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Extracorporeal pumpless interventional lung assist in clinical practice: determinants of efficacy.

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Abstract

Respiratory acidosis can become a serious problem during protective ventilation of severe lung failure. A pumpless arterio-venous interventional lung assist (iLA) for extracorporeal carbon dioxide removal has been used increasingly to control critical respiratory situations. The present study sought to evaluate the factors determining the efficacy of iLA and calculate its contribution to gas exchange.

In a cohort of 96 patients with severe ARDS, hemodynamic parameters, oxygen consumption and carbon dioxide production as well as gastransfer through the iLA were analysed.

Our measurements demonstrated a significant dependency of blood flow via the iLA – device on cannula size (1.59 +/- 0.52 l/min for 15 Fr, 1.94 +/- 0.35 l/min for 17 Fr, and 2.22 +/- 0.45 l/min for 19 Fr, $p < 0.001$) and on mean arterial pressure. The oxygen transfer capacity averaged 41.7 +/- 20.8 ml/min, carbon dioxide removal was 148.0 +/- 63.4 ml/min. Within two hours of iLA treatment, PaO_2/FiO_2 increased significantly and a fast improvement of $PaCO_2$ and pH was observed.

Interventional lung assist eliminates approximately 50 percent of calculated total carbon dioxide production with rapid normalisation of respiratory acidosis. Despite limited contribution to oxygen transfer it may allow a more protective ventilation in severe respiratory failure.

Number of words: 199

Keywords:

Interventional lung assist (iLA), extracorporeal carbon dioxide removal, oxygen transfer, acute respiratory distress syndrome

Introduction

The successful application of prolonged extracorporeal oxygenation in a young patient with posttraumatic acute respiratory failure had been reported more than 35 years ago (1). As technical requirements were very demanding, use of early extracorporeal membrane oxygenation (ECMO) remained limited to few experienced centres. Two controlled prospective clinical studies in adults with ARDS could not demonstrate a significant survival advantage (2, 3). The need for systemic anticoagulation due to the large foreign surface of early devices led to severe bleeding complications in these trials. Therefore ECMO – treatment in adults did not gain much acceptance in the past. Animal experiments proved in the 1980s that total extracorporeal carbon dioxide removal was possible with a pumpless artery-to-vein shunt (4). Optimized technical design, especially the development of low-resistance oxygenators made the use of pumpless devices in humans possible. Early clinical results of small series of patients were encouraging (5-8) and meanwhile interventional lung assist (iLA) is commercially available. Prospective controlled trials, which are still lacking, have been demanded (9) and have commenced recently.

Low tidal volume ventilation is today common practice in the treatment of acute lung failure, often accompanied by hypercapnia and respiratory acidosis. In this context extracorporeal carbon dioxide elimination could be an opportunity to avoid potentially dangerous decreases in pH.

Up to now there have been no investigations analysing systematically the physical and hemodynamic factors that determine the efficacy of iLA in clinical use. It is not exactly known what effective contribution iLA has in carbon dioxide removal and oxygen transfer in relation to pulmonary gas transfer. In order to address these

questions we analysed the hemodynamic and gas exchange parameters during iLA treatment in patients with acute respiratory distress syndrome (ARDS).

Methods

Technical data and implantation of iLA

Between 1996 and 2007 a total of 168 patients have been treated with an interventional lung assist (iLA, NovaLung GmbH, Talheim, Germany) in our institution. Technical data of iLA as well as the process of implantation has been described in detail recently. Some of the dataset used for this study has been included in the patient outcome data Bein et al have reported previously (8), therefore the presentation of patient outcome data is not intention of this study. In principle iLA is an artificial arterio-venous shunt with an interposed membrane oxygenator (Figure 1). After ultrasonographic measurement of the femoral artery and the contralateral femoral vein the cannulas are implanted in Seldinger technique. The size of the arterial cannula has to be selected smaller than the diameter of the vessel to ensure sufficient peripheral flow. The venous cannula is generally 2 French (Fr) larger to achieve a low flow resistance. The primed oxygenator that has a total exchange surface of 1.3 m² and a very low inherent resistance, is then connected to the flushed cannulas. The membrane of the oxygenator is made of polymethylpentene with the advantage of no plasma leakage. As the whole system is coated with heparin, a strong systemic anticoagulation is not necessary and an activated partial thromboplastin time (aPTT) of 1.5 of normal is generally sufficient. Oxygen is used as sweep gas with a flow of up to 12 l/min. The blood flow through the iLA is generated by the arterio-venous pressure difference, so that a pump is not needed. Prerequisite for the employment of iLA is a normal left ventricular function with a mean arterial pressure of more than 70 mm Hg. In patients with cardiac insufficiency or peripheral atherosclerosis the use of iLA is contraindicated.

Calculation of oxygen and carbon dioxide exchange

Altogether 96 out of 168 patients had been equipped for clinical reasons with a pulmonary artery catheter (PAC, Swan Ganz Catheter, Edwards Life Sciences, Irvine, US) and in these total body oxygen consumption and carbon dioxide production were calculated. Patients were suffering from severe ARDS (PaO_2/FiO_2 = 69 +/- 29 mm Hg, $PaCO_2$ = 66 +/- 25 mm Hg, positive endinspiratory pressure = 38 +/- 6 cm H_2O, positive endexspiratory pressure = 16 +/- 5 cm H_2O, tidal volume 458 +/- 131 ml). By measuring the content of oxygen and carbon dioxide before and after the iLA in parallel, we could calculate the relative contribution of iLA to total gas transfer via the lung. Measurements were done before iLA start, 2 hours, 24 hours and 48 hours after iLA implantation, before stop of iLA and one day after iLA treatment.

Oxygen content (C_aO_2) was calculated according to the following formulas:

$C_aO_2 = (Hb \times 1.31 \times S_aO_2) + (P_aO_2 \times 0.003)$

(C_aO_2 = oxygen content, Hb = hemoglobin, S_aO_2 = arterial oxygen saturation, P_aO_2 = arterial partial pressure of oxygen).

Oxygen delivery capacity (DO_2) per minute:

$DO_2 = C_aO_2 \times CO \times 10$

Analogous the oxygen content of mixed venous blood (C_vO_2) was determined. The difference between arterial and mixed venous oxygen delivery capacity gives the oxygen consumption (VO_2), which is equivalent to the oxygen transfer via the lungs:

$VO_2 = (C_aO_2 – C_vO_2) \times CO \times 10$

The oxygen transfer capacity of the iLA was calculated by multiplying the difference between oxygen content pre iLA (= C_aO_2) and post iLA with the blood flow:

$\text{Oxygen transfer}_{iLA} = (C_{post\ iLA}O_2 - C_aO_2) \times \text{bloodflow}_{iLA} \times 10$

VO_2 after implantation of iLA is calculated as the combination of natural lung oxygen transfer and membrane lung oxygen transfer:

$VO_2 = (C_aO_2 - C_vO_2) \times CO \times 10 + (C_{post\ iLA}O_2 - C_aO_2) \times bloodflow_{iLA} \times 10$

Cardiac output (CO) was determined with the thermodilution method, and the blood flow through the iLA was measured by ultrasound (NovaFlow Ultrasonic Flowmeter, NovaLung GmbH, Talheim, Germany). Blood gas analysis was done with Radiometer 700 and 615 (Radiometer, Copenhagen, Denmark). The carbon dioxide content of plasma was calculated by these analysers with consideration of the Henderson – Hasselbalch equation, measured plasma PCO_2 and pH. Similar to the C_aO_2 it was measured at three sites: arterial = pre iLA (C_aCO_2), post iLA ($C_{postiLA}CO_2$) and mixed venous blood (C_vCO_2). With known CO and blood flow of the iLA, approximated total carbon dioxide production and carbon dioxide removal by the lungs and by the iLA device was calculated.

Approval for this study was obtained from the Ethics Committee of the University of Regensburg.

Statistical Analysis

Variables are reported as means +/- standard deviations, if not told otherwise, and were compared by Student-t-test. The relationships between dependent variables were evaluated by ANOVA on rank and linear regression analysis. A p-value of less than 0,05 was considered statistically significant. For statistical analysis, we used SPSS version 15.0 (SPSS Inc, Chicago, IL) and SigmaPlot version 9.0 (Systat Software Inc, San Jose, California).

Results

Blood flow through the iLA

In total 326 blood flow measurements taken in 96 patients at different times were evaluated. 17 measurements were carried out in arterial 15 Fr cannulas, 175 measurements in arterial 17 Fr cannulas, and 134 measurements in arterial 19 Fr cannulas. Blood flow through the iLA averaged 1.59 +/- 0.52 l/min with 15 Fr cannulas. With 17 Fr cannulas a blood flow of 1.94 +/- 0.35 l/min and with 19 Fr cannulas a blood flow of 2.22 +/- 0.45 l/min was measured ($p < 0.001$).

Mean arterial pressure (MAP) was 85.0 +/- 16.6 mm Hg and was similar between the three groups with different cannula size. In analyzing the dependency of blood flow through the iLA upon MAP we found a linear correlation between both variables, which is depicted in Figure 2 ($r = 0.53$, $p < 0.01$).

Cardiac output (CO) was documented simultaneously with 262 iLA – blood flow measurements and was on an average 9.1 +/- 2.6 l/min for all patients (mean norepinephrine dose: 1.67 +/- 2.18 mg/h). Patients with a 19 Fr cannula had a higher CO (9.6 +/- 2.6 l/min) than patients with a 17 Fr cannula (8.9 +/- 2.7 l/min, $p < 0.05$) or a 15 Fr cannula (8.5 +/- 2.0 l/min). Figure 3 shows a significant ($r = 0.22$, $p < 0.01$), but less obvious correlation between CO and blood flow through the iLA.

CO rose from 8.76 +/- 2.6 l/min pre iLA implantation to 9.45 +/- 2.6 l/min two hours after implantation ($p < 0.001$). The Horowitz index (PaO_2/FiO_2) increased rapidly from 68.9 +/- 29.9 mm Hg pre implantation to 93.7 +/- 48.4 mm Hg two hours post implantation of the device ($p < 0.001$).

Effects on oxygen transport

Taken together all 326 measurements, the oxygen transfer via the iLA averaged 41.7 +/- 20.8 ml/min. During treatment the PO_2 at the Novalung – inlet was 83 +/- 26 mm

Hg and 500 +/- 85 mm Hg at the outlet on an average. Table 1 summarizes the results and factors that influence oxygen transfer 2 hours after iLA implantation, at day 1 and day 2 and before removal. Oxygen transfer over time decreases and was calculated with 33.6 +/- 11.7 ml/min shortly before removal of iLA ($p < 0.005$ to 2 hours). This reflects both a significantly lower blood flow and a higher arterial oxygen saturation. The oxygen transfer capacity of the iLA depends on the arterial oxygen saturation ($r = -0.78$), the blood flow through the device ($r = 0.43$) and the hemoglobin content of blood ($r = 0.23$, each $p < 0.01$) (Figure 4a-c). A slight correlation was found to sweep gas flow through the device ($r = 0.22$, data not shown). Therefore, oxygen transfer is increased in low arterial oxygen saturation, higher blood flow through the system and higher hemoglobin content of blood.

Arterial oxygen delivery capacity (DO_2) rose from 1024 +/- 338 ml/min before iLA treatment to 1187 +/- 350 ml/min 2 hours after iLA implantation ($p < 0.001$). The total oxygen consumption (VO_2) was measured altogether 272 times and was calculated with 295.4 +/- 97.8 ml/min for all patients. We did not observe a significant change of VO_2 over time. In comparing simultaneously VO_2 and oxygen transfer through the iLA, the relative contribution of the device to total calculated VO_2 can be predicted. On an average we found a proportion of 16.0 +/- 8.3 %, which iLA contributes to total calculated oxygen transfer. Pre removal it decreased to 10.7 +/- 2.4 %.

Effects on carbon dioxide elimination and pH

Before iLA start all patients had a pronounced hypercapnia with a $PaCO_2$ of 66.7 +/- 25 mm Hg. Two hours after iLA implantation $PaCO_2$ decreased to 39.5 +/- 12.1 mm Hg ($p < 0.001$), and declined further to 35.8 +/- 7.6 mm Hg ($p < 0.005$) 24 hours later. $PaCO_2$ then remained stable during continuation of iLA and increased to 49.8 +/- 14.7 mm Hg after removal of iLA ($p < 0.001$).

Taken all measurements during iLA treatment together (n = 243) PCO_2 averaged 37.5 mm Hg at the Novalung – inlet and 23.5 mm Hg at the – outlet. The device removed 148.0 +/- 63.4 ml/min CO_2, which equals about 50 % of the calculated total CO_2 production of 291 +/- 124 ml/min. The capacity of the iLA to remove CO_2 increased with higher $PaCO_2$ ($r = 0.34$, $p < 0.01$), higher sweep gas flow ($r = 0.27$, $p < 0.01$) and with higher blood flow through the device ($r = 0.23$, $p < 0.01$) (Figure 5a-c). No correlation was found to hemoglobin content of blood (data not shown). We saw a CO_2 elimination of 135.6 +/- 30.2 ml/min with 15 Fr cannulas, of 144.1 +/- 68.6 ml/min with 17 Fr cannulas, and of 154.3 +/- 58.1 ml/min with 19 Fr cannulas ($p < 0.001$).

The reduction of $PaCO_2$ resulted in a rapid and sustained normalization of respiratory acidosis. The pH level rose within two hours after iLA implantation from 7.24 +/- 0.13 to 7.41 +/- 0.12 ($p < 0.001$) (Figure 6). During extracorporeal CO_2 removal the pH remained stable. After termination of iLA the pH level fell significantly to 7.36 +/- 0.09 ($p < 0.001$).

Discussion

The current study is the first to systematically investigate the efficacy of iLA on oxygen transfer capacity and carbon dioxide removal in a large human study population with severe ARDS. It provides detailed information regarding the factors that influence iLA performance and supports the use of iLA as a highly effective method in severe lung injury with hypercapnia and respiratory acidosis.

Blood flow through the iLA

Blood flow through the iLA depends on both total inherent resistance of the device and on the pressure difference across the system. The flow resistance of the oxygenator is low and causes a pressure drop of about 10 mm Hg at a blood flow of 2 l/min. Thus the flow resistance of the cannulas is the predominant factor of total resistance of the device. According to the Hagen – Poiseuille equation blood flow is most strongly influenced by the diameter of the cannula:

blood flow = $\pi \Delta p \, r^4 / (8 \, l \, \eta)$

(Δp = pressure difference, l = length of cannula, η = viscosity, r = radius of cannula).

Our measurements in vivo confirmed these considerations as well as animal data previously published (10, 11). An increase in cannula size of 2 Fr resulted in an additional flow of about 300 ml/min. This means that using a 15 Fr arterial cannula a blood flow of about 1.6 l/min, using a 17 Fr cannula a blood flow of about 1.9 l/min and using a 19 Fr cannula a blood flow of about 2.2 l/min can be achieved at a MAP of 85 mm Hg.

The second important factor for blood flow through the device is the difference of pressure before (mean arterial pressure, MAP) and after the system (central venous pressure, CVP). As the CVP fluctuates within close limits, MAP is the decisive variable for blood flow and we could demonstrate a strong correlation between MAP

and blood flow through the iLA. In clinical practice MAP is the only relevant parameter for iLA flow at a given cannula size that can be influenced.

Cardiac output (CO) per se is for blood flow through the iLA not important. Blood flow amounted to 20 % of CO with 15 Fr cannulas and up to 25 % of CO with 19 Fr cannulas on average. Comparable numbers have been found in animal experiments (12, 13). In patients with lower CO and normal MAP due to high systemic vascular resistance, a higher proportion of CO is diverted through the iLA, which may amount to more than 30 % of CO (Figure 7). In most patients a significant increase of CO after start of iLA was observed. This can be explained by two mechanisms: firstly by creating an artificial low resistance arterio–venous shunt and secondly by rapid correction of acidosis resulting in improved vasotonus and possibly cardiac pump function.

Effects on oxygen transport

The average oxygen transfer capacity of the iLA of 42 ml/min that we measured in our patients matches well with animal data presented by Zick et al (12) and Brederlau et al (14). Another study mentioned an oxygen transfer of up to 225 ml/min (15), which does not correspond to our results and is physically not plausible. The oxygen transfer capacity of the iLA is mainly limited by the fact that arterial blood, already well oxygenated, is fed into the device, and therefore only a small additional amount of oxygen can be bound to hemoglobin.

Most studies in humans described a significant rise in PaO_2 after implementation of iLA (6-8, 16-18). The patients we evaluated had a PaO_2/FiO_2 of 69 mm Hg before iLA, which increased to 94 mm Hg within 2 hours ($p < 0.001$). This rise in PaO_2 , according to the law of Dalton, is caused mainly by a reduction of alveolar PCO_2 and a concommitant increase in alveolar PO_2. Because PaO_2 is an inaccurate parameter

for oxygen supply, we calculated the arterial oxygen delivery DO_2. The rise of DO_2 from 1024 ml/min before iLA treatment to 1187 ml/min 2 hours after iLA implantation ($p < 0.001$) was caused by a small increase of CO and a higher CaO_2. However it is important to consider that part of CO is diverted through the artificial a-v shunt of the iLA and therefore does not participate in peripheral perfusion. The effective DO_2, which is available for supply of the organism, may even be smaller than prior to iLA implantation. Particularly this is to be expected in patients with a low CO and high dose vasopressors, when a comparably high proportion of CO will flow through the iLA (Figure 7). In patients with reduced CO, therefore, iLA therapy is probably not indicated. Brunston et al analysed the perfusion of organs at different blood flow rates through a pumpless extracorporeal membrane oxygenator using colored microspheres and reported a mild reduction in endorgan perfusion (19). However at a maximal shunt flow of 25 % of CO a reduced perfusion of the cerebrum of up to 26 % and of skeletal muscle of up to 43 % was observed.

Total oxygen consumption (VO_2) of our patients was calculated with 295 ml/min. This is comparable to former studies in critically ill patients (20, 21). At the beginning of extracorporeal therapy the oxygen transfer through the iLA accounted for 16 % of VO_2, at the end of iLA treatment the oxygen transfer amounted to 11 % of VO_2. These results are in accordance with animal experiments, which found the relative share of iLA treatment of total VO_2 to be between 12.5 % and 19.5 % (12, 14). However, as we only did a blood phase calculation of oxygen consumption and carbon dioxide production, the metabolic rate of the lung itself is not taken into consideration. Therefore, the relative numbers may be an overestimation.

After implementation of iLA treatment mixed venous oxygen saturation (SvO_2) rose within 2 hours from 62 % to 74 % ($p < 0.001$). The consequences of this increase of

oxygen supply in the pulmonary artery in combination with a rapid normalization of the pH have not yet been investigated in humans.

Effects on CO_2 elimination

Gattinoni et al had demonstrated 20 years ago using a pumpdriven device that extracorporeal carbon dioxide removal can allow a more protective ventilation, albeit he was not able to show a survival benefit (22). As the necessary blood flow for clinically significant extracorporeal carbon dioxide removal is relatively small, the application of a pumpless arterio – venous system with a low inherent flow resistance is possible. Brunston et al proved that a near-total CO_2 elimination can be done with such a system in sheep (10, 23). We saw a rapid initial decrease of $PaCO_2$ in our patients from 67 mm Hg pre iLA to 40 mm Hg two hours post iLA implementation. During the following 24 hours we observed a further, but smaller reduction in $PaCO_2$. This is probably explained by the transport and storing kinetics of CO_2, which is transported in physical solution, protein bound and in the form of bicarbonate. The physically dissolved proportion, which can be measured as $PaCO_2$, can be eliminated quickly. However, the predominant part of CO_2 is stored and transported as bicarbonate ions, which have to be dissociated within red blood cells in the presence of carbonic anhydrase. Due to the liberation of bicarbonate out of slow compartments it takes several hours until a stable equilibrium of the CO_2 level is readjusted.

This biphasic elimination kinetic of CO_2 is mirrored in several clinical reports (8, 16, 24, 25). The quantity of CO_2, which was removed through the iLA in our patients, was 148 ml/min and accounted for approximately 50 % of total calculated CO_2 production. Conrad et al (26) and Zwischenberger et al (24) reported in their small clinical trials on 8 and 5 patients a complete respectively 70 percent removal of CO_2 with the use of an Affinity oxygenator. This oxygenator has a surface area of 2.5 m², which is

almost double the size of the Novalung oxygenator. With arterial 12 Fr cannulas they reached a maximal blood flow of one liter per minute through the device and found a CO_2 removal of more than 100 ml/min, measured at the outlet of the sweep gas flow and in the exhaled ventilator gas. This differs to our method to determine the CO_2 removal, which was done by calculating the CO_2 content of blood before and after the iLA and the lungs, respectively. By using the Henderson Hasselbalch equation the CO_2 content is calculated by the blood gas analyzer with known pH, bicarbonate, hemoglobin and PCO_2. The calculated total CO_2 production of 291 ml/min in our patients corresponds well to the measured VO_2 of 296 ml/min. In animal studies an extracorporeal CO_2 elimination of 62 – 104 ml/min in pigs (13) and up to 120 ml/min in sheep (23, 27) has been reported. The amount of removed CO_2 depends closely on $PaCO_2$ and sweep gas flow according to our data. Conrad et al observed in their analysis of contributing factors to carbon dioxide transfer a significant regression to $PaCO_2$, pH, sweep gas flow and blood flow through the device (26).

Extracorporeal CO_2 removal resulted in a rapid improvement of respiratory acidosis. A retrospective clinical trial has demonstrated that with rising pH the dose of vasopressors could be diminished and the invasiveness of mechanical ventilation was decreased (8). In large animal ARDS models , extracorporeal CO_2 – removal enabled a less invasive ventilation with reduced levels of inflammatory cytokines (28, 29).

Conclusion

In conclusion we found that an average extracorporeal CO_2 – elimination of about 50 % of total production is possible with the iLA device in patients with ARDS. To achieve this, the use of arterial cannulas of 15 Fr or 17 Fr size is sufficient. Larger cannulas may cause an undesirably large a – v shunt fraction and carry a higher risk

of vascular complications, as has been reported previously (8). In some patients with low body weight and less severe respiratory acidosis even 13 Fr cannulas may be suitable but could possibly result in earlier occlusion of the oxygentor due to lower blood flow. A rapid decrease in $PaCO_2$ and normalization of pH may allow a more protective ventilation with even lower tidal volumes and therefore possibly a reduction of ventilator – induced lung injury. ILA does improve arterial oxygenation and transfers about 45 ml/min of oxygen, however this not necessarily means that oxygen delivery is increased as well. According to our data, ILA therefore should probably not be used in patients with most severely impaired oxygenation or in patients with reduced cardiac output. Whether the survival of acute respiratory failure can be improved with the implementation of iLA as a method to reduce invasiveness of ventilation, needs further study through controlled clinical trials.

References

1. Hill JD, O´Brien TG, Murray JJ, Doutigny L, Bramson ML, Osborn JJ, Gerbode F. Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome). Use of the Bramson membrane lung. N Engl J Med 1972;286:629-634.
2. Zapol WM, Snider MT, Hill JD, Fallat RJ, Bartlett RH, Edmunds LH, Morris AH, Peirce EC, Thomas AN, Proctor HJ, Drinker PA, Pratt PC, Bagniewski A, Miller RG. Extracorporeal membrane oxygenation in severe respiratory failure. A randomised prospective study. JAMA 1979;2193-2196.
3. Morris AH, Fallace CJ, Menlove RL, Clemmer TP, Orme JF, Weaver LK, Dean NC, Thomas F, East TD, Pace NL, Suchyta MR, Beck E, Bombino M, Sittig DF, Böhm S, Hoffmann B, Becks H, Butler S, Pearl J, Rasmusson B. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO_2 removal for adult respiratory distress syndrome. Am J Respir Crit Care Med 1994;149:295-305.
4. Barthelemy R, Galetti PM, Trudell LA, MacAndrew J, Richardson PD, Puel P, Enjalbert A. Total extracorporeal CO2 removal in a pumpless artery-to-vein shunt. Trans Am Soc Artif Intern Organs 1982;28:354-358.
5. Philipp A, Behr R, Reng M, Kaiser M, Birnbaum D. Pumpless extracorporeal lung assist. J Extra-Corporeal Technol 1998;30:38-41.
6. Reng M, Philipp A, Kaiser M, Gruene S, Schoelmerich J. Pumpless extracorporeal lung assist and adult respiratory distress syndrome. Lancet 2000;356:219-220.

7. Liebold A, Reng CM, Philipp A, Pfeifer M, Birnbaum DE. Pumpless extracorporeal lung assist – experience with the first 20 cases. Eur J Cardiothorax Surg 2000;17:608-613.
8. Bein T, Weber F, Philipp A, Prasser C, Pfeifer M, Schmid FX, Butz B, Birnbaum D, Taeger K, Schlitt H. A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. Crit Care Med 2006;34:1372-1377.
9. Morris AH. Extracorporeal support and patient outcome: Credible causality remains elusive. Crit Care Med 2006;34:1551-1552.
10. Brunston RL, Tao W, Bidani A, Cardenas VJ, Traber DL, Zwischenberger JB. Determination of low blood flow limits for arteriovenous carbon dioxide removal. ASAIO J 1996;42:M845-M849.
11. Zhou X, Loran DB, Wang D, Hyde BR, Lick SC, Zwischenberger JB. Seventy-two hour gas exchange performance and hemodynamic properties of NOVALUNG iLA as a gas exchanger for arteriovenous carbon dioxide removal. Perfusion 2005;20:303-308.
12. Zick G, Frerichs I, Schädler D, Schmitz G, Puletz S, Cavus E, Wachtler F, Scholz J, Weiler N. Oxygenation effect of interventional lung assist in a lavage model of acute lung injury: a prospective experimental study. Critical Care 2006;10:R56.
13. De Somer F, Van Belleghem Y, Foubert L, Caes F, Francois K, Dubrulle F, Van Nooten G. Feasibility of a pumpless extracorporeal respiratory assist device. J Heart Lung Transplant 1999;18:1014-1017.
14. Brederlau J, Muellenbach R, Kredel M, Schwemmer U, Anetseder M, Greim C, Roewer N. The contribution of arterio-venous extracorporeal lung assist to gas exchange in a porcine model of lavage-induced acute lung injury. Perfusion 2006;21:277-284.

15. Iglesias M, Jungebluth P, Sibila O, Aldabo I, Matute MP, Petit C, Torres A, Macchiarini P. Experimental safety and efficacy evaluation of an extracorporeal pumpless artificial lung in providing respiratory support through the axillary vessels. J Thorac Cardiovasc Surg 2007;133:339-345.
16. Fischer F, Simon AR, Welte T, Hoeper MM, Meyer A, Tessmann R, Gohrbandt B, Gottlieb J, Haverich A, Strueber M. Bridge to lung transplantation with the novel pumpless interventional lung assist device NovaLung. J Thorac Cardiovasc Surg 2006;131:719-723
17. Bein T, Prasser C, Philipp A, Müller T, Weber F, Schlitt HJ, Schmid FX, Taeger K, Birnbaum D. Pumpenfreie extrakorporale Lungenunterstützung mit arteriovenösem Shunt beim schweren akuten Lungenversagen des Erwachsenen. Anaesthesist 2004;53:813-819.
18. Zimmermann M, Bein T, Philipp A, Ittner K, Foltan M, Drescher J, Weber F, Schmid FX. Interhospital transportation of patients with severe lung failure on pumpless extracorporeal lung assist. Br J Anaesth 2006;96:63-66.
19. Brunston RL, Tao W, Bidani A, Traber DL, Zwischenberger JB. Organ blood flow during arteriovenous carbon dioxide removal. ASAIO J 1997;43:M821-M824.
20. Hayes MA, Timmins AC, Yau E, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 1994;330:1717-1722.
21. Gattinoni L, Brazzi L, Pelosi P, Latini R, Rognoni G, Pesenti A, Fumagalli R. A trial of goal-orientated hemodynamic therapy in critically ill patients. N Engl J Med 1995;333:1025-1032.
22. Gattinoni L, Pesenti A, Mascheroni D, Marcolin R, Fumagalli R, Rossi F, Iapichino G, Romangnoli G, Uziel L, Agostoni A, Kolobow T, Damia G. Low-

frequency positive-pressure ventilation with extracorporeal CO_2 removal in severe acute respiratory failure. JAMA 1986;256;881-886

23. Brunston RL, Zwischenberger JB, Tao W, Cardenas VJ, Traber DL, Bidani A. Total arteriovenous CO_2 removal: simplifying extracorporeal support for respiratory failure. Ann Thorac Surg 1997;64:1599-1605.
24. Zwischenberger JB, Conrad SA, Alpard SK, Grier LR, Bidani A. Percutaneous extracorporeal arteriovenous CO_2 removal for severe respiratory failure. Ann Thorac Surg 1999;68:181-187.
25. Elliot SC, Paramasivam K, Oram J, Bodenham AR, Howell SJ, Mallick A. Pumpless extracorporeal carbon dioxide removal for life-threatening asthma. Crit Care Med 2007;35:945-948.
26. Conrad SA, Zwischenberger JB, Grier LR, Alpart SK, Bidani A. Total extracorporeal arteriovenous carbon dioxide removal in acute respiratory failure: a phase I clinical study. Intensive Care Med 2001;27:1340-1351.
27. Zwischenberger JB, Alpard SX, Tao W, Deyo D, Bidani A. Percutaneous extracorporeal arteriovenous carbon dioxide removal improves survival in respiratory distress syndrome: A prospective randomised outcomes study in adult sheep. J Thorac Cardiovasc Surg 2001;121:542-552.
28. Schmalstieg FC, Chow J, Savage C, Rudloff HE, Palkowetz KH, Zwischenberger JB. Interleukin-8, aquaporin-1, and inducible nitric oxide synthase in smoke and burn injured sheep treated with percutaneous carbon dioxide removal. ASAIO J 2001;47:365-371
29. Vertrees RA, Nason R, Hold MD, Leeth AM, Schmalstieg FC, Boor J, Zwischenberger JB. Smoke/burn injury-induced respiratory failure elicits apoptosis in ovine lungs and cultured lung cells, ameliorated with arteriovenous CO_2 removal. Chest 2004;125:1472-1482.

Tables

	all	2 hours	day 1	day 2	pre explant
number	326	91	81	61	46
O_2-transfer (ml/min)	41.7 +/- 20.8	46.1 +/- 26.4	42.7 +/- 13.5	39.4 +/- 14.6	33.6 +/- 11.7 **
blood flow (ml/min)	2.05+/- 0.44	2.11 +/- 0.44	2.16 +/- 0.41	2.09 +/- 0.44	1.95 +/- 0.42*
MAP (mm Hg)	85.1 +/- 16.5	85.3 +/- 14.7	89.6 +/- 15.4*	87.8 +/- 16.4	84.9 +/- 13.8
Hb (g/dl)	10.4 +/- 1.6	10.2 +/- 1.8	10.6 +/- 1.5*	10.5 +/- 1.4	10.3 +/- 1.2
aO_2-Sat (%)	94.2 +/- 6.0	93.4 +/- 6.9	95.0 +/- 3.2*	94.9 +/- 3.7	96.3 +/- 2.4*
PO_2 post iLA (mm Hg)	500 +/- 85	510+/- 85	506 +/- 78	491 +/- 94	492 +/- 79
DO_2 post iLA (ml/min)	310 +/- 81	315 +/- 83	332 +/- 76*	320+/- 81	293 +/- 70*

Table 1: Oxygen transfer through iLA and factors that influence transfer (MAP = mean arterial blood pressure, Hb = hemoglobin, aO_2-Sat = arterial O_2-saturation, DO_2 post iLA = oxygen delivery post iLA. * $p < 0.05$; ** $p < 0.005$ to 2 hours).

Figures

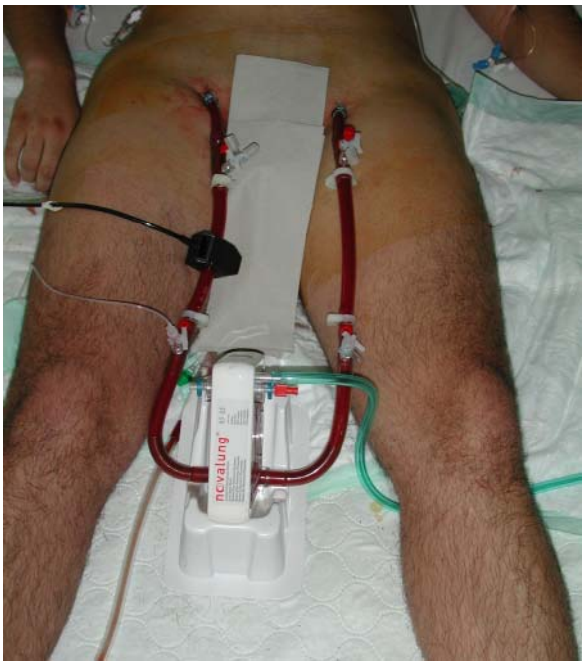


Figure 1: Interventional Lung Assist (iLA)

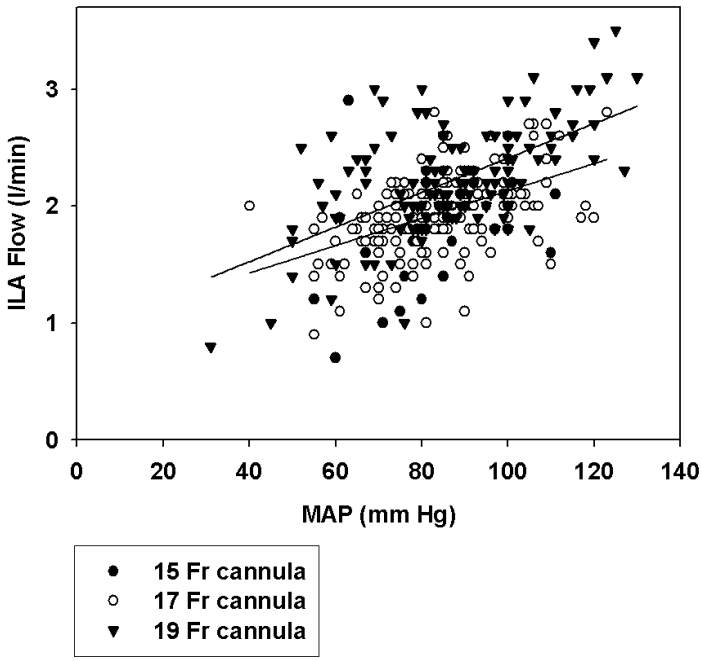


Figure 2: Dependancy of blood flow through the iLA on mean arterial pressure (MAP), different cannula sizes (regression lines are depicted for 17 Fr and 19 Fr cannulas)

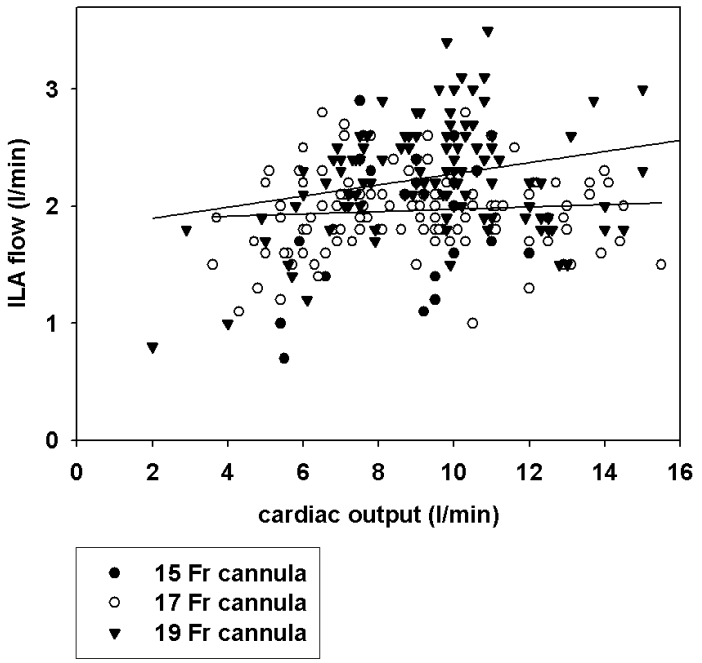
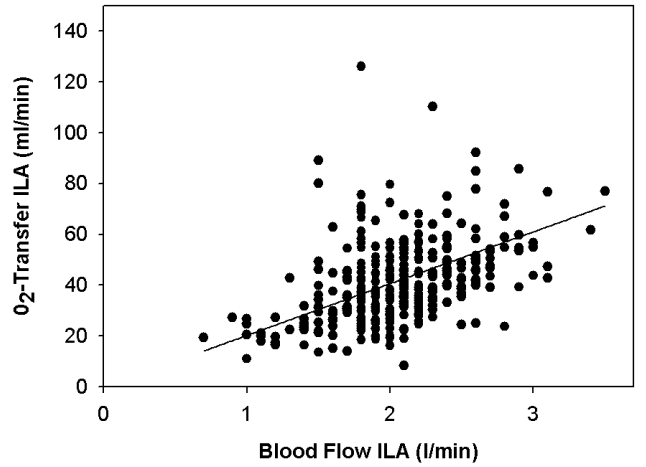
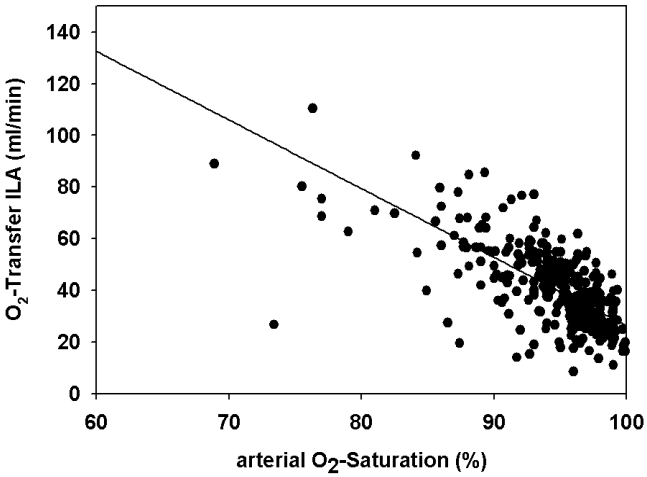


Figure 3: Dependancy of blood flow through the iLA on cardiac output (CO), different cannula sizes (regression lines are depicted for 17 Fr and 19 Fr cannulas)





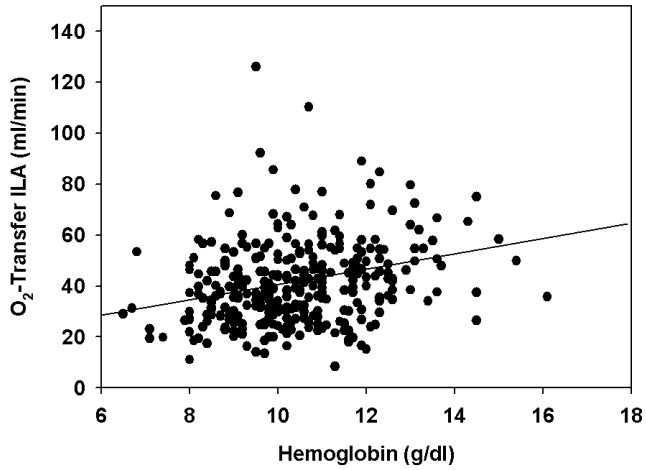
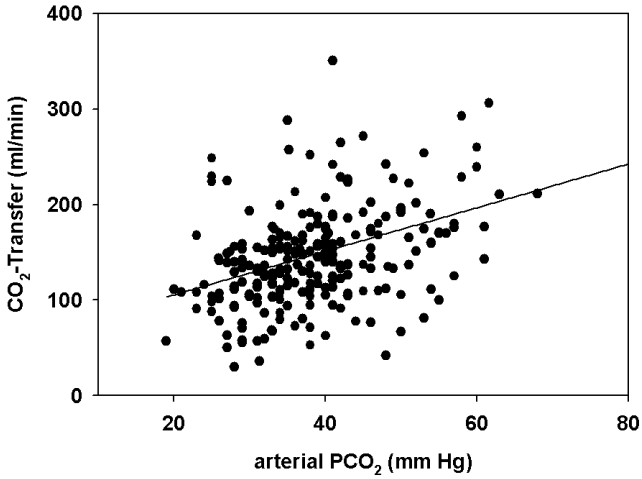
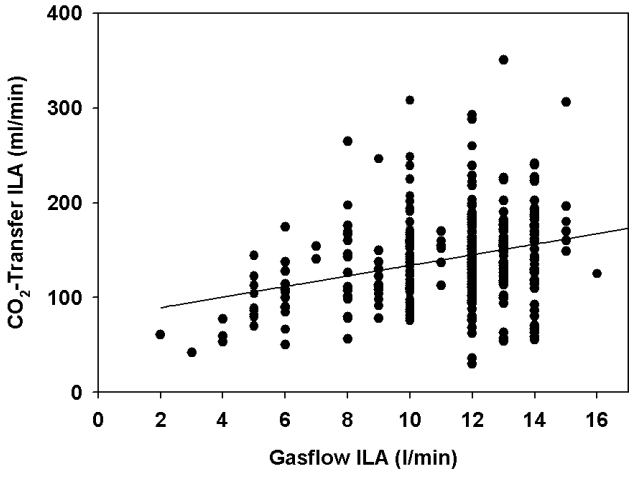


Figure 4a - c: Influence of blood flow, arterial oxygen saturation and hemoglobin content on O_2-transfer through the iLA





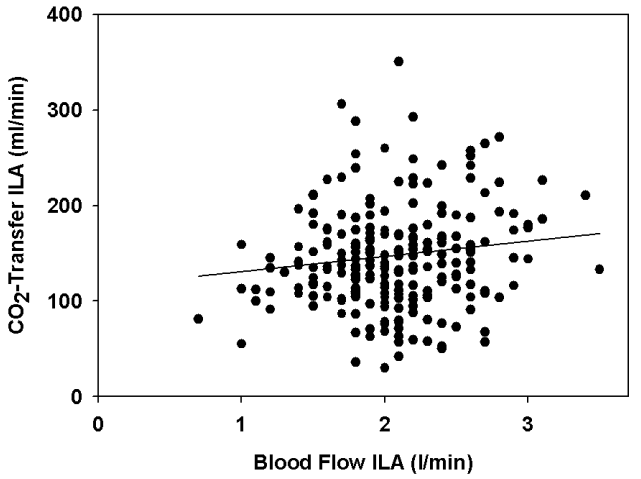


Figure 5 a-c: Influence of $PaCO_2$, sweep gas flow and blood flow on CO_2-transfer through the iLA

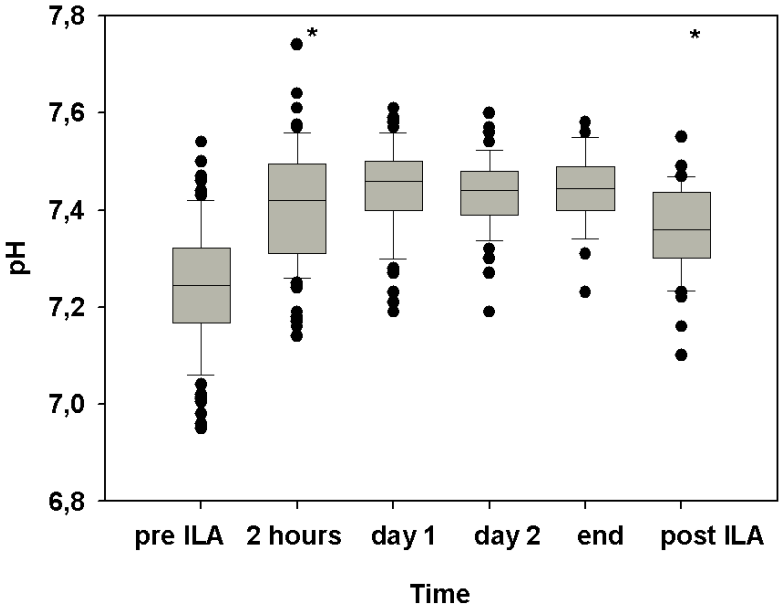


Figure 6: arterial pH before, during and after iLA treatment (* $p < 0.001$)

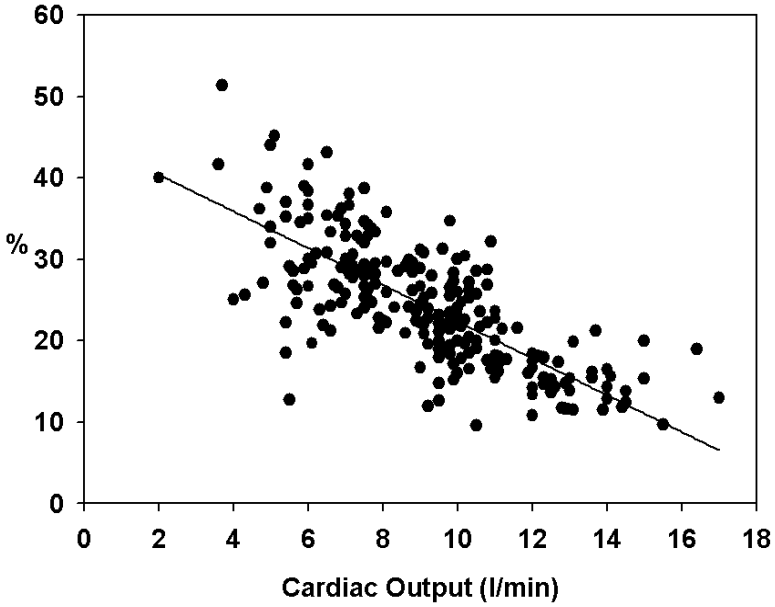


Figure 7: Blood flow through the iLA expressed as percentage of cardiac output and total cardiac output ($R = –0.74$, $p < 0.01$)