Perfusion 2003; **18:** 171–177

New technologies for respiratory assist

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'The artificial lung especially has lingered behind progress with artificial hearts and ventricular assist devices, not because the need for lungs has not been recognized, but because we have not had a full understanding of the engineering problems and the unique material requirements until recent years.'[1]
Brack Hattler, MD PhD

The development from the first clinical use of haemodialysis over five decades ago to widespread chronic treatment took more than two decades. The histories of other artificial organ technologies, such as artificial hearts, follow similar long development paths. For five decades, due to a lack of technology, artificial lungs have been limited to use with a heart-lung machine for cardiopulmonary bypass (CPB) or extracorporeal membrane oxygenation (ECMO). The advent of pumpless biocompatible artificial lungs will open new treatment options for patients with acute or chronic lung failure. *Perfusion* (2003) **18,** 171–177.

Lung disease is the third leading cause of death in developed countries. Chronic obstructive pulmonary disease (COPD) alone costs the USA economy an estimated $31.9 billion a year[2] and, in 1998, caused more than 112 000 deaths. The disease affects tens of millions of Americans. One estimate is that 16 million patients have been diagnosed with some form of COPD and another 16 million more are undiagnosed.[3] Other diseases leading to chronic lung failure include pulmonary fibrosis and cystic fibrosis. Improvements in the treatment of cystic fibrosis have allowed most of these patients to reach adulthood, but despite other cystic fibrosis related problems, 90% of these young adults ultimately die from lung failure.[4]

Over the past decades, critical care medicine has made tremendous contributions to improve outcomes in patients suffering from acute lung failure. Positive pressure ventilation to keep lung failure patients alive during lung failure has steadily improved, but, due to ventilator-induced injury, can be a double-edged sword. The search for options to bridge acute lung failure patients to recovery or, if recovery is not possible, to temporarily or permanently replace the lung with an artificial or bioartificial lung, has been frustrating.

The high mortality associated with acute respiratory failure and further exacerbation of the lung injury by mechanical ventilation continue to pose a challenge in the management of critically ill patients. The current methods for supporting patients with lung disease are not adequate or efficient enough to act as a bridge to recovery or transplant or to permanently support gas exchange. Although occasionally successful as a bridge to recovery or transplant, ECMO requires multiple transfusions and is complex, labour intensive, time limited, costly, nonambulatory and prone to infection. The first intravascular oxygenator and carbon dioxide (CO_2) removal device (IVOX), conceived by Mortensen, was capable of removing 30% of CO_2 production of an adult at normocapnia with a measurable reduction in ventilator requirements. The first generation intravena caval devices failed after initial clinical testing.[5]

Patients with end-stage lung disease, i.e., chronic lung failure, require more permanent lung replacement technology unless they have a chance to temporarily recover from pulmonary decompensation with a short-term lung-assist device. Lung transplantation is a limited option because the shortage of donor lungs causes patients to wait an average of two years for an organ: 80% die before receiving a lung transplant. Currently, 4000 Americans are waiting for a lung or heart-lung transplant,[6,7] a number that rises sharply each year, but dramatically underestimates the dimension of this problem because most patients sick enough for a transplant are not eligible for lung transplantation.

The clinical application of extrapulmonary lung assist began with ECMO with a heart-lung machine. The first patients were an adult trauma patient treated by Don Hill in 1972, and Robert Bartlett's first successful neonatal ECMO case, performed in 1975. ECMO has been discussed and studied extensively, and shall not be the subject of this

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10.1191/0267659103pf684oa

manuscript. However, it is possible that the technological advances in artificial lungs can be employed to make ECMO a biologically less invasive treatment option.

Pumpless interventional lung assist devices and artificial lungs have not been available in the 20th century, due in part to a lack of technologies to reduce the pressure gradient across membrane lungs. With the advent of this technological advance, lung assist devices will soon equal the physiological pulmonary impedance,[8] thus allowing pumpless attachment to the pulmonary circulation. Key technologies for artificial lungs include diffusion membranes to avoid plasma leakage in prolonged applications, long-term coating technologies and homogeneous distribution of blood flow (Table 1). Together, these technologies allow the design of artificial lungs that will create new options for the treatment of acute and chronic lung failure. Extrapulmonary lung assist may complement mechanical ventilation because it gives the lung time to heal while ventilation can be optimized with respect to lung protection. The option of extrapulmonary lung assist without mechanical ventilation is currently being explored.

Currently, three concepts are being discussed; a proposed classification is shown in Table 2.

Intravascular gas exchange devices for single-needle venous access have been designed for implantation in the vena cava or the pulmonary artery. A pulsating balloon in the membrane bundle or an impeller blood pump can be employed to optimize blood flow around the gas exchange fibres or across the device.

Interventional lung assist devices for percutaneous attachment to the systemic circulation creating an arteriovenous shunt. Preferably, the femoral artery and vein are cannulated. These simple devices for single use do not require a blood pump.

Total artificial lungs to completely replace pulmonary gas exchange function. Surgical attachment to the pulmonary circulation in parallel, in series or in a hybrid mode is being discussed. Initially, these will be paracorporeal devices with implantable artificial lungs being the ultimate goal.

Table 1 Engineering

Low pressure gradient
Homogeneous blood flow
Long-term coating
Long-term diffusion membranes
Vascular access

Table 2 Classification of artificial lungs

Device type
A. Oxygenator plus pump (heart lung machine, ECMO)
B. Lung assist device (pumpless, interventional attachment to systemic circulation)
C. Total artificial lung (pumpless, surgical attachment to pulmonary circulation)
D. Bioartificial lung (can be used with B and C)
Anatomic position
Intravascular
Extra/paracorporeal
Implantable
Vascular connection
Intravascular implantation
Interventional cannulation
Surgical anastomoses

Intravascular lung assist

The IVOX is an intracorporeal, hollow-fibre membrane oxygenator and CO_2 removal device that is surgically inserted into the vena cava. Oxygen is pulled through the hollow fibres by a vacuum pump. There is no extracorporeal circulation of blood. Inlet and outlet gas conduits exit a small skin incision.[9–11] About 10 years ago, clinical testing of the device was halted because the device's design did not allow for sufficient gas exchange.

The new intravascular membrane oxygenator (IMO) created by William J Federspiel and Brack Hattler is expected to allow for more efficient gas exchange.[12] Blood is exposed to less than 0.5 m^2 of foreign surface. Key to its design, and a distinction from the IVOX device that failed, is a central balloon within the fibres that inflates and deflates at a rate of 300 beats per minute to move the fibres and mix the blood. This allows for more efficient gas exchange. To drive the pulsating balloon, an extracorporeal control console will be required. This device has been designed for patients with acute respiratory failure, and it is currently being tested in animals (Figure 1).[13] The device is not envisioned to be used for prolonged support or as a total replacement of the lungs.

An advanced intravascular gas exchange device combined with a catheter pump that overcomes the pressure gradient across the device (HIMOX: highly integrated membrane oxygenator) is being developed by Professor Reul's group in Aachen.[14]

In 1996, Baskaran and coworkers, from Pennsylvania State University, tested small intrapulmonary artery lung prototypes, consisting of a central gas supply catheter from which are tethered a large number of blind-ended microporous fibres of equal length. Mathematical modelling of gas transfer was performed for these prototypes.[15]

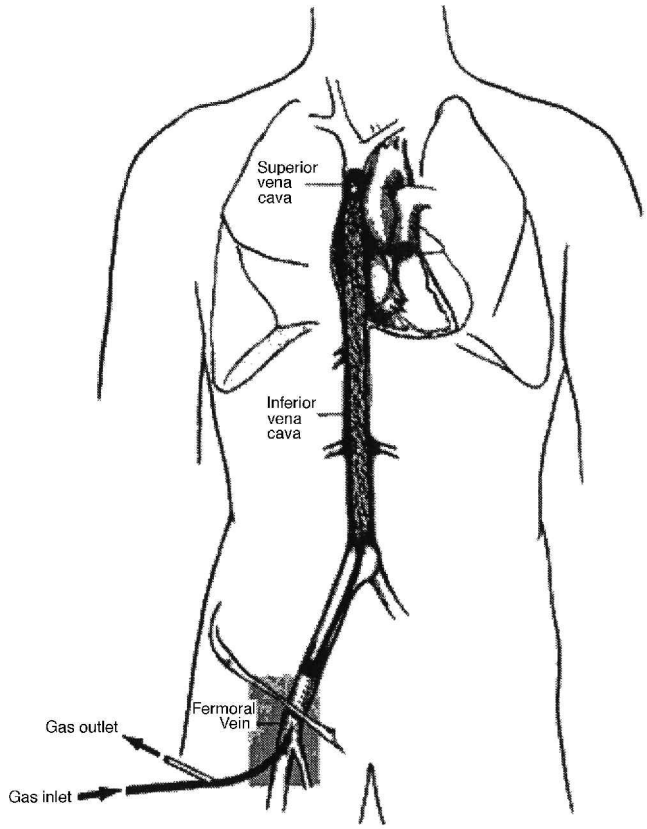

Figure 1

Interventional lung assist or pumpless extracorporeal lung assist

The heart pumps blood through the pumpless lung assist device via a femo-femoral shunt created by percutaneous arterial and venous cannulation (Seldinger technique) with high-flow cannulae. The low impedance of the lung assist device avoids the use of an artificial blood pump. Due to this principle, adequate mean arterial pressure is mandatory and low cardiac output or cardiogenic shock are contraindications for interventional lung assist.[16] This type of device is attached to the systemic circulation and receives only part of the cardiac output for extracorporeal gas exchange. This allows complete CO_2 removal, which can be controlled by varying sweep gas flow. Oxygenation depends on shunt, arterial oxygen saturation and other variables. The lung adds whatever it can.[17] The limited oxygenation provided can be life saving in severe arterial hypoxemia, such as in lung trauma.[18]

The concept of interventional lung assist had first been mentioned in 1967,[19] Rashkind proposed a pumpless oxygenator for temporary lung assist in cystic fibrosis, adult respiratory distress syndrome (ARDS) and congenital heart disease. This vision could not be realized with the technologies available at that time. In 1996, Cappelletti[20] and in 1999, de Somer and colleagues[21] demonstrated the feasibility of pumpless lung assist in animal trials. In 1998 and 1999, Zwischenberger and colleagues,[22,23] who had proposed this concept earlier, confirmed the clinical feasibility of this approach. One year later, Reng *et al.*[17] reported clinical use of the first device developed for pumpless use. The technique seems attractive because of its simplicity and independence from machines. The safety and feasibility of the first commercially available pumpless lung assist device (Novalung ILA, Novalung GmbH, Hechingen, Germany, Figure 2) has been shown in more than 150 clinical applications. It is based on a low resistance lung assist device designed for pulsatile blood flow with tight diffusion membranes and a protein matrix coating. The gas exchange surface amounts to 1.3 m^2. Pressure gradient across the Novalung device and cannulae is shown in Figure 3 with flow for various cannula sizes. Table 3 shows indications from the first 150 clinical cases.

In the vast majority of patients treated with interventional lung assist, this treatment modality has been an adjunct to mechanical ventilation that allowed optimized lung protective ventilation, thus giving the lung time to heal. However, in a few cases, interventional lung assist has been employed

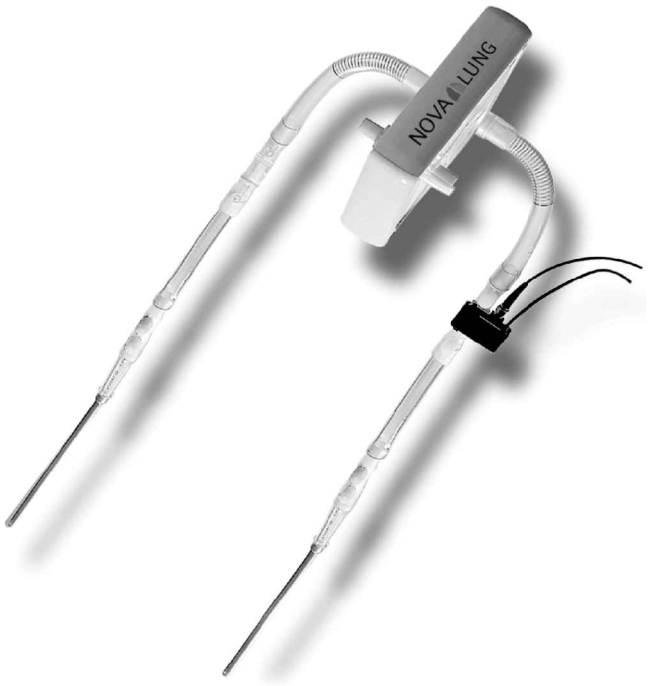

Figure 2 The symmetrical lung assist device is shown with two low resistance cannulae attached. The system's low pressure gradient allows use without a mechanical blood pump in an arteriovenous shunt created between femoral artery and vein.

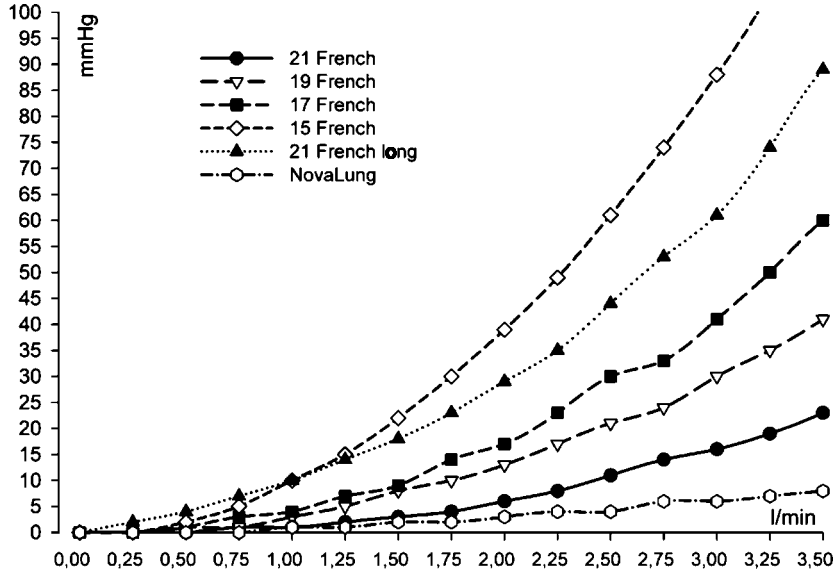

Figure 3 Pressure gradient of cannuale (NovaLung® Cannula 15–21 Fr) and lung assist device (NovaLung) as a function of flow. The lung assist device has a maximum pressure gradient of 7.0 mmHg between 0.5 and 3.0 L/min. Data evaluation was performed in the laboratory at Hb 9.0 g/dL and temperature of 36.0°C. Pulsatile flow was generated by an axial-flow pump (Deltastream® , Medos AG, 52222 Stolberg, Germany). The cannula marked with '21 Fr long' is a standard femoral venous cannula (CB 96605-021 Medtronic) for CPB.

without mechanical ventilation in the awake, non-sedated patient.

Total artificial lung

The first total artificial lung, the BioLung (MC3 Inc., Ann Arbor, MI, USA; Figure 4) has undergone intensive bench testing and animal trials. It is expected to be tested clinically within two years.[24,25] This device could eventually help lung transplant candidates stay alive and mobile for six months or more outside the hospital, and allow them to stay healthy enough to remain at the top of the transplant list. It may also prove suitable for patients with end-stage COPD, pulmonary fibrosis or cystic fibrosis.

The BioLung was shown to produce better survival and less lung injury than a conventional ventilator in five-day tests on damaged sheep lungs.[26] The device prototype is well tolerated in series with the normal sheep pulmonary circulation. Using a lethal dose 80–100% smoke/burn ARDS sheep model, the BioLung was compared with volume-controlled mechanical ventilation (VCMV) in a prospective, randomized, controlled, unblinded, five-day outcome study, where the BioLung wet/dry ratio was significantly lower than VCMV. The BioLung decreased ventilator-induced lung injury to improve five-day survival. Six of eight sheep with the BioLung versus one of six with VCMV survived. Hemodynamic parameters with the BioLung remained stable, and the BioLung showed a very low pressure gradient. Forty-eight hours after injury, the PaO_2/FiO_2 had normalized with the BioLung, and ventilator settings were significantly lower, including FiO_2 reduced from 100% to 21%.

Just like interventional lung assist, the BioLung uses no mechanical pump, instead relying on the heart's own pumping force to send blood from the pulmonary artery through the device. The device is rigidly housed, noncompliant and has a very low resistance to blood flow. When used in series, this device resulted in a 50% incidence of right heart failure in sheep.[27] These results have been improved by a new design for the device, based on computer modelling and prototyping. The alterations have reduced the device's size, made it more flexible and improved blood flow, thereby enhancing the lung's performance and reducing the risk of clotting and infection.[28] Matching the impedance of an

Table 3 Indications for interventional lung assist

Bridge to recovery
trauma
severe pneumonia
ARDS
pulmonary fibrosis
airway obstruction
Bridge across thoracic surgery
pneumonectomy despite severely impaired lung function
Weaning from mechanical ventilation
Bridge to transplant

Figure 4 BioLung total artificial lung prototype.

artificial lung for pulmonary replacement to native pulmonary impedance is important in preventing right ventricular dysfunction. Further development, therefore, addressed this problem by introducing an inflow compliance chamber, an inlet blood separator and modification of the artificial lung outlet geometry, all to reduce resistance and mimic the compliance of the pulmonary vascular bed.[8] The hybrid implantation mode, with inflow to the artificial lung from the proximal pulmonary artery, outflow branches to the distal pulmonary artery and the left atrium, a band around the pulmonary artery between the two anastomoses, and a band around the outlet graft to the left atrium, has been proposed as a compromise between haemodynamic performance and preservation of some portion of the nonpulmonary functions of the natural lungs.[29]

This type of device will initially be used in a paracorporeal fashion, i.e., with grafts connected to an extracorporeal artificial lung. This allows safe and rapid nonsurgical exchange, while an implanted artificial lung would require surgery to replace the device. Therefore, the treatment intervals will not necessarily be limited by the durability of the individual device. Artificial lungs will initially require an extracorporeal oxygen source such as a concentrator or a tank.

In preparation for clinical trials, a survey of transplant program directors at lung transplant centres in the USA was performed by Haft and colleagues.[30] The findings suggest widespread interest and anticipation, with a majority saying that animal trials of one month or less would be sufficient as final preclinical testing. The respondents overwhelmingly said that patients with idiopathic pulmonary fibrosis would be the best candidates for the first clinical trials. They, typically, have the highest waiting list death rate, and their disease progresses rapidly without responding to therapy. Because the lung transplant system currently allocates organs based only on waiting time, size of organ needed and blood type, a clinical trial of an artificial lung as a bridge to transplant would require a change to allocation policy for participants. The survey found support for this shift, which would prioritize transplants for those on the artificial lung, among 67% of transplant program directors. Still others voiced partial support.

Bioartificial lungs

Turning mouse stem cells into cells needed for pulmonary gas exchange may allow the regeneration of damaged lung tissue, and ultimately the creation of artificially grown lungs may make it possible to repair lungs that have been damaged by disease, by implanting fully functioning cells to repopulate damaged areas. Unlike transplantation from a donor, the cells can be developed in such a way that the

body will not reject them. Anne Bishop and her team from London (Imperial College London Tissue Engineering and Regenerative Medicine Centre at Chelsea and Westminster Hospital) now plan to begin development of a living construct, using bioactive foams and scaffolds. They will provide a frame on which the cells can grow and then be transplanted.[31]

Bishop and her colleagues took mouse embryonic stem cells, placed them in a specialized growth system and encouraged them to change into cells that line the lung where O_2 is absorbed and CO_2 is excreted. They have begun to replicate their findings using human embryonic stem cells. The transformed cells could help reline the lungs in patients who had lung damage or in premature infants whose lungs were not fully matured. Unlike transplanted cells from a donor, these cells could be developed so the body would not reject them. Currently, these cells are grown on natural and artificial scaffolds, and the aim there is to construct lung tissue that could be used in implantation.

As an alternative gas exchange concept, the feasibility of a bioregenerative artificial lung has been shown.[32] The photosynthetic capacity of algae (*Chlorella pyrenoidosa*) was maximized at a cell density of 25 million cells/mL to serve as an oxygen producer and CO_2 remover. A reservoir containing blood was interfaced with this system via a gas transfer membrane. A maximum gas transfer rate of 0.55 mol/L/hour was achieved. The projected rate of 1.0 mol/L/hour required for physiological applications is not totally absurd, with a modified setup in the form of regulating the photosynthetic pathway or genetically engineering a hybrid strain with enhanced O_2 production and suppressed photoinhibition capacity.

Perspectives

In conclusion, the development of artificial lungs to assist or replace the failing lung temporarily or permanently has gained increasing momentum in recent years. This decade will see a growing body of clinical experience and a number of trials to define a role for the treatment options enabled or complemented by these new devices.

References

1 Hattler B. Invited keynote lecture, 21st Annual Meeting of the International Society for Heart and Lung Transplantation, Vancouver, British Columbia, April 26, 2001.
2 American Lung Association Fact Sheet. Chronic Obstructive Pulmonary Disease (COPD), September 2000.
3 Petty TL. A new national strategy for COPD. *J Respir Dis* 1997; **18**: 365–69.
4 Hirche TO, Smaczny C, Mallinckrodt C, Krüger S, Wagner TOF. Pulmonale Manifestation der Mukoviszidose im Erwachsenenalter. *Deutsches Ärzteblatt* 2003; **100**: A264–270.
5 Zwischenberger JB, Tao W, Bidani A. Intravascular membrane oxygenator and carbon dioxide removal devices: a review of performance and improvements. *ASAIO J* 1999; **45**: 41–46.
6 2000 Annual Report of the US Scientific Registry for Transplant Recipients and the Organ Procurement and Transplantation Network. Transplant Data: 1990–1999. US Department of Health and Human Services, Health Resources and Services Administration, Office of Special Programs, Division of Transplantation, Rockville, MD; United Network for Organ Sharing, Richmond, VA, 2000.
7 Hosenpud JD. The registry of the International Society for Heart and Lung Transplantation, 17th official report – 2000. *J Heart Lung Transplant* 2000; **19**: 909–31.
8 Haft JW, Bull JL, Rose R *et al.* Design of an artificial lung compliance chamber for pulmonary replacement. *ASAIO J* 2003; **49**: 35–40.
9 Zwischenberger JB, Cardenas VJ Jr, Tao W, Niranjan SC, Clark JW, Bidani A. Intravascular membrane oxygenation and carbon dioxide removal with IVOX: can improved design and permissive hypercapnia achieve adequate respiratory support during severe respiratory failure? *Artif Organs* 1994; **18**: 833–39.
10 Niranjan SC, Clark JW, San KY, Zwischenberger JB, Bidani A. Analysis of factors affecting gas exchange in intravascular blood gas exchanger. *J Appl Physiol* 1994; **77**: 1716–30.
11 Zwischenberger JB, Cox CS Jr. A new intravascular membrane oxygenator to augment blood gas transfer in patients with acute respiratory failure. *Tex Med* 1991; **87**: 60–63.
12 Lund LW, Hattler BG, Federspiel WJ. A comparative in vitro hemolysis study of a pulsating intravenous artificial lung. *ASAIO J* 2002; **48**: 631–35.
13 Hattler BG, Lund LW, Golob J *et al.* A respiratory gas exchange catheter: *in vitro* and *in vivo* tests in large animals. *J Thorac Cardiovasc Surg* 2002; **124**: 520–30.
14 Press Release, Bundesministerium für Bildung und Forschung, Berlin, 8 December 2002.
15 Baskaran H, Nodelman V, Ultman JS *et al.* Small intrapulmonary artery lung prototypes. Mathematical modelling of gas transfer. *ASAIO J* 1996; **42**: M597–603.
16 Liebold A, Philipp A, Kaiser M, Merk J, Schmid FX, Birnbaum DE. Pumpless extracorporeal lung assist using an arterio-venous shunt. Applications and limitations. *Minerva Anestesiol* 2002; **68**: 387–91.
17 Reng M, Philipp A, Kaiser M, Pfeifer M, Gruene S, Schoelmerich J. Pumpless extracorporeal lung assist and adult respiratory distress syndrome. *Lancet* 2000; **356**: 219–20.

18 Schmid FX, Philipp A, Link J, Zimmermann M, Birnbaum DE. Hybrid management of aortic rupture and lung failure: pumpless extracorporeal lung assist and endovascular stent-graft. *Ann Thorac Surg* 2002: **73**: 1618–20.
19 Rashkind WJ, Miller WW, Falcone D, Toft R. Hemodynamic effects of arteriovenous oxygenation with a small-volume artificial extracorporeal lung. *J Pediatr* 1967: **70**: 425–29.
20 Cappelletti DD, Olshove V, Tallman RD. Pumpless arterial-venous extracorporeal CO_2 removal during acute lung injury. *J Extracorp Circ* 1996; **28**: 6–12.
21 De Somer F, Van Belleghem Y, Foubert L *et al.* Feasibility of a pumpless extracorporeal respiratory assist device. *J Heart Lung Transplant* 1999; **18**: 1014–17.
22 Conrad SA, Brown EG, Grier LR *et al.* Arteriovenous extracorporeal carbon dioxide removal: a mathematical model and experimental evaluation. *ASAIO J* 1998; **44**: 267–77.
23 Zwischenberger JB, Conrad SA, Alpard SK, Grier L, Bidani A. Percutaneous extracorporeal arteriovenous CO_2 removal for severe respiratory failure. *Ann Thorac Surg* 1999; **68**: 181–87.
24 Fazzalari FL, Montoya JP, Bonnell MR, Bliss DW, Hirschl RB, Bartlett RH. The development of an implantable artificial lung. *ASAIO J* 1994; **40**: M728–31.
25 Zwischenberger JB, Anderson CM, Cook KE, Lick SD, Mockros LF, Bartlett RH. Development of an implantable artificial lung: challenges and progress. *ASAIO J* 2001; **47**: 316–20.
26 Zwischenberger JB, Wang D, Lick SD, Deyo DJ, Alpard SK, Chambers SD. The paracorporeal artificial lung improves 5-day outcomes from lethal smoke/burn-induced acute respiratory distress syndrome in sheep. *Ann Thorac Surg* 2002; **74**: 1011–16; discussion 1017–18.
27 Lick SD, Zwischenberger JB, Alpard SK, Witt SA, Deyo DM, Merz SI. Development of an ambulatory artificial lung in an ovine survival model. *ASAIO J* 2001; **47**: 486–91.
28 Lick SD, Zwischenberger JB, Wang D, Deyo DJ, Alpard SK, Chambers SD. Improved right heart function with a compliant inflow artificial lung in series with the pulmonary circulation. *Ann Thorac Surg* 2001; **72**: 899–904.
29 Boschetti F, Perlman CE, Cook KE, Mockros LF. Hemodynamic effects of attachment modes and device design of a thoracic artificial lung. *ASAIO J* 2000; **46**: 42–48.
30 Haft JW, Griffith BP, Hirschl RB, Bartlett RH. Results of an artificial lung survey to lung transplant program directors. *J Heart Lung Transplant* 2002; **21**: 467–73.
31 Ali NN, Edgar AJ, Samadikuchaksaraei A *et al.* Derivation of type II alveolar epithelial cells from murine embryonic stem cells. *Tissue Eng* 2002; **8**: 541–50.
32 Basu-Dutt S, Fandino MR, Salley SO, Thompson IM, Whittlesey GC, Klein MD. Feasibility of a photosynthetic artificial lung. *ASAIO J* 1997; **43**: 279–83.