Toward a Long-Term Artificial Lung

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Only a very small portion of end-stage organ failures can be treated by transplantation because of the shortage of donor organs. Although artificial long-term organ support such as ventricular assist devices provide therapeutic options serving as a bridge-to-transplantation or destination therapy for end-stage heart failure, suitable long-term artificial lung systems are still at an early stage of development. Although a short-term use of an extracorporeal lung support is feasible today, the currently available technical solutions do not permit the long-term use of lung replacement systems in terms of an implantable artificial lung. This is currently limited by a variety of factors: biocompatibility problems lead to clot formation within the system, especially in areas with unphysiological flow conditions. In addition, proteins, cells, and fibrin are deposited on the membranes, decreasing gas exchange performance and thus, limiting long-term use. Coordinated basic and translational scientific research to solve these problems is therefore necessary to enable the long-term use and implantation of an artificial lung. Strategies for improving the biocompatibility of foreign surfaces, for new anticoagulation regimes, for optimization of gas and blood flow, and for miniaturization of these systems must be found. These strategies must be validated by *in vitro* and *in vivo* tests, which remain to be developed. In addition, the influence of long-term support on the pathophysiology must be considered. These challenges require well-connected interdisciplinary teams from the natural and material sciences, engineering, and medicine, which take the necessary steps toward the development of an artificial implantable lung. *ASAIO Journal* XXX; XX:00–00.

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Chronic obstructive pulmonary disease is the third most frequent cause of death worldwide, with an increasing mortality. Despite noninvasive ventilation, patients suffer from extreme shortness of breath because of insufficient pulmonary oxygen transfer into the blood and CO_2 elimination from the blood, become immobile, and are mostly no longer able to cope with stress. Furthermore, there is a long-term need for continuous gas exchange support in patients with cystic fibrosis, a congenital disease (frequency, 1:2,000) in which patients mostly require transplantation in the 3rd decade of life because of respiratory insufficiency that can no longer be stabilized but die before organ availability.

Lung transplantation remains the only long-term therapy for these irreversible, terminal lung diseases.[1] However, the availability of donor lungs is severely limited,[2] so there is a great need for a permanent, implantable lung support system. Today's conventional lung support systems (mostly referred to as extracorporeal membrane oxygenators [ECMO]) consist mainly of blood pump, heat exchanger, oxygenator, and cannulae.

The oxygenator module contains bundles of hollow fibers made of polypropylene (PP) or polymethylpentene (PMP) which are predominantly antithrombogen-coated. In contrast to dialyzers, in which blood flows inside the hollow fiber, blood flows around the fibers within these bundles, and oxygen flows through them. Depending on the indication (cause and severity of the gas exchange disorder), the required blood flow through the gas exchange module can be generated by a pump connected to the patient's venous vascular system or far less commonly, passively by connecting to the patient's arterial system.[3]

Despite its antithrombogenic coating and the simultaneous low-dose administration of anticoagulants, the oxygenator module often has to be replaced after a relatively short period of use, ranging from days to a few weeks, because of clot formation. In addition, gas exchange *via* the membrane oxygenator is usually limited after a relatively short time because of a membranous structure (composed of fibrin, single cells, and cell clusters) that covers large areas of the PMP-fibers, which increases the diffusion barrier.[4]

Today's technology allows the use of lung support systems for only a very limited period of time, ranging from days to a few weeks, because of the complexity of the systems and the simultaneous biocompatibility problems. Therefore, lung support systems are currently by no means a permanent support

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option for terminal benign lung diseases.[5] Based on the current state of the related technology and clinical needs, the following seven research fields have been identified as crucial on the way to an implantable lung (**Figure 1**):

1. Research on new anticoagulation regimes and biomarker development
2. Analysis and design of biocompatible membrane and system surfaces
3. Analysis of inflammatory mechanisms and therapy for inflammatory processes induced by the artificial lung
4. Investigation of technical solution corridors for miniaturization, structural integration, and connection of the essential components of a lung support system
5. *In silico* sand *in vitro* analysis of blood flow and gas exchange
6. *In vitro* verification and *in vivo* validation methods development for lung assist systems
7. Influence of long-term lung support on pathophysiology

Activation of Coagulation and Anticoagulation Strategies

The large artificial surfaces encounter activation of the coagulation system even with the best currently available surface coatings. In addition, nonphysiologic flow processes activate leukocytes and thrombocytes, causing additional prothrombogenic activity. Therefore, an efficient and easily controllable anticoagulant is required.

Currently, unfractionated heparin is used as standard therapy for anticoagulation in extracorporeal circulatory systems. Heparin, which is systemically administered intravenously, acts by enhancing antithrombin activity and can be dosed based on various laboratory parameters (activated clotting time, activated partial thromboplastin time, and anti-FXa levels). However, heparin can lead to severe complications, such as bleeding and heparin-induced thrombocytopenia, even in the therapeutic range. In addition to the systemic application of heparin, the blood-exposed surfaces are coated with heparin to reduce their coagulation activation. However, the standard antithrombogenic coating (heparin, phosphorylcholine, poly-2-methoxyethylacrylate, *etc.*) of the blood-bearing components of lung support systems is not sufficient to prevent thrombus formation.[6] Surface-bound heparin is thought to be washed out and degraded by plasmatic enzymes such that its anticoagulant effect is not permanent; the use of surface-bound heparin therefore does not appear optimal for chronic applications. Furthermore, heparin cleavage by ficolin-2, which should lead to activation of the complement system *via* the lectin pathway, has been described.[7] Therefore, heparin does not appear to be optimal for chronic applications.

Anticoagulation strategies with thrombin inhibitors (*e.g.* dabigatran and argatroban) and thrombocyte function inhibitors (*e.g.* prostacyclins) have been pursued experimentally.[8] Furthermore, acetylsalicylic acid and nitric oxide (NO), which both inhibit platelet signaling pathways, were tested in experimental systems.[9] Although all these anticoagulation strategies reduce thrombotic occlusions in the circulatory system and oxygenator, these strategies are associated with an increase in bleeding tendency, which can lead to severe life-threatening bleeding in patients with lung support systems.[10]

An anticoagulation strategy without bleeding complications is recently under development. Recombinant humanized antibodies against activated factor XII were generated. In a large animal model, the antibody 3F7 completely blocked the formation of occlusive thrombi in the extracorporeal circulation, without increasing the tendency to bleed.[11,12]

Currently, however, there is no reliable way to analyze the state of the anticoagulant coating in lung assist systems in clinical settings. Furthermore, there are no predictive biomarkers

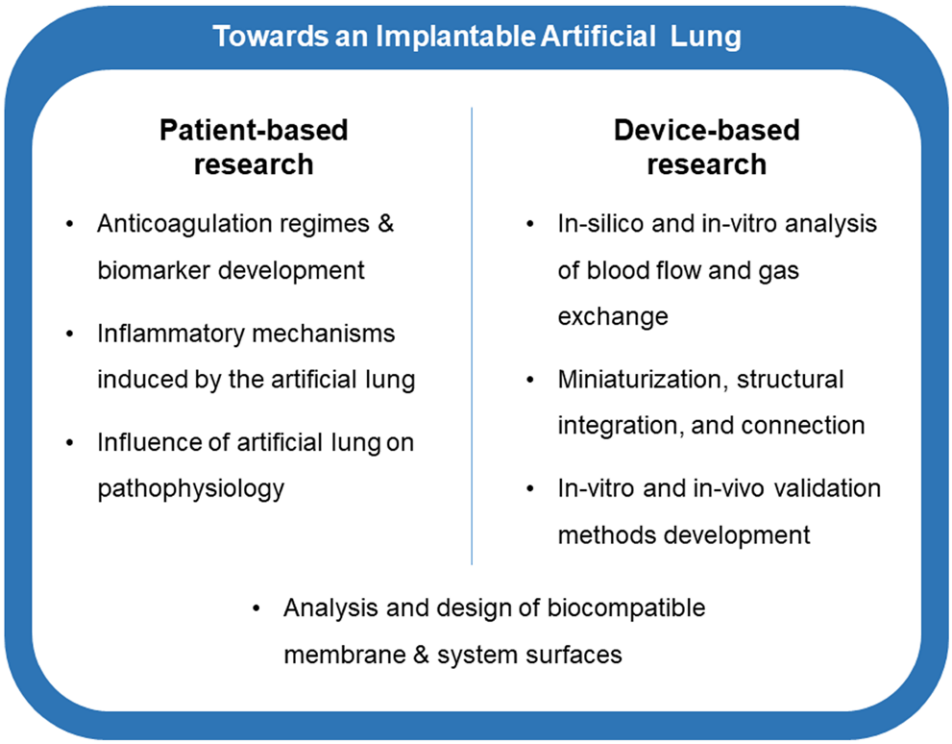

Figure 1. Research fields toward an implantable lung.

indicating coagulation activation in the early phase or occlusions of the circulatory system. Routine laboratory methods (single factor determinations, rotational thromboelastometry, determination of the prothrombin time/international normalized ratio ratio, activated partial thromboplastin time, and similar methods), experimental laminar flow chamber systems, and thrombin determination (endogenous thrombin potential) are used to analyze coagulation. Research on hemocompatibility has also led to fundamental insights into the influence of surface modifications on the activation of different blood cascade systems, particularly the complement system.[13] In addition, the effects of different systemic anticoagulation strategies on hemocompatibility have been investigated.[14,15] Furthermore, the administration of activated factor XII inhibitor antibodies could minimize thrombus formation in the extracorporeal circulation.[11]

However, there is still no reliable, easy to use method, which allows the prediction of thrombus formation at an early stage to adapt the anticoagulation strategy to the acute demand of the patient.[16] Special magnetic resonance imaging (MRI) methods make it possible to visualize thrombus formation in the system, but they require completely nonferromagnetic circuit components and imply a high level of technical and medical complexity.[17,18]

Analysis and Design of Biocompatible Membrane and System Surfaces

Despite a multitude of experimental approaches to surface modification, the goal of creating an antithrombogenic surface per se or a modification that allows stable endothelial cell adhesion has still not been achieved.

All efforts are aimed at preventing the activation and adhesion of thrombocytes on contact between biomaterial and blood. One approach, for example, was the physical modification of the blood-contacting surfaces of cardiovascular implants using nano- and microstructuring.[19,20] Chemical modification represents another approach (*e.g.* coupling of anticoagulants, NO-releasing (NOrel) coatings, cell type–specific peptide sequences). In this context, the use of so-called NOrel polymers,[21] which, similar to endothelial cells, release NO in the membrane and thus at least temporarily prevent platelet activation,[22] is promising.[23] A combination of NOrel polymers with covalent binding of the thrombin inhibitor argatroban[24] is also conceivable. Another example is the creation of a hydrophilized surface by polymerizing polyethylene glycol onto PP hollow fibers.[25] The variety of chemical modifications is also reflected in a process described by Federspiel *et al*.[26] that couples immobilized carboanhydrase to hollow fiber membranes and thus accelerates CO_2 exchange by the natural conversion of CO_2 into bicarbonate.

Physical and chemical modifications are also used to achieve the stable binding of endothelial cells to polymer surfaces. Endothelialization of surfaces exploits the physiologically induced antithrombogenicity of endothelial cells.[27] The endothelialization of PMP fiber bundles is possible, but requires chemical modification[27–29] or a special procedure to ensure that gas transfer is not impaired. Colonization with human endothelial progenitor cells on heparin/albumin-coated PMP membranes has also been shown.[30] Functionalization of the PMP surface by the covalent coupling of cell type–specific peptide sequences (*e.g.* cRGD, cyclic arginine–glycine asparagine) by means of copper-free "click" chemistry[30] or by coating with titanium oxide improved the adhesion of endothelial cells. The possibility of cellularization directly from the bloodstream (*in vivo* endothelialization) *via* the specific coupling of peptide sequences to polymer surfaces would also facilitate the approval procedure as a medical device.[31]

The particular challenge of all procedures lies in the interaction between optimal hemocompatibility and efficient gas transfer. Despite a variety of ideas and efforts to improve the hemocompatibility of surfaces exposed to blood by physical, chemical, or biologic methods, there is still no clinically available coating that can effectively and permanently prevent both coagulation activation and thus clot formation, as well as protein adsorption.

Analysis of Inflammatory Mechanisms and Therapy for Inflammatory Processes Induced by the Artificial Lung

Inflammatory processes are of decisive importance for the therapy and prognosis of the patient, especially in long-term treatment with lung support systems. However, little is known about the mechanisms and complex inflammatory reactions involved in extracorporeal circulation. Examples include activation of the complement system, expression of the procoagulant tissue factor, increases in chemokines and cytokines, and activation of neutrophil granulocytes with the formation of networks (neutrophil extracellular traps [NETs]). Clinically, the formation of edema is an important therapeutic challenge. Inflammatory mediators increase vascular permeability, and the outflow of plasma and protein components leads to tissue swelling. It has long been known that neutrophil granulocytes play an important role in inflammatory processes.[32] New studies show that, in addition to the production of oxygen radicals by neutrophil granulocytes[33] and their ability to migrate,[34] networks of DNA threads from activated neutrophil granulocytes (so-called NETs) are an important mechanism by which neutrophil granulocytes contribute to inflammatory processes.[35] The analysis of these NETs in extracorporeal circulatory systems offers new perspectives for anti-inflammatory therapy.[36] In addition, research on hemocompatibility using mass spectrometry[37] and biomarker analyses[38,39] has led to fundamental insights into the influence of surface modifications on the activation of different cascade systems of the blood, particularly the complement system.

Investigation of Technical Solution Corridors for the Miniaturization, Structural Integration, and Connection of the Essential Components of a Lung Support System

To achieve implantation of a lung support system, miniaturization (oxygenator unit, pump, *etc.*), reduction (tubes) or even the renunciation of individual components (pumpless systems) with regard to all system components is being pursued. Some promising concepts for miniaturization have already been proposed. At RWTH Aachen University, for example, a highly integrated ECMO with an integrated rotary pump that can be used as an ECMO system with significantly reduced external contact surfaces was developed.[40] Because of its compact design, this system is easy to handle and can be placed directly at the patient's bed, but still cannot be implanted. For

pediatric applications, this system has been further miniaturized[41] to reduce filling volumes. In another system, an oxygenator system with pulsating flow is generated with the aid of flexible, thin-walled silicone tubes within the fiber bundle; this system yielded promising results in previous *in vitro* tests.[42,43] A modular system that can be used both as a heart-lung machine and extracorporeal lung support is intended to facilitate the transition from operation-related heart-lung support to permanent extracorporeal lung support and the exchange of components.[44]

In the area of cannulation, a pumpless system that is connected to the umbilical cord of premature infants and also has pediatric applications was developed at RWTH Aachen University, Germany (**Figure 2**).[45] Connection techniques based on performance requirements, the type of gas exchange desired (oxygenation or primarily decarboxylation), and underlying lung disease are also being investigated for adults. An acute animal experiment in sheep showed that the combined replacement of the right ventricle and lung from the right to the left atrium using a pump-driven lung support system is possible.[46,47] At the University of Michigan in Ann Arbor, efforts were initially directed toward a pumpless system that is centrally cannulated and arranged either in parallel or serially to the lung circulation. However, problems such as right heart failure and bleeding occurred.[1,48]

Another development direction was the design of an intracaval, implantable membrane oxygenator, which was preclinically tested.[49] However, the overall gas transfer rates for both O_2 and CO_2 were too low, as the fiber bundles of this oxygenator were compressed by the vena cava itself, and the blood flow passed only the outer membrane fibers. Various systems for CO_2 elimination have been developed and are already in clinical use[50,51] (*e.g.* ILA system, Xenios AG, Heilbronn, Germany; Hemolung, ALung Technologies Inc., Pittsburgh, Pennsylvania). The oxygenators described so far are all based on hollow fiber membranes, which are currently the best solution for clinical use in terms of plasma tightness, permeability, and pressure drop.[52] Polydimethylsiloxane—a material with very good biocompatibility and oxygen diffusivity—serves as the basis for printing novel membranes with good material transport properties.[53] Polydimethylsiloxane was also used for novel microfluidic concepts of an artificial lung, which showed good gas transfer properties *in vitro* in small-scale models and very good hemocompatibility through the use of a polyethylene glycol coating,[54] but lack in large-scale producibility, yet.[55]

Figure 2. Miniaturized, pumpless extracorporeal lung support for premature neonates (research device, priming volume of complete circuit: ≤20 ml) tested in a lamb model with cannulation of the umbilical cord vessels.

Another important aspect of a miniaturized system is the demand-oriented regulation of gas transfer in an artificial lung. Changing conditions (resting phases, movement, stress, *etc.*) on a lung support system, especially in mobile patients, requires automated gas transfer regulation. For this reason, the first automated feedback systems that automatically recognize different levels of demand and then ultimately control pump flow were developed.[56,57]

In Silico and *In Vitro* Analysis of Blood Flow and Gas Exchange

The understanding of the flow conditions of blood and the gas exchange in the oxygenator is further deepened by the application of computational fluid dynamics (CFD)–based flow and gas exchange simulations, experimental flow measurement technology, visualization of the flow by particle image velocimetry (PIV) or particle tracking velocimetry, and MRI. This enables further system optimization, which is essential for the use of the oxygenator as a permanently implantable system.

Currently, observations of mass transport in oxygenators using CFD often use a characteristic number-oriented analytical description. Here, the hollow fiber module in its entirety is regarded as a compact porous medium whose fluid dynamics and membrane properties are described by means of indices.[58] Different research groups pursue CFD flow simulations in oxygenators with different approaches. In addition to flow simulations in oxygenators in which the fiber bundle is modelled as an isotropic, porous medium,[59] a method to determine anisotropic properties in fiber bundles *in vitro* and to implement anisotropic properties in flow simulations were developed (**Figure 3**).[60,61] At the same time, approaches to numerically calculate flow with realistic fiber geometries at high resolution are being pursued using powerful computational clusters. In addition, simulation models in which gas exchange processes in the blood can be examined on a microscopic level have already been developed and validated *in vitro* using identical geometries. The results showed good agreement between the theoretical and experimental values for PP fibers; thus, the correctness of the model was shown.[62,63] Of particular importance in the context of gas exchange is the diffusion path of the gas, which is significantly influenced by the thickness of the fiber membrane and the effective positions of the red blood cells (erythrocytes) in the blood. Therefore, it is essential to take the erythrocyte dynamics into account, transferred to the artificial flow channels of oxygenators. An attempt to consider realistic erythrocyte behavior (their tumbling motion as well as deformation under shearing action) together with elastic vessel wall behavior *via* so-called fluid–structure coupling is being made by means of smoothed particle hydrodynamics.[64]

The special fluid properties of blood are taken into account in various approaches made by international teams to model the multiphase nature of blood.[65–70]

PIV as method for the quantitative measurement and qualitative visualization of flow, as well as to validate numerical

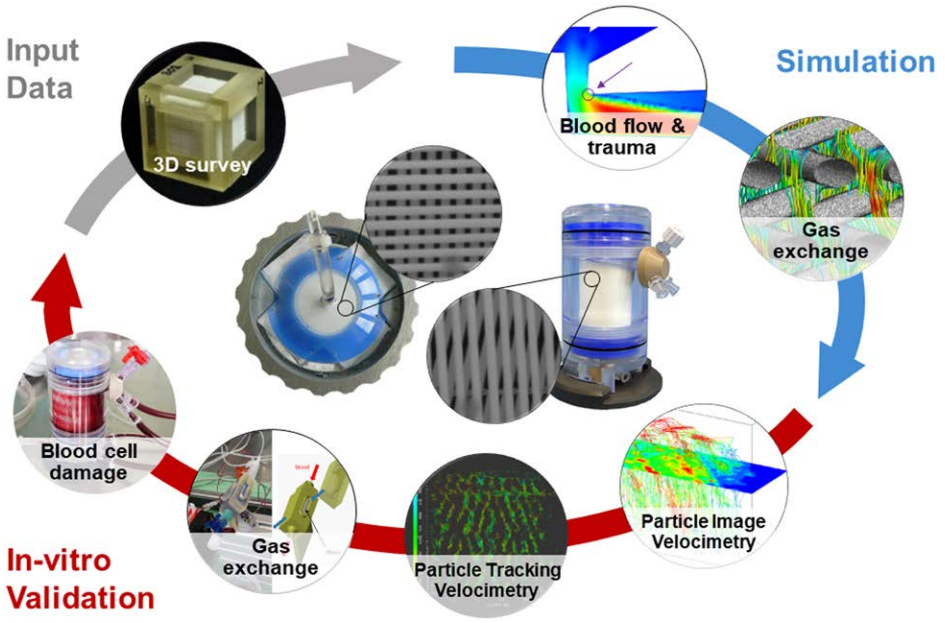

Figure 3. *In silico* and *in vitro* analysis of blood flow and gas exchange.

simulations was developed and established for scaled-up models of oxygenators.[71,72] In addition, PIV-capable erythrocytes freed from hemoglobin (so-called "ghost cells") are currently under development that can be used for realistic flow visualization and for the temporal and spatial resolution of hemolysis.[73]

MRI, on the contrary, is not limited to transparent media or models and can directly follow the flow of blood in the oxygenator, although the temporal and spatial resolution of MRI is lower than that of PIV. MRI makes it possible to look into the blood-filled aggregate[74] without influencing the functioning of the oxygenator. In addition, by using special MRI methods, it is possible to visualize thrombosis in the system where a blocked perfusion compartment is immediately reflected in the image.[17,18] Therefore, MRI is one of the most important methods for the analysis of coagulation in the oxygenator. Furthermore, MRI can be used to measure velocity or even acceleration field by using additional gradient pulses.[75] However, for an analysis by MRI, the oxygenator must be introduced into an external magnetic field and therefore be nonmagnetic.

All approaches for the analysis of blood flow described here provide basic knowledge to be used for the hemodynamically optimized design of oxygenator geometry and fiber modules to develop more efficient and hemocompatible artificial lungs with regard to long-term gas exchange.

Development of Verification and Validation Methods for Lung Assist Systems

The use of suitable and graduated *in vitro* and *in vivo* (animal) models before clinical evaluation are required for the translation of lung assist systems into the clinic. Above all, there is a need for standardized long-term test methods because current test standards such as ISO 7199:2016 cover only short-term testing.[42,76] The development of a long-term test method, which closely resembles physiology and simulates physiologic and pathologic flows and pressures and enables the online measurement of O_2/CO_2, is urgently needed.

Under specific substitution conditions, the test period in a test circuit could be extended to 12 hours without exchanging the blood in the circuit. Not only the gas transfer rates over 12 hours but also coagulation activation, as well as some hemocompatibility parameters could be analyzed.[77] However, mainly because of blood deterioration it has not yet been possible to simulate long-term functionality *in vitro* for a relevant time frame as compared with therapy durations. In addition, to date, these tests are carried out with blood from healthy animals without the respective disease. Whether coagulation activation or inflammation initiated before the start of the test influences the performance of the devices under test remains unknown. Therefore, animal models must be used for this purpose, although these animal models are not standardized. Accordingly, the results of different research groups can rarely be evaluated in a comparative way. This situation is aggravated by the fact that there are no suitable large animal models of chronic lung failure, which occurs as a late consequence of chronic obstructive pulmonary disease. The first animal model of chronic lung failure was used at the University of Michigan, Ann Arbor; an implantable pediatric artificial lung was tested in sheep for up to 4 days.[78] However, acute and chronic lung diseases manifest themselves in so many different variations that the transferability of animal studies to humans remains doubtful.

In addition to animal models, human upper and lower respiratory models are also available as *in vitro* systems to test and optimize new materials[79] with medical device approval. Simulations of the flow properties of different fluids or gases and their interactions with cellular components[80] of the planned implantation site are used for production and optimization.[66] Furthermore, the foreign body reaction in humans can be investigated through *in vitro* test systems in long-term experiments.[81]

Influence of Long-Term Lung Support on Pathophysiology

Increased CO_2 levels are known to have a variety of effects on the human body, including changes in vascular regulation, especially cerebral and pulmonary perfusion, renal function, and cardiac and immunological functions.[82–84] Kielstein *et al*. assumed that the mitigation of respiratory acidosis caused by ECMO may improve renal function. However, in a retrospective, single center study, patients who required ECMO therapy but no renal replacement showed no reduction in elevated serum creatinine after 1 day of treatment as compared with the day of ECMO implantation.[85] Roy *et al*.[86] evaluated the effect of veno-venous ECMO on renal function and fluid balance in neonates with severe respiratory failure in a retrospective, single-center, comparative study and concluded from 30 patients (12 without, 18 with ECMO) that veno-venous ECMO is associated with transient impairment in renal function and marked fluid retention. In addition, the long-term interaction of the ECMO system with the underlying disease has not been systematically studied, yet.

Summary

The loss of organ function can be permanently compensated only by an artificial organ or a transplant. Because of the low availability of transplantable organs, however, lung transplantation is limited to a small percentage of patients. Although artificial organ replacement of the kidney or heart has been a real therapeutic option for several years, lung function can be replaced by an artificial lung for only a very limited period of time. However, for patients with chronic lung diseases in the final stages, an artificial lung could bring survival, a better quality of life outside the hospital, and reintegration into the social community.

Despite the technological developments, biocompatibility problems and suboptimal flow conditions in the oxygenator cause the formation of blood clots in the oxygenator, pump, or cannulas, and protein/fibrin is deposited on the gas exchange membranes, which increases the diffusion distance and thus impairs the gas exchange capacity of the oxygenator. In addition, the red blood cells are damaged (hemolysis).[87–89]

Therefore, extracorporeal lung support is currently used worldwide for only the short-term bridging of insufficient gas exchange, such as that in acute lung failure, in which the lung usually recovers sufficiently within days to a few weeks or as a short-term bridging strategy until transplantation. Although partial successes have been achieved in the past in both the field of biocompatibility optimization[90–93] and clinical application[94–96] by individual groups, the goal of a wearable or even an implantable lung support system is not yet within reach, and the road to this goal is still long.

Overcoming the limitations described above requires a fundamental and interdisciplinary approach to open research questions at the interfaces between the life sciences, natural sciences, engineering, and materials sciences, combining existing core competencies and enabling successful translation and implementation of a long-term therapeutic option.

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