REVIEW ARTICLE

The Current status of the longterm use of Ventricle Assist Devices (VADs) in the management of advanced heart failure

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SUMMARY

Incidence of advance heart failure has raised substantially across the globe. Limited number of cardiac donor organs are available to match cardiac transplant waiting list. Revolutionary work in biomedical engineering created long-term ventricular assist devices. Clinical results of long-term VADs usage has established their definitive role in management of end-stage heart failure in many faces like bridge to recovery, bridge to transplant and as destination therapy etc. Objective of this review is to elaborate the current status of their contributory role in advance heart failure management.

Keywords:
Advance heart failure, Ventricular assist devices, Bridge to transplant, Destination therapy

BACKGROUND

Cardiac disease are number one killer of world population [1]. Heart failure is the end result of many cardiac disease. American College of Cardiology (ACC)/ American Heart Association (AHA) has classified heart failure into four stage (A,B,C & D) on the basis of severity like cancer staging system. Around 5.7 million people in USA and 23 Million people worldwide have heart failure and 20% of this proportion has end-stage heart failure [2]. One-year and 2-year survival of stage D heart failure is 50% and 38% respectively on maximum medical therapy [3]. Cardiac transplantation is gold standard treatment for this group of heart failure that can improve survival [4]. Insufficient number of cardiac donor organs are available to match needs and this dilemma is expected to persist in

future as well. Revolutionary work in biomedical engineering has created an alternative option to successfully mange the end-stage heart failure. Mechanical circulatory support (MCS) or Ventricular assist devices (VADs) include growing number of medical devices that provide blood pumping facility to body.

Objective of this review is to appraise the role of rapidly expanding VADs technology in management of advance heart failure over time and its future. Concise description of types, clinical indication, volume of their use in clinical practice and future prospective of long-term ventricular assist devices will be elaborated.

ERA OF LONGTERM VAD TECHNOLOGY

History of VADs technology can be divided into two eras on the basis of publication of REMATCH trial in year 2001. Pre-Rematch Era starts from initial implantations of VADs by pioneer workers like Michael DeBakey in 1966 and their contemporaries. During this whole era, extensive experimentation figured out the design of VADs, type of pumps etc. The results of REMATCH trial validated the superiority of VADs over medical therapy and hence brought a major change in practice of heart failure management [5]. Slaughter et al did a remarkable randomized controlled trial comparing pulsatile vs. Continuous flow pump VADs (CF-VADS) and proved far better complication profile and durability of CF-VADs [6].

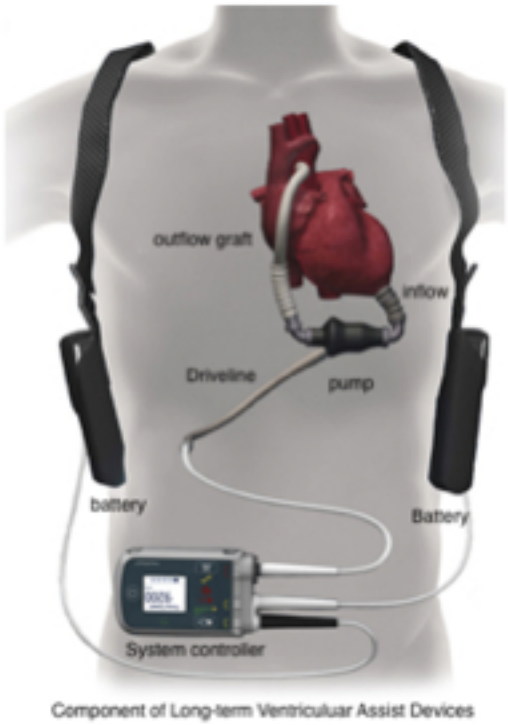
Shift from pulsatile to non-pulsatile VADs in clinical practice is greatest change that happened

Table 1
List of Long-term Ventricular Assist devices

Device Name	Generation of VADs	Comments
HeartMate XVE (Thoratec)	1st generation / Pulsatile	FDA approval for BTT(2001) & DT (2003). Out-dated in clinical practice because of durability concerns
PVAD (Thoratec)- Paracorporeal IVAD (Thoratec)-Intracorporeal	1st generation / Pulsatile	Both CE-mark authorized. FDA BTT approved in 1995 and 2004
Novacor (World Heart)	1st generation / Pulsatile	No more manufacture
HeartMate II (Thoratec)	2nd generation /Axial flow pumps	FDA approved for BTT(2008) and DT(2010). Highest number of implants in the world
HeartAssist 5 (Reliant Heart)	2nd generation /Axial flow pumps	Approved for use in European Union. Pediatric version are FDA approved
Jarvik 2000 (Jarvik heart)	2nd generation /Axial flow pumps	FDA approved investigational device. CE-Mark certified
MicroMed DeBakey VAD-(MicroMed)	2nd generation /Axial flow pumps	FDA approved investigational device
HeartWare (St Jude)	3rd generation / Centrifugal pump with hydromagnetic levitation	FDA approval for BTT (2012) and DT (2017)
DuraHeart (Terumo)	3rd generation / Centrifugal pump with hydromagnetic levitation	FDA approved trials going on
HeartMate III (Thoratec)	3rd generation / Magnatically levitated axial flow pump	FDA approval trial going on

* few more devices like Excor, Incor, MVAD, VentrAssist, etc. are also available for use

in post-REMATCH era. The VAD industry has grown enormously and a number of long term devices are available. Over the years the main aims of industry were to reduce the size of devices without compromising their safety profile. List of common available long term VADs is shown in Table 1. For the sake of discussion, the Ventricular Assist Devices are divided into fallowing generations on the basis of pump technology.



Component of Long-term Ventriculuar Assist Devices

Figure 1

First generation VADs:

These are out-dated pulsatile devices. Less durability and fatal complication vanished their clinical use. Examples include EXCOR (Berlin Heart), Thoratec PVAD & XVE etc.

Second Generation VADs:

Continuous flow/non-pulsatile device with axial flow pump are included in this generation e.g. HeartMate II. This generation has highest number of VADs implants and the first one to earn FDA title for Bridge to transplant and Destination therapy.

Third generation VADs:

Continuous flow/ non-pulsatile device with centrifugal pumps devices like HeartWare, HeartMate III etc. are included in this generation. Miniaturized devices are implantable in the pericardial cavity with magnetic and hydraulic levitation making pump free of wear and tear.

Basic component of long term VADs have an inflow to be inserted into ventricle, a pump, outflow to be anastomosed to aorta or pulmonary artery. Pump is driven by electric supply through a driveline coming out of body as shown in Figure-1. Continuous modification in technology of pumps, accessories related to inflow and outflow component, driveline material component, power source technology, controller softwares and other fine details of VADs technology is going on to improve durability and VADs related complication profile.

INDICATIONS & LONGTERM CLINICAL USES OF VENTRICULAR ASSIST DEVICES

Heart Failure can be divided into left ventricular failure (LVF), Right Ventricular failure (RVF) or both. The assist devices can be customized as Left Ventricular Assist Device (LVAD), Right Ventricular Assist Device (RVAD) or Bi-ventricular Assist Device (BiVAD) according to its type of implantation.

Table 2
INTERMACS PATIENT PROFILES

INTERMACS SCALE	DESCRIPTION
1	Critical cariogenic shock
2	Progressive decline on intravenous inotropes
3	Stable but dependent on intravenous inotropes
4	Resting dyspnea
5	Exertion intolerance
6	Exertion limited
7	NYHA Class III

Dyspnea of cardiac origin having New York Heart Association (NYHA) classes III-b & IV are hallmark of advanced heart failure. The NYHA classification lacks many fine details that are needed to guides management plan in mechanical circulatory support decision making. Inter-agency Registry for mechanical Assist Circulatory Support (INTERMACS) has stratified NYHA-IV

class in more comprehensive way to seven different categories. More grade of heart failure severity in NYHA-IV and hence justification of VAD urgency can be determined from INTERMACS 1-7 scales as shown in Table 2.

Almost 80% VADs implantations have been performed in INTERMACS 2-3, INTERMACS 1 has 1-year survival of 76%, INTERMACS 2-3 has 80% while INTERMACS 4-7 have 82%.

Left ventricular failure is most frequently encountered VAD indication. In addition to NYHA & INTERMACS class, clinical parameters that make indication for LVAD implantation include LVEF of less than 25%, Pulmonary Capillary Wedge Pressure(PCWP) > 20 mmHg, systolic blood pressure less than 80 mmHg, Cardiac Index (CI) of less than 2 liter/min/m^2 despite of continuous intravenous inotropes or intra-aortic balloon pump (IABP) [7]. Isolated RVF mandating RVAD implant is relative rare. Post-LVAD implant RV failure is frequent and it respond well to temporary MCS along with medical therapy in most of cases [8].

Clinical use of VADs can be divided into following different themes:

1. *Bridge-to-bridge therapy (BBT):* Treatment theme when patient of advance heart failure is on short term MCS I.e. Extracorporeal Membrane Oxygenator (ECMO), Tandem-heart etc. and need shift to long term MCS. This theme is becoming popular for INTERMACS category 1 when emergent temporary MCS is indicated for too sick patient. Stabilization of patient to INTERMACS 2 or 3 and then switching to long-term VADs have shown to improve outcome.
2. *Bridge-to-Recovery (BTR):* MCS is indicated for weeks or months as myocardial recovery is expected in this theme of treatment e.g. Viral myocarditis. Very few data of successful BTR for is available.
3. *Bridge to Transplant Therapy(BTT):* This is most frequent theme of MCS therapy in clinical practice. Most of advance heart failure patient are too sick to enjoy quality of life on maximum medical therapy and not expected to live long while on cardiac transplant waiting list. Data has shown that prior VADs implant reduce morbidity and mortality of cardiac transplant.[9] Reduction in pulmonary hypertension due to prolong advance heart failure while on VAD therapy have beneficial impact on right ventricle of donor heart.[10] Improved organ perfusion in VADs patient is thought to improve patient risk factor profile and thus have impact on transplant outcome. 30-38% of BTT are successfully transplanted within 1-year of VAD implantation [11].
4. *Destination Therapy (DT):* In non-transplant candidates with advance heart failure, life long survival dependency on VADs is called destination therapy. Classically, patients over 65 years of age with comorbidity like chronic renal disease/insuline dependent diabetes mellitus with end organ disease etc. preclude them from transplant candidacy. NYHA IIIb/IV not responding to maximum medical therapy for more than 45days , V02 Max less than 12 ml/kg/min and EF less than 25% earn the indication for VAD-DT [11]. One-year survival for VAD-DT is 69% and 5-year survival is 35% [12,11].

Contraindication of long-term VAD implantations include risk of massive bleeding, irreversible organ damage i.e. liver, lungs, brain etc., active infection, aortic regurgitation, prior mechanical aortic valve implantation, neuropsychiatric illness etc. Various risk models have been describe for risk stratification for LVAD patients i.e. Lietz-Miller Score. The factors implicated for increased morbidity and mortality of VADs surgery include old age, female gender, right ventricular dysfunction and renal disease [13].

CURRENT FACTS & FIGURES OF VENTRICULAR ASSIST DEVICES IN HEART FAILURE MANAGEMENT

Limited number of cardiac organs and growing population of advanced heart failure compelled to over-spreading use of long-term VADs. More than 22,000 HeatMate II and more than 10000 HeartWare are implanted to-date.[14] Since June 2006 to December 2016, 22866 FDA approved long-term VADs have been implanted by more than180 hospital around the globe who are participating in INTERMACS. 18987 were primary left ventricular assist implants with 17634 non-pulsatile newer generations and 957

pulsatile devices as BTT or DT. 3845 newer implants were in prior VADs patients and 34 were isolated RVADs.[11] In addition, numbers of investigational and trial based implants of VADs (HeartMate III, HeartWare etc.) is also substantial and is not enrolled in INTERMACS.

The one-year and two-year survival of longterm CF-LVADs implant is 81% and 70% respectively. The major causes of death in early post-VAD implantation are multi-organ failure, right ventricular failure and stroke. After 6 months to 4-year follow up, stroke remain the major cause of death.Other major adverse events during first 3 months of VADs implantation include gastrointestinal bleeding and infection. VADs survival is comparable to Cardiac transplant which is 85-90% at 1 year and 75% at 3 years. The other greatest contribution of VADs in overall management of advance heart failure is the improvement in quality of life both in BTT and DT [15].

FUTURE OF VENTRICULAR ASSIST DEVICES

Number of cardiac transplant across the globe is 5000 per year versus 50,000 candidates on waiting list [16]. Limited availability of cardiac donor organs is constant fact. Figures of orthotropic heart transplant had remain steady around 2000 implant per year in last two decade in USA [16]. INTERMACS statistics for 1st Decade of registry had shown that VADs implantation is stepping parallel to cardiac transplant in USA and is expected to move ahead. Long-term VADs have made a steady progress in it development and indication over the course of time. HeartMate I earned it FDA approval as BTT in 2001 and then as DT in 2003. HeartMate II was approved as BTT in 2008 and as DT in 2010. HeatWare achieved it FDA-BTT approval in 2012 and DT title in September 2017 after results of ENDURANCE and ENDURANCE supplemental trials [17]. Data has shown that >90% of device implant in last 10 years are CF-VADs and out of that nearly 50% are used as DT [11].

Miniaturization, durability, safety of new generation pumps, more variety of FDA-approved devices, more clinical data etc. make long-term VADs as most value gaining treatment option in overall management of advance heart failure in up-coming years.

Conclusion:

Limited cardiac donor availability has created a lot of space for VADs use. Promising results in clinical practice have established their definitive role in overall management of advance heart failure in many faces. More safe, more durable and smaller VADs will have more implants in upcoming years.

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