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

Review Article

Author(s):
Schmid Daners, Marianne; Kaufmann, Friedrich; Amacher, Raffael; Ochsner, Gregor; Wilhelm, Markus J.; Ferrari, Aldo; Mazza, Edoardo; Poulikakos, Dimos; Meboldt, Mirko; Falk, Volkmar

Publication date:
2017-08

Permanent link:
https://doi.org/10.3929/ethz-b-000229689

Originally published in:
Annals of Biomedical Engineering 45(8), https://doi.org/10.1007/s10439-017-1858-9

Annals of Biomedical Engineering, Vol. 45, No. 8, August 2017 (© 2017) pp. 1836–1851
DOI: 10.1007/s10439-017-1858-9

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

Marianne Schmid Daners,[1] Friedrich Kaufmann,[2] Raffael Amacher,[3] Gregor Ochsner,[1,4] Markus J. Wilhelm,[5] Aldo Ferrari,[6] Edoardo Mazza,[7,8] Dimos Poulikakos,[6] Mirko Meboldt,[1] and Volkmar Falk[2]

[1]Product Development Group Zurich, Department of Mechanical and Process Engineering, ETH Zurich, Zurich, Switzerland; [2]German Heart Center Berlin, Berlin, Germany; [3]Wyss Zurich, ETH Zurich and University of Zurich, Zurich, Switzerland; [4]Institute for Dynamic Systems and Control, Department of Mechanical and Process Engineering, ETH Zurich, Zurich, Switzerland; [5]Department of Cardiovascular Surgery, University Hospital Zurich and University of Zurich, Zurich, Switzerland; [6]Laboratory of Thermodynamics in Emerging Technologies, Department of Mechanical and Process Engineering, ETH Zurich, Zurich, Switzerland; [7]Institute for Mechanical Systems, Department of Mechanical and Process Engineering, ETH Zurich, Zurich, Switzerland; and [8]Swiss Federal Laboratories for Materials Science and Technology, EMPA, Dübendorf, Switzerland

(Received 16 January 2017; accepted 22 May 2017; published online 31 May 2017)

Associate Editor Andreas Anayiotos oversaw the review of this article.

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.

Address correspondence to Marianne Schmid Daners, Product Development Group Zurich, Department of Mechanical and Process Engineering, ETH Zurich, Zurich, Switzerland. Electronic mail: marischm@ethz.ch

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 report[59] 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 project[125] 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 transcutaneous 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 1976[104] 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

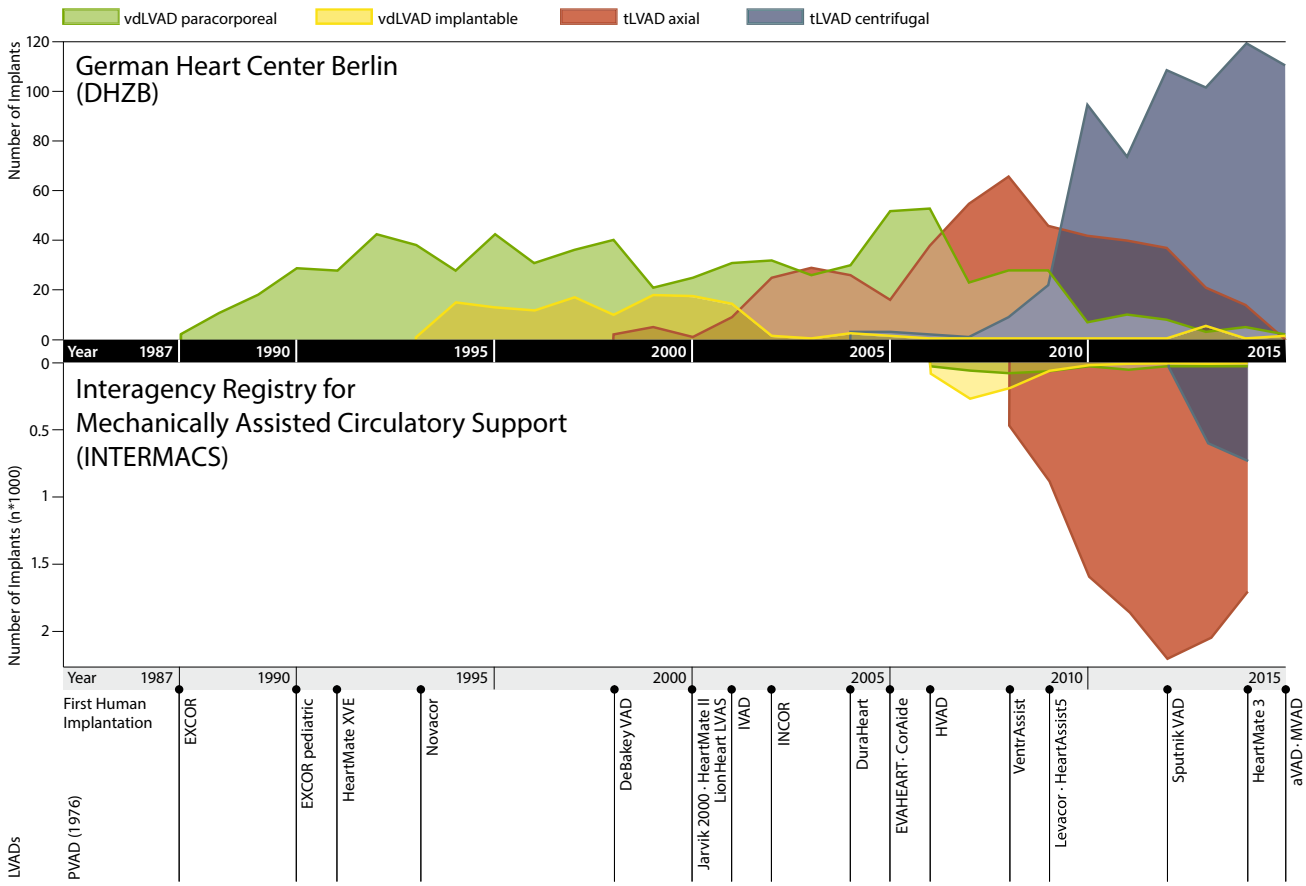

FIGURE 1. Illustration of the various left ventricular assist devices (LVADs). The numbers are exemplary and are taken from the DHZB (top panel, time period 1987–2015) and the seventh INTERMACS study[59] (middle panel, time period 2006–2014). Note the different scaling of the two axes of the number of 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, Excor, Excor 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 (Ventracor 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 optimal 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 TETS[73] resulting in a reduced infection rate[85] 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	Mechanical pivot bearing, ultrasound flow sensor	Telemetric surveillance, adaptive control options
	aVAD	Intraventricular pump position (aVAD only)	
	Jarvik 2000	Blood immersed ceramic bearing, post-auricular driveline, very small pump	Very low infection rate, pediatric application
	Heartmate II	Mechanical pivot bearings	Most implanted device
	Incor	Integrated sensor (rotor position), actively levitated, different length of inflow cannulas	Flow estimations derived from pressure difference and rotor position
	Sputnik VAD	Radial magnetic and axial mechanical pivot bearing	Low cost device
	MVAD	Very small pump, pericardial placement, hybrid suspension: passive magnetic and hydrodynamic, qPulse cycle	First in man application, no clinical approval as yet
Centrifugal pumps			
	DuraHeart*	Active electromagnetic bearing, indirect flow estimation based on the electric current requirement and blood viscosity	Flat pressure-flow diagram, flow estimations derived from motor power and speed, spiral groove hydrodynamic back up bearing[120]
	EVAHEART LVAS	Hydraulic levitation, water cooling and lubrication, special rotor design	Specific rotor design allows pressure pulses to pass the pump with little attenuation
	HVAD	Hydrodynamic thrust bearing, Lavare cycle	Flow estimations derived from motor power and speed, small pump, pediatric and right heart support possible
	VentrAssist*	Hydrodynamic bearing	Physiological control approaches in *in vivo* trials to avoid suction events
	CorAide*	Passive magnetic/hydrodynamic bearing	"Diamond-like" coating, speed adapting algorithm[32]
	Levacor*	Active magnetic bearing	*In vitro* investigation on recirculation zones caused by contractions of the heart[106]
	Heartmate 3	Magnetically levitated, large gap size, artificial pulse mode	No pump thrombosis reported as yet

*Devices no longer commercially available.

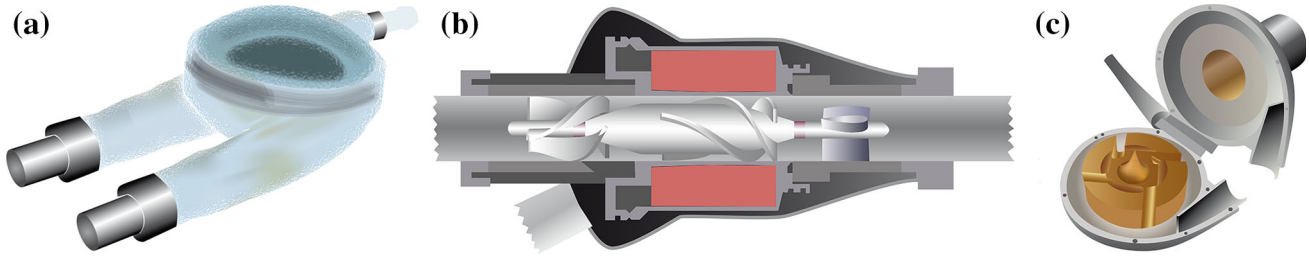

FIGURE 2. Conceptual drawings of (a) volume displacement (EXCOR)[37] as well as (b) turbodynamic axial (Heartmate II) and (c) centrifugal left ventricular assist devices (HVAD).[67]

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 3[14] 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* trials[33] 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 EVAHEART 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 hydrodynamic[27] 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 heparin[107] 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 substate 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

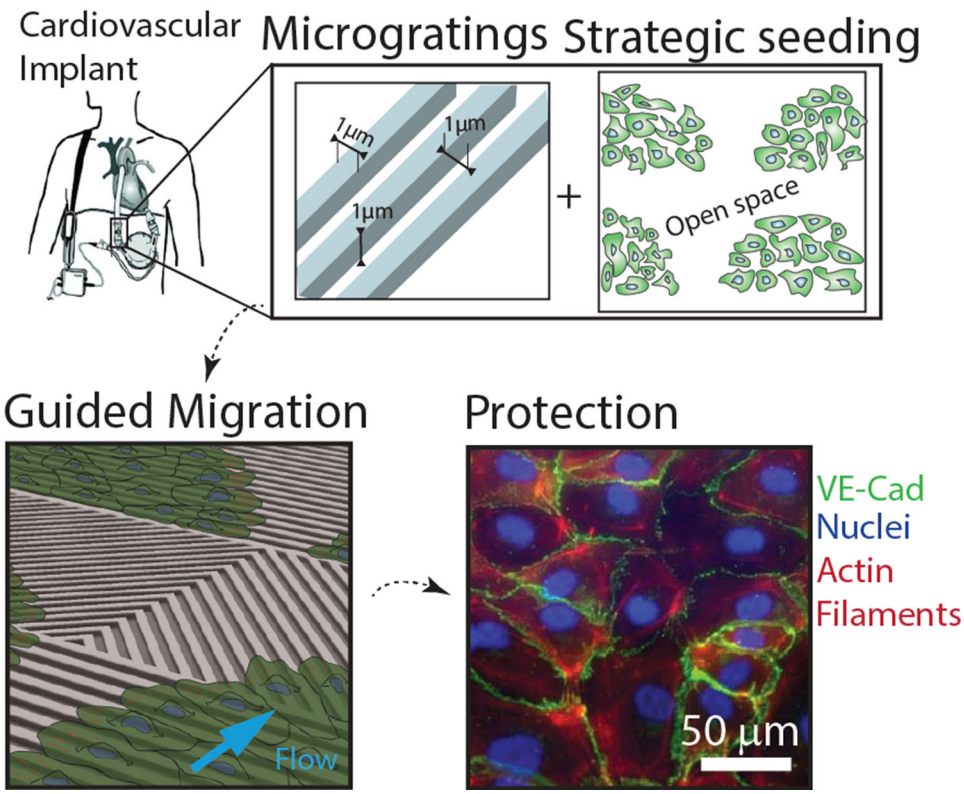

FIGURE 3. Schematic illustrating the novel hybrid endothelialization strategy. Substrates are engineered with rationally designed surface textures connecting islands of strategically seeded endothelial cells yielding suboptimal initial coverage (top). Endothelial cell migration under flow is supported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

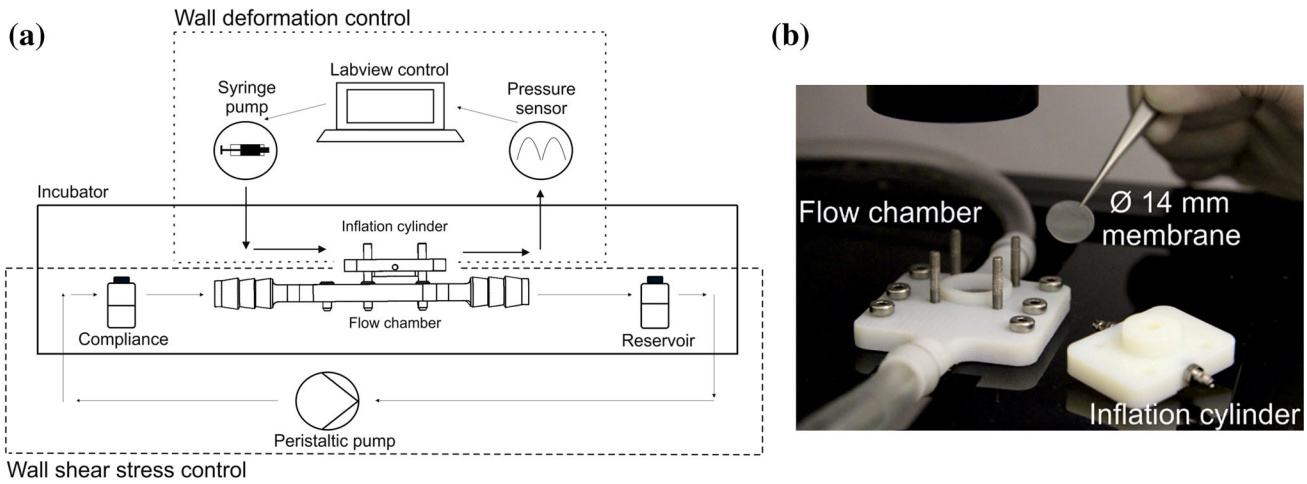

FIGURE 4. Sketch of flow chamber with its control mechanisms (left) and image with a membrane to be tested (right). A peristaltic system is used to generate a liquid flow of medium exposing the cells inside the flow chamber to shear stress (see large tubes in image on the right) while a syringe pump 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]

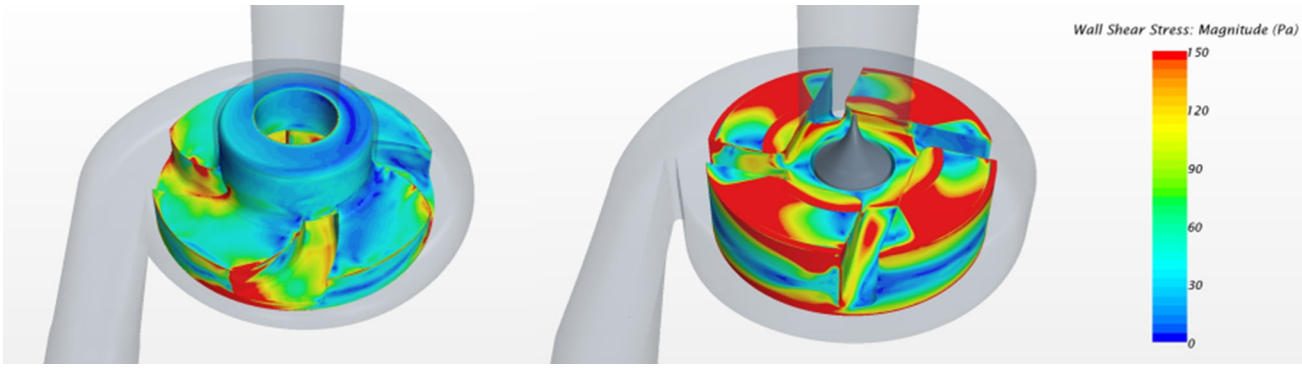

FIGURE 5. Shear stress values at the surface of the rotor of a pump prototype with adjusted rotor design (left) and of the turbodynamic LVAD HVAD (right). Red zones correspond to areas with high shear stress (≥150 Pa) that are prone to cause blood damage. (Images courtesy of Lena Wiegmann, University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

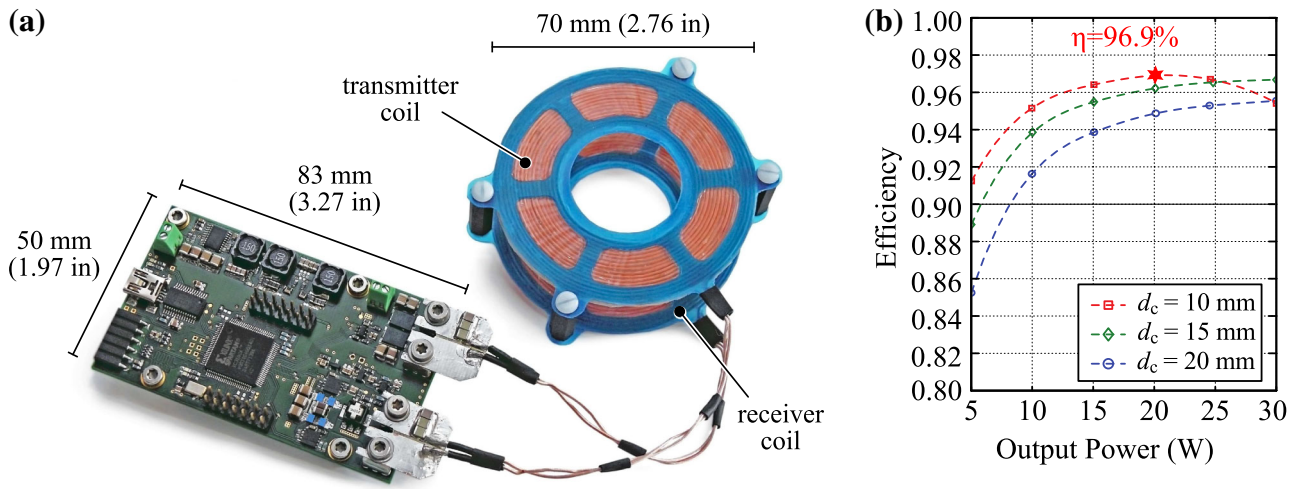

FIGURE 6. Novel wireless energy transmission prototype (left) with measurements of the inductive power transfer link DC–DC efficiency (right). Over a distance of 10 mm, 20 W can be transmitted at an efficiency of almost 97%. Reprinted, with permission, from Knecht *et al.*[61]. © 2015 IEEE.

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 burden[15] 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 field[73] 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 FreeD[121] 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 volume[82] and Petrou *et al.*[90] based on systolic LV pressure. Both controller performances were investigated *in vitro* on the hybrid mock circulation[81] (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 profiles[101] with limited pulsatility. Remaining myocardial contractions superimpose pulsations.[87] On the one hand, tLVADs are unable to produce counterpulsation flow modalities, which support LV unloading[75] because tLVADs lack a capacitance necessary for a phase shift between heartbeat and pump flow. On the other hand, with

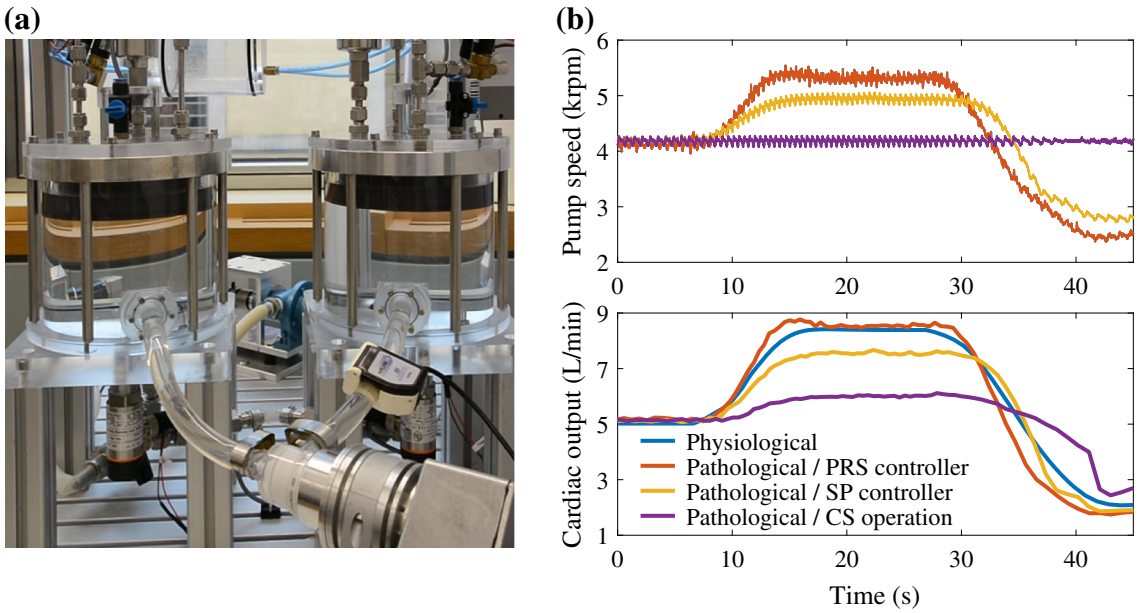

FIGURE 7. (left) Hybrid mock circulation that allows to test volume displacement and turbodynamic ventricular assist devices (VADs) as well as new control approaches.[81] (right) *In-vitro* results of the physiological preload responsive speed (PRS) controller based on the left ventricular volume[82] and the systolic pressure (SP) controller based on systolic LV pressure[90] 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 factor[21] and less events of gastrointestinal bleeding[2,22] than observed with tLVADs. A possible reason for the gradual increase of multisystem organ failure after 12 months[59] 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 heartbeat.

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-

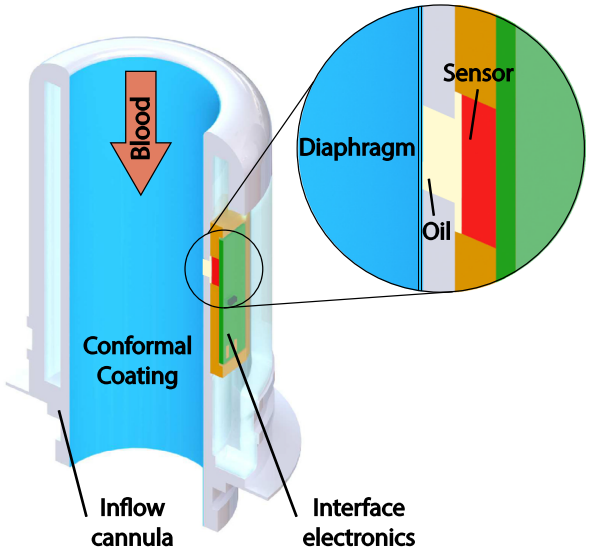

FIGURE 8. Pressure sensor integrated in the inflow cannula of an LVAD. Reprinted, with permission, from Staufert and Hierold[112] © 2016 Elsevier.

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 full[28] 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 LVAD[112] (see Fig. 8). The Parylene-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.

ACKNOWLEDGMENTS

The authors thankfully acknowledge the financial support by the Baugarten Foundation, the Georg und Bertha Schwyzer-Winiker Foundation, the IMG Foundation, the Mäxi Foundation, the Propter Homines Foundation, the Stavros Niarchos Foundation, and the Uniscientia Foundation as well as the ETH Zurich Foundation and the UZH Foundation. This work is part of the Zurich Heart project under the umbrella of University Medicine Zurich. Graphic design of Figs. 1 and 2 by mnemosyne Basel, Switzerland.

CONFLICT OF INTEREST

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

REFERENCES

[1]Agarwal, S., and K. M. High. Newer-generation ventricular assist devices. *Best Pract. Res. Clin. Anaesthesiol.* 26:117–130, 2012.

[2]Akhter, S. A., A. Badami, M. Murray, T. Kohmoto, L. Lozonschi, S. Osaki, and E. B. Lushaj. Hospital readmissions after continuous-flow left ventricular assist device implantation: incidence, causes, and cost analysis. *Ann. Thorac. Surg.* 100:884–889, 2015.

[3]Almond, C. S., H. Buchholz, P. Massicotte, R. Ichord, D. N. Rosenthal, K. Uzark, R. D. Jaquiss, R. Kroslowitz, M. B. Kepler, A. Lobbestael, *et al.* Berlin Heart EXCOR Pediatric ventricular assist device investigational device exemption study: study design and rationale. *Am. Heart J.* 162:425–435, 2011.

[4]Amacher, R., J. Asprion, G. Ochsner, H. Tevaearai, M. J. Wilhelm, A. Plass, A. Amstutz, S. Vandenberghe, and M. Schmid Daners. Numerical optimal control of turbo dynamic ventricular assist devices. *Bioengineering* 1:22–46, 2014.

[5]Amacher, R., G. Ochsner, A. Ferreira, S. Vandenberghe, and M. Schmid Daners. A robust reference signal generator for synchronized ventricular assist devices. *IEEE Trans. Biomed. Eng.* 60:2174–2183, 2013.

[6]Amacher, R., A. Weber, H. Brinks, S. Axiak, A. Ferreira, L. Guzzella, T. Carrel, J. F. Antaki, and S. Vandenberghe. Control of ventricular unloading using an electrocardiogram-synchronized Thoratec paracorporeal ventricular assist device. *J. Thorac. Cardiovasc. Surg.* 146:710–717, 2013.

[7]Anand, J., S. K. Singh, D. G. Antoun, W. E. Cohn, O. H. B. Frazier, and H. R. Mallidi. Durable mechanical circulatory support versus organ transplantation: past, present, and future. *Biomed Res Int* 2015:849571, 2015.

[8]Angud, M. Left ventricular assist device driveline infections: the Achilles' heel of destination therapy. *AACN Adv Crit Care* 26:300–305, 2015.

[9]Arndt, A., P. Nüsser, K. Graichen, J. Müller, and B. Lampe. Physiological control of a rotary blood pump with selectable therapeutic options: control of pulsatility gradient. *Artif. Organs* 32:761–771, 2008.

[10]Asgari, S. S., and P. Bonde. Implantable physiologic controller for left ventricular assist devices with telemetry capability. *J. Thorac. Cardiovasc. Surg.* 147:192–202, 2014.

[11]Bachmann, B. J., L. Bernardi, C. Loosli, J. Marschewski, M. Perrini, M. Ehrbar, P. Ermanni, D. Poulikakos, A. Ferrari, and E. Mazza. A novel bioreactor system for the assessment of endothelialization on deformable surfaces. *Sci. Rep.* 6:38861, 2016.

[12]Bhagra, S., C. Bhagra, F. Özalp, T. Butt, B. Ramesh, G. Parry, C. Roysam, A. Woods, N. Robinson-Smith, N. Wrightson, *et al.* Development of de novo aortic valve incompetence in patients with the continuous-flow HeartWare ventricular assist device. *J. Heart Lung Transpl.* 35:312–319, 2016.

[13]Bottan, S., F. Robotti, P. Jayathissa, A. Hegglin, N. Bahamonde, J. A. Heredia-Guerrero, I. S. Bayer, A. Scarpellini, H. Merker, N. Lindenblatt, D. Poulikakos, and A. Ferrari. Surface-structured bacterial cellulose with guided assembly-based biolithography (GAB). *ACS Nano* 9:206–219, 2015.

[14]Bourque, K., C. Cotter, C. Dague, D. Harjes, O. Dur, J. Duhamel, K. Spink, K. Walsh, and E. Burke. Design rationale and preclinical evaluation of the HeartMate 3 left ventricular assist system for hemocompatibility. *ASAIO J.* 62:375–383, 2016.

[15]Brouwers, C., J. Denollet, N. de Jonge, K. Caliskan, J. Kealy, and S. S. Pedersen. Patient-reported outcomes in

left ventricular assist device therapy: a systematic review and recommendations for clinical research and practice. *Circulation* 4:714–723, 2011.

[16]Callington, A., Q. Long, P. Mohite, A. Simon, and T. K. Mittal. Computational fluid dynamic study of hemodynamic effects on aortic root blood flow of systematically varied left ventricular assist device graft anastomosis design. *J. Thorac. Cardiovasc. Surg.* 150:696–704, 2015.

[17]Carpentier, A., C. Latrémouille, B. Cholley, D. M. Smadja, J.-C. Roussel, E. Boissier, J.-N. Trochu, J.-P. Gueffet, M. Treillot, P. Bizouarn, *et al.* First clinical use of a bioprosthetic total artificial heart: report of two cases. *Lancet* 386:1556–1563, 2015.

[18]Cheung, A., K. Chorpenning, D. Tamez, C. Shambaugh, Jr, A. E. Dierlam, M. E. Taskin, M. Ashenuga, C. Reyes, and J. A. LaRose. Design concepts and preclinical results of a miniaturized HeartWare platform: the MVAD system. *Innovations* 10:151, 2015.

[19]Cowger, J., V. Rao, T. Massey, B. Sun, K. May-Newman, U. Jorde, and J. D. Estep. Comprehensive review and suggested strategies for the detection and management of aortic insufficiency in patients with a continuous-flow left ventricular assist device. *J. Heart Lung Transpl.* 34:149–157, 2015.

[20]Crestanello, J. A., D. A. Orsinelli, M. S. Firstenberg, and C. Sai-Sudhakar. Aortic valve thrombosis after implantation of temporary left ventricular assist device. *Interact. Cardiovasc. Thorac. Surg.* 8:661–662, 2009.

[21]Crow, S., D. Chen, C. Milano, W. Thomas, L. Joyce, V. Piacentino, R. Sharma, J. Wu, G. Arepally, D. Bowles, *et al.* Acquired von Willebrand syndrome in continuous-flow ventricular assist device recipients. *Ann. Thorac. Surg.* 90:1263–1269, 2010.

[22]Crow, S., R. John, A. Boyle, S. Shumway, K. Liao, M. Colvin-Adams, C. Toninato, E. Missov, M. Pritzker, C. Martin, D. Garry, W. Thomas, and L. Joyce. Gastrointestinal bleeding rates in recipients of nonpulsatile and pulsatile left ventricular assist devices. *J. Thorac. Cardiovasc. Surg.* 137:208–215, 2009.

[23]da Rocha e Silva, J. G., A. L. Meyer, S. Eifert, J. Garbade, F. W. Mohr, and M. Strueber. Influence of aortic valve opening in patients with aortic insufficiency after left ventricular assist device implantation. *Eur. J. Cardiothorac. Surg.* 49:784–787, 2016.

[24]DeBakey, M. E. A miniature implantable axial flow ventricular assist device. *Ann. Thorac. Surg.* 68:637–640, 1999.

[25]Diakos, N. A., C. H. Selzman, F. B. Sachse, J. Stehlik, A. G. Kfoury, O. Wever-Pinzon, A. Catino, R. Alharethi, B. B. Reid, D. V. Miller, *et al.* Myocardial atrophy and chronic mechanical unloading of the failing human heart: implications for cardiac assist device-induced myocardial recovery. *J. Am. Coll. Cardiol.* 64:1602–1612, 2014.

[26]Dual, S. A., G. Ochsner, A. Petrou, R. Amacher, M. J. Wilhelm, M. Meboldt, and M. Schmid Daners. R-wave magnitude: a control input for ventricular assist devices. In: Proceedings of the 8th International Workshop on Biosignal Interpretation (BSI 2016), 2016, pp. 18–21.

[27]Esmore, D., P. Spratt, R. Larbalestier, S. Tsui, A. Fiane, P. Ruygrok, D. Meyers, and J. Woodard. VentrAssist left ventricular assist device: clinical trial results and clinical development plan update. *Eur. J. Cardio-Thorac. Surg.* 32:735–744, 2007.

[28]Farrar, D. J., P. G. Compton, J. H. Lawson, J. J. Hershon, and J. D. Hill. Control modes of a clinical ventricular assist device. *IEEE Eng. Med. Biol.* 5(1):19–25, 1986.

[29]Franco, D., F. Milde, M. Klingauf, F. Orsenigo, E. Dejana, D. Poulikakos, M. Cecchini, P. Koumoutsakos, A. Ferrari, and V. Kurtcuoglu. Accelerated endothelial wound healing on microstructured substrates under flow. *Biomaterials* 34:1488–1497, 2013.

[30]Fraser, Jr, C. D., R. D. Jaquiss, D. N. Rosenthal, T. Humpl, C. E. Canter, E. H. Blackstone, D. C. Naftel, R. N. Ichord, L. Bomgaars, J. S. Tweddell, *et al.* Prospective trial of a pediatric ventricular assist device. *N. Engl. J. Med.* 367:532–541, 2012.

[31]Fujisawa, N., L. A. Poole-Warren, J. C. Woodard, C. D. Bertram, and K. Schindhelm. A novel textured surface for blood-contact. *Biomaterials* 20:955–962, 1999.

[32]Gazzoli, F., A. Alloni, F. Pagani, C. Pellegrini, A. Longobardi, D. Ricci, M. Rinaldi, and M. Viganò. Arrow coraide left ventricular assist system: Initial experience of the cardio-thoracic surgery center in Pavia. *Ann. Thorac. Surg.* 83:279–282, 2007.

[33]Gibber, M., Z. J. Wu, W.-B. Chang, G. Bianchi, J. Hu, J. Garcia, R. Jarvik, and B. P. Griffith. In vivo experience of the child-size pediatric Jarvik 2000 heart: update. *ASAIO J.* 56:369–376, 2010.

[34]Giridharan, G. A., T. J. Lee, M. Ising, M. A. Sobieski, S. C. Koenig, L. A. Gray, and M. S. Slaughter. Miniaturization of mechanical circulatory support systems. *Artif. Organs* 36:731–758, 2012.

[35]Gregory, S. D., M. C. Stevens, J. P. Pauls, E. Schummy, S. Diab, B. Thomson, B. Anderson, G. Tansley, R. Salamonsen, J. F. Fraser, *et al.* In vivo evaluation of active and passive physiological control systems for rotary left and right ventricular assist devices. *Artif Organs.* 40:894–903, 2016.

[36]Healy, A. H., S. H. McKellar, S. G. Drakos, A. Koliopoulou, J. Stehlik, and C. H. Selzman. Physiologic effects of continuous-flow left ventricular assist devices. *J. Surg. Res.* 202:363–371, 2016.

[37]Hetzer, R., E. Hennig, A. Schiessler, N. Friedel, H. Warnecke, and M. Adt. Mechanical circulatory support and heart transplantation. *J. Heart Lung Transpl.* 11:S175–S181, 1991.

[38]Hetzer, R., T. Krabatsch, A. Stepanenko, E. Hennig, and E. V. Potapov. Long-term biventricular support with the heartware implantable continuous flow pump. *J. Heart Lung Transpl.* 29:822–824, 2010.

[39]Hetzer, R., F. Kaufmann, E. Potapov, T. Krabatsch, and E. M. D. Walter. Rotary blood pumps as long-term mechanical circulatory support: a review of a 15-Year Berlin experience. In: Seminars in Thoracic and Cardiovascular Surgery, Elsevier, 2016.

[40]Hetzer, R., V. Alexi-Meskishvili, Y. Weng, M. Hübler, E. Potapov, T. Drews, E. Hennig, F. Kaufmann, and B. Stiller. Mechanical cardiac support in the young with the Berlin Heart EXCOR pulsatile ventricular assist device: 15 years' experience. In: Seminars in Thoracic and Cardiovascular Surgery: Pediatric Cardiac Surgery Annual, Elsevier, vol. 9, 2006, pp. 99–108.

[41]Hetzer, R., Y. Weng, E. V. Potapov, M. Pasic, T. Drews, M. Jurmann, E. Hennig, and J. Müller. First experiences with a novel magnetically suspended axial flow left ventricular assist device. *Eur. J. Cardiothorac. Surg.* 25:964–970, 2004.

[42]Hirohashi, Y., A. Tanaka, M. Yoshizawa, N. Sugita, M. Abe, T. Kato, Y. Shiraishi, H. Miura, and T. Yambe. Sensorless cardiac phase detection for synchronized control of ventricular assist devices using nonlinear kernel regression model. *J. Artif. Organs* 19:114–120, 2016.

[43]Holtz, J., and J. Teuteberg. Management of aortic insufficiency in the continuous flow left ventricular assist device population. *Curr. Heart Fail. Rep.* 11:103–110, 2014.
[44]Hoshi, H., T. Shinshi, and S. Takatani. Third-generation blood pumps with mechanical noncontact magnetic bearings. *Artif. Organs* 30(5):324–338, 2006.
[45]http://news.mit.edu/2014/world-wireless-power-witricity-1028.
[46]http://reliantheart.com/2015/04/07/dualis-medtech-and-reliantheart-partner-on-fully-implantable-tet-system-for-the-heartassist5-lvad/.
[47]Hui, S. Y. R., W. Zhong, and C. K. Lee. A critical review of recent progress in mid-range wireless power transfer. *IEEE Trans. Power Electron.* 29:4500–4511, 2014.
[48]Inci, G., and E. Sorgüven. Effect of lvad outlet graft anastomosis angle on the aortic valve, wall, and flow. *ASAIO J.* 58:373–381, 2012.
[49]Jansen-Park, S.-H., S. Spiliopoulos, H. Deng, N. Greatrex, U. Steinseifer, D. Guersoy, R. Koerfer, and G. Tenderich. A monitoring and physiological control system for determining aortic valve closing with a ventricular assist device. *Eur. J. Cardio-Thorac. Surg.* 46:356–360, 2014.
[50]John, R., S. Lee, P. Eckman, and K. Liao. Right ventricular failure—a continuing problem in patients with left ventricular assist device support. *J. Cardiovasc. Transl. Res.* 3:604–611, 2010.
[51]John, R., K. Mantz, P. Eckman, A. Rose, and K. May-Newman. Aortic valve pathophysiology during left ventricular assist device support. *J. Heart Lung Transpl.* 29:1321–1329, 2010.
[52]Kar, B., R. M. Delgado, III, O. Frazier, I. D. Gregoric, M. T. Harting, Y. Wadia, T. J. Myers, R. D. Moser, and J. Freund. The effect of LVAD aortic outflow-graft placement on hemodynamics and flow. *Tex. Heart Inst. J.* 32:294–298, 2005.
[53]Kaufmann, F., and T. Krabatsch. Using medical imaging for the detection of adverse events ("incidents") during the utilization of left ventricular assist devices in adult patients with advanced heart failure. *Expert Rev Med Devices.* 13:463–474, 2016.
[54]Kim, N. J., C. Diao, K. H. Ahn, S. J. Lee, M. V. Kameneva, and J. F. Antaki. Parametric study of blade tip clearance, flow rate, and impeller speed on blood damage in rotary blood pump. *Artif. Organs* 33:468–474, 2009.
[55]Kirklin, J. K., R. Cantor, P. Mohacsi, J. Gummert, T. De By, M. M. Hannan, R. L. Kormos, S. Schueler, L. H. Lund, T. Nakatani, *et al.* First annual IMACS report: a global ISHLT registry for mechanical circulatory support. *J. Heart Lung Transpl.* 35:407–412, 2016.
[56]Kirklin, J. K., D. C. Naftel, R. L. Kormos, F. D. Pagani, S. L. Myers, L. W. Stevenson, M. A. Acker, D. L. Goldstein, S. C. Silvestry, C. A. Milano, *et al.* Interagency registry for mechanically assisted circulatory support (INTERMACS) analysis of pump thrombosis in the HeartMate II left ventricular assist device. *J. Heart Lung Transpl.* 33:12–22, 2014.
[57]Kirklin, J. K., D. C. Naftel, R. L. Kormos, L. W. Stevenson, F. D. Pagani, M. A. Miller, J. T. Baldwin, and J. B. Young. Fifth INTERMACS annual report: Risk factor analysis from more than 6,000 mechanical circulatory support patients. *J. Heart Lung Transpl.* 32:141–156, 2013.
[58]Kirklin, J. K., D. C. Naftel, F. D. Pagani, R. L. Kormos, L. W. Stevenson, E. D. Blume, M. A. Miller, J. T. Baldwin, and J. B. Young. Sixth INTERMACS annual report: a 10,000 patient database. *J. Heart Lung Transpl.* 33:555–564, 2014.
[59]Kirklin, J. K., D. C. Naftel, F. D. Pagani, R. L. Kormos, L. W. Stevenson, E. D. Blume, S. L. Myers, M. A. Miller, J. T. Baldwin, and J. B. Young. Seventh INTERMACS annual report: 15,000 patients and counting. *J. Heart Lung Transpl.* 34:1495–1504, 2015.
[60]Klotz, S., M. C. Deng, J. Stypmann, J. Roetker, M. J. Wilhelm, D. Hammel, H. H. Scheld, and C. Schmid. Left ventricular pressure and volume unloading during pulsatile versus nonpulsatile left ventricular assist device support. *Ann. Thorac. Surg.* 77:143–150, 2004.
[61]Knecht, O., R. Bosshard, and J. Kolar. High efficiency transcutaneous energy transfer for implantable mechanical heart support systems. *IEEE Trans. Power Electron.* 30:6221–6236, 2015.
[62]Krabatsch, T., M. Schweiger, M. Dandel, A. Stepanenko, T. Drews, E. Potapov, M. Pasic, Y.-G. Weng, M. Huebler, and R. Hetzer. Is bridge to recovery more likely with pulsatile left ventricular assist devices than with nonpulsatile-flow systems? *Ann. Thorac. Surg.* 91:1335–1340, 2011.
[63]Kwan-Gett, C. S., M. J. Crosby, A. Schoenberg, S. C. Jacobsen, and W. J. Kolff. Control systems for artificial hearts. *Trans. Am. Soc. Artif. Intern. Organs* 14:284–290, 1968.
[64]LaRose, J. A., D. Tamez, M. Ashenuga, and C. Reyes. Design concepts and principle of operation of the HeartWare ventricular assist system. *ASAIO J.* 56:285–289, 2010.
[65]Laumen, M., T. Kaufmann, D. Timms, P. Schlanstein, S. Jansen, S. Gregory, K. C. Wong, T. Schmitz-Rode, and U. Steinseifer. Flow analysis of ventricular assist device inflow and outflow cannula positioning using a naturally shaped ventricle and aortic branch. *Artif. Organs* 34(10):798–806, 2010.
[66]Lee, J., T. J. Billich, D. H. LaForge, M. Ryan, B. Sohrab, J. S. Jassawalla, and P. M. Portner. Control electronics for the Novacor totally implantable left ventricular assist system. In: Engineering in Medicine and Biology Society, 1988. Proceedings of the Annual International Conference of the IEEE, pp. 72–73, 1988.
[67]Lima, B., M. Mack, and G. V. Gonzalez-Stawinski. Ventricular assist devices: the future is now. *Trends Cardiovasc. Med.* 25:360–369, 2015.
[68]LionHeart™ LVD2000 Clinician's Manual, Arrow Intl., P/N: LV-L2000-001 (rev. S0_070200), pp. 2-2 and 3-2.
[69]Loh, J. P., I. M. Barbash, and R. Waksman. Overview of the 2011 food and drug administration circulatory system devices panel of the medical devices advisory committee meeting on the cardiomems champion heart failure monitoring system. *J. Am. Coll. Cardiol.* 61:1571–1576, 2013.
[70]Long, C. C., A. L. Marsden, and Y. Bazilevs. Fluid–structure interaction simulation of pulsatile ventricular assist devices. *Comput. Mech.* 52:971–981, 2013.
[71]Long, C. C., A. L. Marsden, and Y. Bazilevs. Shape optimization of pulsatile ventricular assist devices using FSI to minimize thrombotic risk. *Comput. Mech.* 54:921–932, 2014.
[72]McCarthy, P. M. Heartmate implantable left ventricular assist device: bridge to transplantation and future applications. *Ann. Thorac. Surg.* 59:S46–S51, 1995.
[73]Mehta, S. M., W. E. Pae, G. Rosenberg, A. J. Snyder, W. J. Weiss, J. P. Lewis, D. J. Frank, J. J. Thompson, and W. S. Pierce. The LionHeart LVD-2000: a completely implanted left ventricular assist device for chronic circulatory support. *Ann. Thorac. Surg.* 71:S156–S161, 2001.

[74]Meineri, M., A. E. Van Rensburg, and A. Vegas. Right ventricular failure after LVAD implantation: prevention and treatment. *Best Pract. Res. Clin. Anaesthesiol.* 26:217–229, 2012.

[75]Moazami, N., W. P. Dembitsky, R. Adamson, R. J. Steffen, E. G. Soltesz, R. C. Starling, and K. Fukamachi. Does pulsatility matter in the era of continuous-flow blood pumps? *J. Heart Lung Transpl.* 34:999–1004, 2015.

[76]Moazami, N., K. Fukamachi, M. Kobayashi, N. G. Smedira, K. J. Hoercher, A. Massiello, S. Lee, D. J. Horvath, and R. C. Starling. Axial and centrifugal continuous-flow rotary pumps: a translation from pump mechanics to clinical practice. *J. Heart Lung Transpl.* 32:1–11, 2013.

[77]Molina, E. J., and S. W. Boyce. Current status of left ventricular assist device technology. *Semin. Thorac. Cardiovasc. Surg.* 25:56–63, 2013.

[78]Najjar, S. S., M. S. Slaughter, F. D. Pagani, R. C. Starling, E. C. McGee, P. Eckman, A. J. Tatooles, N. Moazami, R. L. Kormos, D. R. Hathaway, *et al.* An analysis of pump thrombus events in patients in the heartware advance bridge to transplant and continued access protocol trial. *J. Heart Lung Transpl.* 33:23–34, 2014.

[79]Netuka, I., Y. Pya, D. Zimpfer, T. Krabatsch, J. Garbade, V. Rao, M. Morshuis, S. Marasco, F. Beyersdorf, P. Sood, *et al.* HeartMate III, fully magnetically levitated left ventricular assist device for the treatment of advanced heart failure—results from the CE mark trial. *J. Cardiac Fail.* 21:936, 2015.

[80]Noviani, M., R. M. Jamiolkowski, J. E. Grenet, Q. Lin, T. A. Carlon, L. Qi, A. E. Jantzen, C. A. Milano, G. A. Truskey, and H. E. Achneck. Point-of-care rapid seeding ventricular assist device with blood-derived endothelial cells to create a living antithrombotic coating. *ASAIO J.* 62:447–453, 2016.

[81]Ochsner, G., R. Amacher, A. Amstutz, A. Plass, M. Schmid Daners, H. Tevaearai, S. Vandenberghe, M. J. Wilhelm, and L. Guzzella. A novel interface for hybrid mock circulations to evaluate ventricular assist devices. *IEEE Trans. Biomed. Eng.* 60:507–516, 2013.

[82]Ochsner, G., R. Amacher, M. J. Wilhelm, S. Vandenberghe, H. Tevaearai, A. Plass, A. Amstutz, V. Falk, and M. Schmid Daners. A physiological controller for turbodynamic ventricular assist devices based on a measurement of the left ventricular volume. *Artif. Organs* 38:527–583, 2014.

[83]Ochsner, G., M. J. Wilhelm, R. Amacher, A. Petrou, N. Cesarovic, B. Röhrnbauer, M. Meboldt, and M. Schmid Daners. In vivo evaluation of physiological control algorithms for LVADs based on left ventricular volume or pressure. *ASAIO J* 2017. doi:10.1097/MAT.0000000000000533.

[84]Ong, C., S. Dokos, B. Chan, E. Lim, A. Al Abed, N. Osman, S. Kadiman, and N. H. Lovell. Numerical investigation of the effect of cannula placement on thrombosis. *Theor. Biol. Med. Modell.* 10:35, 2013.

[85]Pae, W. E., J. M. Connell, A. Adelowo, J. P. Boehmer, R. Korfer, A. El-Banayosy, R. Hetzer, M. Vigano, and A. Pavie. Does total implantability reduce infection with the use of a left ventricular assist device? The LionHeart experience in Europe. *J. Heart Lung Transpl.* 26:219–229, 2007.

[86]Park, Y. H. Current mechanical circulatory support devices for end stage heart failure. *Korean Circ. J.* 39:1–10, 2009.

[87]Patel, S. R., and U. P. Jorde. Creating adequate pulsatility with a continuous flow left ventricular assist device: just do it! *Curr. Opin. Cardiol.* 31:329–336, 2016.

[88]Patel, N. D., E. S. Weiss, J. Schaffer, S. L. Ullrich, D. C. Rivard, A. S. Shah, S. D. Russell, and J. V. Conte. Right heart dysfunction after left ventricular assist device implantation: a comparison of the pulsatile HeartMate I and axial-flow HeartMate II devices. *Ann. Thorac. Surg.* 86:832–840, 2008.

[89]Pereda, D., and J. V. Conte. Left ventricular assist device driveline infections. *Cardiol. Clin.* 29:515–527, 2011.

[90]Petrou, A., G. Ochsner, R. Amacher, P. Pergantis, M. Rebholz, M. Meboldt, and M. Schmid Daners. A physiological controller for turbodynamic ventricular assist devices based on systolic left ventricular pressure. *Artif. Organs* 40:842–855, 2016.

[91]Pitsis, A. A., A. N. Visouli, V. Vassilikos, V. N. Ninios, P. D. Sfirakis, N. E. Mezilis, P. S. Dardas, G. S. Filippatos, G. I. Bougioukas, D. T. Kremastinos, and J. W. Long. First human implantation of a new rotary blood pump: design of the clclinic feasibility study. *Hell. J. Cardiol.* 47:368–376, 2006.

[92]Portner, P. M., P. E. Oyer, D. G. Pennington, W. A. Baumgartner, B. P. Griffith, W. R. Frist, D. J. Magilligan, G. P. Noon, N. Ramasamy, P. J. Miller, *et al.* Implantable electrical left ventricular assist systems: bridge to transplantation and future. *Ann. Thorac. Surg.* 47:142–150, 1989.

[93]Potthoff, E., D. Franco, V. D'Alessandro, C. Starck, V. Falk, T. Zambelli, J. A. Vorholt, D. Poulikakos, and A. Ferrari. Toward a rational design of surface textures promoting endothelialization. *Nano Lett.* 14:1069–1079, 2014.

[94]Prisco, A. R., A. Aliseda, J. A. Beckman, N. A. Mokadam, C. Mahr, and G. J. Garcia. Impact of LVAD implantation site on ventricular blood stagnation. *ASAIO J* 2017. doi:10.1097/MAT.0000000000000503.

[95]Rebholz, M., R. Amacher, A. Petrou, M. Meboldt, and M. Schmid Daners. High-frequency operation of a pulsatile VAD—a simulation study. *Biomed. Tech.* 62:161–170, 2017.

[96]Robotti, F., D. Franco, L. Bänninger, J. Wyler, C. T. Starck, V. Falk, D. Poulikakos, and A. Ferrari. The influence of surface micro-structure on endothelialization under supraphysiological wall shear stress. *Biomaterials* 35:8479–8486, 2014.

[97]Rose, E. A., A. C. Gelijns, A. J. Moskowitz, D. F. Heitjan, L. W. Stevenson, W. Dembitsky, J. W. Long, D. D. Ascheim, A. R. Tierney, R. G. Levitan, J. T. Watson, and P. Meier. Long-term use of a left ventricular assist device for end-stage heart failure. *N. Engl. J. Med.* 345:1435–1443, 2001.

[98]Rose, E. A., H. R. Levin, M. C. Oz, O. H. Frazier, Q. Macmanus, N. A. Burton, and E. A. Lefrak. Artificial circulatory support with textured interior surfaces. A counterintuitive approach to minimizing thromboembolism. *Circulation* 90:87–91, 1994.

[99]Saito, S., K. Yamazaki, T. Nishinaka, Y. Ichihara, M. Ono, S. Kyo, T. Nishimura, T. Nakatani, K. Toda, Y. Sawa, *et al.* Post-approval study of a highly pulsed, low-shear-rate, continuous-flow, left ventricular assist device, EVAHEART: a Japanese multicenter study using J-MACS. *J. Heart Lung Transpl.* 33:599–608, 2014.

[100]Salamonsen, R. F., E. Lim, J. Moloney, N. H. Lovell, and F. L. Rosenfeldt. Anatomy and physiology of left ventricular suction induced by rotary blood pumps. *Artif. Organs* 39:681–690, 2015.

[101]Schima, H., K. Dimitrov, and D. Zimpfer. Debate: creating adequate pulse with a continuous flow ventricular

assist device: can it be done and should it be done? Probably not, it may cause more problems than benefits!. *Curr. Opin. Cardiol.* 31:337–342, 2016.

[102]Schima, H., M. Vollkron, U. Jantsch, R. Crevenna, W. Roethy, R. Benkowski, G. Morello, M. Quittan, M. Hiesmayr, and G. Wieselthaler. First clinical experience with an automatic control system for rotary blood pumps during ergometry and right-heart catheterization. *J. Heart Lung Transpl.* 25:167–173, 2006.

[103]Schmid, C., M. Jurmann, D. Birnbaum, T. Colombo, V. Falk, G. Feltrin, A. Garatti, M. Genoni, G. Gerosa, P. Göttel, *et al.* Influence of inflow cannula length in axial-flow pumps on neurologic adverse event rate: results from a multicenter analysis. *J. Heart Lung Transpl.* 27:253–260, 2008.

[104]Schumer, E. M., M. S. Ising, J. R. Trivedi, M. S. Slaughter, and A. Cheng. Early outcomes with marginal donor hearts compared with left ventricular assist device support in patients with advanced heart failure. *Ann. Thorac. Surg.* 100:522–527, 2015.

[105]Selishchev, S., and D. Telyshev. Ventricular assist device Sputnik: description, technical features and characteristics. *Trend Biomater. Artif. Organs* 29:207, 2015.

[106]Shu, F., S. Vandenberghe, J. Brackett, and J. F. Antaki. Classification of unsteady flow patterns in a rotodynamic blood pump: Introduction of non-dimensional regime map. *Cardiovasc. Eng. Technol.* 6:230–241, 2015.

[107]Sin, D.-C., H.-L. Kei, and X. Miao. Surface coatings for ventricular assist devices. *Expert Rev. Med. Devices* 6:51–60, 2009.

[108]Slaughter, M. S. Long-term continuous flow left ventricular assist device support end end-organ function: prospects for destination therapy. *J. Card. Surg.* 25:490–494, 2010.

[109]Slaughter, M. S., M. A. Sobieski, S. C. Koenig, P. S. Pappas, A. J. Tatooles, and M. A. Silver. Left ventricular assist device weaning: hemodynamic response and relationship to stroke volume and rate reduction protocols. *ASAIO J.* 52:228–233, 2006.

[110]Sonntag, S. J., T. Kaufmann, M. R. Büsen, M. Laumen, F. Gräf, T. Linde, and U. Steinseifer. Numerical washout study of a pulsatile total artificial heart. *Int. J. Artif. Organs* 37:241–252, 2014.

[111]Starling, R. C., N. Moazami, S. C. Silvestry, G. Ewald, J. G. Rogers, C. A. Milano, J. E. Rame, M. A. Acker, E. H. Blackstone, J. Ehrlinger, L. Thuita, M. M. Mountis, E. G. Soltesz, B. W. Lytle, and N. G. Smedira. Unexpected abrupt increase in left ventricular assist device thrombosis. *N. Engl. J. Med.* 370:33–40, 2014.

[112]Staufert, S., and C. Hierold. Novel sensor integration approach for blood pressure sensing in ventricular assist devices. *Proc. Eng.* 168:71–75, 2016.

[113]Stefopoulos, G., F. Robotti, V. Falk, D. Poulikakos, and A. Ferrari. Endothelialization of rationally microtextured surfaces with minimal cell seeding under flow. *Small* 12:4113–4126, 2016.

[114]Stepanenko, A., and F. Kaufmann. A novel total artificial heart: search for haemocompatibility. *Lancet* 386:1517–1519, 2015.

[115]Stepanenko, A., T. Krabatsch, E. Hennig, F. Kaufmann, B. Jurmann, N. Dranishnikov, H. B. Lehmkuhl, M. Pasic, Y. Weng, R. Hetzer, *et al.* Retrospective hemolysis comparison between patients with centrifugal biventricular assist and left ventricular assist devices. *ASAIO J.* 57:382–387, 2011.

[116]Stewart, G. C., and M. R. Mehra. A history of devices as an alternative to heart transplantation. *Heart Fail. Clin.* 10:S1–S12, 2014.

[117]Stulak, J. M., M. E. Davis, N. Haglund, S. Dunlay, J. Cowger, P. Shah, F. D. Pagani, K. D. Aaronson, and S. Maltais. Adverse events in contemporary continuous-flow left ventricular assist devices: a multi-institutional comparison shows significant differences. *J. Thorac. Cardiovasc. Surg.* 151:177–189, 2016.

[118]Tchantchaleishvili, V., J. G. Y. Luc, C. M. Cohan, K. Phan, L. Hübbert, S. W. Day, and H. T. Massey. Clinical implications of physiological flow adjustment in continuous-flow left ventricular assist devices. *ASAIO J.* 63:241–250, 2016.

[119]Thamsen, B., B. Blümel, J. Schaller, C. O. Paschereit, K. Affeld, L. Goubergrits, and U. Kertzscher. Numerical analysis of blood damage potential of the HeartMate II and HeartWare HVAD rotary blood pumps. *Artif. Organs* 39:651–659, 2015.

[120]Timms, D. A review of clinical ventricular assist devices. *Med. Eng. Phys.* 33:1041–1047, 2011.

[121]Waters, B. H., A. P. Sample, P. Bonde, and J. R. Smith. Powering a ventricular assist device (VAD) with the free-range resonant electrical energy delivery (FREE-D) system. *Proc. IEEE* 100:138–149, 2012.

[122]Wheeldon, D. R., D. H. LaForge, J. Lee, P. G. Jansen, J. S. Jassawalla, and P. M. Portner. Novacor left ventricular assist system long-term performance: comparison of clinical experience with demonstrated in vitro reliability. *ASAIO J.* 48:546–551, 2002.

[123]www.ethz.ch/content/dam/ethz/common/docs/media/globe/2016/WEB_ETH_Globe_3-16_DS_en.pdf.

[124]www.zurichheart.ethz.ch/hybridmembrane/.

[125]www.hochschulmedizin.uzh.ch/en/projekte/zurichheart.html.

[126]Yamane, T. The present and future state of nonpulsatile artificial heart technology. *J. Artif. Organs* 5:0149–0155, 2002.

[127]Yang, F., R. L. Kormos, and J. F. Antaki. High-speed visualization of disturbed pathlines in axial flow ventricular assist device under pulsatile conditions. *J. Thorac. Cardiovasc. Surg.* 150:938–944, 2015.