

Lung, Artificial: Current Research and Future Directions

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INTRODUCTION

Artificial lungs are medical devices designed to take over or supplement the respiratory function of the lung: oxygenating the blood and removing carbon dioxide. They are generally classified as extracorporeal, paracorporeal, intravascular, or intrathoracic devices (Fig. 1). The artificial lungs used clinically today are extracorporeal blood oxygenators, primarily used in operations requiring cardiopulmonary bypass, but also used less frequently for support of patients with respiratory failure. The growing incidence of lung disease associated with the aging population has spurred recent work toward next-generation artificial lungs that may be used to successfully treat patients with a variety of respiratory failures. Next-generation artificial lungs include 1) paracorporeal approaches (wearable devices that will be attached directly to patients); 2) intravascular approaches (respiratory catheters placed within the vena cava through a peripheral vein); and 3) intrathoracic approaches (devices that will be placed internally within the thoracic or abdominal cavities). Intravascular artificial lungs are aimed primarily at treatment of acute respiratory failures, whereas paracorporeal and intrathoracic artificial lungs are aimed primarily at bridge-to-transplant respiratory support because of the more invasive procedures required to implement them. This article reviews the current state of research on next-generation artificial lungs for support of patients with failing lungs. The basic operational principles of artificial lungs and the current clinical applications of standard blood oxygenators are reviewed in a companion article (*Lung, Artificial: Basic Principles and Current Applications*).

ARTERIOVENOUS CARBON DIOXIDE REMOVAL

Arteriovenous carbon dioxide removal (AVCO₂R) is more the development of a new respiratory support technique than a next-generation artificial lung device. AVCO₂R represents a simpler means of extracorporeal respiratory support and involves a blood oxygenator (either a standard blood oxygenator or one developed specifically for the

application) connected directly from the arterial to venous circulations in a paracorporeal approach, thus obviating the need for a blood pump and associated tubing in the extracorporeal circuit. The goal of AVCO₂R is to provide lung rest to patients suffering from acute respiratory distress syndrome (ARDS) or other acute lung failures^[1] by reducing the tidal volume, minute ventilation, and pressures associated with mechanical ventilation.^[2,3] The specific technique used in AVCO₂R consists of diverting blood flow through a femoral arterial cannula to a commercial blood oxygenator (as the artificial lung) and back to the patient through a femoral venous cannula (Fig. 2). The AVCO₂R circuit principally removes CO₂ before returning the blood back to the patient, but some oxygenation of the blood occurs as well. The flowrate is much lower than in typical extracorporeal membrane oxygenation (ECMO) circuits and is dictated by the arterial-to-venous pressure difference of the patient and the hydraulic resistance of the artificial lung. Although AVCO₂R eliminates the need for a mechanical blood pump, it ideally requires an oxygenator/artificial lung with a sufficiently low hydraulic resistance to ensure adequate blood flow from the arteriovenous pressure difference to remove a sufficient amount of CO₂.

Recent animal studies using healthy adult sheep have characterized the flowrate and gas exchange capabilities of an AVCO₂R system.^[4] The artificial lung used in the AVCO₂R application was a 2.5 m² AffinityTM blood oxygenator connected to the left carotid artery via an 18-French (Fr) cannula and the left jugular vein via a 22-Fr cannula. Blood flowrates through the AVCO₂R circuit were 25–29% of cardiac output during the 6-hour study, with a pressure drop across the oxygenator of less than 10 mm Hg. Maximum CO₂ removal was approximately 100 ml/min, or 96% of total CO₂ production by the animal. Importantly, the study showed a decrease in minute ventilation from approximately 10 l/min before AVCO₂R to 0.5 l/min, and peak inspiratory pressure also decreased from 41 cmH₂O to 20 cmH₂O in subsequent hours after initiation of the therapy. The effect of AVCO₂R blood flow on organ perfusion was investigated using colored microspheres in a conscious ovine model with the carotid-to-jugular arteriovenous circuit using the AffinityTM 2.5 m² oxygenator.^[5] AVCO₂R

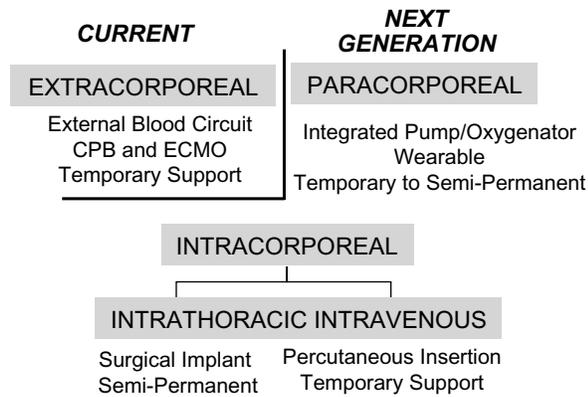


Fig. 1 Classification of artificial lung technology.

flow varied from 5–25% of baseline cardiac output and organ flow was measured using microsphere techniques. A 10–20% decrease in organ perfusion accompanied a 5% shunt, but organ perfusion did not decrease further with increased shunt flow through the AVCO₂R device. Hemodynamic parameters such as heart rate, mean arterial, and pulmonary arterial pressures remained unchanged throughout the study, indicating that blood shunting through the AVCO₂R system was well-tolerated by the animals.^[5]

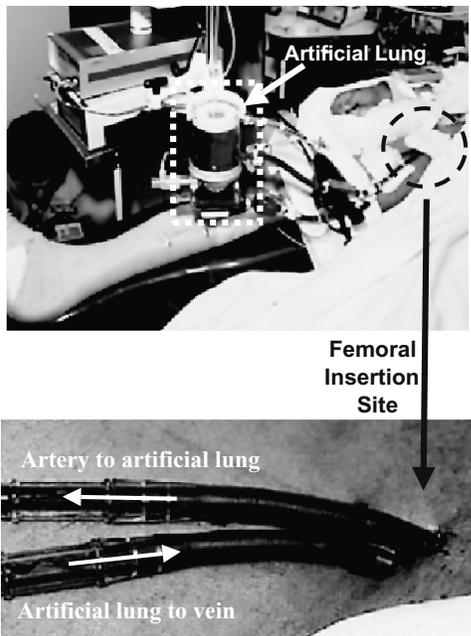


Fig. 2 This simple circuit consists of the inlet cannula, the artificial lung, and the return cannula to the patient. The insertion site in this case is the femoral artery and vein in the patient’s right leg. (Courtesy of Joseph B. Zwischenberger, University of Texas Medical Branch, Galveston, TX.)

A 7-day study of AVCO₂R in sheep using a smoke-inhalation injury model of severe respiratory failure showed gas exchange capabilities similar to those in previous AVCO₂R studies using the same Affinity™ blood oxygenator with no statistically significant changes in heart rate, cardiac output, mean arterial pressure, or pulmonary artery pressure.^[6] Increased survival among sheep managed with AVCO₂R versus ventilator-managed sheep has also been shown for this ARDS model.^[7] In the latter study, 18 sheep received an LD₅₀ severe smoke inhalation and a 40% third-degree burn on their external flanks. Animals were randomized to either a ventilator-managed sham group (*n* = 9) or an AVCO₂R therapy group (*n* = 9) and treated for 7 days. AVCO₂R allowed significant ventilator reductions in tidal volume, peak inspiratory pressure, minute ventilation, respiratory rate, and FIO₂ (Fig. 3). All AVCO₂R-managed animals survived the study, whereas only three of the ventilator-managed sheep survived the duration of the study.

Respiratory support with AVCO₂R has recently expanded into human clinical trials. In a pilot study of feasibility and safety, percutaneous AVCO₂R was studied in five patients suffering from severe ARDS and CO₂ retention who were unresponsive to standard mechanical ventilation protocols.^[8] AVCO₂R was initiated for 72 hours using the 2.5 m² Affinity™ blood oxygenator with 12- to 15-Fr venous and 10- to 12-Fr arterial cannulae inserted percutaneously into the femoral vein and artery, respectively. Average blood flowrates through the artificial lung ranged from approximately 600–1100 ml/min with maximum CO₂ removal rate of 208 ml/min. The

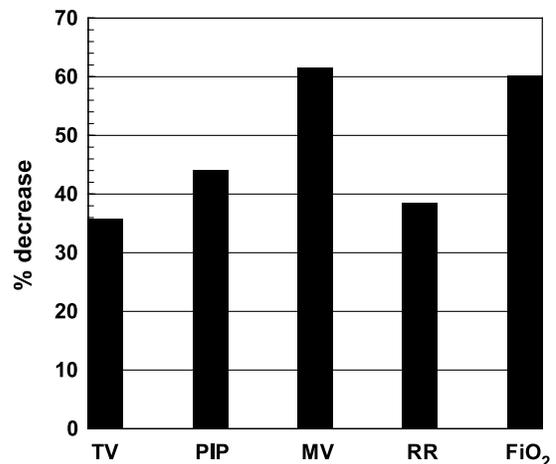


Fig. 3 Decreased ventilator parameters after instituting AVCO₂R in sheep with burn and smoke-inhalation-induced ARDS. This study lasted 7 days. TV: tidal volume; PIP: peak inspiratory pressure; MV: minute ventilation; RR: respiratory rate; FIO₂: fraction of inspired O₂.

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minute ventilation was significantly decreased from 7.2 ± 2.3 l/min before initiation of AVCO₂R to 3.4 ± 0.8 l/min after 24 hours of AVCO₂R therapy. A follow-up phase I clinical study lasting 72 hours in eight patients with acute respiratory failure and hypercapnia was also conducted.^[9] Blood gas measurements, ventilator parameters, and hemodynamics were measured before and after initiation of AVCO₂R. The arterial CO₂ concentration decreased from 90.8 ± 7.5 mm Hg to 51.8 ± 3.1 mm Hg, and minute ventilation was reduced from 6.92 ± 1.65 l/min to 3.00 ± 0.53 l/min after 2 hours of AVCO₂R. Hemodynamic changes were not significant, nor were any major complications associated with AVCO₂R reported during the study. Zwischenberger and colleagues from the University of Texas Medical Branch continue work in this area, focused on developing AVCO₂R into a standard therapy for respiratory support during severe respiratory failure.

INTRAVASCULAR RESPIRATORY CATHETERS

Intravascular artificial lungs have been studied and are being developed as a less expensive, less personnel-intensive alternative to respiratory support with extracorporeal artificial lungs. Anatomical and physiological constraints of device placement in major blood vessels of the human body impose significant challenges in developing intravascular artificial lungs. Most of the

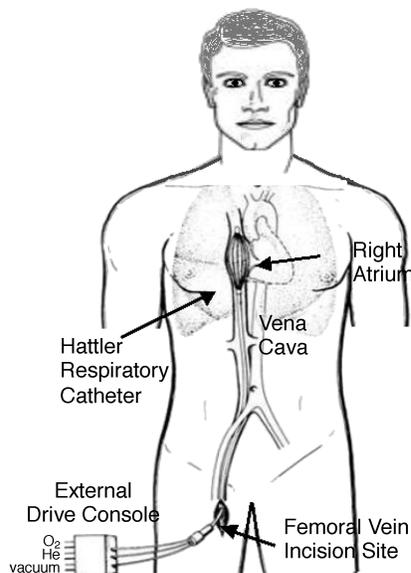


Fig. 4 Schematic of intravascular artificial lung or respiratory support catheter placed within the human vena cava.

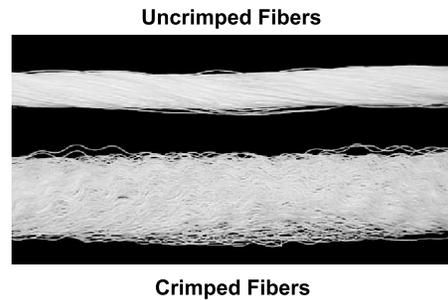


Fig. 5 Crimped fibers were used in the IVOX device to minimize fiber clumping and disrupt blood flow. (View this art in color at www.dekker.com.)

intravascular devices that have been developed are intended for insertion through a peripheral vein (femoral or jugular) and placement in the vena cava, the largest blood vessel in the body through which blood returns to the heart (Fig. 4). The adult human inferior vena cava ranges on average from 2.2 cm to 3.3 cm in diameter and the superior vena cava ranges from 1.5 cm to 2.2 cm.^[10] Intravascular artificial lungs must be compact for insertion, yet possess sufficient membrane area to achieve adequate respiratory support. The primary objective of intravascular artificial lungs is to supplement the gas exchange of a failing lung, but not completely replace it. Respiratory support at 40–60% of the body's resting metabolic needs has generally been considered an appropriate target for intravascular artificial lungs.^[11]

Four principal development efforts have tackled the challenge of intravascular artificial lungs since the 1980s. Mortensen and colleagues at CardioPulmonics, Inc. (Salt Lake City, UT) developed the IVOX, the only intravascular artificial lung that has undergone human clinical trials.^[12–14] The IVOX consisted of a bundle of crimped hollow fiber membranes joined at the distal end to the inner lumen of a dual-lumen gas conduit, and at the proximal end to the outer lumen of the gas conduit, which led outside the body to a console for providing sweep gas flow through the fibers. The crimped fibers (Fig. 5) of the IVOX helped minimize fiber clumping in the vena cava and also helped disturb blood flow and diffusional boundary layers on fiber surfaces to improve overall gas exchange permeance.^[15,16] A total of 160 patients with severe acute respiratory distress were studied in applications that lasted up to 28 days of support.^[12] The clinically tested IVOX ranged from 0.21 m² to 0.51 m² in membrane area, and the average rates of O₂ and CO₂ transfer accomplished in the trials ranged from 40 to 70 ml/min, or about 20–30% of baseline metabolic needs. The IVOX demonstrated that intravascular artificial lungs can be implanted within the vena cava and perform for



extended periods without significant complications in situ (for example, from blood thrombosis). About 30% of the patients showed improvement in blood gases that allowed reduction in mechanical ventilation, but overall the level of respiratory support provided was considered marginal.^[12] The choice of a clinical trial without a random prospective control arm hampered efforts at gaining Food and Drug Administration (FDA) approval, and CardioPulmonics eventually discontinued its attempt at FDA approval and halted further device development.

Several innovative intravascular artificial lung prototypes were developed at Northwestern University as the ILAD, for intravascular lung assist device.^[17–19] To enhance gas exchange, an active or dynamic D-ILAD device was developed, consisting of sheets of short microporous fibers stacked, folded, and twisted around a central shaft to create a helical or screw-like arrangement of fiber surfaces.^[20] Rotation of the entire D-ILAD device increased blood convection across the fiber surfaces, thus improving gas transfer performance while also providing some pumping motion to blood flow. In pilot experiments, oscillatory motion of the D-ILAD bundle showed increased gas exchange compared to steady rotational motion. Prototype D-ILAD devices with membrane areas from 0.1 to 0.5 m² accomplished O₂ and CO₂ transfer rates of 208 ml/min/m² and 310 ml/min/m², respectively, in bench tests involving bovine blood flow through a mock vena cava at 2 l/min.^[21] The D-ILAD only achieved adequate gas exchange with significant fiber rotation, which may be difficult to implement in the vena cava; the efforts of the Northwestern group have shifted to developing a total artificial lung device.^[22,23]

An intravascular artificial lung designed to be placed through the right ventricle into the pulmonary artery (PA) was developed at Penn State University as the PENSIL, for Penn State Intravascular Lung.^[24,25] Placement within the PA allows the entire cardiac output to flow past the fiber surfaces to help maximize gas exchange. The PENSIL consisted of a central core catheter with spaced manifold sleeves around it from which blind-ended hollow fibers emanated. The central catheter served as the spine of the PENSIL, and the fibers emanating from the manifold resembled long bristles of a bottle brush. The use of blind-ended fibers meant that sweep gas must diffuse into fibers rather than being convected through them, as in most artificial lungs. Oscillation of the pressure in the central catheter was studied as a method to provide some oscillatory convection of sweep gas in and out of the blind-ended fibers.^[26] PENSIL devices were fabricated with membrane areas ranging from 0.04 to 0.38 m² and, compared to the IVOX, achieved reasonable O₂ exchange efficiencies at 140 ml/min/m². CO₂ exchange (corrected to a blood PCO₂ driving force of 50 mm Hg) was low, however, at only 25 ml/min/m².

Catheter vibration was recently considered as a means of improving gas exchange in the PENSIL,^[14] but other than this effort, the development of the PENSIL appears dormant.

The only currently active development program on intravascular artificial lungs is the effort at the McGowan Institute for Regenerative Medicine at the University of Pittsburgh. This intravascular artificial lung or respiratory support catheter (also known as the Hattler Catheter, and formally referred to as the intravenous membrane oxygenator (IMO)) uses a centrally positioned pulsating balloon within a fiber bundle made from fiber fabric wrapped around the central balloon (Fig. 6). Balloon pulsation pumps blood around the hollow fiber surfaces at greater blood flow velocities than would otherwise flow in the vena cava, and as a result enhances gas exchange by decreasing diffusional boundary layers. Development efforts over the past seven years have led to improvements in balloon pulsation (faster possible pulsation rates) and balloon-bundle design to further increase the gas exchange of the respiratory catheter. The design of the respiratory catheter has evolved substantially from earlier prototypes^[27–31] and has been tested extensively in animals, including ex-vivo tests^[29] used to make comparisons with the IVOX, acute animal implants,^[32] and some limited chronic implant tests.^[33] Initially intended for surgical insertion in the femoral vein through a cut-down procedure, the respiratory catheter is now undergoing further development to reduce catheter insertion size and allow for percutaneous insertion.

The pulsating balloon has been a key component of our respiratory support catheter that allows for greater gas exchange than a passive device like the IVOX. Recent ex-vivo tests^[29] were conducted by placing the catheter in a mock vena cava vessel (1-inch tube) connected in an extracorporeal circuit to a calf, a test and setup analogous to those used to study the clinically tested IVOX.^[11] Figure 7

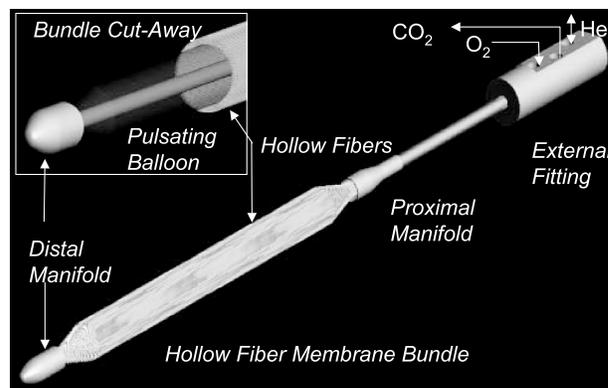


Fig. 6 Respiratory support catheter. (View this art in color at www.dekker.com.)



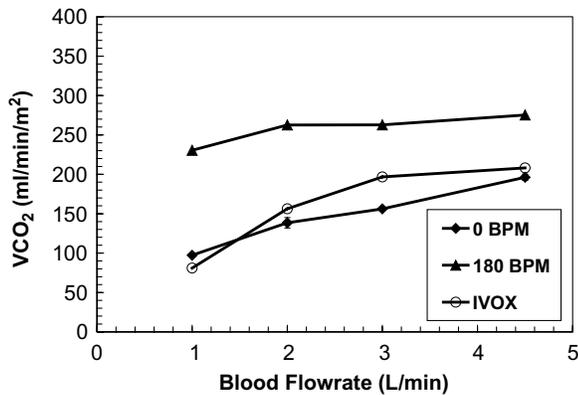


Fig. 7 Ex-vivo results for pulsating respiratory catheter (at 0 and 180 beats per minute) versus IVOX as function of blood flowrate.

shows the CO_2 removal rate achieved with the respiratory (Hattler) catheter (HC) tested ex vivo in comparison to the IVOX over a range of relevant blood flowrates through the mock vena cava. Balloon pulsation increased gas exchange 200–300% at the lowest blood flowrate, compared to 50–100% enhancement at the highest blood flowrate. In this manner balloon pulsation eliminated much of the dependence of the gas exchange rate on blood flowrate as seen in passive oxygenators, suggesting that the respiratory catheter may exhibit less gas exchange variability related to cardiac output variability in patients. In the ex-vivo studies, the CO_2 and O_2 gas exchange rates of the catheter at maximal balloon pulsation varied from approximately 250 to 300 ml/min/m² and, depending on the blood flowrate, were from 50–500% greater than IVOX gas exchange in these tests.^[34] In a series of acute implants of the respiratory catheter in calves,^[7] the CO_2 transfer rate was 320 ml/min/m², comparable to that achieved in the ex-vivo tests.

TOTAL ARTIFICIAL LUNGS

Several research groups are developing total artificial lung (TAL) devices for treating chronic respiratory failure, primarily as bridge-to-lung transplant devices. Whereas implantable total artificial lungs that can be placed in the thoracic or abdominal cavities may be an ultimate goal, the initial implementation and testing of total artificial lungs appears to favor paracorporeal applications, with the TAL external to but immediately attached to the patient. The attachment mode of the TAL is an important design consideration, and in-series, in-parallel, and hybrid configurations have been studied.^[35] The in-series configuration connects the artificial lung to the proximal

pulmonary artery, diverting all the cardiac output through the device and returning it to the distal pulmonary artery immediately upstream of the natural lungs. Although this mode enables the natural lung to be an effective embolic filter, the mechanical load on the right heart increases because it must provide the pumping energy for blood flow through both the natural and the artificial lung. An estimated 0.11 W/(l/min) is required by the right ventricle with the TAL in-series configuration.^[36] The in-parallel configuration attaches the artificial lung between the pulmonary artery and the left atrium so that only a fraction of the blood flow diverts through the artificial lung. The fraction of blood flow through the artificial lung depends on its impedance relative to that of the natural lung. The in-parallel configuration has the clear advantage that the right heart workload is reduced, but only a fraction of total cardiac output receives respiratory support from the artificial lung and that fraction is not exposed to the metabolic and filtering functions of the natural lung. The power requirement of the in-parallel configuration (assuming $\frac{2}{3}$ of total flow through the TAL and $\frac{1}{3}$ through the natural lung) is roughly half that for the in-series configuration.^[36] The hybrid configuration attaches the inlet of the artificial lung to the proximal pulmonary artery, and uses a split return to the distal pulmonary artery (and natural lung) and to the left atrium. The hybrid configuration allows all the cardiac output to flow through the artificial lung with less resistance than the in-series configuration, and also allows greater flow through the natural lung than the in-parallel configuration. The power requirement of the right heart for this configuration depends on the amount of blood flow through the artificial lung relative to the natural lung, and has been estimated at between approximately 0.08 W/(l/min) and 0.10 W/(l/min).^[36] Patients with a weak or failing right ventricle would require either the in-parallel or hybrid configurations because of the reduced power required for adequate perfusion of the artificial lung and natural lung.

The implantable Intrathoracic Artificial Lung (ITAL) under development at Northwestern University focuses on resting the lung in acute respiratory failure and as a bridge-to-lung transplantation in chronic lung failure.^[37] Mathematical models were developed to estimate the required surface area for 200 ml/min of oxygen transfer at a blood flowrate of 5 l/min with a pressure drop of less than 15 mm Hg.^[38] Based on these analyses a prototype implantable artificial lung with the design specifications shown in Table 1 was fabricated and tested.^[39] In-vitro gas exchange rates in bovine blood were 150–200 ml/min of O_2 and over 200 ml/min of CO_2 at 4 l/min blood flow. The device was implanted in two Yorkshire pigs for less than 6 hours, and gas exchange rates were approximately 99 ml/min of O_2 and 86–144 ml/min of CO_2 . The pressure drop across the device was approximately 10 mm Hg. The



Table 1 Specifications of a first ITAL prototype

Specification	Design target
O ₂ transfer rate	>200 ml/min
Blood-side pressure drop	<15 mm Hg
Blood flowrate	3–5 l/min
Fiber outer diameter	0.038 cm
Surface area	2.2 m ²
Priming volume	240 ml

ITAL was later modified to reduce the resistance to flow of the device. These changes included increasing the device porosity—or void fraction—from 0.53 to 0.74, reducing the surface area from 2.2 m² to 1.83 m², increasing the inlet and outlet grafts to the device from 1/4" to nearly 3/4", and adding an inlet compliance chamber made of thin-walled latex tubing 1 inch in inner diameter.^[37] The device, tested on three Yorkshire pigs, had average gas exchange ranging from 156–204 ml/min of O₂ and 187–242 ml/min of CO₂. The power requirements of the right ventricle were determined to be approximately 0.06 W/(l/min) for full blood flow through the ITAL. The effects of the device housing and inlet graft compliance on the right heart power requirements have also been studied using a computational model.^[36]

The BioLungTM total artificial lung under development at MC3, Inc. (Ann Arbor, MI) and the University of Michigan is intended for complete respiratory support as a bridge to transplant for 1–6 months (Fig. 8). Initial BioLung prototypes were evaluated paracorporeally and connected in series with the natural lung.^[22] Five of 7 sheep survived with 75–100% of cardiac output diverted through the device during a 24-hour study with oxygen transfer rates of approximately 150–240 ml/min. Two of the animals did not tolerate complete occlusion of the pulmonary artery; therefore total cardiac output was not diverted through the artificial lung in these animals. A 168-hour study found 50% of the sheep died of right heart failure when the device was placed in series with the natural lung due to increased flow impedance caused by the device.^[23] Several changes to the TAL were made to reduce its flow resistance (or impedance), including addition of an inflow cannula compliance chamber, and inlet blood flow separator and modification of the outlet geometry. A 72-hour healthy sheep survival model using the modified device showed 6 of the 7 sheep exhibited good cardiac function with gas exchange averages of 220 ml/min of O₂ and 166 ml/min of CO₂.^[40] The most recent study has compared volume-controlled mechanical ventilation to the modified BioLung TAL in a 5-day smoke inhalation/burn ARDS sheep study. Six of 8 animals survived when treated with the artificial lung, and only 1

of 6 animals survived when treated with mechanical ventilation.^[41] Average gas transfer rates for the artificial lung were 218.6 ± 17.7 ml/min O₂ and 183.0 ± 27.8 ml/min CO₂. Latest developments on the BioLung device have focused on using computational fluid dynamics (CFD) to optimize the device.^[42] A flow separator has been placed in the inner core of the fiber bundle and the axial length of the fiber bundle has been shortened, reducing the surface area from 2.1 m² to 1.6 m². A second outlet has also been added, which decreased the pressure drop across the device 10–40%. The newer design exhibited higher O₂ transfer efficiency (almost 300 ml/min/m² versus less than 250 ml/min/m² in the old design) in a 6-hour study of 6 adult male sheep at a flowrate of 6 l/min.^[42]

A paracorporeal total artificial lung for chronic respiratory support (Chronic Artificial Lung, or CAL) is under development at the University of Maryland as a continuation of earlier work at the University of Pittsburgh. The CAL is intended as a bridge-to-transplant device with the goal of 21-day support of basal metabolic needs using a device less than 0.5 m² in fiber membrane area.^[43] The CAL uses active mixing from a rapidly rotating disc made of microporous hollow fiber membranes that enhance gas exchange by increasing blood flow velocity past fiber surfaces and reducing diffusional boundary layers. The disc rotates within a housing and the centrifugal motion imparted to blood enables the CAL to pump blood (which may reduce the impact of the CAL on the right heart in its intended in-series attachment mode). The motor controller directing disc rotation can generate pulsatile or nonpulsatile flow. The CAL generated 5 l/min flow against a 100 mm Hg pressure head at 1600 rpm during steady flow in bench tests using bovine blood, but adding pulsatility to the flow decreased pumping. Published data are lacking but



Fig. 8 BioLungTM artificial lung prototype from MC3, Inc. The center port is the blood inlet, and the two side ports are blood exit ports. (Courtesy of MC3, Ann Arbor, MI.)



the gas exchange efficiency of the CAL appears promising, with 550 ml/min/m² and 450 ml/min/m² reported for O₂ and CO₂ exchange efficiencies, respectively, in scaled-down prototypes.^[43]

OTHER EFFORTS IN ARTIFICIAL LUNGS

Several other artificial lung technologies are in various stages of development. The Integrated Heart–Lung Assist Device (IHLAD) combines the functions of a blood pump and artificial lung into one device with the goal of functioning as emergency percutaneous cardiopulmonary support.^[44] The IHLAD incorporates a central six-vane impeller driven by a magnetic coupling to an outer motor. The impeller is surrounded by gas-exchanging hollow fiber membranes. The blood-contacting surfaces are treated with covalently-bonded heparin to reduce thrombogenicity and allow preprimed storage for emergency use. This IHLAD has a surface area of 0.85 m² and was evaluated in an in-vivo goat study with the device attached paracorporeally in a venoarterial bypass. Transfer rates of 180 ml/min O₂ and 110 ml/min CO₂ were achieved at 5 l/min of blood flow with sweep gas flows of three to five times the blood flowrate. The impeller enables pumping performance of 9 l/min output at 400 mm Hg pressure head at 3000 rpm. After 3 months of preprimed storage, the device was tested for gas exchange rates in an ex-vivo goat experiment. Whereas O₂ transfer rates were unaffected by storage, the CO₂ removal decreased approximately 30% after 3 months.

One artificial lung concept involves rotating an annular fiber bundle to promote active mixing and increased gas exchange, in addition to generating a pumping force.^[45]

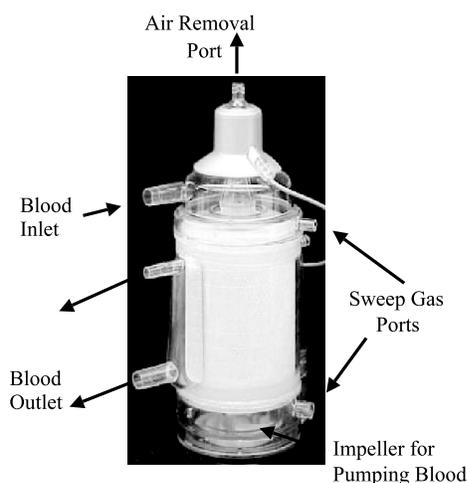


Fig. 9 The CORx[™] integrated pump-oxygenator from cardiovention, Inc. (View this art in color at www.dekker.com.)

The annular fiber bundle is potted around a stationary central flow diffuser for distributing blood flow throughout the length of the rotating bundle. This is similar in concept to the CAL, in that the rotation of the fibers increases the relative velocity of blood flow past fiber surfaces to increase the efficiency of gas transfer, so less fiber membrane area is required for gas exchange, helping to reduce priming volume and adverse blood–material interactions. A prototype with a priming volume of 1250–2500 ml and 0.2 m² of membrane area exhibited a transfer rate of approximately 60 ml/min of O₂ at a rotational speed of 600 rpm.

The CORx[™] System developed by Cardiovention in California consists of a hollow fiber membrane bundle similar to those used in typical commercial artificial lungs attached directly to an impeller pump (Fig. 9).^[46] The pump generates enough pressure to perfuse the artificial lung and return oxygenated and decarbonated blood back to the patient, thus achieving the primary gas exchange requirements and blood flowrates of standard cardiopulmonary bypass (CPB). The device also includes a special technology for removing air that inadvertently enters the circuit during the surgical procedure. This compact unit has a total blood-contacting surface area of less than 1.4 m², which reduces the blood surface contact area and minimizes hemodilution of the patient. The device has recently been approved by the FDA and is currently used for cardiac procedures at hospitals across the United States.^[46]

A novel photolytic artificial lung is under development that uses photosynthesis to convert CO₂ to O₂, obviating the need for O₂ to supply gas (as in membrane artificial lungs).^[47] The device consists of a blood pump, photolytic module of stacked cells, and a light source. The photolytic cells are created with vacuum-deposited titanium metal, a coating of photolytically sensitive TiO₂, and a layer of MnO₂ adhered to the surface of a glass substrate. In the photolytic modules, bicarbonate is protonated to form carbonic acid, which is converted to water and CO₂ in the presence of the carbonic anhydrase. The resultant water is converted to active oxygen at the TiO₂ catalyst when exposed to light, and the active oxygen is converted to dissolved oxygen at the MnO₂ catalyst.^[47] Many such photolytic units will be integrated into a functional device to achieve relevant rates of O₂ production and CO₂ removal.

CONCLUSION

The next-generation artificial lungs described here derive directly in a conceptual sense from the hollow fiber membrane and membrane module technology used in standard clinical blood oxygenators. Many of these



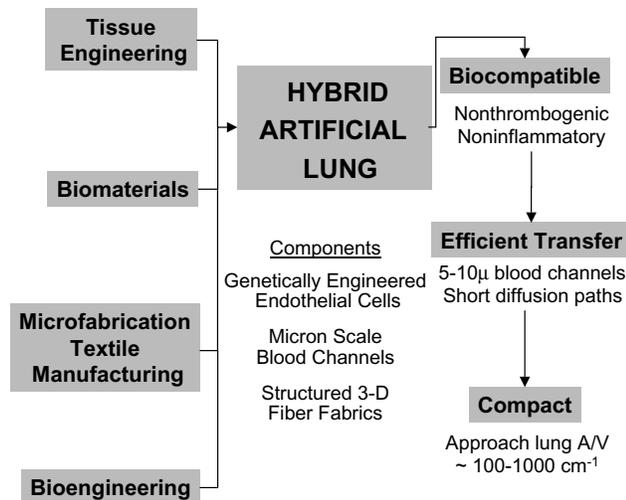


Fig. 10 The future of artificial lungs. (View this art in color at www.dekker.com.)

artificial lung devices will hopefully achieve some clinical success in the next five to ten years. On a more distant horizon, the future of artificial lungs may depart significantly from the use of purely synthetic devices based on existing hollow fiber membranes fabricated into modules resembling those used today. The natural lung is a remarkable gas exchange organ because of the microvascular scale of blood pathways combined with the intimate micron-scale juxtaposition of its blood and gas pathways (see the article titled “Lung, Artificial: Basic Principles and Current Applications” in this encyclopedia). Future artificial lung technologies are likely to be biohybrid artificial lungs, combining both synthetic and natural tissue components, into gas exchange units aimed at mimicking the scale and function of the alveolar-capillary units of the natural lung. Biohybrid artificial lungs of the future (Fig. 10) may involve micron-scale blood channels intimately contacting gas channels to provide not only for short diffusion paths and efficient gas exchange but to also create compact devices with surface area to blood volume ratios approaching those of the natural lung. The challenge of biocompatibility inherent in making these microvascular-scale blood channels, with an extensive blood contact area, nontrombogenic and noninflammatory may require the use of endothelial cells, perhaps genetically engineered for enhanced performance or for the robustness required in this application. Significant advances in tissue engineering, biomaterials, microfabrication, and bioengineering will all need to be harnessed for the technological development of these future artificial lungs. At the same time, the need for artificial lungs in the distant future may be eclipsed by

significant advances in regenerative medicine that enable tissue repair and regeneration of the failing lung.

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ARTICLES OF FURTHER INTEREST

Lung, Artificial: Basic Principles and Current Applications, p. 910
Lung Surfactants, p. 932

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