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Physiology of the Assisted Circulation in Cardiogenic Shock, a State of the Art Perspective

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Abstract

Mechanical circulatory support (MCS) has made rapid progress over the last three decades. This was driven by the need to develop acute and chronic circulatory support as well as by the limited organ availability for heart transplantation. The growth of MCS was also driven by the use of extracorporeal membrane oxygenation (ECMO) after the worldwide H1N1 influenza outbreak of 2009. The majority of mechanical pumps (ECMO and left ventricular assist devices) are currently based on continuous flow pump design. It is interesting to note that in the current era, we have reverted from the mammalian pulsatile heart back to the continuous flow pumps seen in our simple multicellular ancestors. This review will highlight key physiological concepts of the assisted circulation from its effects on cardiac dynamics to principles of cardiopulmonary fitness. We will also examine the physiological principles of the ECMO-assisted circulation, anticoagulation and the hemocompatibility challenges that arise when the blood is exposed to a foreign mechanical circuit. Finally, we conclude with a perspective on smart design for future development of devices used for MCS.

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Brief summary

Mechanical circulatory support has changed the prognosis of patients with advanced heart failure, especially in the setting of organ shortage and limited access to heart transplantation. Current devices provide continuous flow to the systemic circulation and are strongly dependent of loading conditions. Despite advances in device technology over the past two decades, limited exercise capacity and hemostasis-related adverse events remain major issues.

Keywords

mechanical circulatory support; ventricular assist device; physiology; circulation; extracorporeal membrane oxygenation

Part I. Introduction

Since its inception in the 1970s, extracorporeal membrane oxygenation (ECMO) has been applied to treat life-threatening cardio-pulmonary collapse.¹ The ECMO circuit combines a circulatory assist device (pump) and a gas exchange system (oxygenator) to maintain sufficient tissue oxygen delivery, supplementing pulmonary and/or cardiac function. ECMO can be divided into two general types, depending on whether the oxygenated blood is returned to the venous (veno-venous, VV) or arterial system (veno-arterial, VA). VV ECMO is used in patients with severe lung injury but preserved cardiac function (Figure 1). For patients with profound cardiogenic shock, oxygenated blood is delivered to the arterial circulation and this support is referred to as VA ECMO. Improvement in technologies and in patient management has led to the rapid growth in the implementation of ECMO, allowing many patients to recover from their critical illness or to be successfully bridged to transplantation.²

In the absence of cardiogenic shock, an implantable left ventricular assist device (LVAD) is preferred for destination therapy, as a bridge to transplantation, or as bridge to a decision of transplant candidacy.³ There are a number of devices currently available or under development, underscoring both the growing demand for durable MCS and the need for further improvement in mechanical assist device development. The first generation of pulsatile flow (PF) devices has been progressively replaced by rotary pumps providing continuous flow (CF). Slaughter et al. compared outcomes for CF vs. PF-devices and found that CF devices were associated with an improved 2-year survival, a lower incidence of stroke and a decreased incidence of pump dysfunction requiring surgical replacement.⁴ Along with device miniaturization and improved quality of life, there has been a shift from extracorporeal to intracorporeal durable MCS, and from pulsatile flow (PF) to continuous flow (CF) physiology over the last two decades.⁵ First generation CF devices were based on axial flow that pumps blood via a rotating impeller. Since their introduction, more than 40,000 patients worldwide have been implanted with rotary pumps.^{3, 6} More recently, engineers have improved the efficiency of CF-devices by developing magnetically levitated centrifugal pumps (e.g., Heartware ventricular assist device (HVAD, Medtronic Inc., Minnesota, USA) and the Heartmate 3 (HM3, Abbott Inc., Chicago, USA)). Centrifugal pumps have several advantages over axial flow pumps including: (i) easier surgical

implantation with apical sewing ring; (ii) smaller dimensions allowing the device to be more compatible with a larger patient population; (iii) lower procoagulation profile attributed to magnetically levitation technology and (iv) lower rates of hemolysis due to a lower average pump speed (<5,800 RPM vs. >8,000 RPM for axial pumps). According to data from the International Registry for Mechanically Assisted Circulatory Support (IMACS), encompassing outcomes from 16,286 patients from America, Asia-Pacific and Europe, the installation of centrifugal pumps now outpaces axial flow pumps.³

Part II. Selection of the appropriate mechanical support strategy

One of the key principles of MCS is that the circulatory support should meet but not exceed the need of the patient, with ECMO reserved for patients in cardiogenic shock with concomitant respiratory failure or in whom timely initiation of acute circulatory support system is needed. Several factors come into consideration in the selection of the optimal MCS solution including the acuity and severity of the heart failure syndrome (from decompensated heart failure to cardiogenic shock), its phenotype (biventricular or with predominantly right heart failure with normal or elevated pulmonary vascular resistance) and its response to initial medical, reperfusion therapy or basic mechanical support strategies. Compared to other devices such as intra-aortic balloon pump (IABP) or Impella (Abiomed, Danvers, USA), VA-ECMO provides complete cardiopulmonary support with the highest cardiac outflow. The indications for VA-ECMO have dramatically increased over the last decade, not only as a result of a growing number of patients requiring urgent MCS, but also thanks to easier and faster implantation techniques, better hemocompatibility, as well as improved management by multidisciplinary teams including intensivists, cardiologists and cardiothoracic surgeons. The potential reversibility of CS, as well as the presence of end-organ perfusion or predominant right ventricular failure, have to be considered in the decision to implant temporary MCS including pumpless PA-LA oxygenators in pulmonary arterial hypertension as illustrated in Figure 1. Indicators of poor probability for ECMO weaning should be taken into account, as well as the transition from temporary to durable support or to heart transplantation, especially in patients with major comorbidities, advanced age or multiple chronic end-organ failure.

Rotary pumps used for LVADs and ECMO circuits are fluid-dynamic pumps providing unidirectional and continuous flow. These pumps are preload and afterload-dependent and are best suited to generate high flow in a low-resistance circulation.⁷ In contrast, the heart is a positive-displacement pump and generates pulsatile flow. LVADs are expected to work in concert with the native heart, while ECMO provides flow to the arterial system but opposes native cardiac flow (Figure 2). These opposing forces increase LV afterload and therefore LV stroke work and myocardial oxygen consumption. This can potentially impede cardiac recovery and reinforce the importance of having adequate transition strategies from ECMO support.

Part III. Specific consideration of the ECMO circulation

Cannulation strategy

VA ECMO can be performed via different cannulation strategies. Peripheral cannulation via percutaneous or vascular cut-down access provides prompt VA-ECMO initiation outside of the operating room or during peri-arrest situations.⁸ Central cannulation defined as arterial cannulation of the ascending aorta improves oxygenated blood flow to cerebral, aortic arch and coronary vessels.^{8, 9} Central cannulation is more frequently performed for refractory cardiogenic shock after cardiac surgery but carries a risk of mediastinal bleeding and the need for chest re-opening at the time of ECMO decannulation.⁹ In addition to circuit/cannula configuration, cannulation size directly impacts circuit flow as it relates to the vascular resistance via Poiseuille's Law ($Q = \frac{P \Delta r^4}{8 \eta l}$) where radius (r) and pressure gradient (P) drive flow (Q).

North-South syndrome

In peripheral VA-ECMO, a significant physiologic consideration is the phenomenon of differential hypoxia also termed "North-South syndrome" or "Harlequin syndrome." This occurs when blood ejected by the LV is poorly oxygenated as determined by severely compromised native lung function. As such, the watershed area (i.e., point of admixture from the oxygenated blood of ECMO circuit and deoxygenated blood from the pathologic (e.g., severe pulmonary edema) native lungs) creates a source for differential oxygenation, placing the head vessels at risk for hypoxemia (Figure 2).⁹ The ability to maintain adequate oxygenation is dependent on the total volume of oxygenated ECMO blood delivered to the patient being greater than the volume of deoxygenated blood from the native circuit's cardiac output. The addition of another cannula improves the limited venous drainage flows in smaller patients as well as mitigates the potential for ischemia with the venous admixture/differential hypoxia. VV-A cannulation provides increased drainage from the venous system reducing the venous return of poorly oxygenated blood to the left heart.^{8, 10} With a baseline peripheral VA-ECMO circuit, V-AV cannulation is employed when the initial configuration shows evidence of differential hypoxia; a reinfusion limb of oxygenated blood is added to the internal jugular vein return cannula improving cerebral and coronary oxygenation.⁸ When hybrid cannulation strategies are performed, caution should be made to maintain adequate flows (> 1 LPM) in each limb to prevent line thrombosis.¹¹

Left ventricular overload and purpose of decompression

LV dysfunction and supraphysiologic afterload due to VA-ECMO retrograde flow are major risk factors for LV overload and hydrostatic pulmonary edema, occurring in 20 to 30% of patients.¹² *In situ* thrombosis (left atrium, LV, aortic root) is also a major complication that may result in LV distension, especially in the case of failure of the aortic valve to open despite high LV end-diastolic volume and LV end-diastolic pressure.^{13, 14} Ostadal et al., suggested that in absence of end-organ failure, ECMO blood flow should be maintained as low as possible to avoid negative effects on LV function and recovery.¹⁵

There is no consensus definition of LV distension in the setting of VA-ECMO support. The use of inotropes is the first approach to maintain LV ejection and aortic valve opening.

Diuretics or ultrafiltration can also be employed to decrease hydrostatic pulmonary edema.¹⁶ In case of an aortic pulse pressure lower than 10 mmHg, preventive LV decompression is usually considered. Increased pulmonary edema, echocardiographic evidence for blood stagnation within the left heart cavities, and ventricular arrhythmias are all indications for LV decompression. While specific patient populations and optimal LV unloading techniques have yet to be defined, current practice employs both surgical and percutaneous methods for LV decompression.¹⁷ Table 1 summarizes the various strategies employed for LV decompression as well as their advantages and limitations.^{18,9}

Limb ischemia

Arterial cannulation for peripheral VA-ECMO usually occludes the common femoral artery leading to a dramatic decrease in blood flow for the lower limb. Acute leg ischemia can be prevented by the insertion of a reperfusion line into the superficial femoral artery (6 to 8 Fr. sheath), directly connected to the arterial canula for continuous antegrade perfusion. In case of severe peripheral artery disease with chronic occlusion of superficial femoral arteries, the reperfusion line can be cautiously placed in the deep femoral artery. Similarly, the large venous canula for blood drainage can impair venous return and is frequently associated with lower limb edema and sometimes deep venous thrombosis below the cannulation site. In patients with severe peripheral artery disease, especially in case of an inability to establish lower limb reperfusion, the venous canula can be introduced on the contralateral common femoral vein to avoid impaired venous return that may increase the malperfusion of the lower limb. Arterial switch to the axillary artery or to central cannulation can be utilized in case of persistent leg ischemia despite the above preventive approaches.

Part IV. Specific consideration of the LVAD

Compared to the ECMO circuit, the LVAD operates in parallel to the left ventricular ejection in the presence of aortic valve opening (Figure 3a). In the presence of ventricular ejection, the LVAD will therefore modify the pressure-volume characteristics of the operating LV ventricle (Figure 3b). In addition, since the pulmonary circulation remains in series with the left sided circulation, the pulmonary flow can be used as a gauge of effective stroke volume in the absence of pulmonary regurgitation or shunting.

Comparative characteristics of continuous and pulsatile flow blood pumps

The main advantages and disadvantages of PF and CF (including centrifugal and axial blood pumps) LVADs are summarized in Table 2. PF-LVADs were usually set up in a “fill to empty” mode working synchronously with the native left ventricle. PF-devices are known to be more efficient for LV volume unloading than CF-devices, whereas CF-LVADs need positive pressure in the left ventricle for optimal pump flow.^{19, 20} Recent experimental studies have shown that axial CF-pumps are associated with higher LV unloading than contemporary centrifugal pumps, suggesting a lower risk of LV suction with CF centrifugal technology.²¹

Artificial pulsatility of continuous flow devices

The long-term physiologic impact of CF-devices is more complex than simply the lack of pulsatility for end-organ perfusion. Mild to moderate pulsatility of the systemic circulation is often observable, while pulsatility of the pulmonary circulation is preserved. The systolic increase in LV pressure causes an increase in pump flow. Clinical pulsatility can be quantified on CF-LVADs as the pulsatility index (PI) defined as $V_{\max} - V_{\min} / V_{\text{mean}}$ with (V) as blood flow velocity with maximum flow during systole. Higher PI values reflect the higher contribution of LV contractility to effective cardiac output at steady RPM. To enhance the pulsatility of MCS, contemporary CF devices (e.g., HM3) provide an artificial pulse due to transient changes in pump speed. This periodic washout of the pump chamber is designed to reduce blood stasis and thrombosis.²² Insights from the secondary analysis of the Momentum 3 trial showed a significantly lower rate of pump thrombosis and other hemocompatibility-related adverse events in patients with HM3 compared to patients with HM2 axial flow pump after 6 months of follow-up.²³ Among these events, pump thrombosis was significantly less frequently observed with the HM3 centrifugal pump, suggesting that intrinsic pulsatility may protect against blood stasis.²³ Currently, there is still a controversy whether these changes in flow dynamics with the HM3 will lead to a decreased incidence of debilitating stroke.

Long-term consequences of continuous flow physiology

One of critical benefit of systemic circulation pulsatility is to prevent blood stasis and thrombosis due to impaired flow. Aortic root thrombosis can be observed in patients with CF-LVADs due to a lack of aortic valve opening as a result of complete LV unloading and poor native heart contractility. Another consequence of persistent CF physiology is the elevated shear stress resulting in red blood cell injury, as well as platelet activation. Impaired renal function, gastrointestinal bleeding, arteriovenous malformations, aortic valve insufficiency due to leaflet fusion, stroke and thromboembolic events are also some of the complications observed in patients with non-pulsatile blood flow.⁷ Preliminary reports of mid-term outcomes of the HM3 centrifugal pump suggest that gastrointestinal bleeding and detrimental stroke remains a burden despite advances in device hemocompatibility and artificial pulsatility, especially for patients with durable support.^{24, 25}

Another major feature of pulsatile flow is to deliver kinetic energy to the vasculature.²⁶ While the aorta and its collateral branches share a high compliance, arterioles and capillaries have a lower compliance and a higher resistivity. End-organ perfusion is therefore more dependent of pulse pressure for than of mean flow velocity.²⁷ Lastly, pulsatile blood flow is considered necessary for maintaining cardiovascular autonomic homeostasis. Baroreflex dysfunction with increased sympathetic activity is commonly observed in patients with end-stage heart failure. Regulation of muscle sympathetic nerve activity may however be preserved in patients with CF-LVADs as was recently described by Tank et al.²⁸ This is particularly relevant when considering vascular tone and exercise physiology in the setting of long-term MCS.

Interaction between LVAD, right ventricle and pulmonary circulation

In patients with heart failure and pulmonary vascular disease impeding candidacy for heart transplant, LVAD or biVAD implantation often leads to reversal of pulmonary hypertension (PH) after 3 to 6 months of support.²⁹ However the importance and implication of PH should not be underestimated. Preoperative transpulmonary gradient > 10 mmHg has been shown to negatively affect 1-year post-transplant survival in patients bridged with CF-LVAD.³⁰

Right ventricular failure (RVF) occurs in 20 to 40% of patients after LVAD implantation and is a major cause of poor outcomes and reduced survival during the first post-operative year.³¹ An international definition for RVF secondary to LVAD implantation has been established, including an elevated central venous pressure (CVP) >16 mmHg with decreased cardiac index below 2 liters/min/m², in the absence of increased PCWP, requiring RV assist device implantation or prolonged inotropic therapy or inhaled pulmonary vasodilators (> 7days).³²

RV response to LV unloading after LVAD implantation depends on the balance between hemodynamic benefits and mechanical disturbances for the right ventricle (Supplemental Table 1). The substantial rise in cardiac output after LVAD implantation results in marked and instantaneous increase in RV preload due to elevated systemic venous return. RV afterload is also expected to decrease after LVAD implantation. On the other hand, changes in septal motion dynamics due to changes in myocardial perfusion and geometry may lead to RV systolic dysfunction.¹⁹ Despite septal dysynergy, RV myocardial efficiency and output can be maintained by increasing preload and reducing afterload.^{33, 34} Other LVAD-independent risk factors for RVF include: excessive fluid administration, moderate to severe tricuspid regurgitation, coronary artery embolism, prolonged cardio-pulmonary bypass times, acute lung injury especially in the setting of excessive transfusion of blood products, arrhythmias and ventricular asynchrony.^{35, 36}

Basic principles of the LV flow mechanics

LV durable circulatory support is a unique model of parallel systemic circulation for blood flow between the LV and the aorta (Figure 3a). The determinants of pump flow include preload, afterload, pressure gradient between inflow and outflow cannula and pump speed. Revolutions per minute are fixed, while loading conditions are exposed to intracycle, circadian and other biological variability. The interactive physiology between the native LV and contemporary LVADs are summarized in Table 3.

Preload sensitivity—Preload sensitivity is a major determinant of optimal right and left atrial pressures to ensure a balanced flow between rotary pumps and the systemic circulation. This is analogous to the Frank-Starling mechanism characterized by increased ventricular contractility (pump flow) in response to increased preload, at any given afterload and heart rate (LVAD pump speed (RPM)).²⁰ LVAD sensitivity to preload, defined as the capacity to increase pump flow with increasing preload, can be quantified as the ratio of pump output to filling pressures (L/min/mmHg). Any decrease in LV filling pressure

(hypovolemia, RV dysfunction, cardiac tamponade) may result in suction events and/or ventricular arrhythmias.

Afterload sensitivity—Rotary pumps and the left ventricle share the same inverse relationship between afterload and blood flow. However, CF-pumps are nearly three-times more sensitive to increased afterload (hypertension, vasopressors) than that of the native LV.²⁰ Low flow events and decreased output can therefore be frequently observed despite optimal filling pressure if afterload is too high emphasizing the importance of blood pressure control in patients with LVADs.

Pressure gradient dependency—Flow rate of CF-pumps is strongly dependent on the pressure gradient between the LV (preload, inflow pressure) and the aorta (afterload, outflow pressure).³⁷ A slight increase in systemic vascular resistance (SVR) or any obstruction of the LVAD outflow graft results in increased pressure gradient, also known as pump differential pressure. CF-LVAD flow is inversely related to the pressure gradient and this relationship is characterized by pressure-flow curves (Figure 3c). Therefore, any increase in pump afterload, at fixed RPM and LV filling pressure, results in decreased output. Rotary pumps are 3 to 4 times more sensitive to changes in systemic blood pressure than the normal heart.³⁸ Rosebaum et al., investigated the pressure gradient or differential across the pump and its correlation with LV filling pressures at different ranges of loading conditions, and in the setting of pump dysfunction (thrombosis, outflow graft compression) and found that (i) the pressure gradient was strongly correlated with pump speed; and (ii) that the pressure gradient is a relevant marker of LV unloading with an optimal range between 20 and 40 mmHg.³⁹

Pump speed—Because the LV and LVADs share the same preload, any increase in pump speed results in decreased LV filling pressure. Similarly, a decrease in pump speed results in an increase in LV end-diastolic pressure and potentially an increased blood flow into the LV outflow tract, aortic valve opening and increased systemic pulsatility. At different pump speeds (RPM), the LVAD will therefore operate on a different HQ curve (Figure 3c). Optimization of pump speed is challenging at the time of LVAD implantation since many factors influence loading conditions: mechanical ventilation, RV dysfunction and arrhythmias impact preload, while vasoplegia and vasopressors influence LVAD afterload. Figure 3d shows LV PV loops at different ranges of LVAD speed and in different loading conditions. Changes in LVAD parameters (power, pump flow, pulsatility index) as a consequence of variations in loading conditions are described in Supplemental Table 2. Of note, pump flow is a calculated and not a measured parameter in the LVADs.

Non-invasive monitoring of LVADs using echocardiography

In addition to estimated LVAD flows dynamics, blood pressure and activity level, echocardiography is often useful in assessing LVAD function and systemic circulation (Figure 3e, f). The parasternal views and the apical views are particularly useful in assessing aortic valve opening (a gage of LV output), septal position (a marker of unloading and ventricular interactions), right ventricular function as well as valvular function. Because the pulmonary flow remains pulsatile and in series with the left circulation, assessing of mid

pulmonary velocity time integral may be useful during RAMP protocol to evaluate the effects on effective stroke volume. In the laboratory, we usually average 5 to 10 beats.

Part V. Exercise physiology of contemporary left ventricular assist devices

LVAD implantation not only improved survival but also physical activity when compared to matched patients with advanced heart failure. In a recent study by Moreno-Suarez et al., LVAD implantation improved physical activity when compared to matched patients with heart failure; in this study physical activity was measured by an activity monitor (Actiheart, CanNtech, Cambridge, UK) as well as peak oxygen consumption (peak VO_2).⁴⁰ The increase in exercise capacity may, however, not be as extensive when compared to matched patients who have undergone cardiac transplantation. For example, in a study by Dunlay et al., peak VO_2 increased post-transplant but did not change significantly following LVAD implantation, and 72% of post LVAD patients' peak VO_2 remained less than 14 mL/kg/min (HM2 device).⁴¹ Interpretation of these studies needs to take into account the type of device used as well as baseline frailty, fitness and contractile ability of the native heart.

Exercise capacity is a complex process that not only depends on peak cardiac output but also on arterio-venous oxygen extraction, peripheral muscle strength and respiratory function. By design, LVADs have not yet incorporated activity or exercise modulation algorithms which would allow for an increase in cardiac output during exercise. The peripheral muscle system is also emerging as a key factor in explaining the variability in exercise tolerance. Gross et al., showed that exercise capacity as measured by peak VO_2 was mainly associated with intrinsic contractile and chronotropic reserve rather than a change LVAD flow rate.⁴² In patients with LVAD support, Rosenbaum et al., found that pulsatility index, peak heart rate and lower pump speed were moderately associated with peak VO_2 also pointing towards the importance of intrinsic contractile and chronotropic reserve.⁴³ Although this study may suggest an inverse relationship between pump speed and peak VO_2 , Vignati et al., found that modulating pump speed improved VO_2 .⁴³ Other studies have also investigated the role of adaptative speed modulation during exercise. Jung et al., investigated fixed versus incremental pump speeds found that incremental increase in RPM every 2 minutes was associated with an increase in peak VO_2 (15.4 ± 5.9 mL/kg/min vs. 14.1 ± 6.3 mL/kg/min; $P=0.012$). Similarly, Apostolo et al., tested the incremental increase in pump speed hypothesis on patients with Jarvik 2000 LVAD devices and found a small but significant increase in peak VO_2 (12.5 ± 2.5 mL/min/kg vs 11.7 ± 2.8 mL/min/kg; $p = 0.001$).⁴⁴ As with most studies on this subject, the number of patients was too small to allow more granular analysis of the effects of speed modulation on response to therapy. A better understanding of the effect of pump flow modulation on exercise capacity will however require a comprehensive assessment of both contractile and chronotropic reserve as well as flow reserve provided but the increment in pump speed.

Exercise testing may also have a role in identifying potential candidates for explantation. In a pilot study, Christle et al., tested the feasibility of serial cardiopulmonary exercise testing (CPET) in patients considered for explantation.⁴⁵ CPET was performed at both high and low

LVAD speeds in patients on CF devices. These patients had equivalent or higher exercise performance at low LVAD speeds compared to high speeds, which was reflective of increased contractile reserve. Peak VO_2 and METs were 1.2 ml/kg/min and 1 MET higher, peak LV end diastolic diameter (EDD), stroke volume (SV) and SV reserve were higher with minimal LVAD support. However, the external generalizability of these findings may be limited as all patients studied were potential explant candidates, suggesting a clinically significant amount of native cardiac recovery. Baseline CPET may also reveal profiles of patients more susceptible to explantation as it assesses dependence on LVAD flow support. In a proof of concept study of patients on PF-LVAD, the two patients that were explanted achieved higher workload, higher peak VO_2 and lower VE/ VCO_2 slopes.⁴⁶

Despite the improvement noted in physical activity after LVAD implantation, exercise capacity is still limited compared to healthy volunteers. Grosman-Rimon et al., reported that chronotropic response was still impaired despite improvement in the percentage of heart rate reserve.⁴⁷ The European Extra-HF study found that of the 77 LVAD centers, 45 (58%) reported having an exercise training program for LVAD patients.⁴⁸ There have only been a few small studies on the effects of exercise training, suggesting that moderate to high intensity exercise may be beneficial and lead to improvements in peak exercise capacity.^{49–51} Haddad et al., published a more thorough review of the response of LVAD patients to cardiac rehabilitation.⁵² In addition, the “Exercise Training in Patients with a Left Ventricular Device (Ex-VAD)” trial is an ongoing study with the potential to improve our understanding of the effects of exercise training in LVAD patients.⁴⁹

Part VI. Impact of ECMO and LVADs on hemostasis and hemocompatibility

Despite major technological advances over the last two decades, thrombotic and bleeding events remain two common complications related to the use of MCS that significantly affect the assisted circulation. Here we will summarize the impact of the assisted circulation on the physiology of the hematologic system (summarized in Table 4 and Figure 4).

Concomitant risk of bleeding and thrombosis under ECMO support

The most common mechanical complication of ECMO is clot formation requiring circuit exchange and the most common patient complication is bleeding. Contact with non-endothelial lined surfaces leads to activation of the coagulation pathways involving platelets, leukocytes and complement system.^{53, 54} The inflammatory state of the patient and the potential presence of sepsis, renal and hepatic injury further compound the issue, resulting in a pathological hematologic profile. The delicate balance between bleeding and thrombosis is compounded by the need for anticoagulation, as extracorporeal surfaces lack the innate mediators that protect against contact pathway activation.⁵⁵ Furthermore, the risk of ECMO-related thrombosis may be increased by low blood flow rates (< 2 LPM). Conversely, lower levels of anticoagulation may be employed at higher blood flow rates (> 4–5 LPM).

ECMO-related coagulopathy

Contact between the blood and the non-biologic surfaces of the ECMO circuit leads to a profound inflammatory response, resulting in activation and adsorption of coagulation factors including prekallikrein, and high molecular weight kininogen, von Willebrand factor (vWF), and fibrinogen. This creates a relative coagulopathy, and acts as an anchor for platelets to adhere, leading to significant thrombocytopenia.

Thrombocytopenia—There has been much debate about the general presumption of the association between ECMO and the development of thrombocytopenia explained by consumption within the circuit, platelet dysfunction, aggregation and adherence to oxygenator membrane. The odds of developing severe thrombocytopenia increases by 35% for every 5 point increase APACHE II (odd ratio (OR): 1.35) and by 35% for every $25 \times 10^9/L$ below a mean platelet count ($188 \times 10^9/L$) at cannulation (OR: 1.35).⁵⁶ Platelet dysfunction caused by aberrant platelet adhesion and activation has also been studied.⁵⁷ In addition, adverse drug reactions such as heparin induced thrombocytopenia can lead to profound thrombocytopenia compounded by the presence of heparin coated ECMO tubing.⁵⁸

Hyperfibrinolysis—Hyperfibrinolysis occurs when there is an over activation of the fibrinolytic system and leads to a bleeding tendency similar to that seen during trauma and liver transplant.⁵⁹ There is a paucity of data on the role of the fibrinolytic system in ECMO. Circuit related hyperfibrinolysis can occur in older circuits and typically resolves with a circuit change. A hyperfibrinolytic profile may also be seen in the setting of oxygenator thrombosis where fibrinogen is being consumed, an ominous sign of impending oxygenator failure and need for circuit replacement.⁶⁰

ECMO-related hemolysis

The incidence of hemolysis in adults may be as high as 8.1% for VV-ECMO and 5.1% for the VA-ECMO patients.⁶¹ Current ECMO pumps are nonocclusive, however red blood cells (RBC) can still be impacted by positive (arterial limb) and negative pressures (venous limb) created by the centrifugal pump.⁶²

The impact of positive in-line pressures on hemolysis—Depending on the degree of cardiac dysfunction ECMO circuits may be run at high flow rates (> 5 LPM), resulting in high outlet (post-pump) pressures (>300 mmHg). Blood can stagnate and heat up in the pump head leading to thrombus at low flows or if there is an occlusion in the outlet line. The work generated by the pump, results in high pump temperatures and shear stress particularly at tubing connector points, which can greatly increase the risk of hemolysis. The seal-less Maquet magnetic rotaflow pump introduced in 1995 was able to reduce heat generation and improve hydraulic efficiency with less RBC damage.⁶³

The impact of negative in-line pressures on hemolysis—Excessive venous line pressures may also result in RBC damage. When negative pressures at the inflow cannula exceed the volume of blood in the cannulated vein the line will visually bounce (often referred to as chugging or chatter), this is the result of vein walls collapsing over the inlet

ports of the cannula. When the blood is exposed to rapid changes in negative pressure, dissolved gas (nitrogen and oxygen) can form small gas filled cavities. When these cavities experience higher arterial line pressures, they collapse (i.e. cavitation), resulting in pressure waves that damage RBCs.⁶⁴ Strategies to minimize the risk of cavitation-induced hemolysis include: (i) increasing preload with volume support; (ii) reducing the pump speed; (iii) echocardiographic verification of cannula position; and (iv) troubleshooting cannulas for malpositioning, kinking and areas of clot in the tubing or oxygenator.

Current laboratory metrics in anticoagulation

Regardless of therapeutic strategy, monitoring the level of anticoagulation is critical to minimize bleeding and thrombotic events, however, in practice there is great variability in what is monitored. A recent international survey of ECMO centers showed that activated clotting time (ACT; 97%) is the most frequently measured, followed by the activated partial thromboplastin time (aPTT; 93%), then anti-factor Xa (FXa; 65%), and finally thromboelastography (TEG; 43%).^{65, 66} There are no major studies that have evaluated which combination of these metrics is optimal to minimize thrombosis or bleeding, and there is frequently discordance in among these values adding to clinical confusion. Supplemental Table 3 provides an overview of assays used to monitor anticoagulation on ECMO, and the evidence underlying the advantages and disadvantages of each assay.

LVAD coagulopathy and thromboembolic risk: specific considerations compared to ECMO

Conditions that increase risk for pump thrombosis in LVAD patients are summarized in Supplemental Table 4 and include device-related, clinical and surgical factors. LVAD-related coagulopathy has been well described by Susen et al.⁶⁷ Briefly, loss of vWF function combined with platelet dysfunction are the main mechanisms associated with early hemorrhagic risk after LVAD initiation. These hemocompatibility issues are usually well managed after the immediate post-operative course (< 48 hours), whereas ECMO-related coagulopathy becomes more severe as the duration of MCS increases (> 10 days). After several months of circulatory support, bleeding events observed in CF-LVAD patients are a leading cause of readmission, but are more likely to be related to persistently low pulse pressure than to interactions between blood and non-biologic materials on the device inner surfaces. Acquired von Willebrand syndrome with excess cleavage by ADAMTS13 has also been well described (Figure 4). Angiodysplasia of the gastrointestinal tract may result in significant bleeding and is more frequently observed with CF-LVAD than with the previous generation of pulsatile devices (Figure 4).^{4, 68} Another major difference in hematologic-specific outcomes between patients managed on ECMO compared to LVAD patients is the morbidity and mortality associated with these adverse events (Supplemental Table 5). ECMO-related complications are usually managed medically whereas LVAD-related bleeding or thrombosis require more often invasive or surgical treatment. In the case of ECMO circuit component clots, the risk of both hemodynamic collapse and thromboembolic complication is low, and a simple change of the ECMO circuit is necessary. In stark contrast, LVAD thrombosis, regardless of the clot location (inflow, pump body, or outflow), can result in stroke and pump dysfunction. This devastating complication is associated with up to 50% mortality in patients not eligible for pump exchange or urgent HTx.⁶⁹

Part VII. Conclusions and Future Perspectives

Several potential improvements to ECMO circuits are being explored and include improvement in oxygenator and pump efficiency, as well as technical advances in cannula materials that will allow for a lower level of anticoagulation for the circuit. For patients with respiratory failure or in patients with right ventricular pressure overload with a maintained intrinsic contractility despite depressed systolic function, pumpless extrapulmonary gas exchange system will likely expand their role. Among the most significant advancements is the development of pumpless extrapulmonary gas exchange system (i.e., Novalung interventional lung assist, Xenios AG, Germany). This system has the potential for use as a destination therapy device for respiratory failure, analogous to the LVAD. While this device has been approved in Europe, FDA approval has yet to be obtained. Until a destination device for respiratory failure is developed further ECMO research is needed to refine appropriate patient selection for ECMO support. As ECMO use continues to expand and the duration of ECMO therapy increases continued research is needed to understand the physiology of recovery from critical illness, the effect of MCS on the immune system and the medium and long-term sequelae of MCS.

Speed modulation is currently the only way to adapt MCS technology to human circulation. None of the current rotary pumps have an autoregulation system for pump speed and therefore can not automatically adapt to daily changes in LV loading conditions. Preclinical studies have investigated *in vivo* performance of pressure or volume sensors to improve the real-time management of patients supported with durable LVADs (Figure 5).⁷⁰ Real-time measurement of blood viscosity in LVAD patients has also been recently reported to improve the management of centrifugal pumps.⁷¹ Similarly, real-time monitoring of aortic valve opening associated with automatic feed-back adjustment of LV unloading has been investigated in sheep by Jansen-Park et al.⁷² Additional research is being applied to make pressure-regulated rotary blood flow closer to the physiology of the normal heart. Contemporary CF-LVADs provide artificial pulsatility, however the hemodynamic and functional benefit especially on end-organ perfusion and hemocompatibility remains to be investigated. Analysis of wave forms is clinically available with the HVAD centrifugal flow pump and will be in the next few years with the HM devices. These data provide evidence for early detection of adverse events (pump thrombosis) but are also useful to optimize pump speed and fluid expansion in the postoperative course after LVAD implantation.⁷³ Autoregulation of pump speed due to integrative analysis of wave forms could be a major advance for the next generation of LVADs. Remote hemodynamic monitoring using intrapulmonary pressure sensors is another promising approach for the management of LVAD patients, during the early postoperative course and later for decision to bridge the patient to HTx, based on the level of pulmonary hypertension (Figure 5).^{74, 75}

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Wolfson PJ. The development and use of extracorporeal membrane oxygenation in neonates. *The Annals of thoracic surgery*. 2003;76:S2224–S2229. [PubMed: 14667691]
2. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. *The New England journal of medicine*. 2001;345:1435–1443. [PubMed: 11794191]
3. Goldstein DJ, Meyns B, Xie R, et al. Third Annual Report From the ISHLT Mechanically Assisted Circulatory Support Registry: A comparison of centrifugal and axial continuous-flow left ventricular assist devices. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation*. 2019;38:352–363.
4. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. *The New England journal of medicine*. 2009;361:2241–2251. [PubMed: 19920051]
5. Holman WL, Naftel DC, Eckert CE, Kormos RL, Goldstein DJ, Kirklin JK. Durability of left ventricular assist devices: Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) 2006 to 2011. *The Journal of thoracic and cardiovascular surgery*. 2013;146:437–441.e431. [PubMed: 23490245]
6. Kirklin JK, Naftel DC, Pagani FD, et al. Seventh INTERMACS annual report: 15,000 patients and counting. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation*. 2015;34:1495–1504.
7. Moazami N, Dembitsky WP, Adamson R, et al. Does pulsatility matter in the era of continuous-flow blood pumps? *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation*. 2015;34:999–1004.
8. Broman LM, Taccone FS, Lorusso R, et al. The ELSO Maastricht Treaty for ECLS Nomenclature: abbreviations for cannulation configuration in extracorporeal life support - a position paper of the Extracorporeal Life Support Organization. *Critical care (London, England)*. 2019;23:36.
9. Rao P, Khalpey Z, Smith R, Burkhead D, Kociol RD. Venoarterial Extracorporeal Membrane Oxygenation for Cardiogenic Shock and Cardiac Arrest. *Circulation. Heart failure*. 2018;11:e004905. [PubMed: 30354364]
10. Pavlushkov E, Berman M, Valchanov K. Cannulation techniques for extracorporeal life support. *Annals of translational medicine*. 2017;5:70. [PubMed: 28275615]
11. Rao P, Mosier J, Malo J, et al. Peripheral VA-ECMO with direct biventricular decompression for refractory cardiogenic shock. *Perfusion*. 2018;33:493–495. [PubMed: 29466925]
12. Demondion P, Fournel L, Golmard JL, Niculescu M, Pavie A, Leprince P. Predictors of 30-day mortality and outcome in cases of myocardial infarction with cardiogenic shock treated by extracorporeal life support. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2014;45:47–54. [PubMed: 23616484]
13. Schafer A, Burkhead D, Bauersachs J. Haemodynamic simulation and the effect of early left ventricular unloading in pre-shock acute coronary syndrome. *ESC heart failure*. 2019;6:457–463. [PubMed: 30861640]
14. Weber C, Deppe AC, Sabashnikov A, et al. Left ventricular thrombus formation in patients undergoing femoral veno-arterial extracorporeal membrane oxygenation. *Perfusion*. 2018;33:283–288. [PubMed: 29172999]
15. Ostadal P, Mlcek M, Kruger A, et al. Increasing venoarterial extracorporeal membrane oxygenation flow negatively affects left ventricular performance in a porcine model of cardiogenic shock. *Journal of translational medicine*. 2015;13:266. [PubMed: 26275717]

16. Cevasco M, Takayama H, Ando M, Garan AR, Naka Y, Takeda K. Left ventricular distension and venting strategies for patients on venoarterial extracorporeal membrane oxygenation. *Journal of thoracic disease*. 2019;11:1676–1683. [PubMed: 31179113]
17. Meani P, Gelsomino S, Natour E, et al. Modalities and Effects of Left Ventricle Unloading on Extracorporeal Life support: a Review of the Current Literature. *European journal of heart failure*. 2017;19 Suppl 2:84–91. [PubMed: 28470925]
18. Schrage B, Burkhoff D, Rubsamen N, et al. Unloading of the Left Ventricle During Venoarterial Extracorporeal Membrane Oxygenation Therapy in Cardiogenic Shock. *JACC. Heart failure*. 2018;6:1035–1043. [PubMed: 30497643]
19. Capoccia M Mechanical Circulatory Support for Advanced Heart Failure: Are We about to Witness a New “Gold Standard”? *Journal of cardiovascular development and disease*. 2016;3.
20. Fukamachi K, Shiose A, Massiello A, et al. Preload sensitivity in cardiac assist devices. *The Annals of thoracic surgery*. 2013;95:373–380. [PubMed: 23272869]
21. Senage T, Fevrier D, Michel M, et al. A mock circulatory system to assess the performance of continuous-flow left ventricular assist devices (LVADs): does axial flow unload better than centrifugal LVAD? *ASAIO journal (American Society for Artificial Internal Organs : 1992)*. 2014;60:140–147. [PubMed: 24577368]
22. Wiegmann L, Thamsen B, de Zelicourt D, et al. Fluid Dynamics in the HeartMate 3: Influence of the Artificial Pulse Feature and Residual Cardiac Pulsation. *Artificial organs*. 2019;43:363–376. [PubMed: 30129977]
23. Uriel N, Colombo PC, Cleveland JC, et al. Hemocompatibility-Related Outcomes in the MOMENTUM 3 Trial at 6 Months: A Randomized Controlled Study of a Fully Magnetically Levitated Pump in Advanced Heart Failure. *Circulation*. 2017;135:2003–2012. [PubMed: 28385948]
24. Mehra MR, Goldstein DJ, Uriel N, et al. Two-Year Outcomes with a Magnetically Levitated Cardiac Pump in Heart Failure. *The New England journal of medicine*. 2018;378:1386–1395. [PubMed: 29526139]
25. Mehra MR, Salerno C, Cleveland JC, et al. Healthcare Resource Use and Cost Implications in the MOMENTUM 3 Long-Term Outcome Study. *Circulation*. 2018;138:1923–1934. [PubMed: 29807933]
26. Li Y-SJ, Haga JH, Chien S. Molecular basis of the effects of shear stress on vascular endothelial cells. *Journal of Biomechanics*. 2005;38:1949–1971. [PubMed: 16084198]
27. Burton AC. Relation of structure to function of the tissues of the wall of blood vessels. *Physiological reviews*. 1954;34:619–642. [PubMed: 13215088]
28. Tank J, Heusser K, Malehsa D, et al. Patients with continuous-flow left ventricular assist devices provide insight in human baroreflex physiology. *Hypertension (Dallas, Tex. : 1979)*. 2012;60:849–855.
29. Moayedifar R, Zuckermann A, Aliabadi-Zuckermann A, et al. Long-term heart transplant outcomes after lowering fixed pulmonary hypertension using left ventricular assist devices. *European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery*. 2018;54:1116–1121. [PubMed: 29905775]
30. Uriel N, Imamura T, Sayer G, et al. High Transpulmonary Artery Gradient Obtained at the Time of Left Ventricular Assist Device Implantation Negatively Affects Survival After Cardiac Transplantation. *Journal of cardiac failure*. 2019.
31. Kochav SM, Flores RJ, Truby LK, Topkara VK. Prognostic Impact of Pulmonary Artery Pulsatility Index (PAPi) in Patients With Advanced Heart Failure: Insights From the ESCAPE Trial. *Journal of cardiac failure*. 2018;24:453–459. [PubMed: 29597051]
32. Lampert BC, Teuteberg JJ. Right ventricular failure after left ventricular assist devices. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation*. 2015;34:1123–1130.
33. Farrar DJ, Compton PG, Dajee H, Fonger JD, Hill JD. Right heart function during left heart assist and the effects of volume loading in a canine preparation. *Circulation*. 1984;70:708–716. [PubMed: 6478570]

34. Moon MR, Castro LJ, DeAnda A, et al. Right ventricular dynamics during left ventricular assistance in closed-chest dogs. *The Annals of thoracic surgery*. 1993;56:54–67. [PubMed: 8328877]
35. Denault AY, Haddad F, Jacobsohn E, Deschamps A. Perioperative right ventricular dysfunction. *Current opinion in anaesthesiology*. 2013;26:71–81. [PubMed: 23235519]
36. Haddad F, Couture P, Tousignant C, Denault AY. The right ventricle in cardiac surgery, a perioperative perspective: II. Pathophysiology, clinical importance, and management. *Anesthesia and analgesia*. 2009;108:422–433. [PubMed: 19151265]
37. Khalil HA, Cohn WE, Metcalfe RW, Frazier OH. Preload sensitivity of the Jarvik 2000 and HeartMate II left ventricular assist devices. *ASAIO journal (American Society for Artificial Internal Organs: 1992)*. 2008;54:245–248. [PubMed: 18496273]
38. Lim HS, Howell N, Ranasinghe A. The Physiology of Continuous-Flow Left Ventricular Assist Devices. *Journal of cardiac failure*. 2017;23:169–180. [PubMed: 27989869]
39. Rosenbaum AN, Frantz RP, Kushwaha SS, Stulak JM, Maltais S, Behfar A. Novel Left Heart Catheterization Ramp Protocol to Guide Hemodynamic Optimization in Patients Supported With Left Ventricular Assist Device Therapy. *Journal of the American Heart Association*. 2019;8:e010232. [PubMed: 30755070]
40. Moreno-Suarez I, Liew S, Dembo LG, Larbalestier R, Maiorana A. Physical Activity Is Higher in Patients with LVADs Compared to Chronic Heart Failure. *Medicine and science in sports and exercise*. 2019.
41. Dunlay SM, Allison TG, Pereira NL. Changes in cardiopulmonary exercise testing parameters following continuous flow left ventricular assist device implantation and heart transplantation. *Journal of cardiac failure*. 2014;20:548–554. [PubMed: 24893345]
42. Aymami M, Donal E, Guihaire J, et al. Rest and Exercise Adaptation of the Right Ventricular Function in Long-Term Left Ventricular Assist Device Patients: A Prospective, Pilot Study. *Journal of cardiac failure*. 2016;22:240–241. [PubMed: 26705752]
43. Vignati C, Apostolo A, Cattadori G, et al. Lvad pump speed increase is associated with increased peak exercise cardiac output and vo2, postponed anaerobic threshold and improved ventilatory efficiency. *International journal of cardiology*. 2017;230:28–32. [PubMed: 28038810]
44. Apostolo A, Paolillo S, Contini M, et al. Comprehensive effects of left ventricular assist device speed changes on alveolar gas exchange, sleep ventilatory pattern, and exercise performance. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation*. 2018;37:1361–1371.
45. Christle JW, Moneghetti K, Haddad F, et al. P1833Serial echo-cardiopulmonary exercise test ramping for evaluation of patients with VAD. *European Heart Journal*. 2018;39.
46. Imamura T, Kinugawa K, Nitta D, et al. Novel scoring system using postoperative cardiopulmonary exercise testing predicts future explantation of left ventricular assist device. *Circulation journal: official journal of the Japanese Circulation Society*. 2015;79:560–566. [PubMed: 25746540]
47. Grosman-Rimon L, McDonald MA, Pollock Bar-Ziv S, et al. Chronotropic incompetence, impaired exercise capacity, and inflammation in recipients of continuous-flow left ventricular assist devices. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation*. 2013;32:930–932.
48. Ben Gal T, Piepoli MF, Corra U, et al. Exercise programs for LVAD supported patients: A snapshot from the ESC affiliated countries. *International journal of cardiology*. 2015;201:215–219. [PubMed: 26301640]
49. Bobenko A, Schoenrath F, Knierim JH, et al. Exercise training in patients with a left ventricular assist device (Ex-VAD): rationale and design of a multicentre, prospective, assessor-blinded, randomized, controlled trial. *European journal of heart failure*. 2019.
50. Jung MH, Gustafsson F. Exercise in heart failure patients supported with a left ventricular assist device. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation*. 2015;34:489–496.

51. Christie JW, Boscheri A, Pressler A, et al. Interval exercise training increases maximal and submaximal exercise performance in heart failure with biventricular assist device therapy. *International journal of cardiology*. 2015;187:104–105. [PubMed: 25828324]
52. Mahfood Haddad T, Saurav A, Smer A, et al. Cardiac Rehabilitation in Patients With Left Ventricular Assist Device: A SYSTEMATIC REVIEW AND META-ANALYSIS. *Journal of cardiopulmonary rehabilitation and prevention*. 2017;37:390–396. [PubMed: 28727672]
53. Doyle AJ, Hunt BJ. Current Understanding of How Extracorporeal Membrane Oxygenators Activate Haemostasis and Other Blood Components. *Front Med (Lausanne)*. 2018;5:352–352. [PubMed: 30619862]
54. Fischer M, Sperling C, Tengvall P, Werner C. The ability of surface characteristics of materials to trigger leukocyte tissue factor expression. *Biomaterials*. 2010;31:2498–2507. [PubMed: 20035991]
55. Cho HJ, Kim DW, Kim GS, Jeong IS. Anticoagulation Therapy during Extracorporeal Membrane Oxygenator Support in Pediatric Patients. *Chonnam Med J*. 2017;53:110–117. [PubMed: 28584789]
56. Abrams D, Baldwin MR, Champion M, et al. Thrombocytopenia and extracorporeal membrane oxygenation in adults with acute respiratory failure: a cohort study. *Intensive care medicine*. 2016;42:844–852. [PubMed: 27007099]
57. Lukito P, Wong A, Jing J, et al. Mechanical circulatory support is associated with loss of platelet receptors glycoprotein Iba1 and glycoprotein VI. *Journal of thrombosis and haemostasis : JTH*. 2016;14:2253–2260. [PubMed: 27601054]
58. Natt B, Hypes C, Basken R, Malo J, Kazui T, Mosier J. Suspected Heparin-Induced Thrombocytopenia in Patients Receiving Extracorporeal Membrane Oxygenation. *The journal of extra-corporeal technology*. 2017;49:54–58. [PubMed: 28298667]
59. Chapin JC, Hajjar KA. Fibrinolysis and the control of blood coagulation. *Blood reviews*. 2015;29:17–24. [PubMed: 25294122]
60. Lubnow M, Philipp A, Foltan M, et al. Technical complications during veno-venous extracorporeal membrane oxygenation and their relevance predicting a system-exchange--retrospective analysis of 265 cases. *PloS one*. 2014;9:e112316. [PubMed: 25464516]
61. Conrad SA, Rycus PT, Dalton H. Extracorporeal Life Support Registry Report 2004. *ASAIO journal (American Society for Artificial Internal Organs : 1992)*. 2005;51:4–10. [PubMed: 15745126]
62. Lawson DS, Ing R, Cheifetz IM, et al. Hemolytic characteristics of three commercially available centrifugal blood pumps. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*. 2005;6:573–577.
63. Mendler N, Podecht F, Feil G, Hiltmann P, Sebening F. Seal-less centrifugal blood pump with magnetically suspended rotor: rot-a-flot. *Artificial organs*. 1995;19:620–624. [PubMed: 8572962]
64. Lequier L, Horton SB, McMullan DM, Bartlett RH. Extracorporeal membrane oxygenation circuitry. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*. 2013;14:S7–12.
65. Bembea MM, Annich G, Rycus P, Oldenburg G, Berkowitz I, Pronovost P. Variability in anticoagulation management of patients on extracorporeal membrane oxygenation: an international survey. *Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies*. 2013;14:e77–84.
66. Winkler AM. Managing the Precarious Hemostatic Balance during Extracorporeal Life Support: Implications for Coagulation Laboratories. *Seminars in thrombosis and hemostasis*. 2017;43:291–299. [PubMed: 28166602]
67. Susen S, Rauch A, Van Belle E, Vincentelli A, Lenting PJ. Circulatory support devices: fundamental aspects and clinical management of bleeding and thrombosis. *Journal of thrombosis and haemostasis : JTH*. 2015;13:1757–1767. [PubMed: 26302994]
68. Eckman PM, John R. Bleeding and thrombosis in patients with continuous-flow ventricular assist devices. *Circulation*. 2012;125:3038–3047. [PubMed: 22711669]

69. Starling RC, Moazami N, Silvestry SC, et al. Unexpected abrupt increase in left ventricular assist device thrombosis. *The New England journal of medicine*. 2014;370:33–40. [PubMed: 24283197]
70. Cysyk J, Newswanger R, Popjes E, et al. Cannula Tip With Integrated Volume Sensor for Rotary Blood Pump Control: Early-Stage Development. *ASAIO journal (American Society for Artificial Internal Organs : 1992)*. 2019;65:318–323. [PubMed: 29757760]
71. Hijikata W, Maruyama T, Suzumori Y, Shinshi T. Measuring real-time blood viscosity with a ventricular assist device. *Proceedings of the Institution of Mechanical Engineers. Part H, Journal of engineering in medicine*. 2019;233:562–569.
72. Jansen-Park S-H, Spiliopoulos S, Deng H, et al. A monitoring and physiological control system for determining aortic valve closing with a ventricular assist device. *European Journal of Cardio-Thoracic Surgery*. 2014;46:356–360. [PubMed: 24499877]
73. Grinstein J, Rodgers D, Kalantari S, et al. HVAD Waveform Analysis as a Noninvasive Marker of Pulmonary Capillary Wedge Pressure: A First Step Toward the Development of a Smart Left Ventricular Assist Device Pump. *ASAIO journal (American Society for Artificial Internal Organs : 1992)*. 2018;64:10–15. [PubMed: 28604571]
74. Kilic A, Katz JN, Joseph SM, et al. Changes in pulmonary artery pressure before and after left ventricular assist device implantation in patients utilizing remote haemodynamic monitoring. *ESC heart failure*. 2019;6:138–145. [PubMed: 30350926]
75. Veenis JF, Manintveld OC, Constantinescu AA, et al. Design and rationale of haemodynamic guidance with CardioMEMS in patients with a left ventricular assist device: the HEMO-VAD pilot study. *ESC heart failure*. 2019;6:194–201. [PubMed: 30614639]

Figure 1. Comprehensive approach for mechanical circulatory support in cardiogenic shock. ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device; right ventricular assist device; RVAD, right ventricular assist device.

Figure 2. Complications related to the opposite blood flow in patients under femoral VA-ECMO. ECMO, extracorporeal membrane oxygenation; VA, venoarterial; VAV, venoarterial venous; LA, left atrium; LV, left ventricle.

Figure 3. The LVAD system and intrinsic ventricular function, a parallel circulatory configuration.

(A) The LVAD system is organized in parallel with the left ventricle with the pulmonary flow serving as a gage of the effective circulatory output. (B) The change in the LV-pressure volume loop secondary to implantation of the LVAD. (C) the HQ LVAD flow curves highlighting the importance of pressure differential on pump flow with greater differential associated with lower flows as well as the effects of RPM on flow curves. (D) increasing RPM speed during RAMP protocols can alter pressure-volume curves by increasing unloading and therefore affecting the ability of the LV to eject blood. (E) and (F) highlight selected parameters useful in echocardiographic monitoring of LVAD including aortic valve opening, LV dimensions, septal position, right ventricular function as well as valvular function. Monitoring of estimated PA flows can be useful during RAMP optimization of LVAD flow. *White plots, end-systolic point; Black plots, end-diastolic point; Dash lines = LVAD support*

Figure 4. Schematic representation of selected elements associated with increased risk of bleeding in LVAD patients.

Continuous flow LVAD can contribute to acquired vonWillebrand syndrome as well as angiodysplasia (especially the gastrointestinal bed). With anticoagulation and antiplatelet therapy, these two factors can significantly increase the risk of bleeding in patients with LVAD.

Figure 5. Schematic representation of an autoregulated smart LVAD design.

Sensor technology including pump flow curve analytics, pressure-flow sensors, heart rate and rhythm sensors and activity sensors could be integrated in an autoregulated LVAD system enabling modulation of RPM as well as early complication detection algorithms allowing early therapeutic intervention. Activity, heart rate and blood pressure sensors can in the future also be incorporated for optimization of blood pressure, fluid management or detection of systemic complications such as bleeding.

Table 1.

Indications and approaches for left ventricular decompression under VA-ECMO support.

Indications		
<i>Clinical</i>	<i>Hemodynamic</i>	
- ventricular arrhythmias	- pulse pressure <10 mmHg	
- pulmonary edema	- PCWP >25 mmHg	
<i>Echocardiographic</i>		
- absence of aortic valve opening		
- dilated and hypocontractile LV		
- blood stagnation within LV or LA		
Approaches	Advantages	Disadvantages/Risks
IABP	Percutaneous Bedside implantation	Thromboembolic events Migration Insertion site (bleeding, infection)
Percutaneous atrial septostomy (Rashkind)	Percutaneous No implantable device	Percutaneous closure in case of myocardial recovery Surgical closure in case of LVAD implantation
Impella	Percutaneous Progressive weaning (LV ejection) Prevent aortic root thrombosis	Stroke, Hemolysis Aortic valve injury (regurgitation) Insertion site (infection, bleeding)
TandemHeart	Percutaneous Dual lumen canula for unloading of left and right atria	Transseptal approach Migration
LV / LA vent	Direct unloading of LV / LA Progressive weaning (LV ejection)	Surgical approach for implantation and explantation Canulation site (bleeding, infection)

IABP, intra-aortic balloon pump; LA, left atrium; LV, left ventricle; PCWP, pulmonary capillary wedge pressure.

Table 2.

Comparative characteristics of pulsatile and continuous flow left ventricular assist devices.

	PF VADs	CF VADs
Device (weight)	<ul style="list-style-type: none"> - Berlin Heart EXCOR (45 to 140 gr.) - Thoratec IVAD (339 gr.) - Thoratec PVAD (419 gr.) - Novacor (1000 gr.) - Heartmate 1 XVE (1150 gr.) 	<i>Axial pumps:</i> <ul style="list-style-type: none"> - Jarvik 2000 (90 gr.) - Heart Assist 5 (92 gr.) - Berlin Heart INCOR (200 gr.) - HM2 (281 gr.) <i>Centrifugal pumps:</i> <ul style="list-style-type: none"> - Heartware (145 gr.) - HM3 (200 gr.)
Constitution	<ul style="list-style-type: none"> - one compliance chamber (10 to 65 mL according to device type) - inflow and outflow valves - inflow and outflow cannula 	<ul style="list-style-type: none"> - <i>Axial pumps:</i> inflow cannula, impeller inside a small pump chamber, pre-coated outflow graft - <i>Centrifugal pumps:</i> integrated inflow cannula, single suspended rotor with impeller blade, small pump chamber (50 mL), pre-clotted outflow graft with bend relief
Physiology of blood flow	Volume displacement	Fluid acceleration <ul style="list-style-type: none"> - <i>Axial pumps:</i> hydrodynamic forces and partial magnetic levitation using hemodynamic bearings, seals impeller (HVAD) - <i>Centrifugal pumps:</i> full magnetic levitation of a spinning rotor using a single stator (HM3)
Implantation	Intraperitoneal or extracorporeal	Intrathoracic
Energy transfer	Periodic changes in working space	Rotation of the impeller (axial pump) or of the spinning rotor (centrifugal pump)
Flow adaptation	Systole/diastole duration ratio	Pump speed: <ul style="list-style-type: none"> - 8,000 to 12,000 (axial) - 2,400 to 2,900 (HVAD) - 4,800 to 5,800 (HM3)
Output range	4 to 8 L/min	4 to 10 L/min
Durability	<5% at 2 years	70% at 2 years
Sensitivity to preload	"Fill to empty mode": synchronization with the native ventricle	Preload-dependent: suction events in case of low LV preload
Sensitivity to afterload	Low	High (centrifugal > axial)

LVAD, left ventricular assist device; CF, continuous flow; PF, pulsatile flow; HVAD, heartware ventricular assist device; HM2, heartmate 2; HM3, heartmate 3.

Table 3.

Comprehensive interactive physiology of the normal heart and contemporary ventricular assist devices.

	Normal Left Ventricle	Rotary Blood Pumps
Characteristics of blood flow	Pulsatile	Continuous Low-pulsatility waveform with centrifugal pumps [*]
Functional Anatomy	Chamber + outflow tract including valves	Inflow cannula + pump + outflow cannula
Determinants of blood flow	Preload Afterload Contractility Heart rate, heart rhythm	Preload $\approx$ LV pressure Afterload $\approx$ aortic pressure Pressure gradient across the pump Pump speed
Shear stress	Low	High
Adaptation to changes in loading conditions	Heterometric autoregulation	Fixed pump speed Modulation based on pressure gradients
Changes in preload	Frank-Starling relationship	
- $\searrow$ preload	$\searrow$ SV, $\searrow$ SWi, $\searrow$ CO	$\nearrow$ pressure gradient, $\searrow$ pump flow
- $\nearrow$ preload	$\nearrow$ SV, $\nearrow$ SWi, $\nearrow$ CO	$\searrow$ pressure gradient, $\nearrow$ pump flow
Changes in afterload		
- $\searrow$ afterload	Mild to Moderate effects on cardiac output (<i>acute setting</i>)	$\searrow$ pressure gradient, $\nearrow$ pump flow
- $\nearrow$ afterload		$\nearrow$ pressure gradient, $\searrow$ pump flow

^{*} Waveforms with low pulsatility can be observed due to native ventricular contraction and cyclical variations of pump speed in centrifugal pumps.

CO, cardiac output; LV, left ventricle; SV, stroke volume; SWi, stroke work index. Pressure gradient across the pump = Aortic blood pressure – left ventricular pressure.

Table 4.

Summary of hematologic complications in patient on ECMO support

Complication	Cause
Thrombosis	Low blood flow rate Low flow at tubing connections/tube kinking Inadequate anticoagulation – antithrombin deficiency Disseminated intravascular coagulation Heparin induced thrombocytopenia
Bleeding	Supratherapeutic anticoagulation Surgical complications Acquired von Willebrand disease Liver disease Disseminated intravascular coagulation Thrombocytopenia Platelet dysfunction – loss of glycoprotein receptors Hyperfibrinolysis
Thrombocytopenia	Illness severity Underlying thrombocytopenia Sepsis/septic shock Disseminated intravascular coagulation Heparin induced thrombocytopenia
Hemolysis	Disseminated intravascular coagulation Excessive pump speed – high positive pressures resulting in shear stress and heating of pump Excessive negative pressures – cavitation of dissolved gas (nitrogen, oxygen)