

OXYGEN (Comment)

Using saturation to monitor the need for supplemental oxygen

People who only started to care for preterm babies in the last twenty years may, perhaps, be forgiven for not appreciating how the delivery of oxygen was monitored when it first came into widespread use, along with the invention of the enclosed Perspex incubator, in the early 1940s. In fact, until the first study appeared in 1952¹ suggesting that too much oxygen could cause blindness due to what was initially called retrolental fibroplasia [but is now called retinopathy of prematurity (ROP) because it only occurs in preterm babies], oxygen was hardly monitored at all. Once the outcome of the first three trials became known in 1956²⁻⁴ the initial strategy was not to let babies have more than 40% oxygen. However it became fairly clear over the next decade and a half that this was probably killing more babies than it was saving from blindness,^{5,6} and it came to be accepted that what matters is not the amount of oxygen in the inspired gas (Fraction of inspired oxygen or FiO_2 – expressed as a percentage), but the amount of oxygen in the arterial blood. The amount of oxygen in the blood is expressed in terms of the partial pressure of oxygen (PaO_2) and measured in units of pressure (kiloPascals - kPa).

Periodic arterial sampling soon took off in those units lucky enough to have an 'on-site' blood gas analyser, but this could only 'calibrate' the clinical judgement of the cot-side nurse once every few hours. It worked well for the first week or so if steps had been taken to get an umbilical artery catheter inserted while this was still technically possible, but these catheters did not remain patent indefinitely, so this offered little guidance for babies still needing oxygen when more than a week old. Arterial lines could also trigger thrombotic complications. The arrival of continuous transcutaneous oxygen monitoring in the early 1980s (using a probe that warmed a small area of skin until the capillaries became so dilated that the blood in them contained almost as much oxygen as there was in arterial blood) was, therefore, a huge technical advance. Those who had to care for babies in the 1970s will tell you that, before this, the only available cot-side approach to preventing 'hyperoxia' had been to reduce the amount of oxygen given until the baby became clinically desaturated (which, as the first of the two vertical dotted lines in fig 1 shows, only occurs when saturation is down to about 80% and arterial partial pressure is ~5 kPa) and then increase the inspired oxygen by an arbitrary 10%.

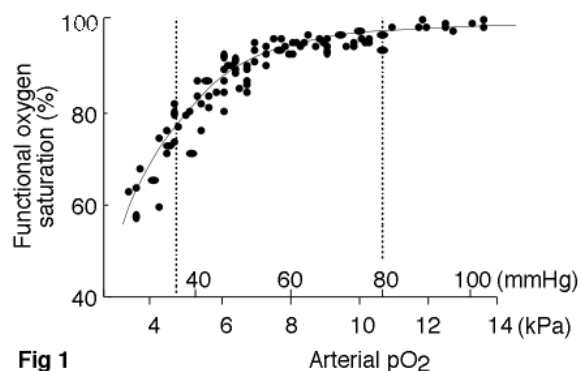


Fig 1

Amazingly only one trial was ever done to see whether transcutaneous monitoring, as an add-on to routine blood sampling, could reduce the incidence of ROP, and this failed to show benefit.⁷ An analysis undertaken by Flynn⁸ using data collected during Bancalari's trial did, however, have a profound impact on nursing care when it was finally published in 1992, because it showed that, in the 101 babies who survived long enough for the incidence of ROP to be documented, serious ROP was much more common in those who had been exposed to an arterial oxygen partial pressure (PaO_2) in excess of 80 mm Hg (~10.7 kPa). Hence, the second of the two dotted lines in fig 1. Ever since this paper first appeared, and basically on the basis of just this one study, it has been generally accepted that an attempt should be made to keep PaO_2 below this threshold value in babies in whom the vascular development of the retina is not yet complete if they are still having oxygen (or any other form of respiratory support for that matter). However, in the meantime another much more convenient device for measuring oxygen in the bloodstream became available – the pulse oximeter.

Pulse oximeters started to come into widespread use very rapidly⁹ at much the same time as the outcome of Bancalari's trial first became known. However, a pulse oximeter can only define the proportion of arterial haemoglobin that is combined (saturated) with oxygen, expressed as a percentage (SaO_2) and the corresponding PaO_2 can vary. No further studies of a similar nature to the Bancalari's were ever attempted and, more shamefully, no such question was asked of the new approach using arterial oxygen saturation.

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While arterial lines are still widely used to obtain a direct measure of PaO_2 in the first few days of life, they can only provide a series of intermittent 'spot' readings, and retaining arterial access is also technically challenging in babies more than a few days old. Transcutaneous sensors and pulse oximeters, on the other hand, are noninvasive and provide continuous information. Though transcutaneous probes measure the crucially important PaO_2 they require calibration and checking against a true blood oxygen measurement every few hours. Pulse oximeters have the advantage of not requiring calibration and it is perhaps not surprising, therefore, that most monitoring of oxygenation in intensive care units is done using pulse oximetry. They have the disadvantage of providing the less informative measure of oxygen saturation (SaO_2) and not the more important measure to which it is variably related, PaO_2 .

Clinicians think they know what the safe working range is for PaO_2 in the very preterm baby, but, even now, almost twenty years after pulse oximeters first came into common use, there is still great uncertainty as to what constitutes the optimum working range for oxygen saturation. Early studies of the relationship reported how partial pressure related to *fractional* saturation, but most pulse oximeters now display *functional* saturation, and this is what more recent studies have reported.

For those wanting to explore the complex relationship between FiO_2 , SaO_2 and PaO_2 in more detail please see the commentary entitled “Oxygen – non-invasive assessment of pulmonary oxygen exchange.”

Functional and fractional saturation The haemoglobin molecule can be modified in a range of different ways. *Functional* Haemoglobin molecules are molecules that are capable of transporting oxygen. They are called oxyhaemoglobin when carrying oxygen and deoxyhaemoglobin when not carrying oxygen. *Dysfunctional* haemoglobin molecules are not able to carry oxygen. This may be because the molecule has become impaired or become strongly bound to a molecule *other* than oxygen. Such competitive binding happens, for example, in carbon monoxide poisoning (when carboxyhaemoglobin is formed), or when treatment with nitric oxide, or a number of other drugs, results in methaemoglobin being formed (as outlined in the *Formulary’s* monograph on methylene blue – that condition’s primary antidote). *Functional saturation* (the number now displayed by most non-invasive saturation monitors) is the ratio of oxyhaemoglobin to all other functional haemoglobin while *fractional saturation* is the ratio of oxyhaemoglobin to **all** haemoglobin (including any dysfunctional haemoglobin). Thus the results from the two types of oximeters will be different when significant amounts of dysfunctional haemoglobin are present. Typically, in a healthy baby, fractional saturation is about 2% less than functional saturation.

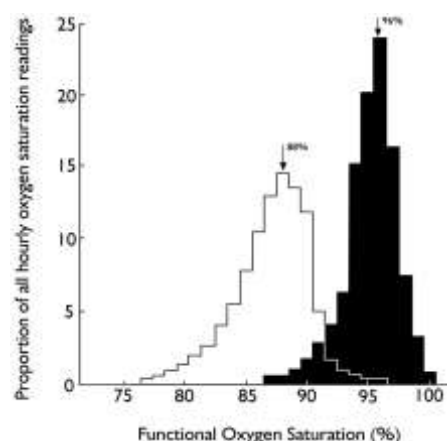
So what are reasonable ‘safe limits’? The shocking thing is that half a century after everyone came to realise that, as with any drug, it is possible to give too much, as well as give too little, we still do not really know how much oxygen we should be giving the preterm baby.

A safe upper limit: Fig 1 would suggest that, if the safe limit suggested by the Flynn study⁸ can be relied on, the logical thing is to set the upper saturation alarm so it is triggered when functional saturation exceeds 95%, but that is to forget that with most oximeters it is possible to adjust the sampling time during which the data from which the saturation is calculated is gathered. This can be varied from about 2 second to about 16 seconds. There would be endless self-cancelling alarms if there was no delay mechanism in place because anyone who has ever spent any time watching a monitor will know just how variable the individual readings can be. Furthermore, once the alarm has been cancelled by the observer it remains disabled for up to 2 minutes. A baby could, therefore, spend quite a lot of time with a saturation in excess of 95% without the alarm ever being triggered as long as no one spell lasts more than two minutes, and there is evidence to suggest that this happens quite a lot.

There is another complication. The data shown in fig 1 were obtained in Edinburgh at a time when staff were trying to keep the babies somewhere between 86 and 94% saturated.¹⁴ It differs quite significantly from the data obtained by Professor Poets in Tübingen, Germany, in 2002.¹¹ Arterial blood samples taken when the oximeter suggested that the blood was 95% saturated had a mean PaO_2 of 7.2 kPa in the Scottish study, but a mean PaO_2 of 9.7 kPa in the German study. No sample had a PaO_2 above 9.5 kPa in the Scottish study, but 5% had a PaO_2 above 11.0 kPa in the German study. All the babies in the Scottish study were premature, but many of the babies in the German study were relatively mature, so there was not the same focus on trying to keep saturation below 95% (see Appendix). This may well be one the reason why the two studies came up with rather different findings. Interestingly staff in Edinburgh decided, once the outcome of their study became known that, to prevent multiple short periods of hyperoxaemia that do not individually last long enough to trigger the alarm, they would in future set their upper pulse oximeter alarm limit for oxygen-dependent preterm babies at 93% (as did Castillo *et al.*¹³).

A safe lower limit: If little is known about the safe upper limit, even less is known about the safe lower limit for functional saturation. The various international BOOST trials are currently addressing this very issue. In December 2010 a meta-analysis of the data presented to the Data Monitoring Committees of these studies (BOOST-II UK, BOOST-2 Aust/NZ and COT) together with the data from the SUPPORT study showed a clear increase in survival to 36 weeks gestation in the groups randomized to a target saturation range of 91%-95%. As a result the various BOOST studies ceased recruiting on 24th December 2010. Follow up of all participants, including the vitally important neuro-developmental assessments at 2 years of age, will continue in order to address the other endpoints.

Before this development the only valid information available came from an observational study reported by units in the UK’s Northern Neonatal Network in 2001¹⁵ and 2004.¹⁶ They followed a group of babies of less than 28 weeks gestation born between



1990 and 1994 until they were in their teens and were able to show that the long term outcome for the babies in a unit where staff aimed for a functional saturation of between 82 and 91%* was at least as good as that of a closely matched group cared for in a unit where staff aimed for a saturation of between 92 and 97% (see fig 2), and that serious ROP was four times more common in the babies cared for in the unit that targeted the higher saturation range.

One thing that fig 1 shows is that, even when functional saturation is as high as 90-92%, quite a few babies have an arterial PO_2 of less than 5 kPa. Clinicians initially trained to rely on partial pressure rather than saturation to guide respiratory support had long been taught that it was important to keep partial pressure much higher than this.¹³ Indeed Anne Greenough's book on *Neonatal Respiratory Disorders* used to say that staff should aim to keep partial pressure between 8 and 12 kPa,¹⁷ and even more liberal guidelines have usually recommended a target range of somewhere between 5 and 11 kPa.¹⁸

The American Academy of Pediatrics still suggests that staff should aim for a PaO_2 of 50–80 mm Hg (6.7 – 10.7 kPa).¹⁹ However, all these guidelines were merely based on 'received opinion'. There was never much evidence to support any of these arbitrary, but much-quoted, limits. The findings summarised by fig 1 suggest that it is actually perfectly safe to allow arterial PO_2 to fall to 4 kPa, and that there is hardly any more risk of it falling this low when functional saturation is 85% than there is when it is 90%. Indeed, more than three quarters of all arterial blood gas samples taken when saturation is as low as 80% will still come up with an arterial PO_2 of at least 4 kPa. However, even if there are grounds for accepting a PaO_2 of 4 kPa for a short time, this still does not establish whether sustained exposure to an arterial partial pressure this low is equally safe.

In truth, therefore, nobody really knows what the safe lower limit is. What matters in the end of course is not just how much oxygen each red cell is carrying to the tissues, but how many red cells there are and how well the circulation is carrying those cells to the body's most vulnerable tissues – including the brain. The follow up study undertaken by Win Tin (still, as yet, only reported in abstract)¹⁶ certainly suggests that as long as tissue perfusion remains good the blood does not need to be as well oxygenated as many have long thought, and that sustained periods with a saturation in the low 80s are not detrimental (fig 2). And, if this is true, the consequences could be more profound than many have yet appreciated. In the Northern Neonatal Network study half the babies of less than 28 weeks gestation in the unit targeting a functional saturation of 82-91%* had been extubated by seven days, but this took 21 days in the unit targeting a saturation of 88-97%.¹⁵ When that unit changed the alarm limit settings from 88 and 98% to 75 and 93% they found they had halved the time it took to get half the babies of 24–28 weeks gestation free from the perceived need to have a tracheal tube in place.²⁰

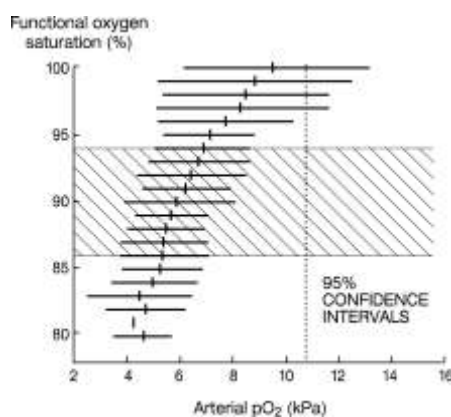


Fig 2

Keeping saturation 'on target'

It is, of course, one thing to say that saturation should be kept within a specified range and quite another to achieve this. The AVIOx 'audit' in 2006 of the extent to which 14 units from three different countries were managing to keep saturation within a target range that they had set for themselves if the baby was in oxygen or on some other form of respiratory support, found that "centers maintained infants within their intended range 16% to 64% of the time, but were above range 20% to 73% of the time,"²¹ Ngheim has, more recently, explored some of the reasons why compliance can be so variable,²² and Clucas *et al.*, from Melbourne, have courageously shown how often the upper alarm is not set where it is supposed to be.²³ Pulse oximeters often display more transient changes than a transcutaneous monitor and, if staff respond to these just as the displayed reading starts to return to where it was before this could actually cause increased lability and increase the time spent 'off target'.²⁴ An unrealistically 'tight' target range also makes compliance more difficult.²¹

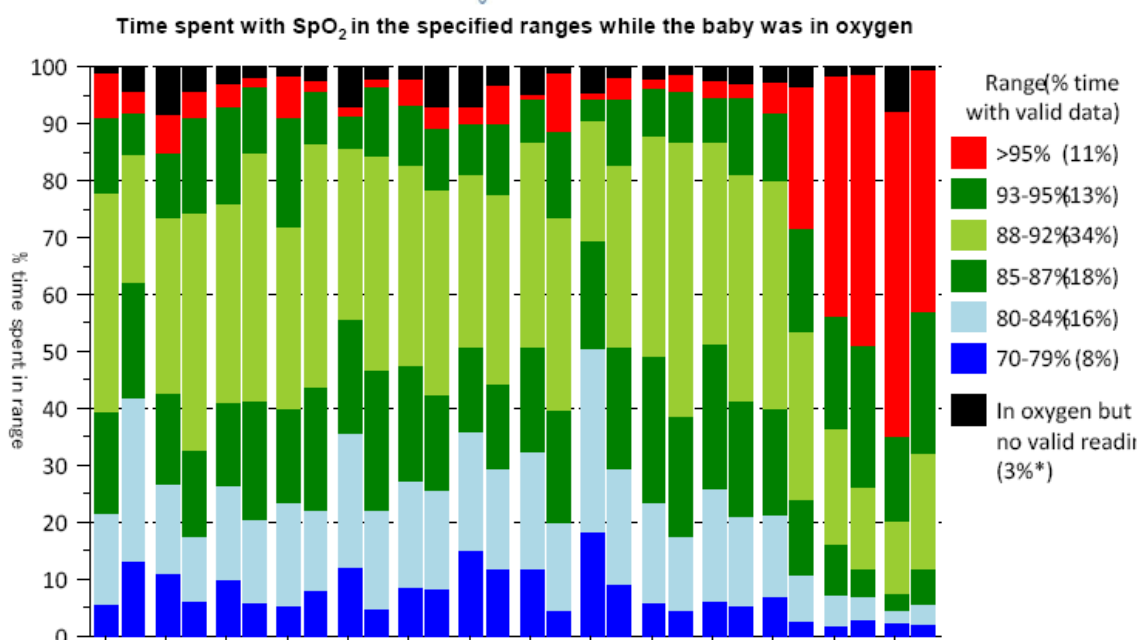


Fig 3

In the various international BOOST trials, where cot-side nurses were being asked to keep the baby's blood between 85% and 95% saturated, even experienced staff have found it hard to keep the baby 'in range' much more than two thirds of the time – the light and dark green part of each colour bar in fig 3 (where each bar of the histogram shows the spread of saturation actually achieved during each 12 hour care-shift over a two week period). The amount of time spent with a saturation above 95% (even though the alarm was supposed to be triggered if saturation exceeded 94% for more than two minutes) increased over time, as in other studies,²³ as the baby got older and as care was taken over by less experienced staff.

Conclusion Our understanding of the factors that cause ROP to develop in the very preterm baby is still very incomplete,²⁵ and it is important to remember that retinal surgery does not 'cure' ROP in the way that ligation 'cures' a persistent PDA – 40% of the babies treated in the CRYO-ROP trial were still seriously disabled (a corrected visual acuity of $\leq 6/60$) 10 years later.²⁶ However unless the move away from giving as much oxygen as has been common in the recent past²⁷⁻³¹ is studied in a **controlled** way there is a serious risk that today's clinicians will make the same mistake as their colleagues did fifty years ago, and do more harm than good.^{32,33} Even achieving such a change is going to be difficult unless a simple audit programme can be developed that allows staff to see how widely the saturation of an individual baby has varied by producing a graphical summary similar to the one shown in fig 3.

And if clinicians are right to be concerned when the functional saturation of an extremely immature baby rises above 94% in the first few weeks of life because they are being given more oxygen than we judge really necessary, should they not be equally worried when this happens to a baby whose perceived respiratory needs are being supported not with oxygen but with a ventilator, CPAP, or a high flow of humidified air through a nasal cannula?³⁴⁻⁶ If a high P_aO_2 really *is* potentially damaging then it is presumably just as important to prevent this when a very preterm baby is being ventilated in air, or is being supported by CPAP in air, as it is when the baby is in supplemental oxygen. The AVIOx study robustly classified all three situations as offering potentially 'modifiable hyperoxia'.²¹ While it may not prove possible to abolish the 'hyperoxia' by reducing the respiratory support, any more than it is always possible to do this by reducing the inspired oxygen concentration, it must surely be important to try.

* The unit in question was using pulse oximeters that displayed fractional rather than functional saturation when the study was done, with upper alarms set so that they were activated, after a one minute delay, when saturation, as displayed, reached 90%. In the second unit they were set so that they were activated when functional saturation reached 98%. To prevent confusion the target range is being quoted here in terms of what it *would* have been had these oximeters displayed functional rather than fractional saturation.

References

1. Patz A, Hoek LE, de la Cruz E. Studies on the effect of high oxygen administration in retrolental fibroplasia. I. Nursery observations. *Am J Ophthalmol* 1952;**35**:1248–53. [RCT]
2. Lanman JT, Guy LP, Dancis J. Retrolental fibroplasia and oxygen therapy. *JAMA* 1954;**155**:223–6. [RCT]

3. Patz A. Oxygen studies in retrolental fibroplasia. IV. Clinical and experimental observations. *Am J Ophthalmol* 1954;**38**:291–308. [RCT]
4. Kinsey VE, Jacobus JT, Hemphill F. Retrolental fibroplasia: cooperative study of retrolental fibroplasia and the use of oxygen. *Arch Ophthalmol* 1956;**56**:481–543. [RCT]
5. Avery ME, Oppenheimer EH. Recent increase in mortality in hyaline membrane disease. *J Pediatr* 1960;**57**:553–9.
6. Bolton DPG, Cross KW. Further observations on cost of preventing retrolental fibroplasia. *Lancet* 1974;i:445–8.
7. Bancalari E, Flynn J, Goldberg RN, *et al.* Influence of transcutaneous oxygen monitoring on the incidence of retinopathy of prematurity. *Pediatrics* 1987;**79**:663–9. [RCT]
8. Flynn JT, Bancalari E, Snyder ES, *et al.* A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. *N Engl J Med* 1992;**326**:1050–4.
9. Brockway J, Hay WW, Eyzaguirre M. Neonatal pulse oximetry: accuracy and reliability. *J Pediatr* 1989;**83**:717–22.
10. Brockway L, Hay WW. Prediction of arterial partial pressure of oxygen with pulse oximeter oxygen saturation measurements. *J Pediatr* 1998;**133**:63–6.
11. Bohnhorst B, Peter CS, Poets CF. Detection of hyperoxaemia in neonates: data from three new pulse oximeters. *Arch Dis Child* 2002;**87**:F217–9.
12. Gerstmann D, Berg R, Haskell R, *et al.* Operational evaluation of pulse oximetry in NICU patients with arterial access. *J Perinatol* 2003;**23**:378–83.
13. Castillo A, Sola A, Baquero H, *et al.* Pulse oxygen saturation levels and arterial oxygen tension values in newborns receiving oxygen therapy in the neonatal intensive care unit: is 85% to 93% an acceptable range? *Pediatrics* 2008;**121**:882–9.
14. Quine D, Stenson BJ. Arterial oxygen tension (PaO₂) values in infants <29 weeks of gestation at currently targeted saturations. *Arch Dis Child* 2009;**94**:F51–3.
15. Tin W, Milligan DW, Pennefather P, *et al.* Pulse oximetry, severe retinopathy, and outcome at one year in babies of less than 28 weeks gestation. *Arch Dis Child* 2001;**84**:F106–10.
16. Bradley S, Anderson K, Kelly T, *et al.* Early oxygen exposure and outcome at 10 years in babies of less than 28 weeks gestation. [Abstract] *Pediatr Res* 2004;**55**:373A.
17. Robertson NRC. Intensive care. In: Greenough A, Milner AD, Robertson NRC, eds. *Neonatal respiratory disorders*. London: Arnold, 1996: p185.
18. American Academy of Pediatrics, and American College of Obstetricians and Gynecologists. *Guidelines for perinatal care*. 5th ed. Elk Grove Village IL: American Academy of Pediatrics, 2002 p 246.
19. Northern Neonatal Network. *Neonatal Formulary*. 1st ed. London: BMJ Books 1996; 111–2.
20. Tin W, Wariyar U. Giving small babies oxygen: fifty years of uncertainty. *Semin Neonatol* 2002;**7**:361–7.
21. Hagadorn JL, Furey AM, Nghiem T-H, *et al.* Achieved versus intended pulse oximeter saturation in infants born less than 28 weeks' gestation: the AVIOx study. *Pediatrics* 2006;**118**:1574–82.
22. Nghiem T-H, Hagadorn JL, Terrin N, *et al.* Nurse opinions and pulse oximeter saturation targets for preterm infants. *Pediatrics* 2008;**121**:e1039–46.
23. Clucas L, Doyle LW, Dawson J, *et al.* Compliance with alarm limits for pulse oximetry in very preterm infants. *Pediatrics* 2007;**119**:1056–60. (See also 1195–6.)
24. Quine D, Stenson BJ. Does monitoring method influence stability of oxygenation in preterm infants? A randomised cross-over study of saturation versus transcutaneous monitoring. *Arch Dis Child* 2008;**93**:F347–50. [RCT] (See also F330–1.)
25. Adams G.(ed). Retinopathy of Prematurity. [A six article symposium] *Early Hum Devel* 2008;**84**:71–106.
26. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity. Ophthalmological outcomes at 10 years. *Arch Ophthalmol* 2001;**119**:1110–8.
27. Sun SC. Relation of target SpO₂ levels and clinical outcome in ELBW infants in supplemental oxygen. [Abstract] *Pediatr Res* 2002;**51**:350A.
28. Chow L, Wright KW, Sola S. Can changes in clinical practice decrease the incidence of severe retinopathy in very low birth weight infants? *Pediatrics* 2003;**111**:339–45.
29. Anderson CG, Benitz WE, Madan A. Retinopathy of prematurity and pulse oximetry: a national survey of recent practices. *J Perinatol* 2004;**24**:164–8.
30. Deulofeut R, Critz A, Adams-Chapman I, *et al.* Avoiding hyperoxia in infants ≤1250 g is associated with improved short- and long-term outcomes. *J Perinatol* 2006;**26**:700–5.
31. VanderVeen DK, Mansfield TA, Eichenwald EC. Lower oxygen saturation alarm limits decrease the severity of retinopathy of prematurity. *JAAPOS* 2006;**10**:445–8.
32. Silverman WA. A cautionary tail about supplementary oxygen: the albatross of neonatal medicine. *Pediatrics* 2004;**113**:394–6.
33. Tin W, Gupta S. Optimum oxygen therapy in preterm babies. [Review] *Arch Dis Child* 2007;**92**:F143–7.
34. Sreenan C, Lemke RP, Hudson-Mason A. High-flow cannulae in the management of apnea of prematurity: a comparison with conventional nasal continuous positive airway pressure. *Pediatrics* 2001;**107**:108–13.
35. Finer N. Nasal cannula use in the preterm infant: oxygen or pressure. *Pediatrics* 2005;**116**:1216–7.
36. Shoemaker MT, Pierce MR, Yoder BA, *et al.* High flow nasal cannula versus nasal CPAP for neonatal respiratory disease: a retrospective study. *J Perinatol* 2007;**27**:85–91.
37. Claude N, D'Ugard C, Bancalari E. Automated adjustment of inspired oxygen in preterm infants with frequent fluctuations in oxygenation. *J Pediatr* 2009;**155**:640–5. [RCT] (See also 606–8.)

Appendix

How high can functional saturation be allowed to go before there is at least a 5% chance that arterial oxygen pressure (P_{aO_2}) has exceeded 80 mm Hg (~10.7 kPa) ?

Study	Pulse oximeter reading	Mean arterial pO ₂ (and 95% confidence interval)
Brockway and Hay,* 1998 ¹⁰	94%	7.6 (5.1 to 10.1) kPa
	96%	8.8 (6.7 to 10.9) kPa
Bornhorst <i>et al.</i> , 2002 ¹¹	92%	8.7 (4.9 to 10.8) kPa
	93%	8.9 (5.3 to– 11.6) kPa
Castillo <i>et al.</i> , 2008 ¹³	94%	
	95%	
Quine and Stenson, 2008 ¹⁴	96%	7.7 (5.1 to 10.3) kPa
	97%	8.3 (5.1 to 11.6) kPa

* Oximeters measuring fractional saturation were used in this study. A 2% correction has been applied to make the findings reasonably compatible with those obtained in the other three studies