

## OXYGEN (Comment)

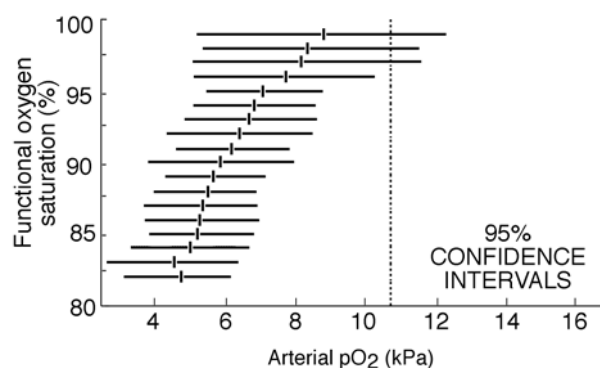
## Using saturation to monitor the need for supplemental oxygen

People who only started to care for preterm babies twenty years ago 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 1952<sup>1</sup> 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], it was hardly monitored at all. Once the outcome of the first three trials became known in 1956<sup>2-4</sup> the initial strategy was not to let babies have more than 40% oxygen, but it became fairly clear over the next decade and a half that this was probably killing more babies than it was saving from blindness,<sup>5,6</sup> and it came to be accepted that it was obviously the amount of oxygen getting into the blood, and not the amount of oxygen in the air, that matters.

Periodic arterial sampling soon took off in those units lucky enough to have on '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 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 fig 1 of this *Formulary's* oxygen monograph shows, only occurs when saturation is down to about 80% and arterial partial pressure is ~5 kPa) and then empirically increase the inspired oxygen by a somewhat arbitrary 10%.

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, possibly, in part, because it was not big enough.<sup>7</sup> Indeed, because pulse saturation monitors started to come into widespread use very rapidly<sup>8</sup> at much the same time as the outcome of Bancalari's trial first became known, no further studies of a similar nature were ever attempted and, more shamefully, no such question was asked of the new approach using saturation. Data collected during Bancalari's trial did, however, have a profound impact on nursing care when it was finally published in 1992, because analysis 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).<sup>9</sup> Since that time, and basically on the basis of this one study, it has been generally accepted that  $PaO_2$  should be kept 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).

The challenge is that the need for oxygen is now nearly always judged using a pulse oximeter to measure saturation rather than a transcutaneous sensor, or arterial line to measure  $PaO_2$  direct. The first four editions of this *Formulary* used data collected by Brockway and Hay back in 1989, but only published in full in 1998,<sup>10</sup> to show what the manufacturers have always admitted but staff frequently forget – that any one reading from such an oximeter may be in error by  $\pm 2\%$  and, in certain parts of the saturation range, by more than this.<sup>11</sup> The version of the relationship shown in fig 2 of the monograph on oxygen in the current (fifth) edition used data published by Professor Poets in 2002<sup>12</sup> using a Masimo monitor (a monitor that is thought to be better at 'editing out' false and unreliable readings) and this, in turn, will be replaced, when the next edition appears, with data recently published by Quine and Stenson.<sup>13</sup> The data they presented (see fig 1), and the conclusions they reached, closely parallel the conclusions also reached earlier this year by Castillo and colleagues.<sup>14</sup> Saturations higher than 95% risk breaching the somewhat imperfectly defined 80 mm Hg 'threshold' defined by Flynn but, since any saturation in the 84–89% range implies a  $PaO_2$  of ~5 kPa, much current concern about allowing saturation to drop into the mid 80s is probably ill-founded.



**Functional and fractional saturation** The data collected by Brockway and Hay related to *fractional* saturation, and this was what most monitors in use in the early 1990's displayed. The data collected by Poets, and more recently by Quine and Stenson, relate to *functional* saturation. Some basic understanding of the nature of the haemoglobin molecule is necessary to comprehend the difference between functional and fractional saturation. Haemoglobin may be referred to as functional or dysfunctional. Functional Haemoglobin is haemoglobin that is capable of transporting oxygen (and is 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).

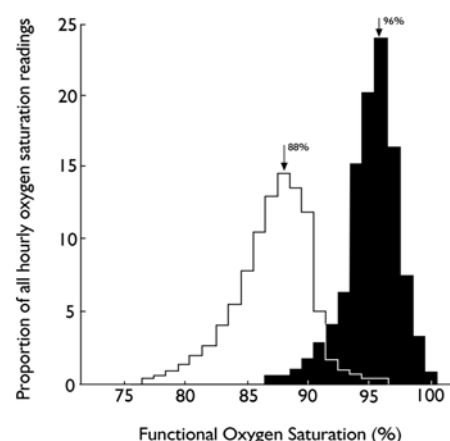
*Functional saturation* (the number now displayed by most non-invasive saturation monitors) is the ratio of oxyhaemoglobin to all other functional haemoglobin whereas *fractional saturation* is the ratio of oxyhaemoglobin to **all** haemoglobin (including any dysfunctional haemoglobin). Thus the results from the two types of oximeters will be different when significant amounts of dysfunctional haemoglobin are present. Typically, even 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 don't really know how much oxygen we should be giving.

**A safe upper limit:** Fig 1 would suggest that, if the safe limit suggested by the Flynn study<sup>9</sup> 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 there is an in-built delay before the alarm is activated and, in the various BOOST trials currently going on round the world, this has been set at two minutes. There would be endless self-canceling 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 even though these are, themselves, the average of all the readings actually taken over about 8 seconds. 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.<sup>13</sup> It differs quite significantly from the data obtained by Professor Poets in Tübingen, Germany, in 2002.<sup>11</sup> 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%. It has to be assumed that this is 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 hyperoxia that do not individually last long enough to trigger the alarm, they would in future set their upper pulse oximeter alarm limit for oxygen-dependant preterm babies at 93%.

**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. The only valid information available at the moment comes from an observational study reported by units in the UK's Northern Neonatal Network in 2001<sup>15</sup> and 2004.<sup>16</sup> 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.

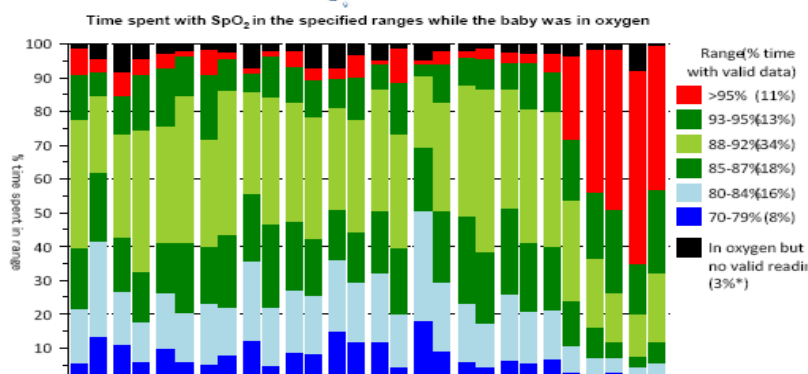


One thing that fig 1 shows is that, even when functional saturation is as high as 90-92%, quite a few babies with have an arterial  $PO_2$  of less than 5 kPa. Clinicians initially trained to rely on partial pressure rather than saturation to guide respiratory support had long been taught that it was important to keep partial pressure much higher than this.<sup>13</sup> 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,<sup>17</sup> and even more liberal guidelines (mindful that cyanosis begins to become detectable when partial pressure falls below 5 kPa) have usually recommended a target range of somewhere between 5 and 11 kPa.<sup>18</sup> 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).<sup>19</sup> However, all these guidelines were merely based on 'received opinion'. There was never much evidence to support any of these somewhat 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)<sup>16</sup> 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%.<sup>15</sup> 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 an endotracheal tube in place.<sup>20</sup>

### 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,"<sup>21</sup> Ngheim has, more recently, explored some of the reasons why compliance can be so variable,<sup>22</sup> and Clucas *et al.*, from Melbourne, have courageously shown how often the upper alarm is not set where it is supposed to be.<sup>23</sup> 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'.<sup>24</sup> An unrealistically 'tight' target range also makes compliance more difficult.<sup>21</sup> In the various international BOOST trials, where cot-side nurses are currently 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,<sup>23</sup> 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,<sup>25</sup> 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.<sup>26</sup> However unless the move away from giving as much oxygen as has been common in the recent past<sup>27-31</sup> 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.<sup>32,33</sup> 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.

\* 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.

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