

Left Ventricular Assist Devices: Challenges Toward Sustaining Long-Term Patient Care

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Abstract—Over the last few decades, the left ventricular assist device (LVAD) technology has been tremendously improved transitioning from large and noisy paracorporeal volume displacement pumps to small implantable turbodynamic devices with only a single transcutaneous element, the driveline. Nevertheless, there remains a great demand for further improvements to meet the challenge of having a robust and safe device for long-term therapy. Here, we review the state of the art and highlight four key areas of needed improvement targeting long-term, sustainable LVAD function: (1) LVADs available today still have a high risk of thromboembolic and bleeding events that could be addressed by the rational fabrication of novel surface structures and endothelialization approaches aiming at improving the device hemocompatibility. (2) Novel, fluid dynamically optimized pump designs will further reduce blood damage. (3) Infection due to the paracorporeal driveline can be avoided with a transcutaneous energy transmission system that additionally allows for increased freedom of movement. (4) Finally, the lack of pump flow adaptation needs to be encountered with physiological control systems, working collaboratively with biocompatible sensor devices, targeting the adaptation of the LVAD flow to the perfusion requirements of the patient. The interdisciplinary Zurich Heart project investigates these technology gaps paving the way toward LVADs for long-term, sustainable therapy.

Keywords—Adverse events, Heart failure, Cardiac surgery, Surface structure, Hemocompatibility, Fluid dynamics, Implantability, Physiological control.

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ABBREVIATIONS

| | |
|-----------|--------------------------------------------------------------------|
| LVAD | Left ventricular assist device |
| vdLVAD | Volume displacement LVAD |
| tLVAD | Turbodynamic LVAD |
| BTT | Bridge to transplant |
| DT | Destination therapy |
| CF | Continuous flow |
| LV | Left ventricular, left ventricle |
| AV | Aortic valve |
| TETS | Transcutaneous energy transmission system |
| DHZB | German Heart Center Berlin |
| INTERMACS | Interagency registry for mechanically assisted circulatory support |

INTRODUCTION

Over the past 15 years, a variety of turbodynamic left ventricular assist devices (tLVADs) has been introduced for the treatment of end stage heart failure.^{1,67,126} These devices have largely replaced volume displacement LVADs (vdLVADs)^{86,116} and are almost exclusively used for destination therapy (DT). The reported survival rates of patients with a tLVAD or a vdLVAD were 80 and 65% after 1 year and 70 and 45% after 2 years, respectively.^{57,59} The freedom from device exchange was 95% for tLVADs and 90% for vdLVADs after 1 year. After 2 years, this difference increased dramatically with 92% for tLVADs and only

40% for vdLVADs.⁵⁷ In the first IMACS report, the 1-year survival rates for tLVAD and vdLVAD were 81 and 78%, respectively.⁵⁵ Since 2008, according to the seventh INTERMACS report⁵⁹ focusing on two turbodynamic devices, the HVAD and the Heartmate II, the survival rate of patients with continuous flow (CF) devices (centrifugal and axial) was 84/76% (bridge to transplant (BTT)/DT) after 1 year. The 2-year survival rate for centrifugal pumps was 80% while for axial tLVADs it decreased to 72%. Device malfunction of tLVADs is rare but poses a constant risk over time.

The Zurich Heart project¹²⁵ is a multidisciplinary and inter-institutional cooperative research effort of the University of Zurich, the University Hospital Zurich, the University Children's Hospital Zurich, the German Heart Center Berlin (DHZB), the Swiss Federal Laboratories for Materials Science and Technology and ETH Zurich, which aims at developing new technologies and radical improvements for VADs. The consortium's research is motivated by the fact that long-term LVAD therapy is a viable alternative to heart transplantation,⁷ which is mainly limited by donor shortage. A significant rate of adverse events that is associated with LVAD therapy and the technical challenges to overcome such problems demand for in depth research.^{34,59,104,111}

This review discusses the state of the art, summarizes technology gaps for future LVAD technology and reports on broad contributions of the Zurich Heart consortium that addresses the corresponding needs. To this end, the different working principles and technological implementations of LVADs are assessed with respect to their impact on adverse events. The performance of LVADs is analyzed considering four specific key aspects that need improvement: (1) The high risk of thromboembolic and bleeding events that can be addressed by novel surface structures and endothelialization approaches to improve the device hemocompatibility. (2) Fluid dynamically optimized pump designs that can further reduce blood damage. (3) Enabling full implantability of the LVADs with the help of a transcatheter energy transmission system (TETS) and pump size reduction to reduce infection and improve freedom of movement. (4) Pump flow adaptation that allows adjusting the LVAD flow to the perfusion requirements of the patient based on physiological control systems working collaboratively with biocompatible sensor devices and considering pulsatile pump operation.

The target audience of this review are scientist and engineering communities aiming at promoting very much needed innovation to the critically important LVAD technology.

PAST AND CURRENT LVAD DESIGNS

The top panel in Fig. 1 depicts the number of implanted devices at the DHZB. vdLVADs are distinguished in paracorporeal and implantable devices and tLVADs in axial and centrifugal pumps. The middle panel shows the number of implanted devices reported in the seventh INTERMACS study,⁵⁹ showing the majority use of axial tLVADs due to the large number of Heartmate II implantations in the US. The bottom panel depicts the various devices at their year of first implantation in humans. The device specific features are listed in Table 1. In the subsequent sections, the various LVADs are introduced according to their working principles and grouped into vdLVADs and tLVADs. Conceptual drawings of a volume displacement (EXCOR) as well as a turbodynamic axial (HeartMate II) and a turbodynamic centrifugal LVAD (HVAD) are shown in Fig. 2.

VOLUME DISPLACEMENT LVADS

The paracorporeal and pneumatically driven volume displacement pump Heartmate PVAD and the Berlin Heart Excor are representatives of the first LVAD generation available on the market. They were first implanted in 1976¹⁰⁴ and 1987,³⁷ respectively. Their operation was noisy (tilting valves and pneumatic drive) and therefore, caused a high psychological burden.¹⁵ The major adverse events were pump thrombosis, stroke, bleeding and infection.⁵⁷ Both pumps allowed visual inspection of the blood chambers for thrombus formation. The Excor is still used but mainly for pediatric applications as it is the only pump that is available in different sizes and therefore, can be implanted in infants and pump chamber exchange with growth is easily accomplished.⁴⁰ In 2011 it was approved by the Food and Drug Administration (FDA) for BTT in the pediatric population.^{30,57} The Excor is available with tilting discs or polyurethane leaflets as valves depending on the pump size.

First generation implantable vdLVADs had to be deployed in the abdominal cavity due to their large volume. The Novacor had electromagnetically loaded springs. They set the adjacent pusher plates in motion and squeezed a blood sac propelling the blood out of the pump with biological valves. The valves were placed in the proximal part of the inflow and outflow graft, which connected the pump with the apex of the left ventricle and the ascending aorta.⁹² The Heartmate XVE and LionHeart models consisted of a blood chamber, which was divided from the actuator by a membrane driven by a pusher plate.^{73,97} The pusher plate was in turn driven by an electric motor with a

Challenges Toward Sustaining Long-Term LVAD Therapy

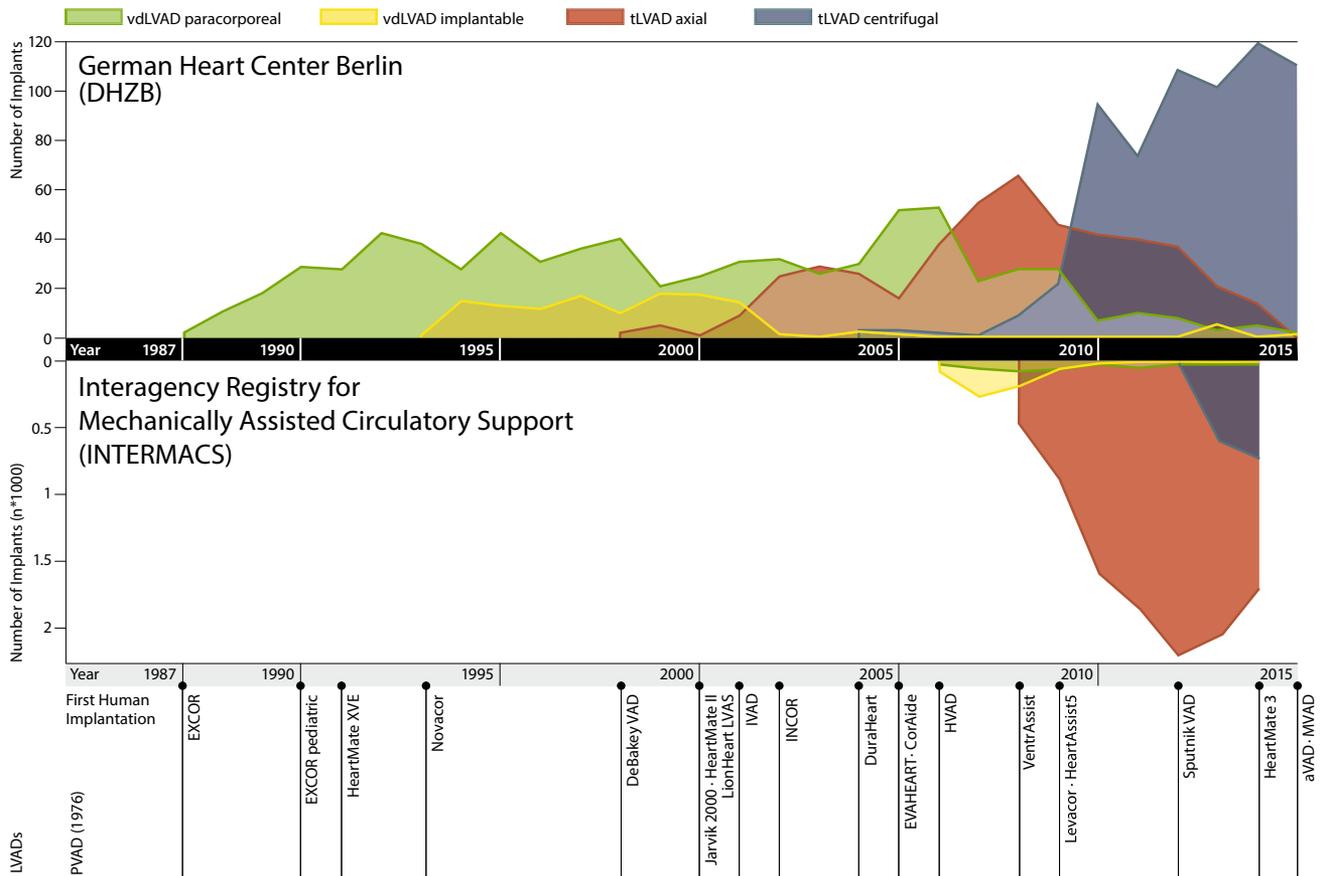


FIGURE 1. Illustration of the various left ventricular assist devices (LVADs). The numbers are exemplary and are taken from the DHZB (top panel, time period 1987–2015) and the seventh INTERMACS study⁵⁹ (middle panel, time period 2006–2014). Note the different scaling of the two axes of the number of implants, e.g., the maximum number of centrifugal turbodynamic LVADs (tLVADs) at the DHZB were 120 in the year 2014 whereas there were 2200 of axial tLVADs implanted in the US in the year 2012. In the bottom panel the diversity of LVADs are listed at their respective year of first implantation in humans according to literature^{37,104,105,122} and the DHZB's database. An overview of the specific device features and aspects is given in Table 1. Heartmate PVAD and IVAD, Heartmate XVE, Heartmate II and 3, (Abbott, Abbott Park, IL, USA); Novacor (WorldHeart Inc., Salt Lake City, UT, USA); Berlin Heart Incor, Excior, Excior pediatric (Berlin Heart GmbH, Berlin, Germany); LionHeart (Arrow International Inc., Reading, PA, USA); Jarvik 2000 FlowMaker (Jarvik Heart Inc., New York, NY, USA); DeBakey VAD/HeartAssist 5 and aVAD (ReliantHeart Inc., Houston, TX, USA); VentrAssist (Ventricor Ltd, Sydney, NSW, Australia); HeartWare HVAD and MVAD (Medtronic, Minneapolis, MN, USA); DuraHeart (Terumo Corp, Tokyo, Japan); EVAHEART (Sun Medical Technology Research Co, Japan); Levacor (WorldHeart Inc., Salt Lake City, UT, USA); Sputnik VAD (Zelenograd innovative technology center, Moscow, Russia).

cam follower (Heartmate XVE)⁷² or by a reversing ball screw mechanism (LionHeart).⁶⁸

With a blood contact surface of sintered microspheres of the titanium housing and textured polyurethane membrane of the Heartmate XVE, low anticoagulation regimens could be achieved and thrombus formation inside the pump was rarely observed.⁹⁸ On the other hand, the cam follower mechanics were prone to wear and had a high incidence of mechanical defects.⁹⁷ The Novacor driving mechanics were less complex and thus not so fragile. Longer operation times of five to six years could be reached until worn out bearings made a pump exchange necessary. Furthermore, this device featured a heart rate synchronized operation mode, which allowed for optimal unloading of the heart and opti-

mal coronary perfusion because of the resulting counter pulsation mode.⁶⁶

Heartmate XVE and Novacor had only one electrical driveline. An additional lumen, terminated with an air filter, allowed for the necessary volume compensation functioning as a vent. For the Heartmate XVE model, pneumatic emergency operation *via* a hand pump was possible in case of mechanical or electrical breakdown of a component.⁷² The LionHeart incorporated a TETS⁷³ resulting in a reduced infection rate⁸⁵ and an increased freedom of movement. Thus far, this has been the first and only commercially available fully implantable LVAD with TETS. The necessary volume exchange was enabled with an additional implanted air chamber. Air volume losses due to diffusion had to be compensated by regular

TABLE 1. List of device specific features and aspects.

| LVADs | Devices | Features | Specific aspects | |
|--------------------------|------------------------------|----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Volume displacement (vd) | PVAD* | Paracorporeal, automated control | Preload sensitive | |
| | IVAD* | Implantable PVAD | Implantation in pre-peritoneal position, only two percutaneous drivelines in BIVAD application | |
| | Excor/Excor pediatric | Paracorporeal, available in various pump sizes | Pediatric application | |
| | Novacor LVAS* | Implantable in abdominal cavity, heart rate synchronized operation, electrical driveline | Good for recovery and weaning | |
| | Heartmate XVE* | Implantable in abdominal cavity, asynchronous mode, textured surfaces within the blood chamber, electrical driveline | Cellular lining helps prevent blood clots and infection | |
| | LionHeart LVAS* | Fully implantable in abdominal cavity plus intrathoracically located components, only TET system | Freedom of movement, reduced infection rate | |
| | Implantable turbodynamic (t) | Axial pumps | DeBaKey VAD/HeartAssist 5 | Telemetric surveillance, adaptive control options |
| | | | aVAD | Intraventricular pump position (aVAD only) |
| | | | Jarvik 2000 | Blood immersed ceramic bearing, post-auricular driveline, very small pump |
| | | | Heartmate II | Mechanical pivot bearings |
| Incor | | | Integrated sensor (rotor position), actively levitated, different length of inflow cannulas | |
| Sputnik VAD | | | Radial magnetic and axial mechanical pivot bearing | |
| MVAD | | | Very small pump, pericardial placement, hybrid suspension: passive magnetic and hydrodynamic, qPulse cycle | |
| DuraHeart* | | | Active electromagnetic bearing, indirect flow estimation based on the electric current requirement and blood viscosity | |
| EVAHEART LVAS | | | Hydraulic levitation, water cooling and lubrication, special rotor design | |
| HVAD | | | Hydrodynamic thrust bearing, Lavare cycle | |
| Centrifugal pumps | | VentrAssist* | Hydrodynamic bearing | |
| | | CorAide* | Passive magnetic/hydrodynamic bearing | |
| | | Levacor* | Active magnetic bearing | |
| | | Heartmate 3 | Magnetically levitated, large gap size, artificial pulse mode | |
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*Devices no longer commercially available.

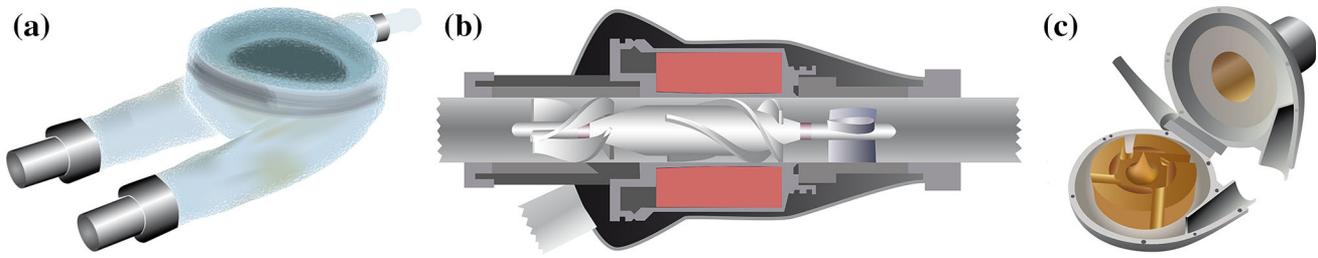


FIGURE 2. Conceptual drawings of (a) volume displacement (EXCOR)³⁷ as well as (b) turbodynamic axial (Heartmate II) and (c) centrifugal left ventricular assist devices (HVAD).⁶⁷

refills *via* a skin port. This device is no longer in use mainly due to its large size and thus, the need for abdominal implantation. In addition, the LionHeart model was designed only for chronic support of patients, in cases where orthotopic heart transplantation was not an option.⁶⁸ The time was not ripe for DT and thus, the number of implanted devices was low, which was an economic challenge for the manufacturer.

TURBODYNAMIC LVADS

The tLVAD Heartmate II device is an axial flow pump,⁶⁷ which represented a great improvement over the vdLVAD Heartmate XVE. Its rotor supported by pivot bearings is the only moving part. The device durability is longer and it is easier to be implanted compared to the Heartmate XVE. The Heartmate II received FDA approval for BTT in 2008 and DT in 2010.⁶⁷ Until today, it has been the only tLVAD with FDA approval for DT, which is depicted in the middle panel of Fig. 1. The next generation of this pump family is the Heartmate 3¹⁴ that obtained Conformité Européenne (CE) mark approval in 2015.⁷⁹ The HVAD is a small fully implantable tLVAD with a hydrodynamic thrust bearing.⁶⁴ It has FDA approval for BTT since 2012.⁶⁷ The occurrence of pump thrombosis remains a problem for the HVAD and the Heartmate II.^{56,78} As compared to the Heartmate II, the HVAD showed a higher incidence of stroke. Patients with the Heartmate II had a higher incidence for driveline infections and driveline damage resulting in pump exchanges.¹¹⁷ Fluid dynamic characterizations of the two devices with respect to their blood damage potential did not show significant differences.¹¹⁹

The HeartAssist 5 (DeBakey VAD) is an electromagnetically actuated system. The rotor is suspended by a mechanical pivot.²⁴ The recently CE approved aVAD integrates the same pump in a smaller housing without the curved rigid inflow cannula of the HeartAssist 5. This miniaturized version is directly implanted at the left apex. Both devices integrate an

ultrasonic flow sensor for independent real-time flow measurements. The Jarvik 2000 in addition to the standard abdominal driveline (FDA approved version suitable for BTT treatment) is available also with a driveline that is tunneled subcutaneously up to the ear with a post-auricular connector leading to a very low infection rate.⁷⁷ Additionally, it is a very small axial pump that is directly implanted at the left apex. A child-size pediatric Jarvik 2000 is under *in vivo* trials³³ and first implantations in children have been reported.³⁹ Until today, there is no specific pediatric tLVAD available on the market.³ Few case reports exist on children with a body weight above 15 kg that underwent HVAD implantation for left and biventricular support.³⁹

The Berlin Heart Incor is the first tLVAD with an active electromagnetic bearing. The rotor position can be determined with the help of the magnetic bearings and the pressure difference is measured with an integrated sensor. Based on this information, the pump flow can be computed.⁴¹ The DuraHeart device was the first electromagnetically levitated centrifugal pump. Different to all other tLVADs, it consisted of more than one moving part with a separate motor turning the magnetically levitated impeller.⁷⁶ The EVA-HEART LVAS design is hydraulically levitated and water-cooled.⁹⁹ Large cannulas combined with the rotor design enable the pressure pulses to travel through the pump less attenuated than in other tLVAD designs resulting in a pump characteristic with a flatter head pressure over flow curve than other tLVADs. The VentrAssist device had a hydrodynamic²⁷ and the Levacor an active magnetic bearing.⁹¹ An alternative tLVAD is the Russian Sputnik device that is partly comparable to the Heartmate II and the HeartAssist 5 devices.¹⁰⁵

TECHNOLOGY GAPS

Surface Structures

The surface of biomaterials can be engineered at the nano- and microscale to produce interfaces, which ei-

ther demote or promote cell adhesion in order to increase hemocompatibility. Various approaches have been proposed, such as texture modifications like sintered titanium surfaces,⁸⁰ different surface coatings with e.g., titanium nitride, diamond-like carbon and heparin¹⁰⁷ or a textured surface with micro-fibers and polyurethane vascular patches.³¹ The Carmat total artificial heart (CARMAT SA, Vélizy-Villacoublay, France)¹⁷ incorporates a bovine pericardial tissue treated with glutaraldehyde.

In general, topographical features can be used to avoid the onset of inflammatory processes.¹³ Alternatively, engineering approaches to support the formation and maintenance of a living cell layer at the luminal surface of the device can also be envisioned. The microstructuring of the blood-to-pump interface with specifically engineered gratings (alternating lines of ridges and grooves) enables endothelial cell migration and adhesion under flow^{93,96,113} up to the generation of a fully confluent endothelial monolayer. Importantly, rationally-designed surface topographies can support the maintenance of a well-connected endothelium beyond the physiological limits and to a maximum wall shear stress of 12 Pa (see Fig. 3).^{29,96}

Recently, Bachmann *et al.*¹¹ have proposed a novel bioreactor as a model system to evaluate different approaches to endothelialization (see Fig. 4). The bioreactor is designed to expose the endothelial cell layer to a variety of conditions of flow and substrate deformation. Topography and mechanical properties of the substrate were shown to influence the integrity of the endothelium when subjected to mechanical loads. With the goal to develop a hyperelastic hybrid membrane aiming at full hemocompatibility, the substrate was tested with representative loads comparable to those present within a vdLVAD.¹²⁴

Fluid Dynamic Aspects

With the help of fluid structure interaction, fluid dynamic aspects of volume displacement devices were assessed regarding the geometrical configuration of the valve angle as well as the position of in- and outlet ducts. This investigation revealed that the valve angle in a pulsatile total artificial heart hardly influenced the washout performance, which is an important measure for pump thrombosis prevention.¹¹⁰ The washout performance was rather dependent on the number of

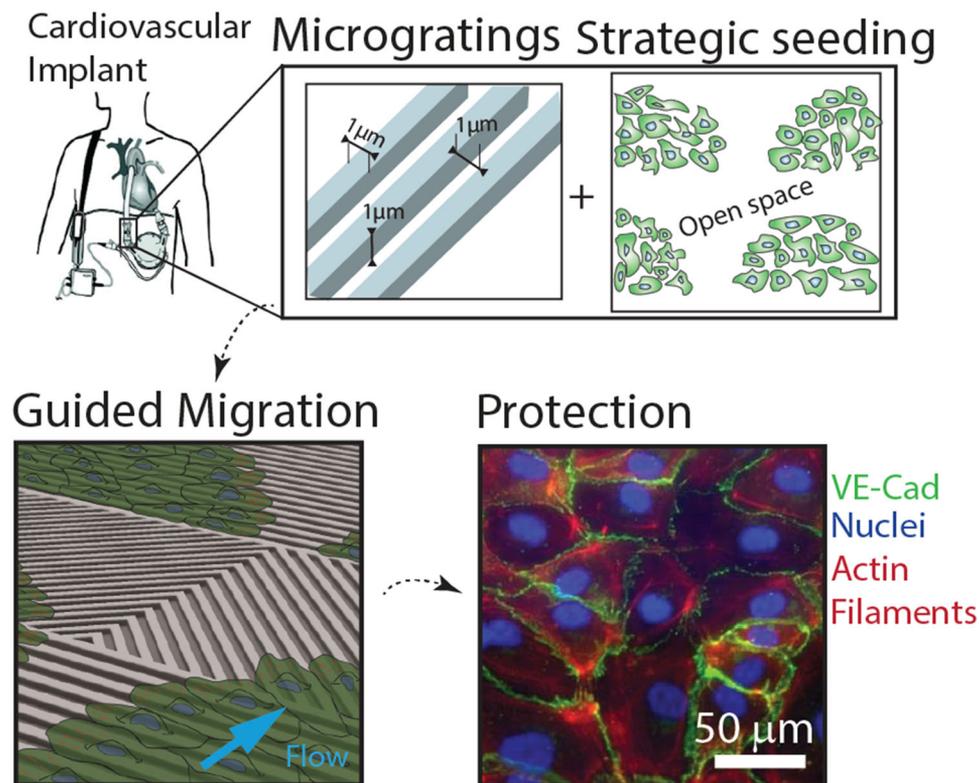


FIGURE 3. Schematic illustrating the novel hybrid endothelialization strategy. Substrates are engineered with rationally designed surface textures connecting islands of strategically seeded endothelial cells yielding suboptimal initial coverage (top). Endothelial cell migration under flow is supported by topography to promptly yield full coverage from a differentiated and functional endothelium (bottom).^{113,124}

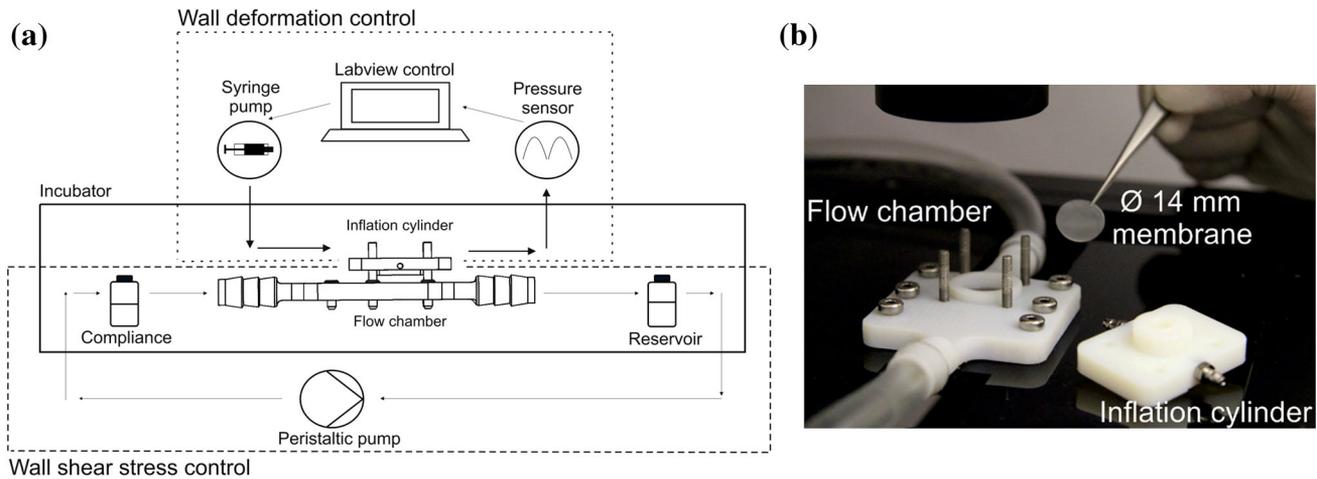


FIGURE 4. Sketch of flow chamber with its control mechanisms (left) and image with a membrane to be tested (right). A peristaltic system is used to generate a liquid flow of medium exposing the cells inside the flow chamber to shear stress (see large tubes in image on the right) while a syringe pump controlled through a PC/LabVIEW (National Instruments Corporation, Austin, TX, USA) interface actuates the membrane through the inflation cylinder using water as an inflation liquid. The system is assembled by placing a 14-mm elastomer membrane in the flow chamber (cells facing down) before closing the system with the inflation cylinder and connecting the latter to the syringe pump.¹¹

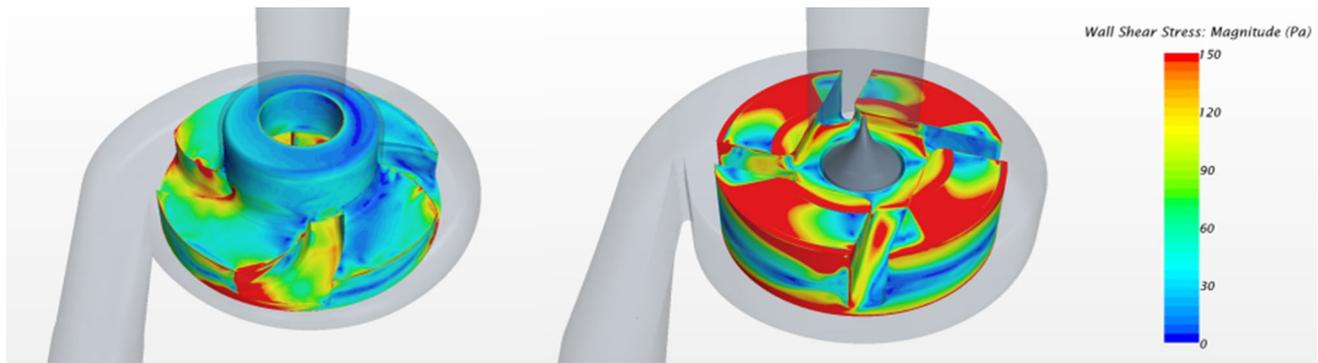


FIGURE 5. Shear stress values at the surface of the rotor of a pump prototype with adjusted rotor design (left) and of the turbodynamic LVAD HVAD (right). Red zones correspond to areas with high shear stress (≥ 150 Pa) that are prone to cause blood damage. (Images courtesy of Lena Wiegmann, University of Zurich and Stefan Boës, ETH Zurich).¹²³

pump cycles, as after three cycles the chamber was almost completely washed out in any tested configuration. The vdLVAD's in- and outlet duct configuration was optimized to minimize the particle residence time in the chamber and maximize the effective throughput efficiency.⁷¹ The ideal configuration was characterized by parallel, vertically positioned ducts. The membrane deformation was investigated during one stroke of a vdLVAD and showed a random buckling of the rather stiff membrane.⁷⁰

Current tLVAD designs vary in their impeller, bearing and actuation concepts. The geometrical configuration of the impeller influences fluid dynamical aspects, such as hydraulic efficiency and blood stagnation zones.¹¹⁹ Kim *et al.*⁵⁴ reported that low flow occurrences have a higher impact on hemolysis than previously assumed. This finding was supported by investigations on low flow behavior of the Heartmate

II.¹²⁷ The geometrical configurations of impeller and bearing principles vary,^{44,76} e.g., the HVAD's impeller geometry appears not to be hydraulically optimized. The hydrodynamic bearing seems inferior over the full impeller levitation with respect to blood cell strain and damage.^{78,79} An acoustic test was developed for the turbodynamic HVAD that can identify a pump thrombosis independently from system parameter changes, which may not change significantly in the early stage of pump thrombosis.⁵³

The question of the optimum size of a tLVAD is debated, as there is a lower limit.³⁴ There is a tradeoff between the tLVAD's size and geometry and the blood cell damage, which restricts its miniaturization. The geometry of a pump prototype was investigated and several blood damage related indices based on computational fluid dynamic simulations calculated (see Fig. 5).¹²³ Among others, areas of critically elevated

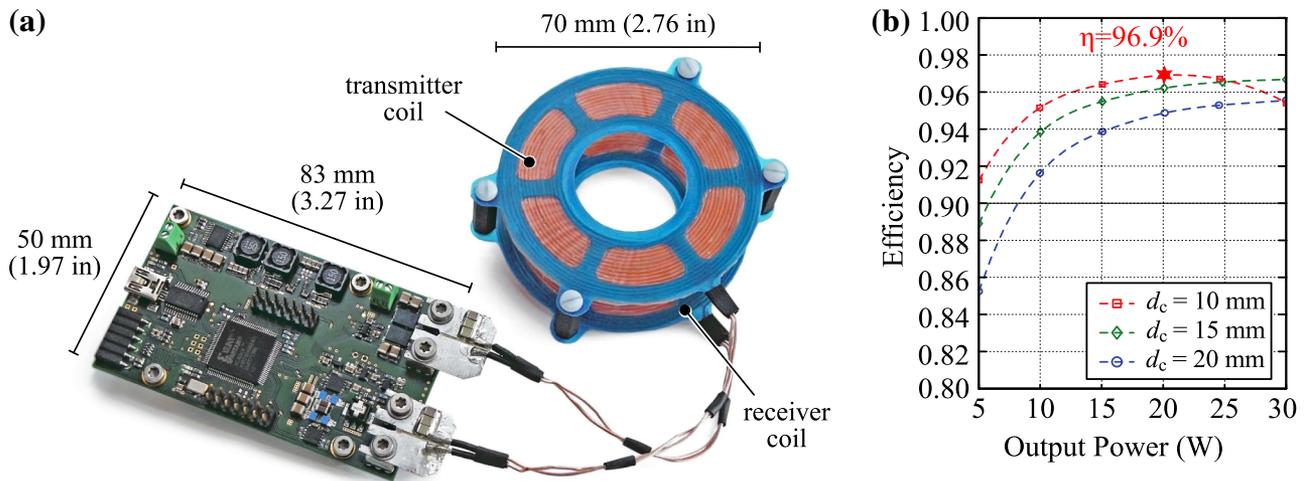


FIGURE 6. Novel wireless energy transmission prototype (left) with measurements of the inductive power transfer link DC–DC efficiency (right). Over a distance of 10 mm, 20 W can be transmitted at an efficiency of almost 97%. Reprinted, with permission, from Knecht *et al.*⁶¹. © 2015 IEEE.

wall shear stress (≥ 150 Pa) on the rotor surface are significantly reduced compared to the HVAD rotor design. Clearly, the adjusted rotor design highlights the potential to reduce blood damage considerably.

For a successful and long-term LVAD support, not only the pump itself matters, but also the inflow and outflow cannula placement. Depending on the inflow cannula length penetrating the apex and its surface structure of the blood contact area, cellular overgrowth can be stimulated.^{78,103} The exact placement of the inflow cannula at the apex influences the flow characteristics around the cannula, resulting in stagnation zones and thrombus formation.^{84,94} A prospective patient study revealed that there is no myocardial atrophy caused by long-term LVAD support and mechanical unloading due to the volume drainage out of the left ventricle.²⁵

The geometrical arrangement of the outflow cannula in the thorax, its connection to the LVAD and its alignment to the ascending aorta largely influence the corresponding compartmental fluid dynamic behavior. The anastomosis angle affects the flow pattern in the aorta and may cause reverse-flow regions toward the aortic valve, which could lead to aortic valve dysfunction.^{16,48} Earlier studies have shown that the placement of the outflow cannula to the ascending aorta is favorable over the anastomosis to the descending aorta due to the effect on flow and hemodynamic conditions.⁵² Using particle image velocimetry, the inflow and outflow cannula tip configuration and placement was investigated. The results revealed that the cannulas positioning and orientation have a great impact on the washout behavior of the left ventricle and the flow pattern in the aorta, respectively.⁶⁵

FULL IMPLANTABILITY

Traditionally, full implantability of an LVAD system is referred to the pump, the cannulas and the actuator. This is in contrast to the configuration of historic, pneumatically powered vdLVADs with external driving units and percutaneous cannulas penetrating the abdominal skin causing a significant psychological burden due to the visibility of the device as well as the audible noise of the tilting valves and the pneumatic actuation. Additionally, these vdLVADs were prone to infection.⁹⁷ Since the introduction of tLVADs, the actuator representing an electric motor is in general integrated into the tLVAD so that the “full implantability” criterion is given in these devices. Yet, tLVADs are still powered and controlled *via* a percutaneous electrical driveline. The size of the skin penetration is remarkably decreased, the electrical drivelines are more flexible than cannulas and the device burden sitting externally on the abdomen is avoided.³⁹ However, infections^{8,89} and the psychological burden¹⁵ induced by continuous violation of the body surface have remained.

Full implantability has therefore to be extended to the controller and energy storage system—rechargeable batteries plus a charging appliance coupled to the TET system,¹⁰ usually a pair of electric coils using inductive coupling to transport electric energy *via* the intact skin of the patient. Technically, the LionHeart has already proven its feasibility in the clinical field⁷³ and independent providers of such TET systems are waiting to sell their subsystems.⁴⁶ Knecht *et al.*⁶¹ developed a wireless energy transmission system that achieves a DC–DC efficiency of the wireless power link of up to 97%, which reduces the power loss in the implanted energy-receiving coil significantly and means a great step towards a

clinical use (see Fig. 6). In an *in vivo* trial, it was shown that the system is capable of transmitting 30 W of power through the skin, causing a temperature rise in the surrounding tissue of less than 2 °C.

So far, the major advantage of eliminating the permanent wound at the percutaneous exit site of any driveline has, however, clearly not been perceived to be important enough to compensate for the disadvantages involving safety, economic and administrative aspects.

Safety aspects include an electronic design with a high intrinsic breakdown resistance to be realized by over-dimensioning and redundancy. This goes along with increased costs and carries the burden of increased size and weight, which stands in contrast to the demand for a reduced size of the device. Heat dissipation is also of greater concern and software reliability of greater importance than with an external and easy to exchange component. The state of the art concerning battery lifetime and reliability is still not satisfactory, which is important because maintenance or exchange would not be an option with implanted components. The Heartmate 3, the first pump with integrated controller hard- and software has shown 100% reliability so far. In contrast, with the first implanted Carmat total artificial heart, system failures of integrated electronics have been reported.^{17,114}

Another reason for continued hesitance to switch to tetherless energy supply in an LVAD system may be the economic risk. Probably each device manufacturer has already established prototypes of such solutions. The market advantage of being the first to introduce this into clinical use is small because the competitors are likely to follow in a very short time. Against it stands the risk of disappointing results not meeting the proclaimed aims or the occurrence of adverse events connected with the new product, which might damage the good reputation of a device manufacturer.

It should be highlighted that with the existing technology, secure coupling of the sending coil with the internal receiving coil is essential. This may demand certain skills, manual and intellectual, on the part of the patient, which in some cases may be questioned with the ever-growing age range of LVAD patients. Failure to find the correct position for the coil or to fix it safely could eventually lead to depleted batteries, which in remote areas may cause hazardous situations. An extended range for coupling would be a favorable solution offering, for instance, truly tetherless sleep with a sending coil integrated in the mattress, as well as ensuring greater safety. Yet, solutions like Witricity^{45,47} or FreeD¹²¹ seem not to be able to be implemented because of the high-energy transfer rate demanded by the LVAD systems.

In addition to the tetherless energy supply, the LVAD size and weight determine the ability to fully implant the device independent of the patient's body size. Of the clinically available vdLVADs only a few could be implanted in patients with large body size: the Novacor, the Heartmate XVE LVAS and the LionHeart devices. A size reduction of a vdLVAD could be compensated by increasing the pump rate to still guarantee full support. Rebholz *et al.*⁹⁵ therefore investigated the influence of increased pump rates with numerical simulations. A synchronized operation with a pump rate of up to the threefold of the physiological heart rate showed that the aortic valve (AV) opening could be controlled, the right heart loading was physiological and the left ventricle could be unloaded at the same time. The pump size reduction has the positive effect that the inner surface to be controlled towards hemocompatibility would also be reduced.¹²⁴

PUMP FLOW ADAPTATION AND PULSATILITY

Pump Flow Control

Salamonsen *et al.*¹⁰⁰ showed the negative effects of LV suction *in vivo* and supported the need for physiological control as a method to avoid suction events. Already in the 1960s, first feedback control approaches were investigated *in vivo*.⁶³ In 2006 physiological tLVAD adaptation was clinically evaluated by Schima *et al.*¹⁰² The group has developed a preload sensitive controller based on pump power and the measured pump flow of the DeBakey VAD. Arndt *et al.*⁹ calculated the pulsatility index from the pressure difference over the rotor assessed in the bearings of the Incor, which allowed to adjust the pump speed according to the rotor deflection.

Over the last years, various concepts of physiological control systems have been developed.¹¹⁸ Ochsner *et al.*⁸² developed a physiological controller based on LV volume⁸² and Petrou *et al.*⁹⁰ based on systolic LV pressure. Both controller performances were investigated *in vitro* on the hybrid mock circulation⁸¹ (see Fig. 7) and *in vivo*⁸³ and their physiological performance compared with a CF pump.

However, tLVADs normally run continuously at a fixed speed or at fixed, periodic speed profiles¹⁰¹ with limited pulsatility. Remaining myocardial contractions superimpose pulsations.⁸⁷ On the one hand, tLVADs are unable to produce counterpulsation flow modalities, which support LV unloading⁷⁵ because tLVADs lack a capacitance necessary for a phase shift between heartbeat and pump flow. On the other hand, with

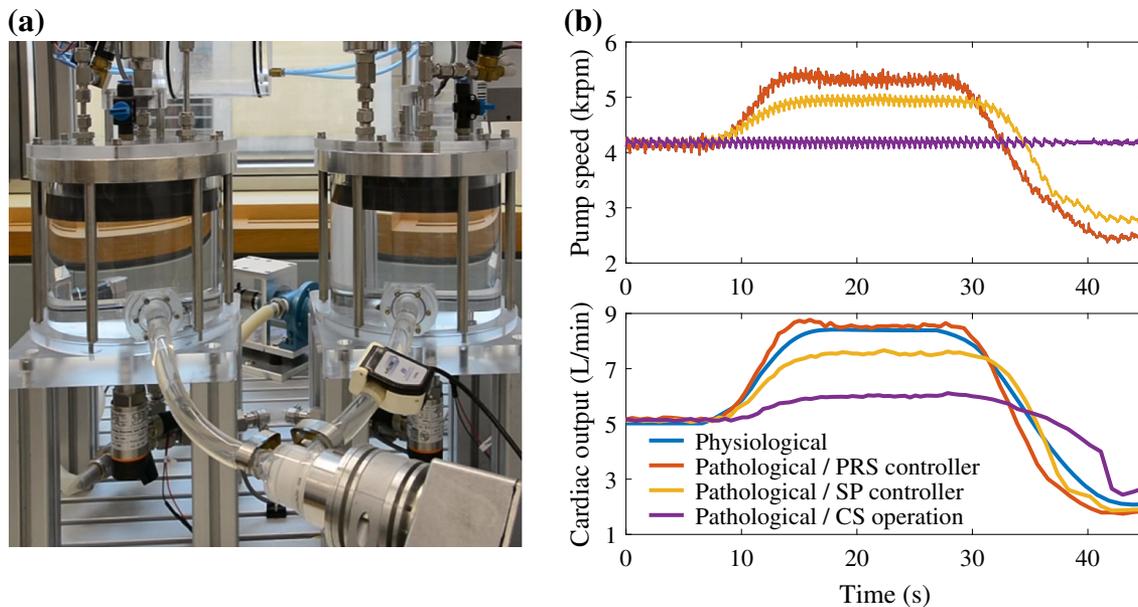


FIGURE 7. (left) Hybrid mock circulation that allows to test volume displacement and turbodynamic ventricular assist devices (VADs) as well as new control approaches.⁸¹ (right) *In-vitro* results of the physiological preload responsive speed (PRS) controller based on the left ventricular volume⁸² and the systolic pressure (SP) controller based on systolic LV pressure⁹⁰ compared to constant speed (CS) VAD operation. The simulated cardiac output (CO) of the PRS controller mimicked the physiological behavior well. The CO with the SP controller was 1 L/min below the physiological case during preload increase, but the two matched well during preload decrease. The constant speed VAD operation adjusted the CO marginally only due to preload changes.

vdLVADs a physiological arterial pulsatility is being restored. Yet, the amount of required pulsatility is unknown.

Pulsatility

The discussion on the importance of the pulsatile operation of an LVAD is ongoing.^{87,101} The obvious supportive argument is the fact that due to the pulsing nature in the physiological case, the flow of a vdLVAD would be analogous to the physiological condition.⁷⁵ Patients supported with vdLVADs show less decrease of the von Willebrand factor²¹ and less events of gastrointestinal bleeding^{2,22} than observed with tLVADs. A possible reason for the gradual increase of multi-system organ failure after 12 months⁵⁹ could be the missing pulsatility over the long period of time.¹⁰⁸ Nevertheless, the importance of pulsation is questioned and further research in this area is needed.¹⁰¹

Aortic Valve Insufficiency

To avoid aortic valve (AV) insufficiency, the AV should intermittently be opened during LVAD support to avoid continuous pressure load on the closed valve.^{23,51} An AV insufficiency results in aortic regurgitation through the AV and causes blood to flow in reverse direction back from the aorta into the LV during diastole.⁴³ AV insufficiency has a big influence on the treatment outcome.¹⁹ A further

problem of a non-opening AV is the potential thrombus formation at the aortic root due to the resulting stasis in this region.²⁰ Amacher *et al.*⁴ performed *in silico* and *in vitro* studies on an optimized controller for tVADs, which could either maximize flow through the AV or minimize LV stroke work. In another study, the pump speed was adjusted based on the AV closure according to the LV loading state.⁴⁹ Newer turbodynamic devices like the HVAD (Lavare cycle),¹² the Heartmate 3 (artificial pulse mode)⁷⁹ and the MVAD (qPulse cycle)¹⁸ have periodic pump speed changes for pump washout and in order to enable active AV opening. However, all these periodically applied changes are not synchronized to the heart-beat.

Right Heart Dysfunction

Right heart dysfunction is another problem during LVAD support.⁵⁰ The incidence of right heart dysfunction for the Heartmate XVE (volume displacement) and Heartmate II (turbodynamic) pumps was comparable.⁸⁸ One could argue that the non-physiological and unsynchronized LVAD control may promote interventricular septum shift because during constant pump speed operation an increased preload can cause LV overload and a reduced preload can cause suction events, corresponding to a left or right septal shift, respectively.⁷⁴ To avoid right ventricular failure, tLVADs have also been implanted for biven-

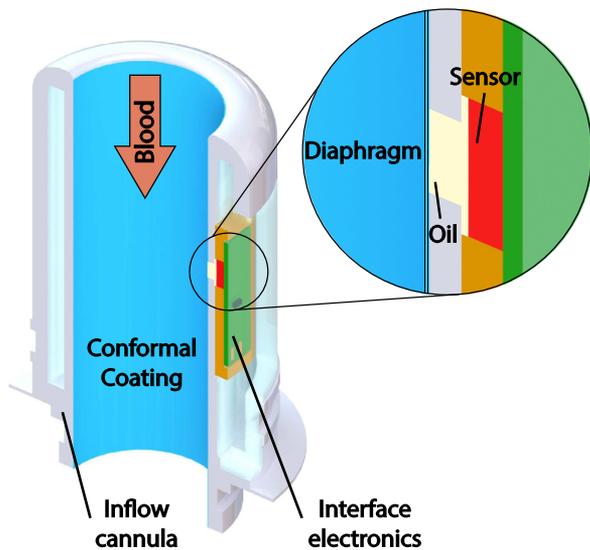


FIGURE 8. Pressure sensor integrated in the inflow cannula of an LVAD. Reprinted, with permission, from Stauffert and Hierold¹¹² © 2016 Elsevier.

tricular support (BiVAD), e.g., the HVAD, which was not designed for BiVAD support. In fact, the system can be implanted at the right side with adjustments of the outflow graft diameter to account for the pressure conditions of the pulmonary circulation.³⁸ In an *in vivo* study, the performance of compliant inflow and outflow cannulas combined with an adaptive speed control based on pressure and flow was tested with promising results.³⁵ Generally, the number of CF BiVAD compared to LVAD implantations per year has decreased by 16% from the first to the second time period reported in the seventh INTERMACS report.⁵⁹ Yet, the hemolysis rates of BiVAD support were comparable to LVAD support.¹¹⁵

Synchronization to Cardiac Cycle

Current and past vdLVADs have fixed stroke volumes and are operated by a preset pressure and pumping frequency. The flow rate and the stroke volume depend on the geometry of the device. Their regular operation is not synchronized to the heart rate except for the Novacor.^{66,92} Several groups have investigated synchronized pump operation. With the help of a regression model based on current and rotational speed, the corresponding heart rate was estimated,⁴² or by using the electrocardiogram signal, the control of VADs was synchronized to the cardiac cycle and, additionally, arrhythmia was detected.⁵ Both studies were validated on a hybrid mock circulation. In an *in vivo* study, Amacher *et al.*⁶ showed that depending on the timing of the PVAD stroke (synchronized to the cardiac cycle using custom-made

electronics and software) a treatment strategy with maximum unloading or gradual reloading of the LV can be achieved. In the regular automatic mode, the PVAD is preload sensitive as the blood volume is ejected when the pump is full²⁸ and therefore, this vdLVAD effectively implemented feedback control.

Bridge to Recovery

Bridge to recovery followed by device explantation is reported to be below 1% of all tLVADs implanted.⁵⁸ Krabatsch *et al.*⁶² found that the outcome for recovery of patients supported with vdLVADs was superior over the one of patients supported with a tLVAD. They reported up to a threefold chance for myocardial recovery with vdLVADs, which may be attributed to the vdLVAD' synchronization ability. Slaughter *et al.*¹⁰⁹ investigated the influence of vdLVAD stroke volume reduction on myocardial recovery *in vivo*. While LV pressure unloading of pulsatile and non-pulsatile devices was comparable, LV volume unloading was more distinct with vdLVADs.^{36,60} This could explain the increased potential for myocardial recovery under vdLVAD support.

Sensor Technology

One of the great challenges for physiological control is the long-term stable integration of sensors. The HeartAssist 5 (DeBakey VAD) and the aVAD are the only LVADs with an integrated flow sensor available on the market today. New approaches for sensor integrations are under investigation. LV volume or volume changes can be derived from the R-wave magnitude assessment of the intracardiac electrocardiogram or the end-diastolic pressure.²⁶ LV pressure can be measured with the help of a pressure sensor that is integrated in the inflow cannula of an LVAD¹¹² (see Fig. 8). The Polyethylene-C diaphragm proves long-term stability. CardioMEMS is an FDA approved implantable pressure sensor that measures pulmonary arterial pressure and is used to monitor heart failure patients.⁶⁹ Its measure could also be used as an LVAD control input.

Outlook

Although the LVAD technology has been transformatively improved from its initial large and noisy paracorporeal volume displacement state to small implantable turbodynamic pumps, there remains a high demand for further improvements on the way toward reaching the goal of long-term patient care with minimal or no post-operative invasion needs.

Looking into the future, we identify the following areas where progress must intensively continue aiming

at reaching this goal. The largest challenge in the LVAD application are post-operative neurologic events like stroke. The benefit of novel surface structuring and endothelialization leads towards enhanced device hemocompatibility and needs to be achieved *in vivo*. The performance of pumps that are miniaturized and fluid dynamically optimized must be further understood and tested. Especially the blood-pump surface interaction needs to be investigated. The risk of infection due to paracorporeal drivelines must be avoided through adaptation and integration of TETS technology, which will additionally increase the freedom of movement. The patient well-being with the help of physiological controllers needs to be furthered and validated in long-term chronic animal and clinical trials. Patient specific LVAD operation should be provided, including the integration of sensors that will allow the pump to adapt to the respective perfusion demand.

In addition to the above, entirely new approaches should be devised and investigated, departing fully from existing technology, such as the use of appropriate bioinspired soft materials that, decades down the line, could aid the development of soft implantable heart assist devices.

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CONFLICT OF INTEREST

Aldo Ferrari and Dimos Poulidakos participate in a Spin-off, aiming at the commercialization of biomedical materials and devices for soft tissue repair.

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