation and replaces cardiac ventricles that are diseased or damaged[10]. The TAH is implanted in an orthotopic position and replaces both the left and right ventricle of the native heart. In 1969, a TAH was implanted in a patient for the first time[11]. However, TAHs have so far primarily been implanted as a temporary bridging therapy for patients with advanced heart failure who are awaiting heart transplantation. The SynCardia TAH (SynCardia Systems, Tucson, AZ, USA) is the TAH that is most frequently implanted as a bridge to heart transplantation therapy and is under investigation in a clinical trial to assess its applicability as destination therapy[12]. However, the limitations of the SynCardia device, which include bulkiness, short durability, high complication rates and low patient quality of life owing to the need for percutaneous hoses and frequent hospitalizations, have so far precluded its approval for this indication. An urgent need for destination therapies for (biventricular) end-stage heart disease exists because the majority of patients have no prospect of recovery with currently available therapies. The rapidly emerging technologies in wireless energy transmission, biocompatible materials and soft robotics provide a promising outlook for TAH development. Many teams across the world have tried different approaches to develop various types of TAHs, of which only a few are still under development. In this Review, we describe the historical milestones and lessons learned during TAH development and discuss the current generation of TAHs and the differences in their working mechanisms. We also highlight new technologies that will promote TAH development in the coming decade.

History of TAH development

Animal experiments

The development of TAHs dates back to the previous century. One of the first experiments with a TAH was reported in 1958, when pioneers Willem Kolff and Tetsuzo Akutsu at the Cleveland Clinic (Cleveland, OH, USA) implanted a TAH in a dog after removing its native heart[13]. The TAH sustained blood circulation in the dog for 90 min[13]. More experiments in dogs were conducted at the Cleveland Clinic in the 1960s, including implantation of a mechanical TAH with two blood chambers that were alternately emptied by a motor pendulum[14] and implantation of two different pneumatically driven TAHs[15]. In the same period, Domingo Liotta (School of Medicine, Cordoba, Argentina) implanted a pneumatic TAH, named the Liotta Heart, in dogs[16]. These experiments inspired more researchers across the world to start developing TAHs. In Japan in 1963, Kazuhiko Atsumi (Tokyo University School of Medicine, Tokyo, Japan) developed several types of pneumatic and mechanical TAH and tested them in 56 dogs[17]. In 1964, a national artificial heart programme was initiated in the USA, sponsored by the National Heart, Lung and Blood Institute. This big nationwide project, led by Frank Hastings, aimed to develop novel technical advances (similar to the aims of the USA space programme) for generating TAHs. Boosted by the national artificial heart programme, TAH experiments were conducted in numerous research centres in the USA, such as at the Penn State Milton S. Hershey Medical Center[18] and the Cleveland Clinic[19].

First TAH implantation in humans

In 1969, Denton Cooley (Texas Heart Institute, Houston, TX, USA) performed the first TAH implantation in humans, implanting the Liotta–Cooley TAH in a patient aged 47 years[11] (Fig. 1). The Liotta–Cooley device was a rigid pneumatic TAH with two ventricles implanted orthotopically. An external pump moved compressed air into a pneumatic chamber inside the ventricle, which pushed a diaphragm and caused the ejection of blood from the blood chamber on the other side of the membrane. The Liotta–Cooley TAH supported the patient for 64 h, after which the patient underwent heart transplantation[11]. The patient died owing to sepsis 32 h after the heart transplantation. Furthermore, the poor biocompatibility of the valves and the surfaces that were in contact with the blood might have contributed to haemolysis and renal impairment[11]. Therefore, although the first TAH implantation was ground-breaking, it was not considered a success[20]. However, this first implantation of a TAH in humans proved the concept that such technology could support a patient as a bridge to heart transplantation. However, the procedure sparked ethical and legal controversy regarding improper consent and experimentation[21]. In the years after the first implantation in humans, further research on TAH prototypes was conducted solely in large animal models by researchers from the University of Alberta (Edmonton, Alberta, Canada)[22]; the University of Utah College of Medicine (Salt Lake City, UT, USA)[23,24,25,26]; the University of Mississippi Medical Centre

(Jackson, MS, USA)[27,28]; the Cleveland Clinic[29,30]; the Baylor College of Medicine (Houston, TX, USA)[31]; and the US Atomic Energy Commission (University of Utah, Salt Lake City, UT, USA)[32,33,34]. It took 12 years from the first TAH implantation in humans until the next human TAH implantation in 1981, again at the Texas Heart Institute, when the pneumatic Akutsu III TAH was implanted as a bridge to transplantation in a man aged 36 years[35]. The Akutsu III TAH worked similarly to the Liotta–Cooley TAH, with two inflatable air sacs to displace blood. The Akutsu III TAH supported the patient for 55 h, after which the patient received heart transplantation. However, in the last 27 h before the transplantation surgery, the patient could not be fully supported by the TAH and died 7 days after the heart transplantation owing to multiorgan failure[35]. The third TAH implantation in humans occurred in 1982 at the University of Utah, where William DeVries and Willem Kolff implanted the Jarvik-7 TAH as destination therapy in a patient aged 61 years with congestive heart failure[36]. The Jarvik-7 was a pneumatic device with a similar working mechanism to the Liotta–Cooley TAH. After implantation of the Jarvik-7 TAH, the patient was conscious and able to communicate with his family. Progressive circulatory shock led to his death 112 days after TAH implantation[36]. This first successful clinical outcome with the Jarvik-7 TAH encouraged many teams across the world to continue developing TAHs (Fig. 1). Most TAHs developed by the first pioneers were pneumatically or hydraulically driven; later, researchers developed TAHs with different working mechanisms. Currently available TAHs can be classified into three types on the basis of their working mechanism: fluid-driven TAHs, mechanical TAHs and continuous-flow TAHs (Fig. 2), which are discussed below.

Working mechanisms of TAHs

Fluid-driven TAHs

Fluid-driven TAHs are the oldest type of TAH, with a working mechanism similar to that of the Liotta–Cooley and Jarvik-7 TAHs. Fluid-driven devices have blood chambers separated by a membrane from a chamber filled with fluid (air or liquid). A pressure rise in the fluid chamber moves the flexible membrane so that the blood chamber empties and the blood is ejected (Fig. 2a). A pump is required to increase the pressure in the pneumatic or hydraulic chamber. Often, these pumps are placed outside the body, which requires percutaneous hoses to move the pressurized fluid from the pump to the TAH. Depending on the type of pump used in these pneumatic and hydraulic devices, the left and right chamber eject blood either simultaneously or alternatingly. More recently developed TAHs (such as the Carmat TAH (Aeson; Carmat, Vélizy-villacoublay, France)) are designed to have the pump implanted in the body, avoiding the need for percutaneous pneumatic or hydraulic pressure hoses. However, percutaneous cables to supply power to the TAH are often still needed.

Historical devices

Several pneumatic TAHs were developed in the 1980s, such as the Brno TAH (Vacord Bioengineering Research Company, Brno, Czech Republic)[37], Penn State pneumatic TAH (Pennsylvania State University, Hershey, Pennsylvania)[38], Phoenix (Southern Taiwan University, Tainan, Taiwan)[39,40], Poisk TAH (Institute of Organ and Tissue Transplantation, Moscow, Russia)[41,42], POLTAH (Artificial Heart Laboratory, Zabrze, Poland)[43] and Vienna TAH (University of Vienna, Vienna, Austria)[44]. In the same period, the electrohydraulic TAH (EHTAH) was developed in Japan (Artificial Organs Department, Osaka, Japan)[45]. Development of the hydraulically driven AbioCor (Abiomed, Danvers, MA, USA) started in the 1990s[46,47,48]. AbioCor was the first fully implantable system designed without any percutaneous cables; it consisted of four internal components and a transcutaneous energy transfer (TET) system. The characteristics of all the TAHs discussed in this Review are summarized in Table 1.

Current devices

Two fluid-driven devices, SynCardia[49] and the Carmat TAH, are currently in use as a bridge to transplantation and are undergoing further evaluation as destination therapy. Another fluid-driven TAH, SoftHeart (ETH Zurich, Zurich, Switzerland)[50], is currently under development[51,52]. The working mechanism of these three prototypes is very similar to the earliest devices, such as the Liotta–Cooley and Akutsu III TAHs. The history of the development of SynCardia dates back 40 years to 1982, when Kolff and DeVries performed the first successful implantation of a TAH in a patient[36]. This TAH, the Jarvik-7, is now known as

SynCardia. SynCardia is a pneumatically driven TAH consisting of two independent ventricles that collect and eject blood simultaneously in a pulsatile manner. A four-layer polyurethane membrane separates the blood in the ventricle from the pneumatic chamber. The pressures in the pneumatic chamber are generated by a pump placed outside the body and connected via percutaneous drivelines. SynCardia is the first TAH that received CE approval (in 1999) and FDA approval (in 2004) for temporary use as a bridge to heart transplantation in eligible candidates who are at risk of imminent death from end-stage biventricular failure[53,54]. This TAH has been implanted in over 1,700 patients worldwide[55]. The Carmat system is a hydraulic TAH developed in France that received CE approval as a bridge to transplantation therapy in 2020. The Carmat TAH consists of left and right blood chambers separated from the hydraulic pressure chamber by a two-layer biocompatible membrane made from bovine pericardium. The pumps that pressurize the hydraulic pressure chambers of the Carmat TAH are built within the TAH itself, making this device larger than SynCardia. Furthermore, the Carmat TAH ejects blood from the left and right blood chambers alternatingly. Although percutaneous pressure hoses are not required to pressurize the hydraulic chamber, the Carmat system requires percutaneous cables to deliver the required electrical power to the TAH. The Carmat TAH has been implanted as a bridge to transplantation in 24 patients in clinical trials (as of February 2022)[56]. SoftHeart is a pneumatically driven TAH entirely made of silicone rubber (except for its mechanical heart valves), and is the only completely soft TAH developed so far. SoftHeart has been tested only in vitro[50,57]. Although the durability of SoftHeart has been improved compared with earlier iterations, it is still limited to only 110,000 cycles (approximately 30 h)[50,57].

Mechanical TAHs

The functionality and clinical applicability of fluid-driven TAHs were demonstrated in the early 1990s, but some of their disadvantages also became apparent. These TAHs were bulky, had poor durability and required percutaneous air pressure hoses and external drivers, which led scientists to explore alternative working mechanisms and shift the focus to mechanically actuated TAHs[58]. Mechanically actuated TAHs have many similarities to fluid-driven TAHs: both have two chambers to collect and eject blood, and inlet and outlet valves to direct the flow (Fig. 2b). Like fluid-driven TAHs, mechanical TAHs have a moving membrane to empty the blood chambers. However, instead of emptying the blood chambers with the use of pressurized gas or liquid (as in fluid-driven devices), mechanically actuated TAHs have an electric motor that drives a pusher plate against the blood chambers. Compared with fluid-driven TAHs, mechanical TAHs are less bulky and, most importantly, do not require large external drivers.

Historical devices

Multiple mechanical TAHs were developed in the 1990s by different teams and institutions: AnyHeart (Seoul University, Seoul, South Korea)[59,60,61], Baylor TAH (Baylor College of Medicine)[62,63], Cleveland Nimbus (Cleveland Clinic)[64,65], eccentric roller TAH (Hiroshima University, Hiroshima, Japan)[66], Linear TAH (Shinshu University, Nagano, Japan)[67,68], MagScrew (Cleveland Clinic)[69], Milwaukee Heart (Milwaukee Heart Project, Milwaukee, WI, USA)[70], Ovalis (Humboldt University, Hamburg, Germany)[71] and Penn State electric TAH (Pennsylvania State University)[72]. These TAHs can be classified on the basis of their working mechanism as TAHs with mechanical actuation parts with either linear or rotary motion.

Current devices

We have identified three mechanically actuated devices that are still under development: Realheart TAH (Linköping University, Linköping, Sweden)[73,74], ReinHeart (Helmholtz Institute, Aachen, Germany)[75] and RollingHeart (University of Lausanne, Lausanne, Switzerland)[76]. None of these devices has been assessed in clinical trials. Realheart and ReinHeart are fully implantable systems, including a TET system and internal battery packs. Both TAHs are actuated with magnets and are being assessed in animal studies. The RollingHeart is a mechanically actuated TAH developed in Switzerland and has only been tested in vitro. This TAH has a spherical shape, and two moving disks divide the spherical cavity into four chambers. An electrical motor moves the disks and thereby changes the volume of the chamber over time, which enables the filling and ejection of the blood. The design is unique because it does not require any valves. However, issues in the design of this TAH related to the recirculation and mixing of oxygenated with deoxygenated blood need to be addressed[76].

Continuous-flow TAHs

A major disadvantage of the above-mentioned fluid-driven and mechanical devices is that they require several indispensable components, such as blood collecting chambers, flexible membranes and valves. As a result, these devices are often bulky and usually do not fit inside petite patients, such as children and some women. The flexible membranes present in these devices are often prone to wear and tear because they deform with every heartbeat (about 35 million times a year). Continuous-flow pumps were introduced as an alternative to traditional pulsatile devices. Because blood is pumped continuously in these devices, they do not require valves, membranes or blood collecting chambers. Therefore, continuous-flow TAHs are smaller and lighter than other types of TAHs. In addition, their lifetime is longer owing to the absence of flexible membranes and the continuous rotation of their motors in a single direction. In the past two decades, substantial progress has been achieved in the field of continuous-flow LVADs, whose efficacy has been proved in clinical trials[77]. The longest reported duration of LVAD support without mechanical failure is 13 years[77,78]. These positive results inspired many TAH researchers to use continuous-flow pumps for TAH development, mainly because of their superior power-to-size ratio and durability compared with fluid-driven and mechanical TAHs. After implantation of a regular continuous-flow LVAD, some blood flow pulsatility remains because the native heart is left in place. By contrast, continuous-flow TAHs eject blood continuously and generate a true continuous blood flow. Given that the physiological response to long-term continuous blood flow is unclear[79,80,81], most of the investigators developing continuous-flow TAHs are exploring the possibility of modulating the flow to provide some level of pulsatilily[79]. So far, achieving the same pulsatility index as with the native heart or the pulsatile TAHs has not been possible.

Historical devices

The first continuous-flow TAHs were developed in the 1990s. We have identified three continuous-flow TAH devices, which are no longer in use: the flow-transformed pulsatile TAH (University of Tokyo, Tokyo, Japan)[82], the undulation pump TAH (UPTAH) (University of Tokyo, Tokyo, Japan)[83] and the Impeller TAH (Jiangsu University, Zhenjiang, China)[84].

Current devices

Although LVADs were developed to assist the native left ventricle, these devices are powerful enough to take over the function of the native ventricle completely. Therefore, several research groups have investigated the efficacy of two commercially available LVADs (such as HeartMate II, Heartmate III, HeartWare HVAD, Jarvik 2000 and HeartAssist 5) combined into a TAH configuration after removing the native heart[85,86,87,88,89,90,91,92,93,94]. The configuration of two LVADs functioning as a TAH has been tested in animal studies and clinical trials[85,86,87,88,89,90,91,92,93,94]. In this Review, we refer to the configuration of two commercially available LVADs functioning as a TAH as 'LVAD–TAH'. Many TAH developers have used continuous-flow pump technology to develop custom-built TAH devices. Several continuous-flow TAHs are currently under development: BiVACOR (BiVACOR, Houston, TX, USA)[95], Cleveland continuous-flow TAH (CFTAH)[96,97] and helical-flow TAH (HFTAH) (University of Tokyo, Tokyo, Japan)[98] are being assessed in chronic animal experiments, and Hybrid CFTAH (Drexel University, Philadelphia, PA, USA)[99] and OregonHeart (OregonHeart, Portland, OR, USA)[100,101] are undergoing in vitro testing.

Balancing right and left cardiac outputs of TAHs

A major issue that must be addressed for successful TAH implantation is the balancing of the right and left cardiac outputs[20]. In a physiological setting, the cardiac output of the left ventricle is slightly greater than the cardiac output of the right ventricle[102], because part of the oxygen-rich blood from the aorta goes into the bronchial arteries that supply the lung parenchyma, which then drains back to the left atrium[103,104]. Therefore, part of the blood ejected by the left ventricle returns to the left atrium without passing through the right circulation, resulting in a larger systemic flow than pulmonary flow. In healthy individuals, the bronchial shunt flow is approximately 1% of the cardiac output[103]. However, various pulmonary diseases increase the bronchial shunt flow to up to one-third of the left ventricular output[103]. A study showed that three out of five patients with an implanted AbioCor TAH had increases in bronchial flow of up to 1.4 l/min, which is 28% of a cardiac output of 5 l/min[105]. The native heart continuously

balances the systemic and pulmonary flows by ventricular interdependence, via the Frank–Starling mechanism[102], but this balancing mechanism is difficult to implement in TAHs. If a TAH cannot compensate for flow differences in venous return, severe complications such as lung oedema and respiratory failure will arise[20]. Therefore, balancing the outputs to the systemic and pulmonary circulations during TAH support is one of the biggest challenges in TAH design[20,106]. Pulsatile TAHs can alter the stroke volume of one of the blood chambers if a sudden change in atrial pressure occurs. The stroke volume can be adjusted in two ways: by adjusting the filling volume inside the chamber or by adjusting the ejection fraction. This adjustment is an active process that requires either manual control or automatic control by feedback from incorporated sensors. In the Carmat system, many internal electronics, microprocessors and sensors are needed to constantly monitor different internal pressures, as well as an ultrasound transducer to monitor the position of the membrane[107]. In SynCardia, the system parameters are manually set to fill the ventricles to 70–85% of their capacity, to create a buffer that passively enables the augmentation of venous return[108]. As a result, SynCardia is sensitive to preload, demonstrating Frank–Starling-like behaviour under normal conditions[108]. Therefore, Syncardia can provide increased output in response to increased preload. However, the shape of the Syncardia Frank–Starling curve differs from that of the human heart, because this TAH is inelastic[108,109]. ReinHeart's design uses the concept of passive and active limitation of the right-sided filling, in combination with the right ventricle having a fixed volume that is 10% smaller than that of the left ventricle[110]. A balancing mechanism is also required for continuous-flow TAHs, because a sudden drop in atrial pressure quickly results in negative atrial pressures (suction event). Continuous-flow TAHs that have two separate pumps for the left and right circulation (such as in the LVAD–TAH, Hybrid CFTAH and HFTAH) have some inherent flow-balancing capacity[98,99,106]. However, a study testing the performance of several types of continuous-flow TAHs made from two separate pumps in an in vitro set-up in which systemic and pulmonary resistance were changed to mimic the human cardiovascular system during daily activities showed that, although all the devices had some flow-balancing capacity, none was able to accommodate all resistance settings[106]. Cleveland CFTAH, BiVACOR and OregonHeart use a single moving rotor to perfuse the pulmonary and systemic circulations. The rotor of the OregonHeart is typically set to pump 60% of each beat time to the left circulation and 40% to the right circulation, but this ratio can be adjusted manually to meet the needs of a wide range of physiological conditions[101]. BiVACOR incorporates an axial magnetic levitation system, which enables active control of the position of the single moving rotor[95]. A leftward shift of the rotor causes an increase in left-sided flow[95]. The Cleveland CFTAH uses a similar mechanism, but in this TAH, the rotor can have passive axial movements inside the stator, enabling the TAH to balance the left and right outputs passively, without any sensors[111]. The axial position of the rotor is determined by the pressure gradient between the left and right blood chambers. When the pressure drops in one of the blood chambers, the rotor passively moves to that side, which helps to prevent atrium wall suction and balances the cardiac outputs[111]. This low-complexity passive feedback mechanism inherently reduces the risk of device failure compared with the complex active feedback mechanisms in other TAHs.

Chronic animal trials

Chronic animal trials are an important step in the preclinical testing of new TAHs. Chronic animal trials have been conducted for AbioCor, AnyHeart, Baylor TAH, BiVACOR, Brno TAH, Carmat TAH, Cleveland CFTAH, Cleveland Nimbus, EHTAH, HFTAH, LVAD–TAH, MagScrew, Penn State electric TAH, Penn State pneumatic TAH, Phoenix, ReinHeart, SynCardia, UPTAH and Vienna TAH (Table 2). Calves are the most frequently used animal model for TAH implantation, followed by goats and sheep. In most of the older chronic animal trials, the animal was implanted with a TAH and was followed up until death. In contemporary studies, researchers often terminate the experiments after a given follow-up period (usually 30–90 days, according to FDA regulations), by taking out the TAH. For the latter studies, elective termination is assigned as the cause of death in Table 2. Nevertheless, the follow-up time in chronic animal trials is often short. Only ten TAH devices were associated with a maximum survival time exceeding 100 days (AbioCor[112], Brno TAH[37], Cleveland Nimbus[113], EHTAH[114], HFTAH[98], Penn State electric TAH[115], Penn State pneumatic TAH[38], SynCardia[25], UPTAH[83] and Vienna TAH[44]) and only one device was associated with a maximum survival time of over a year (Penn State electric TAH)[115]. Overall, the most frequently reported cause of death in chronic animal trials is mechanical failure of the device. Examples of mechanical failure that occurred in chronic animal trials include an electrical short circuit caused by fluid

entering the electronics, dislocation of TET coils, obstruction of the inflow or outflow grafts of the TAH, membrane ruptures, air leakage in pneumatic devices, failure of the implantable battery and a defect or lock in pump bearings[26,69,83,93,98,114,116,117,118,119]. The second- and third-most frequently reported reasons of death are thromboembolic complications and respiratory failure, respectively.

Clinical trials

Since the first successful implantation of a TAH in humans in 1982, a total of nine different TAH devices have been assessed in patients in clinical trials: AbioCor, Brno TAH, Carmat TAH, LVAD–TAH, Penn State pneumatic TAH, Phoenix, Poisk TAH, SynCardia and Vienna TAH (Table 3). These TAHs are pneumatic or hydraulic pulsatile devices, except the continuous-flow LVAD–TAH.

Early studies in humans

Several fluid-driven TAHs were tested in humans in the 1980s and 1990s. Overall, the outcomes were poor, and many patients died within the first days after receiving a TAH or could not successfully receive a heart transplant[120,121,122]. The Brno TAH, developed in the Czech Republic, was implanted in six patients[120]. All patients died of serious complications related to poor device biocompatibility, with a maximum survival of 10 days[120]. The Phoenix TAH was implanted in two patients[121,123]. One patient received a heart transplant on the same day as TAH implantation but died 1 day after receiving the heart transplant[121]. The other patient was successfully bridged to heart transplantation after 15 days of support with the Phoenix TAH[123]. The Poisk TAH was developed in Russia and has been implanted in 13 patients[122]. Of these patients, 12 died during support with the Poisk TAH, for unknown reasons. The maximum period of support was 15 days[122]. The Vienna TAH was implanted in five patients, and three of these patients were successfully bridged to heart transplantation[44,124]. The maximum duration of support was 22 days[44,124]. The Penn State pneumatic TAH was implanted in three patients[38]. Two of the patients were bridged to heart transplantation, and the third patient did not receive a heart transplant because a suitable donor was not found. After 70 days of support, the patient had a cerebrovascular accident, manifested by aphasia. The TAH support stopped on day 379 when this patient had a respiratory arrest and could not be resuscitated[38].

Latest clinical trials

AbioCor, the first fully implantable TAH that used a TET system, was implanted in 14 patients between 2001 and 2003[48]. The maximum duration of support was 512 days, which occurred in a patient who died owing to a membrane rupture in the device[125]. The most frequently observed causes of death were thromboembolic complications and multiorgan failure[125]. The development of AbioCor stopped in 2007 owing to concerns related to the high number of patients who died because of complications of stroke (caused by an ineffective anticoagulation regimen), the low quality of life of the patients and the poor commercial viability[20,79]. Since 2011, several teams worldwide have studied the use of a combination of two commercially available rotary LVADs (HeartMate II, HeartMate III or HeartWare HVAD) adapted to a TAH configuration to replace the native heart completely[86,87,89,90,91,94]. These LVAD–TAHs have been implanted in nine patients[86,87,89,90,91,94], with a maximum reported duration of support of 6 months[89]. The most frequently reported complications were related to thromboembolic and haemorrhagic events[86,87,89,90,91,94]. The pneumatically actuated SynCardia, the first TAH that became commercially available as a bridge to transplantation therapy, is currently available in two sizes (70 cm3 or 50 cm3 ventricles), which enables its implantation in patients of various body sizes. The youngest recipient of a 50 cm3 SynCardia is a boy aged 10 years[126]. So far, Syncardia has been implanted in over 1,700 patients worldwide, with a maximum reported duration of support of 4.5 years receiving permanent SynCardia support[55,127]. Despite the poor prognosis that the SynCardia recipients have before TAH implantation, the long-term survival of recipients of a heart transplant after temporary support with SynCardia is encouraging and comparable with the long-term survival of recipients of a heart transplant who did not receive SynCardia support[128]. Twelve months after the SynCardia implantation, 55% of the patients had received heart transplantation, 14% were still supported by the SynCardia device and 31% died before undergoing a heart transplantation[129]. SynCardia is currently being evaluated in an approved investigational device exemption clinical trial for use as destination therapy[12].

The care of patients receiving SynCardia support remains challenging[128]. The percutaneous hoses are frequently associated with driveline infections, and the TAH material itself often causes mediastinitis and constrictive pericarditis[128]. The period after heart transplantation is associated with a high risk of (temporary) haemodialysis owing to impaired renal perfusion and postoperative compression of the donor heart[128]. The risk of post-transplantation complications increases with prolonged TAH support[128]. The most frequently reported causes of death during support with a SynCardia device are multiorgan failure (40%), thromboembolic complications (13%) and infection (10%)[129,130,131,132,133,134,135,136]. Although minor device malfunctions are frequently described in the literature, severe device malfunctions that lead to death are rare (<2% of the deaths during SynCardia support)[129,130,131,132,133,134,135,136]. The hydraulic TAH developed by Carmat received CE approval as bridge to transplantation therapy in 2020, but the company is continuing clinical research with the aim of ultimately using the Carmat TAH as destination therapy[56]. The Carmat TAH has been implanted as a bridge to transplantation in 24 patients (as of February 2022)[107,137,138]. Patient enrollment for the second clinical trial on the Carmat TAH is ongoing[56]. Although the Carmat TAH was designed to promote biocompatibility, given that its diaphragms and valves are made from bovine pericardium, all patients must receive a strict anticoagulation regimen[138]. Thus far, the clinical outcomes of 11 recipients of the Carmat TAH have been described in the literature[107,138], with a maximum support duration of 308 days[138]. Of these patients, six died during TAH support, and the other five were successfully bridged to heart transplantation[107,138]. The causes of death were multiorgan failure (50%), mechanical failure (33%) and respiratory failure (17%). No thromboembolic complications were observed[107,138]. To date, no TAH has been approved as destination therapy. Only the SynCardia and Carmat TAH are approved as temporary therapy to bridge a severely ill patient to heart transplantation. The percutaneous drivelines of both TAHs are associated with low quality of life and a high risk of infection[128]. Long-term support with the SynCardia TAH is associated with serious risks such as stroke and multiorgan failure[128,129,130,131,132,133,134,135,136].

Technological advances and future perspectives

TET systems to improve quality of life

The TAHs currently available for clinical use (SynCardia and Carmat TAH) have percutaneous cables to supply power to the devices. Percutaneous drivelines are associated with a high risk of infection and reduce the patient's quality of life owing to the limited freedom of movement of the patient. Therefore, TAH devices intended for approval as destination therapy should ideally omit these percutaneous cables. Percutaneous cables can be avoided when all TAH components are implanted inside the body and the electrical power is wirelessly transferred via a TET system.A TET system transfers all the electrical power required by the TAH across the patient's skin via an internal and external coil. Part of this energy is stored in internal battery packs, enabling the patient to have free-from-charging periods. In the past decade, batteries have become smaller and have longer battery life, enabling implantation in the body. In addition to small and high-capacity batteries, high efficiency of the TAH is also essential when energy is provided through a TET system. Figure 3 shows the efficiencies of all types of TAH. The methodology we used to calculate the efficiencies is described in Box 1. Generally, fluid-driven TAHs are slow systems because they first have to move fluid or air to empty the blood-containing chambers. Therefore, emptying the chambers in fluid-driven systems is easier and more efficient at low beat rates than at high beat rates. Fluid-driven TAHs generally show a decline in efficiency at high beat rates. For example, the efficiency of the hydraulic EHTAH declines at cardiac outputs exceeding 6 l/min (Fig. 3a). Like fluid-driven TAHs, mechanical TAHs also have blood chambers, and higher cardiac output can be achieved by maximizing stroke volume and, if needed, by increasing the beat rate. In general, mechanical TAHs become more efficient at higher beat rates and, therefore, at higher cardiac outputs (Fig. 3b). The highest efficiency reported for mechanical TAHs is often reached at a cardiac output of approximately 10 l/min[60,63,64,66,69,70.] Compared with pulsatile devices, continuous-flow devices do not have blood-collecting chambers because they pump blood continuously. In general, the efficiency of continuous-flow pumps increases with higher cardiac outputs. The optimal efficiency of most continuous-flow TAHs is at a much higher cardiac output than the average cardiac output of 5 l/min (Fig. 3c).

Prolonging the free-from-charging periods during support with TAHs using TET systems

Efficient TAHs prolong the period that the patient can engage in activities without charging the TAH, which will improve the quality of life of TAH recipients in the future. The most up-to-date battery technology used for TET systems in TAHs has been described by the team developing ReinHeart[139]. The ReinHeart system has implantable 12 volt lithium–iron–phosphate batteries with 1.1 Ah capacity[139]. We have used this battery as a standard to compare the running time (defined as the maximum time in which the TAH recipient can engage in activities without charging the TAH) of current TAHs if they hypothetically had TET systems with this specific internal battery capacity (Fig. 3d). The running time was calculated for a cardiac output of at least 5 l/min against a physiological mean left afterload (≥90 mmHg). The data show that current TAH devices can hypothetically support the patients with a physiological cardiac output for approximately 1 h with the current battery technology (Fig. 3c; Table 4). For reference, the AbioCor (implanted for the first time in 2001) had the capacity to support the patient for up to 20 min without connection to a power source[47]. Our comparison results suggest that continuous-flow devices (Cleveland CFTAH and OregonHeart) are better than mechanically actuated devices in terms of their working time with internal batteries alone because continuous-flow TAHs require less input power than other TAH types to generate a higher cardiac output (Fig. 3d). Among continuous-flow devices, OregonHeart performs slightly better than the Cleveland CFTAH with regards to efficiency and the required input power (Fig. 3d). The mechanical ReinHeart has a relatively high power consumption (12.5 W) and provides less cardiac output than the other four TAHs analysed, resulting in the lowest efficiency (10.8%). Overall, we can conclude that for most TAHs, either the power consumption or the efficiency does not yet reach the levels required to use a TET system. To date, the AbioCor is the only fully implantable TAH that used a TET system that has been implanted in patients. The latest technological advances in TET systems are promising for future TAH development. Battery technology is rapidly evolving, resulting in more powerful and compact batteries. Powerful implantable batteries will prolong the time frame in which the patient can be free from having to use an electrical power source for the TAH. Furthermore, improving the overall efficiency of the TAH itself will help to use the stored energy of the internal battery packs more effectively. Therefore, we expect that transcutaneous charging of a fully implantable TAH with charging-free periods of >1 h will be feasible in the near future.

Bioinspired TAHs aim to improve biocompatibility

Since the beginning of TAH development in the 1960s, TAHs have been associated with limited biocompatibility resulting in frequently occurring pannus and thrombus formation. Although many attempts have been made to improve the design of TAHs, the biocompatibility issues could not be resolved. By the 1970s, the realization came that no implanted artificial material will ever come close to the anti-thrombogenic properties of the patient's endothelium. Current TAH devices are still associated with numerous complications related to biocompatibility. A high number of thromboembolic events have been reported in clinical trials and animal studies. All TAH recipients require a strict anticoagulation regimen that results in a high risk of haemorrhagic events. Devices such as the Carmat TAH improved biocompatibility by using membranes and heart valves containing sheep pericardial tissue. The available data on the Carmat TAH suggest that patients receiving a Carmat TAH need less anticoagulation medication than patients receiving a SynCardia device[138]. Upcoming solutions to address biocompatibility issues can be found in new developments in biomaterials science. If growing endothelium derived from the patient on the blood-contacting surfaces of the TAH becomes possible, this strategy would probably resolve many biocompatibility issues. The developers of the HybridHeart aim to grow a layer of patient-derived endothelium on the inside of the soft ventricles with the use of biofunctionalization and in situ tissue-engineering techniques[140]. However, owing to the large surface area and the continuous movement of the TAH ventricles, applying tissue engineering techniques on TAH devices remains challenging. Even after five decades of research, we are still far from being able to create a living endothelium inside the ventricles of a TAH[141]. The interaction of rigid components with the blood is associated with many adverse effects. These effects have been most widely studied for the rotors in LVAD devices and include risks of thrombus formation and non-surgical bleeding caused by the device-altered haemostatic function[9,142]. The artificial surface of the rotary blood pumps can induce platelet adhesion, which increases the risk of

thrombosis, and the rotating parts can induce loss of haemostasis-related receptors on platelets, which increases the risk of bleeding[142]. Haemolysis is the second-most common LVAD-related complication, presumably caused by the destruction of erythrocytes in the rotating LVAD devices[143]. Problems related to the incompatibility between hard machines and soft human tissue might be solved if the machine is as soft as the human tissue. Soft robotics is an emerging research field that focuses on developing robots made of soft materials. In the past year, a few research groups have shifted their focus to developing TAHs that are completely soft on the inside and outside, such as SoftHeart and HybridHeart[50,144,145.] The primary benefit of developing soft TAHs is that they mimic the natural movement of the heart, potentially reducing the stress on the blood and thereby resulting in fewer adverse effects[57]. The second benefit of soft robotic cardiac devices is that they are compliant because they can stretch, contract or bend. As a result, soft robotic cardiac devices can promote both the contraction and the relaxation phases of the heart[146]. Owing to its elastic behaviour, the ventricle of a soft TAH has higher passive filling and contracts more forcefully at high filling pressures than at low filling pressures. Therefore, the soft robotic cardiac device passively ejects higher cardiac outputs at larger end-diastolic volumes, like the Frank–Starling mechanism of the native heart. This compliance is inherent to soft robotic cardiac devices[147] and works without the need for any sensors or manual control. A soft robotic cardiac sleeve developed in 2017, the first soft robotic cardiac assist device under development, shows Frank–Starling behaviour[146]. This Frank–Starling mechanism could mean that the expansible volume capabilities of future soft robotic TAHs can balance the left and right outputs to achieve Frank–Starling curve behaviour that resembles human physiology. Given that TAHs need to work for a high number of cycles (one cycle for every heartbeat), achieving high durability and reliability remains a major challenge for TAH development. The SoftHeart had a maximum working duration of 110,000 cycles (approximately 30 h), after which a fatigue crack caused device failure[57]. Although current soft TAHs are at early development stages, with future optimization their benefits might outweigh those of traditionally rigid TAH devices.

Conclusions

After more than six decades of TAH research, TAHs have been successfully used in over 1,700 patients as a bridge to heart transplantation, but a TAH suitable for destination therapy has not yet been developed. Some of the major drawbacks of current TAHs are high complication rates, bulkiness, short durability, poor biocompatibility and low quality of life for the patients. These issues need to be resolved before the potential of TAHs as destination therapy can be realized. Nevertheless, the field of TAH research is rapidly evolving, and various approaches are emerging that could potentially improve the quality of life of TAH recipients. With the development of TET systems and improved TAH efficiency, percutaneous cables will no longer be necessary to provide electrical power to the implanted TAH. The field of battery technology is continuously improving, delivering more compact batteries that are easier to implant internally and that prolong the period during which the patient can engage in activities without charging the TAH. New insights into soft robotics might result in the development of completely soft TAHs that reduce the occurrence of adverse effects associated with traditionally rigid TAHs. Meanwhile, smart biomaterials might solve current biocompatibility issues. In the future, these new technologies have the potential to enable the development of the first TAH approved for destination therapy.

Key points

- After decades of research on total artificial hearts, only two devices are clinically available as a bridge to transplantation therapy; a total artificial heart suitable for destination therapy has not yet been developed.
- Currently available total artificial hearts have major drawbacks, including bulkiness, limited durability, poor biocompatibility, high complication rates and low quality of life for the recipients.
- We are on the verge of an era in total artificial heart development in which rapidly evolving technologies from different fields will lead to new approaches in total artificial heart design and development.
- More powerful and more compact batteries and transcutaneous energy transfer systems will omit the need for percutaneous cables and will improve the quality of life of the recipients of a total artificial heart.

- With the rise of soft robotic technologies and smart biomaterials, completely soft total artificial hearts might soon be developed and are likely to have fewer biocompatibility issues than current devices.

Figures

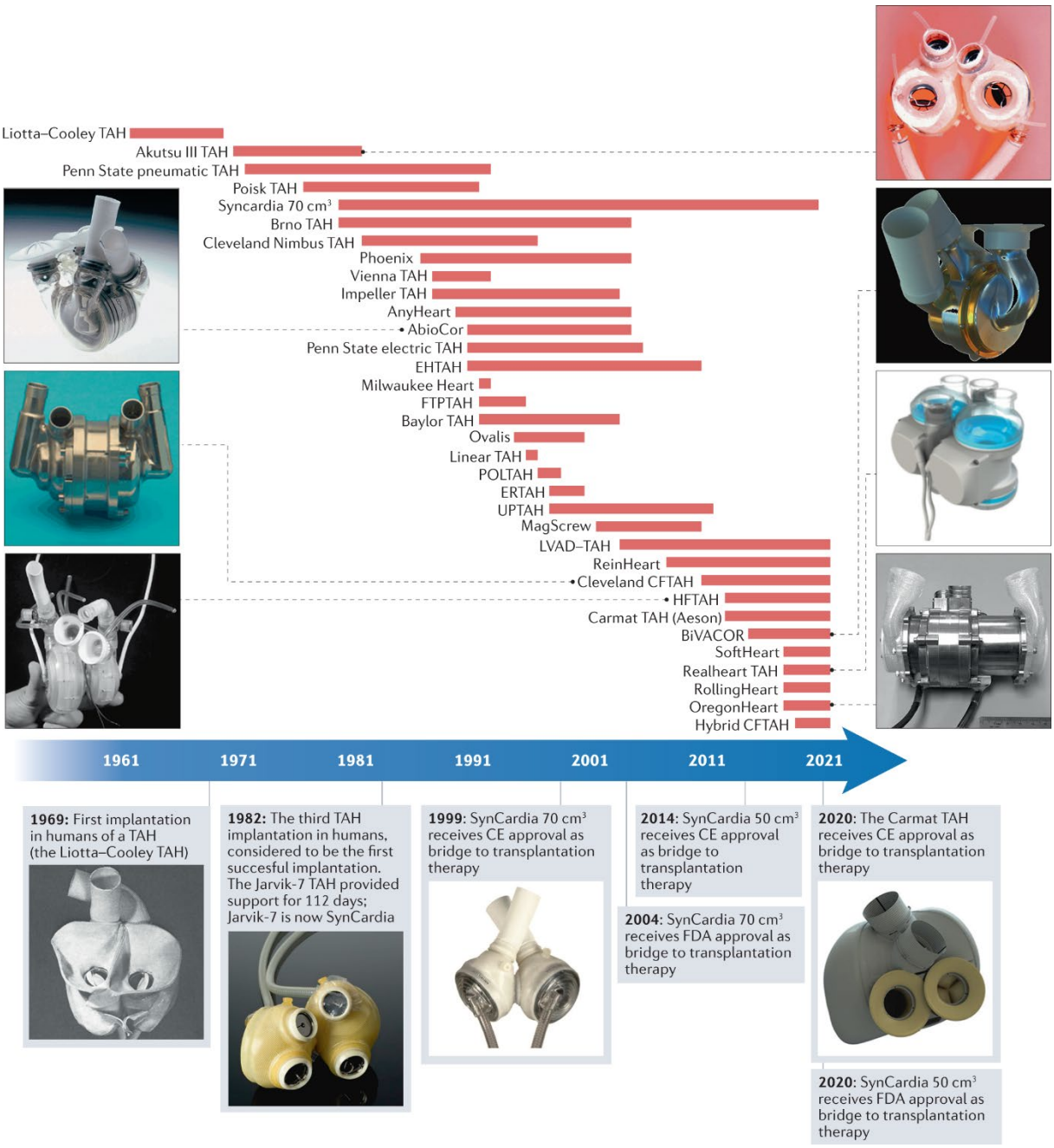

Figure 1. Timeline of the milestones in the development of total artificial hearts
All current TAH devices and the most historically important TAH devices are shown. The red bars represent the period of development and/or reporting of testing results in literature for each TAH. CFTAH, continuous-flow total artificial heart; EHTAH, electrohydraulic total artificial heart; ERTAH, eccentric roller total artificial heart; FTPTAH, flow-transformed pulsatile total artificial heart; HFTAH, helical flow total artificial heart; LVAD–TAH, total artificial heart made with two left ventricular assist devices; UPTAH, undulation pump total artificial heart. Images reproduced with permission from ref.171, Springer Nature (AbioCor); ref.48, Science Museum Group/Academic (Akutsu III); ref.172, Wiley (BiVACOR); ref.173,

Carmat/OUP (Carmat TAH); ref.96, Springer Nature (Cleveland CFTAH); ref.98, Wiley (HFTAH); The Board of Trustees of the Science Museum (Jarvik-7); ref.11, Elsevier (Liotta–Cooley TAH); ref.100, Wiley (OregonHeart); ref.174, Wiley (Realheart TAH); and ref.108, Elsevier (SynCardia).

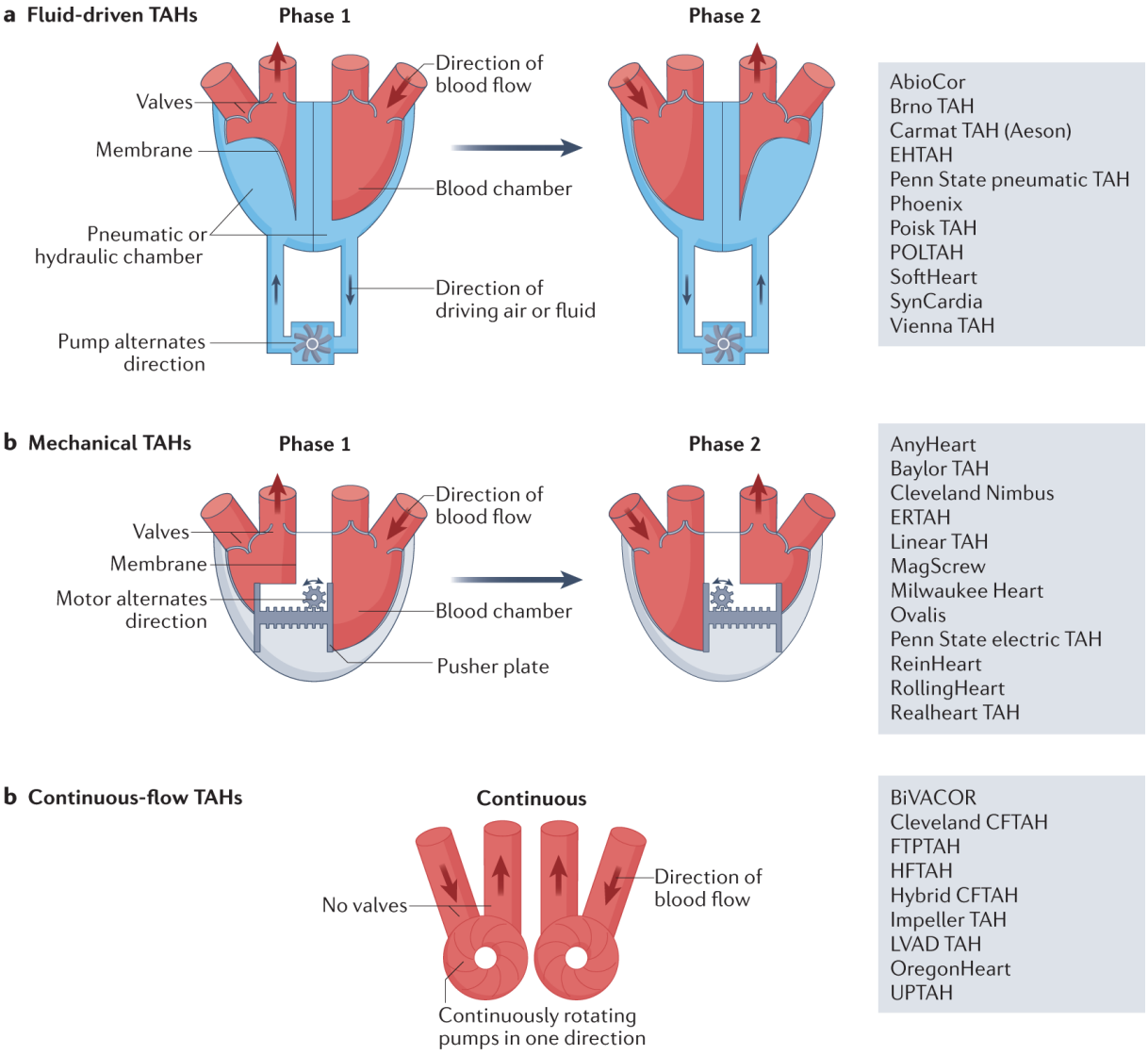

Figure 2. Working mechanism for different types of total artificial hearts

a. Fluid-driven total artificial hearts (TAHs) are composed of blood chambers and pneumatic or hydraulic chambers, which are separated by a membrane. A pump moves pressurized air or liquid into the pneumatic or hydraulic chambers, which moves the membrane and causes the ejection of the blood in a pulsatile manner. In the example shown in the figure, blood is ejected from both blood chambers alternately; however, some devices eject blood simultaneously from both chambers. The pump that moves the air or fluid can be implanted in the body or can be placed externally. For the latter, percutaneous hoses are required. Phase 1 shows the filling of the right blood chamber and the ejection of the left blood chamber. In phase 2, the pump rotates in the opposite direction, resulting in the filling of the left blood chamber and the ejection of the right blood chamber. B. Mechanical TAHs have two blood chambers and a mechanical motor, separated by a membrane. A motor pushes a mechanical part (pusher plate) against the membrane so that blood is ejected from that blood chamber. In the example, blood is ejected from the blood chambers alternately; however, some devices eject blood simultaneously from both chambers. In phase 1, the mechanical motor moves the pusher plate against the membrane of the

left chamber, which ejects blood while the right chamber fills. In phase 2, the mechanical motor moves the pusher plate against the membrane of the right chamber, which ejects blood while the left ventricle fills. c .Continuous-flow TAHs have two continuous-flow pumps that pump blood continuously in one direction. Valves are usually not required. There is no filling or ejection phase because the blood is continuously being pumped. CFTAH, continuous-flow total artificial heart; EHTAH, electrohydraulic total artificial heart; ERTAH, eccentric roller total artificial heart; FTPTAH, flow-transformed pulsatile total artificial heart; HFTAH, helical flow total artificial heart; LVAD–TAH, total artificial heart made with two left ventricular assist devices; UPTAH, undulation pump total artificial heart.

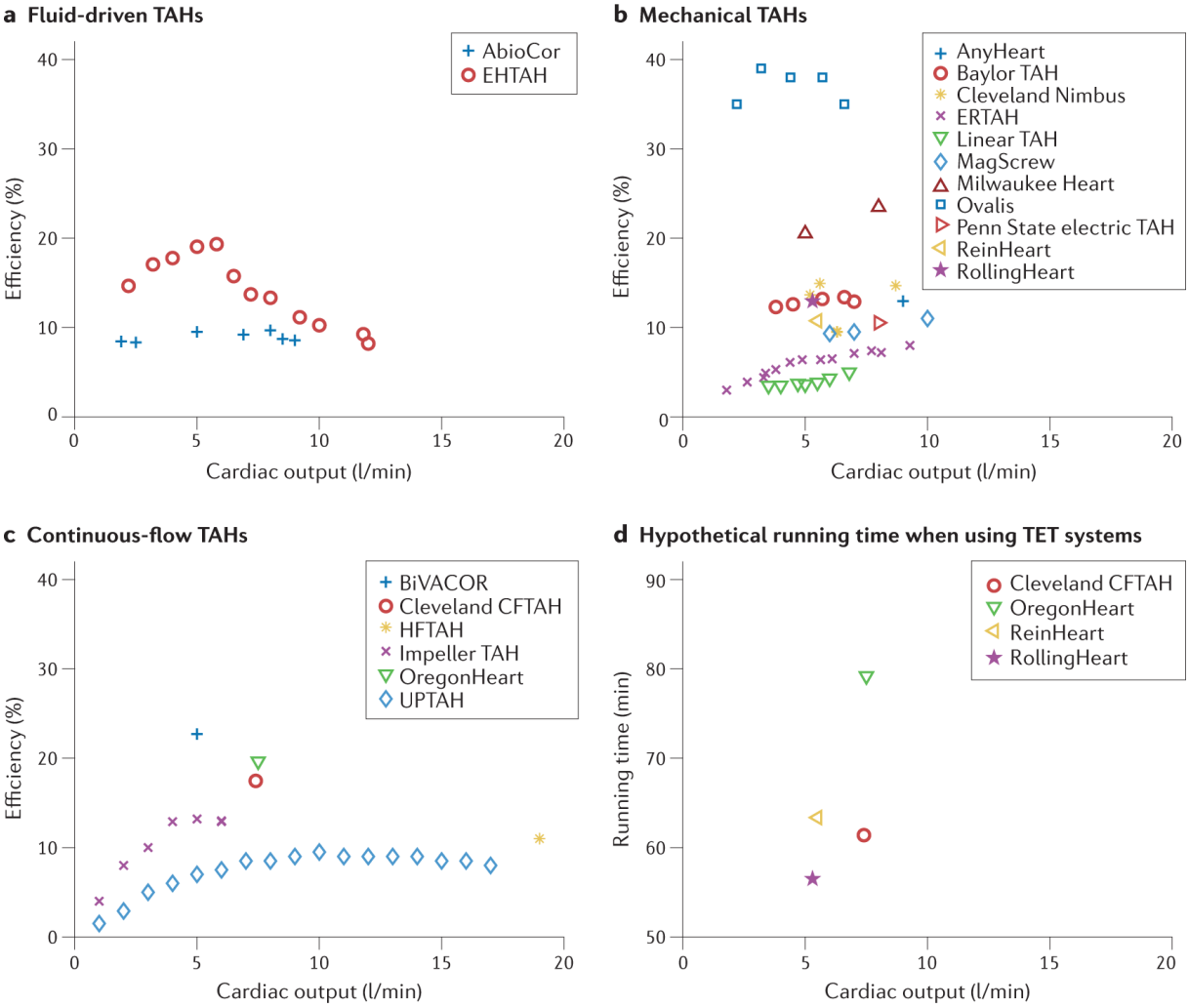

Figure 3. Efficiency of total artificial hearts

Overall efficiencies of total artificial hearts (TAHs) are depicted against the cardiac output. The method of calculation for the overall efficiencies of the TAHs is explained in Box 1. All values are measured under physiological mean left afterload conditions (≥90 mmHg). If right afterload was not reported when tested in a double-sided mock loop, we assumed it to be 20 mmHg. For some TAH devices, we were not able to obtain data to calculate efficiencies. Data for ReinHeart were shared by the authors upon request. a. Overall efficiencies for fluid-driven TAHs[45,175]. b. Overall efficiencies for mechanical TAHs[60,63,64,66,67,69,70,71,76,176]. c. Overall efficiencies for continuous-flow TAHs[84,95,98,157,168,170]. d .Running time (defined as the maximum time in which the TAH recipient can engage in activities without charging the TAH) of TAHs developed since 2015[76,157,170], calculated as though these TAHs hypothetically had transcutaneous energy transfer systems with the internal battery capacity of the most recently available battery technology (from the ReinHeart system). CFTAH, continuous-flow total artificial heart; EHTAH,

electrohydraulic total artificial heart; ERTAH, eccentric roller total artificial heart; HFTAH, helical flow total artificial heart; UPTAH, undulation pump total artificial heart.

Tables

TAH	Region	Type	Dimensions (mm)	Weight (g)	Volume (ml)	Power supply	Valve types	Development stage	Refs
AbioCor	USA	Fluid-driven	85 × 85 × 100	907	723[a]	TET	Mechanical	Stopped	46,47,48
AnyHeart	South Korea	Mechanical	60 × 100 × 100	650	600	TET	Mechanical	Stopped	59,60,61
Baylor TAH	USA and Japan	Mechanical	97 × 97 × 83	620	510	TET	Biological	Stopped	62,63
BiVACOR	USA	Continuous flow	NR	650	NR	Percutaneous	No valves	Animal models	95,148
Brno TAH	Czech Republic	Fluid-driven	NR	NR	NR	Percutaneous	Mechanical	Stopped	37
Carmat TAH (Aeson)	France	Fluid-driven	NR	900	750	Percutaneous	Biological	Approved	51,52
Cleveland continuous-flow TAH	USA	Continuous flow	60 × 60 × 100	486	160	Percutaneous	No valves	Animal models	96,97
Cleveland Nimbus	USA	Mechanical	90 × 97 × 134	NR	700	TET	Biological	Stopped	64,65
Eccentric roller TAH	Japan	Mechanical	100 × 100 × 80	1,800	800[a]	Percutaneous	No valves	Stopped	66
Electrohydraulic TAH	Japan	Fluid-driven	NR	2,492	872	TET	Mechanical	Stopped	45
Flow-transformed pulsatile TAH	Japan	Continuous flow	NR	2,000	550	Percutaneous	Mechanical	Stopped	82
Helical flow TAH	Japan	Continuous flow	80 × 80 × 77	565	493[a]	Percutaneous	No valves	Animal models	98
Hybrid continuous-flow TAH	USA	Continuous flow	50 × 50 × 50[b]	NR	125[a,b]	Percutaneous	No valves	In vitro	99
Impeller TAH	China	Continuous flow	40 × 40 × 80	250	128[a]	TET	No valves	Stopped	84
Linear TAH	Japan	Mechanical	85 × 85 × 94	1,900	560	Percutaneous	Mechanical	Stopped	67,68
LVAD–TAH	Various	Continuous flow	Various	Various	Various	Percutaneous	No valves	Clinical trials	
MagScrew	USA	Mechanical	NR	890	506	TET	Biological	Stopped	69
Milwaukee Heart	USA	Mechanical	83 × 83 × 62	600	490	Percutaneous	Mechanical	Stopped	70
OregonHeart	USA	Continuous flow	85 × 75 × 60[b]	NR	130	Percutaneous	No valves	In vitro	100,101
Ovalis	Germany	Mechanical	75 × 75 × 95	950	560	Percutaneous	Mechanical	Stopped	71
Penn State electric TAH	USA	Mechanical	91 × 91 × 94	700	778[a]	TET	Mechanical	Stopped	72
Penn State pneumatic TAH	USA	Fluid-driven	NR	NR	NR	Percutaneous	Mechanical	Stopped	38
Phoenix	Taiwan	Fluid-driven	70 × 70 × 130	NR	NR	Percutaneous	Mechanical	Stopped	39,40
Poisk TAH	Russia	Fluid-driven	125 × 100 × 70	220	NR	Percutaneous	NR	Stopped	41,42
POLTAH	Poland	Fluid-driven	NR	NR	NR	Percutaneous	Mechanical	Stopped	43
Realheart TAH	Sweden	Mechanical	148 × 126 × 96	800	1,790[a]	TET	Mechanical	Animal models	73,74
ReinHeart	Germany	Mechanical	87 × 87 × 90	940	550	TET	Mechanical	Animal models	75
RollingHeart	Switzerland	Mechanical	80 × 80 × 110	NR	704[a]	Percutaneous	No valves	In vitro	76
SoftHeart	Switzerland	Fluid-driven	NR	136	447	Percutaneous	Mechanical	In vitro	57

SynCardia 70cc	USA	Fluid-driven	NR	240	400	Percutaneous	Mechanical	Approved	49
Undulation pump TAH	Japan	Continuous flow	77 × 77 × 79	660	310	Percutaneous	No valves	Stopped	83
Vienna TAH	Austria	Fluid-driven	72 × 72 × 120	NR	622[a]	Percutaneous	Mechanical	Stopped	44

Table 1. Baseline characteristics of total artificial hearts.

LVAD–TAH, total artificial heart made with two left ventricular assist devices; NR, not reported, TAH, total artificial heart; TET, transcutaneous energy transfer. [a]Calculated with the reported dimensions. [b]Reported target size (not the current prototype).

TAH	Type	Study period	Number of animals	Maximum survival (days)	Most reported causes of death (*n*)	Refs
AbioCor[a]	Fluid-driven	1990–2001	120	108	Elective termination (16), mechanical failure (5)	20,112,117,149,150
AnyHeart	Mechanical	1990	1	4	Respiratory failure (1)	59
Baylor TAH[a]	Mechanical	1993–1994	8	7	NR	151,152
BiVACOR[a]	Continuous flow	2017	15	90	NR	148,153
Brno TAH[a]	Fluid-driven	1983–1995	168	314	Thromboembolic complications (6), mechanical failure (5)	37,119,154,155
Carmat TAH (Aeson)	Fluid-driven	2014–2017	12	10	Thromboembolic complications (4), bleeding (2), respiratory failure (2)	118,156
Cleveland continuous-flow TAH	Continuous flow	2015	17	90	Elective termination (4), bleeding (3)	157
Cleveland Nimbus	Mechanical	1992–1994	12	120	Mechanical failure (10), thromboembolic complications (1), infection (1)	64,113
Electrohydraulic TAH[a]	Fluid-driven	1990–2003	57	159	Mechanical failure (14), thromboembolic complications (7), respiratory failure (7)	114,158,159,160,161,162
Helical flow TAH	Continuous flow	2015	13	100	Mechanical failure (7)	98
LVAD–TAH	Continuous flow	2009–2021	40	92	Thromboembolic complications (23), elective termination (8)	85,88,92,93
MagScrew	Mechanical	2001-2005	12	92	Mechanical failure (5), respiratory failure (3)	69,163
Penn State electric TAH	Mechanical	1990–2000	54	388	Mechanical failure (17), respiratory failure (13)	72,115,164,165,166
Penn State pneumatic TAH[a]	Fluid-driven	1979–1989	47	353	Mechanical failure (22), thromboembolic complications (6)	38,167
Phoenix	Fluid-driven	2001	41	60	Respiratory failure (22), thromboembolic (6), multiorgan failure (6)	40
Reinheart[a]	Mechanical	2015	12	2	NR	75
SynCardia	Fluid-driven	1979–1981	31	268	Thromboembolic complications (8), bleeding (5)	25,26
Undulation pump TAH	Continuous flow	2000–2011	68	153	Mechanical failure (30), bleeding (15)	83,116,168,169
Vienna TAH[a]	Fluid-driven	1991	15	180	Mechanical failure (3)	44

Table 2. Total artificial hearts assessed in chronic animal trials

All devices that have been assessed in published chronic animal trials are listed. The cause of death of the animals was not always reported in the literature, especially for AbioCor, Baylor TAH, BiVACOR, Brno TAH, electrohydraulic TAH, ReinHeart, Penn State pneumatic TAH and Vienna TAH. LVAD–TAH, total artificial heart made with two left ventricular assist devices; NR, not reported; TAH, total artificial heart. [a]Devices with high numbers of missing animal data.

TAH	Type	Number of implanted devices	TAH support duration (days)		Number implanted as bridge to transplantation (%)	Number of deaths during TAH support (%)	Most reported causes of death during TAH support (%)	Refs
			Mean	Maximum				
AbioCor	Fluid-driven	11	142	512	0 (0)	10 (100)	Thromboembolic complications (50), multiorgan failure (33)	125
Brno TAH	Fluid-driven	6	5	10	0 (0)	6 (100)	Thromboembolic complications (50), bleeding (33)	120
Carmat TAH (Aeson)[a]	Fluid-driven	24	166	308	(45)	(55)	Multiorgan failure (50), mechanical failure (33)	107,138
LVAD–TAH	Continuous flow	9	92	180	4 (44)	4 (44)	Multiorgan failure (50), bleeding (50)	86,87,89,90,91,94
Penn State pneumatic TAH	Fluid-driven	3	135	379	2 (67)	1 (33)	Aspiration pneumonia (100)	38
Phoenix	Fluid-driven	2	8	15	2 (100)	0 (0)	–	121,123
Poisk TAH	Fluid-driven	13	5	15	1 (8)	12 (92)	Unknown	122
SynCardia[b]	Fluid-driven	>1,700	94	4.5 years	(65)	(33)	Multiorgan failure (40), thromboembolic complications (13), infection (10)	127,129,130,131,132,133,134,135,136
Vienna TAH	Fluid-driven	5	12	22	3 (60)	2 (40)	Infection (50), multiorgan failure (50)	44,124

Table 3. Total artificial hearts assessed in clinical trials.

All TAH devices that were implanted in patients are listed. LVAD–TAH, total artificial heart made with two left ventricular assist devices; TAH, total artificial heart. [a]The trial on the Carmat TAH is currently enrolling patients[56]; a total of 24 patients received the Carmat TAH (as of February 2022), of which data from only 11 patients are described in the literature; the mean duration of support, bridge to transplantation, death during TAH support and most reported causes of death are based on data from these 11 patients. [b]SynCardia TAHs have been implanted in over 1,700 patients, of which only a fraction has been reported in the literature; we used data from eight clinical trials describing 574 patients implanted with a SynCardia TAH to calculate the mean duration of support, bridge to transplantation, death during TAH support and most reported causes of death[116,117,118,119,120,121,122,123].

TAH	Type	Cardiac output (l/min)	Input power (W)	Output power (W)	Efficiency (%)	Running time without charging (min)	References
Cleveland continuous-flow TAH	Continuous flow	7.4	12.9	1.7	13.3	61	157
OregonHeart	Continuous flow	7.5	10.0	1.7	17.5	79	170
ReinHeart	Mechanical	5.5	12.5	1.3	10.8	63	Unpublished data[a]
RollingHeart	Mechanical	5.3	14.0	2.0	14.1	57	76

Table 4. Power requirements and efficiency of total artificial hearts.

All TAHs currently being investigated with published power requirements are listed. For the TAHs not listed in the table, no power requirements have been reported in the literature. All parameters were measured at a physiological mean left afterload (≥90 mmHg). TAH, total artificial heart. [a]Data for ReinHeart was shared by the authors upon request.

Glossary

Driveline: Percutaneous cable that transmits electrical power from an external driver to the internally implanted device such as a TAH or LVAD.
Transcutaneous energy transfer (TET) system: A wireless power delivery system that uses magnetic fields to transfer power across the skin without the need for direct electrical connectivity.
Bronchial shunt: The physiological passage of oxygenated blood from the aorta to the bronchial circulation. This blood returns directly to the left atrium, thereby bypassing the right side of the heart.
Frank–Starling mechanism: This law states that the stroke volume of the heart increases in response to an increase in the volume of blood in the ventricles before contraction (the end diastolic volume), when all other factors remain constant.
Preload: The filling pressure of the ventricle at the end of diastole, which is determined by the atrial pressure.
Stator: The stationary part of a rotary machine or device.
Investigational device exemption: Type of FDA approval that allows the investigational device to be used in a clinical study in order to collect safety and efficacy data.
Afterload: The amount of pressure that the ventricle needs to exert to eject the blood during ventricular contraction.

Box 1 Calculation of TAH efficiencies

To compare the efficiency of the different types of total artificial heart (TAH) shown in Fig. 3, we used a consistent measure of the power consumed by the TAH (input power) and the amount of work (output power) performed by the TAH to pump blood against physiological pressures. The numerical value of the output power is the product of the difference in outlet and inlet pressure (pressure head) and the flow of blood generated by the heart (cardiac output). For pulsatile TAHs, we calculated the pressure head as the difference between the mean afterload and the intraventricular pressure. We assume that during diastole, the pressure inside the TAH ventricle drops to near 0 mmHg, as in the native heart177. For continuous-flow TAHs, we calculated the pressure head as the difference between the mean afterload and the mean preload. We have used the following equation to calculate the output power of the TAHs:

$$\text{Output power} = Q_{\text{sys}} H_{\text{sys}} + Q_{\text{pul}} H_{\text{pul}}$$

where the output power is in watt, Qsys and Qpul are the resulting cardiac output (in m3/s) for the systemic and pulmonary circulations, respectively, and Hsys and Hpul are the pressure heads (in N/m2) for systemic and pulmonary circulations, respectively, against which the TAH must pump. The input power to the TAH is an individual number unique to the device. Therefore, we analysed only the TAHs that have the corresponding input power reported in the literature. We have used the following equation for calculating the efficiency (η) of a TAH on the basis of input power and output power:

$$\eta = \frac{\text{Output power}}{\text{Input power}} \times 100\%$$

Acknowledgements

The authors are grateful to L. C. van Laake (AMOLF, Netherlands), D. Zrinscak (Scuola Superiore Sant'Anna, Italy) and A. Henseler (evos GmbH, Germany) for their contributions and discussions; D. van Urk (Amsterdam UMC, The Netherlands) for assisting with screening and selecting articles; T. Azami (Amsterdam UMC, The Netherlands) and C. M. van de Beek (Amsterdam UMC, The Netherlands) for assistance with data extraction; C. E. J. M. Limpens (Amsterdam UMC, The

Netherlands) and A. Malekzadeh (Amsterdam UMC, The Netherlands) for their help with the literature search; and ReinHeart TAH GmbH, Germany for providing additional data upon request. The authors' work is part of the HybridHeart project and is funded by the European Union Horizon 2020 research and innovation programme under grant agreement no. 767195.

Contributions

A.V. and M.A. did the major literature search and wrote the first draft. All of the authors contributed to the discussion of content and reviewed and edited the manuscript before submission.

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Competing interests

A.V., M.A., H.K., J.T.B.O. and J.K. are part of the HybridHeart consortium. The other authors declare no competing interests.

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