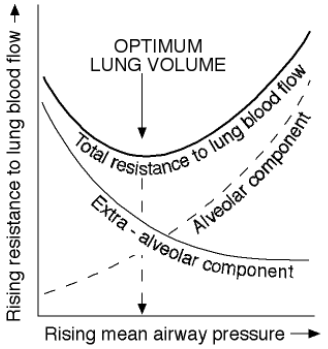
NITRIC OXIDE (Commentary)

When neonatal central cyanosis is not relieved by ventilation

The first need when pulmonary artery pressure does not fall after birth, and a baby presents with features of what used to be called a 'persistent fetal circulation', is to get cyanotic congential heart disease ruled out by an experienced paediatric echocardiographer. While this is being done management, initially, consists of optimising lung expansion, and then optimising left ventricular output and systemic blood pressure before attempting to reduce pulmonary vascular resistance. Babies who are this cyanosed usually require both sedation and paralysis, and many also benefit from treatment with natural surfactant. Sequential ventilator adjustments will help to establish what mean airway pressure provides the best balance between minimising resistance to pulmonary blood flow (see figure) while optimising alveolar ventilation.



It is important to try and determine why desaturated blood is reaching the left side of the heart before instituting treatment. Blood may be passing right-to-left through a patent foramen ovale, or through a patent duct, or passing through the lung without picking up oxygen. There may be a left-to-right shunt between the atria and through the duct, or a right-to-left shunt within the lung – a situation most typically seen in very low birth weight babies with patchy atelectasis or pulmonary interstitial emphysema. Such babies seldom obtain sustained benefit from a pulmonary vasodilator. In term babies without respiratory disease (or with meconium aspiration and asphyxia) cyanosis is usually due to a persistence of the high pulmonary vascular tone normally present before birth. Blood continues to shunt right-to-left across the duct, and a dilated failing right ventricle causes right atrial pressure to rise resulting in further right-to-left flow across the foramen ovale. A chest x-ray may suggest that pulmonary blood flow is sparse, and pulse oximetry may provide evidence of a ductal shunt with saturation in the ("preductal") right arm higher than elsewhere. This persistence of the fetal circulation is now generally called persistent pulmonary hypertension, although the hypertension is usually more relative than absolute.

Once mean airway pressure and left ventricular function have been optimised it may be appropriate to try to manipulate pulmonary vascular tone. A physiological approach should be tried before resorting to drugs. Hypoxia, acidosis and a high arterial pCO_2 (carbon dioxide pressure) may need correction since all increase pulmonary vascular tone. Hyperventilation can cause volume/pressure damage to the lung, and potentially harmful cerebral vasoconstriction, so it may be more appropriate to raise the pH above 7·4 by infusing base. If cyanosis persists and systemic blood pressure is satisfactory then IV tolazoline or epoprostenol (a more expensive vasodilator) should be considered. These will have some effect at once if they are going to work at all. Magnesium sulphate may also be of some value (although no comparative trials have yet been undertaken) but this only seems to work more slowly. However all these agents affect systemic as well as pulmonary vascular tone, and lower systemic as well as pulmonary arterial blood pressure. Intratracheal tolazoline and nebulised epoprostenol have been used experimentally with good effect, and this approach minimises the risk of systemic vasodilatation. Treatment with inhaled nitric oxide has, however, now become the treatment of choice when other treatment strategies fail, even though commercial supplies of the gas now make treatment very expensive.

Use of nitric oxide in term, and near term, babies and in older patients

Nitric oxide treatment has been very widely used in adults with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) for fifteen years, and it often improves oxygenation at least marginally for at least a few days. However a whole series of relatively small randomised trials have failed to provide evidence that use improves survival, and meta-analysis of 12 trials involving 1237 patients published in 2007 showed that while the PaO_2/FiO_2 ratio improved for a time, it delivered no reduction in pre-discharge hospital mortality, or time on a ventilator, and there was some evidence that use actually increased the risk of renal dysfunction (Achikari *et al*., 2007) even when the dose used is kept below 20 ppm. On the basis of this evidence the routine use of nitric oxide in adults has now started to decline.

Nitric oxide *is* however now accepted as being the most effective pulmonary vasodilator in babies of more than 34 weeks gestation. While nitric oxide use does not seem to improve survival, it does reduce the need for ExtraCorporeal Membrane Oxygenation (ECMO). Neither of these strategies should be delayed until the baby is *in extremis,* and prompt referral to a centre capable of providing ECMO should be considered if the oxygenation index (OI) approaches 300, [or 40 if arterial oxygen pressure (pO_2) is being measured in mmHg rather than kPa], and does not fall at least 20% after 4 hours of treatment with nitric oxide. The formula for calculating the oxygenation index is:

OI = mean airway pressure (cm H_2O) x % oxygen in inspired air / post ductal arterial pO_2 (kPa)

Because administration during inter-hospital transfer is not easy, and babies respond badly if treatment is interrupted even briefly once started (even when there seems to have been no response to treatment) use is difficult to justify In units that lack echocardiographic expertise and ready access to an ECMO facility. The results from seven trials involving 847 babies (NINOS, 1997; Roberts *et al.,* 2007; Wessel *et al.,* 1997; Davidson *et al.,* 1998; Christou *et al.,* 2000; Clark *et al.*, 2000, Field *et al.,* 2006) show that while neonatal treatment with nitric oxide does not reduce mortality it can reduce the number of babies needing ECMO by 40% (Relative risk 0·62 [95% CI 0·52, 0·73]). Six trials (NINOS, 2000; Ellington *et al.,* 2001; Lipkin *et al.,* 2002; Clark *et al.,* 2003; Field *et al.,* 2007; Konduri et al., 2007) have now reported long term outcomes. There is no evidence that treatment with nitric oxide is harmful, but it has not yet been found to do anything to reduce the burden of long term disability, which is often significant in babies who have been as ill as this. Nitric oxide can also be of use in some rather older children.

Use of nitric oxide in babies of less than 34 weeks gestation

Although it is now well established that inhaled nitric oxide can reduce the number of term and near babies requiring ECMO treatment for severe hypoxic respiratory failure, evidence that the drug is of use in the *preterm* baby remains illusive. One influential early trial could find no evidence that giving nitric oxide to preterm babies with severe established lung damage did any good (Subhedar *et al.,* 1997), and later follow up assessment confirmed this (Bennett *et al.,* 2001). The focus since then has been on whether earlier treatment, or even 'preventive' treatment, might be more effective. Unfortunately few of these trials (other than the trials reported by Schreiber and van Meurs) have yet reported what the long term outcome was, and it is increasingly clear that many of the features seen on the cranial ultrasound scans that were done during these trials are relatively poor predictors of long term disability. While serious neurosensory disability can be predicted with some certainty when there is clear evidence of parenchymal brain damage, the *absence* of such an appearance does not guarantee lack of disability two years later (Laptook *et al*., 2005). Scans done 6–8 weeks after birth are better at picking up periventricular leukomalacia, porencephalic change, and cortical atrophy with or without features of ventriculomegally, but these were seldom done or reported in these trials

Late treatment for moderate disease: One recent trial (Ballard *et al.,* 2006) recruited 582 babies who weighed 1250 grams of less at birth (mean gestation 26 ± 1·5 weeks) and who had no evidence of severe intracranial bleeding but who were still ventilator dependent when 7–21 days old, and exposed them to a slowly decreasing dose of nitric oxide for at least 24 days. Most of these babies were only moderately oxygen dependent at recruitment (with an OI that was normally between 5 and 9 when arterial pO_2 is measured in mm Hg units). There was a marginal increase in the number of babies who were alive and no longer oxygen dependent at a postmenstrual age of 36 weeks (43·9 *v.* 36·8%) and, in a subgroup analysis that had not been pre-specified before the trial began, they found that benefit was only seen in those starting treatment 7–14 days after birth. However, there was no difference in the number surviving (94·6 v. 93·7%), and it is arguable whether treatment of this nature, which is inevitably expensive, can be justified simply because it reduces the length of time a baby remains oxygen dependent (as judged using the Walsh test). Children recruited into the active arm of the trial received rather less medication in the year after discharge, but they were no less likely to need readmission to hospital for respiratory problems later in the first year of life (22·6 v. 21·9%). The outcome of the developmental assessment of these children at two years has not yet been reported.

Early treatment for serious established disease: The merged results from four trials of early 'rescue' treatment involving a total of 650 babies of less than 34 weeks gestation with rather more severe lung disease (babies typically had an OI above 10 at recruitment) in whom a variable period of treatment (Kinsella *et al.,* 1999; Field *et al.,* 2005; Van Meurs *et al.,* 2005; and Dani *et al.,* 2006) was started within 7 days of birth, suggest a marginal *decrease* in the number of babies still oxygen dependent at a postmenstrual age of 36 weeks, but an equally marginal *increase* in the number of deaths. There seemed to be no difference in the incidence of severe (grade 3–4) intraventricular haemorrhage and/or periventicular leukomalacia, and reports on the surviving babies from the Van Meurs trial, and from the smaller Field trial, suggest that use in babies who are already very ill did not improve the long term survival or the neurodevelopmental progress made by those who did survive (Hintz *et al.,* 2007; Field *et al.*, 2007).

Early 'prophylactic' treatment for the ventilator dependent baby: Schreiber *et al.*, 2003, randomised 207 ventilated babies of less than 34 weeks gestation to receive *early* inhaled nitric oxide or placebo for 7 days before they were three days old. The infants in this single centre study all had a birth weight of less than 2000g (mean 989 grams) and had a median OI of 7 when recruited, and those randomised to treatment with 5–10 ppm of nitric oxide were less likely to be dead or still oxygen dependent at a postmenstrual age of 36 weeks. They were also less likely to have severe intraventricular haemorrhage. However benefit was most noticeable in those babies who only had moderate respiratory distress when recruited (OI <7), and an unusually large number of the control babies had an intraventricular haemorrhage or were still oxygen dependant at 36 weeks. Those with severe disease seemed to derive little benefit. Findings at follow up at two years were in line with the findings at the time of discharge (Mestan *et al,* 2005).

Kinsella *et al.,* 2006 recruited a further 793 babies who weighed 1250 grams or less at birth and were less than 34 weeks gestation. All were intubated and all were still less than 48 hours old when recruited. Half of those recruited were then randomised to treatment with low dose (5ppm) nitric oxide for up to 21 days. Most of the babies only had moderate disease when recruited (mean OI [SD] 5·6 ± 5·9). There was no difference in the primary outcome (death or continued oxygen dependency at a postmenstrual age of 36 weeks), or in any of the individual secondary outcomes, but there was a marginal decrease (17·5 v. 23·9%) in the number of babies with some form of cerebral insult (either severe intraventricular bleeding, or haemorrhagic ventriculomegally or periventricular leukomalacia) in those given continuous low dose nitric oxide for three weeks (or until extubation). There was, however, no difference in outcome at one or two years (Kinsella *et al.,* 2009; Watson *et al.,* 2009).

What is a little surprising in these two trials is that treatment failed to significantly reduce the incidence of bronchopulmonary dysplasia – the condition for which nitric oxide was ostensibly being given – although it did reduce the number of deaths (relative risk for the two trials combined 0·77 [95% CI 0·61 – 0·98]). This failure is all the more remarkable because 56% of the babies in Schreiber's trial and 73% of the babies in Kinsella's trial had died or were still oxygen dependent at a postmenstrual age of 36 weeks. The mean gestation of the babies in Schreiber's trial was 27·2 weeks, and the mean gestation of those in Kinsella's trial was 25·6 weeks. These were, therefore, the very babies where the need to minimise the risk of chronic lung damage is highest. A further more recent trial involving 800 European babies, so far only published in abstract (Mercier *et al.,* 2009) failed to find any evidence of pre-discharge benefit for any outcome or for any trial subgroup.

Use where there is clear evidence of pulmonary hypertension: The suggestion that treatment in babies of more than 34 weeks gestation is generally successful, while treatment of babies less mature than this is, at most, of marginal value is, of course, almost certainly an over-simplification and there is one study (Tanaka *et al.,* 2007) that suggests that treatment with nitric oxide can be of value in babies of less than 34 weeks gestation who have clear evidence of persisting pulmonary hypertension.

Does treatment increase the risk of intracranial bleeding? There has been concern that exposure to nitric oxide might increase the risk of intracerebral bleeding in the very preterm baby, but there seems to be little evidence of this. Indeed two large trials (Schreiber *et al.,* 2003; Kinsella *et al.,* 2006) of early prophylactic treatment have presented sub-group analyses suggesting that early treatment can actually *decrease* the incidence of grade 3–4 intraventricular haemorrhage. Sub-group analyses of this type (especially if not pre-specified) can easily find differences that subsequent trials fail to confirm. On the other hand nitric oxide exposure was associated with a significant *increase* in the number of babies developing a grade III-IV intraventricular haemorrhage among the 420 babies in the van Meurs trial and, on follow up, Hintz *et al.,* 2007 found that more babies so treated did not survive or survived with quite severe cerebral palsy. It will, therefore, be very instructive to see what the outcome of the large, industry funded, EuNO trial that is currently recruiting in Europe turns out to be. This is a trial looking at the value of giving early sustained low dose nitric oxide to babies of less than 29 weeks gestation who have been given surfactant, or found to need an inspired oxygen of 30% or more when offered nasal CPAP (at a pressure of ≥ 4 cm H_2O), within 24 hours of birth. Outcome will be assessed not only when the babies reach a post-menstrual age of 36 weeks, but also two years after they were due to be born.

In the interim we have the illogical situation that many clinicians now find themselves tempted use nitric oxide as a treatment of last resort when faced with a seriously ill preterm baby because there is nothing to loose and nothing else to do, although trials suggest that such treatment is of little benefit, but remain reluctant to advocate early prophylactic use even though these are the babies where there is most evidence, at the moment, that treatment can be of benefit. One reason for this reluctance must be because sustained early use is extremely expensive. Stark (2006) quotes a figure of $3,000 a day for the current cost of using nitric oxide in North America, and use in babies offered early 'rescue' treatment to babies who were chronically ventilator dependent 7-14 days in the Ballard trial did not significantly decrease total pre-discharge costs (Zupancic *et al.,* 2009). A second reason may be that the recent Mercier and Kinsella trials found no evidence that early prophylactic use was beneficial. In the mean time simpler, less aggressive, strategies of respiratory support, and the wider use of caffeine citrate (q.v.), look set to do more than nitric oxide to reduce the risk of chronic lung scaring and long term oxygen dependency in the very preterm baby. The case for using nitric oxide in these babies when there is no evidence of persisting pulmonary hypertension is probably going to depend on whether it proves possible to corroborate current claims that such treatment can be 'neuroprotective' and there is, at present, very little evidence of this.

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