OPINION

Total artificial hearts: past, present, and future

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Abstract | A practical artificial heart has been sought for >50 years. An increasing number of people succumb to heart disease each year, but the number of hearts available for transplantation remains small. Early total artificial hearts mimicked the pumping action of the native heart. These positive-displacement pumps could provide adequate haemodynamic support and maintain the human circulation for short periods, but large size and limited durability adversely affected recipients' quality of life. Subsequent research into left ventricular assist devices led to the use of continuous-flow blood pumps with rotating impellers. Researchers have attempted to integrate this technology into modern total artificial hearts with moderate clinical success. The importance of pulsatile circulation remains unclear. Future research is, therefore, needed into positive-displacement and rotary total artificial hearts.

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Introduction

The need for a practical mechanical replacement for the failing human heart has motivated scientists and clinicians for more than half a century. The deceptive simplicity of the heart and the magnitude of the unmet clinical need associated with advanced heart failure (HF) have attracted a diverse group of innovators, including Charles Lindbergh, Paul Winchell, Alexis Carrel, Willem Kolff, and Robert Jarvik. Most efforts have focused on creating total artificial hearts (TAHs) with pulsatile output, composed of two volume-displacement pumps, each with unidirectional inlet and outlet valves. TAHs with self-contained actuation mechanisms have been devised, but all have been limited by large size and poor durability. Some TAHs have performed well in chronic animal studies and even in small clinical pilot studies. Encouraging results notwithstanding, the only artificial heart that has been implanted with any frequency employs an external pneumatic actuation mechanism that is connected to the device via a pair of transcutaneous air hoses. As a result, this device is used almost exclusively as a bridge to transplantation. The search for a permanent (destination therapy), totally implantable artificial heart continues. Although newer self-contained volume-displacement TAHs might succeed where earlier devices failed, interest is also being shown in leveraging continuous-flow rotary blood pump technology.

Heart disease remains the leading cause of death in the USA and most of the developed world. Each year, almost 400,000 people die from HF-related causes in the USA alone,[1] and this number is likely to increase. Cardiac transplantation is an effective treatment, but limited donor-organ availability has resulted in a modest epidemiological effect. For the past 20 years, only 2,000–2,500 hearts have been transplanted annually in the USA and, therefore, a very small proportion of patients have benefitted from them.[2] Many patients who are not selected for transplantation and who have HF that primarily affects only the left ventricle can be treated with a permanent left ventricular assist device (LVAD), and some have had implanted pumps for >1 decade. Nevertheless, many patients have severe biventricular failure or other conditions that would make LVAD implantation difficult or unwise, such as refractory HF and large recent infarctions, intractable arrhythmias, postinfarction ventricular septal defects, previously implanted prosthetic valves, or complex native valve disease. These patients would benefit from development of self-contained, energy-efficient, durable TAHs.

TAH device requirements

Multiple technical challenges are associated with the development of a self-contained, implantable TAH for use as destination therapy. The device must fit within the mediastinum of a high percentage of patients with HF and must be configured to facilitate suturing to the left and right atrial remnants and the great vessels after the diseased native heart is excised. The TAH must generate adequate cardiac output to accommodate the physiological needs of the patient and some level of exertion, and the device must do so without injuring the formed elements of the blood or generating thromboemboli. Devices must be biocompatible, must not generate excessive heat, and must last for ≥5 years—all without consuming excessive amounts of power. If a transcutaneous energy transfer system is used, an internal battery must have the capacity to power the TAH long enough to allow repositioning of the external component if necessary. Perhaps most challenging is the need for the TAH to balance the systemic and pulmonary circulations despite a wide variety of haemodynamic perturbations.

The entire output of the right ventricle is pumped through the pulmonary circulation to the left atrium, but the same is not true of the left ventricular output. Bronchial arterial branches arising from the descending thoracic aorta drain through the pulmonary veins. A substantial proportion of the left ventricular output, therefore, returns to the left rather than the right atrium. Consequently, the output of the left ventricle might be 10–15% greater than that of the right ventricle. If this balance is not properly maintained, the lesser-functioning side will rapidly develop atrial hypertension. Left atrial hypertension results in pulmonary oedema and respiratory failure. Right atrial hypertension results in anasarca, ascites, and renal and hepatic insufficiency. Efforts to decrease excessive atrial pressure in a TAH recipient who develops pulmonary–systemic imbalance can result in suction events on

Competing interests
D.L.T. is the founder of BiVACOR, Inc. The other authors declare no competing interests.

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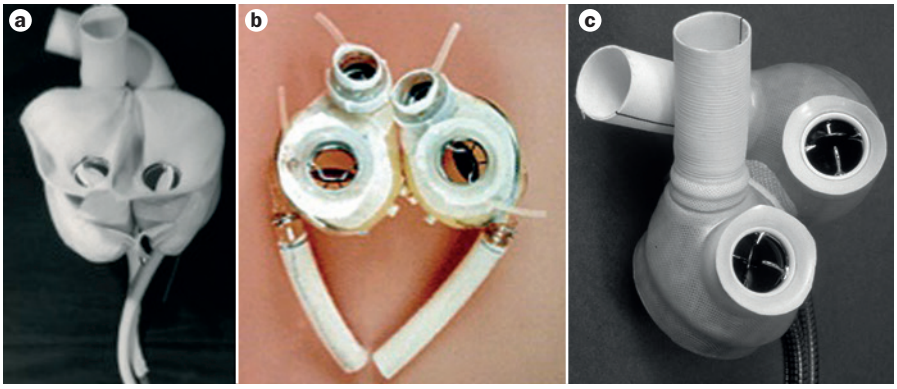

Figure 1 | Three early TAHs. **a** | Liotta–Cooley TAH. **b** | Akutsu III TAH. **c** | Jarvik 7 TAH. Abbreviation: TAH, total artificial heart. All images © Texas Heart Institute.

the low-pressure side, which might lower cardiac output. A mechanism that autonomously assesses and maintains proper balance is essential.

Early beginnings

One of the first descriptions of an artificial heart was made by Leonardo da Vinci in the 15th century, but it was not until 1957 that a TAH was completely implanted into an animal by Akutsu and Kolff.[3] This milestone sparked a boom in the research of TAHs that culminated in Michael DeBakey's successful request to US President Lyndon B. Johnson for financial support for a TAH programme, which was established in 1964. The challenge was set to produce a fully functional artificial heart by the time that humans set foot on the moon.

Liotta–Cooley TAH (1969)

In 1961, Domingo Liotta, who had already been working on a TAH at the University of Cordoba, Argentina, was recruited to work in DeBakey's laboratory at Baylor College of Medicine in Houston, TX, USA. Liotta performed numerous experiments in calves with limited success. The TAH used an external compressor to cyclically deliver and evacuate compressed air to and from two 100 ml rigid, flocked chambers lined with Dacron® (Du Pont de Nemours, USA), each partitioned into two halves—one for blood and the other for compressed air—by a flexible silicone-elastic and Dacron® diaphragm. One of the rigid chambers served as the systemic pump, the other as the pulmonary pump. Two pairs of unidirectional DeBakey ball valves at the inlets and outlets of the blood-filled half of each of the two chambers ensured that blood flow was unidirectional (the DeBakey ball valves were subsequently replaced with Wada–Cutter hingeless valves by Cooley immediately before clinical implementation). Dacron® skirts attached to the inlet valves were sutured to the left and right atrial remnants after the native heart was excised. Knitted Dacron® tube grafts attached to the outlet valves were sutured end to end to the pulmonary artery and aorta. When 70–80 cm^3 of compressed air from the external drive console was used to inflate the pneumatic side of the flexible diaphragm, a similar volume of blood was displaced from the opposite side of the rigid chamber through the outlet valves into the aorta and pulmonary artery. When the air was rapidly withdrawn, the left and right chambers refilled with blood from the pulmonary and systemic veins, respectively. By repeating this cycle 70 times per minute, an output of 5 l/min could be achieved.

On 4 April 1969, 3 months before the first lunar landing, Denton A. Cooley, of the Texas Heart Institute, Houston, TX, USA, became the first surgeon to implant a TAH in a human.[4] Cooley, an associate of DeBakey at the time, offered the experimental therapy to a patient aged 47 years as a bridge to transplantation if resection and repair of his extensive left ventricular aneurysm were impossible. The patient could not be weaned from cardiopulmonary bypass and, therefore, the Liotta–Cooley device (Figure 1a) was implanted. The patient remained haemodynamically stable with the device for 64 h, until transplantation was performed. He was extubated on the first day after surgery, but died 32 h after transplantation, partly owing to sepsis. Notably, haemolysis and progressive renal impairment were seen in the early period after implantation. These effects were attributed to the poor function of the hingeless valves used in the device and to the flocked Dacron® lining of the inner surface. At post-mortem examination, the surfaces of the device that came into contact with blood were observed to be lined with a smooth neointima of platelets and fibrin. Therefore, although implantation of the Liotta–Cooley TAH was a momentous clinical and engineering feat, ultimately it was not considered a success.

Akutsu III TAH (1981)

On the basis of this initial clinical experience with a TAH, Akutsu and colleagues working in the Texas Heart Institute Cullen Cardiovascular Research Laboratory developed the Akutsu III artificial heart (Figure 1b). As with the Liotta–Cooley heart, this device used compressed air and inflatable air sacs to displace blood, but the blood-contacting surfaces were constructed from smooth, multisegmented polyurethane, and the device contained four Björk–Shiley carbon-pyrolytic tilting disc valves. In 1981, after numerous successful implantations in animals, the Akutsu III TAH was used as a bridge to transplantation in a patient aged 36 years who had developed refractory ventricular fibrillation after undergoing CABG surgery.[5] The TAH provided adequate haemodynamic support, but after 24 h, the patient developed profound hypoxia requiring venovenous extracorporeal membrane oxygenation, probably because of pulmonary venous obstruction by the device. The TAH supported the patient for 55 h until transplantation. The patient died 1 week later from multiorgan failure. No haemolysis was seen during implantation, presumably because of improved materials.

Jarvik 7 TAH (1982)

Meanwhile, Kolff and Jarvik had been developing the Jarvik 7 TAH (Figure 1c).[6] As with the Akutsu III TAH, the Jarvik 7 was constructed from multisegmented polyurethane and had four Björk–Shiley tilting valves. After extensive validation in large animals, approval was obtained from the FDA for a small series of clinical implantations as destination therapy. The first implantation was performed by DeVries in a patient with end-stage ischaemic HF.[7] The patient lived for 112 days with the device. Over the next year, the Jarvik 7 TAH was implanted in four further patients, one of whom lived for 620 days. Among the five patients, two had debilitating strokes. One died from haemorrhagic complications, and the other four died from septic complications. Therefore,

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the risk of infection was clearly seen to increase with the duration of support. In 1983, approval of the immunosuppressant drug ciclosporin led to dramatic improvements in long-term survival after cardiac transplantation and to a resurgence in interest in this therapy. As a result, the focus shifted from developing permanent replacements for failing hearts to bridging patients with biventricular failure to heart transplantation.

The Jarvik 7 heart trials were temporarily suspended by the FDA in 1990,[8] but resumed after extensive technical refinements were made to the device. The device has been renamed several times to the Symbion Artificial Heart, the CardioWest TAH, and (for the past 13 years) the SynCardia temporary TAH (SynCardia Systems Inc., USA).[9] Refinements have included reduced size of the pumping chambers from 100 cm^3 to 70 cm^3, integration of a specifically designed modified Medtronic–Hall carbon-pyrolytic tilting disc valve that is more suitable for the high closing forces than the previous valves (because of rigid mounting), and improvements in manufacturing techniques. The device received CE mark approval in 1999 and was the first TAH approved by the FDA, in 2004, for use as a bridge to heart transplantation.[10]

Various iterations of the SynCardia temporary TAH have subsequently been implanted in >1,300 gravely ill patients, around 80% of whom have been successfully bridged to heart transplantation (1-year survival is 70%).[11] A total of 241 patients have survived for >6 months, 92 for >1 year, 16 for >2 years, and three for >3 years; the longest duration of bridging so far is 1,374 days.[10]

A further intended development is to make a 50 cm^3 device, which could substantially improve access to this technology for children and small adults. A portable miniature compressor that weighs 6.1 kg and can function for 3 h on fully charged batteries has improved quality of life by enabling patients to participate in a wide range of activities, such as golf or bike riding, that were not possible with earlier compressors.[12]

The use of external drivers for the SynCardia temporary TAH has several advantages over internal drivers. By integrating the electronic components and most of the mechanical complexity in the paracorporeal pneumatic compressor, the components that need to be implanted could be decreased in size and mechanistically simplified, which facilitated implantation in smaller patients. In addition, those parts that are most likely to fail because of cyclic fatigue are outside the body, where they can be closely monitored and promptly exchanged. At present, external drivers are exchanged pre-emptively every 6–12 weeks. The flexible components implanted in the chest—the pneumatically actuated diaphragms—also have limited durability, because they must flex between 30 million and 50 million times per year. The transcutaneous air hoses are an important physiological liability, because of the increased incidence of ascending driveline infections in patients undergoing long-term support. Although device infections have caused few deaths in patients awaiting transplantation, the mean duration of SynCardia support is 15–90 days at different centres. In a large series of 171 patients, 60% were supported by the SynCardia device for <2 weeks, and the average duration of support was 24 days.[13] A total of 37% of patients experienced severe infectious complications necessitating urgent transplantation.

Totally implantable TAH technology

Although the results of heart transplantation continued to improve after the introduction of better immunosuppressive agents, the supply of donor hearts remained a limiting factor. The National Heart, Lung, and Blood Institute increased funding in 1988 to develop a completely implantable TAH with the aim of producing a practical long-term heart-replacement device. Many ambitious attempts were made to develop durable, self-contained, volume-displacement TAHs with internal actuation mechanisms that eliminated the need for an external driver and percutaneous drivelines or pneumatic hoses. The resulting devices included the Sarns-3M TAH (3M Health Care, USA, in conjunction with the Pennsylvania State University, University Park, PA, USA), the Nimbus TAH (Nimbus, USA, in conjunction with the Cleveland Clinic, Cleveland, OH, USA), the AbioCor® TAH (ABIOMED, USA, in conjunction with Texas Heart Institute and the Jewish Hospital in Louisville, KY, USA), and the electrohydraulic TAH (developed at the University of Utah, Salt Lake City, UT, USA). Each of these devices met the National Heart, Lung, and Blood Institute criteria for success, which included the capacity to pump 8 l/min against a mean systemic blood pressure of 110 mmHg and a mean pulmonary artery pressure of 25 mmHg while maintaining a filling pressure of ≤10 mmHg on the right side and 15 mmHg on the left.[14] All these TAHs were powered by transcutaneous energy transfer systems based on inductive coupling of radiofrequency alternating current through the intact skin without the need for a percutaneous driveline. An implanted battery provided continuous operation in the event of transient disconnection of the transcutaneous energy transfer system. In addition, TAHs were developed in parallel at the National Cerebral and Cardiovascular Center, Suita, Osaka Prefecture, Japan,[15] and the Vacord Bioengineering Research Company, Brno, Czech Republic.[16,17]

Sarns-3M TAH

The Sarns-3M TAH (Figure 2) was designed by pioneering innovator Dick Sarns and used a reciprocating brushless direct-current motor and translating roller screw to alternately actuate left and right pusher plates, which alternately compressed systemic and pulmonary blood sacs made from seamless polyether polyurethane urea to provide stroke volumes of up to 90 ml.[18,19] While one side of the TAH ejected, the other side filled. A total of 4.5 rotations of the motor caused the screw to travel 19 mm. The pump displacement was 64 cm^3, and the maximum output was 8 l/min at 125 bpm. Motor direction was reversed when the left pump filled, as detected by three Hall-effect sensors on the left pump membrane and by monitoring of the motor current. The pusher plates were not attached directly to the blood sacs which could, therefore, fill passively. Early left pump filling was evidence of high atrial pressure, which resulted in an autonomous decrease in right pump stroke volume to restore balance between the systemic and pulmonary circulations. The space between the blood sacs was connected to a gas-filled compliance chamber, which required percutaneous injection of additional air every 6 weeks. As in other TAHs, each chamber was fitted with Björk–Shiley inlet and outlet valves. The internal battery provided 45 min operation in the event of transient disconnection of the transcutaneous energy transfer system.

In mock circulation loop testing, the device could accommodate a wide range of preload pressures without suction events, autonomously increased pump output if left atrial pressure rose (1 l/min/mmHg), and showed relative insensitivity to afterload. Flow balancing was achieved by estimating the left pump's end-diastolic volume on the basis of motor speed and voltage,

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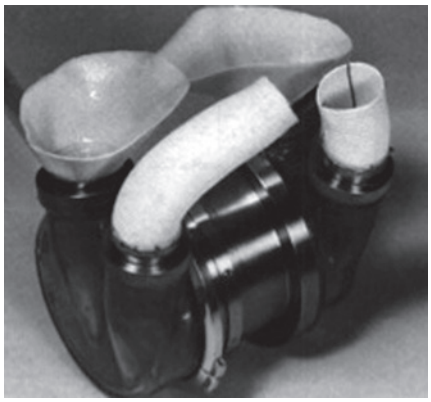

Figure 2 | Sarns-3M positive-displacement total artificial heart (3M Health Care, USA, and Pennsylvania State University, University Park, PA, USA). Reprinted with permission from Rosenberg, G. *et al.* A roller screw drive for implantable blood pumps. *ASAIO J.* **28** (1), 123–126 (1982).

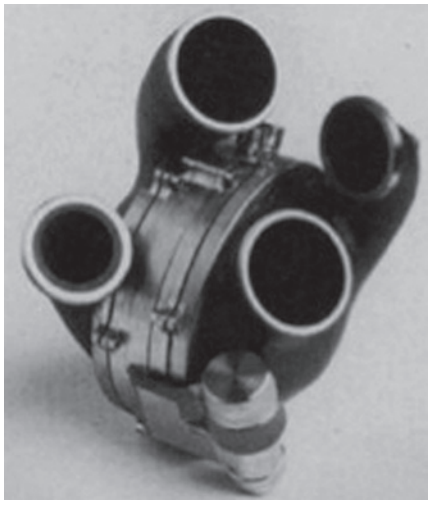

Figure 3 | Nimbus positive-displacement total artificial heart (Nimbus, USA, and Cleveland Clinic, Cleveland, OH, USA). Reprinted from McCarthy, P. M. *et al.* The Cleveland Clinic-Nimbus total artifical heart. In vivo hemodynamic performance in calves and preclinical studies. *J. Thorac. Cardiovasc. Surg.* **108** (3), 420–428 © (1994), with permission from Elsevier.

and by adjusting the right pump's diastolic time.[20] Devices were implanted in 14 calves by 1993, and the longest survival was 150 days.[21] Causes of premature termination of the experiment included respiratory failure, infection, and device failure. Formal review of design readiness began in 1999. Despite moderate success, performance was never considered adequate for human implantation, especially because of the device's large size, poor system reliability, and limited durability.

Nimbus TAH

The Nimbus TAH (Figure 3) used a brushless direct-current motor and gear pump to generate hydraulic pressure, which actuated a hydraulic piston.[14] A spool valve redirected hydraulic fluid to reverse the piston direction. On either end of the reciprocating piston were flat plates that alternately compressed systemic and pulmonary blood sacs, but were not attached to them in order to allow passive filling, as in the Sarns-3M TAH. The hydraulic mechanism was positioned in the 21 mm space between the blood sacs, which was vented to a gas-filled intrathoracic compliance chamber. The blood-contacting surfaces of the pumps were lined with a seamless coating of glutaraldehyde cross-linked gelatin, which was deemed biocompatible and was intended to eliminate the need for systemic anticoagulation. Four bovine pericardial tissue valves (or, in some iterations, human dura mater valves) were integrated into the two blood sacs. The outer shell of the device was constructed from epoxy reinforced with carbon fibre.

The hydraulic cylinder stroke length was 13.2 mm, and the maximum stroke volume was 64 cm^3, but the normal operating stroke volume was 53 cm^3. Maximum output was 9.6 l/min at 150 bpm. As with the Sarns-3M device, in mock circulation loop testing the Nimbus TAH maintained systemic–pulmonary balance and autonomously increased pump output if left atrial pressure rose (0.5 l/min/mmHg).[14] Iterations of the device were implanted in 12 calves, which survived for an average of 32 days (longest survival 120 days).[22] Several animals could exercise on a motorized treadmill for an average of 22 min. Despite these encouraging results, many experiments had to be terminated prematurely because of mechanical failures and, ultimately, the risk was deemed prohibitive to proceeding to human implantation.

AbioCor® TAH (2001)

The AbioCor® TAH (Figure 4) was the only fully implantable self-contained TAH from this era to be used in humans. Again, the device consisted of two pumping chambers with flexible membranes alternately compressed by an internal mechanism.[23] The actuation mechanism, however, was unique in that there were no pusher plates. A centrifugal pump was used to pressurize hydraulic fluid, which alternately compressed the flexible medial aspects of the two blood pumps directly. The centrifugal pump, which rotated at 4,000–8,000 rpm, shuttled silicone oil from

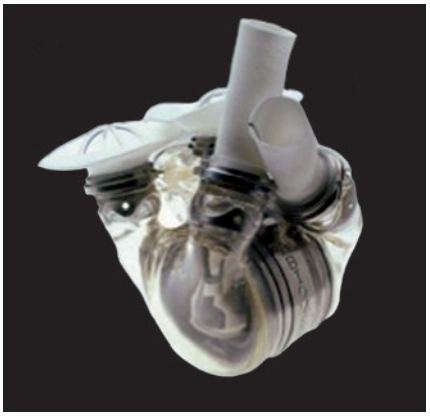

Figure 4 | AbioCor® positive-displacement total artificial heart (ABIOMED, USA). Permission obtained from ABIOMED, USA.

one side of the TAH to the other, so that one blood pump was filling while the other was ejecting. The inlet and outlet ports were positioned on a cylinder that continuously rotated around the hydraulic pump and cyclically changed the direction of the silicone oil without necessitating a change in the rotational direction of the motor. This design was believed to improve mechanical durability.

The blood-contacting surfaces of the AbioCor® were constructed from proprietary multisegmented polyurethane. The TAH was manufactured in such a way that the entire blood path was seamless, including the points of attachment of the four trileaflet valves, which were also fabricated from the same material. The blood-contacting component was housed in a polycarbonate shell. The TAH had a stroke volume of 80 cm^3 and could generate up to 9.6 l/min of blood flow at an ejection rate of 120 bpm. The device was fairly large, measuring 100 mm in width and 85 mm in diameter.

The AbioCor® had a unique mechanism to equalize pulmonary and systemic flow. A small reservoir connected to the right hydraulic space and separated from the left atrium by a thin flexible membrane contained silicone oil. When left atrial pressure became excessively high, the oil was displaced from the reservoir into the right hydraulic space and decreased end-diastolic filling of the right blood pump. As a result, the right pump stroke volume would be decreased for the next heartbeat, resulting in decreased return of blood to the left atrium and an autonomous reduction in left atrial pressure. This technique was refined to produce a sensitivity to preload of 0.4 l/min/mmHg to keep the total volume of blood and hydraulic fluid within the pump constant over time.[24] As a

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result, the AbioCor® was the only positive-displacement device that did not require a gas-filled intrathoracic compliance chamber.

Over a 12-year period, researchers implanted AbioCor® devices into 120 calves; the last 57 of these devices used the electro-hydraulic converter and autonomous pressure equalization system described. Several of the animals survived beyond the 90-day term of the study and could exercise on a motorized treadmill. Formal design readiness testing was begun in 1999, and >200 of the devices were manufactured.

In 2001, Gray and Dowling implanted an AbioCor® TAH in a human.[25] Over the next 2 years, 13 additional TAHs were implanted at four US centres. All the patients were men who weighed 84–120 kg and, therefore, could accommodate the large size of the device. Of these patients, three died in the perioperative period from haemorrhage ($n = 2$) or air embolism ($n = 1$), and six patients died from multiorgan failure within the first 9 months. The remaining five patients survived for 9–15 months, but died from complications related to stroke, infection, or organ failure, except the longest-surviving patient, in whom the device failed because an internal flexible membrane ruptured. No serious complications related to the transcutaneous energy transfer system were reported. On the basis of these results, study enrolment was suspended.

ABIOMED subsequently refined the device to decrease the overall size and sought approval for 60 additional implantations. The FDA approved the refined device for use in humans, but the project was deemed commercially unviable and prohibitively difficult, and was discontinued in 2007.[26] The prospect of a totally implantable, permanent mechanical heart-replacement device still seemed very far off.

Development of LVADs

Although intense TAH research continued, other groups focused on developing LVAD technology because of the decreased technical demands associated with assisting a weakened heart rather than replacing it.

Positive-displacement pumps

Early short-term paracorporeal LVADs were intended for use in patients who could not be weaned from cardiopulmonary bypass after heart surgery and relied on percutaneous air hoses similar to those used in the initial TAH systems. Development of a pneumatic pump for this intermediate-term application was cost-effective and easily attainable. The implantable HeartMate® pneumatic pump (TherMedics, USA, and later Thoratec Corporation, USA) was first implanted in a human by Frazier in 1986.[27] Although the original intention in developing implantable LVAD systems in the 1970s was to provide a permanent, completely implantable pump for patients with left-sided HF, the introduction of ciclosporin and the success of heart transplantation resulted in a shift of focus to bridging transplantation-eligible patients until a suitable donor heart could be obtained. Development of a pneumatic pump was a comparatively cost-effective and easily attainable goal for this intermediate-term application. As use of the HeartMate® pump increased, the merit of mechanical circulatory assistance of the left ventricle in transplantation candidates became apparent, but its application was restricted by the scarcity of donor hearts and limitations of the pneumatic device.

In an attempt to address these limitations, Thoratec redirected its efforts towards developing the HeartMate® XVE (Figure 5a). This device was first implanted in a human by Frazier in 1991.[28] It was similar to the pneumatic pump, but used a self-contained high-torque motor and rotating follower and cam rather than pressurized air to actuate the pusher plate; therefore, the device needed no external drive console, although a driveline and pneumatic vent were still required to attach to an external battery pack. The device was large, which made it unsuitable for small patients and made the implantation procedure invasive and associated with early morbidity and mortality. The greatest shortcoming, however, was probably limited durability, with few pumps lasting beyond 24 months.

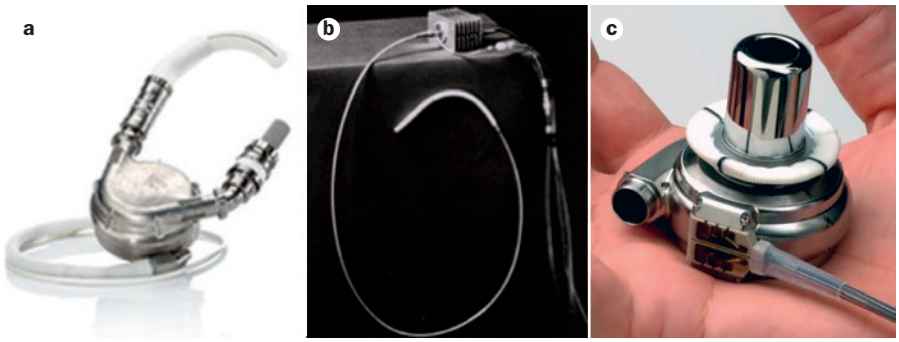

Figure 5 | Transition of positive-displacement pumps to rotary blood pumps (left ventricular assist devices). **a** | HeartMate® XVE (TherMedics, USA, and later Thoratec Corporation, USA). Permission obtained from Thoratec Corporation, USA. **b** | Hemopump (Nimbus, USA). Reprinted from Frazier, O. H. *et al.* First human use of the Hemopump, a catheter-mounted ventricular assist device. *Ann. Thorac. Surg.* **49** (2), 299–304 © (1990), with permission from Elsevier. **c** | HeartWare® HVAD (HeartWare, USA). Image © Texas Heart Institute.

Despite these limitations, many researchers believed that the HeartMate® XVE pump performed well enough to justify a multicentre, prospective, randomized study to compare outcomes with those of optimal medical therapy. In the REMATCH trial,[29] conducted in 129 patients with NYHA class IV HF, 1-year survival was 52% in patients who received the LVAD, compared with 25% in those who received medical management only, and 2-year survival was 24% versus 8%, respectively. LVAD technology was, therefore, deemed to prolong life in appropriately selected patients with end-stage HF primarily affecting the left ventricle. Nevertheless, a smaller, more-durable pump was required.

Rotary blood pumps

Rotary blood pumps were proposed to solve the size and durability challenges posed by positive-displacement pumps, but were initially viewed with scepticism relating to the absence of a physiological pulse. In 1986, Jarvik and Wampler independently approached Frazier about starting animal studies with implantable rotary blood pumps. These efforts resulted in the first two clinically used continuous-flow pumps: the intraventricular Jarvik 2000® (Jarvik Heart, USA) and the temporary Hemopump (Nimbus, USA; Figure 5b).[30–32] Development of these devices showed compellingly that continuous, nonpulsatile blood flow was physiologically tolerated, that rapidly spinning blood pumps could be designed that did not cause haemolysis or liberate particulate emboli, and that rapidly spinning rotors in the blood could be supported by bearings, if the bearings were positioned so that they were continually

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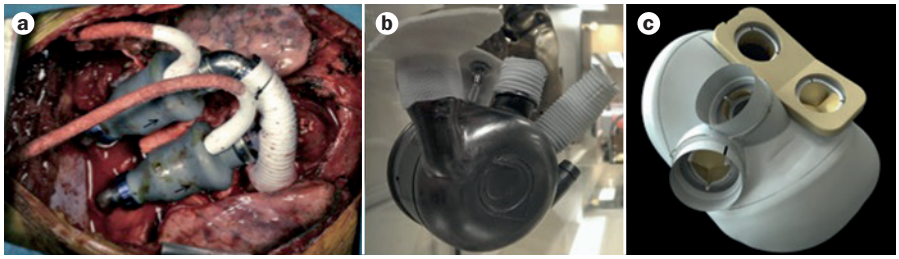

Figure 6 | The future of total artificial heart technology. **a** | Dual HeartMate II® left ventricular assist devices (Thoratec Corporation, USA). Image © Texas Heart Institute. **b** | BiVACOR total artificial heart. Image © Texas Heart Institute. **c** | CARMAT® total artificial heart. Permission obtained from CARMAT, France.

washed by pump flow. The early clinical experience with the Jarvik 2000® also demonstrated convincingly that rotary blood pumps could be made much smaller, quieter, and more durable than volume-displacement pumps. One of the first recipients of this device survived for >7 years with the pump and eventually died from complications arising from a reaction to transfusion.[33] Post-mortem assessment showed almost no wear to the bearings.

In the 1990s, most teams working on mechanical circulatory assistance concentrated on the development of continuous-flow LVADs, including the Jarvik FlowMaker (Jarvik Heart), the HeartMate II® (Thoratec Corporation), the HeartWare® HVAD (HeartWare, USA; Figure 5c), and the HeartAssist 5® (ReliantHeart, USA; formerly MicroMed, USA). Each device is unique, but they share similarities. All devices use a rapidly spinning impeller to add energy to the blood, resulting in pressure and flow. Several devices use an axially oriented Archimedes' screw supported at each end by blood-washed bearings and are classified as axial-flow pumps. Powerful rare-earth magnets integrated into the screw-like impeller cause it to rotate in response to a microprocessor-commutated electromagnetic field produced by the stator surrounding the screw. Rotation of the impeller at 8,000–15,000 rpm results in flow parallel to the axis of rotation. Other devices use a magnetically or hydrodynamically suspended spinning disc-like structure with fins or grooves, and are referred to as centrifugal-flow pumps. They have axisymmetrical inflow, but the outflow arises tangentially from the circumference of the spinning disc.

The first human implantation of the HeartMate II® LVAD was performed in November 2003 by Frazier;[34] since then, >19,000 HeartMate II® pumps have been implanted in >185 countries. Overall, 1-year survival is >80%, and several patients have survived for >8 years.[35] Results with the HeartWare® HVAD have been similarly encouraging. Therefore, continuous-flow LVADs are seen as important tools in the management of end-stage left ventricular HF.

All rotary blood pumps have some degree of inflow and outflow pressure sensitivity.[36] As a result, when continuous-flow LVAD inflow pressure increases, as occurs with each cardiac systole, instantaneous flow through the pump also increases. The pump flow rate, therefore, varies with each ventricular contraction, even when the device is operated at a constant speed. Even when all cardiac output is going through the pump and the aortic valve remains closed throughout the cycle, variation occurs in arterial pressure. Many patients supported by continuous-flow LVADs have marked attenuation of pulse pressure, which is associated with new physiological challenges, such as gastrointestinal haemorrhage (perhaps resulting from destruction of von Willebrand factor) and progressive aortic valve insufficiency. Autonomic regulation of afterload and control of blood pressure are challenging in some patients, perhaps because of an alteration in baroreceptor function. Nevertheless, because of the small size, energy efficiency, and dramatically improved durability of continuous-flow LVADs, these devices have changed the field of cardiac support.

The future of TAH technology

Rotary TAHs

Contrary to the belief that a physiological pulse is essential for TAH application, Golding and colleagues showed in the 1980s that mammalian physiology could be supported long-term by nonpulsatile flow.[37] The first concepts for implantable rotary TAHs were introduced shortly afterwards.[38] After multiple attempts, coupled with the ascendance of rotary blood pump technology as a form of mechanical circulatory assistance in the first decade of the 21st century,[39] the concept of using this technology for TAHs gained traction.

Dual rotary LVADs as TAHs

Researchers at the Texas Heart Institute began to investigate leveraging the promising aspects of continuous-flow LVADs in TAH design. In 2005, they carried out a series of experiments in which the heart of a Corriente-cross calf was excised and replaced with two continuous-flow LVADs, thereby creating a continuous-flow TAH.[40,41] Over 8 years, a wide variety of LVAD pumps, including the HeartAssist 5®, HeartWare® HVAD, HeartMate II®, HeartMate III®, and Jarvik FlowMaker, were implanted in 65 calves.[42] Two calves survived to 90 days, and 29 lived for ≥1 week. Eight calves could exercise on treadmills. Common reasons for premature termination of the experiment included infection in the device and thrombus involving the bearings of the right pump. Use of dual continuous-flow LVADs in this configuration required the fabrication of customized atrial cuffs to allow the inflow cannulas to be attached to the atrial remnants. When dual centrifugal pumps were implanted, modified LVAD sewing rings were used as cuffs. When dual HeartMate II® (Figure 6a) or HeartAssist 5® pumps were implanted, however, the devices were modified by removing the inflow and outflow cannulas and having customized cuffs fitted that would allow the cannulas to be implanted in an acceptable configuration.

The pressure sensitivity intrinsic to all rotary blood pumps was hypothesized to be advantageous to TAH design because it would provide autonomous balance between the systemic and pulmonary sides of the device. Maintaining this balance was a design challenge with positive-displacement TAHs, frequently requiring sensors, compliance chambers, and modulation of stroke volume from beat to beat. By contrast, with a continuous-flow TAH, if a physiological change resulted in hypofunction of the right pump, such as is encountered in transient pulmonary hypertension seen with intense coughing, the corresponding gradual increase in right atrial pressure would autonomously increase the right pump output without any change in pump speed. This effect was proven in numerous animal studies in which right-side pump speed alone was increased, resulting in increased left atrial pressure and moderately, but noticeably, increased left pump flow.[43] In addition, the total continuous-flow TAH output would

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increase autonomously during exercise by means of a similar mechanism.[43]

Different pumps showed different degrees of pressure sensitivity because of differing impeller designs. A hypothesis was formed that an impeller could be designed specifically to optimize this functionality and, therefore, improve autonomous pulmonary–systemic balance.[44] Nevertheless, to accommodate the somewhat reduced pressure sensitivity compared with that of the natural heart, slightly elevated filling pressures would be required to keep the atria from transient collapse. The introduction of feedback control of pump speed was considered as a means of mitigating this problem and improving the capacity of these pumps to balance flows under all conditions.[45]

The thrombotic complications that occasionally occurred in the right pump were thought to be caused by venous thrombi that were liberated from peripheral veins and became entangled in the pump mechanism. This hypothesis was supported by the observation that the left pump was unaffected, presumably because it pumped blood filtered by the lung microcirculation. Modulation of the right pump speed—by transiently decreasing speed by as much as 30% for 0.20 s every 2 s—reduced right pump complications, perhaps by improving pump washout, decreasing the areas of stasis, and facilitating the passage of small thromboemboli arising in the periphery through the right pump.

In 2012, a patient (aged 55 years) with systemic amyloidosis involving the heart, liver, and kidneys was placed on paracorporeal left-heart bypass. The patient was deemed too ill to survive a heart transplantation. Cardiac amyloidosis is generally a contraindication for the SynCardia temporary TAH because of technical issues, and the patient's ventricles were too small to accommodate an LVAD inflow cannula. Frazier and Cohn suggested implanting two HeartMate II® devices to create a continuous-flow TAH.[46] Custom cuffs were fashioned from polypropylene hernia mesh, Dacron® cardiovascular patches, and medical silicone. The inflow cannulas of the two HeartMate II® LVADs were removed, and the pumps were attached to the cuffs by a previously developed technique.[46] The implantation was uneventful, and the patient was extubated on day 2 after surgery in a haemodynamically stable condition. The patient, however, remained anuric on haemodialysis and liver failure continued to progress. After 4 weeks of support with the continuous-flow TAH, the patient developed haemoptysis, and a biopsy revealed amyloid infiltration of the lungs. Hepatic encephalopathy progressed and support was discontinued after 5 weeks.[46] Although no successful long-term outcome was seen in this case, it demonstrated for the first time that a continuous-flow TAH could be used in a human and suggested that assessment was warranted.

Pirk and colleagues performed a similar operation on a patient (aged 38 years) with infiltrating cardiac fibrosarcoma.[47] The procedure was initially successful, but the patient died from a fulminant *Aspergillus* spp. infection after 6.5 months.[48] Other groups have championed the use of dual HeartWare® HVADs, either as biventricular assist devices or as cardiac replacement devices after excision of the ventricles.[49] The clinical experience with continuous-flow pumps for biventricular replacement suggests a possible role for specialized continuous-flow TAHs that leverage the small size, mechanistic simplicity, and improved durability of rotary blood pumps.

Single-device rotary TAHs

In 1987, Qian and colleagues attempted to create a single-device rotary TAH intended for long-term cardiac replacement, but could not adequately balance the left and right circulation.[38] However, after the success of supporting patients with HF using rotary blood pumps, BiVACOR (Houston, TX, USA)[50] and Cleveland Heart (Cleveland, OH, USA)[51,52] each developed a specialized rotary TAH with intrinsic flow-balancing mechanisms. These TAHs contain single rotating elements with systemic and pulmonary impellers on opposing faces. The rotational speed of the left and right impellers is the same, and the different flow characteristics of the systemic and pulmonary circulation are achieved with differences in impeller size and geometry. Similarly, small changes in the position of the rotating element along the axis of rotation result in a substantial change in relative efficiency of the two opposing pumps and provide autonomous systemic–pulmonary flow balance. Although the mechanisms for flow balance differ between the two devices, they both offer the advantages of centrifugal pumps. Specifically, neither has any mechanical bearings or other sources of mechanical wear and no flexible components or valves, and both have only one moving part and are extremely compact and energy efficient.

SmartHeart

The SmartHeart TAH, being developed by Cleveland Heart and Cleveland Clinic, has a cylindrical rotating element supported by a fluid-film hydrodynamic bearing.[51,52] The length of the cylinder is roughly twice its diameter, and the cylinder is capped at both ends by centrifugal flow impellers. When the systemic–pulmonary circulation becomes imbalanced because of a transient perturbation in physiology, the hypofunctioning side of the TAH is exposed to progressively increasing atrial pressure, which creates a hydrodynamic force on the spinning element and shifts the axis of rotation towards the side with lower atrial pressure. Each impeller is positioned in such a way with respect to the volute in which it is spinning that alignment is improved or worsened depending on whether the rotor shifts to the left or right. This change adjusts the relative outputs of the left and right sides of the device and continuously balances pumping efficiency without the need for sensors or feedback algorithms. Chronic testing of the device in animals is ongoing, but 6-week survival has been reported in one experiment.[53]

BiVACOR

The BiVACOR rotary TAH (Figure 6b)[50] originated in Australia and is being developed by BiVACOR and a multinational consortium of research centres. The device uses a different mechanism from the SmartHeart TAH to achieve pulmonary–systemic balance. The rotating element in the BiVACOR TAH is more of a disc than a cylinder, with its diameter being considerably greater than its length. The spinning element is suspended by an active magnetic bearing system, in which stable levitation is maintained by variations in magnetic forces generated by electromagnets in response to position feedback sensors.[54] As in the SmartHeart, small shifts in the position of the rotating element along the axis of rotation substantially change the relative pumping efficiencies of the two pumps, while the rotor position in the BiVACOR device is determined by the differential pressures (forces) acting on the rotor. Specifically, the surrounding pressures cause the magnetic system to pull the rotor automatically towards the underperforming side, which decreases the efficiency of the opposite pump so that the hydrodynamic forces that arise from differences in the left and right atrial pressure are precisely counterbalanced.[55] During *in vitro* testing, the

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device demonstrated a maximum capacity of 16 l/min at 100 mmHg and, when operated with speed modulation, can produce flow pulses of 0–18 l/min and pulse pressures of 120/80 mmHg at 60 bpm.

An early series of nine acute ovine studies demonstrated the hydraulic performance and balancing capacity of the single-rotor concept.[56] Later chronic studies in calves involved seven implantations, with the longest duration being 30 days in a 71 kg calf. The outflow for this calf varied from 7 l/min to 15 l/min and averaged 12 l/min at 100 mmHg at a motor power consumption of 13 W. The animal could exercise on a treadmill for 30 min, and autonomously balanced pulmonary–systemic flow was maintained despite changes in posture and activity, generating flows of 16 l/min without evidence of haemolysis.

Positive-displacement TAHs

Despite the potential benefits of continuous-flow TAHs, whether the physiological limitations imposed by nonpulsatile or reduced-pulsatile perfusion will prove to be prohibitive remains unknown. For this reason, SynCardia is developing a positive-displacement TAH with a 50 cm^3 blood-pumping chamber to enable use in a wider range of patients. Additionally, two European groups have readdressed the challenges in developing a self-contained, totally implantable, durable volume-displacement TAH by applying new technology.

SynCardia

Owing to limited use of the SynCardia temporary TAH device in paediatric and young-adult patients (7% of 1,091 total implantations between 1985 and 2012), the company has been developing a smaller version, called the SynCardia 50/50.[57] The device is intended to be implanted in patients with a body surface area <1.85 m^2. In an attempt to meet the longer-term needs of patients with HF, the device has also been approved by the FDA for use as destination therapy under the Humanitarian Use Device programme.[10]

CARMAT

The CARMAT® TAH (CARMAT, France; Figure 6c), which is under development by Carpentier and colleagues, uses two reciprocating rotary gear pumps to alternately shuttle hydraulic fluid between two blood sacs with compressible diaphragms. Although superficially similar to the AbioCor® TAH, the CARMAT® TAH has four pericardial tissue valves; the blood-contacting surfaces of the blood sacs are lined with a microporous biocompatible material aimed at obviating the need for anticoagulation. In addition, multiple sensors embedded in the device provide autonomous regulation of the pump rate and output in response to activity level and physiological factors. The microprocessor that controls the device is integrated into the pump housing, where it is cooled by silicone oil hydraulic fluid. The device is quite large and heavy (1 kg), but computer-aided anatomical fitting studies have predicted that it will fit 85% of men and 65% of all patients. A percutaneous power lead enters through the posterior scalp and is affixed to a skull-mounted pedestal, as previously described by Jarvik,[58] in an attempt to decrease the incidence of driveline infection.

A CARMAT® TAH was implanted into a patient aged 75 years, who was supported and haemodynamically stable for 74 days, at which point the device suddenly stopped. After an in-depth analysis and subsequent regulatory approval, a second implantation has been performed, and device support was ongoing at the time of writing.

ReinHeart TAH

ReinHeart (Bad Oeynhausen, Germany) and the Helmholtz Institute, RWTH-Aachen University (Aachen, Germany) are developing the ReinHeart TAH. This device has a reciprocating piston to alternately compress two polyurethane sacs as the left and right ventricles. In an attempt to improve durability, a voice-coil and linear actuator combination is used instead of a screw and roller bearings. The stroke volume of the ReinHeart TAH is only 50 ml and, therefore, the size is 84 × 90 mm and the weight is 923 g.[59,60] An implantable compliance chamber allows passive filling of the ventricular sacs, which provides a degree of inherent passive flow balancing. A maximum output of 7 l/min has been demonstrated in calves; the longest survival was 50 h.[61]

Conclusions

Over the past 50 years, researchers have focused on developing a safe, durable, and practical TAH to meet the clinical demands created by end-stage HF. Early devices aimed at replicating the natural physiological pulse were large, heavy, and prone to mechanical failure, dampening enthusiasm for this technology. A shift in focus to LVADs and the success with rotary blood pumps renewed interest and paved the way for new approaches to total heart replacement. Future challenges include gaining additional insights into the effects of reduced or absent pulsatile blood flow. Devices using positive-displacement technology continue to be developed and used clinically. However, given their limitations in terms of durability, they are unlikely ever to be considered a true alternative to transplantation. Instead, initial successful experiments leveraging two LVADs as a TAH suggest that a rotary TAH has potential. The reduced size, improved durability, and reduced power consumption inherent to rotary blood pumps might lead to rotary TAHs succeeding where previous attempts have failed to provide a practical replacement for the human failing heart.

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Author contributions

W.E.C. and D.L.T. researched data for the article. All the authors discussed the content of the article, wrote the manuscript, and reviewed drafts before submission.

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