A New Supportive Therapy for Adult Respiratory Distress Syndrome: Interventional Lung Assist Device

Erişkin Solunum Sıkıntısı Sendromunda Uygulanan Yeni Bir Destekleyici Tedavi: Girişimsel Akciğer Destek Aracı

Zafer ÇUKUROVA, MD, Msc,[a]
Gülay EREN, MD, Msc,[a]
Oya HERGÜNSEL, MD, Msc,[a]
Dilek ALTUN, MD, Msc,[b]
Ayşegül KUŞKU, MD,[a]
Halil ÇETİNGÖK, MD, Msc,[a]
Yücel POLAT, MD,[a]
Ayten ZEYDAN, PhD,[c]
Bülent DURDU, MD, Msc,[d]
Ahmet AKGÜL, MD, Assoc.Prof.[e]

Clinics of
[a]Anesthesiology and Intensive Care,
[d]Infectious Diseases,
[e]Cardiovascular Surgery,
[c]Intensive Care Nurse,
Dr. Sadi Konuk Training and Research Hospital, İstanbul
[b]Clinic of Anesthesiology, Boğazlıyan State Hospital, Yozgat

Geliş Tarihi/*Received:* 03.05.2011
Kabul Tarihi/*Accepted:* 23.09.2011

This case report was presented at 15th National Intensive Care Congress, 5-8 November 2010, İzmir, Turkey.

Yazışma Adresi/*Correspondence:*
Gülay EREN, MD, Msc
Dr. Sadi Konuk Training and Research Hospital,
Department of Anesthesiology and Intensive Care, İstanbul,
TÜRKİYE/TURKEY
glyeren@mynet.com

doi:10.5336/medsci.2011-24584

ABSTRACT Adult respiratory distress syndrome (ARDS) remains a great challenge for physicians in intensive care units with high mortality rates. Although protective lung ventilation is the mainstay of ARDS therapy, it may lead to intractable hypercapnia. Pumpless extracorporeal lung-assist was suggested as an invasive alternative to conventional treatment when gas exchange is not optimized with rigorous mechanical ventilation alone. Here, we report the treatment of a patient with extracorporeal lung-asist in the course of pneumonia-related ARDS due to intractable hypercapnia as a result of failure of protective ventilation strategy and her outcome after treatment. Interventional Lung Assist device (iLA) contains a specially designed low resistance lung membrane, which uses the pressure difference between the arterial and venous circulation. This system enables the use of high airway pressures for oxygenation in combination with very low tidal volumes to avoid ventilator-induced lung injury and this gives time to patient for lung recovery.

Key Words: Respiratory distress syndrome, adult; extracorporeal membrane oxygenation; ventilation

ÖZET Yüksek mortalite hızına sahip olan erişkin solunum sıkıntısı sendromu (ESSS), yoğun bakım ünitesindeki doktorlar için halen önemli bir sorundur. Koruyucu akciğer ventilasyonu ESSS tedavisinin ana dayanağı olsa da, inatçı hiperkapniye yol açabilir. Gaz değişimi tek başına titiz bir mekanik ventilasyonla optimize edilemediğinde, pompasız ekstrakorporeal akciğer yardımı konvansiyonel tedaviye invaziv bir alternatif olarak önerilmiştir. Bu makalede, koruyucu ventilasyon stratejisindeki başarısızlık nedeniyle inatçı hiperkapniye bağlı pnömoni ile ilişkili ESSS sırasında, ekstrakorporeal akciğer yardımı ile tedavi edilen bir olgu sunulmuştur. Girişimsel akciğer yardım cihazı (Interventinal Lung Assit device-iLA), arteriyel ve venöz dolaşım arasındaki basınç farkını kullanan, özel olarak tasarlanmış, düşük dirençli bir akciğer membranına sahiptir. Bu sistem, ventilatör ile ilişkili akciğer hasarından kaçınmayı sağlamak için, oksijenasyon amacıyla uygulanan yüksek hava yolu basınçlarını, çok düşük tidal volümlerle birlikte kullanmaya olanak sağlar ve hastaya, akciğerin iyileşmesi için zaman verir.

Anahtar Kelimeler: Solunum sıkıntısı sendromu, yetişkin; yapay dolaşım membran oksijenizasyonu; ventilasyon

Turkiye Klinikleri J Med Sci 2012;32(1):294-300

Despite substantial advances in the understanding of acute respiratory distress syndrome (ARDS), since its initial description in 1967,[1] the mortality rate is still above 40%.[2,3] In addition to mechanical ventilation, which is still the mainstay of therapy, a number of novel supportive techniques, including partial liquid ventilation, inhaled nitric oxide, surfactant replacement, and extracorporeal techniques have been used.[4-7]

Pumpless extracorporeal lung-assist is a simple and efficient method to support patients with deteriorating gas exchange.[8,9] This device was suggested as an invasive alternative to conventional treatment when optimal gas exchange is not possible by rigorous mechanical ventilation alone.

A new supportive therapy for use in ARDS patients is the Interventional Lung Assist device (iLA), which removes carbon dioxide from the blood. This system contains a specially designed low resistance lung membrane, which uses the pressure difference between the arterial and venous circulation as the driving force for blood flow (Figure 1). The extracorporeal blood flow is approximately 25% of the cardiac output. This system enables the use of high airway pressures for oxygenation in combination with very low tidal volumes to avoid ventilator-induced lung injury and it gives time to the patient for lung recovery.[9] In this report, we described the treatment of a patient requiring extracorporeal lung asist in the course of ARDS secondary to pneumonia and her outcome.

CASE REPORT

A 36 years old woman [weight 88 kg, height 160 cm and ideal body weight (IBW) 52 kg] in the 30th week of pregnancy was referred to our intensive care unit (ICU) from a primary care hospital with the diagnosis of pneumonia-related respiratory insufficiency. On admission, she was on mechanical ventilation with the settings of Synchronized Intermittent Mandatory Ventilation (SIMV), fiO_2 60%, Positive End Expiratory Pressure (PEEP) 10 cmH_2O, pressure over PEEP (PEEP') 18 cmH_2O, frequency 15 min^{-1}, tidal volume (VT) 500 mL and her arterial blood gasses (ABG) analysis revealed respiratory acidosis and hypoxemia (pH 7.21, PCO_2 54.7 mmHg, PO_2 54 mmHg, BE -8.9, saturation 77.9%). Her blood pressure was 112/65 mmHg, heart rate was 148 min^{-1} and her body temperature was 35.8°C. Auscultataion of the lungs revealed basillary inspiratory and expiratory crackles bilaterally. Chest X-ray revealed diffuse bilateral fluffy infiltrates. There was no sign of fetal distress with noninvasive fetal monitoring. Her biochemical blood analysis revealed hyperlactatemia and leucocytosis (lactate 9 mmol/L, leucocyte count 24500 cells/mm^3). Empiric antimicrobial treatment (ampicillin-sulbactam sodium 1gr iv q6hr) was initiated after collection of blood, urine and deep tracheal aspiration specimens for microbiological examinations. After diagnosis of ARDS ventilation settings were immediately changed as pressure controlled with fiO_2 55%, PEEP 14 cmH_2O, PEEP' 15 cmH_2O, fr18, and VT 300 ml. Twenty minutes after the new ventilatory settings, ABG analysis improved; pH 7.29, PCO_2 47 mmHg, PO_2 75 mmHg, BE -6, sat 92%. However, on ventilatory day 3, the patient underwent cesearean section under general anesthesia, due to sustained hypoxemia despite high PEEP settings, in order to prevent any morbidity to the fetus. There was no complication throughout the cesarean section and neonatal APGAR scores were 7 and 10 (at 1 and 5 minutes).

On day 10 in the intensive care unit, the blood cultures revealed *Eschericia coli* infection; antimicrobial treatment was switched to imipenem 500 mg iv q6hr and for the gram-negative septicemia Pentaglobulin therapy was instituted 450 mg/d for 3 days. Thoracic computerized tomography (CT) scanning revealed diffuse, patchy ground glass consolidations with bilateral air bronchograms at lower lobes (Figures 2a and 2b). Percutaneous tra-

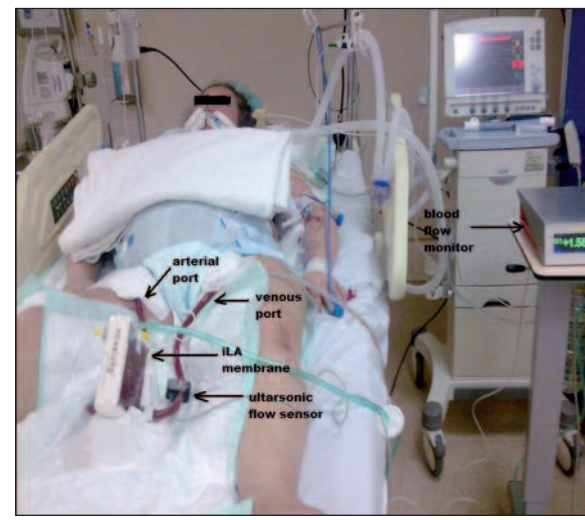

FIGURE 1: Interventional Lung Assist device (iLA) instrumentation of the patient. The system consists of vascular ports connecting the iLA membrane ventilator to the arterial and venous catheters mounted on the patient and the blood flow monitor measuring the flow through the circuit.
(See for colored form http://tipbilimleri.turkiyeklinikleri.com/)

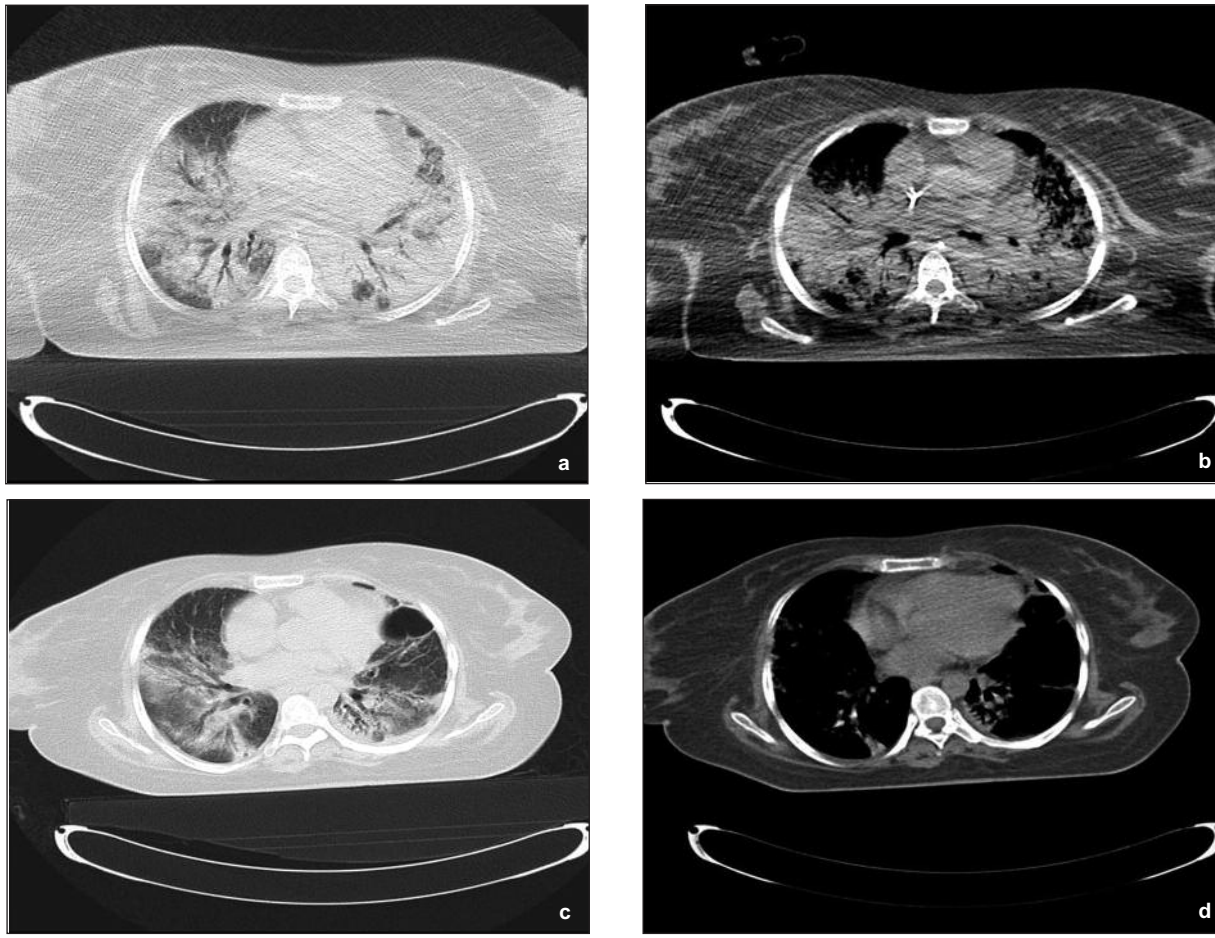

FIGURE 2: Thoracic computed tomography scans revealing diffuse bilateral infiltrations **(a and b)** before Interventional Lung Asisst device (iLA) implementation and apparent improvement after iLA **(c and d)**.

cheostomy was performed on day 15 due to continuation of the ventilatory treatment.

Although she was maintained on protective ventilation via pressure controlled mode with high PEEP and low tidal volumes and with periodical positioning changes as prone v.s. supine, hypercarbia and hypoxemia sustained. On day 24, despite vigorous ventilatory treatment, her clinical status reached a deadlock and in order to give her a chance for treatment as a last choice we decided to implement the pumpless interventional lung assist device (iLA, NovaLung, Hechingen, Germany).

We used the right femoral artery and the left femoral vein respectively for insertion of a 15 French arterial and 17 French venous cannula by the Seldinger technique (Figure 1). After insertion, iLA pre-filled with 0.9% NaCl was connected; initial passive blood flow was 2.1 L min^{-1} and gas flow (oxygen) in the membrane lung was 12 L min^{-1}. Because of the heparin-bonded system, systemic anticoagulation with heparin was targeted only to an activated clotting time of 120-150 s. Blood flow through the extracorporeal system was measured by ultrasonography (Blood Flow Monitoring System, NovaLung®, Hechingen, Germany). Mean arteriovenous shunting with the iLA during treatment was 20-25% of the cardiac output, measured with a thermodilution technique (PiCCO monitor, Pulsion Medical Inc., USA). The targeted mean arterial pressure was 70 mmHg and the minimal cardiac index to ensure sufficient blood flow through the membrane lung was 1.5 L-min^{-1}-m^{-2}. Norepinephrine infusion (maximum dosage 1.5 μg kg^{-1} min^{-1}) was only administered for 24 hrs after starting iLA to reach this index.

TABLE 1: Course of time and change in respiratory mechanics of the patient on Interventional Lung Assist device (iLA).

		Post- iLA				
	Pre-iLA	**4 hours**	**1 day**	**7 days**	**10 days**	**14 days**
FiO_2	**0.6**	**0.7**	**0.65**	**0.5**	**0.5**	**0.45**
PEEP(cmH_2O)	**15**	**18**	**18**	**12**	**8**	**8**
PaO_2/FiO_2	**161**	**55**	**60**	**130**	**196**	**155.5**
P plateau (cmH_2O)	30	27	23	18	17	16
Vt (mL)	400	300	200	200	220	250
Vt ($mL.kg^{-1}$ IBW)	**7.69**	**5.76**	**3.84**	**3.84**	**4.23**	**4.80**
Minute volume ($L.\ min^{-1}$)	**8**	**4.5**	**2.6**	**2.8**	**3.08**	**4**
pH	7.32	7.57	7.53	7.38	7.32	7.33
PaO_2 (mmHg)	**96.8**	**38.5**	**49**	**65**	**98**	**70**
$PaCO_2$ (mmHg)	**86.8**	**44.1**	**42**	**50.7**	**46**	**45.8**
HCO_3^- (mEq/L)	44.2	39.7	35.5	41.7	39	36.5
BE (mEq/L)	13.6	15.7	13	15	12.7	12
SpO_2 (%)	96	80.4	85.3	90	97	93

FiO_2: Inspiratory oxygen fraction; PEEP: Positive end expiratory pressure; PaO_2/FiO_2: ratio of alveolar oxygen pressure to inspiratory oxygen fraction; P plateau: Plateau pressure; Vt: Tidal volume; IBW: Ideal body weight; PaO_2: Alveolar oxygen pressure; $PaCO_2$: alveolar carbondioxide pressure; HCO_3^-: Bicarbonate; BE: Base excess; SpO_2: Oxygen saturation; cmH_2O: Centimetres water; mL: Mililitres; L. min-1: Litres per mimute; mmHg: Milimeter mercury; mEq/L: Miliequivalent per lite.

In the first few hours there was a marked decrease in hypercapnia, as well as an advanced hypoxia; therefore, we had to increase both the fiO_2 and PEEP at the beginning. After the second day following iLA implementation we were able first to reduce fiO_2 stepwise, and then PEEP and mean airway pressure over several days. Tidal volume could be targeted to less than 7 ml kg^{-1} IBW (Table 1). The clinical status of the patient improved and the performance of the iLA was adjusted by reducing the gas flow (oxygen) of the membrane lung. The iLA was stopped 14 days after initiation after a successful trial without gas flow (oxygen) from the membrane lung and the vascular catheters (arterial and venous) were removed.

The management of fluids depended on the PiCCO monitorization of the patient throughout her course in the ICU and no buffer was used for treatment of hypercapnia at any time. She was not given any steroids either as her hemodynamics were not compromised to lead to septic shock any time throughout her treatment.

We observed no iLA related adverse events throughout the treatment. There was marked improvement in the lung as seen on the control thoracic CT after termination of iLA (Figures 2c and 2d). Weaning from ventilation was interrupted by nosocomial pneumonia related to *Pseudomonas aeruginosa*, which responded to appropriate antibiotherapy. On day 50 of admission, the tracheostomy cannula was removed and eventually she was discharged from the hospital on day 63 with recommendation for rehabilitation.

DISCUSSION

In the last few years, there has been a consensus on the ventilation strategies of ARDS on the context of "lung protective ventilation" through which we may face with inevitable hypercapnia.[10] Similarly in our patient, as a result of this lung protective ventilation strategy, we could not manage to overcome the sustained hypercapnia and we decided to establish the iLA for carbon dioxide removal to offer less aggressive ventilation.

Hypercapnic acidosis (HA) is often considered a well-tolerated side effect of lung protective ventilation strategies. There is a growing body of experimental evidence, however, suggesting that HA may be intrinsically protective in ventilator-induced lung injury and acute lung injury (ALI),[11,12] and that buffering HA may be detrimental.[13] Certain patient populations, such as those with car-

diovascular disease or central nervous system injuries, have the potential to be harmed by HA.

Patients with ARDS do not die from respiratory failure per se but rather because of the development of multiorgan failure. However, hypercapnic acidosis appears to exert protective effects on the myocardium.[14] In isolated hepatocytes exposed to anoxia and chemical hypoxia, acidosis markedly delays the onset of cell death and correction of the pH actually accelerates cell death.[15,16] This phenomenon may represent a protective adaptation against hypoxic and ischaemic stress.[15] On the other hand, there is experimental evidence that the beneficial effects of moderate hypercapnia may be counterbalanced by a potential for adverse effects at higher levels. This is supported by experimental evidence demonstrating that protection from the adverse effects of brain ischaemia was better when the inspired carbon dioxide was set at 6% rather than at 9%. Of concern is that, severe hypercapnia produced by 15% carbon dioxide was more recently demonstrated to worsen neurological injury in this context.[17] In isolated hepatocytes, the degree of protection from anoxic injury conferred by metabolic acidosis was greater at a pH of 6.9 than at 6.6.[15]

There are experimental studies reporting that buffering hypercapnic acidosis worsens acute lung injury. The exact mechanisms of the deleterious effects of buffering hypercapnic acidosis are unclear. Specific concerns exist regarding the use of bicarbonate to buffer the acidosis produced by hypercapnia. The effectiveness of bicarbonate infusion as a buffer is dependent on the ability to excrete carbon dioxide, rendering it less effective in buffering a hypercapnic acidosis. In fact, bicarbonate may further raise systemic carbon dioxide levels under conditions of reduced alveolar ventilation, such as ARDS.[18] Furthermore, although bicarbonate may correct arterial pH, it may worsen intracellular acidosis because the carbon dioxide produced when bicarbonate reacts with metabolic acids diffuses readily across cell membranes, whereas bicarbonate cannot.[19] Taken together, these findings suggest that, in the absence of a correction of the primary problem, buffering a hypercapnic acidosis with bicarbonate is not likely to be of benefit. However, there are no long-term clinical outcome data (e.g. survival, duration of hospital stay) to support the buffering of hypercapnic acidosis.[20] With respect to these facts we did not attempt to buffer the hypercapnia in our patient.

Similarly, there is still controversy about the use of steroids in the treatment of ARDS. Most of the sepsis guidelines recommend steroid use only in case of refractory septic shock.[21,22] Trials of high-dose, short-course corticosteroids for early-phase ARDS failed to show improvements in survival.[23,24] Several reports from small case series suggested a benefit of moderate-dose corticosteroids in patients with persistent ARDS.[25,26] A single-center, randomized trial involving 24 patients who had had ARDS for seven or more days reported that moderate dose corticosteroids improved lung function and survival.[27]

The risks associated with corticosteroids in these patients are unclear. Several studies involving patients with sepsis and ARDS have suggested that high-dose corticosteroids increase the risk of secondary infections, yet a meta-analysis of moderate-dose corticosteroids for sepsis did not substantiate this finding.[28] Additional potential risks of corticosteroids include hyperglycemia, poor wound healing, psychosis, pancreatitis, and prolonged muscle weakness with impaired functional status.[29] Considering all these risks with steroid treatment, we did not prefer to use corticosteroids in the course of treatment in the presented case in which no period of refractory hypotension occurred.

The aim of iLA insertion in this reported case was to allow lung-protective ventilation and to improve gas exchange. This allows the native lung function to be supported and the diseased lung may recover better as artificial ventilation can be downgraded. Accordingly, additional iatrogenic lung injury such as barotrauma and volutrauma caused by mechanical ventilation with high tidal volumes and high peak inspiratory pressures can be reduced.[30,31] Our case demonstrates that moderate transfer of oxygen and efficient elimination of carbon dioxide is well achieved with iLA.

The iLA system is characterized by a novel membrane gas exchange device with optimized blood flow integrated into an arteriovenous heparin-coated bypass, established by cannulation of the femoral artery and vein. A passive shunt flow generated by the patient's blood pressure gradient through the gas exchange device allows effective carbon dioxide extraction and moderate improvement in arterial oxygenation. Muller and coworkers[9] showed that interventional lung assist eliminated 50% of calculated total carbon dioxide production with rapid normalization of respiratory acidosis despite limited contribution to oxygen transfer. They found that oxygen transfer capacity was 41.7 ± 20.8 $mL.min^{-1}$ and carbon dioxide removal was 148.0 ± 63.4 $mL.min^{-1}$. The oxygen transfer capacity of the iLA is limited mainly 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 haemoglobin.

In our patient, iLA enabled a safe application of lung protective tidal volume less than 6 $ml.kg^{-1}$ without provoking severe acidosis, by profound carbondioxide elimination. The combination of very low VT with high PEEP allowed the limitation of plateau pressure at 30 cmH_2O or lower and thus the avoidance of barotrauma. The expected hypoxemia was a challenge only for a few days after iLA implementation, which we managed with little incremental manipulations of PEEP and fiO_2. However, it was no more a problem thereafter so that the PaO_2/fiO_2 ratio doubled. Thus, we may suggest that the resultant hypoxemia can be ameliorated by minimal changes of ventilatory parameters.

The system is valuable not only as a means of reducing the need for aggressive ventilation but also for the bridge therapy to lung transplantation[32] and the safe interhospital transport of the critically compromised pulmonary patient,[33] due to ease of use, effectiveness, and relatively low costs. However, cardiovascular stability is mandatory for the use of this treatment modality. Despite using relatively small cannulas, critical ischemia of the distal limb or bleeding at the site of cannulation are possible adverse effects. We used a 15 F cannula for arterial cannulation. No peripheral complications developed in our patient.

The use of extracorporeal technology to accomplish gas exchange, with/without cardiac support, is based on the premise that 'lung rest' facilitates repair and avoids the barotrauma/volutrauma of ventilator management. Interventional, extracorporeal pump-free pulmonary support opens up new possibilities for pulmonary protection. Despite the lack of randomized controlled studies and the possibility of sigificant risks, results are encouraging.

CONCLUSION

Today, low-tidal-volume ventilation is a common practice in the treatment of acute lung failure, often accompanied by hypercapnia and respiratory acidosis. In this context, extracorporeal carbon dioxide elimination could represent an opportunity to avoid potentially dangerous decreases in pH. Interventional lung assist may provide a sufficient improvement at arterial blood gas parametres with easy handling properties and low cost in patients with severe acute respiratory distress syndrome and persistent hypoxia and hypercapnia.

REFERENCES

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet 1967;2(7511):319-23.
2. Mancebo J, Fernández R, Blanch L, Rialp G, Gordo F, Ferrer M, et al. A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. Am J Respir Crit Care Med 2006;173(11):1233-9.
3. Phua J, Badia JR, Adhikari NK, Friedrich JO, Fowler RA, Singh JM, et al. Has mortality from acute respiratory distress syndrome decreased over time?: A systematic review. Am J Respir Crit Care Med 2009;179(3): 220-7.
4. Edis EC, Hatipoglu ON, Celebi D, Celik AD, Uzmezoglu B, Altiay G. [Successfull high PEEP application in a pregnant woman with ARDS]. Turkish Journal of Intense Care Medicine 2010;1(3):73-5.
5. Öztürk GG, Çınar D, Tunç M, Şahin S, Sazak H. [Cases with life-threatening respiratory failure due to influenza A (H1N1) virus infection in intensive care unit]. Turkiye Klinikleri J Med Sci 2011;31(2):490-5.

6. Hirschl RB, Tooley R, Parent A, Johnson K, Bartlett RH. Evaluation of gas exchange, pulmonary compliance, and lung injury during total and partial liquid ventilation in the acute respiratory distress syndrome. Crit Care Med 1996;24(6):1001-8.
7. Alpard SK, Zwischenberger JB. Adult extracorporeal membrane oxygenation for severe respiratory failure. Perfusion 1998;13(1):3-15.
8. Zwischenberger JB, Alpard SK, Conrad SA, Johnigan RH, Bidani A. Arteriovenous carbon dioxide removal: development and impact on ventilator management and survival during severe respiratory failure. Perfusion 1999;14(4):299-310.
9. Müller T, Lubnow M, Philipp A, Bein T, Jeron A, Luchner A, et al. Extracorporeal pumpless interventional lung assist in clinical practice: determinants of efficacy. Eur Respir J 2009;33(3):551-8.
10. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000;342(18):1301-8.
11. Broccard AF, Hotchkiss JR, Vannay C, Markert M, Sauty A, Feihl F, et al. Protective effects of hypercapnic acidosis on ventilator-induced lung injury. Am J Respir Crit Care Med 2001;164(5):802-6.
12. Laffey JG, Honan D, Hopkins N, Hyvelin JM, Boylan JF, McLoughlin P. Hypercapnic acidosis attenuates endotoxin-induced acute lung injury. Am J Respir Crit Care Med 2004;169(1):46-56.
13. Laffey JG, Engelberts D, Kavanagh BP. Buffering hypercapnic acidosis worsens acute lung injury. Am J Respir Crit Care Med 2000;161(1):141-6.
14. Nomura F, Aoki M, Forbess JM, Mayer JE Jr. Effects of hypercarbic acidotic reperfusion on recovery of myocardial function after cardioplegic ischemia in neonatal lambs. Circulation 1994;90(5 Pt 2):II321-7.
15. Bonventre JV, Cheung JY. Effects of metabolic acidosis on viability of cells exposed to anoxia. Am J Physiol 1985;249(1 Pt 1):C149-59.
16. Gores GJ, Nieminen AL, Wray BE, Herman B, Lemasters JJ. Intracellular pH during "chemical hypoxia" in cultured rat hepatocytes. Protection by intracellular acidosis against the onset of cell death. J Clin Invest 1989;83(2):386-96.
17. Vannucci RC, Towfighi J, Brucklacher RM, Vannucci SJ. Effect of extreme hypercapnia on hypoxic-ischemic brain damage in the immature rat. Pediatr Res 2001;49(6):799-803.
18. Sun JH, Filley GF, Hord K, Kindig NB, Bartle EJ. Carbicarb: an effective substitute for NaHCO3 for the treatment of acidosis. Surgery 1987;102(5):835-9.
19. Goldsmith DJ, Forni LG, Hilton PJ. Bicarbonate therapy and intracellular acidosis. Clin Sci (Lond) 1997;93(6):593-8.
20. O'Croinin D, Ni Chonghaile M, Higgins B, Laffey JG. Bench-to-bedside review: Permissive hypercapnia. Crit Care 2005;9(1):51-9.
21. Annane D. Glucocorticoids in the treatment of severe sepsis and septic shock. Curr Opin Crit Care 2005;11(5):449-53.
22. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36(1):296-327.
23. Luce JM, Montgomery AB, Marks JD, Turner J, Metz CA, Murray JF. Ineffectiveness of high-dose methylprednisolone in preventing parenchymal lung injury and improving mortality in patients with septic shock. Am Rev Respir Dis 1988;138(1):62-8.
24. Bernard GR, Luce JM, Sprung CL, Rinaldo JE, Tate RM, Sibbald WJ, et al. High-dose corticosteroids in patients with the adult respiratory distress syndrome. N Engl J Med 1987;317(25):1565-70.
25. Biffl WL, Moore FA, Moore EE, Haenel JB, McIntyre RC Jr, Burch JM. Are corticosteroids salvage therapy for refractory acute respiratory distress syndrome? Am J Surg 1995;170(6):591-5.
26. Keel JB, Hauser M, Stocker R, Baumann PC, Speich R. Established acute respiratory distress syndrome: benefit of corticosteroid rescue therapy. Respiration 1998;65(4):258-64.
27. Meduri GU, Headley AS, Golden E, Carson SJ, Umberger RA, Kelso T, et al. Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial. JAMA 1998;280(2):159-65.
28. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. BMJ 2004;329(7464):480.
29. Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med 2003;348(8):683-93.
30. Moran JL, Bersten AD, Solomon PJ. Meta-analysis of controlled trials of ventilator therapy in acute lung injury and acute respiratory distress syndrome: an alternative perspective. Intensive Care Med 2005;31(2):227-35.
31. Lionetti V, Recchia FA, Ranieri VM. Overview of ventilator-induced lung injury mechanisms. Curr Opin Crit Care 2005;11(1):82-6.
32. Fischer S, Simon AR, Welte T, Hoeper MM, Meyer A, Tessmann R, et al. Bridge to lung transplantation with the novel pumpless interventional lung assist device NovaLung. J Thorac Cardiovasc Surg 2006;131(3):719-23.
33. Zimmermann M, Bein T, Philipp A, Ittner K, Foltan M, Drescher J, et al. Interhospital transportation of patients with severe lung failure on pumpless extracorporeal lung assist. Br J Anaesth 2006;96(1):63-6.