Experimental safety and efficacy evaluation of an extracorporeal pumpless artificial lung in providing respiratory support through the axillary vessels

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Supplemental material is available online.

Objective: We sought to investigate the safety and feasibility of implanting the pumpless interventional lung assist device (Novalung; Novalung GmbH, Hechingen, Germany) to the axillary vessels either by means of direct cannulation or end-to-side graft interposition and the capability of either type of vascular access to provide respiratory support during apneic ventilation in adult pigs.

Methods: Ten pigs were ventilated for 4 hours (respiratory rate, 20-25 breaths/min; tidal volume, 10-12 mL/kg; fraction of inspired oxygen, 1.0; positive end-expiratory pressure, 5 cm H₂O). Thereafter, the interventional lung assist device was surgically connected to the right axillary artery and vein by using direct cannulation (n = 5) or end-to-side ringed polytetrafluoroethylene graft interposition (n = 5), and ventilatory settings were reduced to achieve near apneic ventilation (respiratory rate, 4 breaths/min; tidal volume, 1-2 mL/kg; fraction of inspired oxygen, 1.0; positive end-expiratory pressure, 20 cm H₂O). Hemodynamic and intrathoracic volumes and lung cytokine levels were measured.

Results: Blood flow through the interventional lung assist device was 1.7 ± 0.4 L/min or $30\% \pm 14\%$ of the cardiac output, and the mean pressure gradient across the interventional lung assist device was 10 ± 2 mm Hg. The interventional lung assist device allowed an O₂ transfer of 225.7 ± 70 mL/min and a CO₂ removal of 261.7 ± 28.5 mL/min. Although the amount of blood flow perfusing the interventional lung assist device was significantly higher ($P < .01$) with direct cannulation (2.1 ± 0.3 L/min) compared with that seen in graft interposition (1.3 ± 0.3 L/min), the latter allowed similar respiratory support with reduced hemodynamic instability.

Conclusions: The axillary vessels are a safe and attractive cannulation site for pumpless partial respiratory support. Compared with direct cannulation, graft interposition was equally able to support the interventional lung assist device–driven gas exchange requirements during apneic ventilation with better hemodynamic stability.

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All peripheral artificial lungs (ALs) generated thus far have been attached to either the groin or neck vessels.¹ Unfortunately, this site and the commonly used high-flow cannulae are unsuitable for clinical long-term or ambulatory support because of the potential morbidity (eg, pericannula thrombosis, leak, dislodgments, intimal tear, and dissection) and reduced patient compliance (eg, deambulation and mobilization). A hypothetical solution would be to use the axillary vessels, an access increasingly used in cardiothoracic surgery.²⁻⁶

The pumpless extracorporeal interventional lung assist device (iLA; Novalung; Novalung GmbH, Hechingen, Germany) is a new AL powered uniquely by means of arterial pressure that drives blood flow through a femofemoral shunt created by percutaneous arterial and venous cannulation with low-resistance cannulae, thus avoiding the need for a mechanical blood pump. This device allows complete CO₂

Abbreviations and Acronyms

AL	= artificial lung
ARDS	= adult respiratory distress syndrome
AVCO ₂ R	= arteriovenous extracorporeal CO ₂ removal
CO	= cardiac output
F _{IO₂}	= fraction of inspired oxygen
IL	= interleukin
TNF- α	= tumor necrosis factor α
TV	= tidal volume

removal and minimal oxygenation and has been successfully used thus far as a bridge to lung recovery^{7,8} and transplantation.⁹ Because of these backgrounds, we investigated the safety and feasibility of attaching the iLA to the axillary vessels either by means of direct cannulation or graft interposition and the capability of either access to provide respiratory support during apneic ventilation in pigs.

Materials and Methods

Ten Yorkshire Duroc pigs (Isoquimen S/L, Barcelona, Spain) weighing 55.1 ± 2.7 kg were used. All animals received care in compliance with the "Principles of laboratory animal care" formulated by the National Society for Medical Research and the "Guide for the care and use of laboratory animals" prepared by the Institute of Laboratory Animal Resources, National Research Council, and published by the National Academy Press, revised 1996. The study was approved by the Animal Care and Use Committee of the University of Barcelona (Project N-0001-61399030-F).

Study Design

Animals were ventilated with volume control (Servo 900D; Siemens, Munich, Germany) for 4 hours with the following respiratory settings: respiratory rate, 20 to 25 breaths/min; tidal volume (TV), 10 to 12 mL/kg; fraction of inspired oxygen (F_{IO₂}), 1.0; and positive end-expiratory pressure, 5 cm H₂O. After this observation period (4 hours), the right axillary artery and vein were surgically connected to the iLA through either direct cannulation (group 1, n = 5) or graft interposition (group 2, n = 5), and the ventilator parameters were modified to achieve a near-static (or apneic) ventilation, targeting a respiratory rate of 4 breaths/min and a TV of 1 to 2 mL/kg while maintaining the same F_{IO₂} and gradually increasing the positive end-expiratory pressure to 20 cm H₂O. The study was completed after this 8-hour period. Assignment to either group was aleatory and independent of the diameter or rigidity of the vessel.

Anesthesia and Monitoring

Animals were premedicated with intramuscular azaperone (4 mg/kg) and intravenous thiopental (10 mg/kg) and relaxed with intravenous rocuronium ($6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). Orotracheal intubation was obtained through a 7.5F endotracheal tube under bronchoscopic guidance. Anesthesia was maintained by means of continuous infusion of fentanyl ($1 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) and propofol

Figure 1. Photograph showing a direct cannulation of the axillary artery and vein in the right deltopectoral groove.

($3\text{--}5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) until the study end. Antibiotic therapy included 2 g of intravenous cefazolin at induction of anesthesia. Animals were instrumented with an arterial pressure line (5F) placed transcutaneously in the right femoral artery (PiCCO plus; Pulsion Medical Systems, Munich, Germany) and several peripheral venous catheters and a Swan-Ganz catheter (Edwards Lifesciences, Munich, Germany) placed transcutaneously in the left internal jugular vein. Peripheral oxygen arterial saturation was continuously monitored with a pulse oximeter (BCI, Inc, Waukesha, Wis) placed at the pig's tail and another probe placed on the right arm. Urine output was continuously monitored by placement of a percutaneous bladder catheter. Temperature was maintained at 37°C with heaters and blankets. Intravenous 0.9% NaCl fluids and vasoactive drugs were given if systemic systolic arterial pressure decreased to less than 100 mm Hg, as was intravenous atropine (0.5–1 mg) if heart rate was less than 50 beats/min.

iLA Implantation Technique

Under sterile conditions, a 6- to 10-cm incision over the equivalent of the human right deltopectoral groove allowed easy exposure and encirclement by an umbilical tape of the subclavian and axillary vessels, taking care to preserve the infrascapular portion of the brachial plexus. This site was used because of our previous hemodynamic and surgical experience.¹⁰ Proximal and distal control of the axillary artery was gained, and the umbilical tape was passed through a tourniquet. After systemic heparinization (20 IU/kg), femoral artery clamps were used proximal and distal to the cannulation or implantation site.

In group 1, after a transversal arteriotomy, the axillary artery (15F) and vein (17F) were cannulated with specially designed, short, straight, low-resistance cannulae (Novaport; Novalung GmbH, Hechingen, Germany; Figure 1). The tourniquets were tightened and secured, flow was evaluated on the basis of ante-grade or back bleeding, and, if adequate, the cannulae were clamped. The distal arterial clamp was left in place until the end of the study period, and the perfusion of the distal arm was controlled clinically and with the previously placed pulse oximeter. In group 2 a 1- to 2-cm vertical arteriotomy and venotomy were created, and two 8-mm ringed polytetrafluoroethylene (Jotec GmbH, Hechingen)

Figure 2. Photograph showing graft interposition to the axillary artery and vein in the right deltopectoral groove.

gen, Germany) grafts of 3 cm in length were sewn onto the artery and vein in an end-to-side fashion by using vascular parachute techniques and 5-0 or 6-0 polypropylene sutures (Prolene; Ethicon, Inc, Somerville, NJ; Figure 2) and ultimately connected to the iLA system through silicone straight $1/4 \times 3/8$ rubber connectors (Novalung GmbH). The iLA device and tubing system were completely deaired and filled with normal saline solution (approximately 240 mL). Finally, the tubes were connected to the cannulae or silicone connectors, and the proximal clamps were slowly removed to create a peripheral arteriovenous shunt. A sweep gas tube providing pure O_2 (6-12 L/min) was connected to the iLA and placed at the bedside (Figure E1). Functional control was achieved through a monitor (Blood Flow Monitor, Novalung GmbH), which calculates blood flow through the system by using an ultrasonic flow probe (NovaFlow System, Novalung GmbH) placed at the venous cannula. iLA malfunction was defined as a driving blood flow of less than 0.5 L.

The capability of the iLA to provide additional O_2 was measured by calculating the O_2 content of blood entering and exiting the device and multiplying the difference by the flow rate through the device, according to the following formula:

$$\begin{aligned} \text{Oxygen transfer (mL/min)} \\ &= [(\text{Oxygen content as volume \%}) \\ &\quad \times 10 \text{ dL/L}] \times \text{iLA flow rate (L/min)} \end{aligned}$$

The arteriovenous extracorporeal CO_2 removal ($AVCO_2R$) provided by the iLA was calculated as follows:

$$\begin{aligned} \text{AVCO}_2R \text{ (mL/min)} \\ &= \text{CO}_2 \text{ content in the inflow arterial cannula} \\ &\quad - \text{CO}_2 \text{ content in the venous outflow cannula} \\ &\quad \quad \quad (\text{mL CO}_2/\text{mL blood}) \\ &\quad \quad \quad \times \text{Blood flow iLA (L/min)} \times 10 \end{aligned}$$

Hemodynamics and Lung Function

The following hemodynamic variables were measured hourly (monitor, Hewlett Packard model 685): heart rate, cardiac output

(CO), cardiac index, mean arterial pressure, mean pulmonary arterial pressure, pulmonary capillary wedge pressure, central venous pressure, systolic index, systolic volume, systemic vascular resistance, pulmonary vascular resistance, left ventricular systolic work, right ventricular systolic work, and body temperature through the Swan-Ganz catheter. PiCCO allowed us to measure the extravascular lung water volume, intrathoracic blood volume, and ventricular contractility. Ventilator parameters, including minute ventilation, lung compliance, and peak inspiratory pressure, and arterial and venous blood gases were evaluated hourly as well.

Lung Cytokine Assays

The left lung was lavaged with 40-mL aliquots of sterile saline solution (0.9% NaCl) instilled through the bronchoscope's channel and subsequently aspirated manually before intubation and every hour thereafter. Tumor necrosis factor α (TNF- α), interleukin (IL) 6, and IL-8 levels were measured in bronchoalveolar lavage supernatants by using an enzyme-amplified sensitivity immunoassay based on the quantitative immunometric sandwich enzyme immunoassay technique (Medgenix Diagnostics, Fleurus, Belgium) and PerSeptive (Framingham, Mass). Normal concentration values in our laboratory are as follows: TNF- α , 25 to 120 $\mu\text{g/mL}$; IL-6, less than 39 $\mu\text{g/mL}$; and IL-8, less than 62 $\mu\text{g/mL}$.

Histopathologic Features

Animals were killed 4 hours after iLA implantation or if the animal's condition was deteriorating, by using an intravenous bolus of fentanyl and propofol and potassium chloride (40 mEq). Systemic heparin (100 IU/kg) was also given to avoid postmortem thrombus formation. The lung tissue samples of each lobe were dissected and placed in formalin for 18 hours and then in 70% methanol for 24 hours. Paraffin-embedded lung sections measuring 5 μm were mounted on slides and stained with hematoxylin and eosin. Each section was evaluated to search for acute/chronic interstitial or alveolar inflammation, alveolar edema, and the presence of macrophages, desquamative cells, or polymorphonuclear intra-alveolar cells. Also, infarction or clots in the lung were evaluated. Cannulated or grafted vessels were evaluated for the presence or absence of emboli or thrombi or intimal injury.

Statistical Analysis

Continuous variables were compared by using the independent-samples t test. The odds ratio was calculated to perform between-group comparisons of categorical variables. Results are presented as means $\pm$ standard error of mean. Analyses were made with the SPSS package (version 7.0; SPSS, Inc, Chicago, Ill).

Results

All animals completed the study protocol. Graft interposition was more time consuming (21 ± 5 minutes) than direct cannulation, whereas the latter was technically more demanding, especially during the introduction and antegrade placement of the arterial cannula in the brachiocephalic artery. Except for 1 dislodgement and temporary malfunction of 1 arterial cannula, there were no other neurovascular complications.

Figure 3. Correlation of O_2 transfer and arteriovenous CO_2 removal ($AVCO_2R$) to the blood flow perfusing the interventional lung assist device during apneic ventilation.

The overall blood flow perfusing the iLA was 1.7 ± 0.4 L/min or $30\% \pm 14\%$ of the CO (7.2 ± 2.6 L/min), and iLA declamping induced a peripheral arteriovenous shunt effect (Table E1) that was well tolerated clinically. The mean resistance of the iLA was 10 ± 2 mm Hg. The iLA device supported a mean O_2 transfer and $AVCO_2R$ of 225.7 ± 70 mL/min and 261.7 ± 28.5 mL/min (Figure 3), respectively, and permitted a significant reduction of the ventilatory settings to reach a near-apneic ventilation status (Table 1). Direct cannulation permitted a significantly higher arterial inflow through the iLA device than graft interposition (2.1 ± 0.3 vs 1.3 ± 0.3 , $P < .01$, Figure E2) throughout the entire study period, whereas the latter provided similar iLA-driven respiratory support (Table 2) and more hemodynamic stability (Table E2) during apneic ventilation.

Figure 4 shows the evolution of the bronchoalveolar lavage concentrations of lung cytokines during the different ventilation modes. Final pathological examinations were normal in all specimens.

Discussion

Presently, a long-term intracorporeal AL remains a dream,¹¹ and recent progress¹ suggests a high likelihood of success for ambulatory and extracorporeal devices that can be switched in and out, as in a dialysis setting, with¹¹ or without¹ an integrated pumping system. However, the clinical feasibility and advantages of pumpless devices to provide effective gas exchange when placed in parallel with the native circulation, either centrally (pulmonary artery to left atrium) or peripherally (usually femoral artery and vein,

TABLE 1. Average ventilatory variables during initial ventilation (4 hours) and apneic ventilation under interventional lung assist device support (4 hours)

Variables	Initial ventilation without iLA support	Apneic ventilation with iLA support	P value
TV (mL)	527 ± 62	98 ± 15	$<.001$
RR (beats/min)	21.9 ± 2.8	4 ± 0.3	$<.001$
MV (L/min)	12.1 ± 1.6	0.67 ± 0.5	$<.001$
PIP (cm H ₂ O)	23.4 ± 2.6	22 ± 2.1	NS
PEEP (cm H ₂ O)	5.1 ± 0.3	20 ± 2	$<.001$
Pao_2/Fio_2	479.5 ± 81.3	328.2 ± 120.7	$<.001$
$Paco_2$ (mm Hg)	40.8 ± 7.5	51.6 ± 4.1	$<.001$
LC (mL/cm H ₂ O)	51 ± 9.1	95.7 ± 15.2	$<.001$

iLA, Interventional lung assist device; TV, tidal volume; RR, respiratory rate; MV, minute volume; PIP, peak inspiratory pressure; NS, not significant; PEEP, positive end-expiratory pressure; Pao_2/Fio_2 , arterial oxygen tension/fraction inspired oxygen; $Paco_2$, arterial carbon dioxide tension; LC, lung compliance [(TV/Plateau pressure) – PEEP].

$AVCO_2R$), have been demonstrated experimentally and clinically.^{7,12-16}

The iLA device is a relatively new, commercially available, low-resistance membrane lung designed for pulsatile blood flow with tight diffusion membranes and a protein matrix coating, incorporating a gas exchange surface of 1.3 m^2 . Because the mean pressure gradient of the Novalung cannulae and device is approximately 7 mm Hg with a blood flow of between 0.5 and 2.5 L/min, it can be powered solely by the mean arterial pressure when placed peripherally through an arteriovenous shunt created by percutaneous arterial and venous cannulation with low-resistance cannulae.⁸ Because oxygenation is essentially uncoupled from CO_2 removal, the iLA has successfully been used to allow and optimize advanced lung protective ventilation strategies beyond ARDSnet¹⁷ in patients with adult respiratory distress syndrome (ARDS)⁷ and CO_2 retention syndromes without ventilator-associated lung injury, in recovery from lung injuries, and as a bridge to transplantation.^{8,9} The iLA has also been used in general thoracic patients as intraoperative respiratory support or to treat postoperative noncardiogenic ARDS (personal communication). However, because of its simplicity, low invasiveness, no need for pump support, and access through peripheral vessels, the iLA might have much wider application in an ambulatory configuration as a bridge to transplantation or as an alternative to transplantation (long-term palliation). The minimal O_2 transfer is an obvious limitation of the arteriovenous attachment mode, but hypoxia can be treated by means of low-flow O_2 supplementation to permit O_2 diffusion across the resting native lungs, either as apneic oxygenation¹⁸ or hyperoxygenation.¹⁹

Thus far, extracorporeal ALs have used either the neck (carotid artery–internal jugular vein) or groin (femoral ar-

TABLE 2. Differences in respiratory variables between direct cannulation and graft interposition during apneic ventilation under interventional lung assist device support

Variables	Direct cannulation	Graft interposition	P value
TV (mL)	97 ± 1.9	99.4 ± 9.1	NS
RR (beats/min)	4 ± 0.3	4 ± 0.3	NS
MV (L/min)	0.6 ± 0.2	0.5 ± 0	NS
PIP (cm H ₂ O)	23.5 ± 2.4	21.3 ± 1.9	NS
PEEP (cm H ₂ O)	22.1 ± 4.3	20.3 ± 3.5	NS
PaO ₂ /Fio ₂	350.4 ± 111.1	307 ± 148.6	NS
Paco ₂ (mm Hg)	53.6 ± 8.3	49.1 ± 9.7	NS
LC (mL/cm H ₂ O)	100.9 ± 8.5	95.4 ± 3.6	NS
BFR (L/min)/% CO	2.1 ± 0.3/30.8 ± 12	1.3 ± 0.3/13.3 ± 10	.001
O ₂ transfer (mL/min)	179.8 ± 48	123.7 ± 51.9	NS
AVCO ₂ R (mL/min)	340 ± 28	223 ± 26	.05

TV, Tidal volume; NS, not significant; RR, respiratory rate; MV, minute volume; PIP, peak inspiratory pressure; PEEP, positive end-expiratory pressure; PaO₂/Fio₂, arterial oxygen tension/fraction of inspired oxygen; Paco₂, arterial carbon dioxide tension; LC, lung compliance [(TV/Plateau pressure) – PEEP]; BFR, blood flow rate through the device; CO, cardiac output; AVCO₂R, arteriovenous carbon dioxide removal.

tery and vein) circulation as the site of implantation, both of which are eventually inadequate for long-term use or in ambulatory patients. In this sense the axillary vessels might represent a valid alternative and provide several advantages. First, the subclavian or axillary vein is a routine cannulation site in an ambulatory setting. Second, the axillary artery is rarely and less diseased than the iliofemoral vessels, benefits from a rich collateral blood flow that reduces the hazards of ischemia in the upper extremity, and has already been beneficial for different cardiac open procedures²⁻⁶ and once

for extracorporeal respiratory life support.²⁰ Moreover, it can be safely cannulated either directly or through end-to-side graft interposition.⁶

In the present study we investigated the safety and efficacy of the axillary vessels as a vascular access site for partial extracorporeal respiratory support. The presented results demonstrate that the iLA connected through an end-to-side graft interposition to the axillary artery and subclavian or axillary vein provides respiratory support similar to direct cannulation during apneic ventilation. This finding might have various different clinical advantages; for example, tunneled and high-volume cannulae placed over longer periods of time are more likely to dislodge or induce brachiovascular injuries, can lead to infectious complications, and are less patient friendly. On the contrary, cannulation of a graft attached to the axillary artery might avoid the technical pitfalls described clinically with direct cannulation^{5,6} and greatly simplifies decannulation or device exchange. Indeed, the only disadvantages appear to be the extra time required at the onset to anastomose the graft to the artery (approximately 20 minutes), the occasional bleeding from the suture line, and, last but not least, that the use of the prosthetic graft anastomosed to the artery is more expensive than the provided cannulae and might become infected. However, these pitfalls could be avoided by placing the arterial cannula into a saphenous vein graft²¹ that had been previously anastomosed end-to-side to the axillary vessels, and this would result not only in no extra cost but also in an unlimited availability and more hemostasis.

Axillary arterial cannulation powered significantly ($P = .001$) more blood flow (2.1 ± 0.3 vs 1.3 ± 0.3 L/min) through the iLA than graft interposition, and this might be partly explained by the technique itself and because we did

Figure 4. Evolution of bronchoalveolar cytokines during initial ventilation (0-4 hours) and apneic ventilation (4-8 hours). The initial increase of tumor necrosis factor α (TNF- α ; $P = .05$), interleukin 6 (IL-6; $P < .005$), and interleukin 8 (IL-8; $P < .05$) concentrations during the first phase attenuated to normal values during apneic ventilation and use of the interventional lung assist device. Normal concentrations in our laboratory are as follows: TNF- α , 25 to 120 μ g/mL; IL-6, less than 39 μ g/mL; and IL-8, less than 62 μ g/mL.

clamp the artery distal to the cannulation site during investigation. However, a long-term direct arterial cannulation is unfeasible clinically, and an arterial graft interposition would have the advantage that it would still permit optimal distal arm perfusion, thus minimizing the risks of ischemic injury of the arm and, ultimately, avoiding a compartment syndrome on reperfusion⁵ and allowing more hemodynamic stability because only about less than 15% of the CO would be diverted to it. In any case this blood flow difference did not affect the iLA graft-driven AVCO₂R (223 ± 26 L/min) capacity or O₂ transfer, which are in line with the basal exchange requirements of an adult patient (200 and 240 mL/min, respectively, at a CO of 4-6 L/min). Because no other respiratory variables were different during apneic ventilation, one might speculate that graft interposition in the axillary vessels could provide peripheral gas exchange in a variety of clinical situations in which hemodynamic stability and early mobilization, ambulation, and extubation are desired.

The bronchoalveolar lavage cytokine responses observed in this study cannot be ultimately interpreted because of the small samples. However, one might speculate that the rapid attenuation of the inflammatory response (IL-6, IL-8, and TNF- α) observed during the initial ventilation strategy can be explained by the fact that the combination of apneic (TV, 1-2 mL/kg) ventilation and iLA affords a better lung protection and minimizes more lung overdistention, recruitment, and derecruitment than the ARDSnet ventilation modulus (TV, 6-12 mL/kg).¹⁷ This in turn confirms previous human studies in which low (6 mL/kg) TV ventilation was associated with a more rapid attenuation of the inflammatory response in patients with acute lung injury and ARDS.^{22,23}

In conclusion, the present study demonstrates that the axillary vessels are a safe cannulation site for extracorporeal peripheral partial respiratory support and that the iLA, once attached to this paracorporeal site, provides, with minimal surface area (1.3 m²) and shunt blood flow (approximately 30% of the CO) requirements, an almost total removal of the produced CO₂ and permits near-static or apneic ventilation (TV, 1-2 mL/kg). The minimal shunt blood flow (<15% of the CO) requirements, similar gas exchange capability, and improved hemodynamic stability of graft interposition make this vascular access modality clinically more attractive than direct cannulation and might represent a further step toward ambulatory long-term AL support.

References

- Lick SD, Zwischenberger JB. Artificial lung: bench toward bedside. *ASAIO J*. 2004;50:2-5.
- Sabik JF, Lytle BW, McCarthy PM, Cosgrove DM. Axillary artery: an alternative site of arterial cannulation for patients with extensive aortic and peripheral vascular disease. *J Thorac Cardiovasc Surg*. 1995;109:885-91.
- Baribeau YR, Westbrook BM, Charlesworth DC, Maloney CT. Arterial inflow via an axillary artery graft for the severely atheromatous aorta. *Ann Thorac Surg*. 1998;66:33-7.
- Neri E, Massetti M, Capannini G, et al. Axillary artery cannulation in type A aortic dissection operations. *J Thorac Cardiovasc Surg*. 1999;118:324-9.
- Sinclair MC, Singer RL, Manley NJ, Montesano RM. Cannulation of the axillary artery for cardiopulmonary bypass: safeguards and pitfalls. *Ann Thorac Surg*. 2003;75:931-4.
- Sabik JF, Nemeh H, Lytle BW, et al. Cannulation of the axillary artery with a side graft reduces morbidity. *Ann Thorac Surg*. 2004;77:1315-20.
- 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.
- Matthais G. New technologies for respiratory support. *Perfusion*. 2003;18:245-51.
- Fischer S, Simon AR, Welte T, et al. Bridge to lung transplantation with the novel pumpless interventional lung assist device NovaLung. *J Thorac Cardiovasc Surg*. 2006;131:719-23.
- Macchiarini P, Mazmanian GM, De Montpreville V, et al. Experimental tracheal and tracheoesophageal transplantation. *J Thorac Cardiovasc Surg*. 1995;110:1037-46.
- Wu ZJ, Gartner M, Litwak KN, Griffith BP. Progress toward an ambulatory pump lung. *J Thorac Cardiovasc Surg*. 2005;130:973-8.
- Alpard SK, Zwischenberger JB, Tao W, Deyo DJ, Bidani A. Reduced ventilator pressure and improved P/F ratio during percutaneous arteriovenous carbon dioxide removal for severe respiratory failure. *Ann Surg*. 1999;230:215-24.
- Zwischenberger JB, Alpard SK, Tao W, Deyo DJ, Bidani A. Percutaneous extracorporeal arteriovenous carbon dioxide removal improves survival in respiratory distress syndrome: A prospective randomized outcomes study in adult sheep. *J Thorac Cardiovasc Surg*. 2001;121:542-51.
- Conrad SA, Zwischenberger JB, Grier LR, Alpard SK, Bidani A. Total extracorporeal arteriovenous carbon dioxide removal in acute respiratory failure: a phase I clinical study. *Intensive Care Med*. 2001;27:1340-51.
- Wang D, Lick S, Alpard SK, et al. Toward ambulatory arteriovenous CO₂ removal: initial studies and prototype development. *ASAIO J*. 2003;49:564-7.
- Zwischenberger JB, Conrad SA, Alpard SK, Grier L, Bidani A. Percutaneous extracorporeal arteriovenous CO₂ removal for severe respiratory failure. *Ann Thorac Surg*. 1999;68:181-7.
- The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342:1301-8.
- Wang D, Lick SD, Campbell KM, et al. Development of ambulatory arterio-venous carbon dioxide removal (AVCO₂R): the downsized gas exchanger prototype for ambulation removes enough CO₂ with low blood resistance. *ASAIO J*. 2005;51:385-9.
- Go T, Altmayer M, Richter M, Macchiarini P. Decompressing manubriectomy under apneic oxygenation to release the median thoracic outlet compartment in Bechterew disease. *J Thorac Cardiovasc Surg*. 2003;126:867-9.
- Yolota K, Fujii T, Kimura K, Toriumi T, Sari A. Life-threatening hypoxemic respiratory failure after repair of acute type A aortic dissection: successful treatment with venoarterial extracorporeal life support using a prosthetic graft attached to the right axillary artery. *Anesth Analg*. 2001;92:872-6.
- Loubani M, Parmar JM, Clones NW, Abid Q. Use of saphenous vein graft in axillary artery cannulation. *Ann Thorac Surg*. 2004;78:1838-9.
- Ranieri VM, Suter PM, Tortorella C, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome. *JAMA*. 1999;282:54-61.
- Parsons PE, Eisner MD, Thompson T, et al. Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. *Crit Care Med*. 2005;33:1-6.

Discussion

Dr Michael S. Mulligan (*Seattle, Wash*). This work adds to the literature underscoring the point that pumpless atrioventricular support of gas exchange has a place in the care of the critically ill. CO₂ removal and O₂ transfer are physiologies that can be uncoupled and supported independently. I have several questions. The most consistent benefit demonstrated in the experience with the Affinity and NovaLung devices relates to improved outcomes with CO₂ removal in patients with ARDS. Entirely adequate rates of CO₂ removal are achievable with device flows as low as 800 to 1000 mL or 10% to 15% of CO. Therefore why is it necessary or desirable to divert 30% to the CO through the device?

The oxygen transfer rate across this device seems high. One would assume that to achieve that, the arterial blood inflow must be desaturated in the range of 65% or so. However, the low-frequency positive-pressure ventilation that you used and not apneic ventilation, in fact, is highly effective at maintaining oxygenation, as per the work of Kolobo. One would expect saturations in that paradigm in the range of 85% to 95%. Can you explain how such high levels of O₂ transfer were achieved across this device? If flows adequate for CO₂ removal are attainable with small percutaneous cannulae, what is the real advantage to axillary arterial dissection and potential grafting in what is likely to be a critically ill and nonambulatory population? Finally, the duration of 4 hours on the device might not reflect a clinically useful interval. Similarly, comparing bronchoalveolar lavage cytokine content from animals that had direct versus graft cannulation does not assess the inflammatory response attributable to pumpless support of gas exchange itself. Do you have any data from animals before and after the institution of support, allowing each animal to serve as its own control? Thank you for sending me the manuscript and for continuing to help advance this important field.

Dr Macchiarini. As senior author, I take the privilege to answer the questions. Thank you for the questions. Thirty percent of the CO is the normal range of the output that you might power through the iLA when you put it on the femoral vessels, and this has been used in almost more than 1000 patients thus far. Therefore what we decided is to have an alternative, to in fact have less CO through the iLA and, as a matter of fact, through the graft interposition. We were able to flow only 10% of the CO, which was approximately 1.2 L/min.

I cannot remember all the questions, but the last one was why we chose this limited time of investigation. First of all, there are articles suggesting that 4 hours is enough at the given tidal volume of 10 to 12 mL/kg to induce a lung injury, and therefore we used

that time frame. Thereafter, the second 4 hours of observation time was simply because there is clinical evidence that the lung cytokine response induced in patients with ARDS can be reversed within 3 days, and probably you, better than I, know that in an animal setting this time corresponds to the 3 days in the clinical issue.

I cannot remember the other questions.

Dr Joseph B. Zwischenberger (*Galveston, Tex*). There are a couple of key points that the discussant brought up that still need to be addressed. First of all, arteriovenous CO₂ gas exchange has been existent for about 10 to 15 years, and many of us have been working on this, and, as you alluded to, there is more than a 1000-patient experience in Europe with the NovaLung. However, there are 2 camps. One camp is the high-flow camp that wants to get 20% to 30% of CO and access the femoral vessels with a large cannula (18F to 20F), and they have about a 25% complication rate with vascular access. Then there is the low-flow camp, to which I belong, that goes for about 10% to 15% of CO and can use a 12F to 14F cannula in which the complication rate is less than 5%. If you use the low-flow strategy, you can accomplish total CO₂ removal, but you do not contribute significantly to oxygenation and therefore rely on the native lungs. The key question in this presentation is why do you report such large O₂ transfer numbers, and why do you think such large flows are necessary, especially in an animal that has normal native lungs and can accomplish oxygenation without difficulty?

Dr Macchiarini. Thank you, Joe.

The issue with the cannula, and you know better than I, is not the volume. It is the resistance that they have. Therefore we might talk about that in a later session. However, the O₂ transfer that we had is probably because, at odds with your studies, we use an FIO₂ of 1 and not lower because we did not want to have 2 different parameters change in the same study, and this might explain why we had more. Therefore because oxygenation was done through the native lungs and not through the oxygenator, I think this could probably explain this, keeping the FIO₂ at 100% at the second phase, the high oxygen transfer.

Dr Mulligan. Are you saying that your O₂ transfer was attributable to the native lung and not the device? That was not clear in the manuscript. Therefore that is what you are saying, that you supported CO₂ scrubbing and O₂ transfer independently, one with the device and one with the native lung with low-frequency positive-pressure ventilation? Is that correct?

Dr Macchiarini. Exactly.

Figure E1. Photograph showing graft interposition to the axillary artery and vein in the right deltopectoral groove and their connections to the rubber connectors and the interventional lung assist device.

Figure E2. Comparison of the type of vascular access and blood flow perfusing the interventional lung assist device.

TABLE E1. Pigs hemodynamic during initial ventilation (4 hour) and apneic ventilation under interventional lung assist device support (4 hours)

Variables	Initial ventilation without iLA support	Apneic ventilation with iLA support	P value
CO (L/min)	6.8 ± 3	7.7 ± 3	NS
MAP (mm Hg)	97.2 ± 17.7	79.7 ± 11.3	.001
MPAP (mm Hg)	28.7 ± 4.7	41.1 ± 6.5	.001
SVR (dyne/cm ⁵)	1072.6 ± 370.6	721.7 ± 383.4	.001
PVR (dyne/cm ⁵)	151.1 ± 137.5	203.1 ± 78.9	NS
PCWP (mm Hg)	19.7 ± 3.9	23.3 ± 4	.001
CVP (mm Hg)	18.4 ± 3.3	23 ± 4.6	.01
DPmax (mm Hg)	689.7 ± 240.8	1025.8 ± 289.4	.001
ELWI (mL/kg)	10.6 ± 5.3	12.9 ± 6.2	.01
ELWV (mL)	533.2 ± 99.1	614.2 ± 214.6	NS

iLA, Interventional lung assist device; CO, cardiac output; NS, not significant; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure; DPmax, ventricular contractility; ELWI, index extra lung volume water; ELWV, extra lung water volume.

TABLE E2. Hemodynamic differences between direct cannulation or through graft interposition during apneic ventilation and interventional lung assist device support

Variables	Direct cannulation	Graft interposition	P value
CO (L/min)	6.8 ± 2.8	9.8 ± 2.7	.02
MAP (mm Hg)	77.3 ± 11.2	79.3 ± 13.8	NS
MPAP (mm Hg)	41 ± 6.9	44 ± 4.0	NS
SVR (dyne/cm ⁵)	912.2 ± 457.8	465.6 ± 213.4	.03
PVR (dyne/cm ⁵)	246.9 ± 65.5	168.1 ± 81.3	.03
PCWP (mm Hg)	23.4 ± 5.6	24 ± 4.7	NS
CVP (mm Hg)	23 ± 6.2	23.5 ± 4.2	NS
DPmax (mm Hg)	1215.4 ± 252.1	812.7 ± 200.5	.01
ELWI (mL/kg)	13.1 ± 7.7	13.1 ± 5.1	NS
ELWV (mL)	748.3 ± 165.3	616.1 ± 176.2	NS

CO, Cardiac output; MAP, mean arterial pressure; NS, not significant; MPAP, mean pulmonary arterial pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure; DPmax, ventricular contractility; ELWI, index extra lung volume water; ELWV, extra lung water volume.