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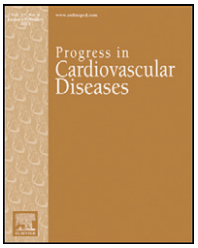

Mechanical Circulatory Support: Current Status and Future Directions

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ARTICLE INFO

Keywords:
Heart failure
Mechanical circulatory support
Left ventricular assist device
Heart transplantation

ABSTRACT

Advance heart failure (AHF) is a growing epidemic with high morbidity and mortality. Left ventricular assist device (LVAD) has come to offer an opportunity to improve survival and quality of life. This form of therapy however, is not free of complications and poses a challenge to apply to a broader population. Adjunct therapies in combination with LVAD therapy and advances in device technology are in the near future, which may lessen the number of adverse events. This review summarizes the history, clinical outcomes and current challenges facing LVAD therapy. Finally, future directions of LVADs in the treatment of AHF are discussed.

Since the 1950s when development first began, mechanical circulatory support (MCS) pumps have evolved at a rapid pace. Advances in technology, better comprehension of flow dynamics, and more discriminating patient selection have contributed to improved outcomes. Not surprisingly, this has resulted in the increased use of this technology in the growing advanced heart failure (HF; AHF) population. Although current therapies have dramatically improved outcomes, the overall clinical course of patients with AHF remains poor. Thus, new therapies are needed, and MCS offers an opportunity to improve outcomes in this challenging population.

Although the durability of MCS devices allows for long-term beneficial effects of mechanical unloading, this strategy is not free of complications and device related issues make this therapy a challenge to apply to a broader population. Data from international registries has improved our ability to select more suitable candidates for MCS and has improved the match between man and machine. As a result more than 10,000 implants have occurred in the past 6 years. However, many questions about MCS remain, with timing of MCS being a moving target. Treating patients with severe compromise is associated with poor outcomes, while initiating this therapy too early in the course may not be beneficial or cost effective. The role of drugs (particularly neurohormonal agents), stem cell therapy or gene transfer in association with MCS to determine the best strategy for achieving recovery of heart function is currently being evaluated in centers around the world. This review focuses on outcomes, challenges and future directions of MCS therapy for patients with AHF.

History of MCS

In the early 1950s, post-cardiotomy shock management shrouded the outcomes of open-heart surgery. The advent of cardiopulmonary bypass and the first heart-lung machine laid the foundation of circulatory support research and by 1964 the National Institutes of Health formed the Artificial Heart Program. In 1966, Dr. Michael Debakey implanted the first successful pneumatic pump for post-cardiotomy weaning and bridge to recovery. However, government budget and technological limitations at the time shifted the goal of funding toward bench research before clinical applications. In 1969, Dr. Denton Cooley implanted the first temporary total

Disclosures/Conflict of Interest: see page 452.

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http://dx.doi.org/10.1016/j.pcad.2016.01.006
0033-0620/

Abbreviations and Acronyms

AHF = advanced heart failure

BTT = bridge to transplant

CF = continuous flow

CVA = cerebral vascular accident

BNP = brain natriuretic peptide

DLI = driveline infection

DT = destination therapy

FDA = Federal Drug Administration

GI = gastrointestinal

HF = heart failure

HMII = HeartMate II

HT = heart transplantation

INR = International Normalized Ratio

INTERMACS = Interagency Registry of Mechanically Assisted Circulatory Support

LDH = lactic dehydrogenase

LV = left ventricular

LVAD = left ventricular assist device

LVEF = left ventricular ejection fraction

MPC = mesenchymal precursor cells

NYHA = New York Heart Association

PF = pulsatile flow

QoL = quality of life

RHF = right heart failure

RVAD = right ventricular assist device

SCT = stem cell therapy

artificial heart into a patient who had post-operative complications until a donor heart was available for heart transplantation (HT). The patient survived 64 hours on the device but died just 32 hours after HT. Due to the risk associated with development of the total artificial heart (TAH), including device malfunction, infection and incompatibility of materials used with human blood, the task force recommended that left ventricular (LV) assist devices (LVADs) should be the preferred area of research and development in the future. It was not until 1975, however, that LVADs were investigated in clinical trials as means of temporary support after open-heart surgery. The results of these trials lead to prioritization of mechanical cardiac assistance for the study of integrated electrical LVAD systems in the immediate post-operative period of open-heart surgery. In 1978, Dr. Phillip Oyer implanted the first LVAD as bridge to transplant at Stanford University. Driven by success in animal studies and technological advancements, the Federal Drug Administration (FDA) awarded Dr. William Devries, Robert Jarvik and Willem Kolf investigational device exemption for a TAH system, the Jarvik-7. The first application of this device was in 1982 to Dr. Barney Clark, a dentist with end stage HF who ultimately lived for 112 days after implantation before succumbing to sepsis. This and other poor outcomes with the use of TAH lead to a decisive conclusion to halt the TAH program and pursue research in clinical application for LVAD systems.[1]

In 1986 the Thoratec TCI pump, a pulsatile flow pump (PF-LVAD) with a pusher-plater system that provided a stroke volume of 85 cc, was approved. The system was activated either pneumatically or electrically and a textured polyurethane interior created a pseudo-intimal layer, which helped reduce risk of thrombosis and embolization. By 1990, the FDA gave approval of LVAD as a bridge to HT therapy, and by 1999 Columbia University reported their 7-year experience of 95 patients implanted with HeartMate XVE (a modified TCI pump), with 75% of the recipients supported for 108 days and eventually transplanted.[2] The success of these trials allowed for development of clinical trials exploring LVAD as enduring long-term therapy (Fig 1).

Success

In AHF, the gold standard for curative treatment remains HT. However, this approach is limited for many years by availability of donor hearts and only ~2300 orthotopic HTs are now performed each year. The supply clearly does not meet the increasing demand as close to 10% of the 6.6 million patients in North America who live with end-stage HF (Stage D). The initial clinical trials assessing outcomes in LVAD therapy as a bridge to HT open the path for consideration of mechanical support as a permanent therapy for patients who are not candidates for HT (also known as destination therapy — DT). The landmark REMATCH trial randomized New York Heart Association (NYHA) class IV patients with LV ejection fraction (LVEF) ≤25% to LVAD vs. inotropic therapy. The greater survival shown by LVAD therapy compared to inotrope at 1 year (52% vs. 25%, $p = 0.002$) led the FDA to approve LVAD therapy as DT.[3] The shortcomings of these pulsatile pumps however were long-term durability that required device replacement in 21% of patients. Innovations in pump design with smaller devices, single high-speed rotary impeller pump providing continuous flow (CF) offered long term durability. The superior design of CF-LVAD was tested in a randomized controlled trial comparing both flow profiles in NYHA IV patients ineligible for HT. The CF group showed superior survival at 1 year (68% versus 55%) and 2 years (58% versus 24%) compared to the pulsatile group. Furthermore, freedom from disabling stroke or reoperation for device malfunction was 11% vs. 46% for CF compared to the PF device.[4]

As LVAD use increased over the years, the Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) was created to record the evolution of LVAD therapy. The more recent registry data reports that >10,000 patients have been implanted nationwide. CF pumps accounted for 100% of the LVAD implanted as DT since 2010. Survival at 1 and 2 years has remained unchanged over the past 5 years with 80% and 70% being alive, respectively.[5] These results are consistent with the post-market approval results showing a survival of 83%, 75%, and 61%, at 1, 3 and 5 years respectively; however, frequent hospitalizations due to non-device and device related issues were noted.[6] The latter adverse events have lessened by advances in technology and improvement in patient care enabling the use of LVAD as an alternative to HT. Thus, the most recent INTERMACS report demonstrates a decrease in MCS as a bridge to HT (BT) strategy approach from 42% in the 2006–2007 periods to 21.7% in the 2011–2013 periods. The opposite trend occurred for MCS use as a DT strategy with an increase from 14.7% to 41.6% during this same period.[5]