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EARLY MECHANICAL CIRCULATORY SUPPORT DEVICES AND TECHNOLOGY DEVELOPMENT

Establishing the Concept

In the 1930s, Carrel and Lindbergh[1] developed an in vitro artificial heart-like apparatus for keeping organs alive outside the body. They removed the hearts, kidneys, ovaries, adrenal glands, thyroid glands, and spleens of small animals to watch them develop and function over the course of several days.[2] Acute animal studies in Russia and the United States followed in the 1940s. However, the meaningful origin of the modern era of mechanical circulation support (MCS) can be traced to the development of the heart-lung machine by Gibbon (Table 1.1) and its first successful clinical use in 1953.[3,4] The device was developed for cardiopulmonary bypass so that surgical cardiac procedures that require hours of circulatory support could be performed. The success of the device and the need for prolonged circulatory support for patients who could not be weaned from the heart-lung machine or whose hearts could recover with longer durations of support provided the initial impetus for developing devices that could provide long-term circulatory support. The optimism in the 1950s and 1960s that circulation could be successfully supported for extended periods by an artificial heart spurred its development by pioneers such as Kolff, Akutsu, DeBakey, Liotta, and Kantrowitz.[5] In 1963, DeBakey and Lederberg testified before the US Congress on the need for an artificial heart in very different domains: for patients otherwise healthy except for their failed heart and for isolated travelers on long space journeys.[6] These hearings coincided with the debate about the implications of the Russian Sputnik Program and unbridled national enthusiasm for taking on large technologic challenges such as the program to put the first man on the moon, which had begun just a few years earlier.

In 1964, with special congressional approval, the National Heart Advisory Council established the mission-oriented Artificial Heart Program (AHP) to design and develop devices to assist a failing heart and to rehabilitate heart failure (HF) patients.[7] In the initial planning stages of the program, cardiology and surgery experts recommended that clinical systems be capable of a cardiac output of 10 L/min, be able to maintain normal blood pressure, and be "biocompatible" (a vague physiological term then and now). These and other physiological parameters represented the defined design goals of the first generation of MCS systems.[2] Despite this limited set of design inputs, engineers, biologists, and clinicians created teams and collaborations and used them, when appropriate, as quantifiable engineering design inputs to achieve the physiological goals in the early MCS systems.

Important progress on these early MCS systems resulted from the cooperation and collaboration fostered by the National Heart, Lung, and Blood Institute (NHLBI). In 1977, following a recommendation from the Cardiology Advisory Committee, the NHLBI Devices and Technology Branch (DTB) started the annual Contractors Meeting.[4,8] The primary purpose of the meeting was to provide a public forum for showcasing the progress of the contract research projects. The DTB viewed the meeting as an opportunity for gathering the branch grantees and contractors together to share ideas and network with other teams. After a decade of successful annual meetings sponsored by the NHLBI, the meeting was moved to Louisville, Kentucky, as the "Cardiovascular Science and Technology: Basic and Applied" meeting under the leadership of Jack Norman,[5] then to Washington, DC, with the guidance of Hank Edmunds,[5] and was finally integrated into the Annual Meeting of the American Society of Artificial Internal Organs by then President Bob Eberhart (1993).[7] This progression has preserved the spirit of collaboration of the original Contractors Meeting, which also includes the highly regarded Hastings Lecture dedicated to the memory of Dr. Frank Hastings, the first chief of the NHLBI Artificial Heart Program.

The annual meetings emphasized the importance of developing collaborative venues for the field to share results, both positive and negative, and develop a common language across disciplines with procedural guidelines, which improve the comparability of data between research teams.

During the early period of the program, spanning from 1963 to 1980, progress on implantable, long-term ventricular assist systems outpaced similar work on the more widely publicized total artificial heart (TAH) systems.[9] In fact, short-term ventricular assist systems were being fabricated for use in initial clinical trials in the late 1970s.[10] The Institute of Medicine Committee report to "Evaluate the NHLBI

TABLE 1.1 Mechanical Circulatory Support Milestones

Year	Event
1953	First successful use of heart-lung machine for cardiopulmonary bypass (Gibbon)
1958	First successful use TAH in a dog (Kolff and Akutso)
1963	First successful use of LVAD in human (DeBakey)
1964	Artificial Heart Program established at NIH Six contracts awarded to analyze issues and need for program
1968	First clinical use of intraaortic balloon pump (Kantrowitz)
1969	First artificial heart implant in humans (Cooley)
1977	NHLBI RFPs for blood pumps, energy converters, and energy transmission NHLBI RFA on blood-material interactions
1980	NHLBI RFP for integration of blood pumps designed for 2-year use
1982	Barney Clark received first TAH implant for destination therapy (DeVries)
1984	NHLBI RFP for 2-year reliability studies First use of Pierce-Donachy VAD (Thoratec PVAD) as BTT (Hill) First implant of Novacor VAD First use of electromechanical VAD (Oyer)
1985	First use of CardioWest TAH as BTT (Copeland)
1988	First use of hemopump in humans (Rich Wampler)—first rotary blood pump used (Frazier) NHLBI awards four contracts to develop portable, durable TAHs
1989	Manual of operations for Novacor VAD NHLBI clinical trial completed
1991	First HeartMate VE implant (Frazier)
1994	FDA approval for pneumatic HeartMate VE as BTT
1996	NHLBI IVAS contracts awarded for Jarvik 2000, HeartMate II, CorAide VADS Pilot trial (PREMATCH) for destination therapy begins NHLBI awards two contracts for TAH Clinical Readiness Program (Abiomed, Penn State)
1998	FDA approval for HeartMate XVE as BTT FDA approval for Novacor as BTT REMATCH trial begins First DeBakey VAD implant (Wieselthaler)
1999	First human implant Arrow LionHeart VAD (first use of TETS) (Korfer)
2000	First HeartMate II implant (Lavee) First Jarvik 2000 implant (Frazier)
2001	REMATCH trial completed First implant of the AbioCor TAH (Dowling)
2002	FDA approval of HeartMate XVE as destination therapy
2003	CMS coverage decision for destination therapy
2004	NHLBI pediatric mechanical circulatory support program launched First implant of DuraHeart VAD (Korfer)
2006	First implant of HeartWare HVAD (Wieselthaler) First implant of Levacor VAD (Long) FDA approval of AbioCor TAH (Humanitarian Device Exemption) INTERMACS registry launched (PI: Kirklin)
2007	First implant of Circulite Synergy device (Meyns); advent of miniature VADs Peter Houghton dies after a record 2714 days of VAD support
2008	HeartMate II BTT clinical trial completed
2009	FDA approval of HeartMate II for BTT HeartMate II destination therapy clinical trial completed 850th implant of the CardioWest TAH
2010	FDA approval of HeartMate II for destination therapy
2012	FDA approval of HVAD centrifugal flow pump for bridge-to-transplant therapy
2014	First implant of HM3 (Schmitto)
2017	FDA approval of HVAD for destination therapy FDA approval of HM3 centrifugal flow pump for bridge-to-transplant and bridge-to-recovery therapy

BTT, Bridge-to-transplant; *CMS*, Centers for Medicare and Medicaid Services; *FDA*, Food and Drug Administration; *HM3*, HeartMate; *INTERMACS*, Interagency Registry of Mechanically Assisted Circulatory Support for End-Stage Heart Failure; *IVAS*, Innovative Ventricular Assist System; *LVAD*, left ventricular assist device; *NHLBI*, National Heart, Lung, and Blood Institute; *NIH*, National Institutes of Health; *PI*, principle investigator; *PVAD*, paracorporeal ventricular assist device; *REMATCH*, Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure; *RFA*, request for application; *RFP*, request for proposal; *TAH*, total artificial heart; *TETS*, transcutaneous energy transfer system; *VAD*, ventricular assist device; *VE*, vented electric.

Artificial Heart Program" contains a useful chronology of research and related important events from 1963 to 1991.[11,12]

The first generation (1980) of implantable MCS systems was designed to meet a 2-year operational goal during benchtop reliability testing.[13] Next followed the NHLBI Readiness Program.[14] This program aimed to ensure the functional reliability of the MCS systems that demonstrated the greatest promise. Each awarded contractor placed 12 MCS systems on "Mock Circulations" to assess their function during a simulated cycle of daily life for 2 years without interruption or maintenance. Success was completing the test with no more than one system failure at 2 years.

Clinical Application and Evolution of MCS

These early MSC programs created the engineering design basis for the HeartMate XVE (HM XVE) (Fig. 1.1) that was used in the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial.[15] In clinical use, the HM XVE and other systems demonstrated that first-generation implantable systems could achieve meaningful physiological objectives for 2 years and improve quality of life. However, many patients suffered serious adverse events such as bleeding, infection, and device malfunction.

Recognizing the initial success of MCS devices by multidisciplinary teams created by the NHLBI programs, in 1994, the NHLBI released the "Innovative Ventricular Assist System" (IVAS) request for proposals to encourage innovation of totally implantable MCS systems that were designed to achieve at least a 5-year functional lifetime with 90% reliability.[16] This program was designed to incorporate the latest advances gained from first-generation MCS systems, the TAH, and in related engineering, clinical, and biology fields.

The IVAS program was crucial to advancing the field of MCS for longer survival and patient quality of life. The program again brought together skilled teams of clinicians, engineers, and biologists working together and collaborating with other teams toward the same defined physiological goals. As a result, the systems with the most promise exceeded the expectations of the program. These included the HeartMate II (HMII) (see Fig. 1.1) and the Jarvik 2000 VAS.[17,18] The HMII, an axial-continuous flow system, became the most clinically successful MCS system. In bench tests, HMII systems met physiological requirements, and some operated indefinitely.

The pivotal clinical trial with the HMII showed significantly improved survival and reduced adverse events for study patients. The unexpected result was underscored in the companion editorial to the release of the multicenter randomized trial. The author compared the REMATCH trial with the HM XVE to the HMII trial using Kaplan-Meier survival graphs.[19] The survival results with HM XVE were exactly the same in 2009 as in 2001, very strongly suggesting that the improved HMII survival was largely due to the engineering design of the systems. This again pointed to the value of the National Institutes of Health/NHLBI initiating the IVAS program.

After the HMII trial, thrombus-related device malfunctions increased without explanation.[20] There was speculation that the dimensionally tight axial-flow channel of the HMII was a contributing factor in thrombus formation. At the same time, magnetically levitated centrifugal-flow systems were on the drawing board. These systems became technically feasible because of advances in permanent magnets. The potential advantage of the centrifugal-flow pump is the dimensionally wider blood flow channels that may reduce the potential for thrombus formation. The importance of design is also seen in the widened internal flow patterns of the HeartMate 3 (HM3), which are likely responsible for the improved rate of "survival free of disabling stroke or reoperation to replace or remove a malfunctioning device" at 2 years compared to the HMII, despite the rates of disabling stroke being similar.[21] The HVAD (Fig. 1.2), also a centrifugal blood pump,

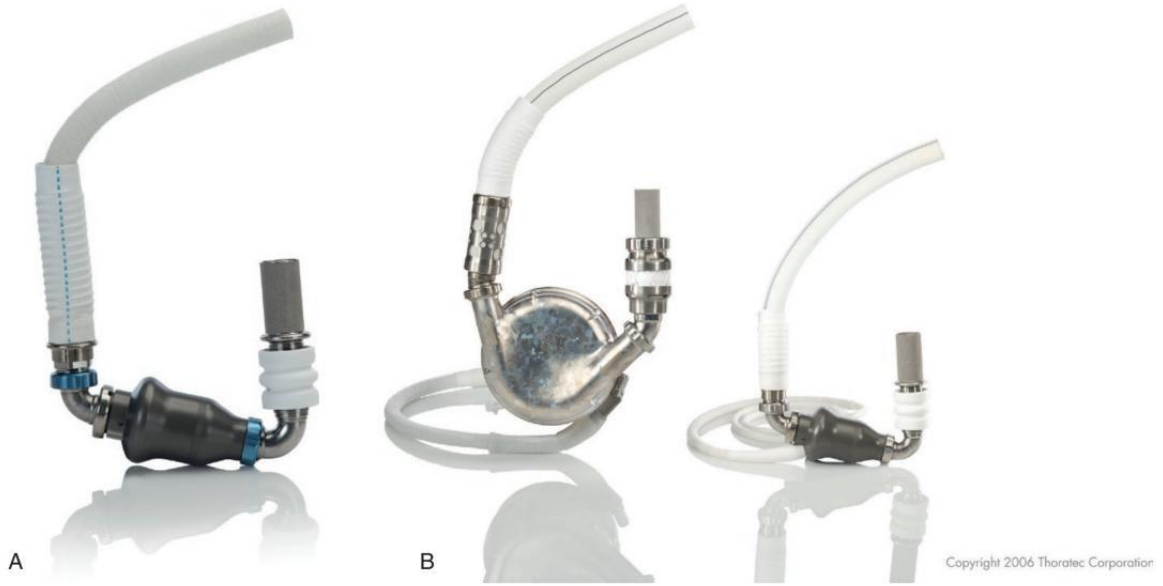

Fig. 1.1 The HeartMate II (A and lower left in B) compared with the Heartmate XVE (B). The HeartMate II was the first rotary ventricular assist device to receive U.S. Food and Drug Administration approval for bridge to transplant and destination therapy. (Courtesy of Abbott.)

Fig. 1.2 The HeartWare HVAD. (Reproduced with permission of Medtronic, Inc.)

Fig. 1.3 The HeartMate 3, like the HeartWare left ventricular assist device, is a centrifugal pump but, rather than using bearings, has a fully magnetically levitated (Full MagLev) rotor. (Courtesy of Abbot Laboratories, Lake Bluff, IL.)

has different internal flow patterns from the HM3 (Fig. 1.3). In 2017, the Heartware system received Food and Drug Administration (FDA) approval for "Destination" therapy, following prior approval in 2012 as a bridge for cardiac transplantation.[22]

With the growth of MCS in the 1990s and early 2000s and its profound impact on patient outcomes, it was recommended that the NHLBI create a mechanism to assess various MCS technologies as they entered clinical use.[11] To fulfill this vision, the NHLBI elected to develop a registry to collect data to improve patient MCS selection, measure quality of life, meet the FDA regulatory requirements, and inform the Centers for Medicare and Medicaid Services (CMS) regarding reimbursement decisions. This led to a solicitation that resulted in the Interagency Registry of Mechanically Assisted Circulatory Support for End-Stage Heart Failure (INTERMACS).[23]

The NHLBI provided the necessary financial support for the contract to develop and run the registry, which was awarded to the University of Alabama at Birmingham. This substantially reduced triagency administrative factors and allowed the three agencies to join together on the steering committee and address questions relevant to their "agency mission" data collection. INTERMACS exceeded expectations for organizing, collecting, and analyzing clinical data and provided Medical Device Reports for adverse events to the FDA and data for CMS payment decisions.

INTERMACS made an early decision to only curate data generated by patients implanted with FDA-approved durable MCS devices (i.e., devices with the potential for patient discharge).[24] This requirement added additional rigor to the INTERMACS database as the implants were under design controls and thus not subject to random design modifications that may directly influence clinical outcomes. Fourteen device systems met this standard. In recent years, of the 14 systems, 3 adult ventricular assist systems, 1 pediatric device, and 1 TAH system became the primary MCS devices in clinical use, thus providing essentially all the Bridge and Destination therapy data for INTERMACS.

ONGOING TECHNOLOGY DEVELOPMENTS AND DEVICES

The development of new MCS devices has been spurred by innovation, as well as building on the success of earlier concepts. Substantial activity has focused on the development of novel TAHs. To date, the SynCardia TAH (Fig. 1.4), based on the Jarvik-7 TAH developed in the early 1980s, is the only one that has received substantial use, accounting for over 95% of the more than 1700 worldwide TAH implants since the first TAH in 1969.[25] Recent efforts to develop a newer generation of TAH include the CARMAT bioprosthetic TAH,[26] the Cleveland Clinic continuous-flow total artificial heart (CFTAH),[27] and the BiVACOR TAH.[28] The CARMAT TAH, like the SynCardia TAH, is a positive displacement device. However, it utilizes bioprosthetic blood-contacting surfaces, electro-hydraulic pumps to activate the membrane between the two ventricles to product pulsatile flow, and an advanced control system involving implanted sensors to provide flows to meet patient demands. Four patients were implanted with the device in a pilot study, which is anticipated to lead to a pivotal study. The Cleveland Clinic TAH and BiVACOR TAH both involve a single moving part, a rotor with impeller blades on each side, with each side driving the flow in the left and right centrifugal continuous-flow pumps that make up the device. These are considerably smaller than positive displacement TAHs, so small that a pediatric version of the Cleveland Clinical CFTAH is being developed for infants down to 0.3 m^2 body surface area (BSA). The continuous-flow TAHs are both at the stage of animal studies.

Novel, advanced ventricular assist devices (VADs) are being designed and developed to address the outstanding issues with adverse events and special populations. These include a minimally invasive intraaortic balloon pump for long-term support (NuPulseCV, Raleigh, NC) and a valveless VAD that uses magnetically driven pistons to create pulsatile flow, known as the TorVAD (Windmill Technologies, Austin, TX).[29,30] They also include newer generations of continuous-flow VADs such as a miniature implantable pump platform, the Revolution, in which minor modifications of components can be implemented to adjust the pump performance to support the right or left side of the heart (Vadovations, Inc., Oklahoma City, OK).[31,32]

Some of the greatest attention has focused on the development of MSC devices for children, specifically small ones. This was spurred on by the NHLBI Pediatric Circulatory Support Program spanning from 2004 to 2009 and the Pumps for Kids, Infants, and Neonates