NATIONAL TECHNICAL UNIVERSITY OF ATHENS
SCHOOL OF ELECTRICAL AND COMPUTER ENGINEERING
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INTERDISCIPLINARY POSTGRADUATE PROGRAMME
"Translational Engineering in Health and Medicine"

The Evolution and Current State of Left Ventricular Assist Device Technology: A Review of Clinical, Computational, and Experimental Studies on Commercial and Research Devices

Postgraduate Diploma Thesis

Dimitrios Karelas

Supervisor: Christos Manopoulos, Assoc. Professor NTUA

Athens, June 2025

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The postgraduate diploma thesis has been approved by the examination committee on 25 June 2025

1st member	*2nd member*	*3rd member*
Christos Manopoulos	*Konstantina Nikita*	*Spyretta Golemati*
Assoc. Professor NTUA	*Professor NTUA*	*Assoc. Professor NKUA*

Athens, June 2025

Karelas Dimitrios
Graduate of the Interdisciplinary Postgraduate Programme,
“Translational Engineering in Health and Medicine”,
Master of Science,
School of Electrical and Computer Engineering,
National Technical University of Athens

Athens, June 2025

Abstract

Heart failure (HF) remains a leading global health burden, with a subset of patients requiring advanced interventions beyond optimal medical therapy. Left ventricular assist devices (LVADs) have emerged as a critical treatment option for patients with end-stage HF, serving either as a bridge to transplantation or as destination therapy. This narrative review explores the evolution, clinical application, engineering development, and future outlook of LVAD technology through clinical, computational, and experimental lenses.

Mechanical circulatory support originated in the mid-20th century with the advent of cardiopulmonary bypass. Early pulsatile LVADs (e.g., HeartMate I, Thoratec) improved hemodynamics but were plagued by infections, thrombosis, and mechanical failures. The REMATCH trial demonstrated survival advantages but highlighted design limitations. The second generation introduced continuous-flow axial pumps like HeartMate II and Jarvik 2000, offering enhanced durability and reduced infection risk but introducing complications from non-physiologic flow, including gastrointestinal bleeding and acquired von Willebrand syndrome. Third-generation centrifugal-flow devices, notably HeartMate 3 with magnetically levitated impellers, improved hemocompatibility and durability. MOMENTUM 3 trial results favored HeartMate 3, showing markedly lower pump thrombosis (0.6% vs. 12.5%) and stroke (2.8% vs. 11.3%) rates compared to HeartMate II.

Nonetheless, complications persist. Right ventricular failure occurs in up to 25% of recipients, often requiring RVAD support. Aortic insufficiency arises in over 30% within two years due to commissural fusion. Stroke and driveline infections remain concerns, although improved designs have reduced thromboembolic events. Engineering advancements—especially computational fluid dynamics (CFD), finite element analysis (FEA), and mock circulatory models—have informed iterative design improvements and anticoagulation strategies. AI and machine learning are being explored for predictive monitoring and automated control of pump function.

Economic evaluations, such as the UK ICER analysis (£47,361 per QALY for HeartMate 3), support LVAD use in select patients but underscore ongoing cost-effectiveness concerns. Looking forward, priorities include fully implantable systems, wireless power transmission, enhanced biomaterials, and integration with tissue-engineered constructs. Optimizing patient selection and minimizing complications through the synergy of clinical, computational, and engineering innovations will be pivotal in expanding the benefits of LVAD therapy.

Keywords: Left Ventricular Assist Devices, Mechanical Circulatory Support, Cardiac Assist Devices, Heart Failure, Continuous-Flow LVADs, Pulsatile-Flow LVADs, Magnetic Levitation Technology, Hemocompatibility, Pump Thrombosis, Bridge to Transplantation, Destination Therapy, Computational Fluid Dynamics

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Table of Contents

List of Abbreviations

Abbreviations	Definitions
ACC	American College of Cardiology
AHA	American Heart Association
AI	Artificial Intelligence
ARVC	Arrhythmogenic Right Ventricular Cardiomyopathy
AUC	Area Under the Curve
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
BSA	Body Surface Area
BTT	Bridge to Transplant
BVS	BiVentricular Support
CABG	Coronary Artery Bypass Grafting
CAP	Continued Access Protocol
CBAS	Carmeda BioActive Surface
CBS	Cardiac Beat Synchronization
CD	Cluster of Differentiation
CE	Conformité Européenne
CF	Continuous Flow
CFD	Computational Fluid Dynamics
CI	Confidence Interval
COMPETENCE	Centrifugal Or Magnetic PumP Induced End-organ funcTION and CliniCal outcomEs
COPD	Chronic Obstructive Pulmonary Disease
CSU	Cool Seal Unit
CT	Computed Tomography
CVD	Cerebrovascular Disease
DCT	Double-Cuff Tipless
DPTI	Diastolic Pressure-Time Index
DT	Destination Therapy
ECG	Electrocardiogram
ECLS	Extracorporeal Life Support
ECMO	Extracorporeal Membrane Oxygenation
EDPVR	End-Diastolic Pressure-Volume Relationship
EDV	End-Diastolic Volume
EF	Ejection Fraction
ELEVATE	Evaluation of VAD Efficiency and Therapeutic Effectiveness
EPPY	Episodes Per Year
ESC	European Society of Cardiology
ESPVR	End-Systolic Pressure-Volume Relationship
ESV	End-Systolic Volume
FDA	Food and Drugs Association
FEA	Finite Element Analysis

FGF	Fibroblast Growth Factor
GDMT	Guideline-Directed Medical Therapy
GFR	Glomerular Filtration Rate
HF	Heart Failure
HFA	Heart Failure Association
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HM	HeartMate
HMII	HeartMate II
HMIII	HeartMate III
HMRS	High-Resolution Magnetic Resonance Spectroscopy
HSP	Heat Shock Protein
HVAD	HeartWare Ventricular Assist Device
IABP	Intra-Aortic Balloon Pump
ICD	Implantable Cardioverter Defibrillator
ICER	Incremental Cost-Effectiveness Ratios
IHD	Ischemic Heart Disease
IMACS	International Mechanically Assisted Circulatory Support
INR	International Normalized Ratio
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
IP	Implantable Pneumatic
IV	Intravenous
KCCQ	Kansas City Cardiomyopathy Questionnaire
LATERAL	Less Invasive Ventricular Assist Device Implantation
LED	Light Emitting Diode
LSFG	Laser Speckle Flowgraphy
LV	Left Ventricle
LVAD	Left Ventricular Assist Device
LVEDP	Left Ventricular End-Diastolic Pressure
LVEF	Left Ventricular Ejection Fraction
LVID	Left Ventricular Internal Diameter in Diastole
LVP	Left Ventricular Pressure
MCS	Mechanical Circulatory Support
MCSD	Mechanical Circulatory Support Devices
MES	Microembolic Signals
ML	Machine Learning
MLWHF	Minnesota Living with Heart Failure Questionnaire
MOMENTUM	Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3
MRI	Magnetic Resonance Imaging
MTTF	Mean Time to Failure
MVO	Myocardial Venous Oxygenation
MWTD	Minute Walk-Test Distance
NASA	National Aeronautics and Space Administration

NHS	National Health Service
NIH	National Institutes of Health
NO	Nitric Oxide
NSE	Neuron-Specific Enolase
NTUA	National Technical University of Athens
NYHA	New York Heart Association
OMM	Optimal Medical Managment
PE	Pneumatic Electric
PF	PediaFlow
PRA	Panel Reactive Antibody
PTFE	Polytetrafluoroethylene
PTV	Particle Tracking Velocimetry
PumKIN	Pumps for Kids, Infants, and Neonates
PV	Pressure-Volume
PVA	Pressure-Volume Area
PVR	Pulmonary Vascular Resistance
QALY	Quality-Adjusted Life Year
REMATCH	Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure
REVOLVE	Refining the Evaluation of a Ventricular Assist Device in Lower Risk Patients with Ventricular Dysfunction
ROADMAP	Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients
RPM	Revolutions Per Minute
RV	Right Ventricle
RVAD	Right Ventricular Assist Device
SHFM	Seattle Heart Failure Model
SPTI	Systolic Pressure-Time Index
STS	Society of Thoracic Surgeons
SUSTAIN	SUrvivability and STAbility IN Long-term MCS
SV	Stroke Volume
SW	Stroke Work
TAH	Total Artificial Heart
TCD	Transcranial Doppler
TETS	Transcutaneous Energy Transmission Systems
TIA	Transient Ischemic Attack
TPG	Transpulmonary Gradient
UK	United Kingdom
UNOS	United Network for Organ Sharing
VAD	Ventricular Assist Device
VD	Dead Volume
VE	Vented Electric
XVE	Extended Ventricular Enhancement

1 Introduction

1.1 Heart Failure

1.1.1 Definition

Heart failure (HF) is a clinical syndrome characterized by cardinal symptoms such as breathlessness, ankle swelling, and fatigue, often accompanied by signs like elevated jugular venous pressure, pulmonary crackles, and peripheral edema. It arises from a structural and/or functional abnormality of the heart, leading to increased intracardiac pressures and/or insufficient cardiac output at rest or during physical activity (McDonagh et al., 2021).

The etiological spectrum of HF demonstrates significant geographical variability, with multiple contributing factors frequently interacting to drive the pathophysiological progression of the condition. Ischemic heart disease (IHD) accounts for approximately 40% of HF cases globally, although its prevalence varies significantly across regions. It is most prevalent in Eastern Europe, the Middle East and Southeast Asia (~60%) and notably less common in Africa (<15%). Hypertension is the underlying cause in about 15% of HF cases, with the highest prevalence observed in Africa. Valvular and rheumatic heart disease remains a significant etiology in Sub-Saharan Africa and low-income regions, while Chagas cardiomyopathy is the leading cause of non-ischemic HF in South America, with increasing cases reported in Europe and the United States due to migration. Data on other potential HF etiologies, such as amyloidosis, human immunodeficiency virus (HIV)-associated cardiomyopathy, sarcoidosis, and other less common cardiomyopathies, remain limited (Savarese et al., 2023).

1.1.2 Classification

Left Ventricular Ejection Fraction (LVEF) is a key parameter used to evaluate left ventricular systolic function, providing insight into the heart's ability to pump blood effectively. It represents the proportion of blood ejected from the left ventricle during systole (contraction phase) relative to the total volume of blood present in the ventricle at the end of diastole (relaxation phase). Mathematically, LVEF is expressed as a percentage, calculated using the formula (1):

$$LVEF = \left[\frac{SV}{EDV}\right] \text{x } 100 \quad (1)$$

where, Stroke Volume *(SV)* is the amount of blood ejected during a single heartbeat, determined as the difference between the End-Diastolic Volume *(EDV)*: the volume of blood in the LV at the end of diastole, and End-Systolic Volume *(ESV)*: the volume of blood in the LV at the end of systole.

HF is categorized into different phenotypes based on LVEF measurements as follows (B. Bozkurt et al., 2021):

- HF with Reduced Ejection Fraction (HFrEF): LVEF ≤ 40%
- HF with Mildly Reduced Ejection Fraction (HFmrEF): 40% < LVEF < 50%
- HF with Preserved Ejection Fraction (HFpEF): LVEF ≥ 50% in patients with HF symptoms and signs, structural and/or functional cardiac abnormalities, and/or elevated natriuretic peptides (NPs).

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

Figure 1. Heart Failure classification based on Left Ventricular Ejection Fraction.

HF: heart failure, HFmrEF: heart failure with mildly reduced ejection fraction, HFpEF: heart failure with preserved ejection fraction, HFrEF: heart failure with reduced ejection fraction, LV: left ventricle, LVEF: left ventricular ejection fraction.

a. Signs may not be present in the early stages of HF (especially in HFpEF) and in optimally treated patients.
b. For the diagnosis of HFmrEF, the presence of other evidence of structural heart disease (e.g. increased left atrial size, LV hypertrophy or echocardiographic measures of impaired LV filling) makes the diagnosis more likely.
c. For the diagnosis of HFpEF, the greater the number of abnormalities present, the higher the likelihood of HFpEF.

The New York Heart Association (NYHA) Functional Classification is a system used to categorize the severity of heart failure based on a patient's symptoms and their impact on daily activities. Established in 1928, it remains a widely utilized tool in clinical practice (Goldman et al., 1981). This classification comprises four classes:

- Class I**:** No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or shortness of breath.
- Class II**:** light limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, shortness of breath, or chest pain.
- Class III**:** marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, shortness of breath, or chest pain.

- Class IV**:** unable to carry on any physical activity without discomfort. Symptoms of heart failure are present at rest; if any physical activity is undertaken, discomfort increases.

Another classification is provided by the American College of Cardiology (ACC) and the American Heart Association (AHA). HF is categorized into distinct stages emphasizing the progression of the disease and its impact on survival (Figure 2) (Heidenreich et al., 2022). Advanced stages are associated with a reduced life expectancy. Therapeutic strategies at each stage focus on specific goals: modifying risk factors in stage A, managing risk and structural heart disease to prevent HF in stage B, and alleviating symptoms while reducing morbidity and mortality in stages C and D.

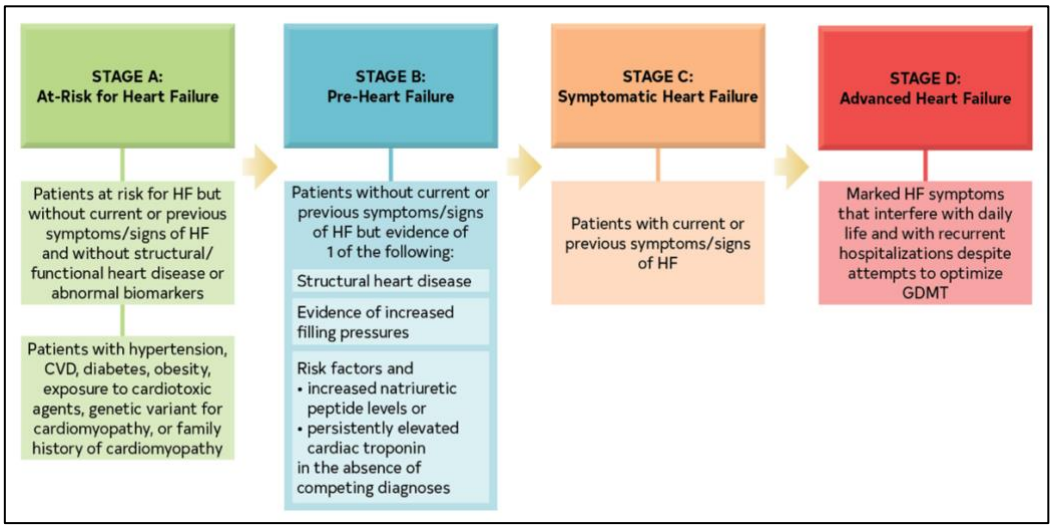


Figure 2. ACC/AHA Stages of HF. The ACC/AHA stages of HF are shown.

[ACC: American College of Cardiology; AHA, American Heart Association; CVD, cardiovascular disease; GDMT, guideline-directed medical therapy; and HF, heart failure.]

1.1.3 Incidence and Prevalence

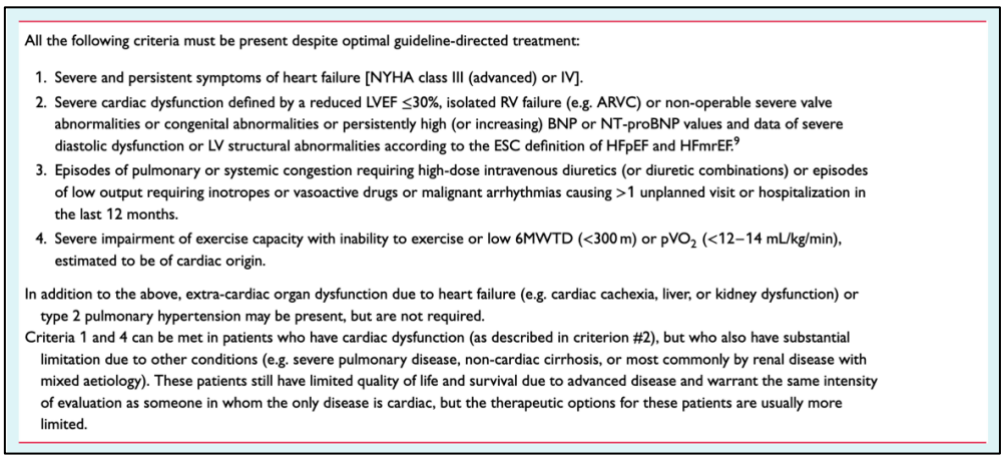
HF represents a significant global health concern, with millions of individuals affected annually. While advancements in the management of cardiovascular diseases have contributed to a reduction in age-adjusted incidence rates in developed nations, the overall incidence continues to increase, primarily driven by an aging population. In Europe, the incidence of HF is estimated at approximately 3.2 per 1,000 person-years, with country-level variation ranging from 1.99 to 6.55 per 1,000 person-years, according to data from the ESC Heart Failure Association Atlas (Seferović et al., 2021). The prevalence of HF demonstrates a strong age-dependent gradient, with a median prevalence of 1.7% across European populations, exceeding 10% in individuals aged 70 years and older. Globally, an estimated 55.5 million people were living with HF in 2021, based on data from the Global Burden of Disease (GBD) Study (Roth et al., 2023). The age-standardized prevalence increased from approximately 648

to 677 cases per 100,000 population between 1990 and 2021, reflecting the combined effects of population aging, improved survival following cardiovascular events, and advances in HF diagnosis and management.

The economic burden of HF is substantial and projected to escalate significantly in the coming decades. In the United States, the direct and indirect costs associated with HF were estimated at $30.7 billion in 2012, with forecasts indicating a 127% increase to $69.8 billion by 2030 (Virani et al., 2021). The prevalence of advanced HF is also rising due to an increasing number of HF cases, an aging population, and improvements in HF treatment and survival. Despite these advances, prognosis remains poor, with 1-year mortality rates ranging from 25% to 75% (Truby & Rogers, 2020; Xanthakis et al., 2016). Overall, this trajectory highlights the necessity for innovative approaches to reduce healthcare expenditures while improving outcomes. Addressing the rising prevalence and associated costs of HF requires a multifaceted strategy encompassing prevention, early detection, and optimization of evidence-based therapeutic interventions.

1.1.4 Advanced Heart failure

Many patients with HF eventually progress to a stage of advanced HF, characterized by persistent symptoms despite receiving maximal therapy. The Heart Failure Association (HFA) - European Society of Cardiology (ESC) criteria for advanced HF are outlined in Figure 3 (Crespo-Leiro et al., 2018). While a severely reduced LVEF is often observed, it is not necessary for an advanced HF diagnosis, as it can also occur in patients with HFpEF. Additionally, advanced HF may be associated with extra-cardiac organ dysfunction, such as cardiac cachexia, liver or kidney dysfunction, or type II pulmonary hypertension. However, these conditions are not mandatory for defining advanced HF.


All the following criteria must be present despite optimal guideline-directed treatment:

1. Severe and persistent symptoms of heart failure [NYHA class III (advanced) or IV].
2. Severe cardiac dysfunction defined by a reduced LVEF ≤30%, isolated RV failure (e.g. ARVC) or non-operable severe valve abnormalities or congenital abnormalities or persistently high (or increasing) BNP or NT-proBNP values and data of severe diastolic dysfunction or LV structural abnormalities according to the ESC definition of HFpEF and HFmrEF.[9]
3. Episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing >1 unplanned visit or hospitalization in the last 12 months.
4. Severe impairment of exercise capacity with inability to exercise or low 6MWTD (<300 m) or pVO_2 (<12–14 mL/kg/min), estimated to be of cardiac origin.

In addition to the above, extra-cardiac organ dysfunction due to heart failure (e.g. cardiac cachexia, liver, or kidney dysfunction) or type 2 pulmonary hypertension may be present, but are not required.

Criteria 1 and 4 can be met in patients who have cardiac dysfunction (as described in criterion #2), but who also have substantial limitation due to other conditions (e.g. severe pulmonary disease, non-cardiac cirrhosis, or most commonly by renal disease with mixed aetiology). These patients still have limited quality of life and survival due to advanced disease and warrant the same intensity of evaluation as someone in whom the only disease is cardiac, but the therapeutic options for these patients are usually more limited.

Figure 3. HFA-ESC criteria for defining advanced heart failure (Crespo-Leiro et al., 2018)

ARVC: arrhythmogenic right ventricular cardiomyopathy, BNP: B-type natriuretic peptide, ESC: European Society of Cardiology, HFA: Heart Failure Association, HFmrEF: heart failure with mid-

range ejection fraction, HFpEF: heart failure with preserved ejection fraction, LV: left ventricular; LVEF: left ventricular ejection fraction, NT-proBNP: N-terminal pro-B-type natriuretic peptide, NYHA: New York Heart Association, pVO_2 : peak exercise oxygen consumption, RV: right ventricular, 6MWTD: 6-minute walk test distance.

Identifying patients in the early stages of advanced heart failure remains a clinical challenge. It has been proposed that individuals experiencing significant exertional limitations (NYHA III) despite receiving guideline-directed optimal medical therapy should be evaluated by a heart failure specialist. Recently, the ACC, through an expert consensus document, introduced the acronym *"I NEED HELP"* to highlight high-risk features that warrant referral for advanced heart failure assessment (Yancy et al., 2018):

I: Inotropes (iv)

N: NYHA IIIb-IV or persistently elevated natriuretic peptides

E: End-organ dysfunction

E: Ejection fraction ≤35%

D: Defibrillator shocks

H: Hospitalizations >1 in prior 12 months

E: Edema despite escalating diuretics

L: Low blood pressure ≤90 mmHg, high heart rate

P: Prognostic medication progressive intolerance/down-titration of guideline-directed medical therapy

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) has developed a classification system comprising seven clinical profiles to describe the severity of advanced heart failure in patients considered for mechanical circulatory support (Kirklin et al., 2008; Lietz, 2010). These profiles range from Profile 1 (critical cardiogenic shock) to Profile 7 (advanced NYHA Class III symptoms). This classification aids in patient assessment and management decisions.

1. Critical Cardiogenic Shock – Life-threatening, requiring immediate intervention.
2. Progressive Decline – Worsening despite therapy, nearing shock.
3. Stable but Inotrope Dependent – Reliant on inotropes but not deteriorating.
4. Recurrent Advanced Heart Failure – Episodic decompensation, frequent hospitalizations.
5. Exertion Intolerant – Severe limitations in daily activities.
6. Exertion Limited (NYHA IIIb) – Moderate activity restriction.
7. Advanced NYHA III – Mild symptoms, not yet severe heart failure.

1.1.5 Management Strategies of Advanced Heart Failure

Management strategies for advanced HF aim to alleviate symptoms, enhance quality of life, and prolong survival. Pharmacological options include inotropes, which temporarily improve cardiac output in cases of refractory HF but are associated with poor long-term outcomes, and vasopressors, reserved for patients with cardiogenic shock and organ hypoperfusion. While these medications play a role in stabilizing patients, their utility is largely limited to bridging patients to more definitive therapies. Device-based interventions such as implantable cardioverter-defibrillators (ICDs) can help reduce the risk of sudden cardiac death in select patients awaiting transplantation. Additionally, ultrafiltration and peritoneal dialysis address fluid overload and congestion in cases of diuretic resistance. Surgical options remain a mainstay for eligible patients, with heart transplantation regarded as the gold standard for those meeting strict eligibility criteria. Other surgical approaches, including coronary artery bypass grafting (CABG) or valve repair/replacement, are considered for patients whose cardiac dysfunction is associated with reversible pathologies (Heidenreich et al., 2022).

Mechanical circulatory support (MCS) has emerged as a cornerstone therapy for advanced HF, especially in patients who are not immediate candidates for heart transplantation or those requiring stabilization as a bridge to decision-making. Short-term MCS devices, such as intra-aortic balloon pumps (IABP), extracorporeal membrane oxygenation (ECMO), and percutaneous devices like the TandemHeart or Impella systems, provide temporary stabilization by improving hemodynamics and restoring end-organ perfusion in acute settings. These devices are critical in bridging patients to more definitive interventions, such as long-term MCS or transplantation. Long-term MCS, primarily represented by left ventricular assist devices (LVADs), has shifted care for patients with advanced HF. These devices serve as a bridge to transplantation, allowing patients to await donor availability, or as destination therapy for those ineligible for transplantation. A meta-analysis of 12 studies found that LVADs as destination therapy significantly improve survival, with a pooled effect size of 0.848 (95% CI: 0.306–1.390, $p = 0.002$), and enhance quality of life, with a standardized mean difference of 0.78 (95% CI: 0.65–0.91). However, complication rates remain high, with infections and bleeding being the most common adverse events, affecting up to 35% and 25% of patients (Khoufi, 2025). Advances in continuous-flow LVADs, such as the HeartMate 3, have significantly improved survival rates and reduced complications, including pump thrombosis and stroke. Despite the progress, challenges like right ventricular failure, bleeding, thromboembolism, and infections continue to pose significant clinical hurdles, underscoring the need for ongoing innovation and comprehensive patient management. In Table 1, indications and contraindications for LVAD implantation are outlined. In Table 2, pivotal randomized control trials which contributed to the establishment of LVAD in advanced HF patients are presented.

Table 1. Indications and Contraindications for LVAD implantation.

Indications	Contraindications					
NYHA Class IV refractory to OMM and conventional surgery	Limited life expectancy	Age >80 y	Active malignancy			
LVEF <25%	Severe comorbidities precluding meaningful outcome	End-stage renal disease (GFR < 30 or CrCl clearance < 30)	Severe liver disease (bilirubin < 2.5 or INR > 2.0 with cirrhosis or portal hypertension)	Severe lung disease (obstructive or restrictive, home O_2); pulmonary infarction within the past 6 weeks	Severe vascular disease; severe arthritis	Unconfirmed neurological status, unresolved stroke, or severe neuromuscular disorder
Reduced functional capacity as measured by a maximal O2 consumption VO_2<14 mg/kg/min	Hematologic	Active severe bleeding; chronic thrombocytopenia	Active infection	Refusal of blood transfusions	Confirmed heparin induced thrombocytopenia	Intolerance to anticoagulation
Exceptions for select patients may include clinical trial protocol requirements	Anatomic	Congenital heart disease	Hypertrophic cardiomyopathy	Large ventricular septal defect	BMI precluding implantation or rehabilitation	
	Hemodynamic	Severe independent right heart failure	PVR >6 or TPG >15 on testing with inhaled NO, epoprostenol sodium, or intravenous nitroprusside	Existing significant aortic insufficiency unable to be corrected		
	Psychosocial	Evidence of ongoing alcohol, smoking or drug use or dependency	Inability to provide informed consent	Inability to adhere to medical regimen	Inability to maintain device (drive line, console)	Active mental illness or psychosocial instability

NYHA: New York Heart Association; LVEF: Left Ventricular Ejection Fraction; VO_2: Maximal Oxygen Consumption; GFR: Glomerular Filtration Rate; CrCl: Creatinine Clearance; INR: International Normalized Ratio; PVR: Pulmonary Vascular Resistance; TPG: Transpulmonary Gradient; NO: Nitric Oxide; BMI: Body Mass Index, adapted from (Han et al., 2018)

Regarding exclusion criteria for LVAD implantation**,** patients are typically deemed unsuitable if they present with conditions such as severe right ventricular dysfunction**,** irreversible end-organ failure**,** active systemic infection, or severe coagulopathy. A comprehensive psychosocial evaluation is also essential, as factors like non-adherence to medication**,** unsafe home environment**,** lack of social support, or substance abuse can adversely affect post-implantation outcomes (Masarone et al., 2023).

Table 2. Randomized Controlled Trials of LVADs (adapted from Sidhu et al., 2020).

Study	Study device	Study population	Primary outcome	2-year survival	Special considerations
REMATCH	HeartMate XVE (Pulsatile flow)	129 patients with advanced heart failure who were ineligible for cardiac transplantation; HeartMate XVE (n=68) vs. optimal medical therapy (n=61) in 1:1 ratio	Survival at 1 and 2 years (52% with HeartMate XVE vs. 25% with optimal medical therapy at 1-year; 23% with HeartMate XVE vs. 8% with optimal medical therapy at 2-years)	23% with HeartMate XVE compared to 8% with optimal medical therapy	Improved quality of life and survival in the device group; higher incidence of infection and bleeding in the device group
HM DT study	HeartMate II (Continuous flow, axial pathway pump)	200 patients with advanced heart failure requiring device as destination therapy; HeartMate II (n=134) vs. HeartMate XVE (n=66) in 2:1 ratio	2-year survival free from disabling stroke or reoperation to repair or replace the device (46% with HeartMate II vs. 11% with HeartMate XVE)	58% in HeartMate II compared to 24% with HeartMate XVE	Both devices improved quality of life and functional capacity, and the HeartMate II improved survival compared to the HeartMate XVE; no difference in the incidence of stroke between the devices noted, but lower rates of right heart failure and infection noted for HeartMate II
ENDURANCE	HVAD (Continuous flow, centrifugal pathway pump)	446 patients with advanced heart failure requiring device use as destination therapy; HVAD (n=297) vs. HeartMate II (n=148) in 2:1 ratio	2-year survival free from disabling stroke or device failure (55.4% with HVAD vs. 59.1% with HeartMate II)	60.2% with HVAD compared to 67.6% with HeartMate II	HVAD had significantly higher incidence of ischemic or hemorrhagic stroke compared to HeartMate II but was non-inferior on primary outcomes
ENDURANCE Supplemental	HVAD (Continuous flow, centrifugal pathway pump)	465 patients with advanced heart failure requiring device use as destination therapy; HVAD (n=308) vs. HeartMate II (n=157) in 2:1 ratio	12-month incidence of transient ischemic attack or stroke with residual deficit 24 weeks post-event (14.7% with HVAD vs. 12.1% with HeartMate II)	—	Intensive blood pressure control (mean arterial pressure ≤85 mmHg if automated pressure and ≤90 mmHg if Doppler pressure) associated with reduced hemorrhagic stroke rates with HVAD; non-inferiority for neurological injury was not met for HVAD
MOMENTUM 3	HeartMate 3 (Continuous flow, centrifugal pathway pump with intrinsic pulse)	1028 patients with advanced heart failure requiring short or long-term support; HeartMate 3 (n=516) vs. HeartMate II (n=512) in 1:1 ratio	2-year survival free from disabling stroke or reoperation to repair or replace a malfunctioning device (76.9% with HeartMate 3 vs. 64.8% with HeartMate II)	79% with HeartMate 3 compared to 77% with HeartMate II	Decreased pump thrombosis, stroke and bleeding, including gastrointestinal bleeding, with HeartMate 3

For the purposes of this MSc thesis, the focus will be on the historic evolution and current state of LVAD technology. This thesis narratively reviews clinical, computational, and experimental investigations, analyzing both commercially available and research-based durable devices. By exploring the development in device design, implementation strategies, and patient outcomes, this thesis aims to provide an overview of the role of LVADs in advanced heart failure management. Special attention will be given to the integration of engineering innovations and clinical practices, highlighting how these developments have shaped the current landscape and addressing the challenges that persist in optimizing LVAD therapy.

2 Methods

A comprehensive literature search of peer-reviewed studies was conducted in PubMed and Google Scholar using a combination of MeSH terms and keywords, including "left ventricular assist device", "mechanical circulatory support", "advanced heart failure", "pressure-volume loop", "axial-flow pump", "continuous-flow pump", "centrifugal pump", "pulsatile pump", "bridge to transplantation", "bridge to recovery", "destination therapy", "computational fluid dynamics", "healthcare cost", "economic evaluation" and "cost-effectiveness." Boolean operators (AND, OR) were used to refine and expand the search. References from selected articles were manually reviewed to identify additional relevant studies, and the search strategy was iteratively refined to maximize coverage of the most relevant literature. Abstracts, conference proceedings, posters, and non-indexed publications were excluded to ensure the inclusion of high-quality, rigorously reviewed literature.

Studies included in this review were categorized into clinical trials, computational and in-silico modeling studies, in-vitro and in-vivo experimental research, and economic evaluations. Randomized controlled trials, prospective and retrospective observational studies, systematic reviews, and meta-analyses were assessed for clinical outcomes such as survival rates, adverse events, and quality of life. Computational studies using computational fluid dynamics (CFD), finite element modeling, and lumped parameter modeling were reviewed to evaluate LVAD hemodynamics, shear stress effects, thrombogenicity, and myocardial unloading. Experimental research included benchtop and animal studies assessing pump performance, blood damage, and biomaterial compatibility. Economic analyses focused on cost-effectiveness, incremental cost-effectiveness ratios (ICER), hospital resource utilization, reimbursement policies, and financial sustainability of LVAD therapy in different healthcare settings.

The review focuses on key aspects of LVAD technology, including survival outcomes, device durability, adverse events such as stroke, gastrointestinal bleeding, pump thrombosis, and right heart failure, as well as quality of life improvements. LVADs were classified based on their generation (first-, second-, and third-generation), flow type (pulsatile vs. continuous), and bearing technology (contact-bearing, hydrodynamic, and magnetically levitated). By integrating engineering, clinical, and economic perspectives, this review aims to provide a comprehensive understanding of LVAD advancements and their implications for future research and clinical decision-making.

3 LVAD: Overview

3.1 Technical Insights

Each LVAD consists of internal (intracorporeal) components (inflow cannula, implantable pump, outflow graft) and external components (driveline, controller, power source). The inflow cannula is surgically implanted into the apex of the left ventricle, where it draws oxygenated blood into the pump chamber. The pump housing contains the impeller or rotor, which propels blood forward using either axial or centrifugal flow mechanisms and is situated in the preperitoneal or pericardial space. The outflow graft then delivers the blood into the ascending aorta, effectively bypassing the weakened LV to restore systemic circulation. The driveline is a percutaneous cable that connects the internal pump to an external controller, which regulates pump speed, power consumption, and alarm functions. Power is supplied through rechargeable lithium-ion batteries or a direct electrical connection to a wall outlet, ensuring uninterrupted device operation. The external controller also provides real-time monitoring of pump parameters, including speed (rotations per minute), estimated flow (L/min minute), and power consumption (watts) (Chaudhry et al., 2022). A schematic representation of an LVAD is depicted in Figure 4.

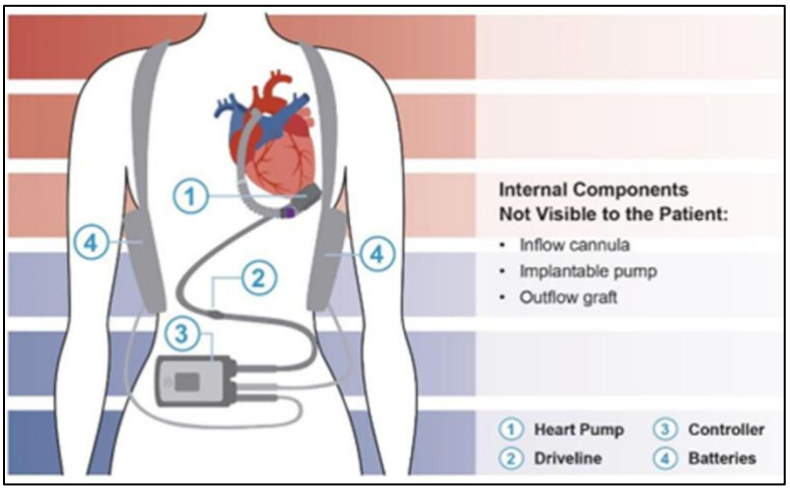


Figure 4. Schematic representation of an LVAD.

The function and performance of an LVAD are governed by several key parameters each of which provides crucial insights into the interaction between the device and the native cardiovascular system:

- **Pump speed**, measured in revolutions per minute (rpm), is the only adjustable parameter in an LVAD.

- **Power** represents the energy output of the pump and is influenced by both speed and flow rate. Higher flow requires more power, while increased resistance (pressure gradient) reduces power.
- **Pulsatility index** (range 1–10) indicates the proportion of cardiac output generated by the native left ventricle. A lower pulsatility index suggests greater LVAD support and severe left ventricular dysfunction but may also result from reduced preload.
- **Flow** is influenced by pump speed and inversely related to the pressure gradient opposing LVAD flow. It is not directly measured but is calculated based on pump power, speed, and blood viscosity.
- **Power and pulsatility index** are measured directly by the LVAD, whereas flow is an estimated value.

(Adapted from Hanna, 2022)

3.1.1 Impellers

The impeller is a critical component of a blood pump, responsible for driving fluid movement and ensuring efficient hydraulic performance while minimizing blood damage. In the context of LVADs, impeller design has evolved through generations to enhance hemodynamic efficiency and hemocompatibility, thereby reducing complications such as hemolysis, thrombosis, and platelet activation. The fundamental role of the impeller is to generate the necessary pressure gradient that moves blood from the left ventricle to the systemic circulation. The impeller operates based on the principles of turbomachinery, where rotational energy is imparted to the fluid, increasing its velocity and converting it into pressure energy. The geometric configuration of the impeller, including the number of blades, blade angles, clearance gaps, and shroud design, has a significant impact on both hydraulic performance and blood compatibility. Increasing speed enhances impeller rotation, leading to greater LV unloading and increased cardiac output, but current devices do not automatically adjust based on physiologic demand (DeVore et al., 2017).

Impellers in LVADs can be categorized based on their design and operational characteristics. Early generations of LVADs utilized axial-flow impellers, which function similarly to propellers, generating flow along the axis of rotation. These designs were relatively simple but exhibited limitations in pressure generation and blood compatibility due to high shear stress. To address these issues, later generations introduced centrifugal impellers, which rely on a radial flow pattern, redirecting blood outward from the center through curved vanes. These designs improved pressure head generation while reducing shear forces, leading to lower hemolysis rates. Modern LVADs employ advanced impeller designs that incorporate magnetic or hydrodynamic bearings to minimize mechanical contact, reducing wear and eliminating the need for mechanical bearings. Magnetic levitation (maglev) impellers use controlled electromagnetic forces to suspend the impeller, enabling contact-free operation that reduces

friction, heat generation, and the risk of clot formation. Hydrodynamically levitated impellers, on the other hand, rely on fluid-dynamic forces to maintain separation between moving parts, offering similar advantages in reducing blood damage and improving long-term durability (Gülich, 2010)

3.2 Pump Flow Types and Generations

The development of continuous-flow rotary pumps represents a major advancement in LVAD technology, replacing the first-generation pulsatile volume displacement pumps with more compact and durable designs. Within this category, a key distinction is made between contact-bearing and non-contact bearing designs, which define second- and third-generation LVADs, respectively. Second-generation LVADs, typically designed with an axial blood flow path, utilize an internal rotor that remains in contact with mechanical bearings to support its motion. However, exceptions to this classification exist, as some axial-flow devices incorporate partial magnetic suspension to reduce mechanical wear. In contrast, third-generation LVADs are characterized by fully non-contact bearing designs, where the impeller or rotor is suspended entirely within the blood flow path using magnetic or hydrodynamic levitation. These devices predominantly feature centrifugal blood flow paths, although axial-flow third-generation devices also exist, such as the Berlin Heart INCOR, which employs magnetic levitation for impeller suspension (Pagani, 2008).

Magnetic and hydrodynamic levitation systems in third-generation LVADs eliminate frictional wear and reduce heat generation, key factors that improve durability and hemocompatibility. Magnetic levitation may be achieved through passive (permanent magnets) or active (electrically induced) mechanisms, while hydrodynamic levitation relies on fluid forces generated by the rotating impeller to maintain suspension. Some LVADs, such as the HeartWare HVAD, use a combination of both magnetic and hydrodynamic forces to achieve impeller stability. Other devices, such as the VentrAssist, rely entirely on hydrodynamic levitation, whereas the DuraHeart and HeartMate 3 use different forms of active and passive magnetic levitation. Active magnetic levitation, which requires position sensors and control systems, offers greater precision in impeller positioning but increases the complexity and size of the device. Hydrodynamic levitation, on the other hand, allows for miniaturization but can result in variable tolerances between the impeller and pump housing, which may lead to intermittent impeller contact, particularly at low rotational speeds (Pagani, 2008).

The classification of third-generation LVADs extends to their motor systems, which determine how the impeller is magnetically coupled to the motor. Three primary designs exist: external motor-drive systems, direct-drive systems, and self-bearing (bearingless) systems. External motor-drive systems use a separate motor to generate magnetic coupling forces for impeller rotation, while a distinct

levitation system maintains suspension. However, this design still requires mechanical bearings to support the motor's rotation. The DuraHeart LVAD follows this design principle. In a direct-drive system, such as the Berlin Heart INCOR, the impeller itself serves as the motor rotor, with a dedicated levitation system integrated to achieve magnetic suspension. This approach simplifies the system by reducing additional motor components. The most advanced configuration is the self-bearing or bearingless system, in which both the drive and levitation coils are embedded within the same stator core. This design eliminates the need for separate bearings or external motors, improving overall efficiency and reducing mechanical complexity. Examples of this include HeartMate 3 which uses bearingless system to achieve full magnetic levitation (Pagani, 2008).

3.3 Hemodynamics

3.3.1 Cardiac Pressure-Volume Loops

LVADs fundamentally alter the hemodynamic profile of the heart by providing continuous mechanical support, thereby influencing ventricular loading conditions, myocardial energetics, and remodeling. A thorough understanding of cardiac mechanics is essential to appreciate how LVADs interact with the cardiovascular system. Evaluating the effects of LVADs on cardiac mechanics necessitates an analysis of pressure-volume (PV) loops, which illustrate the relationship between ventricular pressure and volume throughout the cardiac cycle. Cardiac mechanical load is influenced by preload and afterload, both of which regulate stroke volume through the Frank-Starling mechanism. Preload refers to the ventricular load before systole and is represented by end-diastolic pressure or volume, whereas afterload denotes the resistance the ventricle must overcome to eject blood and is commonly expressed as arterial elastance (Ea), linking end-diastolic and end-systolic volumes. The PV loop consists of four phases: isovolumetric contraction, ejection, isovolumetric relaxation, and filling. The loop's width corresponds to stroke volume, while the enclosed area represents myocardial oxygen consumption (MVO_2), serving as an indicator of cardiac workload.

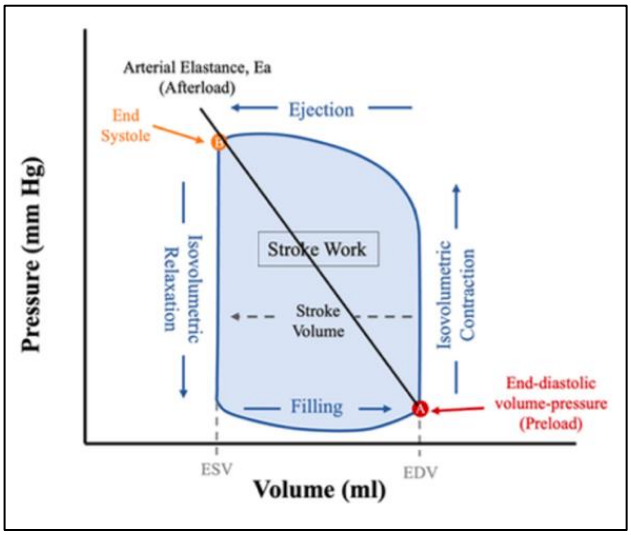


Figure 5. Pressure-Volume (P-V) loop of the LV illustrating the cardiac cycle and key parameters of ventricular function. The loop represents the relationship between pressure and volume during diastole and systole. Point **A** marks end-diastole and reflects preload (end-diastolic volume and pressure), while point **B** marks end-systole, reflecting afterload via arterial elastance (Ea). The shaded area denotes stroke work, and the horizontal span represents stroke volume (EDV – ESV). Phases of isovolumetric contraction, ejection, isovolumetric relaxation, and filling are annotated accordingly.

Time-varying elastance, E(t), is a key measure of cardiac function that remains independent of mechanical load, defined as the ratio of instantaneous ventricular pressure, P(t), to volume, V(t), minus the dead volume (VD) (2), which represents the point below which no pressure is generated (Suga & Sagawa, 1972). End-systolic elastance (Ees), derived from the end-systolic pressure-volume relationship (ESPVR), serves as a load-independent marker of myocardial contractility. An increase in contractility (positive inotropy) shifts the ESPVR leftward and steepens its slope, whereas reduced contractility (negative inotropy) results in a flatter slope, characteristic of a failing heart (Maughan et al., 1984). In HFrEF, a shallower ESPVR makes cardiac output highly sensitive to afterload variations, highlighting the potential benefit of afterload-reducing therapies in improving hemodynamics and clinical symptoms.

$$E(t) = \frac{P(t)}{V(t) - VD} \tag{2}$$

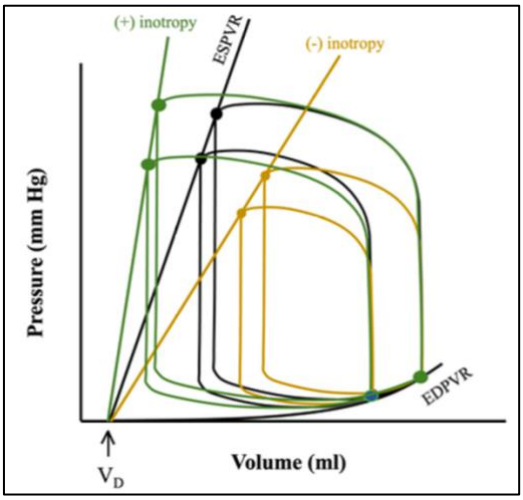


Figure 6. P-V loop under varying preload conditions and contractile states (Ees). Each PV loop is constrained by its respective linear ESPVR, derived from the instantaneous end-systolic pressure-volume points, and the EDPVR, drawn from the corresponding end-diastolic points. The slope of the ESPVR represents Ees, an indicator of intrinsic myocardial contractility, while the x-axis intercept denotes the Vd, the point below which the ventricle is unable to generate pressure.

Diastolic ventricular properties are reflected in the end-diastolic pressure-volume relationship (EDPVR), a nonlinear curve that characterizes ventricular compliance and passive myocardial stiffness (Pfeffer et al., 1991). In advanced heart failure, ventricular dilatation shifts the EDPVR rightward, leading to elevated diastolic pressures for a given volume. Both ESPVR and EDPVR provide critical insights into myocardial tissue properties, serving as key indicators of disease progression and the potential for ventricular recovery following mechanical support.

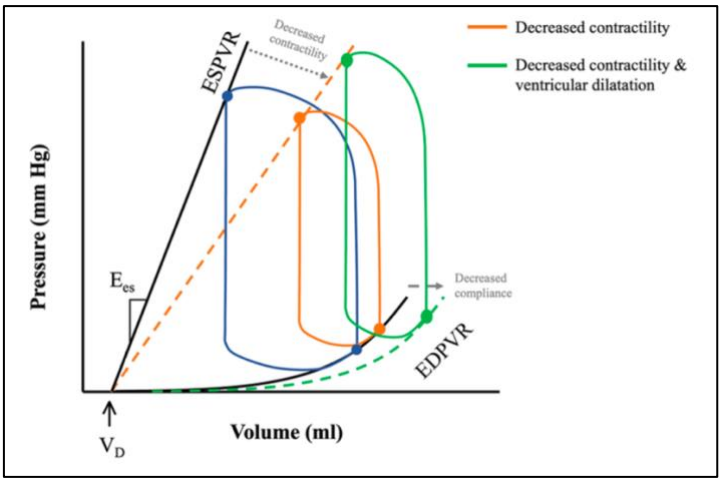


Figure 7. P-V loops in health and disease. ESPVR and EDPVR shift with decreasing contractility and compliance (depicted by grey dotted arrows) during pathological remodeling of the heart. Decreased cardiac contractility in HFrEF shifts ESPVR rightward with a shallower slope (orange dotted line). Progressive ventricular remodeling leads to a rightward shift of the EDPVR (green dotted line) and further downward shifting of the ESPVR, resulting in LV dilation and decreased LV contractility.

3.3.2 Post-LVAD hemodynamics

During LVAD support, blood is continuously diverted from the LV to the aorta, bypassing the normal phases of the cardiac cycle and eliminating isovolumic contraction. This alteration results in a distinct downward and leftward displacement of the PV loop, producing a characteristic triangular shape. The extent of this shift is primarily determined by the LVAD flow rate, which regulates the degree of ventricular unloading (Jain et al., 2019). Higher flow rates contribute to increased cardiac output but also lead to left ventricle-aortic pressure uncoupling, a key indicator of mechanical unloading. The magnitude of unloading is crucial, as it plays a direct role in myocardial remodeling. Following LVAD implantation, there is an immediate reduction in left ventricular end-diastolic pressure (LVEDP), and over time, the EDPVR gradually shifts leftward. Although this adjustment does not completely restore normal myocardial function, it enhances myocardial compliance and alleviates diastolic dysfunction (Burkhoff et al., 2021).

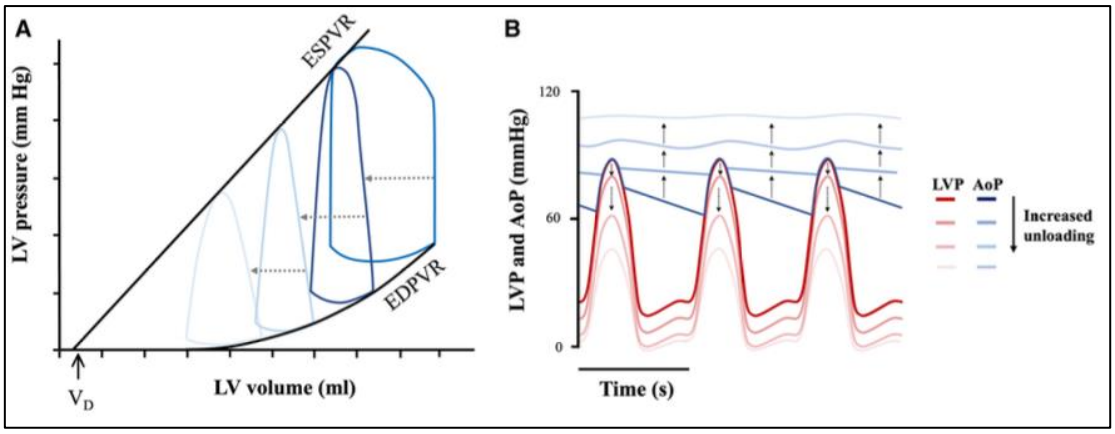


Figure 8. Mechanical circulatory support unloading and effects on cardiac mechanics. (A) Triangular PV loop with progressive leftward and downward shift under mechanical support and (B) LV-aortic pressure uncoupling. LV pressure (LVP—represented by the red theme), and aortic pressure (AoP—represented by the blue theme) progressively uncouple with increased device flow rates.

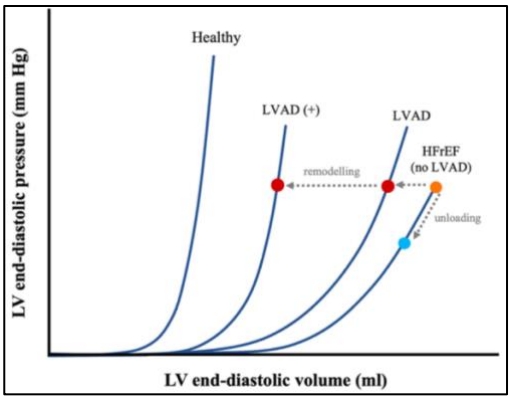


Figure 9. Effect of prolonged mechanical unloading on diastolic function. EDPVR of a healthy vs. HFrEF heart and time-dependent LVAD-associated leftward shifts in EDPVR, with shorter (LVAD)

and longer duration (LVAD+) of unloading. The effect of immediate mechanical unloading on the point of the heart on the EDPVR are also shown (HFrEF diagonal arrow from orange dot to blue dot).

MVO_2 is directly related to the area enclosed by PV loop, which represents the combination of stroke work and potential energy. A larger PV loop area signifies higher oxygen demand (Pamias-Lopez et al., 2023). LVADs contribute to reducing MVO_2 by lowering preload and stroke volume, which in turn decreases myocardial wall stress, as described by Laplace's law. This reduction in workload is particularly advantageous for hemodynamically unstable patients, as it helps prevent ischemic injury.

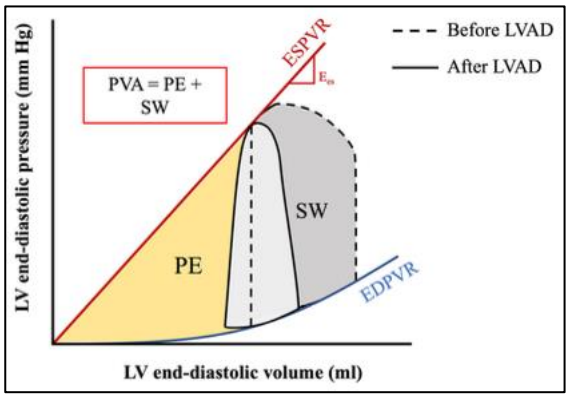


Figure 10. PV area corresponding to oxygen consumption before and after LVAD implantation. The pressure-volume area (PVA) is the sum of stroke work (SW) and potential energy (PE) and represents the total mechanical work of the ventricle per beat. The PVA is directly correlated to the MVO2.

In addition to lowering oxygen demand, LVADs play a crucial role in enhancing myocardial oxygen supply by increasing coronary perfusion pressure. Since coronary blood flow occurs mainly during diastole, it is affected by the pressure difference between the aorta and the left ventricle, quantified as the diastolic pressure-time index (DPTI). By reducing left ventricular diastolic pressure while sustaining or elevating aortic pressure, LVADs facilitate improved diastolic coronary perfusion. Simultaneously, they decrease myocardial workload and systolic left ventricular pressure, thereby reducing the systolic pressure-time index (SPTI), which serves as an indicator of oxygen demand. The balance between myocardial oxygen supply and demand is represented by the DPTI/SPTI ratio, where a higher value suggests enhanced coronary perfusion (Hoffman & Buckberg, 2014).

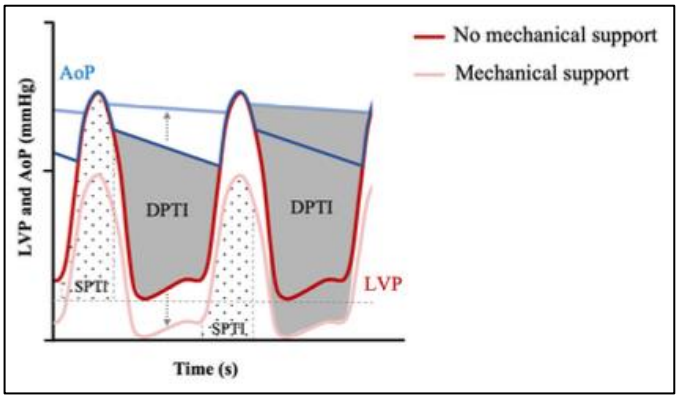


Figure 11. Myocardial O_2 demand (SPTI) and supply (DPTI) with or without mechanical unloading. Modified Wiggers diagram showing progressive mechanical unloading (represented by grey dotted arrow) and uncoupling of LV pressure (LVP-red themed loops) and aortic pressure (AoP-blue themed loops), correlated with increased DPTI (grey overlay) and decreased SPTI (hashed overlay).

3.4 Complications

LVADs are associated with a range of complications contributing to significant morbidity and frequent hospital readmissions (Eisen, 2019; Han et al., 2018). Although LVADs are theoretically beneficial in optimizing myocardial oxygenation, their continuous-flow operation may lead to complications. The lack of pulsatility can interfere with aortic valve opening, potentially increasing the likelihood of coronary artery thrombosis. Additionally, prolonged exposure to non-pulsatile blood flow can trigger structural changes in the coronary vasculature, such as increased collagen deposition and breakdown of the internal elastic lamina, which may progressively impair myocardial perfusion over time (Ambardekar et al., 2018).

Bleeding, particularly of gastrointestinal origin, is among the most common adverse events following LVAD implantation, affecting 15% to 30% of patients within the first year (Chaudhry et al., 2022). Early bleeding is primarily related to the surgical intervention, while late bleeding is often linked to acquired von Willebrand syndrome, chronic anticoagulation therapy, and angiogenesis-related changes. Gastrointestinal bleeding accounts for 60% of all LVAD-associated bleeding episodes, with an incidence varying between 12% and 25% depending on the device type. Risk factors include elevated INR, lower platelet count, history of gastrointestinal bleeding, infections, and destination therapy status (Suarez et al., 2011). Management strategies include proton pump inhibitors, octreotide, omega-3 fatty acids, and temporary anticoagulation modifications, while procedural interventions such as cauterization and arterial embolization may be required in severe cases. Despite various therapeutic approaches, recurrence rates remain high, estimated at 9%.

Thromboembolic events, including pump thrombosis and stroke, have been major concerns in LVAD therapy, though advancements in device design have contributed to a decline in incidence (Chaudhry et al., 2022). Factors contributing to thrombosis risk include suboptimal anticoagulation, turbulent flow, and device geometry. Strict adherence to surgical implantation techniques, optimized anticoagulation regimens, and appropriate pump speed settings are crucial in minimizing thrombosis risk. Stroke remains one of the most severe complications, occurring in 13% to 30% of patients, with ischemic stroke (5.5% annual incidence) being more common than hemorrhagic stroke (3.1%). Embolic sources include thrombus formation in the pump, aortic valve, inflow, or outflow grafts, while hemorrhagic strokes are often related to hypertension, endocarditis, and anticoagulation therapy (Han et al., 2018).

Right heart failure is another common complication following LVAD implantation, occurring in approximately 15% to 25% of patients, with 4% requiring right ventricular assist device (RVAD) support within the first two weeks. It is primarily caused by acute hemodynamic shifts following LVAD activation, leading to increased right ventricular preload, left ventricular unloading, and geometric distortion of the right ventricle (Bouchez et al., 2023). Pre-implant risk factors include elevated pulmonary vascular resistance, right ventricular dysfunction on echocardiography, and high INTERMACS classification. While most cases of right heart failure improve with inotropic support, early RVAD implantation improves outcomes in refractory cases. Late-onset right heart failure, occurring months to years after LVAD implantation in approximately 10% of patients, has been associated with a poor prognosis, with a one-year survival rate of only 38%. Predicting and managing right heart failure remain significant challenges, with treatment options including aggressive diuresis, inotropic therapy, and consideration of heart transplantation in eligible patients.

Aortic insufficiency is an increasingly recognized long-term complication, with over 30% of patients developing moderate to severe aortic regurgitation within two years post-LVAD implantation. The continuous flow generated by LVADs leads to persistent aortic valve closure, promoting commissural fusion and progressive valve dysfunction. This results in blood recirculation within the LVAD circuit, increasing pump workload and exacerbating heart failure symptoms. Optimization of LVAD speed and maintaining some degree of pulsatility have been suggested as protective measures to preserve aortic valve integrity. Surgical interventions, such as aortic valve closure or replacement, may be required in severe cases, but these procedures carry an increased mortality risk. Off-label use of transcatheter aortic valve replacement for managing LVAD-associated aortic insufficiency has been reported, but further studies are needed to evaluate its safety and efficacy (Jorde et al., 2014).

LVAD-related infections, particularly in the driveline, are a leading cause of morbidity, affecting 33% to 43% of patients within the first year of implantation. The driveline exit site serves as a direct

conduit for pathogens, making it the most common site of infection, though infections can also involve the pump pocket or bloodstream. Staphylococcus aureus is the most frequently implicated pathogen, followed by gram-negative bacteria, fungi, and mycobacteria. Risk factors include obesity, diabetes, prolonged hospitalization, prior cardiac surgery, and immune suppression. Infections are associated with increased risks of pump thrombosis and stroke, with hemorrhagic strokes occurring more frequently than ischemic events in the presence of systemic infection. Driveline infections often require aggressive treatment, including oral and intravenous antibiotics, surgical debridement, and, in severe cases, LVAD exchange. Preventive measures such as strict driveline care protocols, sterile dressing changes, and minimizing trauma to the exit site are essential. Despite these efforts, long-term infection risk remains high due to the presence of a percutaneous driveline (B. Long et al., 2019). The development of fully implantable LVADs, which eliminate the need for an external driveline, holds promise for reducing infection-related complications in the future.

4 LVAD Technology Advancements. Past and Present Devices

4.1 Early Conceptualization and Initial Applications

The concept of MCS originated in the mid-20th century with John Gibbons' cardiopulmonary bypass system, initially designed for use in cardiac surgery and later adapted for post-surgical recovery and cardiovascular shock management. Early research focused on total artificial hearts (TAH), with Kolff developing a prototype at the Cleveland Clinic and Liotta advancing similar work in Argentina before joining Baylor's TAH program (Eisen, 2019). Liotta et al. set the foundational milestone in the development of LVADs when they introduced a paracorporeal pulsatile-flow pump powered by an external air system (Liotta et al., 1963). The pump featured Silastic tubing reinforced with Dacron mesh for strength and ball valves for unidirectional blood flow. It was air-driven, synchronized with the cardiac cycle, and placed inside the thoracic cavity. The surgical technique involved cannulation of the left atrial appendage for inflow and the descending aorta for outflow, with the pump fixed to the chest wall and powered by an external air source. This device was designed to offload the left ventricle by diverting blood from the left atrium to the aorta offering temporary or prolonged mechanical support over days or weeks. Experimental work involved 51 canine models to refine the surgical technique and assess the physiological impact of the equipment. The device demonstrated a capacity to effectively reduce left ventricular workload and wall tension while improving coronary perfusion. The first clinical application of the pump was performed on a 42-year-old male with severe congestive heart failure. The LVAD successfully alleviated pulmonary edema and stabilized hemodynamics over four days of use, although the patient ultimately succumbed to complications unrelated to the pump. The device demonstrated that prolonged unloading of the left ventricle could improve cardiac function and systemic circulation. While the study underscored the promise of LVADs, it also revealed significant issues that required further refinement.

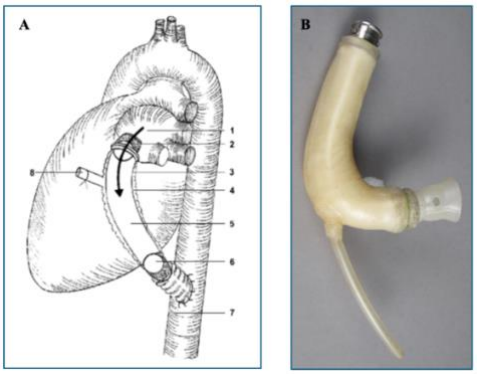


Figure 12. Drawing (A) and clinical prototype (B) developed by Liotta D. at Baylor University, Houston.1: Left Atrium, 2: Inlet Valve, 3: Housing of Silastic reinforced with Dacron Fabric, 4: Air

Chamber, 5: Blood Chamber, 6: Outlet Valve, 7: Descending Aorta, 8: Plastic Tube (Internal Dimension 4mm) for Air Supply.

Liotta's pioneering efforts, in collaboration with DeBakey, provided the foundation for the development of the DeBakey Pump (DeBakey & Kennedy, 1971). Through an iterative process spanning several years, the device evolved from an experimental concept into a more advanced and refined mechanical circulatory support system. Its compact, intrathoracic design allowed for sustained support and minimized complications associated with external devices. The device was used in patients with refractory left ventricular failure, who were unresponsive to medical therapy and in dire need of circulatory support. Clinical outcomes indicated significant improvements in systemic circulation, a reduction in pulmonary edema, and stabilization of cardiac output. Importantly, the pump allowed for partial recovery of the native heart in some cases, serving as a bridge to recovery. However, the device faced challenges, including thrombosis, hemolysis, infections, and limited durability.

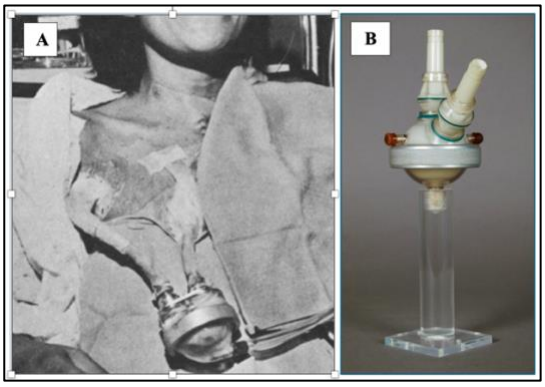


Figure 13. (A) The DeBakey Ventricular Assist Device implanted in a patient and (B) exhibited.

During the 1980s, pulsatile-flow LVADs transfigured MCS by replicating the natural systolic and diastolic phases of the heart, enhancing physiological compatibility and improving outcomes in advanced heart failure. The first major breakthrough came with the development of the Abiomed BVS 5000, designed for short-term biventricular support in acute heart failure. This device received FDA approval in 1992, providing critical stabilization for patients in cardiogenic shock as a bridge to recovery. Shortly after, the Novacor LVAD emerged as one of the first long-term implantable LVADs, demonstrating sustained support for patients with chronic heart failure. The Novacor system was approved by the FDA in 1993 for bridge-to-transplantation use, highlighting its reliability for extended periods of support. At the Penn State University, Dr. William Pierce developed a pneumatic heart assist device, which later became the Thoratec pneumatic VAD, one of the first FDA-approved bridge-to-transplant

(BTT) devices. This technology later evolved into the HeartMate I (Stewart & Mehra, 2014). HeartMate I was a landmark pulsatile-flow LVAD designed for long-term support and was approved by the FDA in 1994. Together, these devices marked a transformative period in the evolution of LVAD technology, establishing a foundation for future innovations in mechanical circulatory support.

4.2 First Generation, Pulsatile-flow LVADs

The development of LVADs has significantly advanced the management of end-stage heart failure, with the evolution of flow dynamics playing a crucial role in improving device performance and patient outcomes. The earliest LVADs utilized pulsatile-flow technology, designed to replicate the natural cardiac cycle by generating rhythmic blood ejections. These devices functioned using diaphragm or pneumatic pumps that mimicked the filling and ejection phases of the native heart. While pulsatile LVADs initially became the standard in mechanical circulatory support, they presented significant limitations, including large device size, mechanical complexity, high energy consumption, and increased risks of infections due to percutaneous drivelines. Their reliance on mechanical valves further predisposed patients to thrombus formation, necessitating stringent anticoagulation protocols.

First-generation LVADs, such as the Novacor and the HeartMate I (IP, VE, and XVE) were pulsatile devices primarily designed for bridge-to-transplantation. These systems employed electromechanical actuation and incorporated Dacron-lined blood-contacting surfaces to mitigate thrombotic risk. However, despite their efficacy in temporarily supporting patients awaiting heart transplantation, these devices had notable drawbacks, including a substantial device footprint, elevated infection rates, hemolysis, and limited long-term durability. Clinical trials, such as the REMATCH study, demonstrated that LVAD therapy provided improved survival compared to optimal medical management, yet complications such as sepsis, bleeding, and mechanical failures remained significant challenges. Over time, these limitations prompted the transition toward continuous-flow LVADs, which offered enhanced efficiency, reduced complication rates, and increased long-term reliability (Lietz et al., 2007).

4.2.1 Abiomed BVS 5000

The Abiomed BVS 5000 has played a pivotal role in the evolution of ventricular assist devices since its introduction in the 1980s and 1990s. Designed as a pneumatically driven, paracorporeal, pulsatile device, it was primarily aimed at providing mechanical circulatory support for bridging patients to recovery, heart transplantation, or further long-term support (Wassenberg, 2000). Its design included a pneumatic dual-chamber system, with an atrial chamber for filling and a ventricular chamber

for pumping, capable of delivering a fixed stroke volume of approximately 80 mL. The BVS 5000 operated asynchronously to the patient's native cardiac rhythm, automatically adjusting to changes in preload and afterload. This adaptability facilitated consistent support without continuous operator input. Connection to the circulatory system was achieved using large-bore atrial and arterial cannulas, externalized to allow for sternal closure post-implantation, while a console provided real-time monitoring and safety adjustments (Morgan et al., 2004).

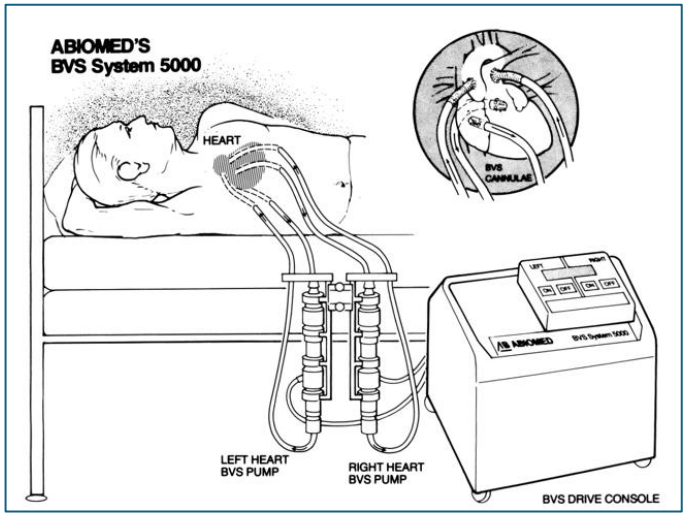


Figure 14. Schematic drawing of the Abiomed BVS 5000 ventricle assist device.

In vitro assessments of the Abiomed BVS 5000 demonstrated that Doppler-controlled preload adjustment (25 mmHg) provided stable flow (5.3 ± 0.7 l/min) with minimal retrograde flow, whereas optical pump height adjustment (35 mmHg) led to high atrial pressures and undetected retrograde flow, highlighting the necessity of Doppler flow monitoring for optimal and stable device performance (Lachat et al., 1999). An experimental study evaluating the Abiomed BVS 5000 in a porcine model of acute myocardial infarction-induced cardiogenic shock demonstrated that, while mean aortic pressure and total flow were comparable to the Gyro pump and Gyro + IABP setups, the BVS 5000 generated significantly higher pulse pressure (48.2 ± 3.3 mmHg) and improved renal arterial blood flow, highlighting its benefits for renal and peripheral circulation (Sezai et al., 2006).

A multi-institutional registry of 420 patients from 60 centers across 15 countries (1987–1994) demonstrated the effectiveness of the BVS 5000, with 55% of post-cardiotomy patients successfully weaned or bridged, 70% of cardiomyopathy patients undergoing transplantation, and an analysis suggesting that ventricular assist may improve outcomes compared to inotropes and IABP (Gray & Champsaur, 1994). A comparative study showed that the Abiomed BVS 5000 outperforms the non-pulsatile Biomedicus pump in postcardiotomy cardiogenic shock, with higher weaning (62% vs. 38%) and survival rates (61.5% vs. 39%), influenced by factors such as younger patient age, shorter resuscitation-to-implantation time, and intraoperative device installation (Minami et al., 1994).

Despite its contributions to advancing mechanical circulatory support, the BVS 5000 has limitations. The absence of active suction mechanisms increased the risk of atrial collapse under low preload conditions, and prolonged support often led to progressive end-organ dysfunction. Device-related complications, such as bleeding and thromboembolic events, remained significant challenges, limiting survival outcomes in some patients.

4.2.2 Novacor

The Novacor represents a pulsatile ventricular assist device that demonstrated efficacy as a bridge to transplantation, with improvements in hemodynamics, myocardial remodeling, and overall survival outcomes compared to the Abiomed BVS 5000 (Pristas et al., 1990). The Novacor system employed a polyurethane blood sac, actuated by a solenoid-driven pump, to generate pulsatile flow with a fixed stroke volume of approximately 70 mL and a flow capacity of up to 8.5 L/min (Wheeldon et al., 2000). Blood entered the device through an inflow cannula implanted in the left ventricle and exited through an outflow cannula connected to the ascending aorta. The pump was powered by an external controller and battery system connected via percutaneous drivelines, which allowed for real-time monitoring and adjustments to the device's performance. Early iterations of the Novacor device used woven polyester conduits, but these were later replaced by gelatin-sealed conduits to reduce embolic phenomena (Dagenais et al., 2001). The system's design advancements, including various operating modes and optimized valve housing designs, have improved flow dynamics and reduced thrombotic risks. Studies highlighted the importance of housing designs like the modified triple sinus, which enhanced washing efficiency and minimized thrombus formation (Sturm et al., 1992). Flow visualization studies revealed that higher beat rates improved surface washing, providing insights for tailored device operation (Woodard et al., 1992).

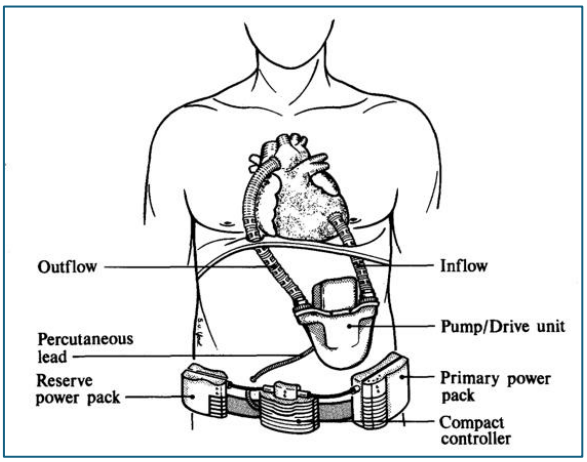


Figure 15. The wearable Novacor LVAD.

In vivo and in vitro testing showed that the Novacor had an 80% reliability for 2-year operation (80% confidence level) through 14.3 years of failure-free system testing, with an estimated mean time to failure (MTTF) exceeding 8.8 years, while ovine experiments with Novacor subsystems, including volume compensators and pump/drive units, have shown long-term durability (Jassawalla et al., 1988). Another study of 58 chronic ovine implants (>7 days) in the Novacor demonstrated that porcine valves exhibited minimal calcification even at 236 days, whereas bovine pericardial valves developed severe calcification and pseudoneointimal proliferation, leading to reduced pump output (Ramasamy et al., 1988).

The Novacor has demonstrated significant hemodynamic and structural benefits in patients with advanced heart failure, particularly those bridged to cardiac transplantation. A study of 16 patients bridged to cardiac transplantation with Novacor support for 2 to 144 days demonstrated significant reductions in total pulmonary resistance and improvements in right ventricular ejection fraction, enabling successful transplantation even in high-risk patients with elevated pulmonary resistance (Gallagher et al., 1991). A hemodynamic study in 10 patients further highlighted that pulmonary vascular resistance, right ventricular stroke work index, and systemic vascular resistance are key determinants of pump output and filling volume, emphasizing the role of right ventricular function and pulmonary resistance in system performance (Miyamoto et al., 1990). Radionuclide angiography and echocardiography showed substantial improvements in left and right ventricular ejection fractions, from 17% ± 7% to 47% ± 19% and from 21% to 32%, respectively, while Doppler echocardiography revealed aortic valve closure during systole in some patients, reflecting the device's impact on ventricular dynamics (Charron et al., 1994). Additionally, in six patients supported for up to 125 days, the Novacor facilitated myocardial reverse remodeling with a 17–54% reduction in left ventricular myocyte cross-sectional area, restoring cell dimensions without evidence of progressive atrophy, confirming effective ventricular unloading while preserving myocardial integrity (Jacquet et al., 1991). The immune and inflammatory responses in heart failure patients supported with the Novacor showed elevated inflammatory markers and suppressed T-cell subsets compared to those receiving medical management, indicating both disease severity and the device's impact on immune homeostasis (Deng et al., 1999). However, prolonged support facilitated neuroendocrine recovery, with normalization of renin, aldosterone, cortisol, and catecholamine levels, although full metabolic recovery required extended support durations (Noirhomme et al., 1999).

The worldwide clinical experience with the Novacor demonstrated its efficacy and reliability as a bridge to transplantation in 768 patients, with 58% successfully transplanted, 41% discharged, and an average support duration of 85 days. While complications such as bleeding (5–10%), infection (5–21%), and cerebrovascular events (5–7%) were noted, the device improved left ventricular function, hemodynamics, and rehabilitation outcomes (Murali, 1999). Introduced in Europe in 1993, the wearable

Novacor, featuring a compact microprocessor-based controller and rechargeable batteries, significantly enhanced patient mobility and quality of life by enabling autonomous function (Robbins et al., 2001). Among 118 patients across 19 centers, with a median implant duration of 115 days, the Novacor demonstrated a 64% overall survival rate and enabled 33% of patients to return home, while infection (14%) and multi-organ failure (6%) were the primary causes of mortality (El-Banayosy et al., 1999).

Explanted Novacor analyses provided insights into thromboembolic risks and tissue responses, revealing that pseudo-intima in inflow conduits was nonadherent and thrombogenic, whereas the outflow conduit exhibited stable collagen structures with smooth muscle cell integration (Houel et al., 1999). Biomaterial composition and conduit rheology influenced these differences, with Dacron inflow and collagen-impregnated Dacron outflow prostheses triggering inflammatory, hemostatic, and fibrinolytic responses that facilitated neovessel development (Fastenau et al., 1999). Thromboembolic complications were a major concern, with a study of 36 Novacor recipients reporting thromboembolic events in 47% of patients, neurologic events in 58%, and microembolic signals in 67%, emphasizing the need for optimized anticoagulation strategies (Schmid, Weyand, et al., 1998). Thrombus deposition studies showed heavier thrombi on the concave side of the inflow valve, correlating with thromboembolic events in 8 of 23 patients and confirming the role of platelet activation and pump dynamics in clot formation (Dewald et al., 1997; Wagner et al., 1993). Infections also significantly impacted survival, with LVAD-related infections reducing transplantation success rates from 85% to 42% (Herrmann et al., 1997). Despite these challenges, advancements in device design and management protocols have successfully reduced bleeding rates to 5–10% and cerebrovascular event rates to 5–7% in newer iterations.

4.2.3 Thoratec

The Thoratec VAD served as the predecessor to the HeartMate (HM) series. Evolving from the early pneumatically driven pulsatile pumps introduced in the 1980s, the Thoratec VAD paved the way for more durable and compact implantable systems, culminating in the development of the pulsatile HeartMate XVE and the subsequent continuous-flow models, HeartMate II and HeartMate 3, which significantly improved device longevity, reduced complications, and enhanced patient mobility.

The device features a pneumatically driven pump that delivers pulsatile blood flow, effectively mimicking the natural cardiac cycle (Farrar, 2000). Its modular design enables univentricular or biventricular support through large-bore cannulas, with inflow cannulas positioned in the heart (e.g., left ventricular apex, left atrial appendage, or left atrium) and outflow cannulas anastomosed to the ascending aorta or pulmonary artery. This setup allows the device to deliver flow rates of 5–7 L/min, meeting the hemodynamic demands of critically ill patients. The blood-pumping chambers and cannulas are constructed from Thoralon (Whittaker & Glanville, 2000). Pneumatic drivers provide alternating

positive and negative air pressures to fill and empty the blood pump at beat rates ranging from 20 to 110 beats per minute. The device predominantly operates in a full-to-empty control mode, dynamically adjusting beat rate and flow output in response to venous return and the body's physiological needs. The system is powered by either a hospital-based pneumatic console or a portable, battery-powered control unit (TLC-II portable VAD driver), enhancing mobility for selected patients. The paracorporeal configuration of the Thoratec VAD simplifies surgical implantation by placing the blood pump on the anterior abdominal wall and connecting it to the heart and great vessels via cannulas that cross the chest wall. This design eliminates the need for abdominal surgery, accommodates a wide range of body sizes, and permits patient ambulation. When biventricular support is required, two pumps can be used in tandem. However, the development of the intracorporeal Thoratec IVAD provided a compact and versatile alternative to large electromechanical LVAD systems, featuring a titanium housing and Thoralon blood sac, controlled via the portable TLC-II VAD driver (Farrar et al., 2000). The TLC-II, an 8 kg pneumatic unit supporting both paracorporeal and implantable Thoratec VADs, enhanced patient mobility and facilitated up to 7 L/min VAD output through multiple power sources, including rechargeable lithium-ion batteries (Farrar et al., 1997).

The Thoratec VAD has been extensively studied for its structural durability, hemodynamic performance, and potential advancements in energy-independent circulatory support. A 14-month study of Thoralon polyurethane blood pumping sacs confirmed their structural integrity, resistance to degradation, and stable physical properties, with no surface erosion or cracking except minor biofilm formation after 336 days, validating their durability for long-term clinical use (Babu et al., 2004). A retrospective study of 28 Thoratec VAD patients found that left ventricular cannulation provided superior hemodynamic support with higher VAD flow at lower preload and better ventricular unloading, though survival was primarily influenced by myocardial recovery, transplant eligibility, and complications rather than cannulation strategy alone (Lohmann et al., 1990). Expanding on its applications, studies on muscle-powered ventricular assist devices (MVADs) assessed the feasibility of using linear contracting skeletal muscle for circulatory support by coupling a porcine latissimus dorsi muscle to a Thoratec VAD via a mechanical-to-hydraulic piston energy converter, with stroke work increasing linearly with preload and achieving a stroke volume of 40 mL at 92 mmHg systolic pressure and 10 mmHg filling pressure, supporting the potential for fully implantable, energy-independent circulatory support as an alternative to cardiac transplantation (Farrar et al., 1994). Further supporting this concept, a study using unconditioned latissimus dorsi muscle in anesthetized goats with a two-stage mechanical-to-hydraulic energy converter linked to a Thoratec VAD found that the largest piston generated the highest force (70.1 ± 10.8 N), the smallest achieved the longest stroke length (4.0 ± 0.7 cm), and the middle-sized piston produced the greatest stroke work (1.2 ± 0.5 J) with an ejected stroke volume of 45 ± 17 mL, highlighting the importance of optimizing energy converter and MVAD actuator

piston ratios to improve efficiency in fully implantable, battery-free circulatory support (Farrar et al., 1995).

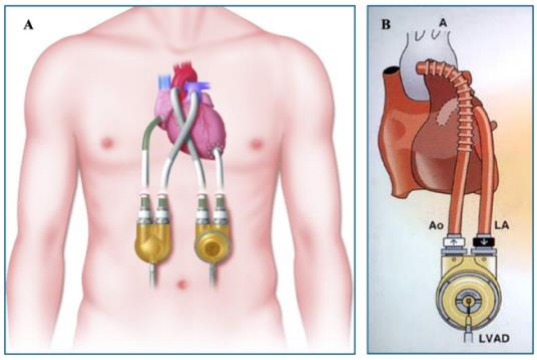


Figure 16. The Thoratec Ventricular Assist Device. A. The Thoratec left and/or right ventricular assist device is positioned paracorporeally on the anterior abdominal wall, with cannulas passing through the chest wall to establish connections between the pump, the heart, and the great vessels. B. LVAD placement with the inflow cannula connected to the left atrium and the outflow cannula connected to the ascending aorta.

The Thoratec VAD has been widely utilized as a bridge to transplantation, with clinical studies evaluating its outcomes across adult and pediatric populations. By October 1991, the Thoratec VAD system had been implanted in 154 patients across 39 centers in 10 countries, with 78% requiring biventricular support, achieving flow rates of 5.0 ± 0.9 L/min (left) and 4.3 ± 0.8 L/min (right), successfully bridging 65% of patients to transplantation after a mean of 17.5 days, resulting in an early post-transplant survival of 84%, overall survival of 54%, and a one-year actuarial survival of 82%, comparable to conventional heart transplantation (Farrar & Hill, 1993). A review of 111 Thoratec VAD patients identified 44 supported for myocardial recovery (mean age 51.9 years) and 67 bridged to transplantation (mean age 41.5 years), with survival rates of 27% and 63%, respectively. Complications included bleeding in 45% of recovery patients and 31% of bridge patients, as well as device-related thromboembolism in 8.1%, while long-term outcomes showed a 10-year actuarial survival of 16% for recovery patients, 22% for bridge patients, and 33% for those successfully transplanted (McBride et al., 1999). Further analysis of 104 Thoratec VAD patients bridged to transplant identified advanced age (>60 years), pre-implant ventilation, and elevated bilirubin as independent predictors of poor survival, with biventricular support associated with worse outcomes compared to LVAD support (El-Banayosy et al., 2000). These findings underscored the necessity of timely VAD implantation before irreversible end-organ dysfunction, particularly in elderly patients. Pediatric outcomes with the Thoratec VAD were found to be comparable to adults, as demonstrated in a retrospective study of 58 children and adolescents, where 60% successfully bridged to transplantation and 10% recovered native heart function (Reinhartz et al., 2001).

4.2.4 HeartMate I

The HeartMate I was a pulsatile-flow LVAD, available as either an implantable pneumatic (IP) or a vented electric (VE) device, featuring a polyurethane blood sac within a rigid titanium shell, controlled by an electro-pneumatic driver to generate stroke volumes of approximately 83 mL per beat and flow rates up to 10 L/min. Unidirectional flow was ensured by tilting-disk mechanical valves, while its textured blood-contacting surface of sintered titanium microspheres promoted pseudoneointima formation, reducing the need for systemic anticoagulation. The device was implanted intracorporeally in the peritoneal cavity, with inflow cannulation at the left ventricular apex and outflow cannulation to the ascending aorta. It was powered via an external console connected through a driveline, allowing portable pneumatic drivers for limited mobility but posing a risk of infection at the driveline exit site. Postoperative management focused on hemodynamic monitoring, infection prevention, and individualized anticoagulation strategies (Dowling et al., 2004).

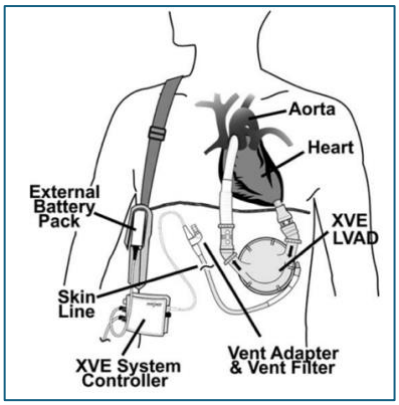


Figure 17. The HeartMate XVE system with cannulation.

Preclinical and experimental studies have further elucidated the mechanisms underlying the success of HeartMate LVADs. Computational modeling has demonstrated that the device's flow dynamics minimize shear stress, reducing hemolysis and thrombus formation (Chiu et al., 2014). Transesophageal echocardiographic studies have shown immediate reductions in left ventricular dimensions after device implantation indicating effective ventricular unloading (Estep et al., 2010). Histological analyses revealed decreased markers of acute myocyte damage, such as contraction band necrosis, although myocardial fibrosis increased over time, reflecting altered loading conditions rather than true myocardial recovery (McCarthy et al., 1995).

Small-scale studies also highlight HeartMate I impact on physiological recovery. The hemodynamic improvements achieved with HeartMate LVADs are profound and immediate. In a study of 19 patients, LVAD support significantly improved cardiac index (1.6 ± 0.2 to 3.2 ± 0.9 L/min/m², $p = 0.0002$), reduced left atrial pressure (22.9 ± 9.5 to 8.0 ± 5.5 mmHg, $p = 0.003$) and decreased pulmonary vascular resistance (5.2 ± 2.6 to 2.0 ± 0.8 Wood units, $p = 0.004$) (McCarthy et al., 1994).

Inhaled nitric oxide reduced pulmonary vascular resistance by over 20% in LVAD patients, with the variable flow mode mitigating left atrial pressure increases (Hare et al., 1997). Post-LVAD, the incidence of de novo monomorphic ventricular tachycardia was significantly elevated (4.5 times more likely), emphasizing the need for vigilant electrolyte management (Ziv et al., 2005). In addition to hemodynamic stabilization, HeartMate LVADs significantly reduce neurohormonal activation. A study of 13 patients found a 92% reduction in plasma renin activity (57 ± 56 to 3 ± 3 ng/mL/h, $p < 0.001$) and a 79% decline in norepinephrine levels (2,953 ± 1,457 to 518 ± 290 pg/mL, $p < 0.001$) during device support (K. B. James et al., 1995). A study at Baylor College of Medicine and Texas Heart Institute demonstrated that prolonged HeartMate LVAD support significantly reduces myocardial fibrosis by 82%, promoting uniform reverse remodeling and improved cardiac function in end-stage cardiomyopathy patients bridged to transplantation (Bruckner et al., 2000).

Clinical studies have evaluated the survival benefits, and long-term outcomes of HeartMate LVADs in both bridge-to-transplant and destination therapy settings. In a multicenter study of 34 patients, the HeartMate 1000 IP LVAD achieved a 65% survival-to-transplantation rate, with 80% of transplanted patients successfully discharged, while control patients without device support experienced 100% mortality within 77 days (Frazier et al., 1992). In a retrospective analysis comparing intravenous inotrope therapy with HeartMate LVAD support in status 1 transplant patients, LVAD use resulted in better clinical and metabolic profiles at transplantation, significantly fewer post-transplant complications, including renal failure (16.7% vs. 52.6%) and right heart failure (5.6% vs. 31.6%), and higher event-free survival (55.6% vs. 15.8%, $p < 0.05$), despite higher overall hospital costs (Bank et al., 2000). In a multicenter trial of 280 candidates, the HeartMate VE LVAD reduced pre-transplant mortality from 67% to 29% ($p < 0.001$), improved one-year post-transplant survival to 84% versus 63% in controls ($p = 0.0197$), and provided an average support duration of 112 days, with significant reductions in bilirubin (1.2 to 0.7 mg/dL) and creatinine (1.5 to 1.1 mg/dL) (Aaronson et al., 2002). A Japanese multicenter trial of the HeartMate VE LVAD reported mean support durations of 478 days (range: 390–575 days) and a one-year survival rate of 100% in device-supported patients (Omoto et al., 2005). An analysis of 377 HeartMate I LVAD recipients found that centers with higher destination therapy implant experience had significantly better one-year survival rates (67.4% vs. 47.8% for ≤ 4 vs. >9 implants, $p = 0.009$), though center volume was not an independent predictor when adjusted for preoperative risk (Lietz et al., 2009). The reliability of HeartMate LVADs has improved significantly over time. A review of 277 devices implanted between 1991 and 2002 reported a marked decline in device failures after 1998 (Navia et al., 2002). The Novacor Vascutek conduit further reduced stroke risk, while the textured surfaces of the HeartMate devices minimized thromboembolic complications (Kaplon et al., 1999).

Comparative studies have highlighted distinct features and outcomes of early first HeartMate devices. A study of 48 patients compared emergency versus elective LVAD implantation (40 Novacor, 8 HeartMate), showing lower bridge-to-transplantation rates (22% vs. 78%, $p < .01$) and higher bleeding complications (66% vs. 30%, $p < .01$) in emergency cases (Schmid, Deng, et al., 1998). The Cleveland Clinic experience with 205 LVADs (Novacor and HeartMate) reported 85% survival to transplantation and higher one-year post-transplant survival for HeartMate-supported patients (92% vs. 78%) (Kasirajan et al., 2000). Similar survival benefits were observed in a study of 264 patients using HeartMate and Novacor devices, reporting a 69% overall survival-to-transplantation rate and a significant reduction in waiting list mortality (Navia et al., 2002). A comparison of the HeartMate VE LVAD and the Novacor system showed lower thromboembolic risks with HeartMate VE (neurologic dysfunction: 27%, thromboembolism: 12%) versus Novacor (41% neurologic deficits), attributed to HeartMate's textured surface requiring minimal anticoagulation, while both devices had similar survival to transplantation (70% vs. 78%), but Novacor exhibited greater long-term reliability (>3 years vs. 1 year for HeartMate VE) (Pasque & Rogers, 2002). A study of 245 patients undergoing LVAD implantation (77% HeartMate, 23% Novacor) identified early RV failure requiring RVAD support in 9% of cases, with significant predictors including preoperative circulatory support (OR 5.3), female gender (OR 4.5), and nonischemic cardiomyopathy (OR 3.3), while elevated pulmonary artery pressure and pulmonary vascular resistance were not associated with RVAD use (Ochiai et al., 2002). A UNOS registry analysis of 1255 HeartMate and 154 Novacor LVAD recipients as a bridge to transplant showed similar one-year survival rates between devices ($HR = 1.49$, $p = 0.127$), but HeartMate recipients had significantly better five-year survival ($HR = 1.53$, $p = 0.043$). Posttransplant infection and rejection rates were comparable between the two devices after adjusting for patient demographics and comorbidities (Shuhaiber et al., 2009). Another study of 231 patients found no significant difference in T-cell sensitization between HeartMate and Novacor devices ($P = 0.8$), with sensitization driven by perioperative factors like transfusions and baseline PRA levels. Long-term LVAD support, using devices like the HeartMate and Novacor, significantly alters myocardial remodeling by reducing fibrosis through phenotypic shifts in mast cells from chymase-positive to chymase-negative, accompanied by decreased levels of fibrogenic mediators such as bFGF and HSP-47, promoting extracellular matrix remodeling and improved cardiac function (Akgul et al., 2004; Skrabal et al., 2004). Finally, a retrospective review with over 60 VAD implantations from The Penn State showed two-thirds successfully bridged to transplant, with the HeartMate 1000 IP offering better portability and quality of life compared to the Thoratec device, emphasizing the importance of early implantation and meticulous perioperative management (Mavroidis et al., 1999).

One study focused on thromboembolic risks associated with HeartMate systems. These surfaces promote neointimal formation, minimizing the need for systemic anticoagulation and reducing thromboembolic complications to 0.2 episodes per patient-year (Rose et al., 1994). These findings were

reinforced by Pasque et al. who noted that the HeartMate system's reduced reliance on systemic anticoagulation made it particularly suitable for patients at high risk of bleeding (Pasque & Rogers, 2002). Despite benefits, the HeartMate LVAD was associated with complications, including thromboembolic events and infections. Thromboembolic events were rare, with an incidence of 0.2 events per patient-year (Rose et al., 1994). A study involving 57 patients supported by the HeartMate LVAD across 11 U.S. centers reported rare thromboembolic complications, with only two patients (3.5%) experiencing cerebrovascular events (Rose et al., 1994). Adjunctive therapies like vitamin K and aprotinin significantly reduced complications in HeartMate LVAD patients, with vitamin K lowering nonsurgical bleeding from 25.9% to 5.1% and aprotinin halving RVAD use, reducing perioperative mortality ($p = 0.05$), and decreasing blood loss and transfusion requirements despite a transient rise in postoperative creatinine levels (Goldstein et al., 1995; Kaplon et al., 1999). HeartMate's higher infection risks make it less suitable for patients with prior infections, whereas the anticoagulation requirements of the Novacor device pose risks for patients with bleeding tendencies. Notably, intraperitoneal device placement was associated with a lower incidence of device-related infections (14%) compared to extraperitoneal placement (46%, $p = 0.025$) (Wasler et al., 1996).

HeartMate LVADs have been instrumental in improving the quality of life and functional capacity of patients with end-stage heart failure. Advances in device technology, such as the introduction of portable and battery-powered models, have extended support durations while improving patient mobility and quality of life (Tamez et al., 1997). Similarly, the HeartPak portable driver demonstrated comparable pump flow indices to the conventional HeartMate 1000 driver while providing enhanced mobility and convenience (Tamez et al., 1997). A longitudinal study of 78 patients found that physical, occupational, and psychosocial quality-of-life measures remained stable or improved over one year of LVAD support (Grady et al., 2004).

The REMATCH trial in 2001 was the landmark study that established the clinical utility of the HeartMate I and laid the foundation for modern LVAD therapy (Rose et al., 2001). The trial showed that LVAD therapy reduced all-cause mortality by 48% ($p = 0.001$) and achieved one-year survival rates of 52% compared to 25% for optimal medical management ($p = 0.002$). The HeartMate vented electric (VE) LVAD used in the trial enabled these outcomes despite high complication rates, including infections (41% of deaths) and device malfunctions (17% of deaths). Nevertheless, LVAD patients exhibited marked improvements in functional status, transitioning from NYHA class IV to class II, and spent significantly more time alive and outside the hospital during follow-up (340 vs. 106 days). A subset analysis of the REMATCH trial further highlighted the benefits of LVAD therapy in patients receiving inotropic support at randomization, with one-year survival rates of 49% compared to 24% in the optimal medical management (OMM) group ($p = 0.0014$) (Stevenson et al., 2004). These patients

also spent significantly more time outside the hospital with LVAD support (255 vs. 105 days), while outcomes for patients not on inotropes showed no significant differences.

Despite its transformative potential, the REMATCH trial revealed challenges with complications. Neurological events, including stroke, were significantly higher in the LVAD group (42 vs. 4 events, $p < 0.001$) (Lazar et al., 2004). However, LVAD therapy reduced the combined risk of stroke or death by 44% ($p = 0.002$), with Kaplan-Meier analysis confirming substantial survival benefits despite a stroke rate of 16%, primarily occurring early postoperatively. Device limitations were also evident, with a system failure rate of 0.13 per patient-year and freedom from replacement at 87% after one year and 37% after two years (Dembitsky et al., 2004). Adverse event rates were higher in the LVAD group (risk ratio 2.29; 95% CI: 1.85–2.84), though non-septic patients exhibited better survival outcomes (58% vs. 48% freedom from sepsis at one and two years).

Following the introduction of the HeartMate XVE model, significant improvements in LVAD performance and patient outcomes were achieved. The XVE model featured reinforced inflow valves, redesigned outflow grafts, updated percutaneous leads, and advanced Opti-Fill software, all of which enhanced durability and reduced failure rates (J. W. Long et al., 2005). These technological advancements, paired with improved infection control and perioperative care, led to a one-year survival rate of 61% for destination therapy patients, an eightfold reduction in sepsis-related deaths (risk ratio 0.12), and a 61% decrease in overall adverse events compared to the REMATCH cohort.

Design enhancements in the HeartMate XVE significantly improved reliability compared to the earlier HMI model (Patel et al., 2008). Martin et al. reported that major device malfunctions decreased from 36 in the HMI to 6 in the XVE group ($p = 0.0003$), with freedom from malfunction at 1 year increasing from 76% ± 6% to 97% ± 2% ($p < 0.001$) (Martin et al., 2006). Another study by Lietz et al. analyzed post-REMATCH outcomes in 280 XVE patients, reporting a 1-year survival of 56% and an in-hospital mortality rate of 27%, with leading causes of death being sepsis, right heart failure, and multiorgan failure (Lietz et al., 2007). Risk stratification demonstrated 1-year survival rates of 81% for low-risk, 62% for medium-risk, 28% for high-risk, and 11% for very high-risk patients, emphasizing the importance of early referral and appropriate candidate selection.

4.2.5 Berlin Heart EXCOR

The Berlin Heart EXCOR is a paracorporeal pulsatile VAD developed in the late 1980s and early 1990s and used extensively as a bridge to transplantation and, in some cases, as a bridge to recovery. The device is unique for its versatility in supporting both pediatric and adult patients, with its pediatric application receiving FDA approval in 2011.

The EXCOR system consists of extracorporeal pneumatic pumping chambers connected to the heart and great vessels through inflow and outflow cannulas. The EXCOR Adult system offers blood pumps in multiple sizes, including 50, 60, and 80 ml volumes, allowing for optimal patient-specific support (https://www.berlinheart.de/en/medical-professionals/excorr-adult/). The pumps feature a transparent polyurethane casing that enables visual inspection to assess filling and detect potential deposits. A flexible triple-layer membrane, incorporating graphite powder between layers, enhances safety by minimizing friction. The blood-contact surfaces are designed with an ultra-smooth, flow-optimized structure and coated with Carmeda BioActive Surface to improve blood compatibility. Additionally, the system includes a safe de-airing mechanism via a designated port, while integrated valves at both the inflow and outflow sections ensure unidirectional blood flow. The blood pumps are available with either tri-leaflet polyurethane valves or bileaflet carbon valves, providing flexibility in clinical application.

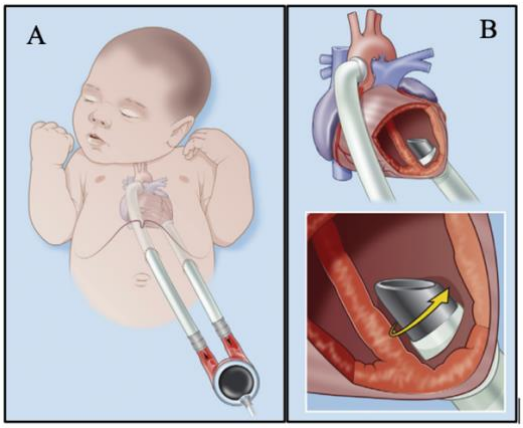


Figure 18. Berlin Heart EXCOR Pediatric. (A) Demonstration of the external pneumatic pumps connected to cannulas inserted into the heart and great vessels of a pediatric patient. (B) Detailed views of the inflow and outflow cannula placement in the heart.

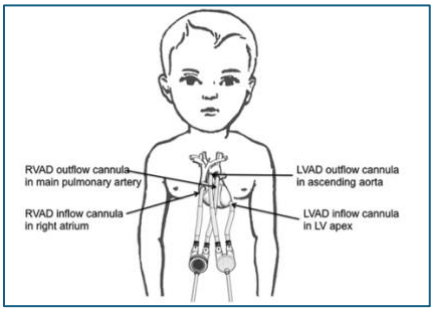


Figure 19. Cannulation for BiVAD in a child.

A study using a novel lumped parameter network to model Berlin Heart EXCOR VAD mechanics demonstrated that increasing systolic pressure and time improved device output, while operating the device at a rate higher than the native heart reduced variability in LV interactions, optimizing cardiac offloading and maintaining output (Yuan et al., 2022). In a computational study

modeling EXCOR support in infants with single-ventricle Norwood physiology, increasing device volume and rate improved cardiac output but did not enhance oxygen delivery, whereas atrial EXCOR optimized cardiac loading in diastolic dysfunction and ventricular EXCOR reduced myocardial stress in milrinone-treated patients, underscoring the model's adaptability for refining BH configurations in diverse clinical scenarios (Yuan et al., 2023).

Clinically, the Berlin Heart EXCOR has been pivotal in treating pediatric heart failure patients who have limited options for mechanical circulatory support. Studies have demonstrated its efficacy in stabilizing hemodynamics and improving survival rates in pediatric patients awaiting heart transplantation (Adachi & Fraser, 2013; Zafar et al., 2021). In a systematic review of 18 studies, mortality rates ranged from 6.3% to 38.9%, transplantation rates from 37.0% to 72.5%, and successful weaning rates from 0.0% to 20.7%, with worse outcomes observed in children under one year of age and those requiring biventricular assist support (Rohde et al., 2019). A single-center study of 94 children supported with EXCOR between 1990 and 2009 reported significant improvements in survival and discharge rates over time, particularly in infants, due to reduced thrombus formation and extended support duration (Hetzer et al., 2011). A larger study of 122 pediatric patients supported with EXCOR between 1990 and 2013 reported a median implantation duration of 63.6 days, with 56 children undergoing heart transplantation and 18 achieving myocardial recovery (Hetzer et al., 2016). For neonates, outcomes have improved dramatically. In a study of 18 infants under one year old supported with EXCOR between 1992 and 2004, survival increased from 0% (1992–1998) to 70% (1999–2004) due to advancements in cannulas, anticoagulation, and perioperative management (Stiller et al., 2005). Another single-center study of 68 pediatric patients up to 18 years old supported with EXCOR between 1992 and 2005 reported a mean support duration of 35 days, with 62% surviving to transplantation or weaning (Hetzer et al., 2006). A multicenter cohort of 204 U.S. children supported with EXCOR across 47 centers between 2007 and 2010 found that 75% survived to transplantation or recovery. However, 29% experienced neurological dysfunction, with smaller patient size, renal dysfunction, hepatic dysfunction, and biventricular support associated with higher mortality (Almond et al., 2013). In the UK, a 7-year study across two pediatric heart transplant centers demonstrated that EXCOR successfully bridged 84% of 102 children to transplant. Independent risk factors for mortality included stroke, ventilation dependence, and non-dilated cardiomyopathy, while overall pediatric transplant numbers remained unchanged (Cassidy et al., 2013). In a multicenter cohort study of 247 pediatric patients implanted with the Berlin Heart EXCOR in the United States between 2011 and 2015, the success rate was 77%, lower than the 90% reported in the original Investigational Device Exemption trial, while bleeding and stroke rates remained similar at 41% and 33%, respectively (Jaquiss et al., 2017). A recent study from the ACTION registry, covering 72 pediatric patients supported with EXCOR from 2018 to 2020, showed improved outcomes compared to a historical cohort (n=320, 2007–2014). The success rate increased from 76% to 86%, with a 44% reduction in stroke and a 40% decrease in pump exchanges,

likely due to advancements in patient selection, anticoagulation strategies, and collaborative care practices (Zafar et al., 2021).

Neurological complications are a major concern. A study of 204 children implanted with EXCOR across 47 centers between 2007 and 2010 found that 29% experienced neurological events, primarily ischemic strokes occurring early during support, making neurological injury the leading cause of death (Jordan et al., 2015). Similarly, a study at Bambino Gesù Children's Hospital found that 36% of 25 children developed brain injuries, with lower weight at implantation significantly associated with risk (Polito et al., 2013). A European Registry cohort of 230 pediatric patients under 19 years old supported with EXCOR between 2011 and 2021 reported a 20% incidence of cerebrovascular accidents, with 70.9% occurring within 90 days post-implantation (Rohde et al., 2022). Immunological complications have also been observed. A study of 13 pediatric patients supported with EXCOR between April 2005 and August 2011 found that 69% developed new anti-HLA antibodies, though the immediate clinical impact was limited (O'Connor et al., 2013).

4.3 Second Generation, Continuous-flow LVADs

Pulsatile-flow devices have largely been replaced by second-generation continuous-flow LVADs, which offer smaller sizes, fewer moving parts, greater energy efficiency, and improved long-term outcomes compared to their predecessors (Atluri & Acker, 2010). These continuous-flow devices have been associated with significantly higher survival rates, particularly in elderly patients requiring long-term circulatory support. Studies have reported a 1-year survival of 36% with non-pulsatile devices compared to 15% with pulsatile systems, while 2-year survival rates were 26% versus 12%, respectively (Drews et al., 2010). Furthermore, non-pulsatile devices have demonstrated superior durability, allowing a greater proportion of patients to be supported beyond one and two years, contributing to extended survival and improved quality of life (Goodman et al., 2022). Despite these advantages, the transition to continuous-flow LVADs has raised concerns regarding the loss of pulsatility and its potential vascular consequences. The absence of a physiological pulse has been implicated in endothelial dysfunction, an increased risk of aortic insufficiency, and a higher incidence of gastrointestinal bleeding due to the formation of arteriovenous malformations (G. S. Allen et al., 1997).

Among continuous-flow LVADs, two primary designs have emerged: axial-flow and centrifugal-flow pumps, each with distinct hemodynamic properties. Axial-flow pumps utilize a helical impeller that propels blood in the direction of the rotational axis, generating a continuous, non-pulsatile flow. These devices operate at high rotational speeds, typically between 8,000 and 15,000 revolutions

per minute (rpm), and exhibit a steep pressure-flow relationship, making them more sensitive to changes in afterload.

The governing equation for axial-flow pumps is based on the Euler turbomachinery equation:

$$\mathrm{H} = \frac{U_2 V_{u2} - U_1 V_{u1}}{g} \tag{3}$$

where H represents the generated head, U is the impeller tip speed, and V_u is the tangential velocity of blood at the inlet (1) and outlet (2).

Because axial-flow devices function at high speeds to maintain adequate blood flow, they generate significant shear stress, which increases the risk of hemolysis and thrombosis. Additionally, these devices are more prone to suction events in cases of low preload, which can collapse the left ventricle and lead to complications such as arrhythmias. Due to their high dependence on preload and afterload, axial pumps may struggle to maintain stable flow under fluctuating physiological conditions (Moazami et al., 2013).

Centrifugal-flow LVADs function by generating radial blood flow perpendicular to the axis of rotation. Instead of relying on a linear impeller, these devices use a spinning disk to create centrifugal force, redirecting blood at a 90-degree angle.

Their design follows the Bernoulli principle, where the impeller generates a centrifugal force given by:

$$F = m \cdot r \cdot \omega^2 \tag{4}$$

where F is the centrifugal force, m is the blood mass, r is the radius of rotation, and ω is the angular velocity of the impeller.

Centrifugal pumps generally operate at lower rotational speeds, typically between 2,000 and 6,000 rpm, and exhibit a flatter pressure-flow curve, making them less sensitive to afterload changes. This reduced sensitivity allows for more stable hemodynamic performance, particularly in patients with fluctuating vascular resistance. Additionally, centrifugal pumps generate some degree of pulsatility due to their inherent preload sensitivity, which may provide physiological advantages in terms of vascular adaptation (Moazami et al., 2013).

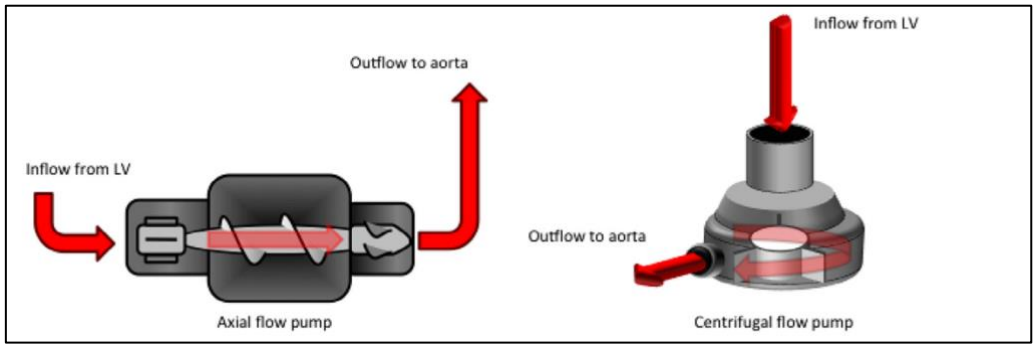


Figure 20. Continuous-flow LVADs classified as either (A) axial-flow or (B) centrifugal-flow (Lim et al., 2017).

The flow rate Q for both axial and centrifugal LVADs can be described using the standard pump performance equation:

$$Q = K(H - H_{loss}) \tag{5}$$

where K is the flow coefficient and H_{loss} represents hydraulic losses due to friction and turbulence.

Axial-flow pumps compensate for hydraulic losses by increasing rotational speeds, which exacerbates shear stress and hemolysis, whereas centrifugal pumps maintain a more stable energy profile with lower dissipation.

Clinical studies comparing axial and centrifugal LVADs have demonstrated key differences in patient outcomes. While both types of devices provide durable circulatory support, axial-flow LVADs have been associated with a higher incidence of adverse events, including pump thrombosis and gastrointestinal bleeding, largely due to elevated shear stress. A retrospective analysis of the IMACS Registry examined 16,286 LVAD recipients from 4 collectives and 24 hospitals, comparing outcomes between axial and centrifugal continuous-flow devices. While survival rates were similar, centrifugal-flow LVADs were associated with lower rates of gastrointestinal bleeding and hemocompatibility-related adverse events, highlighting the ongoing transition from axial to centrifugal pumps in mechanical circulatory support (Goldstein et al., 2019). Furthermore, axial pumps tend to generate higher suction forces at low flow conditions, increasing the risk of ventricular collapse, while centrifugal pumps maintain a more stable flow pattern, reducing the likelihood of suction events. The shift toward centrifugal pumps in modern LVAD therapy has been supported by these advantages, leading to improved durability and mechanical longevity.

Despite the superior performance of centrifugal pumps, the loss of physiological pulsatility in all continuous-flow LVADs remains a concern. One of the key limitations of continuous-flow LVADs

has been their altered preload-afterload relationships. Unlike the native heart, which adjusts ventricular output dynamically, continuous-flow devices exhibit lower preload sensitivity and higher afterload dependence. Axial-flow devices, in particular, have greater preload dependency, making them more susceptible to flow variations and suction events. Centrifugal pumps, with their flatter pressure-flow relationships, provide more consistent hemodynamic performance, making them the preferred choice in patients with fluctuating loading conditions.

Among continuous-flow LVADs, centrifugal pumps have emerged as the preferred choice due to their enhanced hemodynamic stability, lower shear stress, and improved biocompatibility. Ongoing innovations in impeller geometry, inflow cannula positioning, and speed modulation algorithms will continue to refine these devices, ensuring better long-term outcomes for patients with advanced heart failure. Table 3 provides a summary of the differences between axial- and centrifugal- flow pumps.

Table 3. Differences between axial- and centrifugal-flow LVADs

Feature	Axial-Flow LVADs	Centrifugal-Flow LVADs
Mechanical Design	Rotating helical impeller to propel blood along the axis of rotation (inline flow)	Spinning impeller to generate radial blood flow redirected at a 90-degree angle
Flow Characteristics	Higher rotational speeds (8,000–15,000 rpm), steep pressure-flow curves	Lower rotational speeds (2,000–6,000 rpm), flatter pressure-flow curves
Preload Sensitivity	Highly sensitive to preload, prone to suction events in hypovolemia or right heart failure.	Better preload sensitivity, reducing likelihood of left ventricular collapse and suction events.
Afterload Sensitivity	Highly sensitive to afterload; increased systemic vascular resistance impacts flow rates.	Less affected by afterload changes, allowing for more stable hemodynamics.
Hemocompatibility and Shear Stress	Generates higher shear stress, increasing risk of hemolysis, platelet activation, and GI bleeding.	Magnetically or hydrodynamically levitated impellers reduce shear stress and thrombogenic complications.
Risk of Suction Events	More prone to suction events due to higher preload sensitivity.	Exhibit better preload sensitivity, minimizing suction risk.
Pulsatility and Physiological Adaptation	Provides continuous non-pulsatile flow, leading to vascular remodeling and aortic valve fusion.	Some models (e.g., HeartMate 3) incorporate artificial pulse to improve vascular adaptation.
Durability and Wear	Relies on mechanical bearings, leading to wear, pump thrombosis, and more frequent replacements.	Utilize magnetically or hydrodynamically levitated impellers, eliminating mechanical contact and reducing wear.
Clinical Outcomes	Higher rates of pump thrombosis, hemolysis, and bleeding complications requiring aggressive anticoagulation.	Lower rates of thrombotic events and better long-term survival, making them preferred for modern support.

4.4 Axial-flow LVADs

4.4.1 HearMate II

Introduced in the early 2000s the HeartMate II marked a paradigm shift in LVAD technology by transitioning from pulsatile-flow to continuous-flow mechanics. Unlike its pulsatile predecessors, the HeartMate II employed an axial-flow pump with a single rotating impeller that continuously propelled blood from the left ventricle to the ascending aorta reducing overall complexity (Griffith et al., 2001). The absence of a pusher plate or diaphragm allows the device to achieve a much smaller size. The use of continuous-flow mechanics also enhances energy efficiency, allowing for longer battery life and portability. The HeartMate II was designed for long-term use in both bridge-to-transplantation and destination therapy settings.

The pump housing of the HeartMate II is made of titanium. Titanium's use ensures the structural integrity of the device over prolonged periods and minimizes the risk of adverse reactions. The impeller, the rotating component of the axial-flow pump, is reinforced by bearings that are blood-lubricated, eliminating the need for mechanical bearings or external lubrication systems. This design reduces friction, wear, and heat generation, enhancing the pump's operational lifespan and reliability. The inflow and outflow cannulas, which connect the pump to the heart and aorta, are lined with textured surfaces made from titanium microspheres. The inflow cannula is typically inserted into the apex of the left ventricle, and the outflow cannula is connected to the ascending aorta, facilitating seamless blood flow. The diaphragm and seals within the pump are constructed from flexible polymers. These materials are critical for maintaining a secure seal between the blood-contacting components and the mechanical parts of the pump, preventing blood leakage and ensuring the device's efficient operation. Additionally, the percutaneous driveline, which connects the internal pump to the external controller and power source, is coated with high-strength silicone and polyurethane.

Surgically, the HeartMate II was implanted intraperitoneally, simplifying the procedure compared to larger pulsatile devices. Its smaller size and simplified mechanics enabled broader applicability, while continuous-flow operation provided hemodynamic stability with flow rates of up to 10 L/min minute. Patients required lifelong anticoagulation, typically with warfarin, to prevent thromboembolic complications, as the device's continuous flow eliminated natural pulsatility, which raised concerns about long-term vascular and end-organ effects.

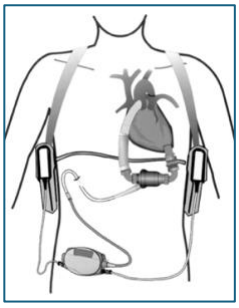


Figure 21. Battery-powered HeartMate II LVAD System.

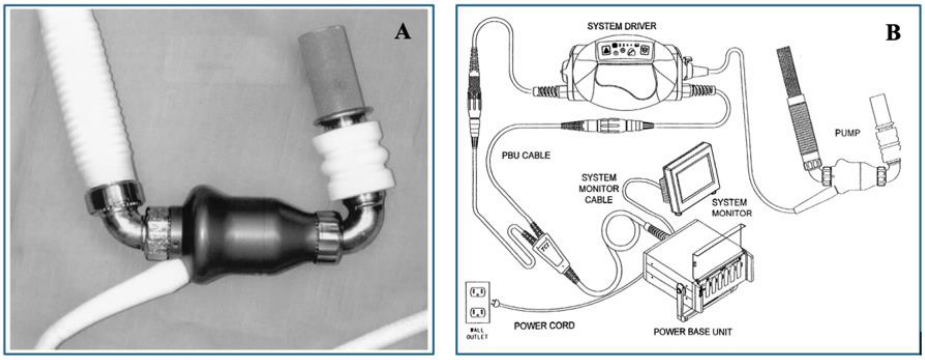


Figure 22. (A) HeartMate II axial flow pump with inlet (right) and outlet (left) conduits. (B) Tethered configuration includes an AC power source and power base unit that recharges the batteries, powers the system driver, and supports the monitor screen.

Hemodynamic optimization of the HeartMate II has been a focus of several studies evaluating flow dynamics, thromboembolic risk, and device durability. A computational fluid dynamics study demonstrated that anterior LVAD cannula placement resulted in more stable flow and reduced wall stress, whereas lateral positioning led to increased turbulence (Karmonik et al., 2012). In another clinical study of 78 HeartMate II patients, an outflow cannula-to-aortic angle of less than 37.5°, an outflow graft anastomosis diameter below 1.5 cm, and lower LVAD speed were associated with an increased stroke risk of 15.4% within one year (Kassi et al., 2023). An analysis of 183 explanted HeartMate II bearings from 181 patients with an average support duration of 363 ± 349 days demonstrated minimal wear (0.59 ± 0.37 μm/year), with an estimated bearing lifespan of 27 to 269 years, confirming that bearing wear is not a limiting factor for long-term device support (Sundareswaran et al., 2013). A retrospective study of 57 HeartMate II patients found that silicone driveline exit site interfaces significantly reduced infection rates (1.7% vs. 20%, $p = 0.026$) and exhibited smoother surfaces with less inflammation compared to velour interfaces, suggesting a potential role in infection prevention and improved healing (McCandless et al., 2015). A multicenter registry study of 200 HeartMate II patients found that the silicone-skin interface tunneling technique reduced driveline infections by 50% at one and two years compared to the traditional velour-to-skin method (HR: 0.49, $p < 0.001$) (Dean et al., 2015).

Clinical trials solidified the HeartMate II's role in heart failure management. The pivotal HeartMate II BTT trial demonstrated the superiority of the HeartMate II (HM II) continuous-flow LVAD over the pulsatile HeartMate XVE (HM XVE) in advanced heart failure patients ineligible for transplantation, with two-year survival rates of 58% vs. 24% ($p = 0.008$) (Slaughter et al., 2009). The HMII significantly reduced device-related failures **(**6 vs. 48 events per 100 patient-years**)** while maintaining comparable hemodynamic support and improving renal and hepatic function. However, HMII patients experienced a 44.3% bleeding incidence, primarily gastrointestinal, due to von

Willebrand factor degradation, necessitating higher transfusion requirements at transplantation ($p < 0.05$). Right ventricular failure occurred in 5% of HM II recipients, significantly lower than historical pulsatile LVAD data, reflecting better right-sided circulatory adaptation. A post-market approval study of the HeartMate II LVAD in bridge-to-transplantation patients showed superior 1-year survival (85% vs. 70% for other devices, including HeartMate XVE), lower 30-day mortality (4% vs. 11%), fewer high-risk INTERMACS profile 1 patients (24% vs. 39%), and comparable or lower adverse event rates, with bleeding as the most common complication, while significantly improving quality of life within three months and sustaining benefits through 12 months (Starling et al., 2011). A UNOS Thoracic Registry analysis of 1,157 bridge-to-transplant patients found similar one- and three-year post-transplant survival rates between HMII and HM XVE (HR = 0.95, CI = 0.64–1.42), but HMII patients had fewer early incidents of allograft rejection and hospitalizations for infection, highlighting the benefits of continuous-flow LVADs in reducing early post-transplant complications (Ventura et al., 2011). The HeartMate II LVAD significantly improved functional capacity and quality of life in advanced heart failure patients, with 82% (BTT) and 80–79% (DT) improving to NYHA class I or II at 6–24 months. In DT patients, the 6-minute walk distance increased from 204 m to 350–360 m, while MLWHF and KCCQ scores showed a 52–55% reduction in symptoms and a 170–178% improvement, respectively (Rogers et al., 2010). Body Mass Index (BMI) extremes were associated with increased bleeding (underweight, $p < 0.001$), infections (extremely obese, $p = 0.041$), and rehospitalization ($p = 0.014$), but survival remained comparable across all BMI categories ($p = 0.83$) (Brewer et al., 2012).

In a retrospective analysis of 1,312 HeartMate II LVAD patients bridged to orthotopic heart transplantation, 90-day survival was 92.3%, with early mortality (13.0%) influenced by recipient and donor factors, while higher-volume centers demonstrated improved outcomes ($p = 0.01$) (Arnaoutakis et al., 2012). The HeartMate II LVAD demonstrated comparable 18-month survival between men (73% ± 5%) and women (73% ± 3%), with women experiencing longer median support duration (238 vs. 184 days, $p = 0.003$), lower transplantation rates (40% vs. 55%, $p = 0.001$), higher hemorrhagic stroke incidence (0.10 vs. 0.04 events/patient-year, $p = 0.02$), and lower device-related infections (0.23 vs. 0.44 events/patient-year, $p = 0.006$), while both groups showed significant functional and quality of life improvements (Bogaev et al., 2011). Another single-center retrospective study analyzed 267 patients who underwent HeartMate II implantation between 2005 and 2014, showing an overall survival rate of 94% at 30 days, 77% at 1 year, and 48% at 5 years, with improved survival in later cohorts ($p = 0.003$) (John et al., 2016). While advancements in HeartMate II implantation led to reduced driveline infections and increased destination therapy use over time, major complications such as hemolysis and pump exchange remain challenges.

HMII complications were also recorded. One study analyzed 956 HeartMate II LVAD patients to identify pre-operative risk factors for late bleeding, stroke, and pump thrombosis (Boyle et al., 2014). Bleeding (0.67 events/patient-year) was more common than hemorrhagic stroke (0.05), ischemic stroke (0.04), and pump thrombosis (0.03), with gastrointestinal bleeding being the most frequent (45%). Risk

factors included older age (>65 years), lower pre-operative hematocrit (≤31%), ischemic etiology, and female sex for bleeding; female sex and younger age (≤65 years) for hemorrhagic stroke; female sex and diabetes for ischemic stroke; and female sex and higher BMI for pump thrombosis. Another study analyzed 6,910 HMII LVAD patients from the INTERMACS database (2006-2013) and found that freedom from pump thrombosis or device exchange decreased from 99% in 2009 to 94% in 2012 ($p < 0.0001$) (Kirklin et al., 2014). Risk factors for pump thrombosis included later implant year, younger age, higher creatinine, larger BMI, white race, LVEF >20%, and elevated lactate dehydrogenase at 1 month ($p < 0.0001$). Despite the increase in thrombosis, overall survival remained high (80% at 1 year), though outcomes after pump exchange were worse than after primary implant. In a retrospective analysis of 1,125 HeartMate II LVAD patients 21% developed atrial arrhythmias, primarily within 60 days post-implantation, with higher serum creatinine (HR 1.49, $p < 0.001$) and lower LVEF (HR 0.98, $p = 0.04$) as independent risk factors, and while survival was unaffected ($p = 0.16$), atrial arrhythmias were associated with poorer quality of life ($p < 0.001$) and delayed functional recovery ($p = 0.016$) (Brisco et al., 2014). Left ventricular recovery leading to HeartMate II LVAD explantation was rare (1.8%) but most likely in young patients (<40 years) with recent-onset (<1 year) nonischemic cardiomyopathy, with 85% surviving at two years in NYHA class I/II and a mean ejection fraction of 42% (Goldstein et al., 2012). Finally, in an in vitro hemocompatibility study comparing HeartMate II and BerlinHeart EXCOR under pediatric flow conditions, both devices showed increasing hemolysis and platelet activation over time, but hemolysis was significantly higher with HeartMate II ($p < 0.001$), while von Willebrand factor degradation was more pronounced with EXCOR (Chan et al., 2018).

The ROADMAP (Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management) study later expanded the clinical understanding of LVAD therapy in ambulatory heart failure patients (Estep et al., 2015). The ROADMAP study was a prospective, nonrandomized, multicenter trial evaluating the efficacy of HMII compared to OMM in ambulatory patients with advanced heart failure (NYHA class IIIB/IV) who were not dependent on inotropic support. The primary endpoint was survival on original therapy with an improvement of at least 75 meters in the 6-minute walking distance at one year. The study demonstrated that LVAD therapy resulted in superior one-year survival (80% vs. 63%, $p = 0.022$) and a greater proportion of patients meeting the primary endpoint (39% vs. 21%, OR: 2.4, $p = 0.012$), despite higher adverse event rates driven primarily by bleeding. Quality of life and depression scores also improved more significantly in LVAD recipients than in OMM patients, supporting its use in functionally impaired, non-inotrope-dependent heart failure patients. At two years, the as-treated analysis continued to favor LVAD therapy, with higher survival rates (70% vs. 41%, $p < 0.001$) (Starling et al., 2017). However, in an intent-to-treat analysis, survival did not differ significantly between groups (70% vs. 63%, $p = 0.307$), as 22% of patients initially assigned to OMM eventually required LVAD implantation. The study also highlighted a decline in key LVAD-related adverse events beyond the first year, reinforcing the need for individualized decision-making in elective LVAD implantation. Importantly, the study demonstrated

that baseline health-related quality of life (hrQoL) played a significant role in patient outcomes (Stehlik et al., 2017). Patients with poor baseline hrQoL had better survival on original therapy with LVADs compared to OMM (82% vs. 58%, $p = 0.004$), while no survival advantage was observed in those with higher baseline hrQoL (75% vs. 70%, $p = 0.79$). Further analyses of the ROADMAP study stratified patients by INTERMACS profiles to assess whether certain subgroups derived greater benefit from LVAD therapy (Shah et al., 2018). Among INTERMACS Profile 4 (IM4) patients, LVAD recipients had significantly higher rates of meeting the primary endpoint (40% vs. 15%, $p = 0.024$) and superior two-year event-free survival compared to OMM (67% vs. 28%, $p < 0.001$). However, in INTERMACS Profile 5 to 7 (IM5-7) patients, the primary endpoint did not significantly differ between treatment groups, though event-free survival was higher in LVAD recipients (76% vs. 49%, $p = 0.025$). While LVAD patients in both IM4 and IM5-7 experienced increased adverse event rates, rehospitalization was significantly higher in the IM5-7 group (93% vs. 71%, $p = 0.016$). Notably, improvements in hrQoL and depression scores were observed only in IM4 patients. The ROADMAP study also assessed the utility of existing prediction models in determining the optimal timing for LVAD implantation. The Seattle Heart Failure Model (SHFM) was a strong predictor of overall survival in OMM patients (HR = 2.98, $p < 0.001$; AUC = 0.71, $p < 0.001$) but failed to predict LVAD-free survival (HR = 1.41, $p = 0.097$; AUC = 0.56, $p = 0.314$), overestimating the likelihood of avoiding LVAD therapy (Lanfear et al., 2017). In LVAD recipients, the HeartMate II Risk Score (HMRS) had only marginal predictive value at three months (AUC = 0.71, $p = 0.026$) and twelve months (AUC = 0.62, $p = 0.122$), underestimating survival across different risk subgroups.

4.4.2 Jarvik 2000

The Jarvik 2000 is a valveless, electrically powered, axial-flow left ventricular assist device designed for both bridge-to-transplantation and destination therapy in patients with end-stage heart failure. With dimensions of 2.5 cm in width, 5.5 cm in length, and a weight of 85 grams, the device features a single moving part, a neodymium-iron-boron magnet impeller housed within a welded titanium shell. It operates at rotational speeds of 8,000 to 12,000 rpm, generating a continuous flow of up to 7 L/min, and is connected to an external controller via a tunneled driveline (Westaby et al., 1998). Over the past 25 years, the device has undergone continuous refinements to improve durability, hemocompatibility, and patient outcomes.

The early iterations of the Jarvik 2000 featured pin bearings, but clinical experience revealed that these components were prone to thrombus formation at the interface between the rotating pin and stationary bearing sleeve (Frazier et al., 2002). To address this issue, cone bearings were introduced, eliminating the circumferential crevice that facilitated clot development. Extensive preclinical testing, including six 60-day calf studies, confirmed that the new design improved thromboresistance, significantly reducing hemolysis and the need for device exchanges. One study analyzed 99 patients

from the Italian Registry who received the Jarvik 2000 LVAD, comparing 39 patients with the older pin-bearing design to 60 with the newer cone-bearing design (Tarzia et al., 2016). Cardiovascular mortality was significantly lower in the cone group (26% vs. 71%, P = .034), with fewer strokes and right ventricular failures, suggesting improved outcomes due to enhanced fluid dynamics. Another key enhancement was the integration of an intermittent low-speed controller, designed to enhance aortic root washout and facilitate intermittent aortic valve opening. By temporarily reducing pump speed for short intervals, this feature allowed the native ventricle to eject blood and maintain physiologic pulsatility, mitigating concerns regarding stagnant flow in the aortic root, which could predispose patients to thromboembolic events and adverse neurologic outcomes.

Further refinements to the Jarvik 2000 included the addition of a radially reinforced polytetrafluoroethylene outflow graft to optimize blood flow dynamics, reducing kinking and ensuring stable hemodynamic support. A major design improvement involved transitioning to a postauricular driveline configuration, which improved long-term device durability and minimized infection risk by eliminating the need for an abdominal driveline exit site. This modification also allowed patients to submerge in water, significantly enhancing their quality of life. External power cables were reinforced to withstand greater mechanical stress, preventing driveline fractures and improving system reliability. The longest reported patient support duration exceeded 9.5 years, demonstrating the robustness of these iterative improvements (Selzman et al., 2023). The evolution of the Jarvik 2000 has been driven by an iterative engineering process focused on reducing thrombotic risk, optimizing aortic valve function, and improving long-term patient outcomes. Its compact intraventricular design, patient-controlled speed settings, and enhanced driveline durability position it as a viable option for both bridge-to-transplant and destination therapy. Future advancements are expected to focus on transcutaneous energy transfer and further refinements in hemocompatibility to ensure continued improvements in mechanical circulatory support technology (Selzman et al., 2018).

Preclinical studies on the Jarvik 2000 demonstrated its ability to effectively unload the left ventricle, reduce end-diastolic pressures, and maintain myocardial oxygen consumption and coronary blood flow ratios. A study in eight calves confirmed that brain and kidney microcirculation remained stable at all pump speeds, indicating that the device provides adequate circulatory support without compromising end-organ perfusion (Tuzun et al., 2004). These findings supported its progression to clinical trials, where it was assessed for long-term reliability and hemodynamic performance. The mechanical reliability of the Jarvik 2000 was evaluated in a retrospective study of 102 patients implanted between 2000 and 2004, with a cumulative pump runtime of 110 years, including 59 years in vivo and 51 years in vitro. The study reported no implantable component failures and a 95% freedom from system failure at four years, although nine cases of external cable malfunctions were documented

(Siegenthaler et al., 2006). These results underscored the device's potential for long-term circulatory support, particularly for critically ill heart failure patients.

The Jarvik 2000's clinical performance was validated in a multicenter bridge-to-transplant study involving 150 UNOS status I patients between 2005 and 2012 (Selzman et al., 2023a). The study achieved its primary endpoint, with 67.3% of the total cohort either successfully transplanted or still listed at 180 days (95% CI: 59.5%-74.3%, p = 0.006). A key modification during the study was the transition from pin bearings to cone bearings, which significantly improved hemolysis rates and reduced end-organ dysfunction. Subgroup analysis demonstrated superior outcomes in the cone-bearing cohort, with a primary endpoint success rate of 91% (95% CI: 72%-97.5%, p = 0.001). Functional capacity and quality-of-life measures improved across all patient groups, reinforcing the device's efficacy in advanced heart failure management (Selzman et al., 2023). However, in a comparative analysis of axial-flow LVADs the Jarvik 2000 demonstrated variable survival rates, with six-month survival ranging from 67% to 91% while the HeartMate II achieved up to 86.9% survival at six months and 96.3% at three years (Savar et al., 2025).

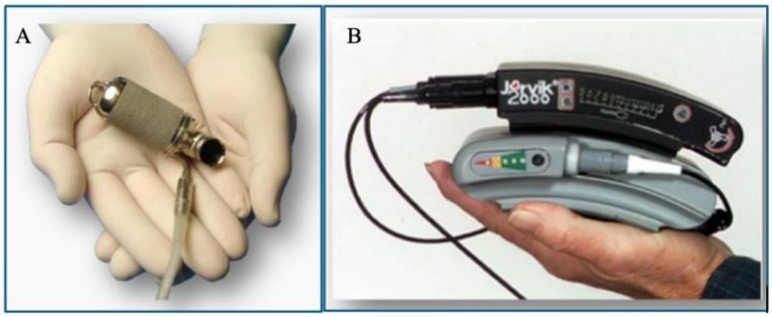


Figure 23. (A) Miniature of the Jarvik 2000 VAD and (B) external control unit and battery pack.

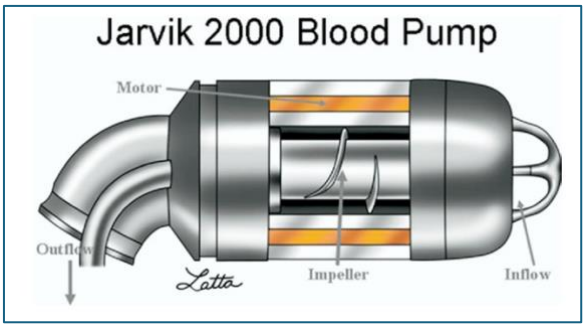


Figure 24. Cross-sectional internal view of the Jarvik 2000 LVAD.

The development of the Pediatric Jarvik VAD has been driven by the need for durable mechanical circulatory support in infants and small children with advanced heart failure (Fukamachi et al., 2018). Given the high mortality rates among pediatric patients awaiting heart transplantation, particularly those with congenital heart disease and low body weight, there has been a significant demand for a device capable of providing effective circulatory support in this population. The Infant Jarvik 2000 VAD was initially developed as a fully implantable, continuous-flow pump designed for small children, but early testing revealed unacceptably high levels of hemolysis. This led to a series of design modifications, resulting in the development of the Jarvik 2015 VAD. The new device features improved impeller blade geometry and an optimized flow profile, significantly reducing shear stress and minimizing blood damage. In vitro hemolysis testing and chronic in vivo animal studies demonstrated that these modifications successfully lowered hemolysis to acceptable levels while maintaining effective hemodynamic support.

The PumpKIN (Pumps for Kids, Infants, and Neonates) clinical trial was initiated to evaluate the safety and efficacy of the Jarvik 2015 VAD as a bridge to heart transplantation in pediatric patients (Baldwin et al., 2017). This trial was designed as a prospective, randomized controlled study comparing the Jarvik 2015 VAD with the Berlin Heart EXCOR, which was the only FDA-approved pediatric VAD at the time. The study aimed to assess key clinical outcomes, including survival rates, adverse events, and overall patient quality of life while on mechanical support. Prior to launching the trial, extensive testing was conducted to ensure the device's compatibility with the anatomical constraints of small children, leading to virtual fit assessments using CT and MRI imaging. The results indicated that the Jarvik 2015 VAD could be implanted in children weighing as little as 8 kilograms, expanding potential treatment options for a vulnerable patient population. The trial represents a critical step in advancing pediatric mechanical circulatory support and addressing the unique challenges associated with device implantation in infants and young children.

The Jarvik 2000 remains a viable option for mechanical circulatory support, with its compact intraventricular design (90 g, 25 cc volume displacement, 25 mm diameter) allowing for patient-controlled speed adjustments and alternative driveline configurations (Zucchetta et al., 2014). It has been implanted in over 1,100 patients across 17 countries, accumulating more than 1,400 patient-years of experience. Optimal pump speed adjustments have been shown to maintain left ventricular unloading while preserving aortic valve opening, ensuring physiological perfusion to end organs such as the brain and kidneys. The overall stroke rate in a study was 21%, with hemolysis occurring more frequently in the pin-bearing cohort (Selzman et al., 2023). Device-related malfunctions were minimal, and no implantable component failures were reported, further supporting its reliability. The transition to cone bearings significantly enhanced hemocompatibility and durability, reducing pump thrombosis and device exchange rates.

4.4.3 MicroMed DeBakey Ventricular Assist Device

The MicroMed DeBakey VAD represents a significant milestone in the field of continuous-flow mechanical circulatory support systems (Noon et al., 2000). Developed through a collaboration between NASA engineers and Dr. Michael DeBakey, the device aimed to address limitations of pulsatile systems, including size, durability, and hemodynamic inefficiency (DeBakey & Teitel, 2005). Systematic refinements of the DeBakey VAD focused on optimizing design parameters such as impeller blade geometry and impeller-stator clearances, achieving flow rates of up to 5 L/min at rotational speeds of 8,000–16,000 RPM while maintaining an exceptionally low hemolysis index of 0.038 g/100 L (Damm et al., 1993). Computational fluid dynamics and flow visualization techniques revealed that design features such as flow straighteners reduced turbulence and laminarized flow, minimizing risks of hemolysis and thrombosis (Wernicke et al., 1995). The inclusion of a hub extension further improved hemocompatibility without compromising pump performance (Fischer et al., 2003).

The DeBakey VAD utilizes an axial-flow mechanism with a single rotating impeller housed within a titanium casing (Potapov et al., 2003). The impeller, suspended by ceramic bearings, reduced friction but encountered wear-related challenges, which led to the development of subsequent magnetically levitated (maglev) systems. Measuring only 5 cm in length and weighing 90 grams, the device is exceptionally compact, facilitating implantation in smaller adults, adolescents, and pediatric patients. This design minimizes surgical complexity and infection risks compared to larger pulsatile devices. Blood enters through an inflow cannula at the left ventricular apex and is propelled by the impeller through an outflow graft connected to the ascending aorta. Operating at speeds of 8,000–12,000 RPM, the device consistently achieved flow rates of up to 10 L/min, ensuring reliable systemic perfusion across diverse patient populations.

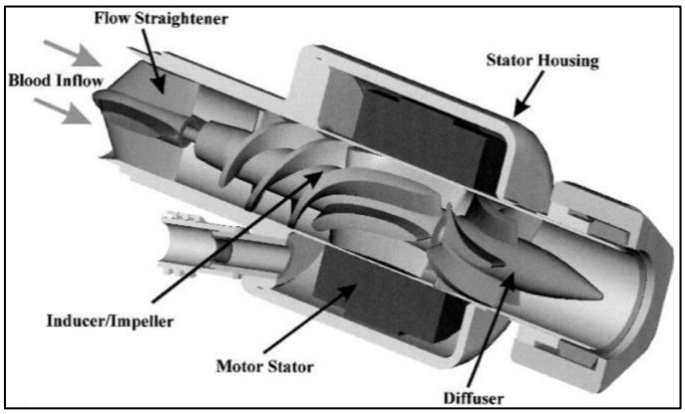


Figure 25. Inside view of the computer designed pump of the MicroMed DeBakey.

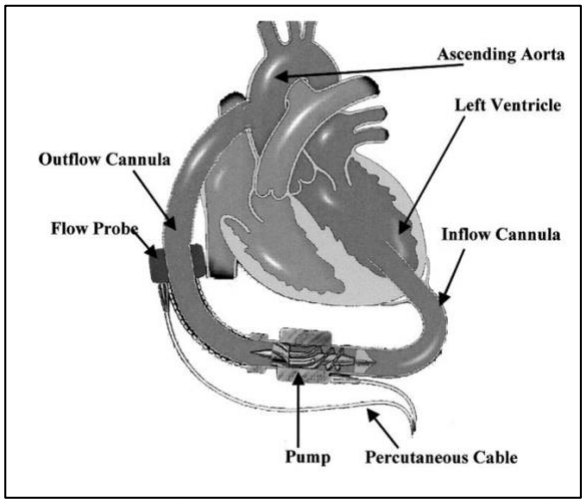


Figure 26. Implantation of the MicroMed DeBakey LVAD. The titanium inflow cannula is connected to the apex of the left ventricle and the Dacron outflow cannula to the ascending aorta.

Hemodynamic performance analyses revealed flow rates ranging from 3.9 to 5.4 L/min and pump indices exceeding 2.3 L/min/m², ensuring sufficient systemic perfusion for patients of various sizes (Hentschel et al., 2008). Experimental studies demonstrated significant reductions in left ventricular pressure (52.2%) and myocardial oxygen demand, with pulmonary artery flow increasing by up to 4.5%, highlighting its role in myocardial recovery (Voitl et al., 2009). Investigations into microvascular perfusion, particularly in the choroid and ophthalmic artery, indicated that while pulsatility decreased under continuous flow, microvascular circulation was preserved, demonstrating the efficacy of the device in maintaining adequate perfusion (Polska et al., 2007). Research on dynamic speed modulation addressed limitations of constant-speed continuous-flow LVADs, such as aortic valve insufficiency. In mock circulatory systems, synchronized speed modulation improved aortic valve ejection duration and valve area, enhancing arterial pulsatility without reducing overall circulatory support (S. Bozkurt et al., 2015). Studies using an ex vivo porcine heart model demonstrated that pulsatile-speed operation doubled arterial pulse pressure and improved pulsatility index compared to constant-speed operation, potentially reducing long-term complications associated with CF-LVADs, such as gastrointestinal bleeding and vascular remodeling (S. Bozkurt et al., 2014). Another ex vivo porcine beating heart model demonstrated that Micromed DeBakey and HeartMate II LVADs accurately estimate left ventricular pressure and dp/dt_{max}, though dynamic models showed limitations in assessing systolic parameters under high heart rates or extreme dp/dt_{max} values (Kassi et al., 2023).

Clinical evaluations confirmed the DeBakey VAD's efficacy in both bridge-to-transplantation and destination therapy. A trial involving 51 patients showed an 81% survival rate at 30 days, with 14 successfully bridged to transplantation (Noon et al., 2001). The device provided consistent pump flows exceeding 4 L/min and improved renal and hepatic function, as indicated by reductions in blood urea nitrogen, creatinine, and bilirubin levels. Studies on reversing fixed pulmonary hypertension demonstrated reductions in pulmonary vascular resistance from 4.3 to 2.0 Wood Units, enabling

successful heart transplantation in previously ineligible patients (Salzberg et al., 2005). Between 1998 and 2002, the DeBakey VAD was implanted in 150 patients, achieving a 50–66% bridge-to-transplantation success rate with a mean support duration of 75 days (Goldstein, 2003). While complications such as bleeding (32%) and hemolysis (12%) were noted, device-related infections were rare. In pediatric applications, the DeBakey VAD demonstrated feasibility as a bridge-to-transplantation (Fraser et al., 2006).

Comparative studies on LVADs, including the MicroMed DeBakey VAD, Novacor LVAD, HeartMate, and Thoratec, highlighted their efficacy in improving outcomes for end-stage heart failure patients. A study of 77 patients found no differences in overall survival or transplantation rates between continuous-flow (MicroMed DeBakey and Berlin Heart Incor) and pulsatile-flow (Novacor) devices but noted fewer blood transfusions and reduced surgical trauma with cLVADs (Garatti et al., 2008). Early elective LVAD use in high-risk cardiac surgery patients resulted in 50% being successfully bridged to transplantation, while 86% of patients without LVADs survived (Schmid et al., 2002). In a comparison of Novacor and DeBakey LVADs, 71.1% achieved transplant, with one- and five-year survival rates of 91.0% and 83.4%, respectively (Vitali et al., 2003). Another study reported significant cardiac function improvements and reductions in myocardial stress markers (BNP and ET-1) with LVAD support, with Novacor achieving the most pronounced outcomes (Thompson et al., 2005). Neurocognitive function has also been assessed in patients with terminal heart failure implanted with either Micromed DeBakey or Thoratec/Novacor devices (Zimpfer et al., 2006). Using cognitive P300 auditory evoked potentials over 12 weeks, researchers observed initial impairments due to chronic cerebral hypoperfusion. Post-implantation, significant improvements in neurocognitive function were reported across all device types, correlating with enhanced cardiac output, though full normalization was not achieved. No differences in recovery were observed between continuous-flow and pulsatile-flow devices, indicating comparable effects on regional cerebral blood flow. Another study compared the DeBakey LVAD and Novacor N100 LVAD in terms of early brain injury (Potapov, Loebe, et al., 2001). Biomarkers S-100B and NSE, indicative of brain injury, returned to baseline levels within days of implantation for both devices. While neurologic complications were noted only in the Novacor group, both devices were deemed neuroprotectively safe. These findings collectively suggest that continuous-flow devices like the DeBakey VAD have a minimal impact on neurocognitive and neurologic outcomes while maintaining effective circulatory support.

The immune response to the DeBakey VAD has been extensively studied. Its biocompatible titanium design reduced HLA sensitization, with no significant IgG antibody formation reported among 14 patients supported for an average of 87 days (Grinda et al., 2005). Nonetheless in another study, inflammatory markers such as interleukin-6 (IL-6) and complement factor C5a were elevated, reflecting immune activation unique to continuous-flow systems (Loebe et al., 2001). The study of platelet

function in patients implanted with the DeBakey VAD highlighted a triphasic coagulation profile, characterized by early impaired hemostasis, hyperaggregability, and a steady-state phase under anticoagulation therapy (Bonaros et al., 2004). Pharmacological interventions, such as aspirin and dipyridamole, proved effective in mitigating thromboembolic risks. However, the complexity of managing coagulation in continuous-flow systems was further emphasized by studies exploring genetic and pharmacological influences on platelet function and coagulation outcomes. One investigation into PlA polymorphism in platelet glycoprotein IIb/IIIa receptors analyzed 41 patients with either pulsatile-flow (Thoratec or Berlin Heart EXCOR) or axial-flow (MicroMed DeBakey VAD) devices (Potapov et al., 2004). Patients with the A1A1 genotype experienced higher bleeding incidences, while those with the A1A2 genotype showed a trend toward thromboembolic complications. Another study comparing coagulation markers such as β-thromboglobulin, platelet factor 4, factor XIIa, and plasmin/α2-antiplasmin complexes found that the axial-flow DeBakey VAD induced greater platelet activation and fibrinolytic activity compared to the pulsatile Novacor LVAD (Koster et al., 2000). Despite these differences, no thromboembolic events were reported. Additionally, research demonstrated aspirin's ability to reduce shear-induced platelet activation by approximately 28% in patients with the DeBakey VAD (Sheriff et al., 2014). However, this effect was transient, returning to baseline within 20 hours post-administration. Notably, device design was shown to influence platelet activation significantly.

Neurological outcomes have also been investigated. Microembolic signals (MES) were evaluated in patients implanted with the MicroMed DeBakey VAD through transcranial Doppler (TCD) studies. In one study monitoring five patients over 10 weeks, MES were undetectable in four patients, while one exhibited a 50% prevalence of MES and transient ischemic attacks, attributed to pre-existing atrial fibrillation and carotid stenosis (Potapov, Nasseri, et al., 2001). Another study reported high levels of MES in 88.9% of patients, primarily gaseous in nature, but found no correlation between MES activity and inflammation, pump dynamics, or thromboembolic events (Thoennissen et al., 2006). Similarly, a study of 23 patients revealed that 87% exhibited MES, mostly gaseous, without a direct link to clinical thromboembolic events (Thoennissen et al., 2005). Oxygen supplementation significantly reduced MES counts, implicating cavitation as a major source, although potential neurocognitive effects of continuous microembolization were noted.

4.4.4 Berlin Heart Incor

The Berlin Heart INCOR is a second-generation, implantable LVAD designed to provide long-term mechanical circulatory support for patients with advanced heart failure (https://www.berlinheart.de/fileadmin/user_upload/Berlin_Heart/Dokumente/Downloads/Downloads_IFU/INCOR/clinic/5000013x13_A08_INC_GA_K_en.pdf). It is an electrically operated axial-flow pump with a magnetically suspended impeller that rotates at a constant speed, generating continuous blood flow. Unlike third-generation devices that feature fully magnetically levitated impellers, the

INCOR relies on magnetic suspension to reduce mechanical wear while maintaining contact bearings. The device is indicated for patients with terminal, medically uncontrollable left ventricular insufficiency classified as NYHA stage III or IV, who have a probable medium- to long-term need for mechanical circulatory assistance. It is used as a bridge to transplantation for patients on a transplant waiting list who can no longer be managed with conservative medical therapy, as a bridge to recovery when myocardial unloading allows for potential heart recovery and device explantation, and as destination therapy for patients with contraindications to transplantation requiring permanent circulatory support.

The INCOR LVAD is contraindicated in patients with predominant right ventricular failure, biventricular heart failure, active infections that do not meet sepsis criteria, sepsis, irreversible multi-organ failure, or intolerance to anticoagulation therapy. The device's blood-contacting surfaces are coated with CBAS (Carmeda BioActive Surface), a heparin-based coating designed to reduce thrombotic complications. While the coating aims to minimize clot formation associated with artificial blood-contacting materials, its long-term effectiveness requires further clinical evaluation.

The design of the INCOR includes a permanently connected percutaneous driveline, encased in a silicone sheath to improve durability and reduce infection risk. The portion of the driveline within the body is additionally coated with an adhesion-promoting polyester velour layer that extends 19 cm from the pump, allowing the driveline to be tunneled so that the silicone portion reaches the skin. This configuration has been associated with a reduced risk of driveline infections in clinical practice. The driveline terminates at the pump socket, where the blood pump's serial number is located, allowing for clear identification even after implantation. A plug coupling facilitates the connection between the pump socket and the control unit cable.

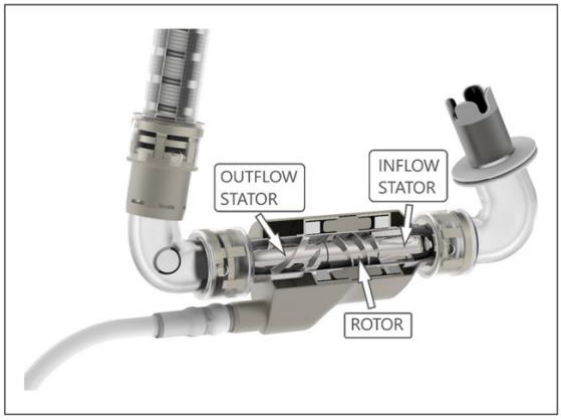


Figure 27. BerlinHeart Incor LVAD, cross sectional view. Hydraulic components of the INCOR LVAD including the inflow stator with straight vanes (right), the outflow stator with diffusor blades (left), and the magnetically suspended rotor in between. Sensor elements in the stator measure the axial position of the rotor and provide in vivo flow rates and pressure heads.

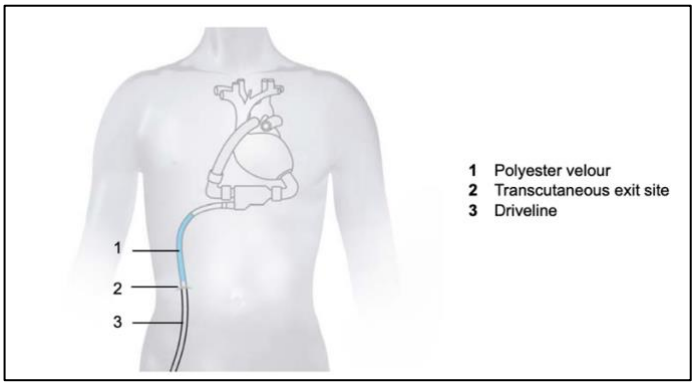


Figure 28. Driveline with polyester velour sheathing.

For outflow cannulation, the INCOR offers two options: a silicone outflow cannula or a graft outflow cannula. The outflow angle section contains a felt pledget to facilitate puncturing, and intraoperative assembly is achieved using snap-in connectors. The inflow cannula features a titanium crown with a textured, sintered titanium surface, which promotes myocardial ingrowth for improved stabilization. The inner portion of the crown and cannula is made of silicone, while a polyester velour suture ring is positioned below the crown to enhance fixation at the implantation site. The device also incorporates a vascular graft prosthesis made of woven polyester for systematic vascular reconstruction. This prosthesis is impregnated with an absorbable, cross-linked protein-based gelatin that eliminates the need for preclotting. The gelatin is hydrolyzed within approximately 14 days and is replaced by normal tissue, reducing thrombogenicity while maintaining structural integrity. However, the vascular graft prosthesis is exclusively indicated for use with the INCOR LVAD and is not suitable for applications such as coronary vessel construction, dialysis fistulas, or pulmonary shunts.

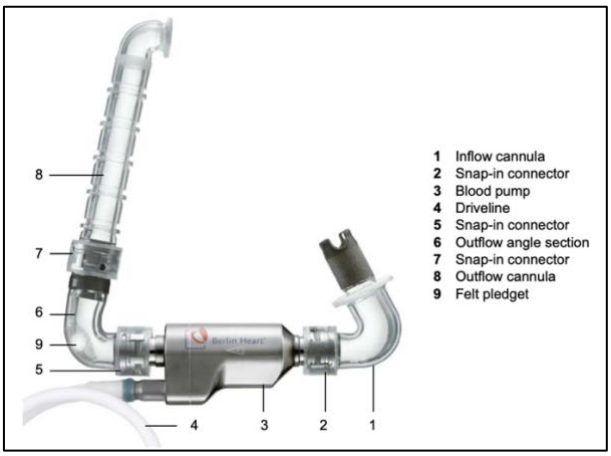


Figure 29. Incor LVAD with cannulae, joined with snap-in connectors.

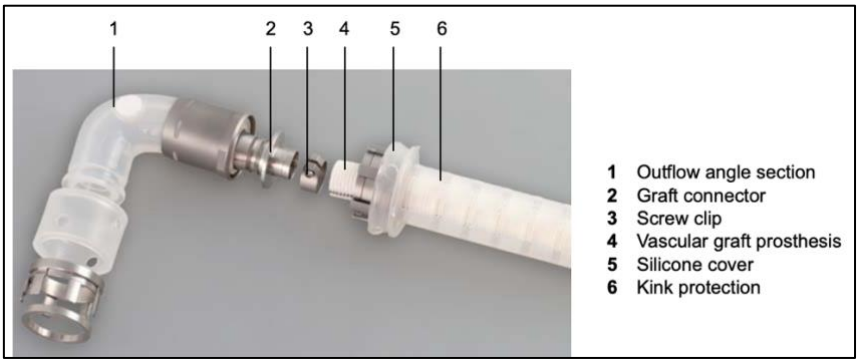


Figure 30. Graft outflow cannula with outflow angle section.

Research focused on optimizing both the mechanical stability of Incor LVAD components and its physiological interaction with the cardiovascular system. One study analyzed the mechanical behavior and stability of the internal membrane in the InCor VAD using structural engineering methods, including large deflection thin-shell theory and finite element modeling (da Costa Teixeira et al., 2001). Experimental testing with a custom-built apparatus validated numerical simulations, confirming that the polyurethane-cotton reinforced membrane can withstand cyclic pressure loading while maintaining structural integrity. Another study presented a computational model for evaluating cardiovascular response in heart failure patients supported by the Berlin Heart INCOR (Shi et al., 2011). Using the CellML modeling language, the researchers investigated the impact of pulsatile impeller pump support by systematically varying pulsation ratios and phase shifts to optimize cardiovascular performance. The results showed that a pulsation ratio of 0.35 and a phase shift of 200 degrees produced the best cardiovascular response, yielding a maximum arterial pulse pressure of 12.6 mmHg without inducing regurgitant flow, while maintaining other hemodynamic parameters within physiological ranges.

Clinical outcomes and patient-specific factors play a crucial role in determining the safety and efficacy of Incor LVAD in advanced heart failure management. In a retrospective study of 42 high-risk advanced heart failure patients implanted with the INCOR LVAD, the device demonstrated effective support with 1- and 2-year survival rates of 74% and 60%, respectively, and no observed cases of gastrointestinal bleeding or pump thrombosis, highlighting its potential advantages over other continuous-flow LVADs (Iacovoni et al., 2015). Another study analyzed 167 patients implanted with the Berlin Heart INCOR LVAD to evaluate the impact of body surface area (BSA) on mortality risk (Komoda et al., 2013). A BSA threshold of 1.867 m² was identified as a critical cut-off, below which patients had a significantly higher risk of death from stroke or systemic bleeding (hazard ratio: 2.665, 95% CI: 1.349-5.265, P = 0.0048), with one-year freedom from these complications being 49.1% in patients with a BSA <1.867 m² compared to 82.7% in those with a BSA ≥1.867 m² (P = 0.0033). A recent systematic review compared the clinical outcomes of commonly used axial-flow pump LVADs, focusing on survival rates and quality of life (Savar et al., 2025). The analysis of second-generation

devices, including the HeartMate II, Jarvik 2000, Berlin Heart INCOR, and DeBakey LVAD, found that HeartMate II had the highest survival rate of up to 96.3% at three years, while Jarvik 2000 showed survival rates ranging from 67% to 91% at six months, both demonstrating significant improvements in patient quality of life.

The Berlin Heart INCOR has been widely utilized as a bridge to transplant and for long-term circulatory support, demonstrating significant hemodynamic improvements in patients with advanced heart failure. However, as a second-generation axial-flow LVAD, it operates with continuous flow, which has been associated with an increased risk of acquired von Willebrand syndrome, gastrointestinal bleeding, and elevated shear stress. Despite these limitations, the device remains a valuable option for patients requiring axial-flow assistance with a magnetically suspended impeller. Ongoing research continues to evaluate its long-term performance, with a focus on hemocompatibility and infection prevention to optimize patient outcomes in LVAD therapy.

4.5 Centrifugal-flow LVADs

4.5.1 EvaHeart

The development of mechanical circulatory support devices in Japan has been shaped by unique challenges, including a historical ban on heart transplantation that lasted until 1997 and a severe donor heart shortage. The earliest clinical MCS were extracorporeal pneumatic devices, such as the Toyobo and Zeon systems, which gained approval in the late 1980s for postcardiotomy support. However, because of their external placement and risk of infection, these devices severely limited patient mobility and quality of life. By the early 1990s, the Novacor and HeartMate I were introduced as implantable alternatives, offering better patient outcomes. Despite their success, these US-made devices were often too large for the average Japanese patient, and their high cost, exceeding $140,000 per unit, restricted widespread use. The national push for developing compact, implantable MCS devices began in 1995, leading to Japan's first wave of rotary blood pump research (Takatani et al., 2005). The late 1990s and early 2000s marked a transition toward continuous-flow MCSDs, with domestic companies developing compact alternatives to imported models. The DuraHeart was one of the first magnetically levitated centrifugal pumps to undergo clinical evaluation, with promising long-term reliability demonstrated in animal studies. In parallel, the EVAHEART employed a mechanical seal with a recirculating cooling system to enhance durability while maintaining hemocompatibility. These advancements allowed for a reduction in the required body surface area (BSA) for implantation, making the devices more suitable for Japanese patients (Takatani et al., 2005).

The EVAHEART system represents an advanced iteration of continuous-flow VADs developed to address limitations in both pulsatile and earlier continuous-flow technologies. EVAHEART I, approved in Japan for clinical use as a bridge to transplantation, incorporates several innovative design features, including a hydraulically levitated impeller and advanced purge mechanisms. The EVAHEART II, a newer evolution, further optimizes hemodynamic performance and miniaturization, designed for broader patient applicability and enhanced portability. The EVAHEART system employs a centrifugal pump design featuring an open-vane impeller. The impeller is lubricated by a thin layer of sterile circulating water, which minimizes friction at the seal interface and cools the shaft, reducing the risk of clot formation and mechanical wear. This hydraulic levitation system allows for smooth, frictionless operation, contributing to the durability and efficiency of the device. The housing and blood-contacting surfaces are constructed with titanium and medical-grade polymers. The pump's open-vane architecture promotes efficient blood washout, preventing areas of stagnation. Additionally, the wide flow gaps between the vanes are optimized to operate at low rotational speeds, reducing shear stress on blood elements and preserving von Willebrand factor levels. The EVAHEART pump operates at rotational speeds between 1,500 and 3,000 rpm, achieving flow rates between 2-10 L/min. The device's Pump Speed Modulation technology introduces variable speed patterns, promoting intermittent opening

of the aortic valve, which mitigates complications such as aortic valve fusion and promotes native ventricular function. Designed with significantly improved anatomical fitting in mind, this technology enhances tissue in-growth and may contribute to a decrease in post- LVAD stroke. These features position EVAHEART as a device capable of maintaining physiological flow dynamics while reducing the risks associated with non-pulsatile flow.

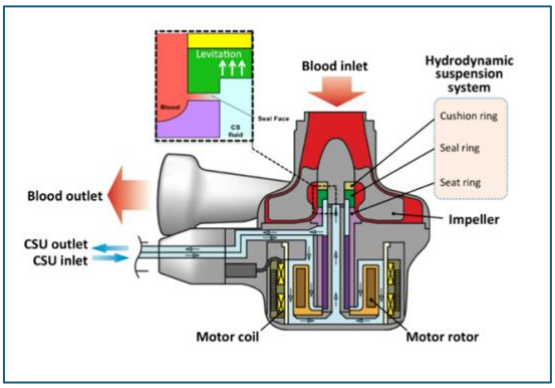


Figure 31. Pump and impeller design. The hydraulically levitated impeller utilizes an ultra-thin layer of circulating sterile water to lubricate the mechanical seal interface and provide cooling around the shaft, reducing the risk of clot formation. The open-vane impeller, designed with large flow gaps, enhances blood washout and enables operation at lower speeds to minimize shear stress. Pump speed modulation allows for controlled speed reductions at predetermined intervals, promoting periodic aortic valve opening.

The EVAHEART has an anti-thrombogenic coating of diamond-like carbon or 2 methacryloyloxyethyl phosphorylcholine to enhance hemocompatibility. The device, measuring 55 × 64 mm and weighing 370 g, has demonstrated excellent long-term performance, with no thrombus formation on blood-contacting surfaces. In in-vivo calf experiments, the EVAHEART maintained flow rates of 5-9 L/min, with a low normalized index of hemolysis (0.005 ± 0.002 g/100L), and exhibited no mechanical failure up to 222 days post-implantation (Yamazaki et al., 2002). A dedicated long-term durability test further confirmed its reliability, with 18 pumps operating for over two years without failure, achieving a ≥90% reliability with an 88% confidence level, and six pumps continuing to function beyond 8.6 years (Kitano & Iwasaki, 2018). These results confirmed the efficacy of the unique water lubrication system in preventing seal and bearing wear, positioning the device as a viable option for both bridge-to-transplant and destination therapy. The J-MACS registry evaluation of 96 patients implanted with EVAHEART in Japan between 2011 and 2013 further validated its long-term safety, showing survival rates of 93.4% at six months and 87.4% at both one and two years, with minimal incidence of gastrointestinal bleeding, right ventricular failure, hemolysis, pump thrombosis, and mechanical failure (Saito et al., 2014). Major complications included ischemic stroke (17.7%), driveline infection (14.6%), and hemorrhagic stroke (13.5%).

The optimization of inflow cannula positioning has been a focus of EVAHEART research, as improper angulation is a known risk factor for thrombus formation and ventricular suction. A mock circulatory loop experiment using a silicone model of a dilated left ventricle demonstrated that a 15° angulation of the inflow cannula toward the septum significantly increased apical stasis, altered vortex dynamics, and reduced kinetic energy, suggesting that optimizing cannula placement could enhance hemodynamic performance and reduce thrombotic risk (May-Newman et al., 2019). To address inflow-related complications, the EVAHEART 2 introduced a novel double-cuff tipless (DCT) inflow cannula designed to improve tissue integration and mitigate malposition risks. Preclinical evaluation in eight bovine models, with intentional malpositioning at an average angle of 58° (range: 30°–77°), confirmed that the DCT cannula effectively prevented ventricular suction, thrombus formation, and intraventricular migration, as evidenced by stable pump parameters and necropsy findings (Motomura et al., 2019). Histopathological analysis revealed minimal pannus formation in two cases associated with warfarin resistance and hyperinflammation at the suture line, but no wedge thrombus formation was detected. These findings support the potential of the DCT inflow cannula to improve long-term hemodynamic stability and reduce thromboembolic risk.

Figure 32. Double cuff tip-less inflow cannula. The novel Double Cuff Tipless (DCT) inflow cannula is designed to promote tissue in-growth, potentially reducing the incidence of post-LVAD stroke (Yamada et al., 2011). Its flush positioning with the endocardium enhances stability and mitigates the impact of malposition.

Beyond hardware modifications, advancements in EVAHEART's control algorithms have aimed to enhance physiological pulsatility. A cardiac beat synchronization control system was implemented to modulate rotational speed in synchronization with the native cardiac cycle, demonstrating improved vascular pulsatility and left ventricular unloading while mitigating adverse effects such as aortic insufficiency (Ogawa et al., 2019). A novel counterpulse mode, which increases pump speed during diastole (e.g., from 1500 rpm in systole to 2500 rpm in diastole), was tested in a mock circulatory loop, revealing a significant reduction in backward flow compared to continuous

mode. Mean backward flow decreased from -4.0 L/min at 1500 rpm continuous mode to -1.0 L/min in counterpulse mode and from -0.5 L/min at 2000 rpm continuous mode to 0 L/min in counterpulse mode, suggesting potential benefits for LVAD weaning and pump-off trials (Ando, Nishimura, Takewa, Ogawa, et al., 2011). In a separate in vivo study involving eight adult goats (61.7 ± 7.5 kg), the pulsatile mode, which increased rotational speed during systole, restored pulse pressure (22.6 ± 9.8 mmHg vs. 11.7 ± 6.4 mmHg in continuous mode, $P < 0.05$) and improved dp/dt max (351.1 ± 137.8 mmHg/s vs. 75.6 ± 36.2 mmHg/s), demonstrating physiological pulsatility comparable to native circulation (Ando, Nishimura, Takewa, Yamazaki, et al., 2011). Another study in ten goats showed that counterpulse mode increased coronary flow primarily by enhancing diastolic perfusion, whereas copulse mode (which increased pump speed during systole) had no significant effect (Ando, Takewa, et al., 2011). These results suggest that counterpulse operation could optimize myocardial perfusion, particularly in patients with ischemic heart failure.

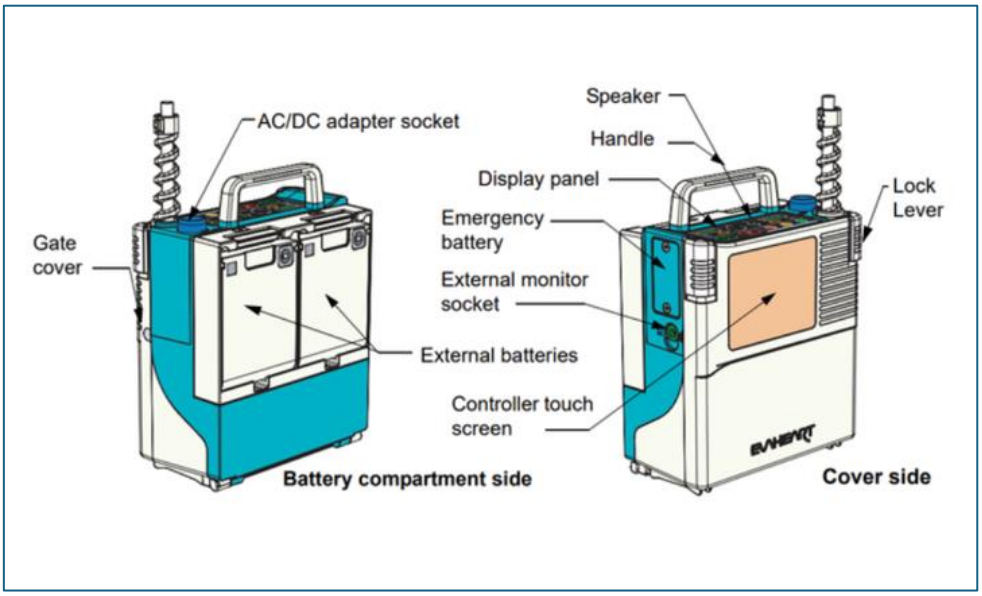


Figure 33. The fully integrated controller serves as the external wearable component that regulates pump speed and Cool Seal Unit (CSU) water pressure. It includes two external battery slots for continuous operation, along with an emergency backup battery for added security. The controller is equipped with two screens: a display panel with LED indicators for charge and status updates, and a touchscreen interface with four tabs providing real-time pump speed data, CSU parameters, battery status, and device settings.

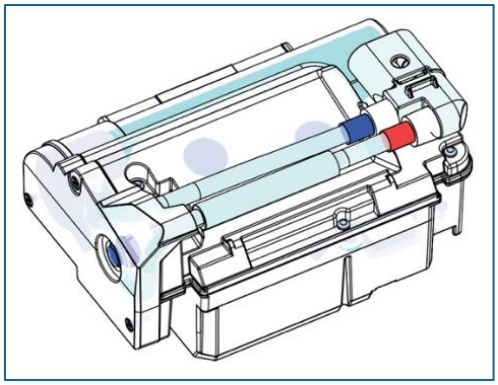


Figure 34. The Cool Seal Unit (CSU) functions as a reservoir and filtration system, ensuring the continuous circulation of sterile water into the pump to levitate the impeller. Combined with the impeller's wide flow gaps, this design enables the device to operate at low speeds while maintaining high blood flow efficiency.

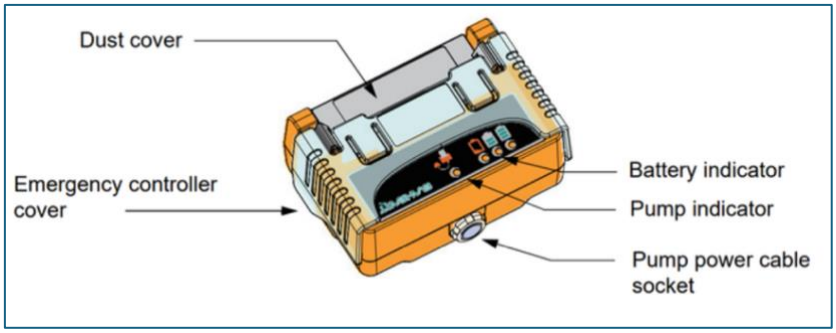


Figure 35. The emergency controller serves as a backup system for the main controller. With only two required connections—an external battery and the blood pump cable—the blood pump automatically powers the controller at a fixed speed.

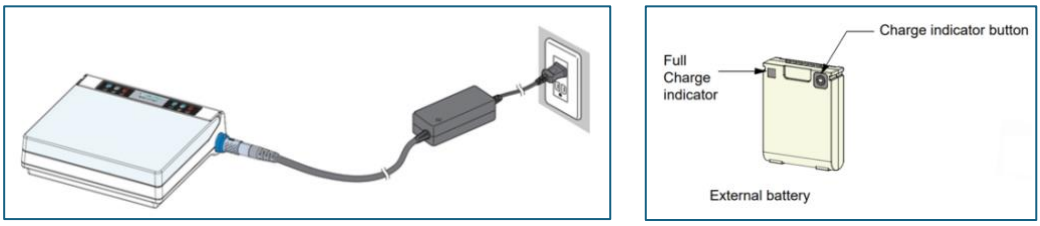


Figure 36. The battery charger and external batteries. Robust battery charger charges two external batteries simultaneously. External batteries provide up to 12 hours of support. Batteries can be charged in the dedicated battery charger or the main controller when connected to AC/DC power.

Further hemodynamic evaluations demonstrated that EVAHEART maintains stable support across varying preload and afterload conditions. In vitro testing revealed that ventricular suction occurs at speeds ≥2,200 rpm when preload is ≤10 mmHg and afterload is ≤60 mmHg but can be avoided at

speeds up to 2,400 rpm when preload is maintained between 10-14 mmHg and afterload at ≥80 mmHg (Ferreira et al., 2012). Peripheral circulation assessment using laser speckle flowgraphy (LSFG) in goats revealed a significant reduction in ocular blood flow pulsatility following EVAHEART implantation, with fluctuation decreasing from 14.7 ± 1.86 to 3.85 ± 0.61 ($p < 0.01$) (Shimamura et al., 2021). This reduction correlated with external carotid artery pulsatility index, indicating that LSFG could be a valuable tool for real-time circulation monitoring during LVAD support.

Hemocompatibility remains a key strength of the EVAHEART design, as demonstrated by ex vivo comparisons with the HeartMate 3. Over six hours of circulation in a mock-loop system using whole human blood, EVAHEART exhibited significantly lower free plasma hemoglobin levels (37 ± 31 mg/dL vs. 503 ± 173 mg/dL in HeartMate 3, $P < .0001$) and lower coagulation activation, as indicated by reduced thrombin-antithrombin complex formation (Zayat et al., 2019). While both devices caused von Willebrand factor degradation, EVAHEART better preserved functional activity, with a significantly lower von Willebrand factor:activity/von Willebrand factor:antigen ratio in the HeartMate 3 group ($P = .009$). A separate 12-hour mock circulatory loop study comparing EVAHEART with the axial-flow HeartMate II showed that the HeartMate II eliminated large von Willebrand factor multimers and increased 10 of 11 von Willebrand factor degradation fragments by 2.0-fold at 6 hours and 2.2-fold at 12 hours, while EVAHEART caused a more modest increase of 1.5-fold and 1.7-fold, respectively (Bartoli et al., 2017). The EVAHEART also significantly reduced the degradation of the 140 kDa von Willebrand factor fragment ($p < 0.01$), highlighting how its lower operational rpm and larger flow gaps mitigate shear stress-induced blood trauma. Another study evaluated the hemocompatibility and flow dynamics of the EVAHEART using a 300% scale-up model, demonstrating optimized vane curvature that prevented flow separations and maintained shear stress levels between 500–2,000 s^{-1}, exceeding the thrombogenesis threshold of 300 s^{-1}. The pump operated efficiently across a wide range of flow conditions (0–8 L/min) at a rotational speed of 2,300 rpm while generating a stable pressure of 100 mmHg, minimizing platelet activation and hemolysis. These findings contributed to the EVAHEART receiving U.S. FDA Investigational Device Exemption in 2009 and Japanese Premarket Approval in 2010, confirming its suitability for long-term mechanical circulatory support with improved hemodynamic stability and reduced thrombotic risk (Yamane et al., 2013).

The EVAHEART has undergone multiple clinical trials primarily in Japan and other select markets. Early studies demonstrated excellent circulatory support, significant improvements in end-organ perfusion, and high survival rates for bridge-to-transplantation patients. Data from these trials also highlighted its efficacy in minimizing complications such as pump thrombosis and bleeding. The results of a comparative study with other VADs indicated that EVAHEART's low shear stress and efficient washout reduced the incidence of von Willebrand factor degradation and gastrointestinal

bleeding. EVAHEART has demonstrated durability, with no recorded mechanical failures over the past decade.

The EVAHEART II, under clinical evaluation in the United States and Japan, has shown promise in further reducing device-related complications while providing long-term support as a destination therapy option. EVAHEART 2 has been further refined to address prior limitations, achieving a 30% reduction in weight and a 26% decrease in displacement volume while retaining identical blood pathway dimensions and pump flow characteristics (https://www.evaheart-usa.com/clinical-trial). These refinements have positioned EVAHEART 2 for broader clinical use, culminating in the ongoing COMPETENCE trial in North America, which is evaluating its safety and efficacy compared to the HeartMate 3 in 399 patients with refractory NYHA Class IV heart failure (S. R. Allen et al., 2023). This prospective, multi-center, unblinded, randomized controlled non-inferiority study assesses primary endpoints, including survival to transplant, recovery, or continued LVAD support free from disabling stroke (Modified Rankin Scale > 3) and severe right heart failure at six months and 24 months. Secondary endpoints include quality of life, six-minute walk distance, rehospitalization rates, reoperations, device malfunctions, and STS-INTERMACS-defined adverse events. A sub-study involving 70 patients (35 EVAHEART 2, 35 HeartMate 3) is also examining von Willebrand factor degradation profiles. As of October 31, 2021, a total of 207 EVAHEART implants, comprising 142 EVAHEART 1 and 65 EVAHEART 2 systems. These advancements solidify EVAHEART 2 as a promising alternative for mechanical circulatory support in patients with advanced heart failure.

Figure 37. Miniaturization of the pump and driveline from the EVAHEART 1 (left) to the EVAHEART 2 (right).

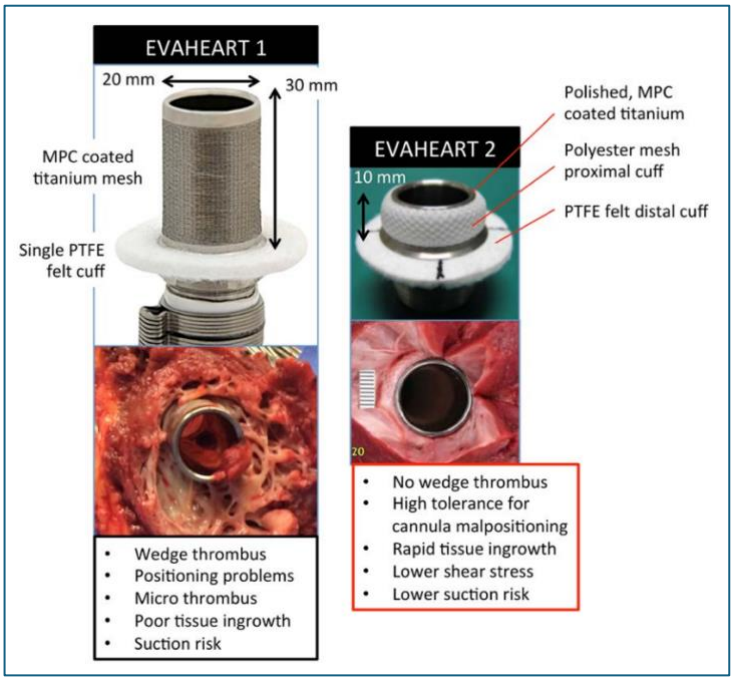


Figure 38. Comparison of a conventional inflow cannula (left) and the newly developed double-cuff tipless inflow cannula (right).

4.5.2 VentrAssist

The VentrAssist LVAD was a centrifugal continuous-flow device aimed to provide long-term support for patients with end-stage heart failure, particularly as a bridge to transplantation or as destination therapy. The VentrAssist LVAD stood out due to its compact size, innovative hydrodynamic design, and biocompatible materials. The VentrAssist LVAD featured a centrifugal pump and the impeller was housed within a titanium casing. The device operated at rotational speeds of approximately 2,000 to 3,000 revolutions per minute, achieving blood flow rates between 4 and 10 L/min (Watterson et al., 2000). The VentrAssist had a shaftless, seal-free, and hydrodynamically suspended impeller and was optimized using computational fluid dynamics to enhance flow paths and minimize axial force imbalance, achieving 18% efficiency in red blood cell suspensions while maintaining stability and reducing hemolysis (Tansley et al., 2000). The pump's rotor-dynamic stability was assessed under varying pump speeds and flow rates, with real-time Hall effect sensor measurements demonstrating that impeller displacement followed a decaying sine wave, confirming increased stiffness and damping with higher flow rates and speeds (Chung, Zhang, Tansley, & Qian, 2004; Chung, Zhang, Tansley, & Woodard, 2004).

In vivo studies in sheep confirmed suitability for chronic implantation, with survival up to 91 days and sustained high-flow performance over 622 days without hemolysis or organ dysfunction, though design challenges such as outflow cannula kinking and electrical malfunctions were addressed (N. L. James, van der Meer, et al., 2003; van der Meer et al., 2003). In vitro studies assessing

hemocompatibility demonstrated minimal hemolysis with a normalized index of hemolysis of 0.000167 g/100 L in whole blood (N. L. James, Wilkinson, et al., 2003). The pump's hydrodynamic profile was further analyzed to assess the effects of viscosity, revealing that while lower viscosity slightly increased pressure rise, overall stability and efficiency were minimally affected (Vidakovic et al., 2000). A paradox in system efficiency was noted, where Haemaccel and phosphate-buffered saline exhibited higher efficiency than aqueous glycerol at the same viscosity, suggesting complex fluid-pump interactions.

Sensorless flow and pressure head estimation using motor speed and input power demonstrated improved accuracy with optimized impeller design, though the choice of blood analogue, beyond just viscosity, influenced precision (Ayre et al., 2000). A study in five greyhound dogs implanted with the pump identified left ventricular suction as a dynamic occlusive process at the pump inlet, leading to end-systolic pressure deficits of 40-160 mm Hg and transient pulmonary venous collapse, highlighting manual pump speed control as a major unresolved clinical challenge (Salamonsen et al., 2015). Further investigations using a mock circulation loop demonstrated that physiological control strategies that mimic the native heart's response to changes in patient state are necessary to prevent ventricular suction, as faster or slower controller responses increased suction risk.

The first international clinical trial in bridge-to-transplant patients demonstrated an 83% success rate with no unexpected safety concerns, leading to European regulatory approval (Esmore et al., 2007). A broader study in 412 patients reported an 81% success rate and significantly reduced hemolysis compared to other ventricular assist devices (Schlensak et al., 2010). The pump maintained circulation and improved end-organ function, with an 82% success rate in bridge-to-transplantation, no deaths due to pump failure, and most adverse events occurred within the first 30 days post-implantation (Esmore et al., 2008). The absence of pulsatility was linked to complications such as gastrointestinal bleeding and arteriovenous malformations due to altered vascular physiology, leading to the development of control algorithms that modulated speed to create a pseudo-pulsatile effect mimicking natural hemodynamics.

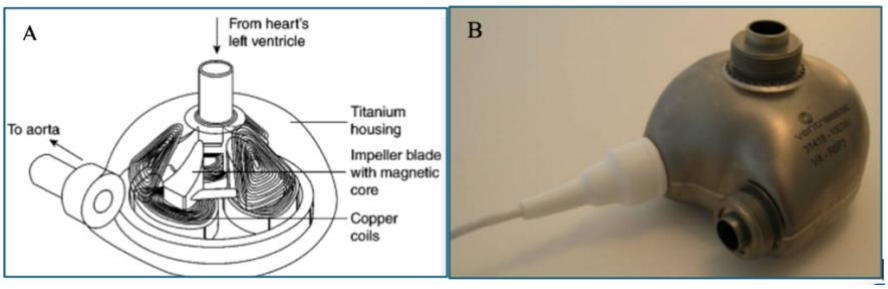


Figure 39. Schematic (A) and Photograph (B) of the VentrAssist LVAD.

Despite its innovative features, the VentrAssist faced significant competition from other LVADs, such as the HeartMate II and HeartWare HVAD, which offered comparable or superior performance with lower complication rates. Financial constraints and the inability to achieve market dominance led to the cessation of Ventracor's operations in 2009. As a result, the VentrAssist LVAD was discontinued, marking the end of its clinical use. The VentrAssist remains an important milestone in the history of LVAD development, demonstrating how engineering ingenuity can advance the field of mechanical circulatory support. Its contributions to centrifugal pump technology and hydrodynamic optimization have influenced subsequent device designs. Lessons learned from the VentrAssist have informed the development of newer-generation LVADs, ensuring better patient outcomes and advancing the management of advanced heart failure.

Figure 40. An exploded assembly view of the pump shows theyokes (outermost), coils, housing, and impeller.

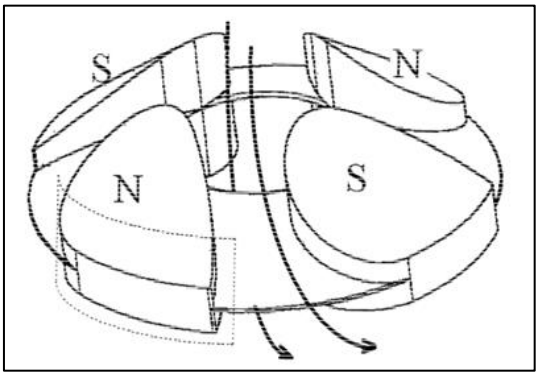


Figure 41. The schema shows the impeller 2.4 ("teardrop shape")indicating fluid flow paths and magnet polarities.

4.6 Third Generation LVADs

The evolution from second- to third-generation MCS devices has been driven by the need to overcome limitations associated with mechanical wear, thrombus formation, and durability concerns inherent in blood-immersed bearings. Second-generation continuous-flow devices demonstrated that long-term support was feasible, yet the presence of mechanical bearings introduced wear-related complications, necessitating design refinements to improve reliability. Third-generation devices address these challenges through the elimination of mechanical contact, utilizing magnetic and/or hydrodynamic levitation to support the rotating impeller. The transition to these third-generation technologies represents a significant advancement in MCS design, yet their complexity and cost necessitate further evaluation to determine their clinical superiority over well-established second-generation devices (Hoshi et al., 2006). A systematic review and meta-analysis of 11 studies, including three randomized trials and eight retrospective and registry studies, demonstrated that third-generation LVADs significantly improve quality of life (QoL) in patients with advanced heart failure (Monteagudo-Vela et al., 2022). The meta-analysis, which synthesized data from four studies using the EuroQol 5L questionnaire, showed a mean increase of 28.9 points six months post-implantation (95% CI: 26.71-31.14), highlighting the substantial benefit of LVAD therapy beyond survival. Another study reviewed over 40 studies on continuous-flow LVADs, including HeartMate II, HeartMate 3, and HeartWare, analyzing their impact on functional capacity and quality of life in end-stage heart failure patients (Mirza & Gustafsson, 2020). While peak oxygen uptake improved to 13.4 ml/kg/min and six-minute walk distance increased to 370 meters, functional capacity remained at 48% of predicted values, with poorer recovery linked to age, diabetes, COPD, and atrial fibrillation. HeartMate 3 showed lower stroke rates of 7.9% vs. 19.1% in HeartMate II and pump thrombosis rates of less than 2% vs. 12%, emphasizing the need for rehabilitation strategies and LVAD optimization to enhance long-term outcomes. These findings support the use of third-generation LVADs not only for improving prognosis but also for enhancing symptom control and patient well-being.

4.6.1 Magnetically Levitated (Full MagLev) LVADs

The third-generation LVADs introduced magnetically levitated impellers to eliminate mechanical bearings, further reducing shear stress and hemolysis (Goodman et al., 2022). These centrifugal pumps aimed to optimize hemodynamics by offering improved hemocompatibility and longer durability. The HeartMate 3, with its fully magnetically levitated rotor, demonstrated superior outcomes in clinical trials, particularly in reducing pump thrombosis and device failure. The HeartWare HVAD combined magnetic and hydrodynamic levitation but was later discontinued due to safety concerns.

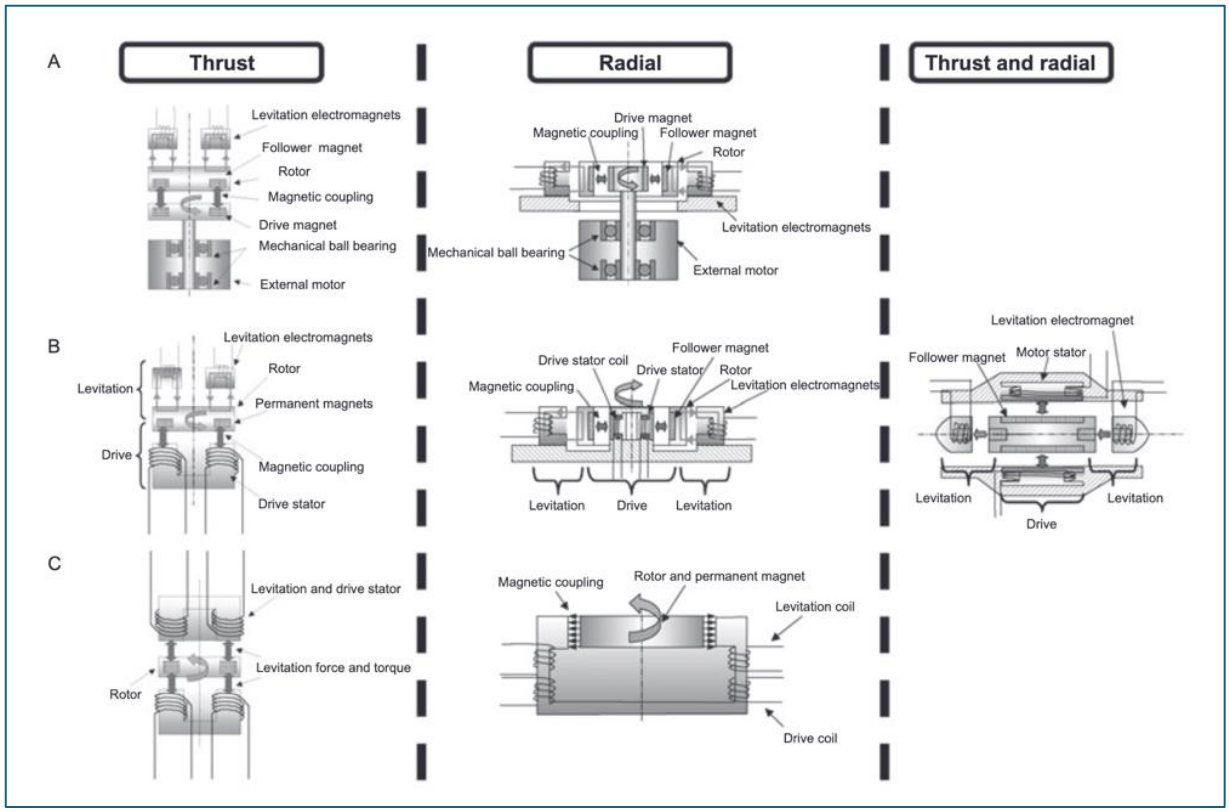


Figure 42. Conceptual representations of maglev systems. They are (A) external motor-driven system, (B) direct-drive system, and (C) self-bearing or bearingless system. Each levitation can be implemented in the thrust or radial direction, or a combination of both.

4.6.1.1 DuraHeart

The DuraHeart represents a defining moment in the evolution of third-generation LVADs. Introduced in the early 2000s, it was the first commercially available LVAD to integrate active MagLev technology into a centrifugal pump design. This innovation addressed limitations of earlier pulsatile-flow and axial-flow devices like mechanical wear, thrombus formation, and hemolysis. The DuraHeart system was designed to provide long-term circulatory aid, particularly as a bridge to transplantation for patients with end-stage heart failure. It received the CE mark in Europe in 2004 and approval in Japan in 2010.

The core of the DuraHeart system is its magnetically levitated impeller, which eliminates the need for mechanical bearings. The impeller is suspended in the blood chamber using active magnetic forces, preventing contact between moving parts and the device housing. This design minimizes friction, reduces heat generation, and virtually eliminates mechanical wear, thereby improving the durability and reliability of the pump. The absence of mechanical bearings also reduces hemolysis and the risk of thrombus aggregation, addressing significant issues observed with earlier devices. The pump housing and blood-contacting surfaces are constructed with biocompatible materials, including titanium and advanced polymers, to further enhance hemocompatibility and reduce inflammatory responses. The

DuraHeart radial-flow, centrifugal pump operates at rotational speeds ranging from 1,200 to 2,400 revolutions per minute, achieving flow rates of up to 10 L/min minute. Its design ensures stable and efficient blood flow, with large gaps around the impeller to promote effective blood washout and minimize areas of stasis and the likelihood of thrombus. With a size of 72 × 45 mm and a weight of 540 g, it is the largest rotary pump, but its 250 µm clearance gaps help reduce blood trauma, and its titanium surfaces are heparin-coated to minimize thrombosis risk (Timms, 2011). The system's external controller and power source allow for precise monitoring and management, while its compact design enables implantation in a broad range of patients, including smaller individuals.

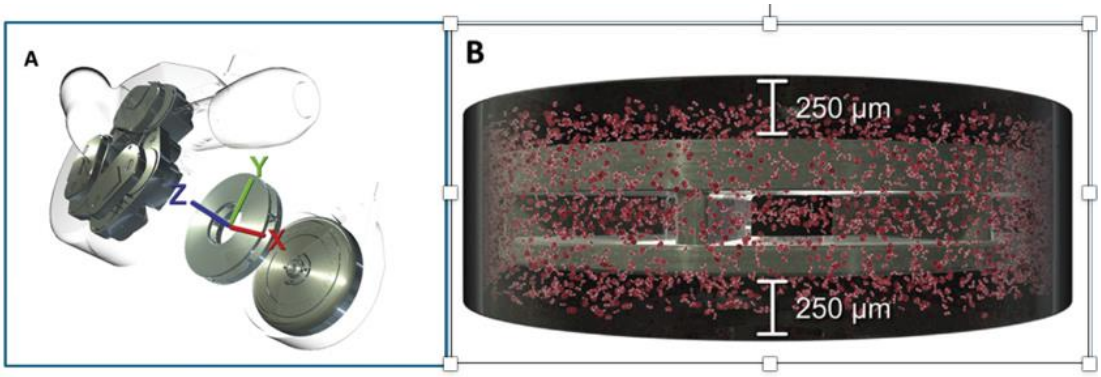


Figure 43. Schematics of the DuraHeart left ventricular assist device. (A) Exploded view: electromagnets and position sensors in the upper pump housing provide magnetic levitation of the impeller, impeller contained within the blood chamber, and drive motor in the bottom pump housing that rotates the impeller through permanent magnetic coupling. (B) The DuraHeart's magnetic levitation system provides wide, stable spacing between the impeller and the blood chamber walls at a distance of 250 mm. Labels X, Y, and Z represent the three axes from right to left, respectively.

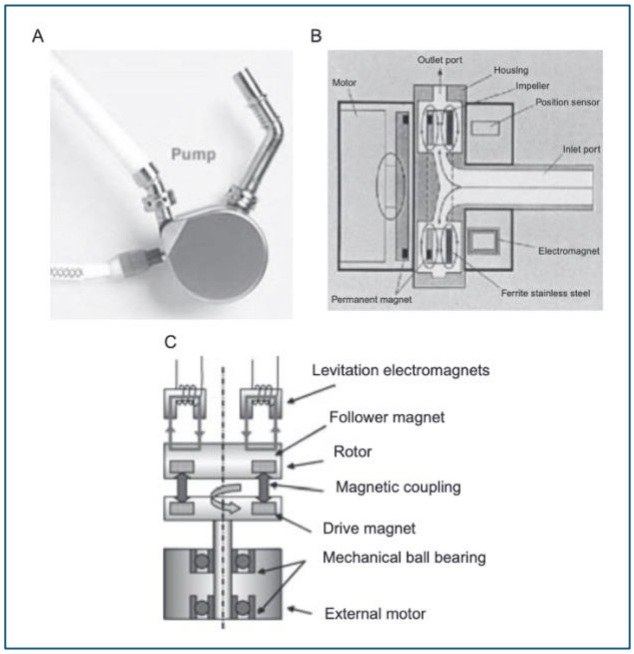


Figure 44. (A) Terumo DuraHeart; (B) schematic representation of the maglev concept; and (C) levitation and drive system schematic.

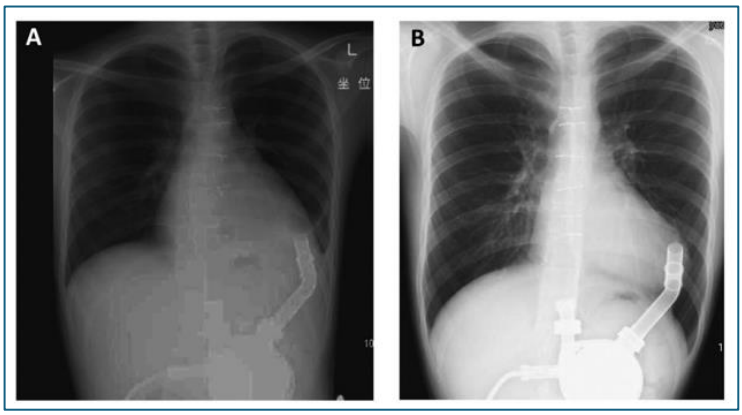


Figure 45. Chest radiograph showing altered orientation of the DuraHeart inflow cannula at implantation (A) and 1 year postoperatively (B).

Clinical trials of the DuraHeart have demonstrated its safety and efficacy in providing long-term circulatory support. In a European multicenter study involving 68 patients, the Kaplan-Meier survival rate was 81% at six months and 77% at one year, comparable to outcomes with other third-generation LVADs (Morshuis et al., 2009). Notably, the study reported no cases of pump thrombosis or mechanical failure. Adverse events were consistent with those observed in other LVAD trials, including driveline infections, bleeding, and right heart failure. The US SUSTAIN trial evaluating the DuraHeart LVAD in 63 advanced heart failure patients demonstrated good hemocompatibility with no clinical hemolysis or pump thrombosis, but highlighted concerns regarding system reliability, as 10% of patients experienced magnetic levitation failure due to cable wire fractures. Despite these issues, the device provided effective hemodynamic support, with 73% of patients achieving the primary endpoint of survival to transplantation, continued device support at 180 days, or recovery (Moazami et al., 2014).

The DuraHeart faced stiff competition from the HeartMate II and HeartWare HVAD, which were more widely adopted due to their smaller size, proven track record, and earlier FDA approvals. Despite its innovative design, the DuraHeart did not achieve significant market penetration, particularly in the US. DuraHeart implantation has been limited to just over 118 patients due to its large size and challenges with inflow cannula placement. Nevertheless, its design principles influenced the development of next-generation LVADs, such as the HeartMate 3.

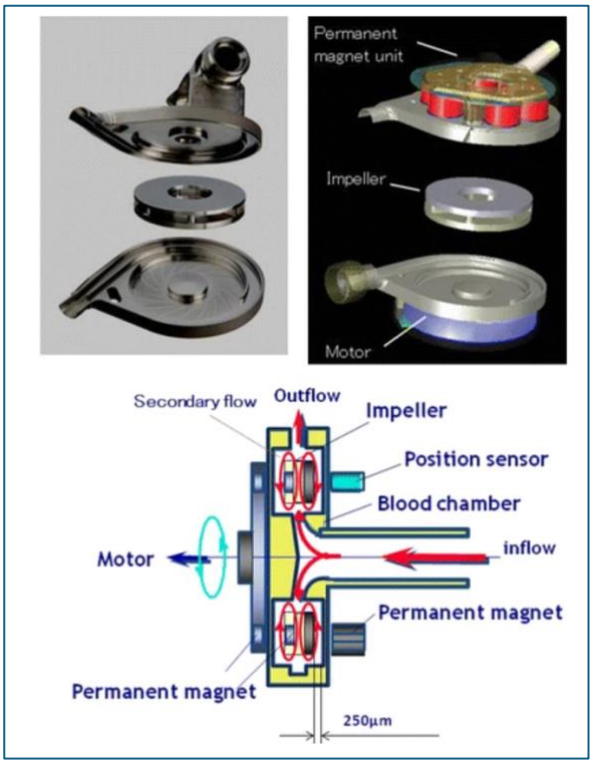


Figure 46. The blood pump of the DuraHeart (upper) device and the structure of the blood pump (lower).

4.6.1.2 HeartMate III

The HeartMate 3 builds upon the foundation laid by its predecessor, the HeartMate II, while addressing key limitations such as hemocompatibility and durability (Bourque et al., 2001). The HeartMate 3 employs a fully magnetically levitated centrifugal-flow pump, which is a significant departure from the axial-flow design of the HeartMate II (Teuteberg et al., 2020). The pump housing of the HeartMate 3 is constructed from titanium (Loree et al., 2001). The blood-contacting surfaces within the device are treated with a proprietary textured coating. Unlike the HeartMate II, which relied on bearings lubricated by blood, the HeartMate 3 uses magnetic levitation to suspend the rotor (Maher et al., 2001). This design ensures near-frictionless operation, virtually eliminating shear stresses and heat generation that could damage blood cells. The HeartMate 3 introduced artificial pulse by periodically reducing pump speed at fixed intervals, creating a pulsatile-like effect that improves vascular function and reduces complications such as stasis, gastrointestinal bleeding, arteriovenous malformations and aortic insufficiency. A numerical model derived from fundamental conservation laws predicts the pressure-flow characteristics of the HeartMate III centrifugal pump, demonstrating that optimal operation occurs at 3,800 rpm**,** while maintaining speeds between 3,100 and 4,500 rpm prevents regurgitant flow and ventricular suction, ensuring effective cardiovascular support (Shi & Korakianitis, 2018). The HeartMate 3 also features a modular driveline system, which connects the internal pump to

an external controller and power source. This driveline has improved materials and design compared to the HeartMate II, reducing the risk of driveline infections. The system's compact size and optimized flow dynamics allow for greater patient mobility and suitability across a broader patient population, including smaller individuals (Farrar et al., 2007).

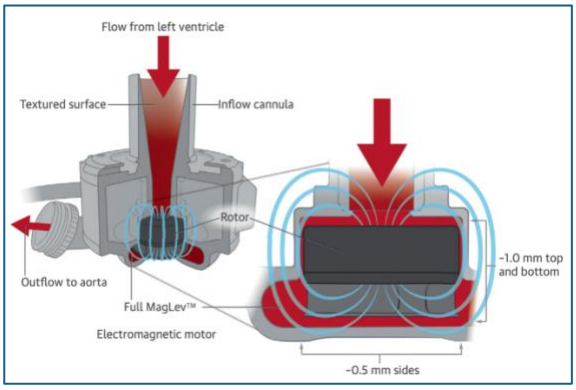


Figure 47. Cross section view of HeartMate 3. The full magnetically levitated rotor allows large pump gaps. Blood flow is received from the left ventricle and is pumped through a graft attached to the ascending aorta. The top portion of the schematic demonstrates the area of internal pump surfaces that are textured and the magnetic field suspending the rotor. The portion of the schematic on the right side demonstrates a magnified view of the gaps around the rotor and the magnetic fields.

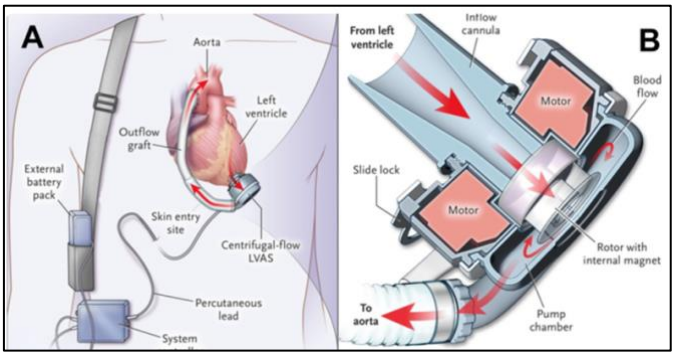


Figure 48. HeartMate 3 Centrifugal-Flow LVAD. **A:** The LVAD system implanted in a patient. An external controller and battery pack connect to the pump via a percutaneous driveline. **B:** Cross-sectional view of the HeartMate 3 pump with a magnetically levitated rotor. Blood flows through the inflow cannula, propelled by the rotor, and exits via the outflow graft. The design eliminates friction, reduces blood trauma, and includes artificial pulse to prevent stasis and complications.

Preclinical testing, including computational fluid dynamics, in vitro hemolysis studies, and in vivo bovine models, demonstrated that HM3 had 50% lower plasma-free hemoglobin levels and only 14% of the hemolysis index observed in HeartMate II, with no pump thrombosis or device failures over 60 days (Bourque et al., 2016). These findings supported the device's progression to clinical trials, leading to CE Mark approval and further evaluation in human patients.

Key differences between the HeartMate 3 and HeartMate II are evident in their performance and clinical outcomes. The HeartMate II, while revolutionary as the first widely used continuous-flow LVAD, had challenges related to pump thrombosis and bleeding due to its axial-flow mechanism. The HeartMate 3, with its centrifugal pump and artificial pulse, addresses these issues, providing improved blood flow dynamics and reducing thrombosis and hemorrhage. Additionally, the HeartMate 3 offers superior durability, with no mechanical contact points to degrade over time, resulting in fewer device replacements. A summary of features of the Thoratec and HeartMate series LVADs is provided in Table 4.

Table 4. Thoratec and HeartMate Series across generations.

Feature	Thoratec	HeartMate XVE	HeartMate II	HeartMate III
Flow Type	Pulsatile	Pulsatile	Continous (Axial)	Continous (Centrifugal)
Pump Mechanism	Pneumatic (air-driven)	Electric Motor	Axial-flow impeller	Fully agLev impeller
Size	Large (paracorporeal)	Large (implantable)	Smaller (intra-thoracic)	Compact (intra-thoracic)
Clinical Use	BTT and BiVAD support	First DT LVAD	Standard LVAD (BTT and DT)	Gold-standard LVAD
Major Limitation	Limited mobility, infection risk	High failure rate	GI bleeding, pump thrombosis	Newer device, requires long-term data

BTT: Bridge to transplantation, BiVAD: BiVentricular Assist Device, DT: Destination Therapy, LVAD: Left Ventricular Assist Device

Clinical trials have established the HeartMate 3 as a pivotal device. In the ELEVATE registry, which included higher-risk patients than the CE Mark trial, 30-day survival remained comparable (95% vs. 98%, $p = 0.46$), with lower cardiac arrhythmia rates (13% vs. 28%, $p = 0.009$), reflecting improved patient management strategies (Garbade et al., 2019). The MOMENTUM 3 trial provided a comprehensive evaluation of the HeartMate 3 (HM3) compared to the HeartMate II in patients with advanced heart failure (Mehra et al., 2019). This randomized trial enrolled 1,028 patients, assessing the primary composite endpoint of survival at two years free of disabling stroke or reoperation for pump malfunction. The HM3 significantly outperformed the HMII, with 76.9% of HM3 recipients achieving the primary endpoint compared to 64.8% of HMII patients (RR=0.84, 95% CI = 0.78–0.91, $P < 0.001$). The centrifugal-flow device was associated with a substantially lower pump replacement rate (2.3% vs. 11.3%, $P < 0.001$) and exhibited lower rates of hemocompatibility-related complications, including pump thrombosis, stroke, and major bleeding. Notably, both ischemic and hemorrhagic stroke rates were reduced in HM3 patients, demonstrating a key advantage of the device's friction-free design and

enhanced blood-flow dynamics. These findings underscore HM3's superiority in long-term durability and safety, reinforcing its role as the preferred LVAD for both bridge-to-transplantation and destination therapy.

Beyond survival and device-related complications, the trial also highlighted HM3's impact on functional outcomes and healthcare utilization. Both LVAD groups demonstrated improvements in exercise capacity, NYHA functional class, and quality-of-life measures, with no significant differences between the devices. However, HM3 patients had fewer hospitalizations and shorter lengths of stay, with a median hospitalization duration of 19 days compared to 17 days in the HMII group. Despite the advantages in hemocompatibility, there was no significant reduction in infection rates, and right heart failure remained a major contributor to morbidity and mortality. Additionally, late complications such as outflow graft occlusion, though infrequent, were identified as unique challenges in HM3 recipients. The final results of MOMENTUM 3 establish the HM3 as the superior LVAD choice, balancing reduced adverse event rates with long-term durability.

Functional outcomes in HM3 recipients have also been favorable. At two years post-implantation, the Kaplan-Meier survival rate was 74±6%, with 64% of patients remaining on LVAD support and 10% undergoing transplantation (Schmitto et al., 2019). Hemocompatibility remained excellent, with no pump thrombosis, hemolysis, or device malfunction. Functional capacity improved significantly, as evidenced by increased six-minute walk distance (239 m to 347 m, $P < 0.0001$), improved NYHA classification (47% in class I, 41% in class II, $P < 0.0001$), and enhanced quality of life scores (EQ-5D: 48.2 to 70.6, $P < 0.0001$). Hemocompatibility advantages with HM3 have been demonstrated across multiple analyses. In a secondary analysis of MOMENTUM 3, HM3 showed a significantly lower risk of hemocompatibility-related adverse events at six months (69% vs. 55% event-free, HR=0.62, 95% CI = 0.42-0.91, $P = 0.012$), driven by reduced pump thrombosis and nondisabling strokes (Uriel et al., 2017). The hemocompatibility score further favored HM3 (101 vs. 137 total points, 0.67±1.50 vs. 0.99±1.79 points/patient), indicating improved biocompatibility. Superior preservation of von Willebrand factor high-molecular-weight multimers, a key marker of reduced shear stress, further supports the reduced thrombotic and bleeding complications observed with HM3 compared to axial-flow devices (Bansal et al., 2019).

At five years, the MOMENTUM 3 trial demonstrated superior survival free of stroke or pump replacement for HM3 recipients compared to HeartMate II (54.0% vs. 29.7%, $P < .001$), with overall survival also significantly higher (58.4% vs. 43.7%, $P = .003$) (Mehra et al., 2022). The reduced stroke incidence (0.04 vs. 0.13 events per patient-year, OR=0.23, 95% CI = 0.08-0.63, $P = 0.01$) and lower rates of pump thrombosis contributed to HM3's clinical superiority. Among discharged patients, five-year mortality was strongly influenced by baseline factors such as elevated blood urea nitrogen and

prior coronary artery bypass grafting or valve surgery, along with postimplant complications including hemocompatibility-related events, ventricular arrhythmias, and impaired renal function at discharge. However, patients without these risk predictors had a five-year mortality of only 22.6%, suggesting that select HM3 recipients may achieve survival rates comparable to transplant candidates, even in destination therapy cohorts (Nayak et al., 2023). Another multicenter registry study evaluated 337 patients bridged from extracorporeal life support (ECLS) to durable mechanical circulatory support, with 140 receiving the HeartMate 3. Compared to other LVADs, HeartMate 3 recipients had significantly lower rates of postoperative stroke (16% vs 28%, P = .01) and pump thrombosis (3% vs 8%, P = .02), with 30-day, 1-year, and 3-year survival rates of 87%, 73%, and 65%, respectively, demonstrating superior outcomes in this high-risk population (Saeed et al., 2024).

Further mechanistic studies have assessed the physiological effects of HM3. In HeartMate 3 recipients, cerebrovascular metabolic reactivity improved compared to HeartMate II, though it remained lower than in healthy controls, suggesting that continuous-flow LVAD therapy does not fully restore cerebral hemodynamics (Stöhr et al., 2021). A study using three-dimensional particle tracking velocimetry (3D-PTV) and computational fluid dynamics identified increased turbulent kinetic energy and wall shear stresses exceeding 150 Pa in low-flow conditions (2.7 L/min), indicating a higher risk of blood damage (Thamsen et al., 2020). From a preclinical perspective, a miniaturized test loop using 450 mL of fresh human blood validated standardized blood damage assessment in LVADs, demonstrating lower hemolysis and better von Willebrand factor preservation with HM3 compared to BPX-80 (Woelke et al., 2021). Endothelial dysfunction and arterial stiffness worsened over 3 to 6 months, as reflected by significant declines in reactive hyperemia index and increases in peripheral augmentation index, underscoring the limitations of artificial pulse in mitigating vascular dysfunction (Ivak et al., 2021). Echocardiographic assessments indicate that HM3 patients experience progressive changes in valvular function. A systematic review of nine studies reported a high and increasing prevalence of aortic regurgitation (33.5% at 12 months), which correlated with worse survival and higher heart failure readmission rates (HR=3.42, 95% CI = 1.48-8.76) (Ohlsson et al., 2024). Mitral regurgitation remained stable (15.0% at 12 months), while tricuspid regurgitation showed an unconfirmed increasing trend (28.5% at 12 months). Data on right ventricular dysfunction were limited, highlighting the need for further research into long-term hemodynamic effects in LVAD patients. Cardiac reverse remodeling following HM3 implantation was evaluated in a multicenter study of 405 patients (Yin et al., 2024). Improvements in LVEF and internal diastolic diameter were similar to older-generation LVADs, with 11.9% of patients achieving full responder status (LVEF $\geq$ 40% and LVIDd $\leq$ 5.9 cm). HM3 provided effective LV unloading and was associated with a lower rate of acute right ventricular failure, but its impact on structural and functional recovery was not superior to earlier devices, emphasizing the need for additional strategies to optimize myocardial recovery. Finally, a study assessed cerebral hemodynamics in 20 patients (mean age 65 ± 9 years, 20% women) before and after

HeartMate 3 LVAD implantation, measuring cerebral autoregulation and cerebrovascular reactivity using transcranial Doppler at four time points (Favilla et al., 2023). Cerebral autoregulation improved at all post-implant visits ($p = 0.004$), while cerebrovascular reactivity showed a delayed improvement at 90 days ($p = 0.04$), despite no significant changes in cerebral blood flow velocity ($p = 0.69$) or mean arterial pressure ($p = 0.61$), suggesting long-term cerebrovascular adaptation.

A network meta-analysis of 49 studies with 31,105 patients found that HM3 is the superior ventricular assist device, with the lowest risk of mortality (99.98), cerebrovascular accidents (99.99), neurologic events (91.45), pump thrombosis (100.00), and bleeding (97.12) compared to HM2 and HVAD (Hanafy et al., 2024). Exchanging HM2 or HVAD to HM3 significantly reduced mortality when complications were present, while hospital admissions were lower in HM3 compared to HM2 (OR: 1.90, 95% CI: 1.15-3.12), supporting HM3 as the preferred choice for LVAD exchange.

Despite these advantages, rehospitalizations remain a challenge. Compared to HeartMate II, HM3 is associated with lower rehospitalization rates (2.1±0.2 vs. 2.7±0.2 per patient-year, $P = 0.015$), fewer hospital days (17.1 vs. 25.5 days per patient-year, $P = 0.003$), and reduced post discharge costs ($37,685±4,251 vs. $76,599±11,889 per patient-year, $P < 0.001$) (Mehra et al., 2018). The primary drivers of these differences were lower incidences of pump thrombosis (0.6% vs. 12.5%, $P < 0.001$) and stroke (2.8% vs. 11.3%, $P = 0.002$), underscoring HM3's economic advantages. Real-world data from Medicare beneficiaries confirmed superior one-year survival for HM3 compared to HeartMate II and other LVADs, with a 36% and 49% lower mortality risk, respectively, and associated reductions in hospitalizations and Medicare expenditures (Pagani et al., 2021).

A systematic review of 134 clinical studies and 19 economic evaluations found that HM3 improved survival (77% at 24 months vs. 59% with HeartMate II) and reduced stroke rates, with an indirect analysis indicating a 75% reduction in mortality risk compared to medical management (RR=0.25, 95% CI = 0.13-0.47) (Beese et al., 2024). However, the incremental cost-effectiveness ratio ranged from £53,496 to £58,244 per quality-adjusted life-year gained, suggesting that further refinement of cost-effectiveness estimates is needed, particularly in the UK National Health Service. An economic analysis compared the cost-effectiveness of the HeartMate 3 against medical therapy for transplant-ineligible advanced heart failure patients in the UK using an indirect comparison of MOMENTUM 3, REMATCH, and ROADMAP trial data (Lim et al., 2022). The incremental cost-effectiveness ratio (ICER) for LVAD therapy was estimated at £47,361 per quality-adjusted life year (QALY) gained, with a 97.1% probability of cost-effectiveness at a £50,000 threshold, and was lower in inotropic-dependent patients (INTERMACS 1-3: £45,616) but higher in ambulatory heart failure patients (INTERMACS 4-7: £64,051). The findings suggest that HM3 LVAD therapy may be cost-

effective for patients requiring inotropic support but exceeds the willingness-to-pay threshold in less-ill ambulatory heart failure patients in the NHS UK-England context.

4.6.1.3 CH-VAD

The CH-VAD is a centrifugal-flow LVAD featuring a fully magnetically levitated rotor. Unlike the HeartMate 3, which employs a bearingless motor, the CH-VAD incorporates an independent electric motor and magnetic bearing system, allowing for an optimized internal space. This results in a compact external profile measuring 47 mm in diameter and 25 mm in thickness, comparable to the HeartWare HVAD, while supporting a larger 33 mm impeller (X. Wang et al., 2024). Operating at 2,800 rpm, the pump delivers a flow rate of 5 L/min at a pressure gradient of 70 mmHg, with a maximum speed of 4,200 rpm supporting flows up to 10 L/min minute. The relatively low rotational speed minimizes turbulence and shear stress, preserving blood integrity and reducing the risk of hemolysis and thrombosis.

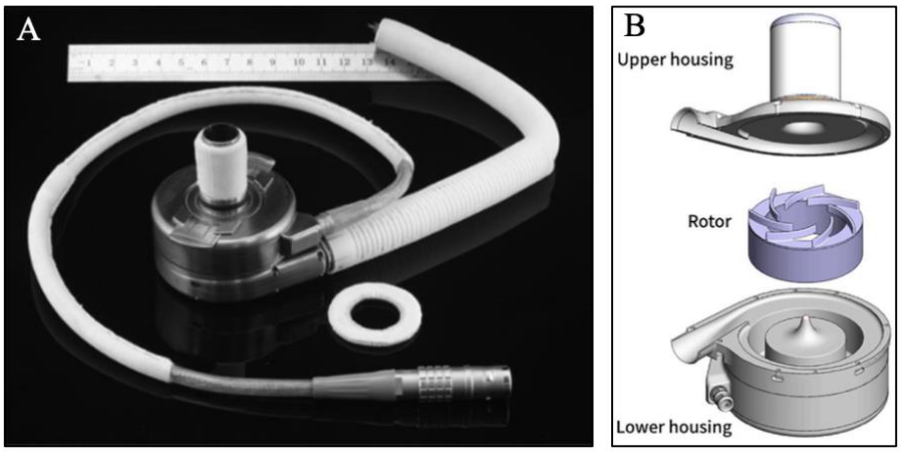


Figure 49. (A) CH-VAD prototype, (B) Exploded view.

The CH-VAD utilizes a dual-flow path system to enhance hemocompatibility. The impeller is mounted on the flat top of the rotor, generating centrifugal flow, while a nose cone structure ensures a smooth transition from axial to radial flow, creating a uniform velocity distribution at the impeller inlet. When magnetic levitation is activated, the rotor maintains a U-shaped levitation gap within the annular pump housing, forming a secondary flow path that improves blood washout. The gap width of 0.25 mm is optimized to balance sufficient washout of blood-contacting surfaces, minimization of exposure to high shear stress, and prevention of Taylor vortices, which can contribute to thrombosis. A computational fluid dynamics analysis comparing the CH-VAD with the HeartWare and HeartMate II demonstrated superior hemocompatibility, with hemolysis indices two times lower than those of the other devices (Zhang et al., 2020). The CH-VAD exhibited the lowest percentage of blood volume

exposed to shear stress above 100 Pa, at 0.4% in normal conditions compared to 1.0% for the HVAD and 2.9% for the HeartMate II. Washout efficiency was also favorable, with over 98% of blood volume cleared from the CH-VAD within 0.4 seconds. Shear stress distributions showed that the CH-VAD had a significantly lower percentage of surface area exposed to high shear stress above 100 Pa, with 7.5% in normal conditions versus 32.7% for the HVAD and 37.8% for the HeartMate II. Under hypertensive conditions, shear stress increased across all devices, but the CH-VAD remained the lowest, with 13.7% of its surface area exceeding 100 Pa compared to 42.7% for the HVAD and 47.1% for the HeartMate II. Another computational fluid dynamics study evaluated blood damage in CH-VAD, HVAD, and HeartMate II (among other) under identical clinical conditions, identifying shear stress above 100 Pa as the primary cause of hemolysis and thrombosis in HVAD and HeartMate II, while CH-VAD exhibited moderate blood trauma risks concentrated in the secondary flow passage and impeller region (Li et al., 2022). Residence time was a critical factor in thrombotic risk for HeartWare and HeartMate II, whereas in CH-VAD, hemolysis and bleeding risks were linked to the hydrodynamic clearance and impeller passage. The multi-indicator analysis demonstrated that among the three devices, HeartMate II had the highest overall risk of blood damage, followed by HeartWare, with CH-VAD exhibiting the lowest hemolysis, thrombosis, and bleeding potential due to its optimized flow path design.

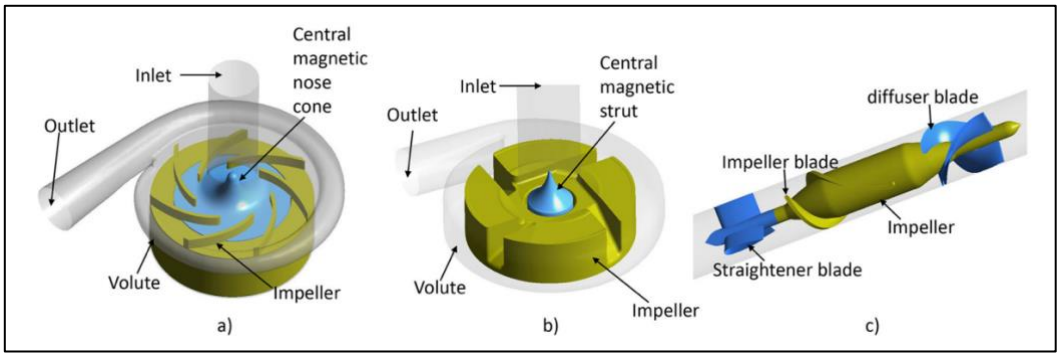


Figure 50. Schematic drawing of the flow domains of the a) CH-VAD, b) HVAD and c) HM II pumps (parts with brown color are the rotary components).

The CH-VAD's flow path design further contributes to its hemocompatibility by reducing turbulence and secondary flow disturbances. A study comparing turbulent flow fields in the CH-VAD and HeartMate III using large eddy simulation showed that the CH-VAD's narrow and long secondary flow path resulted in lower turbulence intensity and reduced shear stress exposure, leading to improved hydraulic efficiency and minimal disturbance to primary flow (Wu et al., 2024). In contrast, the HeartMate III's wider clearance design led to stronger secondary flows, higher turbulence, and increased flow loss, resulting in a steeper performance curve and greater sensitivity to changes in

operating conditions. At higher flow rates, the incidence angle in the HeartMate III increased significantly, causing larger separation zones and a further drop in efficiency compared to the CH-VAD. The CH-VAD's U-shaped secondary flow path allowed for more uniform flow velocity distribution, reducing blood residence time and potential thrombogenic risks.

The CH-VAD has undergone multiple preclinical evaluations to assess its safety, hemocompatibility, and anticoagulation management strategies. In a 14-day calf implantation study, the CH-VAD demonstrated stable pump function, consistent hemodynamic parameters, and negligible hemolysis (Y. Wang et al., 2018). Post-explant analysis revealed no thrombus formation within the device or around the inflow and outflow cannulas, no signs of infection, and only mild-to-moderate adhesions between the pericardial sac and adjacent structures. Gross examination of internal organs was unremarkable, supporting the CH-VAD's potential for safe long-term implantation with superior hemocompatibility due to its large-gap maglev design. A separate 60-day bovine study evaluating hemocompatibility and an anticoagulation regimen demonstrated stable pump performance, no significant thrombus formation or thromboembolic lesions, and low plasma free hemoglobin levels, suggesting minimal hemolysis and paving the way for future good laboratory practice studies (Y. Wang, Smith, et al., 2020). Another study developed a validated anticoagulation regimen for a sheep model testing the CH-VAD, using heparin to maintain an activated clotting time of 326 ± 33 seconds intraoperatively and 157 ± 28 seconds postoperatively, followed by warfarin to sustain an international normalized ratio between 1.2 and 2.0 (Xu et al., 2018). Among six implanted devices, only one case showed thrombus or fibrosis in the pump flow channel, while pathological analysis confirmed no thrombosis, necrosis, or microembolism in major organs, demonstrating effective coagulation control with no bleeding complications.

In vitro hemolysis testing has further validated the CH-VAD's superior hemocompatibility. A study comparing the hemolytic performance of the CH-VAD, HVAD, and HeartMate II in a circulating loop at 4.5 L/min for four hours showed that all three devices generated low hemolysis (NIH < 0.01 g/100 L) (Berk et al., 2019). The CH-VAD had significantly lower hemolysis (0.00135 ± 0.00032 g/100 L) compared to the HVAD (0.00525 ± 0.00183 g/100 L) and HeartMate II (0.00583 ± 0.00182 g/100 L), with reduced platelet activation, suggesting superior hemocompatibility relative to the clinically used devices.

Clinical evaluation of the CH-VAD in patients with end-stage heart failure has further demonstrated its safety and effectiveness. In the largest CH-VAD single-center study, 50 patients at Fuwai Hospital received CH-VAD implantation between June 2017 and August 2023, with a mean support duration of 868 ± 630 days (range 33 days to 6.4 years) (X. Wang et al., 2024). Kaplan-Meier survival rates were 93% at one and two years and 89% at three years. Of the patients, 80% remained on

support, three were bridged to recovery, two received transplants, and five died. Major adverse events included right heart failure in 10%, surgical-related bleeding in 8%, arrhythmia in 8%, driveline infections in 16%, three nondisabling strokes, and one gastrointestinal bleeding, with no reported device malfunctions during follow-up. These results suggest that the CH-VAD is a safe and effective long-term support device, demonstrating high survival rates with relatively low complication rates.

The CH-VAD represents a significant advancement in ventricular assist device technology by integrating magnetically levitated rotor dynamics, optimized flow path geometry, and a miniaturized high-performance pump structure. Future applications will explore its long-term clinical performance, potential for a fully implantable system, and enhanced power delivery mechanisms to further improve patient outcomes.

4.6.1.4 PediaFlow

The PediaFlow LVAD underlines another extension in cardiac function enhancement, uniquely designed to address the need for long-term mechanical circulatory support in infants and toddlers. The PediaFlow VAD is a miniature mixed-flow turbodynamic pump with magnetic levitation. The maglev design allows the impeller to float freely within the pump housing, resulting in nearly frictionless rotation (Noh et al., 2008). This feature enhances energy efficiency and ensures smooth, continuous blood flow, while also minimizing shear stress on blood components. This is particularly critical in pediatric patients, who are more susceptible to hemolysis, platelet activation, and von Willebrand factor degradation. Constructed with biocompatible materials, the PediaFlow LVAD minimizes inflammatory responses and thrombogenicity. The pump housing is primarily made of titanium. Blood-contacting surfaces are coated with medical-grade polymers to reduce clot formation and promote endothelialization. The fully implantable design includes a single, small-caliber percutaneous lead for power and data transmission, smart sensor-based hemodynamic control to monitor cardiac status, and specially designed pediatric cannulae for left and right ventricular support (Wearden et al., 2006). The PediaFlow is an ultra-compact device, specifically engineered to fit within the pericardial space of neonates and infants. The device represents a dramatic improvement in size and usability compared to earlier mechanical circulatory support systems like the Berlin Heart EXCOR. The pump delivers continuous blood flow, operating at rates between 0.3 and 1.5 L/min minute, tailored to the smaller circulatory demands of pediatric patients.

The PediaFlow design was optimized through computational fluid dynamics and weighted objectives analysis, comparing centrifugal and mixed-flow impeller configurations. The axial mixed-flow impeller was selected due to superior biocompatibility, manufacturability, and fluid dynamics performance. Biocompatibility efforts focused on minimizing thrombosis and hemolysis using advanced computational blood damage models tailored for neonates, specialized blood-contacting materials, and microchannel arrays to evaluate red blood cell deformation and shear stress (Gardiner et

al., 2007). Thermal modeling of the PediaFlow VAD using finite element analysis (FEA) and computational fluid dynamics incorporated empirical heat transfer equations to evaluate heat dissipation from motor windings, magnetic bearings, and eddy currents. Results showed that under normal operation, the pump's temperature rise does not exceed 2°C, minimizing the risk of tissue and blood thermotrauma.

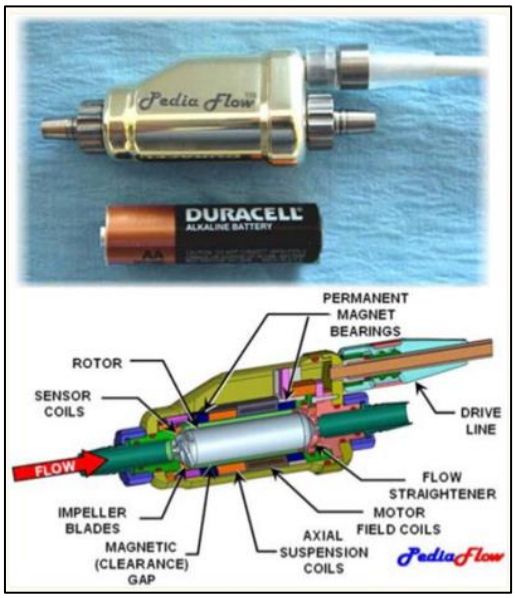


Figure 51. The PediaFlow PF3 magnetically levitated mixed-flow blood pump, approximating the size of an AA-cell battery (top). Partial sectional view displays the principal subsystems (bottom).

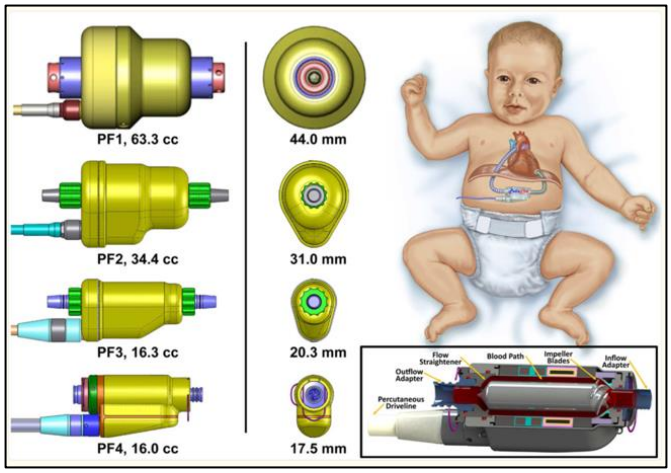


Figure 52. Evolution and miniaturization of the PediaFlow® from the first prototype (PF1) to the 4th generation (PF4) pediatric VAD and pump topology (inset).

In terms of operational dynamics, the PediaFlow includes advanced control systems that allow for precise modulation of flow rates based on the patient's real-time physiological needs. Unlike pulsatile devices, which rely on diaphragms or pusher plates to mimic the heart's natural contraction,

the PediaFlow's continuous-flow mechanism ensures consistent perfusion with fewer mechanical components, thereby reducing the risk of mechanical failure. The simplified design contributes to its compactness and reliability, offering a significant advantage over bulkier, more complex systems.

Preclinical evaluations of the PediaFlow LVAD have demonstrated its effectiveness in maintaining stable hemodynamics and preserving end-organ function in animal models. The first-generation PediaFlow (PF1), a miniature magnetically levitated mixed-flow pump designed for newborns and infants (3–15 kg), demonstrated low hemolysis (NIH = 0.0087 g/100L) and promising hemodynamic performance in 6-hour in vitro tests and chronic in vivo ovine studies (6, 17, and 10 days), validating its magnetic bearing design (Johnson, Wearden, et al., 2011). The second-generation PediaFlow (PF2), a magnetically levitated turbodynamic pump designed for small children with a targeted flow rate of 0.3–1.5 L/min, was evaluated for blood biocompatibility through chronic ovine implantation studies (17, 30, and 70 days) and surgical sham procedures (30 days) (Maul et al., 2011). Platelet activation returned to baseline within two weeks after sham surgery and remained stable in PF2-implanted animals, except for one case of late-term activation linked to a percutaneous cable defect, demonstrating early biocompatibility and providing comparative data for future cardiovascular device assessments in the ovine model (Johnson, Vandenberghe, et al., 2011). A prescriptive, simulation-based design approach was implemented to optimize performance and biocompatibility while minimizing development time and cost. Computational fluid dynamics was used to model blood flow and shear stresses, while finite element analysis was employed to study structural and electromagnetic properties. Multi-disciplinary system-level optimization was performed to balance pump efficiency, hemocompatibility, and anatomical fit. The final PediaFlow PF3 design underwent CFD optimization, ensuring a streamlined flow path that minimizes recirculation zones and thrombogenic potential (Antaki et al., 2010). In vitro and in vivo testing validated the safety and functionality of the PediaFlow design. Bench-top blood analog tests confirmed low hemolysis levels (NIH = 0.0467) and sufficient hydrodynamic efficiency. In vivo testing in ovine models demonstrated excellent hemocompatibility after 72 days of implantation, with no complications such as hemolysis, thromboembolism, or organ dysfunction. The PF3 prototype, roughly the size of an AA battery, is capable of delivering 0.3–1.5 L/min of flow, sufficient for supporting the circulation of a small infant (Antaki et al., 2010).The fourth-generation PediaFlow, a fully magnetically levitated, continuous-flow pediatric ventricular assist device designed for infants as small as 3 kg, underwent extensive computational, in vitro, and preclinical ovine testing, demonstrating minimal hemolysis and excellent hemocompatibility at flow rates of 0.5 to 1.5 L/min. Designated a Humanitarian Use Device by the FDA, these results support its potential for chronic mechanical circulatory support in pediatric patients as a bridge to transplant, surgery, or recovery (Olia et al., 2018).

4.7 Hybrid Suspension (MagLev and Hydrodynamic Suspension)

4.7.1 HeartWare HVAD

The HeartWare HVAD was a third-generation centrifugal-flow LVAD. Designed for intrapericardial placement, the HVAD represented a significant innovation by eliminating the need for a preperitoneal pocket, thereby reducing surgical invasiveness and allowing implantation in smaller patients (Larose et al., 2010). Its compact size and integration of an inflow cannula into the pump housing simplified the implantation process and made it suitable for a wider range of anatomical conditions. The pump featured a magnetically and hydrodynamically levitated rotor, which operated at speeds of 2,400–3,200 rpm to deliver continuous blood flow from the left ventricular apex to the ascending aorta (Molina & Boyce, 2013). This design minimized mechanical wear, reduced blood trauma, and improved durability compared to earlier pulsatile devices. The HVAD was constructed with biocompatible materials such as titanium for durability and polyurethane for blood-contacting surfaces, with textured coatings to reduce thrombogenicity (Rogers et al., 2017).

Figure 53. The blood pump of the device (upper) and the structure of the blood pump (lower).

HeartWare HVAD has been evaluated in various preclinical and clinical studies to assess their performance, safety, and adaptability. In a 90-day preclinical study, the HeartWare HVAD demonstrated excellent hemocompatibility and reliability in healthy sheep, with no thrombus formation,

minimal renal infarction, and stable hematologic and biochemical parameters, even without anticoagulation or antiplatelet therapy (Tuzun et al., 2007). An in vitro hemocompatibility study found the highest hemolysis rates under adult systemic conditions, lower rates in pediatric systemic and adult pulmonary flow, significant von Willebrand factor degradation across all conditions, and no significant platelet activation (Chan et al., 2021). The LATERAL trial demonstrated that HVAD implantation via thoracotomy achieved an 88.1% success rate, reduced hospital stays, and had a favorable safety profile compared to sternotomy (McGee et al., 2019). A two-year follow-up showed low adverse event rates after 6 months and 95% freedom from disabling stroke, reinforcing the long-term benefits of the thoracotomy approach (Wieselthaler et al., 2021). Additionally, the MVAD Pump, a miniaturized axial-flow LVAD, demonstrated reliable hemodynamic support, safety, and feasibility for long-term use in an ovine model, with seven of nine sheep surviving 90 days without device malfunctions or organ compromise (McGee et al., 2014).

HeartWare HVAD has been studied across different patient populations to evaluate its efficacy, safety, and clinical outcomes. The ADVANCE study demonstrated that HeartWare HVAD was noninferior as a bridge to transplantation, with a 90.7% success rate at 180 days and significant improvements in functional capacity and quality of life (Aaronson et al., 2012). The ENDURANCE trial confirmed noninferiority to HeartMate II for 2-year survival, though HVAD had a higher stroke rate (29.7% vs. 12.1%) (Rogers et al., 2017). The ENDURANCE Supplemental Trial found that enhanced blood pressure management reduced hemorrhagic stroke by 50.5% but did not achieve noninferiority for stroke or TIA (C. A. Milano et al., 2018). The ReVOLVE registry analyzed 254 HVAD implants across multiple centers, reporting 87% survival at 6 months, 79% at 2 years, and 73% at 3 years, with transplantation in 22% and a 17% mortality rate (Strueber et al., 2014). A review of 382 ADVANCE BTT and CAP trial HVAD recipients found 19.6% underwent valve procedures, with no significant impact on 1-year survival, though tricuspid valve interventions appeared to reduce late right heart failure in patients with significant preimplant regurgitation (C. Milano et al., 2014). In a global retrospective study of 205 pediatric patients implanted with the HeartWare HVAD, 65.4% underwent heart transplant within 12 months, while mortality (10.7%) was significantly associated with the need for temporary right ventricular support (HR 10.65, $P = 0.001$) and pump exchange (HR 7.9, $P = 0.006$), highlighting the need for further optimization to improve outcomes (Conway et al., 2018).

HeartWare HVAD recipients have been studied extensively to assess complications and outcomes associated with long-term device support. Gastrointestinal bleeding was evaluated in 382 HeartWare HVAD recipients from the BTT trial and CAP found an incidence of 0.27 events per patient-year, with 15.4% of patients experiencing bleeding, mostly due to arteriovenous malformations in the small intestine (Goldstein et al., 2015). In the ADVANCE BTT and CAP trials, 332 HVAD recipients had low rates of driveline infections (16.9%, 0.25 EPPY) and sepsis (17.2%, 0.23 EPPY), though sepsis

was associated with a trend toward reduced survival due to stroke and multi-organ failure (John et al., 2014). Ischemic (6.8%) and hemorrhagic (8.4%) cerebrovascular events were linked to aspirin ≤ 81 mg, atrial fibrillation, mean arterial pressure >90 mmHg, and INR >3.0, while improved blood pressure management reduced hemorrhagic stroke risk from 10.8% to 1.8% ($p = 0.0078$) (Teuteberg et al., 2015). A separate analysis found that pump thrombus occurred in 8.1% of HVAD recipients (0.08 events per patient-year), with risk factors including elevated mean arterial pressure, suboptimal anticoagulation (INR ≤2), and higher INTERMACS profile (≥3) (Najjar et al., 2014). A prospective observational study evaluated myocardial adaptation to the HeartWare LVAD in 37 patients by assessing hemodynamic, structural, and transcriptomic changes (Muthiah et al., 2017). Chronic support led to significant reverse remodeling, with a 4.8-fold reduction in NT-proBNP levels, decreased pulmonary capillary wedge pressure (27.1 ± 6.6 to 14.8 ± 5.1 mmHg, $p < 0.0001$), reduced LV cardiomyocyte size ($2,789.7 \pm 671.8$ to $2,290.8 \pm 494.2$ μm², $p = 0.02$), and improved LV and RV ejection fractions ($p < 0.001$ and $p < 0.02$, respectively). Despite these structural and functional improvements, transcriptomic analysis showed no significant changes in the microRNA profile.

Various comparative studies have explored outcomes, complications, and usability. The HMII and HVAD differ in their flow mechanisms. Computational fluid dynamics comparing HMII and HVAD indicated that while HVAD had larger volumes exposed to shear stresses above 9 Pa and longer residence times, both pumps exhibited similar hemolysis indices, with key hemolysis regions in the rotor and diffuser blades for HMII and the volute tongue for HVAD (Thamsen et al., 2015). Another computational fluid dynamics study analyzed the interaction between patient-specific hemodynamics and different LVAD designs, including the HeartWare HVAD, HeartMate II and HeartMate 3 in both continuous and artificial pulse modes, incorporating anatomical reconstructions from computed tomography and lumped-parameter modeling of systemic circulation from a single patient. The HVAD demonstrated the highest blood velocity in the outflow cannula at 1.74 m/s (range 1.40-2.24 m/s), compared to 0.92 m/s (0.78-1.19 m/s) for HeartMate II and 0.91 m/s (0.86-1.00 m/s) for HeartMate 3, while shear stress and shear rate were also highest in the HVAD at 1.76 Pa and 136 s^{-1}, respectively, versus 1.33 Pa and 91.5 s^{-1} for HeartMate II and 1.33 Pa and 89.4 s^{-1} for HeartMate 3 (Grinstein et al., 2021). Both devices have been shown to effectively reduce pulmonary hypertension and improve transplant candidacy, with significant reductions in mean pulmonary artery pressure (31.9 ± 10.6 to 22.1 ± 6.6 mm Hg, $p = 0.001$) and pulmonary vascular resistance (3.08 ± 1.6 to 1.8 ± 1.0 mm Hg, $p = 0.007$) within seven days of implantation (Pauwaa et al., 2012). Survival outcomes following heart transplantation are comparable between devices, with post-transplant survival rates at 1, 2, and 3 years showing no significant difference (88.4% vs. 87.8%, 79.9% vs. 83.8%, 77.4% vs. 79.9%, $p = 0.843$) (Topkara et al., 2014). However, in destination therapy, survival varies depending on comorbidities, with dialysis-dependent patients showing better outcomes when stabilized before implantation (64.7% at 6 months vs. 14.3% in unstable dialysis patients) (Lamba et al., 2022). Despite comparable survival

rates, thrombotic and hemorrhagic complications remain a concern. A pooled analysis of 734 CF-LVAD recipients showed that HVAD was independently associated with a higher stroke risk (HR: 1.8, 95% CI: 1.25–2.5, P = .003), while HMII had a trend toward more driveline infections, though overall mortality was similar between devices (7.3% vs. 7.5%, P = .95) (Stulak et al., 2016). Long-term anticoagulation discontinuation (≥30 days) led to an 8.5-fold increase in ischemic stroke risk and a 3.9-fold increase in mortality, particularly affecting HVAD recipients (Inchaustegui et al., 2023). Gastrointestinal bleeding was more frequent in HVAD patients (32.5% vs. 24.8% in HMII), with arteriovenous malformations as the primary cause (Kawabori et al., 2020). Additionally, HVAD recipients had significantly higher hemorrhagic stroke rates (44% vs. 10% at one year, p = 0.04) (Lalonde et al., 2013). Both devices provided similar mechanical unloading effects, with comparable improvements in LVEF (18% to 28% in HMII, 26% in HVAD) and reductions in left ventricular volumes over time (Al-Sarie et al., 2016). In a 3D echocardiographic analysis of 31 LVAD patients (19 HeartMate II, 12 HeartWare), both devices increased cardiac output and reduced wedge pressure at higher speeds, but HeartMate II led to greater left ventricular volume reduction (mean Δ = 127 ml vs. 51 ml) and more pronounced right ventricular dilation (mean Δ = 60 ml vs. 22 ml), with its septum becoming more convex, unlike HVAD (Addetia et al., 2018). Right ventricular failure and postoperative acute renal failure occurred at similar rates in both groups, with preoperative central venous pressure elevation identified as a key predictor of worse outcomes (Borgi et al., 2013). Severe preoperative right ventricular dysfunction was also independently associated with a higher risk of gastrointestinal bleeding (62% vs. 33%, P = 0.001; HR: 1.799, 95% CI: 1.089-2.973, P = 0.022) (Sparrow et al., 2015). A multicenter analysis of 497 LVAD recipients found comparable neurologic event rates between HM II and HVAD after covariate adjustment, with advanced age as the only significant predictor (P = 0.02) of adverse neurologic outcomes (Coffin et al., 2015). A study evaluating the usability of HVAD and HMII in emergency scenarios found that 71% of paramedics successfully managed simulated power failures, emphasizing the need for clearer labeling, standardized emergency protocols, and user-friendly design improvements. Finally, a study comparing platelet functionality in 26 LVAD patients (8 HeartMate II, 9 Jarvik 2000, 9 HeartWare) found significantly higher intraplatelet reactive oxygen species generation, mitochondrial damage, and platelet apoptosis in HeartWare recipients, correlating with increased risks of major bleeding, infections, systemic inflammatory response syndrome, and right ventricular failure (Mondal et al., 2015).

HVAD has been used in the pediatric population and compared with other MCS devices. A single-center cohort study conducted between 1986 and 2014 examined 78 pediatric patients who received mechanical circulatory support with either the HeartWare (n=13), EXCOR device (n=63), Berlin Heart INCOR (n=1), or Toyobo (n=1). The findings revealed no significant differences in post-transplant survival among the different devices, suggesting comparable efficacy despite variations in patient selection and ventricular support strategies (Hetzer et al., 2018). Similarly, a retrospective

analysis of 38 pediatric patients supported with EXCOR (n=29) or HeartWare (n=9) between 2008 and 2014 demonstrated comparable survival rates (89.7% vs. 88.9%). However, neurological complications were observed more frequently in HeartWare recipients (33.3% vs. 10.3%), indicating that while both devices are viable long-term support options, they present distinct risk profiles, particularly concerning neurological outcomes (Sandica et al., 2016).

A network meta-analysis of four randomized clinical trials and four observational studies, encompassing 2248 patients, demonstrated that LVADs significantly improve survival compared to medical therapy, with relative risks for death of 0.79 (95% CI 0.60-1.04; P-score 0.89) for HeartMate II, 0.85 (95% CI 0.62-1.17; P-score 0.64) for HeartWare, and 0.88 (95% CI 0.59-1.31; P-score 0.60) for HeartMate 3, whereas medical management had a significantly higher mortality risk (RR: 1.48; 95% CI 1.21-1.80; P-score 0.01) (Cavarretta et al., 2019). Despite no significant differences in survival among newer devices, HeartMate 3 and HeartWare demonstrated lower complication rates, including reductions in bleeding, device thrombosis, hepatic dysfunction, renal dysfunction, respiratory dysfunction, right ventricular failure, and sepsis, underscoring the necessity for further technological refinements to enhance clinical outcomes in end-stage heart failure. Another retrospective observational analysis of 106 patients who underwent continuous-flow LVAD implantation between 2010 and 2020 found no significant differences in overall survival between HeartMate 3 and HeartWare HVAD, with a 4-year survival probability of 54.7% for HM3 and 74.1% for HVAD (P = 0.296). However, after adjusting for confounders, HW was associated with a significantly higher risk of device malfunctions (HR 6.49, 95% CI [1.89, 22.32], P = 0.003), while rates of pump thrombosis and other major adverse events did not differ significantly between the two devices (Mihalj et al., 2022).

In 2021, HVAD application was discontinued due to safety concerns, including an increased risk of neurological events and pump malfunction.

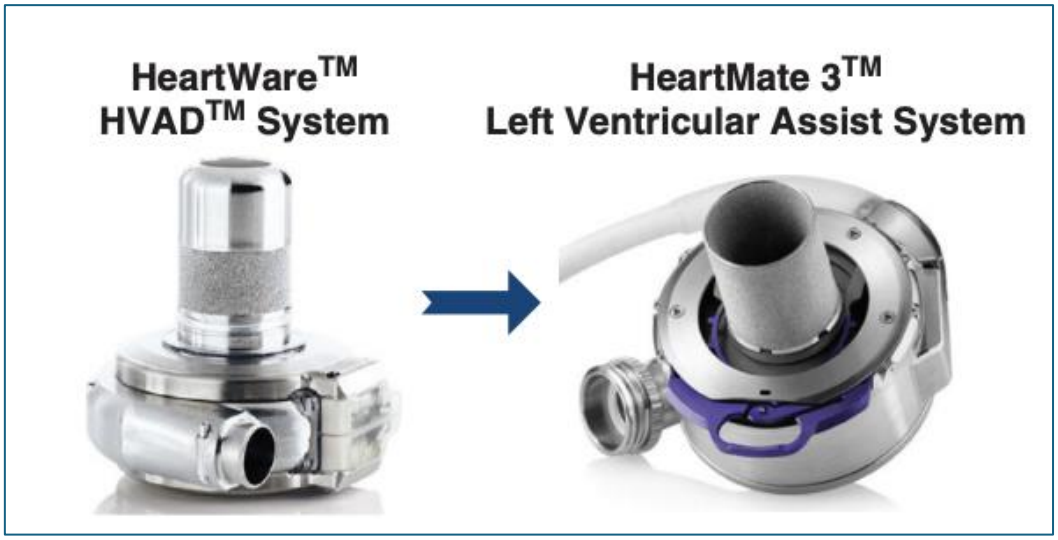


Figure 54. Head-to-Head depiction of HeartWare HVAD system and HeartMate 3LVAD.

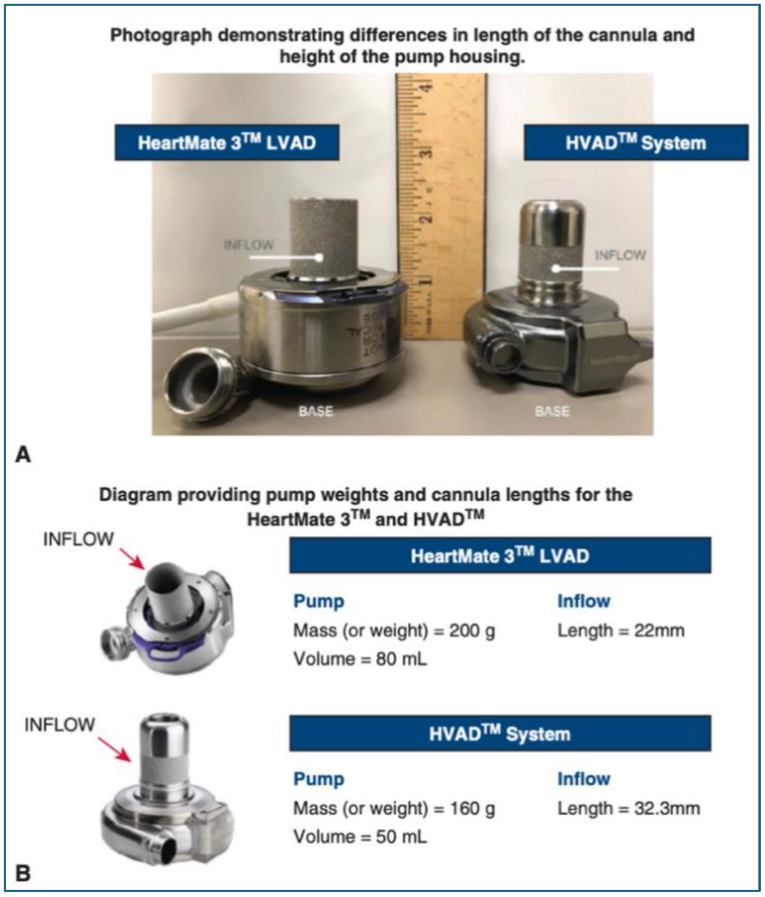


Figure 55. Comparison of the pump dimensions and size for the HeartMate 3 and HeartWare HVAD System.(A) The differences in length of the cannula and height of the pump housing. (B) The pump weights and cannula lengths for the HeartMate 3 and HVAD. The diameter of the inflow cannula of the HVAD is approximately 20.6 mm, and the diameter of the HeartMate 3 inflow cannula is 20.5 mm. The length of the sintering along the inflow cannula is approximately 11.7 mm for the HVAD and approximately 22 mm for the HeartMate 3

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5 Experimental LVADs

5.1 TorVAD

Rotary piston blood pumps have undergone significant evolution over the past several decades as researchers aimed to develop mechanical circulatory support systems that combine the benefits of displacement pumps' pulsatility with the compact design and durability of rotary pumps. The CORA pump, developed in the 1970s, was one of the earliest attempts at this technology, utilizing a cam-driven piston to generate pulsatile flow. Despite demonstrating feasibility, the device faced substantial limitations, including sealing failures, mechanical wear, and hemocompatibility issues, leading to its discontinuation. In the 1990s, the ROTACOR pump introduced an improved rotary piston mechanism with the goal of reducing blood trauma and enhancing durability. However, challenges related to mechanical complexity and suboptimal sealing persisted, resulting in blood infiltration into the drive system. By the early 2000s, renewed interest in rotary piston blood pumps led to the development of various prototypes that aimed to refine sealing techniques and improve efficiency. While these designs sought to eliminate direct mechanical contact to enhance longevity, they encountered issues related to excessive heat generation and inconsistent flow regulation. Research projects, mainly in Japan, further refined MCS technology, with the Miwatec/Baylor biventricular system and various total artificial heart (TAH) prototypes entering experimental phases. The culmination of these iterative advancements is the TORVAD, a toroidal rotary piston blood pump that represents the most refined iteration of this pump type. Unlike its predecessors, TORVAD utilizes magnetically coupled pistons to create synchronized pulsatile flow, significantly reducing shear stress while preserving native aortic valve function. This addresses key complications seen in continuous-flow LVADs, such as gastrointestinal bleeding and aortic insufficiency, which have remained unresolved with traditional rotary pumps. TORVAD also incorporates advanced electromagnetic drive systems that eliminate the wear and sealing failures observed in earlier models, providing a promising alternative to conventional LVADs (Wappenschmidt et al., 2016).

The TORVAD is a next-generation toroidal ventricular assist device designed to provide physiologically pulsatile support for patients with heart failure. Unlike conventional continuous-flow LVADs, which rely on high-speed impellers, the TORVAD uses two independently controlled pistons that enable a unique mechanism of aspiration and ejection within a toroidal pumping chamber. One piston acts as a virtual valve while the other rotates around the chamber, displacing blood through positive pressure. These pistons are magnetically coupled to precision-controlled motors, allowing for fine-tuned regulation of position and motion. Operating at low rotational speeds of 60 to 150 rpm, the TORVAD generates significantly lower fluid shear stress compared to traditional impeller-based LVADs, a feature validated in benchtop and preclinical animal studies. By reducing blood trauma, the

device aims to mitigate common LVAD-associated complications, including hemolysis, gastrointestinal bleeding, and acquired von Willebrand syndrome, which contribute to high morbidity and rehospitalization rates in patients supported by conventional continuous-flow pumps (https://www.windmillcvs.com/).

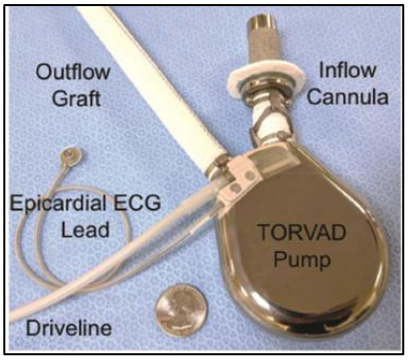

Figure 56. The TorVAD. The core component is a 30-ml displacement torus chamber. The pumping chamber is connected to the left ventricular apex with a sintered titanium inflow cannula and systemic circulation with a 14 mm ePTFE graft. An epicardial ECG sensing lead triggers TORVAD filling and ejection either synchronously (pulsatile or counterpusatile modes) or asynchronously.

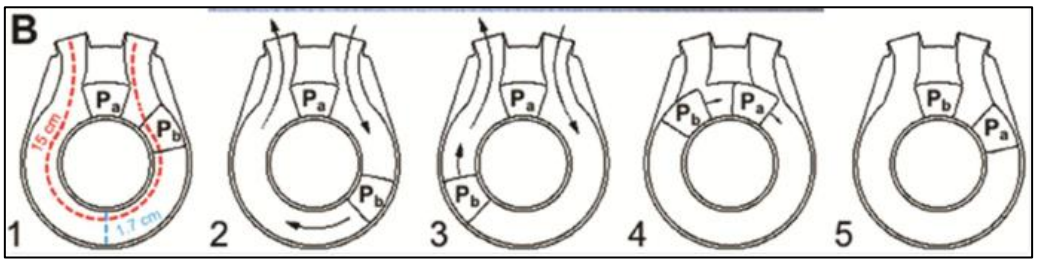

Figure 57. A schematic representation of the TORVAD with two independently controlled pistons. To fill and eject, the TORVAD maintains one of two pistons (Pa) in a stationary position. The other piston (Pb) is actuated around the torus chamber to displace a stroke volume of 30 ml to generate flow (panels 2 and 3). As piston b completes a cycle around the torus and becomes stationary (panel 4), piston a begins a new cycle (panel 5). The result is unidirectional, pulsatile blood flow. Importantly, the TorVAD generates peak shear stress of approximately 10 Pa, which is near physiologic values (2–8 Pa). The dimensions of the wide flow path are show in red and blue.

TorVAD is still in the preclinical phase and has not yet entered clinical trials. The device has been tested in bench-top experiments, computational simulations, and animal studies, demonstrating its unique toroidal rotary piston mechanism designed to provide pulsatile flow while minimizing blood trauma. Currently, there is no current clinical trial registered for TorVAD, and it has not yet received regulatory approval for human implantation. Further preclinical validation is required before TORVAD advances into first-in-human clinical trials.

Hemodynamic modeling has further demonstrated the advantages of the TORVAD over continuous-flow devices (Gohean et al., 2013). A computational cardiovascular system model compared the hemodynamic performance of the TORVAD with the HeartMate II (Gohean et al., 2015). Simulations demonstrated that the TORVAD, with a 30 mL stroke volume and early diastolic counterpulse ejection, maintained comparable systemic support to the HeartMate II (cardiac output 5.7 L/min in both cases) while preserving native aortic valve flow (3.0 L/min vs. 0.4 L/min with HeartMate II) and pulse pressure (26.7 mmHg vs. 12.8 mmHg). The preservation of aortic valve function with TORVAD support could mitigate complications associated with continuous-flow LVADs, such as aortic insufficiency and valve commissural fusion, while reducing shear-related blood trauma. Compared to the HeartMate II, TORVAD support resulted in nearly half the VAD flow (2.7 L/min vs. 5.3 L/min) while achieving the same level of circulatory support, indicating a more efficient unloading of the left ventricle. By preserving the native Frank-Starling mechanism and preventing excessive ventricular unloading, TORVAD may reduce the incidence of suction events and improve long-term hemodynamics in VAD-supported patients.

The preload sensitivity of the TORVAD compared to continuous flow LVADs has been evaluated using lumped parameter models of the cardiovascular system. At low preload (5 mmHg), continuous flow support significantly overpumped the circulation (4.7 L/min vs. 3.5 L/min for TORVAD), leading to ventricular suction events when pulmonary vascular resistance exceeded 0.035 mmHg s/mL. TORVAD counterpulse support, which ejects 30 mL of blood in early diastole, preserved aortic valve flow and maintained physiological preload sensitivity (0.306 L/min/mmHg vs. 0.092 for continuous flow support), reducing the risk of overpumping and suction. This counterpulsation strategy allows TORVAD to adapt to physiological changes while maintaining cardiac output without excessive ventricular unloading (Gohean et al., 2019).

The TORVAD's clinical potential has been validated in preclinical porcine models. In a study of ischemic left ventricular failure, the TORVAD synchronized pulsatile-flow LVAD demonstrated superior hemodynamic performance compared to the continuous-flow BPX-80, achieving significantly higher total cardiac output (5.58 ± 1.58 vs. 5.12 ± 1.19 L/min, $P < .05$), higher mean aortic pressure (67.8 ± 14 vs. 60.2 ± 10 mmHg, $P < .05$), and lower left atrial pressure (11.5 ± 3.5 vs. 13.9 ± 6.0 mmHg, $P < .05$) at the same flow rate (Letsou et al., 2010). In blood trauma studies, the TORVAD, with its lower shear stress and pulsatile flow, demonstrated significantly reduced von Willebrand factor degradation ($-10\% \pm 1\%$ vs. $-21\% \pm 1\%$, $p < 0.0001$), platelet activation (CD 41/61: 645 ± 20 ng/mL vs. $1,581 \pm 150$ ng/mL, $p < 0.001$), and hemolysis (plasma free hemoglobin: 11 ± 2 vs. 109 ± 10 mg/dL, $p < 0.0001$) compared to the HeartMate II (Bartoli et al., 2019). These findings suggest that TORVAD's unique mechanism of synchronized pulsatile ejection reduces hemocompatibility-related complications,

reinforcing its potential to improve clinical outcomes and expand LVAD therapy to patients with less advanced heart failure.

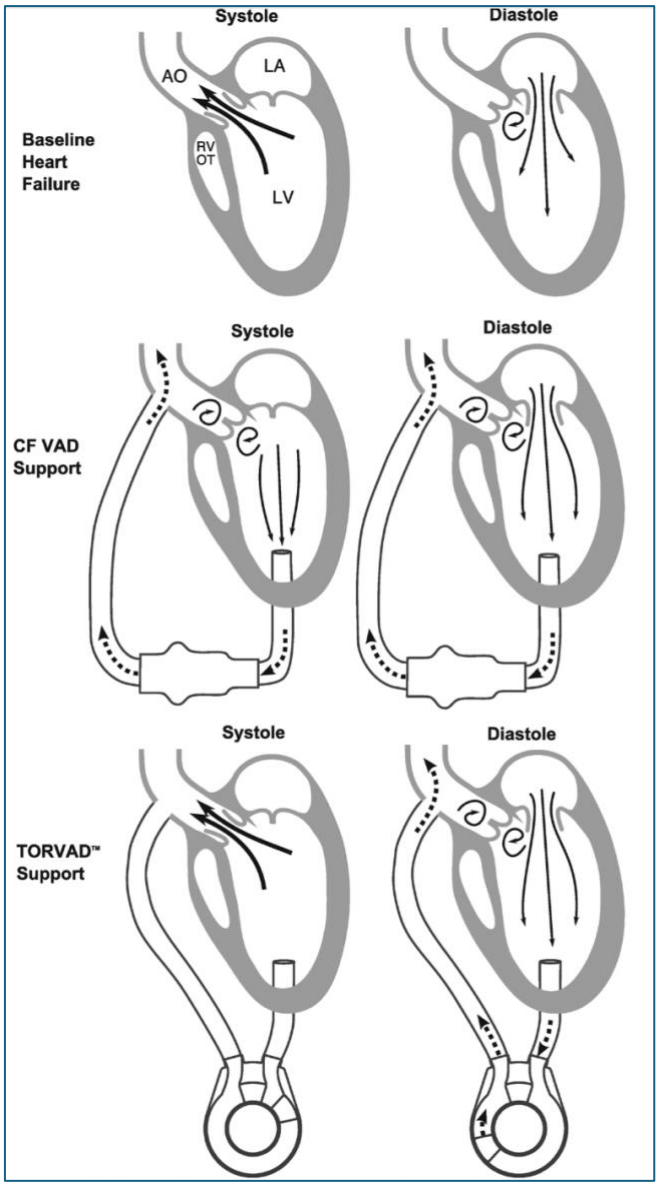

Figure 58. Illustration of continuous flow (CF) and TORVAD support in heart failure.The CF VAD pumps continuously through the cardiac cycle, often eliminating native aortic valve flow during systole. The TORVAD ceases pumping during systole and allows native ejection through the aortic valve, providing full hemodynamic support with only half the VAD flow rate.

The device has also been adapted for pediatric applications (Gohean et al., 2017). Computational modeling determined that a 15 mL stroke volume device with a maximum flow rate of 4 L/min was optimal for pediatric patients with body surface areas ranging from 0.6 to 1.5 m². The TORVAD maintains low shear stress, at least two orders of magnitude lower than continuous-flow VADs, which is critical for reducing complications such as von Willebrand factor degradation and platelet activation. To enhance efficiency and reduce device size, a new radial magnetic coupling

replaced the original C-shaped design, improving torque transmission while reducing overall volume. Finite element modeling optimized motor performance, resulting in improved efficiency, minimal torque ripple, and enhanced heat dissipation. The thermal design ensured that surface temperatures remained within safe limits, with maximum temperature rises of only 0.9°C above ambient levels.

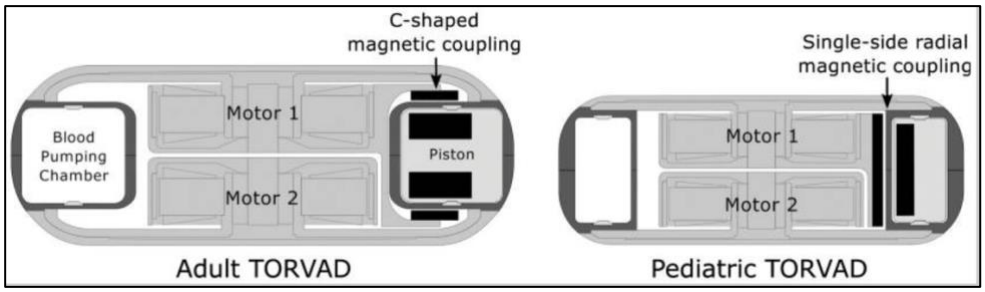

Figure 59. Cross-sections of the adult and pediatric TorVADs, illustrating the location of the motors in the pump and how they are magnetically coupled to the pistons. In this case, motor 1 is shown coupled to a piston, but the piston and magnetic coupling are not shown for motor 2.

5.2 CorWave

The CorWave LVAD is an investigational mechanical circulatory support system designed to provide physiological pulsatile blood flow, setting it apart from traditional continuous-flow LVADs such as the HeartMate 3 (https://www.corwave.com/). Unlike axial- and centrifugal-flow pumps that generate non-pulsatile flow, CorWave utilizes a wave membrane pump that closely replicates the natural heart's pulsatility, both in terms of blood flow speed and rhythm. This innovative design is based on biomimetic wave membrane technology, inspired by the undulating movement of marine animals, where fluid is propelled through oscillatory motion. In CorWave pumps, a polymer membrane remains fixed while an electromagnetic actuator generates oscillations in a magnetic ring, triggering wave propagation along the discoidal membrane. These oscillations propel blood at physiological speeds of 1–2 m/s, significantly lower than the flow speeds observed in rotary pumps, which can exceed 5 m/s. By maintaining a lower shear stress environment, the membrane-based propulsion system reduces blood trauma, preserving blood integrity and minimizing the risk of hemolysis.

A key distinguishing feature of the CorWave LVAD is its ability to provide pulsatile flow at a frequency synchronized with the native heart rate, typically around 60 beats per minute. Unlike continuous-flow turbines, which operate at constant high speeds, the wave membrane has low inertia, allowing for rapid and efficient modulation of its activation frequency and pump flow rate. This dynamic adaptation ensures that the device can respond to changing physiological demands, preserving vascular function and reducing complications such as endothelial dysfunction, gastrointestinal bleeding,

and stroke. Furthermore, the absence of a mechanical impeller significantly reduces shear stress, preserving von Willebrand factor integrity and lowering the incidence of acquired von Willebrand syndrome, a major contributor to bleeding complications in LVAD recipients.

Figure 60. The CorWave LVAD.

Figure 61. The discoidal membrane of the CorWave LVAD. The wave motion can be produced with different membrane geometries, specifically, a discoidal shape and a rectangular shape. The CorWave wave-membrane pump is driven by an electromagnetic actuator, which generates the oscillations of the polymer membrane and translates the propagation of the wave along the membrane (like a sound-speaker), and the propulsion of blood.

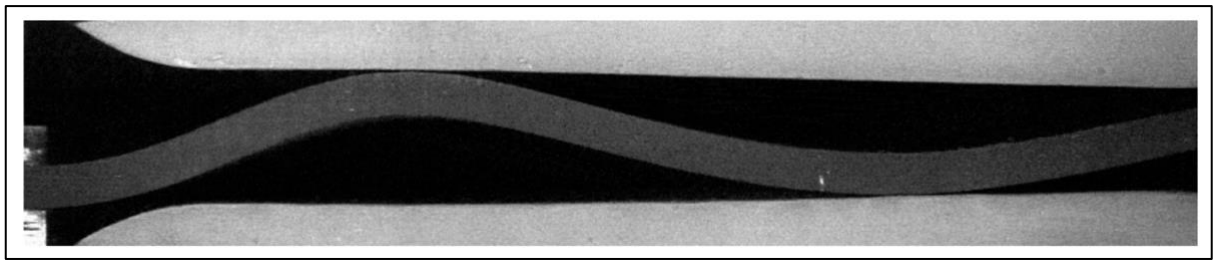

Figure 62. CorWave membrane technology. The wave generated on this membrane moves from the outside to the inside of the disc, radially, propelling blood towards the central orifice.

By integrating physiological pulsatility with reduced blood trauma and lower energy consumption compared to existing continuous-flow devices, the CorWave LVAD represents a promising advancement in mechanical circulatory support. Its ability to reproduce the natural flow patterns of the native heart while minimizing adverse effects associated with non-pulsatile LVADs offers a novel approach to improving patient outcomes and enhancing the long-term durability of LVAD therapy.

Preclinical evaluations have demonstrated promising results confirming the device's ability to maintain pulsatility while reducing hemolysis and thrombosis risk. The pulsatile nature of CorWave has also shown potential advantages in preserving right ventricular function, which is a common limitation of continuous-flow LVADs due to the altered hemodynamic loading conditions they impose on the right ventricle. Preliminary trials are currently assessing the device's long-term safety, efficacy, and durability in human patients. If clinical outcomes align with preclinical expectations, CorWave could represent a significant advancement in LVAD technology by addressing key limitations of existing devices. Further studies are required to evaluate its impact on long-term survival, adverse event reduction, and quality of life improvements for patients with advanced heart failure.

5.3 CorVion

The Corvion LVAD is a fully implantable mechanical circulatory support system designed to enhance the quality of life for patients with severe heart failure (https://corvion.com/technology-corvion/). Unlike conventional LVADs that rely on external components and percutaneous drivelines, the Corvion LVAD is completely internalized, significantly reducing infection risk while improving patient mobility and independence. The system features an advanced hybrid magnetically levitated impeller coupled with a high-efficiency motor, enabling it to operate at a fraction of the power consumption required by existing devices. Drawing less than 1.5 watts to deliver a flow rate of 5 L/min minute, this design optimizes energy efficiency while minimizing blood trauma, reducing the incidence of hemolysis and related complications. The Corvion LVAD incorporates an integrated implantable battery and controller unit, measuring just 13 millimeters in thickness, allowing for pectoral implantation. This system provides up to 12 hours of untethered operation, granting patients the ability to carry out daily activities without dependence on external components. The internal battery, designed for three years of service, can be replaced through a simple surgical procedure. The device's wireless charging system eliminates the need for precise alignment and external connectors, further reducing infection risk. A lightweight external Mobile Charger transmits power through the skin to an internal receiving coil, ensuring simultaneous pump operation and battery recharging. This design allows

patients to sleep without being connected to external battery packs or wall power, greatly enhancing comfort and ease of use.

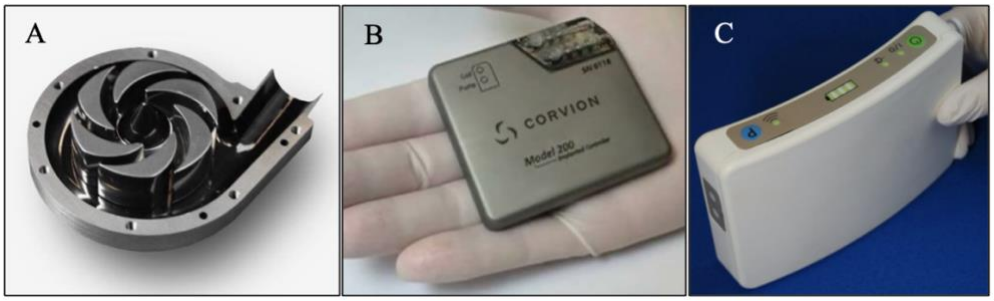

Figure 63. (A) The CorVion LVAD, (B) battery unit, (C) recharger unit.

Recognizing its potential to revolutionize mechanical circulatory support, the Corvion LVAD received Breakthrough Device Designation from the U.S. FDA in December 2020. By integrating a fully internalized system with cutting-edge energy efficiency, the Corvion LVAD represents a significant advancement in circulatory support technology, offering a patient-friendly alternative for individuals suffering from end-stage heart failure.

5.4 CorHeart

The Corheart 6 is a next-generation magnetically levitated continuous-flow left ventricular assist device designed to address key limitations of existing devices, including size constraints, thrombotic complications, and implantation feasibility. With a diameter of only 34 mm and a weight of 90 g, it is significantly smaller than conventional devices such as the HeartMate 3, making it suitable for minimally invasive implantation and for patients with smaller body surface areas. Unlike axial-flow LVADs, which have been associated with higher shear stress and thrombosis risk, the Corheart 6 employs a fully magnetically levitated rotor that eliminates mechanical contact, reducing friction, wear, and power consumption. The CorHeart 6 is mainly used in China (Tu et al., 2024).

Figure 64. Corheart 6 LVAD: 34 mm indiameter, 26 mm in width, and 90 g in weight.

One preclinical study demonstrated that the Corheart 6 provides highly efficient blood washout, achieving 55% clearance in 0.049 seconds and 95% in 0.165 seconds, significantly lowering the risk of thrombus formation (Fang et al., 2023). Computational fluid dynamics simulations confirmed that shear stress values above 150 Pa were localized only at the rotor edges, while overall wall shear stress remained below thrombogenic thresholds. Hemolysis indices remained low across both computational and in vitro studies, with in vitro values ranging from 0.00092 to 0.00134 g/100 L, demonstrating superior hemocompatibility compared to previous-generation LVADs. In vivo testing on ten sheep over a 60-day period at a stable flow rate of 2.0 ± 0.2 L/min confirmed the absence of thrombus formation or hemolysis, further validating its biocompatibility and mechanical performance.

A single-arm, prospective, open-label, multicenter pre-market study is conducted to evaluate the safety and effectiveness of the Corheart 6 LVAD for treating advanced, refractory heart failure in Europe. The study aims to enroll 50 patients across 10 investigational sites in Germany and Austria, with follow-up extending up to five years post-procedure. The primary endpoint is a composite of survival to transplant, cardiac recovery, or six months of device support, free from disabling stroke with a modified Rankin Score greater than three or the need for pump replacement surgery.

6 Economic Evaluation

One study systematically reviewed the cost-effectiveness of LVADs as destination therapy for patients with advanced heart failure who are ineligible for heart transplantation. Among 14 economic evaluations, nine found that LVADs were unlikely to be cost-effective compared to optimal medical management, with incremental cost-effectiveness ratios per quality-adjusted life-year ranging from £52,425 to £273,975 in 2023 prices. The initial implantation cost varied widely, from £104,764 in the United Kingdom to £194,098 in the United States, with total lifetime costs influenced by hospital readmissions, adverse events, and long-term outpatient care. Hospitalization costs accounted for over 60% of total expenses, with stroke and driveline infections being the costliest complications, increasing healthcare expenditures by £30,000 to £50,000 per event. Despite these high costs, two recent evaluations in the United Kingdom and one in the United States suggested that LVADs could be cost-effective under specific conditions, particularly in patients with less severe heart failure classified as INTERMACS profiles 2 to 5, where incremental cost-effectiveness ratios ranged from £64,775 to £72,121 per quality-adjusted life-year. Cost-effectiveness improved in scenarios with lower device costs, reduced hospital readmissions, and longer survival, with models suggesting that extending median survival from 4.5 to 6.5 years could lower incremental cost-effectiveness ratios by 20 to 30%. However, methodological limitations in the reviewed studies, including short time horizons, inconsistent inclusion of adverse event costs, and reliance on outdated medical management comparators, limit the certainty of these findings. The study highlights the need for refined economic models that incorporate real-world data, improved survival estimates, and patient stratification by age, comorbidities, and device type to better inform future health policy decisions (Saygın Avşar et al., 2025).

7 Future

The future of LVAD technology is poised to revolutionize the management of end-stage heart failure, bridging the gap between mechanical circulatory support and cardiac transplantation. As heart transplantation remains the gold standard for treatment, its widespread application is severely limited by donor organ shortages and the long-term complications of immunosuppressive therapy. Mechanical circulatory support has emerged as a viable alternative, with LVADs playing a crucial role as both bridge-to-transplant and destination therapy. However, while the latest generation of LVADs, such as the HeartMate 3, have demonstrated significant improvements in hemocompatibility and clinical outcomes, several limitations persist, including driveline infections, gastrointestinal bleeding, and the requirement for external power sources. Advances in next-generation LVAD design aim to mitigate these issues through improved biocompatibility, physiological pulsatility, and the development of fully implantable systems (Tsiouris et al., 2024).

One of the primary challenges of current LVAD therapy is biocompatibility. Continuous-flow LVADs, while significantly reducing mortality in advanced heart failure patients, still induce acquired von Willebrand syndrome due to increased shear stress, leading to a heightened risk of bleeding and thromboembolic events. Emerging technologies, such as those developed by CorWave, focus on replicating physiological pulsatility while minimizing shear stress, with the goal of reducing hemolysis and improving hemodynamic outcomes. Additionally, advancements in impeller engineering and fluid dynamics seek to enhance blood compatibility, thereby reducing clot formation and mitigating the need for long-term anticoagulation. The incorporation of biocompatible surface materials in next-generation LVADs further improves hemocompatibility by decreasing hematologic and inflammatory pathway derangements, lowering the incidence of adverse events, and allowing for alternative or low-intensity antithrombotic strategies (Berardi et al., 2022).

The development of fully implantable LVADs represents a major breakthrough in mechanical circulatory support, addressing one of the most significant quality-of-life barriers: the need for percutaneous driveline connections. The implementation of transcutaneous energy transmission systems (TETS) has demonstrated the feasibility of wireless power transfer, eliminating the risk of driveline infections and increasing patient mobility. Fully implantable LVADs, such as those being developed by Corvion, integrate wireless energy transfer with advanced hemodynamic control, allowing for improved patient independence and reducing the complications associated with current LVADs. The anticipated benefits of these fully internalized systems extend beyond infection prevention, as they also decrease caregiver burden and allow for untethered device operation, significantly improving patient quality of life. While early iterations of these devices have shown

promise, further advancements in energy efficiency, miniaturization, and long-term reliability will be required before they become widely available for clinical use (Moctezuma-Ramirez et al., 2025).

Beyond hardware improvements, the future of LVAD therapy will be significantly influenced by advances in artificial intelligence and machine learning. Current LVADs operate at fixed or adjustable speeds, requiring clinician intervention to optimize flow settings based on patient status. The integration of machine learning into LVAD control algorithms has the potential to create a truly autonomous, closed-loop system that dynamically adjusts pump flow in response to physiological changes. Early proof-of-concept studies have demonstrated the feasibility of using machine learning to detect VAD suction events, impending pump failure, and arrhythmias. Future LVADs equipped with real-time physiological sensors and AI-driven optimization could continuously modulate pump performance, synchronizing with native cardiac function to enhance overall circulatory efficiency. Additionally, adaptive flow autoregulation through integrated pressure sensors and advanced support titration algorithms promises to improve pump wash-out, optimize right and left ventricular interactions, and increase patient exercise capacity, further enhancing clinical outcomes.

Another revolutionary goal in LVAD development is the creation of a smart VAD capable of modulating flow based on the patient's dynamic physiological needs. Unlike current continuous-flow LVADs, which provide a fixed degree of support, a next-generation smart VAD could adjust pump speed in real-time to better mimic native cardiac function. Early animal model studies have shown promising results, suggesting that dynamic flow modulation could improve cardiac unloading while maintaining adequate perfusion. The introduction of fully pulsatile, valveless miniaturized pumps**,** which use high-frequency oscillating discoidal membranes to propel blood flow, could restore physiologic pulsatility, reducing adverse vascular effects, enhancing end-organ function, and mitigating aortic regurgitation. Such advancements would bring LVAD therapy closer to replicating the physiological benefits of heart transplantation (Bounader & Flécher, 2024).

In addition to improving device functionality, optimizing patient selection criteria remains a crucial factor in expanding the indications for LVAD therapy. Traditionally, LVADs have been reserved for patients with end-stage heart failure who are either transplant candidates or deemed ineligible for transplantation. However, ongoing research suggests that earlier implantation in selected heart failure populations may yield superior long-term outcomes by preventing irreversible end-organ damage and myocardial deterioration. Future clinical trials will play a vital role in refining patient selection algorithms to maximize survival and quality-of-life benefits (Dual et al., 2024).

While LVADs continue to evolve, heart transplantation remains an indispensable treatment for end-stage heart failure, necessitating ongoing efforts to expand the donor pool. Xenotransplantation and ex vivo organ preservation techniques are actively being explored to address donor shortages,

potentially altering the landscape of advanced heart failure management. However, given the complexities of immunologic compatibility and long-term graft survival, mechanical circulatory support remains the most immediately scalable alternative. The convergence of LVAD innovation, artificial intelligence, and biocompatibility improvements suggests that a future generation of mechanical circulatory support devices may achieve outcomes comparable to heart transplantation, ultimately redefining the standard of care for advanced heart failure patients (Bounader & Flécher, 2024).

Despite tremendous advancements in LVAD technology, significant hurdles remain, particularly in reducing adverse events such as bleeding, thrombosis, and infection. Incremental refinements in pump design, energy transmission, and hemodynamic control continue to improve device performance, yet a paradigm shift is required to achieve long-term survival rates equivalent to those of cardiac transplantation. The vision for the future of LVAD therapy is one of continuous evolution, driven by technological innovation and a commitment to optimizing both survival and quality of life. With the advent of fully implantable, AI-powered LVADs and physiologic blood flow-path co-pumping, which synchronizes transvalvular blood stream enhancement to protect right ventricular function and improve septal geometry, the prospect of surpassing transplantation outcomes is no longer a distant aspiration but an achievable reality within the coming decades (Grzyb et al., 2024).

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