Recent Advances in Paediatric Ventilation

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ABSTRACT

Background: *To review the recent advances in ventilatory therapy for acute respiratory failure in children.*

Data sources: *Recent published peer-review articles on mechanical ventilation for acute respiratory failure in children.*

Summary of review: *Advances in conventional treatment for acute respiratory failure (e.g. mechanical ventilation) have not increased survival in children. However, recent therapies including high frequency ventilation, extracorporeal membrane oxygenation, nitric oxide and liquid ventilation have reported improved outcomes. The rationale and use of each are presented.*

Conclusions: *High frequency ventilation exists in three forms, although only high frequency oscillation appears to show any benefit in the management of acute respiratory failure refractory to conventional mechanical ventilation. Extracorporeal oxygenation has halved mortality in neonates with acute respiratory failure, and has been used successfully in non-neonate patients. Inhaled nitric oxide from 6 to 20 parts per million improves oxygenation in paediatric patients with acute respiratory failure and congenital heart disease (particularly in the presence of pulmonary arterial hypertension). Liquid ventilation or perfluorocarbon-associated gas exchange has also been used to treat acute respiratory failure in paediatric patients, with partial liquid ventilation particularly appearing to show promise.*

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Key words: Paediatric ventilation, high frequency ventilation, ECMO, liquid ventilation

Acute respiratory failure (ARF) continues to be a major problem in paediatric critical care. In a recent report from a large paediatric intensive care unit,[1] patients with ARF comprised nearly 3% of all admissions and 8% of total patient days. Mortality in this group was 62% and accounted for 33% of all deaths in the intensive care unit during the 24-month study period. Others report similar findings with mortalities ranging from 40% to 75%.[2-5] Freund and Jorch reviewed four recent reports of acute respiratory distress syndrome (ARDS) in children, reporting an overall mortality of 52%.[6]

Recent advances in conventional therapy for the treatment of ARF and ARDS have not had a major impact on survival. Firstly, the refinements of existing care have had complications, including volutrauma, barotrauma, oxygen toxicity, impairment of cardiac output and nosocomial infections with multiple system organ failure. Secondly, most therapies fail to treat the underlying cause of ARDS and the abnormalities of the surfactant system with accompanying derangements in lung compliance, pulmonary arterial hypertension (PAH), and ventilation-perfusion (V/Q) mismatch.

CONVENTIONAL MECHANICAL VENTILATION (CMV)

All modes of positive pressure ventilation used in adult intensive care units are also used in children, although paralysis or spontaneous breathing with triggered breaths, pressure and volume limited modes are most widely used. Cuffed endotracheal tubes are uncommonly used because of the smaller size of the endotracheal tube (no cuff allows a tube with a larger internal diameter), and the lower bronchial perfusion pressure of children which makes bronchial mucosal injury more likely. Humidification is essential to

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prevent endotracheal tube blockage with inspissated mucous. Diaphragmatic splinting by a distended stomach must be prevented in the spontaneously breathing child because of the dependence of the small child on diaphragmatic function.

Objectives of Mechanical Ventilation

Improve pulmonary gas exchange
- Relieve acute respiratory acidosis or ventilatory failure
- Reverse hypoxemia or hypoxemic respiratory failure

Change pressure-volume relations in lung
- Optimise pulmonary compliance
- Prevent or reverse atelectasis

Reduce or otherwise modulate work of breathing
- Decrease oxygen cost of breathing
- Reverse respiratory muscle fatigue
- Use anaesthesia, sedation, or neuromuscular blockade

Avoid complications
- Decrease or prevent anoxic-hypoxic events
- Prevent barotrauma, volutrauma, and oxygen toxicity

Support lung and airway healing
- Allow time for therapeutic intervention to succeed
- Allow time for lung repair to evolve

Promote independent breathing or independent lifestyle
- Facilitate ventilatory independence
- Provide partial, complete, ambulatory, permanent, or temporary assisted ventilation to support chronic debilitating illness or lung disease

Direct Goals

Oxygenation: Oxygen delivery (DO_2) and oxygen uptake (VO_2) are more important than arterial blood oxygen tension (PaO_2), thus an arterial blood haemoglobin oxygen saturation (SaO_2) of greater than 80% (with no metabolic acidosis) is adequate. Mean airway pressure and inspired oxygen concentration (FiO_2) may be minimised to limit volutrauma, barotrauma and oxygen toxicity.

Ventilation: respiratory acidosis (in the absence of metabolic acidosis) is rarely lethal, thus pH not carbon dioxide is the goal of ventilation (> 7.15). If reactive pulmonary hypertension is present then it may be necessary to have a pH > 7.4.

OTHER THERAPIES FOR ACUTE RESPIRATORY FAILURE

High Frequency Ventilation

High frequency ventilation (HFV) is a nonconventional mode of mechanical ventilation that has been used clinically for almost 15 years in the management of refractory ARF. There are three distinct types of HFV: High frequency positive-pressure ventilation (HFPPV), high frequency jet ventilation (HFJV), and high frequency oscillation (HFO). Important differences between the latter two modes of HFV are summarised in Table 1 and are comprehensively reviewed by Froese and Bryan.[7] Figure 1 illustrates an HFO device. All types of HFV effect elimination of carbon dioxide by the delivery of a very small tidal volume cycled at supraphysiologic respiratory rates.

HFPPV is similar to CMV and accomplishes gas exchange largely through bulk convection, although some bulk convection occurs with the other modes of HFV as well. The tidal volume generated with HFJV and HFV, however, is smaller than the anatomic dead-space volume itself, and thus, other mechanisms must be invoked to explain their effectiveness in ventilation.[8] These mechanisms include pendelluft, asymmetric velocity profiles, Taylor dispersion, and molecular diffusion.

Pendelluft refers to peripheral mixing of gas between alveolar units with variable time constants. During HFV, the respiratory cycle is shorter than the shorter alveolar time constant, and ventilation is considerably augmented as units with longer and shorter time constants empty into one another. Lung diseases in which there is considerable inequality in time constants between alveolar units, such as ARDS, theoretically amplify this effect by 300%.

Asymmetric velocity profiles refer to air flow that has, during inspiration, a parabolic velocity profile; whereas during expiration, it has a flat profile.

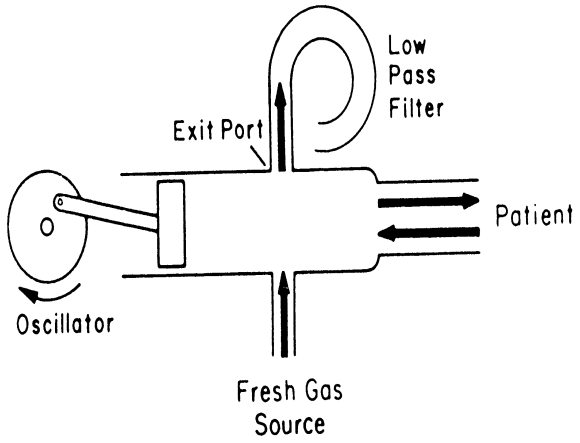

Figure 1. Schematic of a high frequency oscillator. Piston displacement, a function of rate and amplitude, determine "tidal volume". (From Wetzel RC, Gioia FR. High frequency ventilation. Pediatr Clin North Am 1987;34:15.)

Table 1. Differences between high frequency jet ventilation (HFJV) and high frequency oscillation (HFO)

	HFJV	HFO
Rate (H_Z)	1.5-3.0	3.0-15.0
Expiration	Passive	Active
Special ETT/reintubation	Yes	No
Gas exchange		
$\downarrow PaCO_2$	++	++
$\uparrow PaO_2$	±	+
Cardiac output	$\uparrow\downarrow$	$\downarrow$
Tracheal injury	++	?

Accordingly, net convective transport of gas occurs with each respiratory cycle. This mechanism of gas transport is particularly important at points of airway division, where velocity profiles are normally even more skewed.

Taylor dispersion refers to the dispersion of gas within the airway that results from the interaction between the axial velocity profile of the breath and the forces of radial diffusion that act on bases in motion; this effect is enhanced by the turbulent flow encountered at airway branch points and by the high flow velocities seen with HFV. This mechanism contributes significantly to gas mixing during HFV.

Finally, molecular diffusion is no less a factor in gas exchange with HFV than it is with CMV. Figure 2 illustrates those locations within the lung where these various mechanisms of gas exchange are thought to predominate.

HFO appears to be a therapy with great promise for the treatment of ARF refractory to management with CMV. It may also have a role in the prevention of iatrogenic lung injury and in the promotion of lung healing. A strategy that opens alveoli with a sustained inflation maneuver, maintains them open for gas exchange with sufficiently high airway pressure is most likely to achieve improved oxygenation and compliance, and decrease in lung injury.[9]

Proper monitoring of PaO_2, frequent chest radiographs, and serial determination of indices of pulmonary and cardiac function will decrease the potential for barotrauma and low cardiac output that is inherent with this therapy.

Extracorporeal membrane oxygenation (ECMO)

During the early 1970s, numerous cases and small series were reported which led to a multi-institutional ECMO trial in 1975.[10] This study, involving 9 centers over 2.5 years, randomised 90 adults patients with severe ARF to receive ECMO or CMV therapy.

Subsequently criticised for design and methodological flaws, this study failed to demonstrate benefit from ECMO and effectively stopped the use of that therapy in ARF for a time. However, interest in ECMO resurfaced in the early 1980s, led by pediatricians and neonatologists in search of modality that would provide temporising support to premature infants with hyaline membrane disease and persistent pulmonary hypertension of the newborn (PPHN).

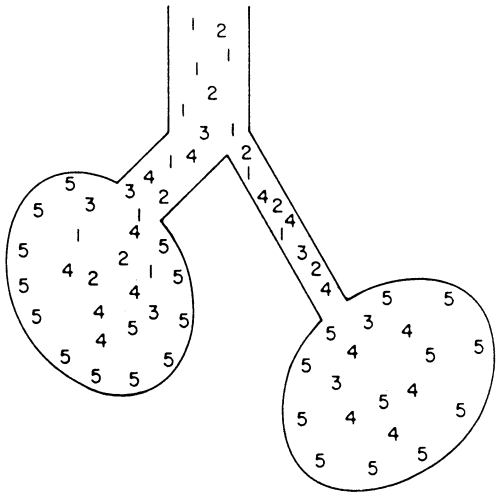

Figure 2. A representation of mechanisms of gas transport that predominate in given lung regions. 1 = bulk convection; 2 = Taylor dispersion; 3 = asymmetric velocity profiles; 4 = pendelluft; 5 = molecular diffusion. (From Wetzel RC, Gioia FR. High frequency ventilation. Pediatr Clin North Am 1987;34:15.)

Indications for neonatal ECMO became more refined as its complications became better understood (particularly bleeding in the more premature patients). A prospective, randomised study was undertaken in 1985 by O'Rourke *et al* in which neonates with ARF who fell into an 80% mortality group, as defined by historically derived predictor data, were randomised to receive either ECMO or conventional therapy.[11] Although the mortality in the control group was only half of that predicted, it was twice that in the ECMO

group, a survival figure that reached statistical significance and established ECMO as a standard therapy for selected groups of neonates, especially those with associated pulmonary arterial hypertension (PAH).

The success of ECMO in the neonatal population inspired renewed interest in applications of this therapy in the non-neonate, and once again, reports of successes in single cases and small series have begun to appear in the literature.[12-15]

Technical aspects

The advantages of veno-arterial compared with veno-venous ECMO include, maintaining a normal pulmonary blood flow, as an aid in lung healing, providing a better coronary blood pH and PaO_2, and maintaining a pulsatile flow. Cerebral embolism is also less likely to occur as the normal pattern of cerebral arterial flow is maintained.

Nitric oxide

Multiple physical and chemical stimuli acting on receptors located on the endothelial cell membrane, activate the intracellular enzyme, nitric oxide synthetase, which catalyses the conversion of L-arginine to nitric oxide (NO). This reaction appears to be dependent on the presence of cofactors, including reduced nicotinamide adenine dinucleotide phosphate (NADPH)[16] and sufficient substate[17] and can be blocked by various arginine analogues.[18] It may also involve active notrosothiol intermediates.[19] The NO so formed diffuses easily and rapidly from the endothelial cells into subjacent vascular smooth muscle cells, where it stimulates guanylate cyclase to increase the concentration of cyclic guanosine monophosphate, which in turn causes smooth muscle relaxtion.[20]

Nitrovasodilators currently in clinical use are thought to act via mechanisms that result in NO release.[21] Any NO that reaches the vascular space is quickly inactivated by binding to the heme ring of haemoglobin, which ultimately is metabolised to methaemoglobin.[22] Guanylate cyclase can also be inactivated by methylene blue,[23] also limiting the effect of NO.

Inhaled NO distributes to aerated lung only, where its localised vasodilating effect improves V/Q matching. Thereafter, any NO that diffuses into the vascular space is quickly inactivated by haemoglobin, so its systemic vasodilatory effects are minimal; thus inhaled NO acts as a selective pulmonary vasodilator.

Laboratory studies prepared the way for trials of inhaled NO in a variety of disease processes characterised by PAH or severe V/Q mismatching. Roberts *et al* used inhaled NO at 80 parts per million (ppm) to treat six infants with PPHN, which increased preductal SaO_2 in all six patients (88% to 97%) and postductal SaO_2 in five of six patients (82% to 90%), without systemic hypotension or significant methaemoglobinaema.[24] Little response was seen with a lower dose of NO and five of six patients manifested rebound PAH when the NO was discontinued after 30 minutes. One patient continued to respond to NO for 23 days.

Kinsella *et al*, reported their experience treating nine neonates with PPHN using NO at 10 to 20 ppm.[25] Within 15 minutes of initiating NO at 10 ppm, the PaO_2 increased from 55 mmHg to 136 mmHg and the oxygenation index (i.e. mean airway pressure x FiO_2 x 100 ÷ PaO_2) decreased from 60 to 26. No patient developed systemic hypotension or meth-aemoglobinaemia. Their first three of nine patients were treated with NO for less than 4 hours and, though they responded, they were referred for ECMO because the PAH persisted when the NO was discontinued. The last six of nine patients were treated for 24 hours with NO, the dose reduced progressively to 6 ppm; all continued to respond to NO administration, and none required ECMO.

In a subsequent report, Kinsella *et al*, again noted a marked improvement in oxygenation with NO for neonates with PPHN.[26] NO was initiated at 20 ppm for 4 hours, then maintained at 6 ppm for 20 hours. Only 1 out of 9 of these ECMO-eligible patients ultimately required ECMO; that patient received primarily left heart support for sepsis-induced low cardiac output and multiple organ system dysfunction. No patients had any haemodynamic compromise because of NO. The blood pressure was well maintained and heart rate fell, indicating a rising cardiac output, even in 2 of 3 of the patients with sepsis. Echocardiographic indices of PAH improved. Methaemoglobin levels peaked at 1.44 ± 0.09% with the "loading dose" of NO but, at 24 hours, were no different than the pretreatment values.

Finer *et al* studied 23 ECMO-eligible neonates treated with conventional medical therapy and surfactant, who continued to have an oxygenation index greater than 20.[27] Fourteen of the 23 patients showed some improvement in oxygenation with NO at 5 to 80 ppm, 1 in 14 responding hours later to NO having not responded initially, but 11 of 23 ultimately required ECMO. Eleven of 13 patients with echocardiographic signs of PAH responded to NO, whereas 7 of 10 with normal pulmonary artery pressures did not.

Abman *et al*, reported a 28-week gestation neonate with PAH secondary to sepsis, who demonstrated improved oxygenation and decreased pulmonary artery pressure (PAP) when treated with low-dose NO.[28] They speculated that NO might prove particularly helpful in the treatment of some preterm patients who were at great

risk for injury with conventional therapy for ARF and PAH, but who were not ECMO-eligible, because of their age and size.

Patients with PAH secondary to congenital heart disease may also benefit, both diagnostically and therapeutically, from NO. Roberts *et al* reported 10 patients, aged from 3 months to 6.5 years, with structural congenital heart disease and PAH; 6 had septal defects with left-to-right shunts, and 5 had trisomy 21.[29] Inhaled NO at 80 ppm was more effective at reducing pulmonary vascular resistance than oxygen at an FiO2 of 0.9. Pulmonary vascular resistance fell 20% with oxygen, 26% with NO at 80 ppm, and 54% with a combination of the two. Patients with the highest pulmonary vascular resistance had the greatest response to NO. A decrease in the systemic vascular resistance did not occur. The authors suggested that, in addition to being a short-term treatment for patients with PAH, NO might be useful in the cardiac catheterisation laboratory to determine which patients have reactive rather than fixed pulmonary vascular disease.

Wessel *et al*, determined the response to an acetylcholine infusion and NO in patients with structural congenital heart disease and PAH following cardiopulmonary bypass and repair.[30] They noted that NO at 80 ppm was a potent and selective pulmonary vasodilator both before and after cardiopulmonary bypass, but that the vasodilatory response to acetylcholine was diminished (37% reduction versus a 9% reduction) after cardiopulmonary bypass. They attributed this finding to cardiopulmonary bypass-induced pulmonary vascular endothelial dysfunction, with failure to release endogenous NO.

Following relief of chronic mitral stenosis with PAH, Girard *et al*[31] (in adults), and Atz *et al*[32] (in children), showed a pulmonary vasodilatory response to NO without a decrease in systemic arterial pressure. Atz *et al*, speculated that in children, where mitral stenosis commonly coexists with important left ventricular outflow tract obstruction, NO might be of particular benefit because systemic diastolic pressure, and therefore coronary artery perfusion, might be better maintained using a selective pulmonary dilator without system vascular effects.

A decrease in endothelium-dependent pulmonary vasodilation has been demonstrated with experimental left-to-right shunts,[33] Eisenmenger's syndrome,[34] idiopathic PAH,[35] and COPD.[36] Rossaint *et al*, treated 10 adults with ARDS using NO at 18 ppm and observed a 19% decrease in mean PAP, a 14% decrease in intrapulmonary shunt, and a 31% increase in PaO_2/FiO_2, the cardiac output and mean arterial blood pressure remained unchanged.[37] Inhaled NO remained effective even when administered continuously in one of these patients for up to 53 days. Methaemoglobin levels remained less than 1.3%.

Considerable potential exists with NO to reduce the short-term mortality and the long-term morbidity of severe cardiopulmonary failure in children. It appears that the long-sought selective pulmonary vasodilator may finally be here.

Liquid ventilation

The concept of liquid ventilation (LV) seems almost anti-evolutionary, yet, as a therapy for ARF, it offers several theoretic advantages compared with CMV for the safe, effective gas exchange in the surfactant-deficient lung.

Forces that determine surface tension may be predicted by considering the Laplace equation;

$$P = 2T/r$$

Where,

P = alveolar distending pressure
T = surface tension
r = radius of the alveolus

This predicts that if surface tension is decreased, lung expansion can be accomplished more easily, and even small alveoli can be maintained open for gas exchange at low distending pressures. The risk of pressure-induced lung injury is also decreased.

It has been reasoned that by using liquid functional residual capacity (FRC) and tidal gas breathing by CMV, oxygenation and carbon dioxide removal may be facilitated and one may improve pulmonary mechanics in the surfactant-deficient lung. Liquid-filled alveoli have a much diminished air-fluid interface, and thus, the surface tension forces that favor alveolar collapse are minimised. Other physical properties of fluid favor its more homogeneous distribution compared with gas, and therefore a more complete expansion of the lung. Oxygenation and ventilation will be directly enhanced if oxygen and carbon dioxide are highly soluble in the fluid used to inflate the alveoli, as the fluid itself will act as a gas exchange reservoir. Finally, the liquid can act mechanically to lavage particulate matter and inflammatory or infectious material from the lung, as well as delivering pharmacological agents to it.

Theoretic advantages of liquid ventilation

- Reduces lung distending pressures;
- Facilitates homogeneous lung expansion;
- Maintains functional residual capacity; and
- Acts as a vehicle for pulmonary administration of drugs to the lung.

Two forms of LV are currently used: total (tidal) liquid ventilation (TLV), and partial liquid (PLV) or perfluorocarbon-associated gas exchange (PAGE). With TLV, a volume of perfluorocarbon equal to the lung's functional residual capacity (FRC) is instilled via an endotracheal tube, and tidal volume (VT) aliquots of liquid are subsequently cycled to effect gas exchange, often utilising highly specialised apparatus. With PLV or PAGE, a volume of perfluorocarbon equal to the lung's FRC is instilled into the trachea, but unlike TLV the subsequent tidal ventilation is performed with respiratory gas administered via a standard mechanical ventilator at conventional settings. An extensive experimental literature has accumulated over the last 25 years for each form of LV, with animal studies documenting its efficacy and safety in mature and immature animals, both with and without a variety of respiratory disease processes. Succinct reviews of this topic have recently been published.[38,39]

Liquid ventilation, especially the technically simpler PLV or PAGE, is a promising therapy, the applications for which are increasing in number. Studies to date have focused on its use to improve gas exchange and increase respiratory compliance in surfactant deficiency states, especially in immature animals. Experimental evidence reported by Fuhrman's group supports its application in lung injury secondary to gastric aspiration[40] and in oleic acid-induced ARDS.[41] PAGE decreases protein loss into the alveoli if initiated prior to inducing ARDS with oleic acid.[42] Perfluorocarbon will also decrease free radical production by alveolar macrophages in vitro,[43] supporting another lung-protective role. Hirschl *et al*, determined that a combination of TLV and PLV improves lung compliance and gas exchange in animals supported with ECMO following oleic-acid-induced lung injury, with LV decreasing the ECMO blood flow requirements.[44] A recent report of gas exchange and compliance change in surfactant deficiency highlights the improvements in this group with PAGE and is summarised in Table 2.

Investigations are also ongoing utilising LV techniques to improve delivery of a wide variety of medications to the lung, for example, antimicrobial agents, surfactants, and NO. "Dose-response" curves for various applications of LV need to be determined and new perfluorocarbons need to be developed, the physical properties of which will hopefully facilitate particular therapies.

CONCLUSION

CMV of patients with ARF has undergone many changes over the past quarter century, with ever more sophisticated strategies and technology being used. Despite these advances, mobidity and mortality have been improved only modestly, at best. Further advances with modification of conventional therapies are likely to be limited by their failure to address the underlying physiologic disturbances which lead to the clinical syndrome of ARF, and their poor success rate in minimising complications associated with the therapy.

New approaches to treatment of ARF usually address some fundamental physiologic principle, for example, surface tension, heart-lung interaction,
normalisation of lung function in the diseased state, or V/Q mismatch, in ways which minimise iatrogenic lung injury.

A number of recently investigated novel therapies, including pressure-controlled ventilation with permissive hypercapnia, high-frequency ventilation, ECMO, inhaled nitric oxide therapy, and per-fluorocarbon liquid ventilation, show promise.

Table 2. Gas exchange and compliance in conventional mechanical ventilation versus perfluorocarbon-associated gas exchange

	CMV		PAGE		
Time (min)	-30	-5	5	30	60
PaO_2 (mm Hg)	61 ± 6	59 ± 6	250 ± 28	251 ± 18	268 ± 38
$PaCO_2$ (mm Hg)	62 ± 6	62 ± 4	50 ± 4	41 ± 3	38 ± 3
pH	7.19 ± .05	7.20 ± .04	7.27 ± .03	7.34 ± .04	7.36 ± .04
C_{Dyn} (ml/cm H_2O/kg)	0.33 ± .03	0.37 ± .04	0.85 ± .09	0.87 ± .08	0.88 ± .10

CMV = conventional mechanical ventilation; C_{Dyn} = dynamic compliance; PAGE = perfluorocarbon-associated gas exchange; $PaCO_2$ = partial pressure of carbon dioxide, arterial; PaO_2 = partial pressure of oxygen, arterial. From Leach CL, Fuhrman BP. Perfluorocarbon-associated gas exchange (PAGE) in surfactant deficiency. Am Rev Respir Dis 1992;145:A454.

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REFERENCES

1. Davis SL, Furman DP, Costarino AT Jr. Adult respiratory distress syndrome in children: Associated disease, clinical course, and predictors of death. J Pediatr 1993;123:35-45.
2. Lyrne RK, Truog WE. Adult respiratory distress syndrome in a pediatric intensive care unit: Predisposing conditions, clinical course, and outcome. Pediatrics 1981;67:790-795.
3. Rivera RA, Butt W, Shann F. Predictors of mortality in children with respiratory failure: Possible indications for ECMO. Anaesth Intensive Care 1990;18:385-389.
4. Tamburro RF, Bugnitz MC, Stidham GL. Alveolar-arterial oxygen gradient as predictor of outcome in patients with non-neonatal pediatric respiratory failure. J Pediatr 1991;119:935-938
5. Timmons OD, Dean JM, Vernon DD. Mortality rates and prognostic variables in children with adult respiratory distress syndrome. J Pediatr 1991;119:896-899.
6. Freund A, Jorch G. Pediatric characteristics of adult respiratory distress syndrome: A meta-analysis. Klin Padiatr 1993;205:411-415.
7. Froese AB, Bryan AC. High-frequency ventilation. Am Rev Respir Dis 1987;135:1363-1374.
8. Wetzel RC, Gioia FR. High frequency ventilation. Pediatr Clin North Am 1987;34:15-38.
9. Gerstmann DR, DeLemos RA, Clark RH. High-frequency ventilation: Issues of strategy. Clin Perinatol 1991;18:563-580.
10. Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. JAMA 1979;242:2193-2196.
11. O'Rourke PP, Crone RK, Vacanti JP, et al. Extracorporeal membrane oxygenation and conventional medical therapy in neonates with persistent pulmonary hypertension of the newborn: a prospective randomized study. Pediatrics 1989;84:957-963.
12. Adolph V, Heaton J, Steiner R, Bonis S, Falterman K, Arensman R. Extracorporeal membrane oxygenation for non-neonatal respiratory failure. J Pediatr Surg 1991;26:326-330.
13. Butt W, Karl T, Horton A, Shann F, Mullaly R. Experience with extracorporeal membrane oxygenation in children more than one month old. Anaesth Intensive Care 1992;20:308-310.
14. Steiner RB, Adolph VR, Heaton JF, Bonis SL, Falterman KW, Arensman RM. Pediatric extracorporeal membrane oxygenation in posttraumatic respiratory failure. J Pediatr Surg 1991;26:1011-1014.
15. Weber TR, Tracy TF Jr, Connors R, Kountzman B, Pennington DG. Prolonged extracorporeal support for nonneonatal respiratory failure. J Pediatr Surg 1992;27:1100-1104.
16. Palmer RM, Moncada S. A novel citrulline-forming enzyme implicated in the formation of nitric oxide by vascular endothelial cells. Biochem Biophys Res Commun 1989;158:348-352.
17. Mitchell JA, Hecker M, Vane JR. The generation of L-arginine in endothelial cells is linked to the release of endothelim-derived relaxing factor. Eur J Pharmacol 1990;176:253-254.
18. Vargas HM, Cuevas JM, Ignarro LJ, Chaudhuri G. Comparison of the inhibitory potencies of N-methyl-, N-nitro and n-amino-L-arginine on EDRF function in the rat: Evidence for continuous basal EDRF release. J Pharmacol Exp Ther 1991;257:1208-1215.
19. Ignarro LJ, Lippton H, Edwards JC, et al. Mechanism of vascular smooth muscle relaxation by organic nitrates, nitrites, nitroprusside, and nitric oxide: Evidence for the involvement of S-nitrosothiols as active intermediates. J Pharmacol Exp Ther 1981;218:739-749.
20. Griffith TM, Edwards DH, Lewis MJ, Henderson AH. Evidence that cyclic guanosine monophosphate (cGMP) mediates endothelium-dependent relaxation. Eur J Pharmacol 1985;112:195-202.
21. Gruetter DY, Gruetter CA, Barry BK, et al. Activation of coronary artery guanylate cyclase by nitric oxide, nitroprusside, and nitrosoguanidine: Inhibition by calcium, lanthanum, and other cations; enhancement by thiols. Biochem Pharmacol 1980;29:2943-2950.
22. Doyle MP, Hoekstra JW. Oxidation of nitrogen oxides by bound dioxygen in hemoproteins. J Inorg Biochem 1981;14:351-358.
23. Gruetter CA, Gruetter DY, Lyon JE, Kadowitz PJ, Ignarro LJ. Relationship between cyclic guanosine 3'-5'monophosphate formation and relaxation of coronary arterial smooth muscle by glyceryl trinitrate, nitroprusside, nitrite, and nitric oxide: effects of methylene blue and methemoglobin. J Pharmacol Exp Ther 1981;219:181-186.
24. Roberts JD, Polaner DM, Lang P, Zapol WM. Inhaled nitric oxide in persistent pulmonary hypertension of the newborn. Lancet 1992;340:818-819.
25. Kinsella JP, Neish SR, Shaffer E, Abman SH. Low-dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn. Lancet 1992;340:819-820
26. Kinsella JP, Neish SR, Ivy DD, Shaffer E, Abman SH. Clinical responses to prolonged treatment of persistent pulmonary hypertension of the newborn with low doses of inhaled nitric oxide. J Pediatr 1993;123:103-108.
27. Finer NN, Etches PC, Kamstra B, Tierney AJ, Peliowski A, Ryan CA. Inhaled nitric oxide in infants referred for extracorporeal membrane oxygenation: dose response. J Pediatr 1994;124:302-308.
28. Abman SH, Kinsella JP, Schaffer MS, Wilkening RB. Inhaled nitric oxide in the management of a premature newborn with severe respiratory distress and pulmonary hypertension. Pediatrics 1993;92:606-609.
29. Roberts JD Jr, Lang P, Bigatello LM, Vlahakes GJ, Zapol WM. Inhaled nitric oxide in congenital heart disease. Circulation 1993;87:447-453.
30. Wessel DL, Adatia I, Giglia TM, Thompson JE, Kulik TJ. Use of inhaled nitric oxide and acetylcholine in the evaluation of pulmonary hypertension and endothelial

function after cardiopulmonary bypass. Circulation 1993;88:2128-2138.
31. Girard C, Lehot JJ, Pannetier JC, Filley S, Ffrench P, Estanove S. Inhaled nitric oxide after mitral valve replacement in patients with chronic pulmonary artery hypertension. Anesthesiology 1992;77:880-883.
32. Atz AM, Adatia I, Jonas RA, Wessel DL. Inhaled nitric oxide in children with pulmonary hypertension and congenital mitral stenosis Am J Cardiol 1996;77:316-319.
33. Fineman JR, Reddy MV, Wong J. Early impairment of endothelium-dependent vasoactive responses in lambs with increased pulmonary blood flow and pulmonary hypertension. Pediatr Res 1994;35:24A.
34. Dinh Xuan AT, Higenbottam TW, Clelland C, Pepke-Zaba J, Cremona G, Wallwork J. Impairment of pulmonary endothelium-dependent relaxation in patients with Eisenmenger's syndrome. Br J Pharmacol 1990;99:9-10.
35. Pepke-Zaba J, Higenbottam TW, Dinh-Xuan AT, Stone D, Wallwork J. Inhaled nitric oxide as a cause of selective pulmonary vasodilation in pulmonary hypertension. Lancet 1991;338:1173-1174.
36. Dinh-Xuan AT, Higenbottam TW, Clelland CA, et al. Impairment of endothelium-dependent pulmonary artery relaxation in chronic obstructive lung disease. N Engl J Med 1991;324:1539-1547.
37. Rossaint R, Falke KJ, Lopez F, Slama K, Pison U, Zapol WM. Inhaled nitric oxide for the adult respiratory distress syndrome. N Engl J Med 1993;328:399-405.
38. Greenspan JS. Liquid ventilation: A developing technology. Neonatal Net 1993;12:23-32.
39. Shaffer TH, Wolfson MR, Clark LC Jr. Liquid ventilation. Pediatr Pulmonol 1992;14:102-109.
40. Nesti FD, Fuhrman BP, Steinhorn DM, et al. Perfluorocarbon-associated gas exchange in gastric aspiration. Crit Care Med 1994;22:1445-1452.
41. Papo M, Paczan P, Burak B, et al. A medical grade perfluorocarbon used during PAGE improves oxygenation and ventilation in a model of ARDS. Crit Care Med 1993;21:S288.
42. Papo M, Holm B, Fuhrman B, et al. Perfluorocarbon associated gas exchange (PAGE) instituted prior to lung injury decreases intra-alveolar protein flux. Crit Care Med 1994;22:A141.
43. Smith T, Steinhorn D, Marcucci K, Thusu K, Dandona P, Fuhrman B. Perflubron (PFB) decreases free radical (FR) production by alveolar macrophages (AM) in vitro. Crit Care Med 1994;22:A196.
44. Hirschl RB, Grover B, McCracken M, Wolfson MR, Shaffer TH, Bartlett RH. Oxygen consumption and carbon dioxide production during liquid ventilation. J Pediatr Surg 1993;28:513-518.