Bud Frazier's 1,000th LVAD at THI

State of the Art of Mechanical Circulatory Support

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Mechanical circulatory support of the failing heart has become an important means of treating end-stage heart disease. This rapidly growing therapeutic field has produced impressive clinical outcomes and has great potential to help thousands of otherwise terminal patients worldwide. In this review, we examine the state of the art of mechanical circulatory support: current practice, totally implantable systems of the future, evolving biventricular support mechanisms, the potential for myocardial recovery and adjunctive treatment methods, and miniaturized devices with expanded indications for therapy. ***(Tex Heart Inst J 2014;41(2):115-20)***

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Mechanical circulatory support (MCS) of the failing human heart is an evolving field that has had a substantial impact on the treatment of heart failure. The first MCS device experiments predate heart transplantation; implantation of a total artificial heart (TAH) was first attempted in the 1950s in animals.[1] Research and development in TAH and left ventricular assist device (LVAD) technologies occurred for decades, until the introduction of cyclosporine in the 1980s. Thereafter, heart transplantation became the major focus of research until limitations in donor-organ availability hindered this surgery's broad application. In the last 20 years, MCS technology has progressed tremendously, and its clinical applications have expanded rapidly since the turn of the 21st century.

Globally, heart failure is the leading killer of human beings.[2] Every year, as many as 50,000 people are considered to be candidates for heart transplantation; however, only 5,000 cardiac allografts per year are available worldwide.[3] Although many challenges remain, MCS has improved the quality of life and survival rates of patients who have end-stage heart failure. The purpose of this review is to examine the state of the art in MCS therapy: current practice, totally implantable devices, biventricular support, myocardial recovery and adjunctive therapy, and future applications.

Current Practice

The development of MCS devices began with attempts to emulate the biological heart, filling and emptying in repetitive cycles, and using a flexible diaphragm with unidirectional valves to achieve systole and diastole. The results of the landmark Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial showed that, among the sickest patients with severe heart failure, Thoratec Corporation's HeartMate® XVE Left Ventricular Assist System (an electrically driven, pulsatile LVAD) resulted in better 1- and 2-year survival rates and quality of life than did optimal medical therapy.[4] Although these pumps were beneficial, they were prohibitively large and had durability issues. Their mechanical complexity and 100,000 ejections per day culminated in uniform device failure after 18 to 30 months of function.

Over time, first-generation volume-displacement pumps were superseded by 2nd- and 3rd-generation continuous-flow (CF) VADs. These pumps use a single, rapidly spinning impeller that is supported by mechanical blood-washed bearings or, in some recent models, by hydrodynamic or magnetic bearings. The newer devices are associated with improved outcomes[5] because they are smaller and easier to implant than their predecessors. Of more importance, the marked reduction in mechanical complexity has dramatically improved durability: these pumps last longer than 10 years on the bench and 8 years or longer in patients. In another seminal trial,[6] the continuous-flow Thoratec HeartMate II® LVAD was shown to be superior to the HeartMate XVE in a cohort of patients as ill as those in the original REMATCH trial.

The XVE has been discontinued, and the HeartMate II is currently the LVAD most often implanted in the United States.[5]

In 2010, results from the ADVANCE trial led to the approval of HeartWare, Inc.'s HeartWare® Ventricular Assist Device (HVAD) as a bridge to transplantation.[7] This 3rd-generation pump uses a centrifugal impeller that is maintained in axisymmetric alignment by magnetic bearings and is levitated from the stator surface by hydrodynamic bearings. The HVAD is more compact than the HeartMate II, enabling its implantation in patients of smaller body habitus. Furthermore, it is designed for intrapericardial placement, so it decreases the risks of major infection and other complications associated with the intra-abdominal or pre-peritoneal pump pocket that previous pump designs have required. HeartWare, Inc., is currently conducting a clinical trial to evaluate the HVAD pump as an option for destination therapy.

Four other continuous-flow LVADs have been undergoing clinical validation but have yet to receive clearance in the U.S. The ReliantHeart HeartAssist 5® (previously called the MicroMed HeartAssist 5), the Jarvik 2000 FlowMaker® LVAD, and the EVAHEART Left Ventricular Assist System each has unique functionality; however, each has exhibited difficulties that have delayed the approval process. The HeartAssist 5 uses blood-washed bearings to support an axial impeller; however, the bearing design has gone through multiple iterations to correct flaws. This device has an integrated Doppler-flow probe that enables accurate determination of pump output, and a wireless telemetry component that facilitates remote monitoring and early intervention in the event of pump dysfunction. The Jarvik FlowMaker is also supported by blood-washed bearings but lacks an inlet cannula, and its pump housing is placed inside the left ventricle (LV). The EVAHEART, somewhat larger than the other 2 pumps, uses a continuous irrigation system to prevent blood from coming into contact with the device bearings. Although this irrigation system makes the device mechanically more complex, excellent durability has been reported.

There are many ongoing challenges in the field of MCS. Stroke and infection remain prevalent.[5] Furthermore, patients supported by CF pumps often undergo substantial alterations in physiology that are not well understood. Although many patients supported with CF pumps retain some degree of pulsatility because of the improved function of the unloaded heart, others have attenuation or absence of a clinically detectable pulse. The consequences of these physiologic changes are largely unknown. Chronic sympathetic vasomotor tone abnormality caused by decreased baroreceptor stretch might alter the regulation of blood pressure, cause hypertension, and increase the risk of stroke. Thrombosis can occur in regions of blood stasis, resulting in pump dysfunction, hemolysis, or embolic complications. Some CF devices have been associated with an increased incidence of gastrointestinal bleeding. The exact mechanism is unknown; mechanical disruption of von Willebrand factor might play a role.[8] These and other issues are undergoing intensive investigation. In the following sections, we examine advances and innovative techniques in MCS that might solve some of the current challenges.

Totally Implantable Systems

The percutaneous driveline—often referred to as the Achilles' heel of MCS—is a barrier to the long-term application of VADs and TAHs as definitive therapies for heart failure. The exit site of the driveline provides a portal of entry for bacteria, and most life-threatening infections affecting implanted LVAD components arise as an extension of a superficial process.[9] Furthermore, prolonged support is associated with increased risk of infection: after one year of support, the VAD recipient's risk of developing a driveline infection can be as high as 94%.[10] Patients with pump infections spend more time in the hospital,[11] consume more healthcare resources, and might have an increased risk of death.[11,12]

Past efforts to create a totally implantable system without a percutaneous driveline have been successful. Two discontinued devices, the AbioCor® TAH (ABIOMED, Inc.; Danvers, Mass) and the LionHeart LVAD (Arrow International, Inc.; Reading, Pa), used transcutaneous energy-transfer systems (TETS) to deliver power through the intact skin. These TETS use inductive coupling, a principle first demonstrated by Nikola Tesla in 1893. Direct current from a rechargeable battery outside the body is converted to alternating current and is delivered to a coil-shaped antenna that is applied to the skin. The energized external coil produces an oscillating magnetic field. A second coil-shaped antenna implanted just beneath the skin is tuned to the frequency of the oscillating field and resonates with it, resulting in the generation of alternating current in the implanted coil. This current is rectified back into direct current, which is used to power the device and charge an internal battery to ensure uninterrupted device function in the event of transient TETS disconnection. Large amounts of energy can be efficiently transferred when the coils are in proximity and proper alignment; however, distance or misalignment decreases efficiency and can cause heat generation. Improved technology has resulted in TETS with higher efficiency and tolerance of imperfect alignment.

Improved clinical outcomes have elicited renewed interest in totally implantable devices. The major VAD manufacturers in the U.S. have announced partnerships with companies that are involved in wireless energy transfer. In 2011, Thoratec Corporation announced its developmental agreement with WiTricity Corpora-

tion (Watertown, Mass) to develop its FILVAS (Fully Implantable Ventricular Assist System) program for the HeartMate II. In 2012, HeartWare, Inc., announced its partnership with DUALIS MedTech GmbH (Seefeld, Germany) to develop TETS to power its HVAD and other MCS devices under development.

Newer TETS, such as those being developed by WiTricity, use the same principle of inductive coupling, but with enhanced-resonance coupling. First demonstrated in 2007 at the Massachusetts Institute of Technology, this technique focuses on transmitter and receiver inductors tuned to resonate at the same frequency in strongly coupled magnetic fields. Energy is transferred over meters rather than centimeters, the transfer does not require strict alignment of coils or line of sight, and the magnetic fields have very little interaction with surrounding objects such as radio-using electronics and biological tissues. This exciting new technology has many potential future applications and is the focus of intensive investigation. Totally implantable MCS systems that use enhanced-resonance coupling are anticipated in the near future, and they might be another milestone in the field.

Biventricular Support

The initial focus of MCS efforts was to develop a TAH. In 1969, Denton Cooley was the first to implant a TAH clinically, supporting a patient for 36 hours until a donor heart could be located.[13] In 1982, Barney Clarke was given the first TAH for permanent support and lived for 112 days.[14] The device, the Jarvik 7, was subsequently implanted in more than 400 patients, one of whom was supported for longer than 600 days.[15] The Jarvik 7 evolved into the CardioWest, which was renamed the SynCardia TAH—the only device currently approved in the U.S. for total cardiac replacement. This TAH relies on 2 pneumatically driven polyurethane ventricles, each with 2 unidirectional mechanical valves that displace blood in a pulsatile manner, much like the native heart. Although excellent results have been obtained with this device (which has been implanted in more than 1,600 patients), there are limitations. The finite cyclic endurance of the flexible membranes adversely affects long-term durability. The current iteration, which has a 70-cc stroke volume, is large and is therefore approved for use only in larger patients (body surface area, ≥ 1.79 m^2); however, a smaller (50-cc) device that will be suitable for adolescents and children is undergoing clinical validation.

Until recently, total cardiac replacement was the only durable option for severe biventricular failure. Although LVAD therapy with short-term right ventricular support is a temporary option, replacement with a TAH often becomes necessary. Third-generation continuous-flow VADs are small enough to fit into the intrapericardial space, which enables surgeons to implant 2 durable devices for biventricular assist device (BiVAD) support without excising the diseased organ. At the Texas Heart Institute, our technique for transdiaphragmatic implantation of an LVAD[16] has even enabled us to use two 2nd-generation HeartMate II devices in patients who need durable BiVAD support.

Total cardiac replacement and BiVAD support each has advantages and disadvantages. Patients who have BiVADs might not be as completely dependent on MCS as patients with a TAH would be, the consequences of unexpected device interruption are far less disastrous with BiVADs than with a TAH, and BiVAD implantation does not negate the possibility of myocardial recovery. On the other hand, BiVAD support requires the use of 2 separate pump controllers, no algorithms exist to balance flow by adjusting left and right pump speeds automatically and interdependently, and the necessary manual adjustment complicates the care of BiVAD patients.

Progress in TAH technology might help to expand options for the treatment of severe biventricular heart failure. French cardiac surgeon Alain Carpentier, in collaboration with European Aerospace and Defense Systems, recently introduced the CARMAT TAH.[17] The 75-year-old man who received the first device (on 18 December 2013) was alive and functional weeks after his operation.[18] The CARMAT is a large, pulsatile-flow TAH that uses bovine pericardium for its blood-contacting surfaces. It contains internal pressure sensors and control algorithms to increase the rate of blood flow with increased ventricular pressure sensation (preload), such as during exercise. Additional human implantations are expected during 2014, and future investigation should yield insights into the associated clinical outcomes and adverse events.

Because the human heart beats 100,000 times per day, the long-term durability of pulsatile devices with multiple moving parts has proved to be problematic throughout MCS history. We at the Texas Heart Institute, in partnership with Dr. Daniel Timms and with the generous support of the McIngvale family of Houston, have made substantial progress in developing a promising continuous-flow TAH. The implantable, single-unit BiVACOR® replaces the function of both sides of the failing heart. It balances pulmonary and systemic blood flow automatically, using a zero-power magnetic suspension system that levitates a single, double-sided impeller. The axial position of the impeller autonomously adjusts in response to the difference between left and right atrial pressure, which in turn determines the relative efficiency of the pulmonary and systemic pumps. The device is small and durable, consumes little power, and has a coupled physiologic control mechanism. Large-animal trials have been initiated, and much progress in this device's development is expected during 2014. We anticipate that the BiVACOR

will become the first practical mechanical replacement for the failing human heart.

Myocardial Recovery and Adjunctive Therapy

In 1994, our center became the first to describe improvement in ventricular function after LVAD therapy.[19] Subsequently, we reported on the first series of patients with advanced nonischemic cardiomyopathy in whom myocardial recovery enabled LVAD explantation. Of the 5 patients who recovered, 1 died of noncardiac causes 10 days after explantation; the other 4 remained alive at 35, 33, 14, and 2 months of follow-up.[20] Other investigators have since described their experiences with ventricular improvement and the concept of enduring myocardial recovery. Retrospective analyses have shown that LVAD therapy enables many patients with nonischemic heart failure to recover myocardial function.[21-25]

Early studies of myocardial recovery were largely retrospective, had no standardized use of pharmacologic heart-failure therapy, and lacked protocols for myocardial evaluation during LVAD support. In 2006, Birks and colleagues[26] described the Harefield strategy, a staged approach to inducing myocardial recovery actively. The first phase targeted the reversal of pathologic hypertrophy and remodeling by combining LVAD therapy with an aggressive, titrated pharmacologic regimen: 25 mg of carvedilol 3 times daily, digoxin 125 mg/d, lisinopril 40 mg/d, losartan 150 mg/d, and spironolactone 25 mg/d. The second stage was initiated when LV diastolic diameter returned to normal and remained at that dimension after 15 minutes of transient discontinuation of LVAD therapy. This stage involved switching the nonselective β-blocker to a β_1 selective blocker so that clenbuterol, a selective β_2 agonist shown to induce physiologic hypertrophy,[27] could be added to the pharmacologic regimen. Eleven of 15 patients (73%) with nonischemic cardiomyopathy who were treated with a first-generation HeartMate LVAD and the prescribed pharmacologic regimen recovered enough myocardial function to enable device explantation after a mean period of 320 ± 186 days of support. Freedom from recurrent heart failure at 1 and 4 years was 100% and 88.9%, respectively. In 2011, the same group reported similar findings with the same protocol but with use of the HeartMate II.[28] Of 20 enrolled patients with nonischemic cardiomyopathy, 12 (60%) had their devices successfully explanted after 286 ± 97 days of support. Among these 12 patients, cumulative freedom from death and recurrent heart failure was 83.3% at 1 and 3 years.

Despite these encouraging results, myocardial recovery is not a frequently pursued outcome at most LVAD centers. The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) team reports that less than 2% of all VAD patients undergo explantation after recovery.[29] Pathologic remodeling of the ventricle involves chronic changes in cardiomyocyte size, calcium handling, extracellular matrix proteins, and neurohormonal signaling pathways. Upon mechanical unloading of the ventricle through LVAD therapy, significant reverse remodeling has been detected, often with near-normalization of structural abnormalities. However, this phenomenon does not always correlate with myocardial recovery. Gene-expression profiling studies have revealed that less than 5% of dysregulated genes revert to normal with LVAD therapy, despite overall structural improvements.[30] One seemingly important factor in predicting myocardial recovery is the degree of myocardial fibrosis at the time of LVAD implantation.

Early studies of myocardial recovery involved first-generation volume-displacement LVADs in patients with nonischemic heart failure and typically did not systematically evaluate myocardial function over time. In 2013, Drakos and colleagues[31] reported their prospective study of 80 consecutive patients who underwent continuous-flow LVAD therapy. The cohort included patients with ischemic and nonischemic heart failure. Serial echocardiography and right-sided heart catheterization were performed during a one-year period. Continuous ventricular unloading resulted in reverse remodeling, with improvements in LV mass, chamber dimension, and ejection fraction. At 6 months, 34% of patients had a relative increase in LV ejection fraction of greater than 50%. Unlike previous investigations, Drakos and colleagues' study showed that the improvements in cardiac function associated with MCS did not manifest themselves fully until after 6 months of support, and that these improvements persisted at the one-year follow-up evaluation. However, no patient underwent LVAD explantation, and it is unknown whether the reported improvements would have persisted had the ventricle been reloaded for an extended period.

Investigators of mechanical unloading through LVAD therapy have documented increases in circulating progenitor cells,[32] as well as myocardial gene expression of stem cell factor and the c-kit receptor.[33] Current trials of combined LVAD and stem cell therapy might yield further insights into the potential for myocardial recovery in selected patients.

Future Applications

Assist-device therapies have shown substantial potential to elicit reverse remodeling in heart-failure patients, and it is speculated that earlier mechanical unloading—before the development of New York Heart Association functional class IV symptoms—could prove to be beneficial. The INTERMACS team, which has provided invaluable information about VAD-patient outcomes, has announced the creation of a new medical arm of the database called MedaMACS (Medical Arm of Mechanically Assisted Circulatory Support). This registry will track patients in earlier stages of heart failure who

are being treated medically, with the goal of identifying populations that might benefit from earlier MCS therapy. Also anticipated is the start of the Randomized Evaluation of VAD InterVEntion before Inotropic Therapy (REVIVE-IT) trial.[34] This prospective, randomized, multicenter trial will compare patients who have continuous-flow LVADs to a control group of patients with moderately advanced heart failure who are ambulatory, not dependent on inotropic agents, and not candidates for heart transplantation. Information from the MedaMACS registry and the REVIVE-IT trial should yield important insights into the appropriate expansion of VAD therapy to earlier time points in heart failure.

As devices become totally implantable, their miniaturization will probably play an increasingly important role in the expansion of MCS therapies. Two devices under development are the HeartMate III (Thoratec Corporation) and the HeartWare Miniaturized Ventricular Assist Device (MVAD). The centrifugal-flow HeartMate III uses a bearingless motor with totally magnetic levitation of its single moving part—an impeller with active suspension in all dimensions. This new design is postulated to produce even less shear force than its predecessor and is capable of large changes in rotor speed to enable induced pulsation of flow. Induced pulsation is an area of increasing investigation, because it might enable the washout of areas of stasis, thereby potentially reducing thrombosis and embolic events. Furthermore, it might negate some of the possible negative effects of CF, such as chronic neurohormonal changes secondary to lack of baroreceptor stretch.

The HeartWare MVAD, a miniaturized axial-flow device similar in form to the Jarvik FlowMaker, is supported by a combination of magnetic levitation and hydrodynamic bearings. It has a wide-blade design to reduce shear force on blood components while providing 1 to 7 L/min of blood flow.[35] This device can be implanted through various minimally invasive approaches that do not necessitate median sternotomy,[36] including a right mini-thoracotomy with placement of a novel inflow cannula through the superior pulmonary vein, into the left atrium, and through the mitral valve into the LV.[37] Clinical trials are anticipated in the near future and are hoped to provide further tools in the armamentarium against end-stage heart failure.

Mechanical circulatory support systems have progressed technologically during the past 50 years—exponentially so since the early 2000s. As of January 2014, INTERMACS data show that more than 11,000 patients are enrolled in the U.S.,[38] and thousands more are assisted by MCS devices worldwide. Through innovation in TETS and total implantability, many earlier concerns about infection might no longer be relevant. As the mechanisms of myocardial recovery are better understood, the indications for MCS therapy might expand. Adjunctive treatment with stem cells, pharmacologic regimens, and other interventions are actively under investigation. Devices for MCS have become smaller and more durable, and they have produced increasingly beneficial outcomes. At the Texas Heart Institute, we have long pioneered MCS, and we remain on the cutting edge of technological progress. We look forward to further achievements in this important and meaningful therapeutic field and anticipate the day when lasting treatment for end-stage heart failure is no longer limited by the number of available donor organs.

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