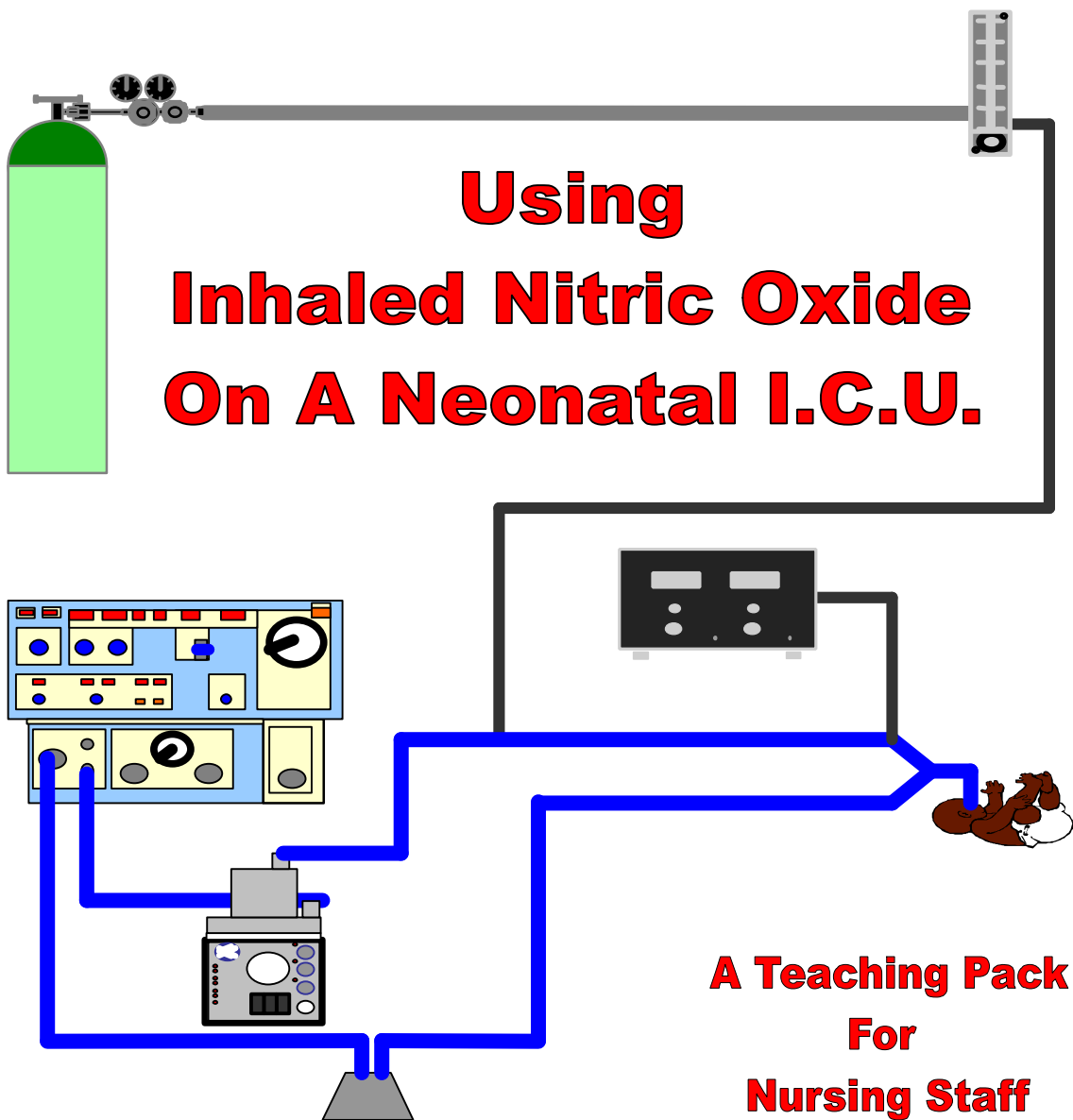


The INNOVO Trial

Neonatal ventilation with **IN**haled **Nitric Oxide**
versus **Ventilatory** support with**Out** inhaled
nitric oxide for severe respiratory failure:

a multicentre randomized controlled trial

Funded by the Medical Research Council



**A Teaching Pack
For
Nursing Staff**

produced by
The INNOVO Trial

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Aim

This teaching pack is aimed at neonatal nursing staff in The INNOVO Trial participating units, using or planning to use inhaled nitric oxide for the treatment of neonates with severe respiratory failure. It brings together an overview of the current evidence, technical information and nursing guidelines.

Introduction

Nitric oxide (NO) is a naturally occurring vasodilator which also plays a part in several other physiological processes, including neurotransmission and platelet aggregation.¹ The introduction of NO therapy for neonates has mainly been to treat babies with pulmonary hypertension and severe hypoxic respiratory failure.² The effectiveness and safety of NO has not yet been fully determined and it is still the subject of ongoing research.

Why is NO used?

Inhaled nitric oxide (INO) is used for its properties as a selective vasodilator. It is administered directly into the lungs mixed with ventilator gases and is absorbed into the pulmonary circulation through aerated alveoli.

Its action as a vasodilator can have the following effects: -

- a) Increased blood flow through aerated areas of the lungs.
- b) Pulmonary artery dilation, reduction in pulmonary artery pressure and reduction in right to left shunting.

The overall result should be an increase in oxygenation.³ A big advantage of NO is that, because of its very short half-life, it only has a local pulmonary effect when given as an inhaled gas. Thus it can reduce pulmonary pressure without causing the systemic hypotension that often results from use of traditional pulmonary vasodilators such as tolazoline and prostacyclin.⁴

What is the evidence base for effectiveness of NO?

Available evidence about the effectiveness of inhaled NO therapy in neonates can be split into two categories: - evidence related to term or near term babies, and evidence related to premature babies.

a) Term Babies

A systematic review published in the Cochrane library⁵ examined 8 trials and revealed that NO can improve short-term oxygenation. It also showed that NO can reduce the need for Extra Corporeal Membrane Oxygenation (ECMO) therapy but does not reduce overall mortality. The reviewers' conclude that use of NO is reasonable in term or near term babies without diaphragmatic hernia. Clark et al⁶ revealed a reduction in the use of ECMO and also a reduction in the need for supplemental oxygen at 30 days of age. Follow up from children in the NINOS trial⁷ do not suggest adverse neurodevelopmental effects from use of NO but there is otherwise currently little data about the long term implications.

b) Preterm Babies

A Cochrane Library review⁸ revealed only one study related to use of NO in preterm babies. This study^{9 10} showed rapid improvement in oxygenation, but no difference in outcome in the short term. Unpublished information from follow-up at 2000 (Subhedar personal communication) showed a very poor outcome overall but numbers were too small to show differential effects. Since then two studies^{11 12} have been published which found that NO did not increase survival but did improve oxygenation and may reduce chronic lung disease. Long term follow up of these trials is not yet available. Rosenberg¹³ in an editorial suggested that use of NO with preterm babies would be reckless practice outside of a randomized, controlled trial even though good reasons for its use exist.

The INNOVO Trial is evaluating the clinical and cost-effectiveness of the use of inhaled nitric oxide in neonates with severe respiratory distress. Thirty-six (as at August 2000) centres from the UK and Europe are collaborating and recruitment will continue until the end of December 2001.

Dosage Used

Reported doses of NO used clinically vary widely. Doses of up to 80 parts per million (ppm) have been used but seem to have no advantage over lower doses when used with term or near term babies.⁵ It is desirable to use the lowest effective dose to reduce the risk of toxicity or side effects.

The dose regimen being used in The INNOVO Trial is as follows:

a) Term babies

In term babies with a gestational age equal to or greater than 34 weeks, the trial starting (and maximal) dosage of INO is 20ppm, which would then be weaned down, after a 1 hour stabilisation period, to the minimum necessary dosage to sustain a clinically significant response. A response is defined as an increase in post ductal PaO₂ of more than 3 kPa (22.5mmHg) in the initial 15 minutes of giving INO.

b) Preterm babies

In preterm babies, gestational age less than 34 weeks, a dose response study is being undertaken to determine the most effective dose. The study will include doses from 5 to 40 ppm. Doses above 40ppm will not be used.

For centres not in the dose response study, until the results of the dose response study are available, a dose level starting at 5 ppm will be used. If no satisfactory response is achieved, the dose will be doubled to 10ppm, then if necessary doubled again to 20ppm, then again if required to 40ppm.

Rebound pulmonary hypertension is a possible problem when reducing or stopping NO even if starting it did not achieve a positive response. For this reason weaning must be done slowly¹⁴ and an increase in FIO₂ can help reduce problems when the NO is turned off.¹⁵

The INNOVO Trial Protocol requires doses to be kept at the minimum effective level and gives details of both dosing and weaning regimes.

Side effects and toxicity

There are several areas in which the use of inhaled NO has the potential to cause problems: -

Raised methaemoglobin levels

NO binds readily to, and is inactivated by haemoglobin forming methaemoglobin. High levels of methaemoglobin can cause a reduction in oxygen carrying capacity, but in practice this potential problem rarely occurs with the doses of NO that are used clinically.¹⁵

Bleeding

NO affects platelet formation and bleeding time, potentially increasing the risk of intraventricular haemorrhage (IVH) and other bleeding disorders.¹ This is a more serious risk with preterm babies who are more prone to IVH.

Nitrogen dioxide (NO₂)

NO mixed with oxygen forms NO₂. If high levels of NO₂ are administered there is a risk of pulmonary oedema or changes in lung tissue.¹⁶ NO₂ and water can combine to form nitric acid, which is also toxic. In practice high NO₂ levels are uncommon with the dose levels of NO used clinically. Risks can be minimised by mixing NO into ventilator circuits fairly near to the patient, flushing delivery systems before use and by constant monitoring of NO₂ levels in ventilator gases.

Use of NO has been theoretically linked with a number of other problems including effects on lung growth and repairs and also damage to DNA.¹ There are concerns that long term neurological and pulmonary follow-up is needed before the effects of NO are fully understood.⁵

NO delivery systems

NO in the UK is usually supplied in cylinders that are light green, with a darker green neck, and contain NO 1000ppm in nitrogen. The gas in these cylinders is under very high pressure. This pressure is reduced to a usable level by means of a regulator. From the regulator the NO is piped to a flowmeter which controls the flow of NO to the patient. From the flowmeter NO is piped to a T-connector in the inspiratory limb of a ventilator circuit, ideally after the humidifier but more than 20cm from the patient. This allows adequate mixing with ventilator gases prior to delivery to the patient but should minimise NO₂ build-up.

Exhaled gas comes from the patient and passes down the expiratory limb of the circuit to the ventilator, where it passes through a scavenging filter which removes NO and NO₂ before gases are exhausted. A monitoring line samples gas continuously to give a readout of NO and NO₂ concentrations being delivered to the patient. This monitoring line can originate either from the inspiratory or the expiratory limb as close to the patient as possible. NO is thus easily delivered into a ventilator or oscillator circuit. It flows at a constant rate to provide a constant dose in relation to the flow of gas in the ventilator. This is known as a constant flow system and is the way NO is usually delivered on neonatal units.

If a ventilator does not have a constant flow of gas, then a constant flow NO delivery system cannot be used as the delivered dose of NO will vary. NO delivery via paediatric and adult ventilators usually needs to be via specialised injection systems, which vary the flow of NO as the flow of ventilator gas changes.

Caution is needed with the Draeger Babylog, which delivers a constant flow of gas in most ventilator modes but may vary its flow slightly in high frequency oscillation (HFO) mode. This could potentially lead to a variation in delivered dose of INO when a constant flow NO system is used. Definitive advice about this is not available from the manufacturer and anecdotal reports vary.

Below are some examples of layouts of constant flow systems: -

- ◆ Figure 1 illustrates a typical generic constant flow system.
- ◆ Figure 2 shows the Sensormedics system, which can be used either with the Sensormedics oscillator or with many neonatal ventilators.
- ◆ Figure 3 shows the SLE Inosys system, which can be used with SLE or with other neonatal ventilators.

Figure 1- Generic constant flow nitric oxide system

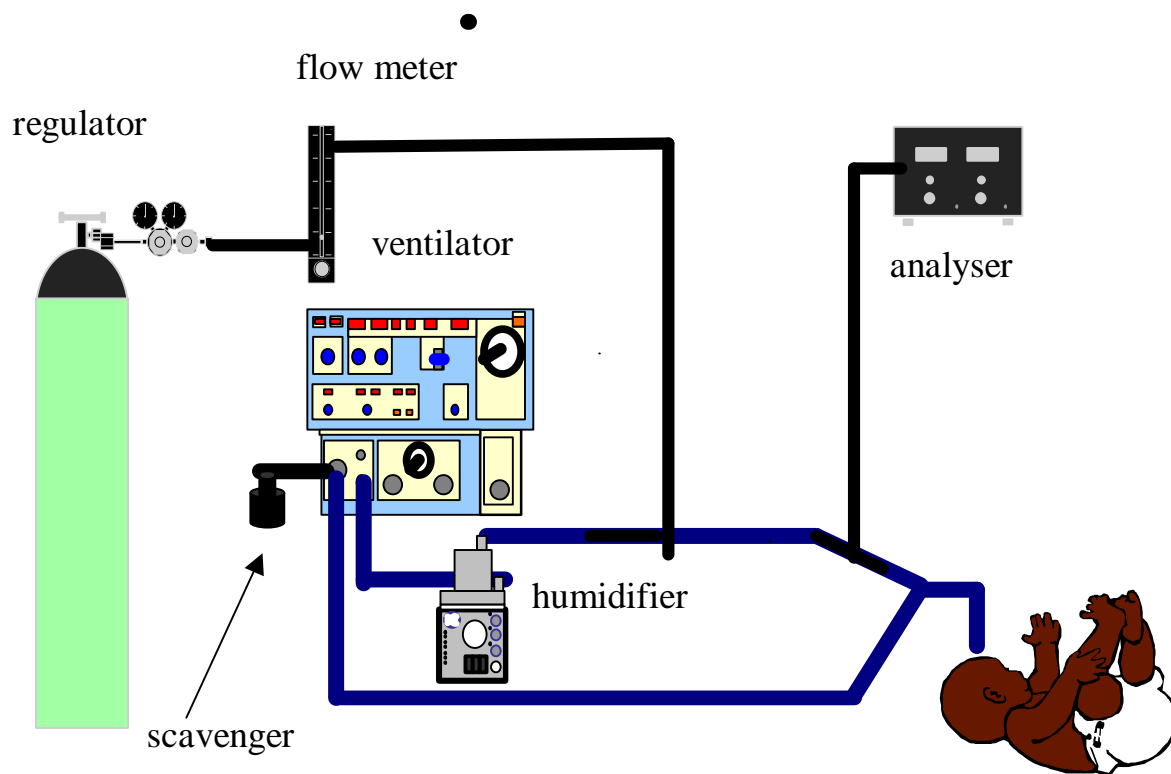


Figure 2- Sensormedics nitric oxide system

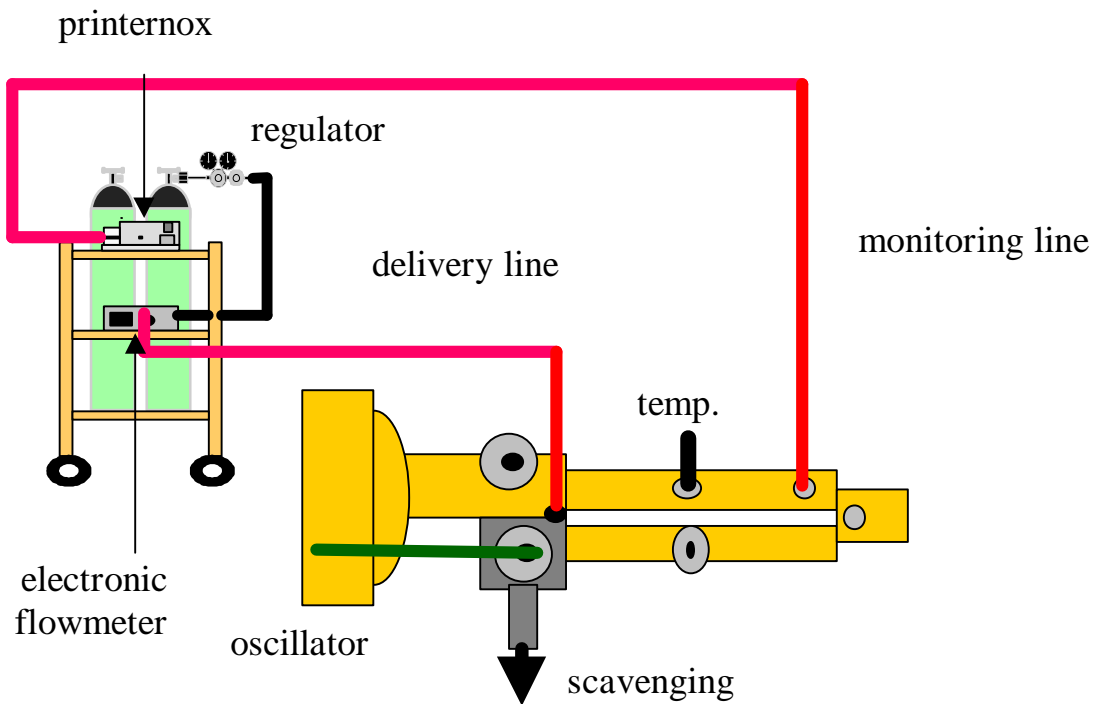
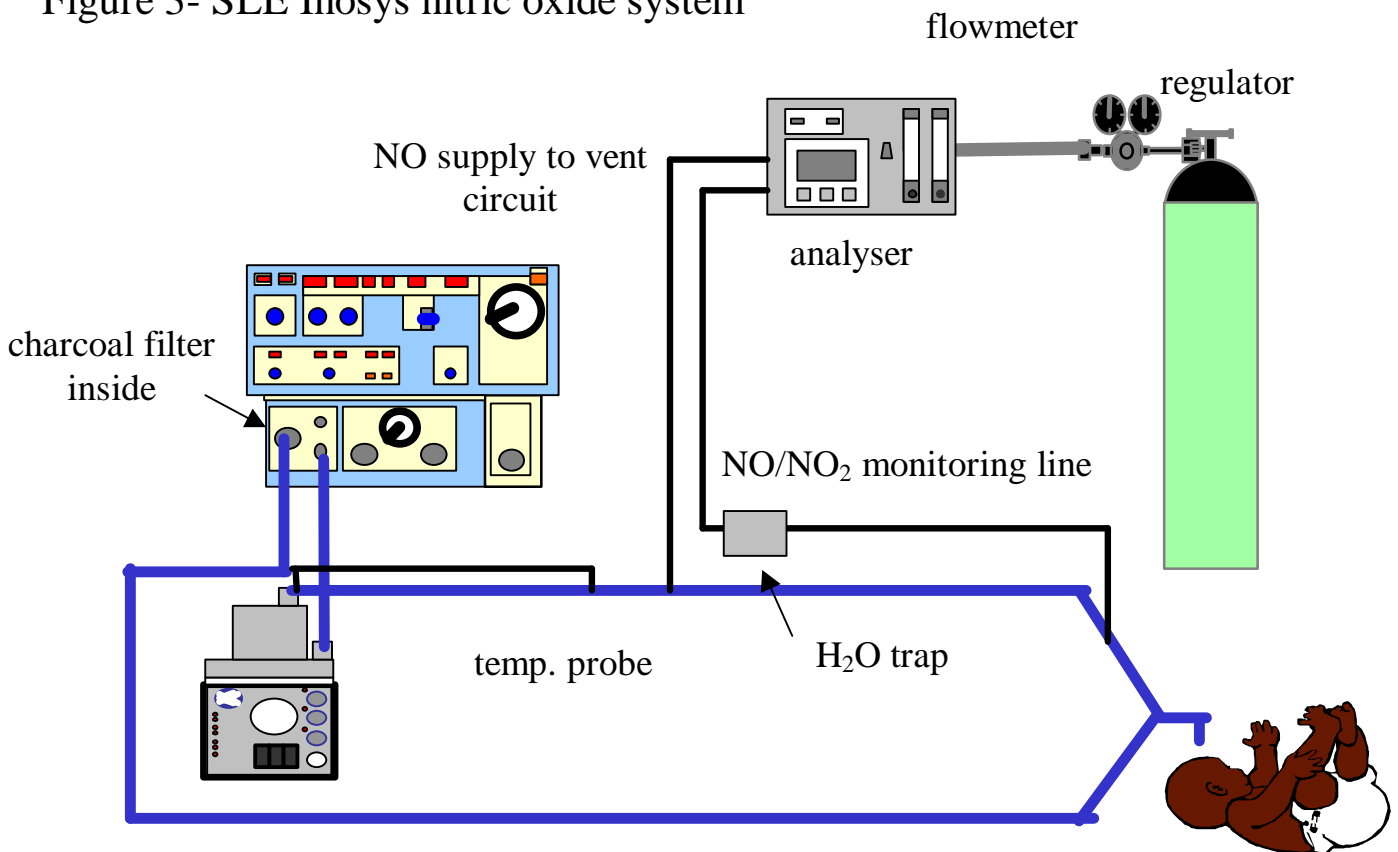


Figure 3- SLE Inosys nitric oxide system

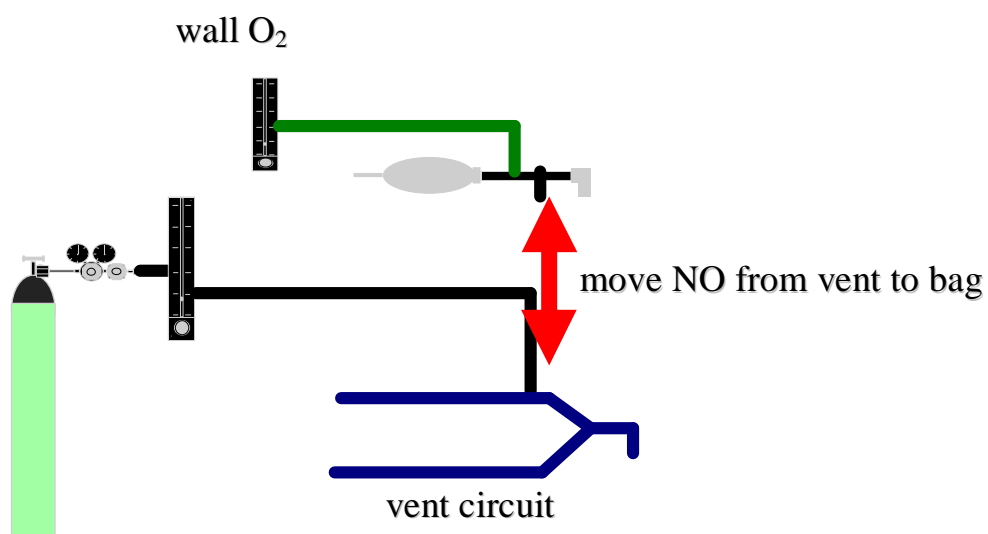


Hand ventilation

NO therapy is a treatment that should be weaned slowly rather than stopped suddenly. This is because it is recognised that dependence can develop and that some patients react badly to its sudden cessation.¹⁷ In the light of this it seems prudent to make provision for supplying NO if, for any reason, a baby is taken off a ventilator and ventilated by hand. Reasons for doing this can include patient deterioration, physiotherapy or ventilator faultfinding.

Hand ventilation systems for use with NO are usually set up in one of two ways. Either a separate NO supply is provided for a bagging circuit, or the NO supply is disconnected from the ventilator circuit and attached to the bagging circuit when required. If a separate NO supply is used then the system must be purged of any NO₂ build-up (by running it for approximately 30 seconds) prior to use. This is not an issue if the NO supply is simply being swapped over, as long as the bagging system is purged after use. Care must be taken during hand ventilation to ensure the NO dose does not change. If bagging circuit flow is different to ventilator flow then the NO flowmeter will need adjusting to compensate. Such adjustments can easily be calculated ahead of time. Use of two people for hand ventilation of babies receiving NO makes what can be a fiddly and stressful process much easier. If Neopuffs are used instead of bagging systems they can easily be adapted for such layouts. Figure 4 shows a typical example of a NO hand ventilation system:-

Figure 4



Setting up

There are currently several different NO systems in use on neonatal units. It is important to be aware of procedures applicable to individual systems when working with them but the general principles of setting them up and using them are universal. Below is The INNOVO Trial checklist, which can help with getting NO up and running accurately and safely. All participating INNOVO Trial units have been supplied with this checklist in poster and A4 format.

Checklist for setting up Nitric Oxide (NO)

1. Collect cylinder and ensure that it contains 1000ppm NO in nitrogen, check label attached to top of cylinder and the value printed on side of cylinder.
2. Check cylinder is turned off then attach regulator to cylinder and make sure it is tight. If regulator is of a type that has its own on/off switch check it is switched off.
3. Take cylinder to bedside and attach regulator to flowmeter, ensure flowmeter is switched off.
4. Make sure cylinder is secured to a wall or trolley - falling cylinder may cause injury or result in accidental discharge of NO.
5. Turn on cylinder (and if applicable, regulator) and check for leaks around cylinder head, regulator and flowmeter by listening or using leak detection spray.
6. Using regulator gauge nearest cylinder check there is sufficient gas supply in the cylinder (see technical guidelines)
7. Attach NO delivery tubing to flowmeter output but not to ventilator circuit.
8. Purge the system of any possible build-up of nitrogen dioxide (NO₂) that has occurred when not in use - individual units should agree how this will be done.
 - If the required ventilator is not in use then at the end of the set-up a test lung can be attached and the system run until a low NO₂ level is confirmed.
 - If the NO is to be attached to a ventilator in use then purging should be done for 30-60 seconds before connecting the flowmeter tubing to the ventilator circuit. Purging can be done into room air away from nearby personnel.
9. Connect the flowmeter output tubing to the ventilator, and the monitoring tubing to the NO/ NO₂ analyser (see Technical Guidelines for sample circuits).
10. Attach scavenger system to the ventilator exhaust.
11. Turn on NO/NO₂ analyser.
12. Set the NO flowmeter to the level required, calculated using the formula:
$$\frac{\text{Nitric Oxide flow rate(Litres/min)} \times 1000\text{ppm}}{\text{Ventilator flow rate(Litres/min)}} = \text{Dose ppm}$$
13. Make sure regulator and cylinder are turned on and if required the output pressure is adjusted to a suitable level (usually 1-2 bar but varies with different systems - check).
14. Allow the analyser a few minutes to settle, then adjust the NO flow as necessary to give the required dose.
15. Set up a hand ventilation circuit as per policy of individual unit.
16. Make sure there are spare cylinders easily to hand to swap with the ones in use when required.
17. Check a methaemoglobin level after 1 hour and then every 12 hours.
18. Monitor NO dose on analyser-adjust flow to maintain desired dose.
19. Monitor NO₂ reading on analyser. High readings may be due to inadequate purging.
20. Ensure environmental monitors are working - maximum recommended levels are 25ppm of NO and 3ppm of NO₂ over an 8 hour period.

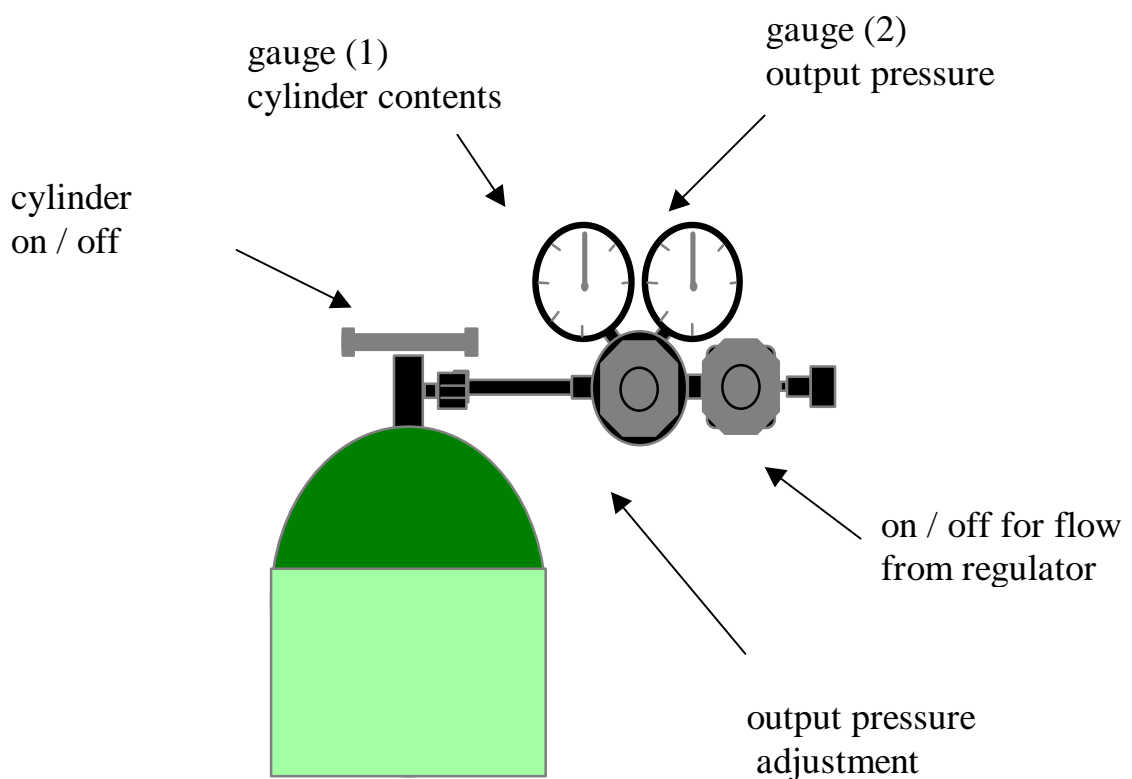
IF HIGH NO FLOWS ARE USED FOR PURGING THEY MUST BE TURNED OFF BEFORE CONNECTION TO A BABY, THEN RESET AT AN APPROPRIATE LEVEL

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Regulators

Regulators are used to reduce gas pressure to a controlled and usable level. It is important that the different parts of the regulator are understood. The gauge (1) nearest the cylinder shows the cylinder contents. This is given as a pressure reading which goes down as the amount of gas in the cylinder reduces. A full cylinder will read about 130 bar.

Figure 5 shows a typical NO regulator attached to a cylinder.



The gauge (2) furthest from the cylinder shows the output pressure of the gas leaving the regulator. The output pressure required varies with different NO delivery systems (i.e. Sensormedics electronic flowmeter needs 3-4 bar and SLE delivery systems need 1-2 bar). Depending on the type of regulator used the output pressure dial may need adjustment to maintain pressure as cylinder contents are used (some regulators do this automatically). Some regulators have an on/off dial, which can stop the flow of gas out of the regulator even if the cylinder is turned on.

Cylinder and regulator safety

NO is supplied in bulky, heavy cylinders which must be handled carefully to avoid potential risks to both staff and patients. A falling cylinder could cause a crush injury, or result in regulator damage and accidental discharge of gas. Poor handling of regulators and circuits can also result in gas discharge or inadvertent NO₂ delivery.

These risks can be minimised by following some basic safety precautions: -

- ◆ Ensure cylinders are well secured to a wall or trolley at all times.
- ◆ Regulators and lines should be flushed of any NO₂ build up prior to use.
- ◆ Environmental monitoring of NO and NO₂ should be carried out to detect possible leaks or problems.
- ◆ Cylinder changes should be planned ahead of time and a spare cylinder kept ready to use – planned, unhurried cylinder changes are more likely to be problem free.
- ◆ Turn off cylinder and discharge pressure before removing regulators.
- ◆ Never turn on a cylinder without a regulator attached.
- ◆ With some regulators the output pressure dial should be turned to low (anti-clockwise) before regulator is swapped from an empty to a full cylinder.
- ◆ Only trained personnel should handle or change regulators.

Shift handover checks

When taking over care of a baby receiving NO there are several checks that should be carried out to help ensure a safe and trouble free shift: -

- ◆ Is the system correctly assembled?
- ◆ Is supply adequate and spare cylinder available?
- ◆ Who will change cylinders/regulators if required?
- ◆ Is hand ventilation system available and ready to use?
- ◆ Is measured NO level equal to that prescribed?
- ◆ Are NO₂ and MetHb levels ok?
- ◆ Is NO flow correct to give measured dose-check formula, Printernox or SLE graph?
- ◆ Does scavenging filter need changing or water trap in monitoring line need emptying/changing?

Nursing care

Nursing care of a baby receiving NO is very similar to the care required by any very sick baby. Minimal handling and close observation is required. There are a few specific points that need to be considered: -

- ◆ Staff should have some knowledge of NO use and of the specific policies and systems of their unit and be aware of who is available to provide support and backup if it is needed.
- ◆ NO and NO₂ levels should be recorded hourly. Met Hb should be recorded at least 12 hourly after the initial level. Raised methaemoglobin can affect accuracy of oxygen saturation monitor readings.¹⁵

- ◆ Check cylinder contents regularly so that cylinder changes can be planned ahead of time. A spare cylinder should however be kept ready for use.
- ◆ A hand ventilation system should be available so that NO can be provided off the ventilator if necessary.
- ◆ NO/NO₂ monitoring lines should be regularly checked for, and emptied of water as this can effect readings. This can be a particular problem with SLE systems. The line can be disconnected and emptied as long as it is clamped to prevent ventilator pressure loss.
- ◆ Ventilator disconnection should be kept to a minimum. Most babies are stable for short disconnections but some are not. Some people are strong advocates of using closed suction systems to avoid this problem¹⁴ but they are expensive and policies vary. When a ventilator is disconnected a small amount of NO is flowing into room air. Staff should keep faces away from circuit ends or cap off the circuit.
- ◆ Staff must know where in the system oxygen concentration is measured from. The NO flow will slightly dilute FIO₂ but this may not be shown by the oxygen analyser.¹⁸
- ◆ When NO is weaned or stopped babies should be monitored closely. Weaning is usually done slowly and an increase in FIO₂ can help stability when stopping.
- ◆ Babies on NO should not be moved either around hospitals or between hospitals unless specialist equipment and staff are available.
- ◆ Staff using SLE ventilators should be aware that if a high pressure alarm is repeatedly reset then there is a potential for pooling and boluses of NO being delivered due to ventilator flow cutting out. To avoid this potential problem high pressure alarms should be set appropriately and reset if necessary.

Staff safety

There are several issues related to staff safety that staff working with NO should be aware of: -

- ◆ Sudden large scale discharge of NO cylinder contents into room air could potentially cause asphyxiation and may necessitate evacuation of a room until it can be well ventilated to clear NO.¹⁹
- ◆ Maximum recommended exposure levels are 25ppm of NO and 3ppm of NO₂ over an 8-hour period.²⁰ In practice it is unlikely environmental levels will reach 1ppm.²¹
- ◆ It is recommended that exhaust gases from ventilators be scavenged unless there is a minimum of 10-12 air changes per hour in the room.²² The INNOVO Trial Technical Guidelines recommend that scavenging be done routinely. Scavenging with charcoal or soda lime filters is easy to do as a routine if wall scavenging systems are not available. Some adult and paediatric units do not scavenge and have not reported problems with environmental NO or NO₂ levels.
- ◆ When NO₂ is being purged from systems into room air, environmental levels will not rise significantly, but it is good practice to direct the flow away from face and other staff.
- ◆ If NO is running through a ventilator circuit during hand ventilation then use of a cap or test lung will reduce environmental exposure. Hand ventilation systems cannot be scavenged so exhaust flow from bag should be away from face.
- ◆ There are no official recommendations about pregnant staff looking after patients receiving NO and many units give pregnant staff a choice about whether they do or not. Working in the same room as a patient receiving NO is not a concern as environmental levels have been shown to be so low.
- ◆ Possible concern has been raised about asthmatic staff working with NO²³ but it is not a common concern and NO is often used to treat adult and paediatric patients with severe asthma.

- ◆ Jones²³ brings together many figures which help to put concerns about NO into perspective. Clinical background levels of NO and NO₂ are much lower than many city centre measurements. Traffic can cause high NO₂ levels and cigarette smoke contains up to 1000ppm of NO. Branson et al¹⁸ discuss suggestions that intensive care unit NO and NO₂ levels are influenced more by outside environmental conditions than by medical use of NO.

Troubleshooting

A properly set up NO system should be fairly trouble free if it is closely monitored. Below are some pointers for possible problems: -

High NO₂ readings

This is usually caused by inadequate purging prior to a system being used or when swapping to a spare cylinder/regulator set-up. Some systems are possibly more prone to this than others. For example some systems have a big deadspace between cylinder and regulator in which NO₂ build-up can occur when not in use.

Measured NO dose reduces

Cylinder may be empty or (if a one stage regulator is in use) the regulator output pressure may need adjusting to maintain pressure as the cylinder empties. The delivery tubing may have become disconnected from ventilator circuit or kinked.

Cylinder empties more quickly than expected

There may be a leak of NO from somewhere in the delivery system. A leaking cylinder should be turned off and replaced.

Increased environmental NO or NO₂ levels

Again there may be a leak or the scavenging system may be faulty or need replacing.

Measured NO and NO₂ fall unexpectedly

This is often caused by water in the monitoring line.

Further Information

- ◆ The INNOVO Trial website located at:
<http://www.innovo-trial.org.uk>
- ◆ The INNOVO Trial protocol June 1999 located in The INNOVO Trial folder on participating units, and on the website.
- ◆ The INNOVO Trial technical guidelines located in The INNOVO Trial folder on participating units, and on the website.
- ◆ SLE manual for the Inosys NO system - contains general information about NO use as well as details about the system
- ◆ Company websites that contain useful articles and information include:
<http://www.sensormedics.com>
<http://www.draeger.com>
<http://www.sle.co.uk>

Contact Paul Cornick (INNOVO Trial research nurse) for further information about this teaching pack or about neonatal nursing issues related to inhaled nitric oxide.

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