

# 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.

(Critical Care and Resuscitation 1999; 1: 85-92)

**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,<sup>1</sup> 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%.<sup>2-5</sup> Freund and Jorch reviewed four recent reports of acute respiratory distress syndrome (ARDS) in children, reporting an overall mortality of 52%.<sup>6</sup>

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 mucus. 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 hypoxic 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 ( $\text{DO}_2$ ) and oxygen uptake ( $\text{VO}_2$ ) are more important than arterial blood oxygen tension ( $\text{PaO}_2$ ), thus an arterial blood haemoglobin oxygen saturation ( $\text{SaO}_2$ ) of greater than 80% (with no metabolic acidosis) is adequate. Mean airway pressure and inspired oxygen concentration ( $\text{FiO}_2$ ) 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**

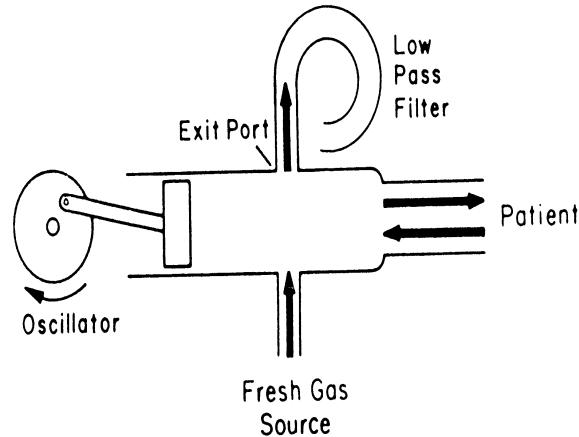
High frequency ventilation (HFV) is a nonconventional mode of mechanical ventilation that has been used clinically for almost 15 years in the management of refractory ARF. There are three distinct types of HFV: High frequency positive-pressure

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.<sup>7</sup> 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.<sup>8</sup> 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 (Hz)	1.5-3.0	3.0-15.0
Expiration	Passive	Active
Special ETT/reintubation	Yes	No
Gas exchange		
↓ PaCO <sub>2</sub>	++	++
↑PaO <sub>2</sub>	±	+
Cardiac output	↑↓	↓
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.<sup>9</sup>

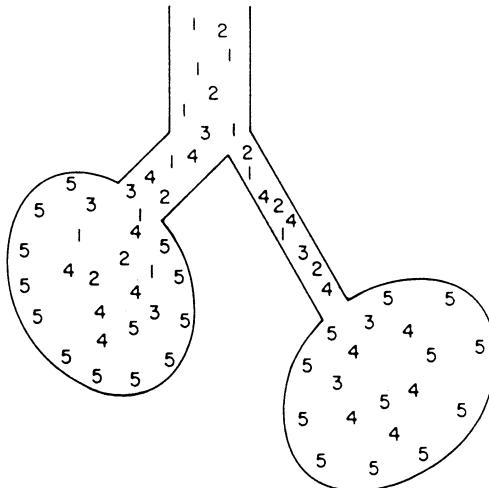
Proper monitoring of PaO<sub>2</sub>, frequent chest radiographs, and serial determination of indices of pulmonary and cardiac function will decrease the potential for barotrauma and low cardiac output that is inherent with this therapy.

#### 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.<sup>10</sup> 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.<sup>11</sup> 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.<sup>12-15</sup>

#### *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<sub>2</sub>, 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)<sup>16</sup> and sufficient substrate<sup>17</sup> and can be blocked by various arginine analogues.<sup>18</sup> It may also involve active notrosothiol intermediates.<sup>19</sup> 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 relaxation.<sup>20</sup>

Nitrovasodilators currently in clinical use are thought to act via mechanisms that result in NO release.<sup>21</sup> Any NO that reaches the vascular space is quickly inactivated by binding to the heme ring of haemoglobin, which ultimately is metabolised to methaemoglobin.<sup>22</sup> Guanylate cyclase can also be inactivated by methylene blue,<sup>23</sup> 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<sub>2</sub> in all six patients (88% to 97%) and postductal SaO<sub>2</sub> in five of six patients (82% to 90%), without systemic hypotension or significant methaemoglobinaemia.<sup>24</sup> 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.<sup>25</sup> Within 15 minutes of initiating NO at 10 ppm, the PaO<sub>2</sub> increased from 55 mmHg to 136 mmHg and the oxygenation index (i.e. mean airway pressure x FiO<sub>2</sub> x 100 ÷ PaO<sub>2</sub>) decreased from 60 to 26. No patient developed systemic hypotension or methaemoglobinaemia. 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.<sup>26</sup> 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.<sup>27</sup> 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.<sup>28</sup> 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.<sup>29</sup> Inhaled NO at 80 ppm was more effective at reducing pulmonary vascular resistance than oxygen at an FiO<sub>2</sub> 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.<sup>30</sup> 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*<sup>31</sup> (in adults), and Atz *et al*<sup>32</sup> (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,<sup>33</sup> Eisenmenger's syndrome,<sup>34</sup> idiopathic PAH,<sup>35</sup> and COPD.<sup>36</sup> 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<sub>2</sub>/FiO<sub>2</sub>, the cardiac output and mean arterial blood pressure remained unchanged.<sup>37</sup> 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.

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