What's New in Acute Respiratory Distress Syndrome in Infants and Children

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Acute respiratory distress syndrome (ARDS) was first described in 1967 by Asbough et al. as a clinical syndrome that occurs 24 to 48 hours after a direct or indirect lung injury [1]. It is characterised by dyspnea, tachypnea, hypoxemia refractory to oxygen therapy, decreased lung compliance, and diffuse alveolar infiltrates on chest X-ray. ARDS is a rare disorder in childhood. The incidence varies from 0.8 to 4.4% among all admissions to the paediatric ICU [2-8]. ARDS is a significant cause of morbidity in critically ill children. While therapeutic interventions remain supportive, the management of evolving acute lung injury is often a controversial issue in the paediatric ICU. There has been significant progress in our understanding of the pathophysiology of acute lung injury and in our understanding of how lung injury is often amplified in the course of mechanical support. This understanding has led to a strategic shift in ventilation style principally geared to optimally recruiting and then maintaining end-expiratory lung volume, preventing the traumatic cycle of derecruitment-recruitment, and finally, limiting alveolar stretching during tidal inflation.

Ventilator induced lung injury (VILI)

The negative impact of mechanical ventilation on the disease process in acute lung injury has been assumed for years, based on animal studies. These studies showed that ventilation with the use of large tidal volumes caused the disruption of pulmonary epithelium and endothelium, lung inflammation, atelectasis, hypoxemia, and the release of inflammatory mediators [9-13]. Thus the traditional approach to mechanical ventilation may exacerbate or perpetuate lung injury in patients with ARDS. Protecting the "normal" population of compliant alveoli within heterogeneous lung necessitates limiting transalveolar pressure to 30-35 cm H₂O. Beyond this limit, it is important to recognize the significance of the upper inflection point in the pressure/volume (P/V) curve. When endexpiratory lung volume is appropriately optimized, avoidance of the upper inflection point generally requires limiting volume-cycled breaths to 4-8 ml/kg. A similar tidal volume may be targeted when the transalveolar pressure excursion is limited by fixing end-expiratory and end-inspiratory pressures. This excursion should be in the general range of 20 cm H₂O.

Permissive hypercapnia (PHC)

In 1990 Hickling et al. introduced the concept of low volume pressure limited ventilation with permissive hypercapnia for patients with severe ARDS [14]. This ventilatory strategy avoided further ventilator induced lung damage while moderate or even severe hypercapnia was well tolerated by the critically ill patients. In this uncontrolled study in patients with severe ARDS Hickling showed that the hospital mortality rate was significantly lower than predicted by Apache II (16% versus 39.6%).

In a recent study on ARDS patients ventilation with lower tidal volumes (6 ml/kg) was compared with traditional tidal volumes (12 ml/kg) [15]. The primary outcome was death before a patient was discharged home and was breathing without assistance. The second primary outcome was the number of days without ventilator use from day 1 to day 28. The trial was stopped after enrolment of 861 patients because mortality was lower in the group treated with lower tidal volumes (31% vs. 39.8%, $p < 0.01$), and the number of days without ventilator use was greater in this group (12 ± 11 vs. 10 ± 11 , $p < 0.01$). The authors concluded that in patients with acute lung injury and ARDS mechanical ventilation with lower tidal volume than is traditionally applied results in decreased mortality and increases the number of days without ventilator use.

There are only few reports on controlled hypoventilation in paediatric patients with ARDS [16-18]. A randomized trial of permissive hypercapnia in preterm infants showed that a ventilatory strategy of permissive hypercapnia is feasible, seems safe, and may reduce the duration of assisted ventilation [19]. There were no differences in mortality, air leaks, intraventricular haemorrhage, periventricular leukomalacia, retinopathy of prematurity, or patent ductus arteriosus.

We used this ventilatory strategy with tidal volumes of 8 ml/kg in 20 paediatric patients with ARDS or acute lung injury. This strategy resulted in PaCO₂ values between 60 and 80 mmHg associated with pH values between 7.25 and 7.35. The overall mortality in these 20 patients was 30%. Baro-volutrauma was observed in 6 patients. Additional therapies included NO inhalation ($n = 17$), surfactant therapy ($n = 11$), and ECMO support ($n = 5$).

Recruitment manoeuvres

There is now further evidence from experimental data that lung recruitment during small tidal volume ventilation allows ventilation on the deflation limb of the pressure-volume curve of the lungs at a PEEP < P_{inflex} [20]. This strategy minimizes lung injury and ensures a lower PEEP, which may minimize the detrimental consequences of high volume ventilation. These sustained inflation manoeuvres for alveolar recruitment are safe in adult patients with ARDS resulting in improved oxygenation [21]. In a recent abstract Gaudencio et al. reported that

lung recruitment manoeuvres with PEEP values between 30 and 40 cm H₂O improved gas exchange in 4 paediatric patients with ARDS without negative haemodynamic effects [22].

High frequency oscillation (HFO)

This form of ventilatory support does not create normal bulk flow ventilatory patterns through changes in lung volume and delivered pressure, but rather maintains lung recruitment via a steady inflating pressure (generally 15 to 30 cm H₂O) around which high-frequency oscillations (range between 4 and 15 Hz with an amplitude of 20 to 60 cm H₂O) generate alveolar ventilation. Tidal volumes are smaller than anatomic deadspace resulting in lower peak alveolar pressures than observed during CMV. Mean airway pressure during HFO is most commonly set above closing pressure and lung volume is maintained steadily without deflation. During HFO lung volume will not travel along the deflation curve to the point of derecruitment. Therefore, the lung may be optimally protected from the stress of cyclic derecruitment that occurs during CMV.

HFO has been widely studied in animal models of acute lung injury [23-25]. It has been shown that HFO improves oxygenation, minimizes histopathologic alterations of acute lung injury when compared to CMV, reduces activated pulmonary neutrophils, and reduces important inflammatory mediators [26, 27]. There is evidence that HFO may be most effective when used early in the course of acute respiratory failure. An optimal lung volume is best achieved with an aggressive initial volume recruitment strategy with relatively high Paw values. There is an important gradient in both peak and mean Paw values from the ventilator to alveolus.

In 1994 Arnold et al. published their experience with high frequency oscillation and conventional mechanical ventilation in 58 paediatric patients with acute respiratory failure [28]. In their prospective, randomized study with crossover design they used a high volume HFO strategy to optimise lung recruitment. Although they used higher Paw during HFO than during CMV the barotrauma frequency was lower during HFO. Of 29 patients enrolled to the HFO group 17 patients (58%) showed a good response to HFO and one patient died. However, 11 patients (38%) crossed over to CMV and 9 (82%) subsequently died. The authors concluded that early institution of a high lung volume strategy using HFO would be the ideal ventilatory approach in paediatric patients with ARDS. Nonresponders to this ventilatory strategy should be considered for alternative approaches such as extracorporeal life support. We used HFO as a rescue therapy in 7 patients with ARDS when conventional respiratory support had failed. In this situation HFO with a high volume strategy improved gas exchange in only one patient. The use of HFO as a rescue strategy when all other therapeutic steps have failed might explain the disappointing results with HFO in our patients.

Partial liquid ventilation (PLV)

The rationale for mechanical ventilation in acute lung injury is to apply a PEEP to prevent end-expiratory collapse of collapsible alveoli and to select a tidal volume to limit overdistension of lung units [29]. Another therapeutic option would be to eliminate the increased forces acting at the air-liquid interface in the acutely damaged lung by filling the lungs with a perfluorochemical liquid [30].

Perfluorocarbon liquids are organic hydrogen molecules in which carbon-bound hydrogen atoms are replaced by fluorine atoms. They are biologically inert, non-biotransformable and immiscible in both aqueous and lipid media. Perfluorocarbon liquids are absorbed minimally by the respiratory epithelium, and are eliminated by evaporation through the lungs. Oxygenated perfluorocarbon liquids have the ability to lower surface tension in surfactant-deficient lungs, to increase functional residual capacity (FRC), and are able to dissolve large amounts of respiratory gases.

In 1991 Fuhrman et al. introduced the technique of perfluorocarbon-associated gas exchange or PLV [31]. This new technique combined liquid ventilation at functional residual capacity and tidal gas volume ventilation using a conventional ventilator. Meanwhile a number of experimental studies have shown that PLV significantly improves oxygenation, lung mechanics, decreases further alveolar damage and decreases serum tumour necrosis factor- α concentration in acute lung injury [32-38]. Most investigators filled up the lung with PFC-liquid at FRC level (30 mL/kg) and used volume-controlled mechanical ventilation with a tidal volume > 15 mL/kg and a PEEP level between 2 and 6 cm H₂O in both the PLV as well as the control groups.

Greenspan and colleagues reported on the first human liquid ventilation experience in preterm infants [39]. Meanwhile the technique of PLV has been studied in neonatal, paediatric, and adult patients [40-42]. Leach et al. reported that partial liquid ventilation resulted in significant improvement in oxygenation in 13 premature infants with RDS after conventional treatment, including surfactant therapy, had failed [40]. A paediatric study in children with ARDS was stopped at enrolment of 182 patients, due to design problems of the study. Series of case reports have shown that partial liquid ventilation in adults is well tolerated and has resulted in improvement in oxygenation. A phase 2 clinical study included 90 patients, 65 of whom were treated with partial liquid ventilation [43]. Overall, the results from this study demonstrated no statistical differences between the treated and control patients. A multicenter study on PLV in adults with ARDS is running involving centres in the USA, Canada, and Europe.

Extracorporeal membrane oxygenation (ECMO)

Rescue therapy with ECMO for patients with severe refractory hypoxia remains of unclear benefit outside the neonatal population. A recent retrospective review by Masiakos et al. showed an overall survival rate of 53% for non-neonatal acute respiratory failure and ECMO support [44]. ELSO registry from July 1999 reported similar survival data of paediatric patients with acute respiratory failure [45]. MOSF and longer time on mechanical ventilation before ECMO predicted worse outcome, whereas duration of ECMO did not influence outcome. In another recent publication from a single institution Swaniker et al. reported an overall lung recovery in paediatric patients with acute respiratory failure of 77% and a hospital survival rate of 71% [46]. Zahraa et al. reported that the outcome of paediatric patients with acute respiratory failure supported by veno-arterial or veno-venous extracorporeal lung support was comparable (survival rate: 55.8% vs. 60%) and that neurological complications were not different between patients supported by veno-arterial or venous-venous bypass [47].

In our series of 11 patients 8 were supported by the veno-venous technique, 1 by veno-arterial technique, and 2 patients switched from veno-venous to veno-arterial bypass. The overall survival rate was 55%.

ARDS-Adjuncts

Surfactant

ARDS is associated with a quantitative decrease in total lung surfactant, changes in phospholipid/surfactant protein ratios, and surfactant inhibition from pathologic events in the alveolar space. While surfactant replacement therapy is well established in preterm and term infants, this therapy remains unproven beyond the neonatal period [48, 49]. In 1999 Wilson et al. showed in a multi-institutional, prospective, randomised, controlled study in 42 children with acute hypoxemic respiratory failure that patients who received surfactant therapy demonstrated rapid improvement in oxygenation, and, on average, were extubated 4.2 days (32%) sooner and spent 5 fewer days (30%) in paediatric intensive care than the control patients [50]. There was no difference in mortality rate or overall hospital stay. In the surfactant group 2 patients were on HFO, one patient inhaled NO, and one patient was on ECMO support, whereas in the control group 6 patients were on HFO, 2 inhaled NO, and one patient was on ECMO support. The overall mortality rate in this study was 11.9%, and only one death was from progressive respiratory failure. In this study 8 of 21 patients received a single dose of surfactant, and 10 patients a second dose. After the second dose the patients did not improve acutely. This is in contrast to the neonatal experience, where multiple doses have been shown to be beneficial. However, this study was not designed to compare single versus multiple doses of surfactant.

Inhaled nitric oxide (NO)

Acute respiratory failure is often associated with severe pulmonary ventilation-perfusion mismatch and pulmonary hypertension. Conventional intravenous vasodilator therapy results in a reduction of both the pulmonary and systemic pressures and worsening of gas exchange caused by a nonselective vasodilation of pulmonary arteries. Inhaled NO is a selective pulmonary vasodilator without any systemic side effects [51]. Inhaled NO rapidly diffuses from the alveoli of ventilated regions to the surrounding tissue causing relaxation of vascular smooth muscle cells. In the blood stream NO is rapidly bound to haemoglobin forming methemoglobin. In 1993 Rossaint et al. reported that inhaled NO reduces the pulmonary artery pressure and increases arterial oxygenation by improving ventilation-perfusion mismatch without producing systemic vasodilation [52]. Abman et al. reported their experience with inhaled NO in 10 paediatric patients with ARDS and 7 with severe viral pneumonias [53]. Inhalation of 20 ppm NO increased PaO₂ levels within 30 minutes by approximately 50% in each group. In addition mean pulmonary artery pressure was lowered from 42 ± 6 mmHg to 31 ± 6 mmHg ($p < 0.01$) and intrapulmonary shunt fraction decreased from $39 \pm 7\%$ to $32 \pm 7\%$ ($p < 0.01$). However, the mortality rate of 50% in the 10 children with ARDS was quite high.

Despite acute physiologic effects, it remains uncertain whether improved oxygenation and pulmonary haemodynamics during iNO therapy are “cosmetic” or actually translate to significant benefits in long-term outcomes. Recent multicenter, randomized trials of iNO therapy have consistently demonstrated improved oxygenation in adults with ARDS, but have not shown a reduction in mortality or morbidity [54]. Recently a randomized multicenter study on iNO therapy in paediatric patients with acute hypoxemic respiratory failure was published by Dobyns et al. [55]. One hundred and eight patients were enrolled for the study. Patients were randomized to iNO (10 ppm) or placebo treatment groups throughout a 3 day study period. Treatment failure defined as OI > 25 for 6 hrs or OI > 40 for 3 hrs was the primary study endpoint. Progressive haemodynamic deterioration, metabolic acidosis, methemoglobinemia or high NO₂ levels were criteria to exit the study and to receive “rescue” therapy. Oxygenation improved over time in both groups, but the response was greater with iNO treatment at 4 and 12 hrs. The rate of treatment failure remained greater in the control group over the first 24 hours. Despite this acute response, the proportion of patients who met treatment failure criteria was not different over the 3-day study. Mortality was not different between both groups (43%), but since cross-over was allowed, this mortality was not an end point of this study. During prolonged therapy the failure rate was reduced in the iNO group patients. The authors concluded that iNO causes an acute improvement in oxygenation in children with severe acute hypoxemic respiratory failure. Two subgroups (immunocompromised and an entry OI > 25) appear to have a more sustained improvement in oxygenation, and the authors speculated that these subgroups may benefit from prolonged therapy.

In a recent paper Ream et al. showed that inhaled NO at doses < 5 ppm improved oxygenation and to a lesser extent ventilation of 62% of children with acute, hypoxic respiratory failure [56]. Mortality was not influenced by prolonged inhalation of NO at doses < 20 ppm. The unpredictable response of patients necessitates individualized dosing of inhaled NO, starting at concentrations of < 1 ppm.

We used inhaled NO in 17 paediatric patients with ARDS. As shown in Table 1 we observed an acute increase in arterial oxygen saturation in 59% of the patients. However, despite this initial improvement in oxygenation, there was no significant difference in duration of mechanical ventilation, ECMO-support, and mortality rate between initial iNO responders and nonresponders.

Table 1. Inhaled NO in pediatric patients with ARDS (*n* = 17)

	Responder	Nonresponder
No. of patients	10	7
Duration of MV(d)	22 ± 5	26 ± 11
iNO (ppm)	4 ± 0.8	9.5 ± 2.1 *
ΔSpO ₂ (%)	9.2 ± 1.7	0.28 ± 0.89*
ARDS (n)		
Primary	5	5
Secondary	5	2
LIS	3.2 ± 0.15	3.3 ± 0.2
OI	29.4 ± 3.8	31.1 ± 5
VI	50.2 ± 5.5	45 ± 6.5
Immunosuppression (n)	2	3
ECMO-support (n)	4	2
Mortality rate (%)	40	43

Responder (ΔSpO₂ > 5%); Nonresponder (ΔSpO₂ < 5%); LIS = lung injury score; OI = oxygenation index (Paw * FiO₂ * 100/PaO₂); VI = ventilation index (PaCO₂ * PIP * RR/1000)

Prone position

There is now some evidence that turning a hypoxemic patient with ARDS from supine to prone position may improve oxygenation [57]. The proposed mechanisms for this improvement are an increase in FRC, change in regional diaphragm motion, redistribution of blood flow to less injured lung units and improved secretion clearance. Studies of experimental lung injury have shown that when turning to the prone position, preferential perfusion does not shift to the ventral part of the lung and that edema is more uniformly distributed along the gravitational axis. There was also no change in FRC or regional diaphragm movement. The explanation for the decreased shunting seen with prone position

seems to be that the gravitational distribution of pleural pressure is much more uniform in the prone position [58]. In the supine position the gravitational forces result in pleural pressure becoming positive in the dependent lung regions and dorsal lung units are below closing volume. This finding suggests that transpulmonary pressure may not exceed airway pressure in this region, resulting in lung collapse. The gravitational pleural pressure differences in the thorax are much less in the prone position, resulting in less of the lung below closing volume and decreased shunt. Recently Curley et al. demonstrated in a prospective case series in paediatric patients with acute lung injury that oxygenation improved without serious iatrogenic injury after prone positioning [59]. On the basis of their clinical findings the authors proposed a prospective randomized study investigating the effect of early and repeated prone positioning on clinical outcomes in paediatric patients with acute lung injury.

Outcome in ARDS

ARDS is a syndrome with many different aetiologies and the outcome will be greatly influenced by the underlying cause. For instance, the mortality in ARDS associated with sepsis is higher than that associated with trauma or patients with single system lung disease without other organ dysfunction. In a published series of adult ARDS patients hypoxemia was the primary cause of death in only 16% of patients, the rest being sepsis and multiorgan failure. Therefore the ability to demonstrate improved oxygenation alone using a non-conventional approach would be unlikely to have a significant impact on outcome unless it could be shown that it either decreases the amount of lung injury or shortens the duration of ventilator support. There is now experimental data showing that lung overdistension results in the release of cytokines which may be responsible for multiorgan injury and dysfunction [60]. This provides a further rationale for the use of ventilator strategies which prevent these events.

Most of the published data on ARDS in paediatric patients are small series reporting mortality rates between 40 and 70% [2-6, 8, 61]. A multicenter prospective study carried out on over 400 paediatric patients with acute respiratory failure, collected over a 1-year period, who required the combination of $\text{FiO}_2 > 0.5$ and $\text{PEEP} > 6 \text{ cm H}_2\text{O}$ for more than 12 hours, reported a mortality rate of 43% [62]. We treated 61 paediatric patients with ARDS over a time period of 16 years, 17 children between 1983 and 1990 with a conventional ventilatory approach and 44 children treated between 1991 and 2000 using a more lung protective approach. Mortality rate in patients treated before 1990 was 59% and the mortality in patients treated after 1990 was 27% (Fig. 1).

Fig. 1. Prognosis of ARDS in children under conventional mechanical ventilation and “lung protective” ventilation

CT: conventional therapy; ECMO: extracorporeal membrane oxygenation; S: responders; NS: nonresponders

Fig. 2. Therapeutic algorithm for children with ARDS

Conclusion

On the basis of experimental and clinical data we now use a treatment algorithm for paediatric patients with ARDS (Fig. 2) and we hope that using this algorithm will help us to decrease the mortality rate of children with ARDS below 20% in the next years.

References

1. Asbough DG, Bigelow DB, Petty TL et al (1967) Acute respiratory distress in adults. *Lancet* ii:319-323
2. Holbrook PR, Taylor G, Pollack MM et al (1980) Adult respiratory distress syndrome in children. *Pediatr Clin North Am* 27:677-685
3. Pfenninger J, Gerber A, Tschappeler H et al (1982) Adult respiratory distress syndrome in children. *J Pediatr* 101:352-357
4. Lyrene RK, Truog WE (1981) Adult respiratory distress syndrome in a pediatric intensive care unit: Predisposing conditions, clinical course, and outcome. *Pediatrics* 67:790-795
5. Timmons OD, Dean JM, Vernon DD (1991) Mortality rates and prognostic variables in children with adult respiratory distress syndrome. *J Pediatr* 119:896-899
6. DeBruin W, Notterman DA, Magid M et al (1992) Acute hypoxemic respiratory failure in infants and children: Clinical and pathologic characteristics. *Crit Care Med* 20:1223-1234
7. Royall JA, Levin DL (1988) Adult respiratory distress syndrome in pediatric patients. I: Clinical aspects, pathophysiology, pathology and mechanisms of lung injury. *J Pediatr* 112:169-180
8. Davis SL, Furman DP, Costarino AT et al (1993) Adult respiratory distress syndrome in children: Associated disease, clinical course, and predictors of death. *J Pediatr* 123:35-45
9. Matthay MA, Folkesson HG, Campagna A et al (1993) Alveolar epithelial barrier and acute lung injury. *New Horizons* 1:613-622
10. Kolobow T, Moretti MP, Fumagalli R et al (1987) Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation. An experimental study. *Am Rev Respir Dis* 135:312-315
11. Dreyfuss D, Soler P, Basset G et al (1988) High inflation pressure pulmonary edema: Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. *Am Rev Respir Dis* 137:1159-1164
12. Tremblay L, Valenza F, Ribeiro SP et al (1997) Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. *J Clin Invest* 99:944-952
13. Dreyfuss D, Saumon G (1998) Ventilator-induced lung injury. *Am J Respir Crit Care Med* 157:294-323
14. Hickling KG, Henderson SJ, Jackson R (1990) Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. *Intensive Care Med* 16:372-377
15. The Acute Respiratory Distress Syndrome Network (2000) 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* 342:1301-1308
16. Sheridan RL, Kacmarek RM, McEtrick MM et al (1995) Permissive hypercapnia as a ventilatory strategy in burned children: Effect on barotrauma, pneumonia, and mortality. *J Trauma* 39:854-859
17. Tibby SM, Cheema IU, Sekaran D et al (1999) Use of permissive hypercapnia in the ventilation of infants with respiratory syncytial virus. *Eur J Pediatr* 158:42-45
18. Trop M, Zobel G, Wanek E et al (1997) Controlled mechanical hypoventilation in pediatric burn patients as treatment of acute respiratory distress syndrome. *Burns* 23:166-169

19. Mariani G, Cifuentes J, Carlo WA (1999) Randomized trial of permissive hypercapnia in preterm infants. *Pediatrics* 104:1082-1088
20. Rimensberger PC, Pristine G, Mullen BM et al (1999) Lung recruitment during small tidal volume ventilation allows minimal positive end-expiratory pressure without augmenting lung injury. *Crit Care Med* 27:1940-1945
21. Lapinsky SE, Aubin M, Mehta S et al (1999) Safety and efficacy of a sustained inflation for alveolar recruitment in adults with respiratory failure. *Intensive Care Med* 25:1297-1301
22. Gaudencio AMAS, Troster EJ, Faria LF et al (2000) Effects of a lung recruitment maneuver keeping PEEP before and after L-Pflex on gas exchange in chilled ARDS patients. *Critical Care* 4[Suppl 1]:S67
23. Hamilton PP, Onayemi A, Smith JA et al (1983) Comparison of conventional and high-frequency ventilation: Oxygenation and lung pathology. *J Appl Physiol* 55:131-138
24. DeLemos RA, Coalson JJ, Gerstmann DR et al (1987) Ventilatory management of infant baboons with hyaline membrane disease: The use of high frequency ventilation. *Pediatr Res* 21:594-602
25. McCulloch PR, Forkert PG, Froese AB (1988) Lung volume maintenance during HFO in surfactant deficient rabbits. *Am rev Respir Dis* 137:1185-1192
26. Sugiura M, McCulloch P, Wren S et al (1994) Ventilator pattern influences neutrophil influx and activation in atelectasis prone rabbit lung. *J Appl Physiol* 77:1355-1365
27. Imai Y, Kawano T, Miyasaka K et al (1994) Inflammatory chemical mediators during conventional and during high frequency oscillatory ventilation. *Am J Respir Crit Care Med* 150:1550-1554
28. Arnold JH, Hanson JH, Toro-Figuero LO et al (1994) Prospective, randomized comparison of high-frequency oscillatory ventilation and conventional mechanical ventilation in pediatric respiratory failure. *Crit Care Med* 22:1530-1539
29. Lachmann B (1992) Open up the lung and keep the lung open. *Intensive Care Med* 18:319-321
30. Lachmann B, Verbrugge S (1996) Liquid ventilation. *Current Opinion in Critical Care* 2:60-66
31. Fuhrman BP, Paczan PR, DeFrancis M (1991) Perfluorocarbon-associated gas exchange. *Crit Care Med* 19:712-722
32. Tütüncü AS, Faithfull NS, Lachmann BL (1993) Intratracheal perfluorocarbon administration combined with mechanical ventilation in experimental respiratory distress syndrome: Dose-dependent improvement of gas exchange. *Crit Care Med* 21:962-969
33. Tütüncü AS, Faithfull NS, Lachmann BL (1993) Comparison of ventilatory support with intratracheal perfluorocarbon administration and conventional mechanical ventilation in animals with acute respiratory failure. *Am Rev Respir Dis* 148:785-792
34. Leach CL, Fuhrman BP, Morin III FC et al (1993) Perfluorocarbon-associated gas exchange (partial liquid ventilation) in respiratory distress syndrome: A prospective, randomized, controlled study. *Crit Care Med* 21:1270-1278
35. Papo MC, Paczan PR, Fuhrman BP et al (1996) Perfluorocarbon-associated gas exchange improves oxygenation, lung mechanics, and survival in a model of adult respiratory distress syndrome. *Crit Care Med* 24:466-474
36. Hirschl RB, Tooley R, Parent AC et al (1996) Evaluation of gas exchange, pulmonary compliance, and lung injury during total and partial liquid ventilation in the acute respiratory distress syndrome. *Crit Care Med* 24:1001-1008
37. Quintel M, Heine M, Hirschl RB et al (1998) Effects of partial liquid ventilation on lung injury in a model of acute respiratory failure: A histologic and morphometric analysis. *Crit Care Med* 26:833-843
38. Rotta AT, Gunnarsson B, Hernan LJ et al (1999) Partial liquid ventilation influences pulmonary histopathology in an animal model of acute lung injury. *J Crit Care* 14:84-92
39. Greenspan JS, Wolfson MR, Rubinstein SD et al (1990) Liquid ventilation of human preterm neonates. *J Pediatr* 117:106-111

40. Leach CL, Greenspan JS, Rubinstein SD et al (1996) Partial liquid ventilation with perflubron in premature infants with severe respiratory distress syndrome. *N Engl J Med* 335:761-767
41. Gauger PG, Pranikoff T, Schreiner RJ et al (1996) Initial experience with partial liquid ventilation in pediatric patients with acute respiratory distress syndrome. *Crit Care Med* 24:16-22
42. Hirschl R, Pranikoff T, Wise C et al (1996) Initial experience with partial liquid ventilation in adult patients with acute respiratory distress syndrome. *JAMA* 275:383-389
43. Bartlett R, Croce M, Hirschl RB et al (1997) A phase II randomized, controlled trial of partial liquid ventilation in adult patients with acute hypoxemic respiratory failure. *Crit Care Med* 25:A135
44. Masiakos PT, Islam S, Doody DP et al (1999) Extracorporeal membrane oxygenation for nonneonatal respiratory failure. *Arch Surg* 134:375-379
45. ELSO report 1999, Ann Arbor, Michigan
46. Swaniker F, Kolla S, Moler F et al (2000) Extracorporeal life support for 128 pediatric patients with respiratory failure. *J Pediatr Surg* 35:197-202
47. Zahraa JN, Moler FW, Annich GM et al (2000) Venovenous versus venoarterial extracorporeal life support for pediatric respiratory failure: Are there differences in survival and acute complications? *Crit Care Med* 28:521-525
48. Long W, Corbet A, Cotton R et al (1991) A controlled trial of synthetic surfactant in infants weighing 1250 g or more with respiratory distress syndrome. The American Exosurf neonatal study group I, and the Canadian Exosurf neonatal study group. *N Engl J Med* 352:1696-1703
49. Auten RL, Notter RH, Kendig JW et al (1991) Surfactant treatment of full-term newborns with respiratory failure. *Pediatrics* 87:101-107
50. Wilson DF, Zaritsky A, Bauman LA et al (1999) Instillation of calf lung surfactant extract (calfactant) is beneficial in pediatric acute hypoxemic respiratory failure. *Crit Care Med* 27:188-195
51. Zapol WM, Hurford WE (1993) Inhaled nitric oxide in the adult respiratory distress syndrome and other lung diseases. *New Horizons* 1:638-650
52. Rossaint R, Falke KJ, Lopez F et al (1993) Inhaled nitric oxide in adult respiratory distress syndrome. *N Engl J Med* 328:399-405
53. Abman SH, Griebel JL, Parker DK et al (1994) Acute effects of inhaled nitric oxide in children with severe hypoxemic respiratory failure. *J Pediatr* 124:881-888
54. Dellinger RP, Zimmermann JL, Taylor RW et al (1998) Effects of inhaled NO in patients with ARDS: Results of a randomized phase II trial. *Crit Care Med* 26:15-23
55. Dobyns EL, Cornfield DN, Anas NG et al (1999) Multicenter randomized trial of the effects of inhaled NO therapy on gas exchange in children with acute hypoxemic respiratory failure. *J Pediatr* 134:406-412
56. Ream RS, Hauver JF, Lynch-RE et al (1999) Low-dose inhaled nitric oxide improves the oxygenation and ventilation of infants and children with acute, hypoxemic respiratory failure. *Crit Care Med* 27:989-996
57. Blanch L, Mancebo J, Perez M et al (1997) Short-term effects of prone position in critically ill patients with acute respiratory distress syndrome. *Intensive Care Med* 23:1033-1039
58. Lamm WJ, Graham MM, Albert RK (1994) Mechanism by which the prone position improves oxygenation in acute lung injury. *Am J Respir Crit Care Med* 150:184-193
59. Curley MA, Thompson JE, Arnold JH (2000) The effects of early and repeated prone positioning in pediatric patients with acute lung injury. *Chest* 118:156-163
60. Ranieri VM, Suter PM, Tortorella C et al (1999) Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: A randomized controlled trial. *JAMA* 282:54-61
61. Zobel G, Kuttig M, Trop M et al (1990) A respiratory severity index for children with ARDS. *Clin Intensive Care* 1:17-21
62. Timmons OD, Havens PL, Fackler FC et al (1995) Predicting death in pediatric patients with acute respiratory failure. *Chest* 108:789-797