

# Retinopathy of prematurity and oxygen therapy: A changing relationship

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## INTRODUCTION

The use of oxygen was implemented in neonatal practice in the absence of any randomized studies. The dose was (and still is in some places) not measured well. Additionally, the newborn's oxygenation levels were not measured routinely until Arterial Blood Gases (ABG's), capillary samples, transcutaneous PO<sub>2</sub> (TcPO<sub>2</sub>) and, more recently, monitoring of oxygen saturation by pulse oximetry (SpO<sub>2</sub>) became available. However, it is one of the drugs most frequently used in NICU's, many times without any limits or control, as repeatedly mentioned in books, editorials and articles, as recent as December 2003 and February 2004<sup>1,2</sup>. The relationship between PaO<sub>2</sub> and saturation is a "changing" one, as reported many years ago. The relation of prematurity, oxygen and ROP has been studied by many<sup>3-8</sup>. However, over the past 63 years, the history of this condition and these relationships continue to evolve. It is our objective to bring up to date some of the important topics in these evolving and changing relationships. In this review we will include, in greater or lesser detail, the definition ROP, the grades of ROP severity and the unsolved issues of its treatment, a few historical aspects, and the population at risk and associated risk factors. We will also discuss the difficulties with accurate statistics in ROP (rates and intercenter and inter-nation variability), the significance of the problem, and the pathophysiology in the developing retina. We will end by providing the best available evidence of the relationship between different oxygenation levels (PaO<sub>2</sub> and TcPO<sub>2</sub>; oxygen saturation, SpO<sub>2</sub>) and of rapid changes and "fluctuation" of oxygenation on ROP. We will also describe how a process of education and of implementation of guidelines to accomplish changes in clinical practice is associated with a clinically significant impact in the prevention of some of the most severe cases of ROP. To end, final comments and a few future studies currently in planning stages will be briefly discussed.

## WHAT IS ROP?

### Definition and Grades of Severity

ROP is a developmental abnormality of the retina and vitreous that occurs in premature infants. It is due to abnormal angiogenesis, in which retinal blood vessels fail to grow and develop normally in infants born prematurely, sometimes resulting in visual impairment and blindness. The disease is associated with, and affected by, survival rates and severity of systemic disease. It is of variable severity, classified after detailed ophthalmologic fundoscopic examination with *INDIRECT* ophthalmoscopy. An International Classification (ICROP) has existed for many years<sup>9</sup>. The classic *stages* described by ICROP are of increasing severity (stages 1-4). The eye is divided in *zones*, according to which area is affected. Zone I ROP occurs when at least one clock hour (sector) of ROP is seen within an imaginary circle in which the radius is twice the diameter from the optic disk to the macula; is the most central zone, close to the optic nerve, and most critical to central vision. It is for this reason worse zone to have abnormal vessel formation. Zone II ROP -intermediate zone, occurs when retinal vessel maturation had not occurred to within 1 disc diameter of the nasal ora serrata. Zone III ROP (peripheral) occurs when retinal vessel maturation is to within 1 disc diameter of the ora serrata on the nasal side, in at least 2 clock hours. Figure 1 is a schematic representation, where "clock hours" of area affected are also represented. Furthermore, terms like threshold; prethreshold and "plus" disease are used. Threshold is used when treatment is indicated. Preshold [places the infant at very high risk for treatment. Plus disease requires at least two quadrants of dilation and tortuosity of posterior pole retinal blood vessels equal to or exceeding that of a standard published photograph. In addition, the ETROP study, published in December 2003<sup>10</sup>, put forth the concept that flat neovascularization in Zone I, even

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without an actual ridge, should be considered Stage 3 and proposed two Types (I and II) to decide on the more severe cases and therapy<sup>10</sup>, based on zone and on the presence or absence of plus disease as follows:

1. *Type 1* (most severe):

- a) Zone I, any stage ROP with plus disease
- b) Zone I, stage 3 ROP with or without plus disease
- c) Zone II, stage 2 or 3 ROP with plus disease

2. *Type 2*:

- a) Zone I, stage 1 or 2 ROP without plus disease
- b) Zone II, stage 3 ROP without plus disease

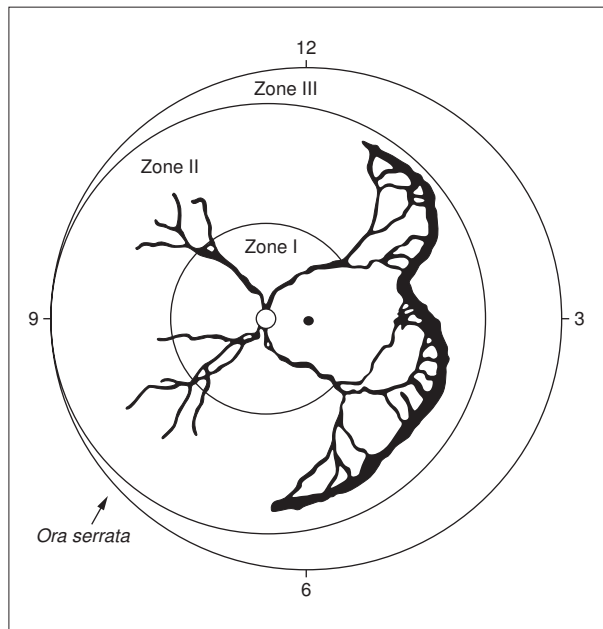
### Treatment and its effectiveness

Unfortunately, to date there is no completely effective “cure” for ROP nor a treatment to stop its progression to the most severe forms. Cryotherapy was used in the past for treatment but laser therapy is the current preferred treatment.

The largest study with published to date with a natural history cohort reporting incidence of ROP is the CRYO-ROP study<sup>11</sup>, however more modern data regarding incidence will soon be reported from the ETROP efforts. The infants in the CRYO-ROP study were born in the USA between January 1986 and November 1987 and the reported incidence in infants < 1,251 grams was 66%. The results showed that cryotherapy was beneficial but many children were left with significant vision loss even after this procedure.

The ETROP study<sup>10</sup> screened 6,998 infants < 1,251 gm in 26 centers in the USA. The infants with high risk pre-threshold ROP were randomized for early versus conventional treatment. The results showed that earlier laser treatment was associated with a reduction of unfavorable visual results at 9 months post conceptional age (PCA): 19.5% vs 14.5%. However, *there was no statistical difference in relation to blindness*. And there were more ‘complications’ during the earlier procedure. By analyzing the data, one can estimate how many would be treated unnecessarily: Type I in cohort: 37% with normal structure never reached threshold. This means that if all infants with type I are treated, for 3 that are treated 1 would not have required the procedure.

Two recent controlled randomized and blind trials assesses whether a strategy of “additional oxygen” in infants > 1 month old reduces progression of retinal damage once the disease process is well underway. The Supplemental Therapeutic Oxygen for Prethreshold ROP trial (STOP ROP)<sup>12</sup>, included infants of about 26 weeks at birth who developed prethreshold ROP in at least one eye and who could not maintain SpO<sub>2</sub> > 94% on room air. Infants were randomized late in the neonatal course once



**Figure 1.** Cartoon of ROP in Zone II with extension of more than 5 contiguous hours. (From Reynolds JD, et al: *N Engl J Med* 338:1572, 1998.)

the diagnosis of threshold ROP had been made to one of two groups: supplemental O<sub>2</sub> to maintain higher SpO<sub>2</sub> target (SpO<sub>2</sub> 96-99%) versus ‘conventional’ SpO<sub>2</sub> (SpO<sub>2</sub> 89-94%). The study failed to show a significant benefit for supplemental oxygen. Progression of prethreshold ROP to threshold was reduced by 28%, but the difference did not reach significance (OR 0.72, 95% CI 0.58, 1.01). A post hoc subgroup analysis of prethreshold ROP *without* plus disease revealed lower risk of progression to threshold among the tiniest infants in supplemental group (46% to 32%, P = 0.004)<sup>12</sup>. However, the reported side effects were much worse in the higher oxygen saturation group. These included pneumonia, exacerbation of BPD, adverse pulmonary events through 3 months corrected age, prolonged need for supplemental oxygen at 50 weeks PMA, and significantly increased use of furosemide. The Australian trial *Benefits of Oxygen Saturation Targeting (BOOST)*<sup>13</sup> randomized 358 infants < 30 weeks gestation who were O<sub>2</sub> dependent at 32 weeks post menstrual age. The oxygen saturation target was 91-94% in the “Standard” group and 95-98% in the High Saturation group. There was a consistent trend but no statistical difference toward reduced need for retinal ablation in higher vs. lower SpO<sub>2</sub> group (RR 0.5, 95% CI 0.3-1.1, p = 0.09). In infants born < 28 weeks gestation (n = 256), ablation was reduced by 48% in the higher SpO<sub>2</sub> group (RR 0.52, 95% CI 0.26, 1.03). There was no evidence that any of several outcomes (hospital stay; growth; major developmental abnormality; neurodevelopmental at 12 months corrected age; parental

stress and infants temperament) were changed. Duration of O<sub>2</sub> therapy & IMV were not improved either. Actually, BPD (O<sub>2</sub> at 36 weeks) was higher in those in the high saturation group (64% vs 46%) and a greater proportion was discharged home on supplemental oxygen (30% v 17%). There were also more respiratory deaths in the higher SpO<sub>2</sub> group<sup>13</sup>. These two trials found no difference in growth, mortality, or major developmental outcomes.

Therefore, the STOP ROP study<sup>12</sup> failed to find convincing evidence that giving additional oxygen significantly reduced the rate at which retinal damaged progressed once this is well underway and the BOOST<sup>13</sup> trial suggests that higher SpO<sub>2</sub> later in the neonatal course may have some role in reducing the progression of existing ROP in some premature infants. More importantly both illustrate potential tradeoffs in safety and efficacy of specific ranges of SpO<sub>2</sub> for different outcomes (i.e.: respiratory versus visual). With small increments in FiO<sub>2</sub> there was evidence for increased pulmonary sequelae and no detectable benefit in growth and neurodevelopmental outcome.

In summary, there is still a need to find a cure and to identify the “right time to treat”, so no missed opportunity exists while at the same time no infant is treated unnecessarily. As importantly, when the diagnosis is made, there is still no treatment that would effectively stop the progress to more severe forms. Above all, there is no definite and completely preventive measure, short of eliminating premature births. Data of STOP ROP and BOOST are important, but they are not relevant to address the optimal SpO<sub>2</sub> level early in the neonatal course which would result in less frequent, less severe ROP and less chronic lung disease. We and others have reported that careful monitoring of O<sub>2</sub> administration and of O<sub>2</sub> saturation, avoiding wide fluctuations and high O<sub>2</sub> saturations soon after birth and for the first several weeks of age, is associated with a lower incidence of severe ROP, less need of laser treatment, less blindness and less BPD.<sup>7,8,14,15</sup> (More details on this are described later).

### A FEW HISTORICAL ASPECTS

Oxygen was discovered more than 200 years ago<sup>16-17</sup>. Scheele in 1773 and Priestley on August 1, 1774 discovered oxygen independently from each other. Priestley was unaware of Scheele's earlier work, since it was not published until 1777. Because of his early publication on March 8, 1775 and subsequent detailed experiments on the nature of this new gas, plus his direct influence on Lavoisier (who actually named the gas “oxygene”, meaning acid-former, and who then initiated the “Chemical Revolution”), Priestley is usually credited with the discovery of oxygen<sup>16</sup>. As far as it is known, Priestley was also the first person ever to inhale air with a greater than normal concentration of oxygen. It seems that in 1780 Chaussier<sup>18</sup> gave oxygen to babies and since

then it has been given to more infants in the world than any other neonatal treatment. Interestingly, Priestley never really knew he discovered oxygen. He insisted to his death that he discovered “dephlogisticated air”. He actually was entangled in an incorrect theory and kept warning others to stick to the evidence and not give in to their prejudices. Claude Bernard, 100 years later wrote, “It is the things we *do* know that are the great hindrance to our learning the things we *do not*.”<sup>16</sup>. In 1917 intragastric administration of oxygen was recommended, a practice that lasted into 1950 and in 1928 Flagg described a method for resuscitation of asphyxiated neonates using oxygen and carbon dioxide<sup>18</sup>.

In the US and other industrialized nations O<sub>2</sub> therapy for neonates was introduced in the 1930's and early 1940's. Its use then became widespread throughout the world. In February of 1941 Dr Clifford a pediatrician in Boston and Dr Chandler, an ophthalmologist, saw a child with roving nystagmus, opacities of the eyes and a “fibro-vascular sheath of the lens”. Within a week another child was seen by them and Dr Terry. These two infants weighed at birth 1.02 and 1.81 kg and they were the forerunners of an epidemic of blindness, with 117 cases between 1942 and 1945. In 1944 Dr Messenger (an ophthalmologist and Latin and Greek scholar) coined the term retrolental fibroplasia (“RLF”). In the early 1950's the relation between O<sub>2</sub> therapy and RLF (name used then for this ROP condition) was discovered. By 1953: 10,000 blinded children by RLF (7,000 born in USA) had been identified. These issues and others are described with factual evidence and elegance by Dr Silverman in his book, “Retrolental Fibroplasia: A Modern Parable”, available on <http://www.neonatology.org/classics/parable/default.htm><sup>19</sup>. This is a must for all in leadership positions in Neonatal-Perinatal Medicine and also enlightening and inspiring for any concerned pediatrician. In brief, the O<sub>2</sub> concentration was turned down in many incubators and there was a reduction in ROP but increased morbidity and mortality. A tragedy happened in the 1950s and 1960s<sup>19-21</sup> when a new and ultimately harmful standard of care that was based on incomplete evidence had been widely implemented. As a few examples, McDonald reported in England that when O<sub>2</sub> was curtailed to 2-6 days, the prevalence of spastic diplegia was as high as 25%, but there was no RLF. When O<sub>2</sub> was maintained for 17-25 days or more, RLF was seen in over 25%, but spastic diplegia only in about 4-5%. Cross<sup>20</sup> reported on the cost in lives in 1973 and Bolton and Cross reported further details in 1974<sup>21</sup>. They found that after oxygen restriction was recommended by consensus the mortality rate in the first 24 hours of age per thousand live births did not continue the significant improvement and downward trend in USA, England and Wales from the

1950's to the 1960's. In addition, based on the excess number of deaths in the first day of life they estimated that "each sighted infant gained may have cost the death of 16 infants". During those days O<sub>2</sub> dose was not measured accurately, and it was impossible to measure levels of oxygenation. Today the relationship is different, and is still evolving.

It has been known since those early days that the proportion of severe visual impairment and blindness due to RLF/ROP in children aged 0-15 years in schools for the blind is inversely related to infant mortality rate, being much higher in industrialized than in developing nations. In data collected by a standard definition and methods between 1991-1996 in developing nations, Gilbert et al<sup>22</sup> reported that the proportion of severe visual impairment and blindness due to ROP in children aged 0-15 years in schools for the blind was 30% in Cuba, 18% in Chile and only 4% in Guatemala, associated again with better infant mortality rates.

Of course much has happened in this last 25-40 years. Blenders became available, as did accurate and simple to use oxygen analyzers, giving clinicians the possibility of controlling and knowing the dose of O<sub>2</sub> (FiO<sub>2</sub>). In the late 1960's and early 1970's PaO<sub>2</sub> measurements became available, as did micro methods for determination of arterial blood gases. This history monitoring of O<sub>2</sub> and blood gas is also very interesting and we have recently summarized it<sup>23</sup>. Non invasive continuous transcutaneous measurement of PO<sub>2</sub> (TcPO<sub>2</sub>) entered practice in the mid-late 1970's and early 1980's and, as useful as it was, is phased out of use. The measurement of oxygen saturation by SpO<sub>2</sub> monitors became available in the 1980's, but its history is still evolving.

In the past 3-4 years several editorial comments have been written on the topics<sup>1,2,24-27</sup> and several original articles have been published just in the last 18 months<sup>7,14</sup>.

However, truly effective care based on systematic reviews of the evidence obtained from randomized controlled trials is still not possible in relation to prevention of ROP, clearly not for O<sub>2</sub> therapy, PaO<sub>2</sub> and SpO<sub>2</sub> levels.

#### **POPULATION AT RISK AND ASSOCIATED RISK FACTORS**

The four major factors clearly associated with ROP are prematurity, oxygen use, male sex and white race. Of course, the problem tends to be more frequent and more severe in infants born at extremely low gestational age (24-27 weeks of gestation) and with ELBW (< 800 grams). However, the disease still exists in many regions of the world in infants who are ≥ 32 weeks' gestation and > 1,750 grams. This was the case 30-40 years ago in industrialized nations, where now ROP is non existent in this gestational age and birth weight groups. These

factors lend more support to the impact of clinical practices on the development of severe ROP.

There are many other factors that have been postulated as associated risk factors, but they have not been clearly confirmed or proven in large well performed studies. Discussing each of them in any detail escapes the objective of this review and they will only be named and only some briefly discussed below. The multiple factors explored in association with ROP include hypoxemia, indomethacin therapy, vitamin E and A deficiency, inositol, patent ductus arteriosus, lack of breastfeeding, postnatal steroids, light exposure, candida sepsis, numerous blood transfusions, early use of iron, the use of erythropoietin (EPO) and hypercapnia.

Post natal dexamethasone may be associated with severe ROP<sup>28-31</sup>. In a randomized trial of ELBW infants (750 grams) ventilator dependent at 15-25 days of age it was associated with a higher proportion of severe ROP (56% vs 45%) and need for ablation (35% vs 20%)<sup>30</sup>. Light reduction was not associated with ROP prevention<sup>32</sup>. Several clinical reports associate candida sepsis with a significantly higher proportion of severe ROP and surgical therapy for ROP<sup>31,33-35</sup>. The effect of blood transfusion on retinopathy of prematurity is still controversial<sup>36-38</sup>. A prospective, randomized study, combining data from both groups, showed no association between hemoglobin hematocrit ratios or transfusion protocol and ROP incidence or severity<sup>36</sup>. Dani et al<sup>38</sup> has nicely described the potential role of blood transfusions and iron intake on ROP. In preliminary reports presented at research meetings it is suggested that EPO use for anemia of prematurity may be associated with an increase incidence of ROP<sup>39,40</sup>. In relation to hypercapnia and apnea and their potential role in ROP we refer the authors to the section on pathophysiology described later.

#### **ROP "STATISTICS" (RATES AND INTERCENTER AND INTER-NATION VARIABILITY), EYE EXAMINATION AND SIGNIFICANCE OF THE PROBLEM**

Unfortunately in many NICU's in the world the rates of ROP are still unknown or the statistics of this condition are inaccurate. This is due to several possible reasons. First and foremost, if neonatal mortality for VLBW is high, the rates of ROP will be "low", particularly so in units that report cases with ROP in relation to admissions. Secondly, with any VLBW mortality rates, the data for ROP should not be reported per VLBW infants admitted to the unit. The numerator should be the *number of infants with ROP* and the denominator should only include *screened infants*. A summary of how data should be reported to allow valid comparisons is shown in table 1. Finally, for accurate statistics on this condition, all babies at risk must be examined and screened correctly before discharge and the screening rate known in the



NICU (table 1). If this is not done, the true rates of ROP in a particular unit will not be accurately known, and could be falsely low and comparisons among different units will not be valid.

The issues mentioned above are related to the variability that exists between centers and of course between regions or nations. However, when all steps are followed, there is still significant inter-center variability. In several large data bases one observes that the rates of severe ROP (III-IV) vary from 2% to more than 12%, and the need for laser treatment varies between 1-4%. This inter-center variability is related to differences in clinical care of oxygen administration and monitoring, and other aspects of care. These differences in care also explain, at least in part, within center variability from one epoch to the next.

To ensure accurate data, the infants considered at risk should be screened following a detailed protocol so that (almost) no infant is missed. Additionally, the eye examination should be methodically performed. The infant's pupils must be dilated (cyclopentolate 0.2% and phenylephrine 1.0%; cyclomydril) to ensure thorough examination. If there is poor dilation, cyclopentolate 0.5% and or phenylephrine 2.5% can be used. The exam involves the use of a sterile eyelid specula and scleral depressors in order to visualize the peripheral retina with a binocular indirect ophthalmoscope, along with a hand-held lens. The infants must be carefully monitored for signs of distress caused by the examination.

There are also guidelines as to when to repeat follow up exams. If there is no ROP during first exam, the infants need to be examined until retinal vessels had developed. In eyes in which ROP is observed, the location and severity must be recorded according to ICROP<sup>9</sup>. Zone I ROP needs to be examined every week. Diagnosis of Zone III ROP requires follow up at least once, 2 weeks

later. Zone II needs to be followed every 1-2 weeks until full maturity or worsening is found.

The significance and impact of ROP is crucial. About 4-5% of survivors < 1,000 grams are legally blind. A larger percentage has significant visual impairment. If one accepts a gross estimate that each year there are 2,000 VLBW infants discharged alive from NICU's in the USA who are blind or severely visually impaired and that the life expectancy for those infants is 70 years, one can calculate that each year there are 140,000 new years of blinded life entering society. Severe ROP not only leads to blindness but is associated with severe abnormal neurodevelopmental abnormalities. VLBW infants with severe ROP fare much worse than those without visual impairment. As ROP severity increases the severe disability rate increases from about 4% to 20% when there is threshold ROP. More than half of the infants with unfavorable vision have severe disability. With unfavorable vision the functional outcomes are worse, with 77% being unable to provide self care, 50% having problems of continence, 43% motor disabilities and 66% altered personal-social skills, 3-10 times more frequent than controls with favorable vision<sup>41</sup>.

Finally, in almost every region that data is obtained from schools for blinded children or adults, the proportion of severe visual impairment and blindness due to RLF/ROP is much higher any other cause (or many causes combined). ROP in these settings is the most common cause of blindness. The significance of this problem is also now being reported from developing nations, where survival of VLBW infants is increasing and a large numbers of infants with severe ROP and/or blindness are entering society<sup>42,43</sup>). The saddest part is that many of these infants are "large" (i.e. > 27 weeks gestation, or > 1,250 gm at birth), similar to what happened, but no longer occurs, in industrialized nations 30-55 years ago.

TABLE 1. Calculation of rates of retinopathy of prematurity to make valid comparisons within the same NICU in different epochs or between different NICU's

<p><b>Rate of ROP</b> Number of infants with the Dx of ROP <math>\times 100</math> Infants who had detailed retinal exams</p>
<p><b>Rate of SEVERE ROP (III-IV):</b> Number of infants with the Dx of severe ROP <math>\times 100</math> Infants who had detailed retinal exams</p>
<p><b>Rate of therapy (Laser, Cryo) for ROP:</b> Number of infants treated for severe ROP <math>\times 100</math> Infants who had detailed retinal exams</p>
<p><b>Rate of screening for ROP:</b> Number of infants screened for ROP <math>\times 100</math> Infants <i>eligible</i> for detailed retinal exams</p>

NICU: Neonatal Intensive Care Unit.

## PATHOPHYSIOLOGY AND THE DEVELOPING RETINA

The two triggering factors are an incompletely vascularized retina (preterm infants) and increased PaO<sub>2</sub> with relative retinal hyperoxia. These leads to vasoconstriction and decrease in growth factors, among them are insulin like growth factor (IGF-1) and vascular-endothelial growth factor (VEGF). This leads to arrest of vascularization and capillary obliteration, which leads to decreased perfusion and subsequent retinal ischemia and hypoxia. In response to this, various growth and angiogenic factors (IGF-1, VEGF and others) are upregulated. If this response is marked and vasogenic factors do not decrease, angiogenesis (i.e.: new blood vessel formation) becomes abnormal and disorganized with significant vasoproliferation. This could finally lead

to inflammation, proliferative retinopathy, significant fibrosis and retinal detachment<sup>44-50</sup>.

Even though hyperoxia and the formation of radical oxygen species are clearly a predominant part of the pathogenesis, other factors like pro-inflammatory cytokines, cyclooxygenase-2 (COX-2), neuropeptide Y, Nitric Oxide (NO) and deficit of trophic factors and anti oxidants have been implicated. COX-2 has pro-angiogenic effects mediated by prostaglandins (PGE<sub>2</sub>) and activation of specific receptors (EP3 receptors). This leads to induction of eNOS expression, the endothelial form of the NO synthase, which would lead to more NO being present. This is why some investigators are exploring COX-2 inhibition to attenuate intra vitreal neovascularization. The neuropeptide Y has 36 amino acids and is upregulated by hyperoxic exposure. Depending on the time and duration of retinal hyperoxia and hypoxia and the expression of the Y2 specific receptor, significant neovascularization can occur<sup>46-48</sup>. Interestingly, in a genetic "knockout" model of Y2 receptors, there is significantly less retinopathy, blood vessel tuft formation, retinal hemorrhage and blood vessel tortuosity despite breathing FiO<sub>2</sub> 75% for five days after day 7 of age<sup>48</sup>. Cyclooxygenase-2 (COX-2) is involved in neurodegenerative events in the rat retina<sup>49</sup>. The role of the soluble receptor of tumor necrosis (sTNFR) was recently evaluated in 14 VLBW infants in a pilot study. It was found that infants who later developed severe ROP had higher serum levels of sTNFR between 3 days and 5 weeks of age<sup>50</sup>. These findings are leading investigators to study different forms of inhibition in an attempt to attenuate abnormal neovascularization.

Regarding hypercarbia, Holmes reports on carbon dioxide-induced retinopathy in the neonatal rat<sup>51</sup>. Furthermore, recent reports in animal model and tissue cultures show that hypercarbia without any hemodynamic effects increases NO synthase (NOS) isoforms in the retinal vasculature, resulting in cytotoxicity of the vasculature<sup>52,53</sup>. When hypercarbia coexists with elevated NO in the retina, the retinal lesions are many fold worse. In addition it has been clearly demonstrated that hypercarbia induces vascular development and prolongs activation of endothelial NOS<sup>52,53</sup>. Finally, the role of VEGF and IGF-1 in a hypercarbic oxygen-induced retinopathy rat model of ROP has been recently described<sup>54</sup>. The clinical information is incomplete and non conclusive<sup>55,56</sup>, but this is not unexpected due to the multifactorial issues involved in the pathogenesis of ROP.

As clinicians we can observe our practices and evaluate if any changes introduced in clinical practice before there is 'enough evidence' of safety and efficacy have any impact on important outcomes. Nowadays many NICU's allow some very ill infants to remain on CPAP early in the infant's life, even if they have high PaCO<sub>2</sub> and show

significant oxygen fluctuation 'down and up' due to intermittent apneic episodes of variable severity. In those cases we are able to document only intermittently a few, limited variables like PaO<sub>2</sub> and PaCO<sub>2</sub>, but as clinicians we cannot see what is happening, if anything, with NOS, NO, COX-2, IGF and VEGF systemically or in the retina. Interestingly, in addition to GA and BW, it was recently reported that apnea and surfactant therapy are significant independent risk factors for ROP. Furthermore, apnea may not only increase the risk of developing ROP, but may also worsen pre-existing ROP<sup>57</sup>.

Until further evidence is made available, the rates of ROP need to be monitored carefully and accurately if clinical practices are modified. The question today is which among the factors related to hypercarbia, hyperoxia and significant and rapid oxygen fluctuation has a greater or lesser impact on ROP. They may all modify the expression of some or all of the factors mentioned above, and may be more detrimental in combination when the infant is more immature and the retina significantly underdeveloped. Unfortunately, it seems that there are regions and centers in the industrialized world which are showing an increase in severe ROP<sup>58-60</sup>, NOT associated with an increased survival of the tiniest infants. One can only wonder and speculate if the introduction of several new practices has a relation with this. Surfactant came in early 1990's and can be associated with rapid improvements in oxygenation. Around the same time, SpO<sub>2</sub> monitors were introduced. In many centers high SpO<sub>2</sub> values were routinely allowed and, therefore, a lack of a fast enough response to the surfactant induced changes in oxygenation could be associated with very high (unknown) PaO<sub>2</sub> levels for varying periods of time early in post natal life. This, in addition to the rapidly fluctuating changes in oxygenation associated with the use of SpO<sub>2</sub> monitors may explain in part the increase and variability in rates described before. CPAP with significant hypercarbia and frequent episodes of low and high oxygen levels early in life may also have an impact on ROP.

### **OXYGEN ADMINISTRATION, OXYGENATION LEVELS, RAPID CHANGES AND ROP**

Oxygen was discovered more than 200 years ago (see before) and it has been administered to more infants in the world than any other neonatal treatment. However, we still do not fully know how much is wise to give or how much infants actually need in relation to variations in illness and gestational and postnatal age. But we have known for many years that "too much oxygen" damages the retina<sup>3-6,61-64</sup>.

### Why choosing between the ‘extremes’ of oxygen dose: 21 % (room air) versus 100 % (‘pure oxygen’)?

In many places, and even in the recent literature, there is a longstanding debate about using 21% oxygen ( $\text{FiO}_2$  0.21) versus 100% or ‘pure’ oxygen ( $\text{FiO}_2$  1.0) during resuscitation<sup>65-72</sup>. This practice of choosing ‘one or the other extreme’ cannot be a correct practice for many infants since it excludes or limits a more reasonable practice, a practice based on using an ‘adequate’ dose of oxygen, assessing each infant’s needs. Placing a pulse oximeter, targeting for an “acceptable”  $\text{SpO}_2$  and using a blender to be able to administer the needed oxygen dose for that target are simple and inexpensive care measures, which are used ‘day in and day out’ in every NICU in many nations. Measuring  $\text{FiO}_2$  and  $\text{O}_2$  saturation (and/or) ABG’s is done routinely in many NICU’s. Why is this not done *routinely from the time of birth* in preterm infants treated in many places through out the world? Why is this practice not done consistently during resuscitation, and at any time in the delivery room, in hospital transit or during hand ventilation? Not to do so is not supported by any literature nor by physiological evidence.

It is well known that resuscitation without oxygen is effective as described by the references just cited above. Additionally, mouth to mouth resuscitation delivers less than room air ( $\text{FiO}_2$  19-20%) and has been known to be effective for decades. The neonatal practice of ‘one or the other extreme’ (21% vs 100%) in the delivery room may be understandable in poor, underdeveloped areas, with no expensive technology and no NICU’s. In such places (and *only* in such places), if severe lung disease is unlikely or ruled out, it seems that the best alternative would be to resuscitate with room air, and change to 100%  $\text{FiO}_2$  in the particular infant who shows no good response. Or alternatively, if in doubt, it may be necessary to start with 100% and wean to room air immediately after signs of initial recovery start to be evident. In any other place in the industrialized world and also in centers in developing countries that are able to afford and have modern expensive technologies and NICU’s, practicing with only two extremes of  $\text{O}_2$  dosing (21% versus 100%  $\text{O}_2$  administration) is just suboptimal.

### Oxygenation levels and ‘bad practices’

Currently oxygenation is measured in neonates in one of two ways: arterial blood gases ( $\text{PaO}_2$ ) and pulse oximetry ( $\text{SpO}_2$ ) monitoring. The history of oxygen monitoring is also very interesting and has been recently summarized<sup>23</sup>. Transcutaneous  $\text{PO}_2$  electrodes were used in the 1970’s and, as useful as they were in the past, they were replaced by  $\text{SpO}_2$  in the mid to late 1980’s. Capillary  $\text{O}_2$  ( $\text{PcO}_2$ ) determinations are not reliable to measure oxygenation, since a  $\text{PcO}_2$  of 45 mmHg may represent a  $\text{PaO}_2$  of 50mmHg or one > 80-100 mmHg.  $\text{SpO}_2$  monitors

are currently widely used and this history is still evolving as new technological advances are entered into practice. In a separate review on pulse oximetry in neonatal medicine<sup>73</sup>, we describe the most important aspects of  $\text{SpO}_2$  and the significant differences in saturation monitors in the market, and how much we know and do not know about oxygenation. Suffice to say here that as with any measuring device there is an accepted variability of  $\pm 0.5\%$  to up to 3% when compared to the ‘gold standard’ (Co-Oximetry). Additionally, one  $\text{SpO}_2$  monitor is not the same as another  $\text{SpO}_2$  monitor. Many  $\text{SpO}_2$  monitors have high rates of false alarms, are not accurate in eliminating noise, have ‘holding periods’ and are more sensitive to light and motion artifacts. In summary, many  $\text{SpO}_2$  monitors may not function well when clinicians need them the most. In addition, some  $\text{SpO}_2$  monitors measure and display functional  $\text{O}_2$  saturation and some fractional  $\text{O}_2$  saturation<sup>73,74</sup>. Some monitors read 1.5%-4% higher or lower than other monitors, even in very stable conditions. Therefore, this information helps us understand that finding the ‘ideal’ or best  $\text{O}_2$  saturation in preterm infants is not easy, and cannot be just one value.

In many places the oxygen dose ( $\text{FiO}_2$ ) is not measured carefully *all* of the time when given to premature infants, due to lack of blenders. The lack of use of blenders in the delivery room, providing 100% ( $\text{FiO}_2$  of 1.0) and no measurement of  $\text{O}_2$  saturation is unacceptable as we have described in a Pediatric textbook<sup>75</sup>. In such cases, unless the lungs are severely affected, the  $\text{PaO}_2$  could be very high (i.e.: 200-400 mmHg) and the real arterial  $\text{O}_2$  saturation would be 100% with an  $\text{SpO}_2$  reading of > 95% (up to 100%), if measured. Until true evidence is available, care providers can argue and struggle about what is the best, ideal,  $\text{SpO}_2$  level and disagree if the “target saturation” for weaning the  $\text{FiO}_2$  should be 93% or 96% or some other%. But this can be done with humility, cognizant of our ignorance of what is “best” and of the caveats regarding monitor’s measurement errors and differences between  $\text{SpO}_2$  monitors<sup>73</sup>. But what ever these and other limitations of our current knowledge may be, using a blender and a measurement of oxygenation (i.e.  $\text{SpO}_2$  monitor) ‘increases the evidence’. In such way, the infant would not be exposed to definitely abnormally high oxygenation levels and the  $\text{FiO}_2$  would be weaned as rapidly as necessary, as tolerated by the infant.

Another ‘bad practice’ is that of manual ventilation in an intubated infant when this is done with gas flowing into a breathing bag directly from the wall  $\text{O}_2$  flow meter (i.e. 100% or  $\text{FiO}_2$  1.0). For many reasons, like intubation in the delivery room, “deterioration” in NICU, change of ET tube, and others, manual ventilation may be necessary. However, we must remind ourselves that the gas “from the wall” is ‘pure oxygen’ and is *cold* and *dry*. These last two issues will change flow dynamics and

affect the lung and the airways. In addition, if the infant was previously receiving  $FiO_2 < 1$  (i.e. 40%; 60%; 70%) and was stable, and now, with this practice of manual ventilation with 'pure oxygen', without a heater humidifier and a blender, the saturation reads 100%, it is *impossible* to know how high is the infant's  $PaO_2$ .

Yet another bad practice occurs in many places when the dose of oxygen ( $FiO_2$ ) is changed significantly without written orders or documentation. Even today, in many places and during many NICU shifts, the  $FiO_2$  is modified significantly during some periods of time by care providers caring for preterm infants. For the most part, these modifications go undocumented in the clinical records. This delivery of clinical care with risk for "abnormally high"  $FiO_2$  and oxygenation levels is described in the following circumstances. A preterm infant in NICU shows a decrease in  $O_2$  saturation (i.e.  $SpO_2 < 75\% - 80\%$ ) and the monitor alarms. The care provider increases the  $FiO_2$  by 5-10-20-30% or more. The infant then "recovers", the  $SpO_2$  reads 98-100% and the infant is left in "good condition", since the  $O_2$  saturation is "as good or better" than before. Many infants are left like this, without accurate documentation. And many monitors' alarms are turned off. Most infants, if not all, do not have an ABG measured during the period just described, when the  $FiO_2$  has been changed significantly. Subsequently, minutes or hours later, when the infant is found by another care provider with an increased  $FiO_2$  and an  $SpO_2$  of 97-100%, a frequent practice is that the  $FiO_2$  is immediately brought back to, or close to, baseline levels. The infant may then be "well oxygenated" with  $O_2$  saturation of 93% and  $PaO_2$  of 45-60 mmHg or "rebound" to low  $SpO_2$ . Therefore, in infants breathing  $FiO_2 > 0.21$  who are exposed to these (too frequent) circumstances, we do not know how high the  $PaO_2$  was during those times when the  $PaO_2$  was not measured but the  $O_2$  saturation was 97-100%. Additionally, the infant may be subject to wide fluctuations in oxygenation. This is what we have come to call 'A LOST RELATION'. A similar situation is observed with the use of nasal cannulas. An infant is with 0.5L/min and  $FiO_2$  0.30 or so, the infant "desaturates" and/or has an apneic episode and the  $SpO_2$  monitor alarms. The  $FiO_2$  is increased to 0.40 or more and/or the flow rate is changed. The saturation "recovers" and reads higher. The infant is left "in good condition" with such treatment. How high is the  $PaO_2$  level?

If during fetal life growth and health occur with saturation of 70-80%, why have we insisted to maintain oxygen saturation  $> 95\%$  in preterm infants receiving supplemental oxygen? This is of particular significance since the pulse oximeters do not give enough information about the blood oxygen tension ( $PaO_2$ ), which could be very high (i.e.  $> 200-350$  mmHg) when an infant breathes supplemental  $O_2$ . Oxygen saturation monitors were

entered into practice in the 1980s not only without randomized trials but also, and probably more importantly, without education of bedside care providers around the world (i.e.: nursing staff, respiratory therapists and also physicians) about the changing relation between  $O_2$  and Hemoglobin,  $PaO_2$  and  $O_2$  saturation. When a preterm infant (and any human being) breathes a gas with oxygen supplementation and has an  $O_2$  saturation of 100% the oxygenation levels and  $PaO_2$  cannot and be predicted, and it can be "as low as" 60-70 mmHg or "as high" as 400 mmHg, or higher. Despite all this, in many places "physiological" targets of  $O_2$  saturation were accepted and entered into practice for preterm infants of all gestational ages and postnatal ages receiving supplemental oxygen based on  $O_2$  saturation levels seen in healthy term or preterm infants breathing room air (median values 96-99% as described in references 76-79).

The optimal or ideal  $SpO_2$  for preterm infants is not known. Therefore evidence based clinical practice is impossible. However, since so many babies receive  $O_2$  and are monitored with  $SpO_2$  monitors, we should make an effort to identify and try to eradicate 'bad practices' like the ones described here.

### **What is the evidence that high $PaO_2$ and $SpO_2$ levels and widely fluctuating levels are 'bad practices'?**

A cohort study in Northern England in relation to infants born between 1990-1994<sup>7</sup> found that infants treated with the intention to maintain the  $SpO_2$  target between 80-90% had similar rates of survival (around 50%) and CP (15-17%) at 1 year of age than those infants maintained at 88-98%. However, only 6% in the first group had threshold ROP versus 28% in infants with  $SpO_2$  in the upper ranges. Additionally, the infants with lower  $SpO_2$  limits had less days of  $O_2$  (40 vs 96 days) and IMV (14 vs 31 days), and their weight fell much less, with only 17% weighing less than the third percentile at discharge, compared to 45% in the high  $SpO_2$  ranges. There were 295 surviving infants, but the policy regarding  $SpO_2$  was found out retrospectively and 4 different types of monitors with different techniques were used.

Several surveys reveal similar situations. The most recent one<sup>14</sup> reported that the range of  $SpO_2$  for VLBW infants varied from 82% to 100% among all responders. The mean minimal  $SpO_2$  was 90% ( $\pm 3$ ); the mean maximal  $SpO_2$  96% ( $\pm 2$ ). The proportion of NB with SEVERE ROP ( $\geq 3$ ) was lower if the objective of maximal  $SpO_2$  is  $< 92\%$  (2.2% VS 6%). Retinal surgery in VLBW infants is less frequent when  $SpO_2$  ranges are  $< 98\%$  in the first two weeks of age (2.5% vs 5%) and also less frequent if  $SpO_2$  is  $< 92\%$  even after 2 weeks of age.

Bornhorst and Poets<sup>80</sup> have shown that using an upper alarm limit of 95%, there is 95% sensitivity with a Masimo<sup>®</sup> oximeter for detecting a  $PaO_2$  above 80 mmHg,



currently the upper limit recommended by the American Academy of Pediatrics<sup>81</sup>.

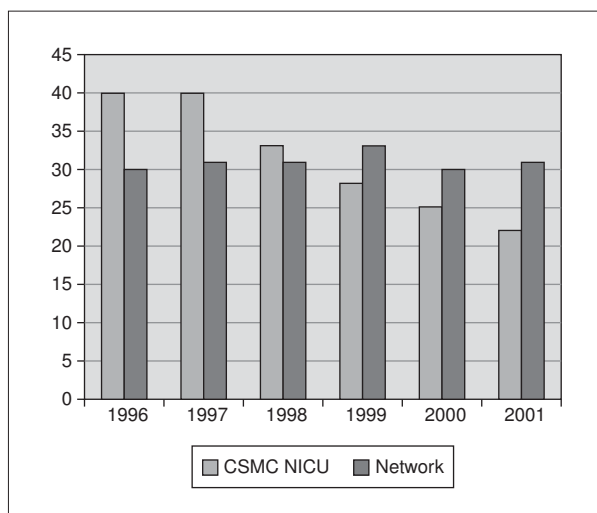
Marlow, commenting on future clinical trials mentioned that SpO<sub>2</sub> climbing too high should be avoided and probably not accepted by ethical committees<sup>82</sup>. After intensive and extensive work of Dr Cole, to try to initiate the POST ROP study, the saturation ranges proposed for the two groups (85-89% and 91-95%) do not include a group of “high O<sub>2</sub> saturation” (i.e. > 95%). Finally, we have recently showed that a strict policy of oxygen administration and monitoring, targeting O<sub>2</sub> saturation 88-93% is associated with a significant reduction of ROP<sup>8</sup>, described in more detail below. Avoiding high oxygen saturation and the possibility of hyperoxia (high P O<sub>2</sub>) is clearly supported in all current studies. Even though we still do not know how low of a SpO<sub>2</sub> is safe, we do know that saturations of 88-93-95% will maintain PaO<sub>2</sub> above 45 mmHg and usually less than 75-80 mmHg. Whether this PaO<sub>2</sub> is too high for some very immature babies remains to be determined, but this concern is what lead some clinicians to try maintain SpO<sub>2</sub> < 92% in the most ELGA infants.

Avoiding hyperoxia may be beneficial for conditions other than ROP, such as BPD and periventricular leukomalacia. Additionally, oxidative stress influences apoptosis and cell growth<sup>83</sup>. This may have some relation to white matter injury and to long term consequences in growth and development and even in carcinogenesis. In this regard it has been reported that oxygen at birth increased the risk of childhood lymphatic leukemia (OR 2.3; 95% CI 1.5-3.6) in a Swedish study<sup>84</sup>.

In relation to fluctuating oxygen levels and ROP, several animal and humans studies lend support to the

relation between fluctuation and retinal damage<sup>85-91</sup>. Penn<sup>85-87</sup> showed that range of PaO<sub>2</sub> and alternating values make retinopathy worse in a model of ROP. A 12 hour cycling of FiO<sub>2</sub> (FiO<sub>2</sub> changing from 40 to 80%) produced neovascularization in 72% of the cases, but while FiO<sub>2</sub> was constant at 80% neovascularization occurred in 18%. The severity was of 5 clock hours in the first group of animals vs 2.3 in the latter. Saito<sup>88</sup> found that the larger the coefficient of variation of PaO<sub>2</sub> the worse was the retinopathy; Cunningham studied the variability of TcPO<sub>2</sub> (31 vs 38 infants) and found worse retinopathy when the variability was larger<sup>89</sup>. Finally, York analyzed arterial blood gases in 231 infants between 1993 and 1995. On average the blood gases were measured every 2.4 h and the coefficient of variation was directly related to the risk of ROP<sup>90</sup>. Very recently, McCole has shown the effects of hyperoxic fluctuation in a rat model<sup>91</sup>.

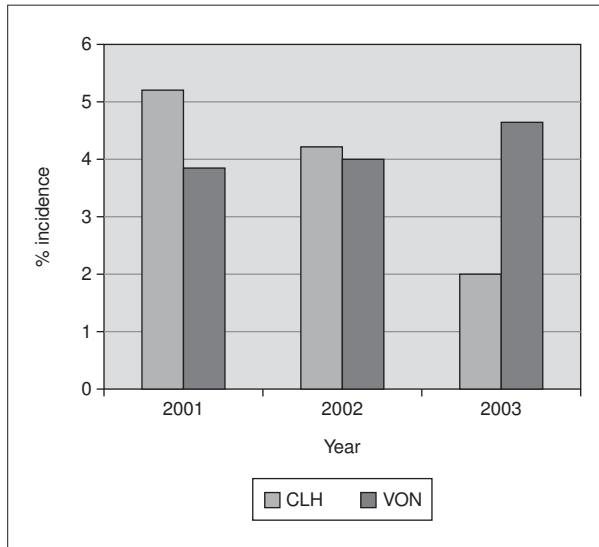
In summary, in the past few years, a number of studies have suggested that the “physiologically normal” O<sub>2</sub> saturation of healthy infants breathing room air, long-accepted by many as targets for SpO<sub>2</sub> in NICU, may be too high for the premature infant, and that allowing significant fluctuation is detrimental. Unfortunately, aiming for “high” O<sub>2</sub> saturation (i.e. > 95%) in preterm infants treated with oxygen has been, and still is in some places at some times, a routine clinical practice, accompanied by a frequent “up and down” in FiO<sub>2</sub>. A “comfort zone” exists, and within this, it is assumed that if the O<sub>2</sub> saturation is “high” the preterm baby is doing well. This needs to change, but the values and ranges of “lower” SpO<sub>2</sub> saturations reported in recent cohort studies cannot be the basis for routine treatment for all premature infants of all gestational and post natal ages. No range should become established practice before questions regarding short and long-term risks and benefits are resolved and until (if ever) the same SpO<sub>2</sub> last generation monitor technology is used universally. However, this is not the same as saying “we’ll continue to deliver care as always because that is the way we have done it”. Eradicating some bad practices is not the same as implementing routinely unproven practices in a rigid way. Increased awareness and education of known and proven facts must be disseminated, since the gap between knowledge and practice is associated with morbidity and can sometimes be lethal.



**Figure 2.** Proportion of infants with BPD (Oxygen at 36 weeks) after implementing a practice guideline regarding oxygen administration and monitoring. (One center: CSMC and data from Vermont Oxford Network, large data base with > 25,000 infants < 1,500 gm).

### CHANGING CULTURE IN NICU'S: PROCESS OF EDUCATION AND IMPLEMENTATION OF GUIDELINES REGARDING OXYGEN ADMINISTRATION AND MONITORING

We recently published a study where a strict practice with adequate SpO<sub>2</sub> monitoring (Masimo®) and a continuous quality improvement process of education



**Figure 3.** Proportion of laser surgery in infants with birth weight 500-1,500 grams. The implementation of education and of a last generation SpO<sub>2</sub> monitor (Masimo®) were associated with a marked decrease. (Single center, compared to VON data base).

and implementation of guidelines to accomplish changes in clinical practice were associated with a clinically significant impact in the prevention of the most severe cases of ROP<sup>8</sup>. The practice change occurred from the time of birth, with implementation of blenders and SpO<sub>2</sub> monitoring in the delivery room, and the acceptance of “lower than usual” SpO<sub>2</sub> values until the retina became mature. We aimed for SpO<sub>2</sub> (85%) 88-93% (95%) and to avoid wide swings in FiO<sub>2</sub> and SpO<sub>2</sub>. In 238 VLBW infants who survived and had detailed eye examinations, the rates of severe ROP decreased from 12 to 2% and there was no laser surgery required. This included 148 survivors and examined infants who had a birth weight of 500 to 1,250 grams<sup>8</sup>. In addition, the rate of BPD decreased significantly also (figure 2). We just had a very similar experience in the last 2 years at a different center (with a decrease from 13% to 3% in rates of severe ROP) and a marked decrease in the need for laser procedure (Unpublished data; figure 3).

In order to accomplish these changes in practice, it was necessary to “change culture”. For this, we studied about the fascinating topic of culture change in health care. We learned that it is important to understand the meaning of organizational culture in NICU, since each facility has its own unique character that strongly influences the quality of care and overall environment. When managing culture change one can try to lead *reform* or *transformation*. We learned that coming to grips with culture in NICU facilities is a serious and necessary undertaking if real transformation is to occur. To implement transformation,

**TABLE 2. Concepts which may be useful for educational process**

1. Oxygen is a potent drug
2. SpO<sub>2</sub> levels for VLBW breathing O<sub>2</sub> were accepted in clinical practice not based on physiological evidence or clinical evidence
3. SpO<sub>2</sub> monitors were introduced into practice without full understanding of “its meaning” by care providers at the bed side.
4. SpO<sub>2</sub> have provided a misleading sense of “accuracy” and security
5. There is mounting evidence that high SpO<sub>2</sub> levels accepted by *some* as “normal” are unnecessary and very likely detrimental.
6. In room air a SpO<sub>2</sub> of 96%-100% can be normal, but the PaO<sub>2</sub> will never be > 65-90 mmHg.
7. The relation between PaO<sub>2</sub> and SpO<sub>2</sub> is lost at “high” SpO<sub>2</sub> levels when an infant is breathing supplemental O<sub>2</sub> (FiO<sub>2</sub> > 21%) and therefore we are ignorant of the infant's PaO<sub>2</sub> in these circumstances.
8. When a premature infant is breathing O<sub>2</sub>, and the SpO<sub>2</sub> is 96%-100% the PaO<sub>2</sub> can be much higher than 90 mmHg
9. “Ranges” of PaO<sub>2</sub> at mid and low levels of O<sub>2</sub> saturation have been evaluated. The relation and predictability of PaO<sub>2</sub> from SpO<sub>2</sub> is pretty good when the SpO<sub>2</sub> is not high.
10. There is a wide spectrum of opinion and care practice, with some saying that SpO<sub>2</sub> must be always > 90%, or always > 93%, or > 95% as ‘mandatory’, while others consider SpO<sub>2</sub> ≤ 92% or 85%-93% as safe and effective.
11. It is impossible with current knowledge to find the “best” practice, but we can eradicate bad practices.
12. SpO<sub>2</sub> monitoring technology has markedly improved in last 5 years and there are significant differences in the various monitors in the market.
13. Currently the upper limit for PaO<sub>2</sub> recommended by the American Academy of Pediatrics is 80 mmHg.
14. A PaO<sub>2</sub> < 80 mmHg when an infant breaths supplemental O<sub>2</sub> can be achieved in the majority of circumstances by keeping the SpO<sub>2</sub> limits (and alarms) at 95%, avoiding higher saturations. However, there is no evidence that saturations of 86-93% are detrimental.

SpO<sub>2</sub>: oxygen saturation by pulse oximetry; VLBW: very low birth weight; PaO<sub>2</sub>: partial arterial pressure of oxygen; FiO<sub>2</sub>: inspired fraction of oxygen.

every member of the leadership team, including medical directors, must be prepared for the hard work and time needed to shift organizational culture. A ‘First Order Change’ implies doing what you do better; by quantitative reproduction and repetition (i.e.: “Change OF culture”). The ‘Second Order Change’, on the other hand, is qualitative growth, something different. (i.e.: “Change IN culture”). This is said to be necessary when an existing culture has begun to stagnate. We also learned that professional values, affirmed over years and decades, are resilient enough to frustrate many attempts to produce change. That is why the actions should not *just* attempt to modify familiar behavior.

One important point in this process was to remind all of us all of the time that, fairly frequently, in relation to

oxygenation and complex physiologic changes, “more important than what we see is what we do not see”. What we believe is that as useful as SpO<sub>2</sub> monitors are, we should not fix ourselves with a SpO<sub>2</sub> value (which we can see) and then chase it. Our approach is somehow different, learning and thinking about oxygen saturation curves, SpO<sub>2</sub> monitors, their differences and the pitfalls of some, and the changes that may be induced on VGEF, IGF-1, and radical oxygen species by transient elevations of PaO<sub>2</sub>, all of which cannot see. Another important point in our own education was to accept that there has never been convincing evidence for the “rational” use of supplemental O<sub>2</sub> in caring for preterm infants but there is physiological evidence and knowledge of the relation between SpO<sub>2</sub> and Hemoglobin. The important concepts in which the educational process can be based and a change in culture be achieved are summarized in table 2.

Based on our findings we can conclude that adequate SpO<sub>2</sub> monitoring equipment (Masimo Signal Extraction Technology®) accompanied by implementation of a strict clinical practice of oxygen administration and monitoring which avoids “high” SpO<sub>2</sub> and minimize wide fluctuations from the time of birth and during the first few weeks of life are associated with a significant decrease in severe ROP. This is accompanied by no increase in mortality, no increase in developmental anomalies and a decrease in BPD. We also concluded that the intercenter (and within center) variability described for ROP rates is related at least in part to differences in clinical practices and with differences in the minute-to-minute handling of O<sub>2</sub> administration and monitoring. We are NOT concluding that blindness can be completely eliminated by strict efforts to keep “FiO<sub>2</sub> < 40%” or that blindness can be completely eliminated by maintaining SpO<sub>2</sub> at 85-93%. Of course we are also not able to conclude which is the best SpO<sub>2</sub> level for very preterm infants.

Avoiding these high saturations (97-100%) in premature infants breathing (*monitored*) supplemental O<sub>2</sub> is not the same as to recommend a set and fixed range of “lower O<sub>2</sub> saturations”. However, HIGH O<sub>2</sub> saturation and HIGH FiO<sub>2</sub> when not needed are practices with increased risk which can, and should, be avoided. The predicament of the clinician and bed side care provider is then which one of the ranges less than 95% is safe and beneficial for different gestational and postnatal ages. This is not known and awaits further study. In our practice we chose a range as a target, with a span of about 9% saturation points (85-93%). We are not saying this is the way to handle all VLBW infants from birth until discharge if they are still breathing supplemental oxygen. In the tiniest of babies some speculate that maybe even lower SpO<sub>2</sub> values (82%-88% or 91%) may be sufficient, with the caveat that when an infant is not able to oxygenate with a possible diagnosis of pulmonary hypertension or when an infant gets older and has BPD

or severe ROP these ranges of SpO<sub>2</sub> are individually decided.

We do recommend education, and expanding the knowledge and understanding of bedside care providers of what is known to be risky. We consider that after an adequate process most would agree what are “bad practices” in this regard. Eradicating practices known to be associated with increased risks and changing a monitor with false readings and alarms and holding periods, could only be beneficial in clinical practice.

What we recommend then is to “change culture”. This includes the following: a) monitor FiO<sub>2</sub> and SpO<sub>2</sub> all the time; b) increase our awareness that when infants breath FiO<sub>2</sub> > 0.21 and the O<sub>2</sub> saturation is > 95% and up to 100% the relation saturation/PaO<sub>2</sub> may be lost; and therefore not to target *high* O<sub>2</sub> saturations when FiO<sub>2</sub> > 0.21 is being used. In addition we advocate: c) avoidance of cycling and wide, and rapid increases in FiO<sub>2</sub>, d) documentation; e) staying by the bedside when the infant is “recovered” after “an episode”; and f) to initiate weaning quickly but to wean slowly after this. In addition, we recommend using reliable last generation pulse oximetry monitoring to avoid responding to “false alarms”; and to maintain alarm limits as long as the infant is receiving FiO<sub>2</sub> > 0.21 during high risk periods of development, starting from the time of birth. Finally, we recommend managing the infant with O<sub>2</sub> saturations which, by known physiologic relations between hemoglobin and O<sub>2</sub>, will be related to a PaO<sub>2</sub> which is “not low or high” by currently accepted standards. We must accept with humility the uncertainty of what the “best” or “ideal” saturation range is for all preterm infants of all gestational ages, at all postnatal ages. This needs further detailed study.

Finally, the worse incidence and progression of ROP seen in some regions or units makes one wonder if any of the many changes that have occurred in clinical neonatal care in the last 12-15 years may be partly responsible for this. Of the entire major therapeutic changes that have entered clinical practice, only one was well studied: exogenous surfactant. This practice is associated with more acute changes in oxygenation early on in life. Unfortunately, around the time of implementation of routine use of surfactant the TcPO<sub>2</sub> monitors were changed to O<sub>2</sub> saturation monitors. Some NICU’s implemented “titration policies” (up and down) potentially associated with large PaO<sub>2</sub> swings. Recently “higher” PaCO<sub>2</sub>’s are being accepted and possibly more apneic episodes are tolerated since CPAP use is more prevalent. How do these combinations affect the developing retina is still not fully known.

### Ongoing and Future studies

The AVIOX study (*Actual Versus Intended OXYgen saturation*) was just presented in preliminary form at a

research meeting<sup>92</sup> in May 2004. This study shows that the proportion of SpO<sub>2</sub> values within intended range varied between 16-71% at different study centers. Most noncompliance was *above* the intended range, lending support to the fact that routine care of tiny premature infants who receive supplemental O<sub>2</sub> varies substantially among different centers.

The POST (*P*ulse *O*ximetry *S*aturation *T*arget) ROP trial is being planned extensively by Dr Cole and a large group of investigators. This will include tiny preterm infants. For this proposed randomized, blinded, controlled trial the target saturation ranges from the time of birth proposed are 85-89% for one group and 91-95% for the other. The results will hopefully help clinicians in better determining the safe and effective saturation to aim for. An editorial from December 2003 in *Pediatrics*<sup>1</sup> advocating the POST ROP trial states that "Evidence of net benefit or harm from one outcome should be considered in the context of other major outcomes. For example, it would be inappropriate to terminate recruitment because of a 3% reduction in severe ROP in the lower oxygen group before the trial had accumulated sufficient power to exclude a 6% increase in mortality or severe neurodevelopmental impairment in the same group. In this case, if the trial were prematurely terminated and lower oxygen became the clinical standard, for every baby whose sight was saved, two would die or survive with major disability." In addition, other smaller trials and basic studies are starting to address new potentially useful drugs for decreasing abnormal retinal angiogenesis. They include exploring in a mouse model with neuropeptide Y expression, somatostatin analogs, ibuprofen and squalamine<sup>93-96</sup> among others, to inhibit neonatal retinal neovascularization and stimulate regression of oxygen-induced retinopathy. This innovative work awaits further confirmation and may become of clinical value in the future.

## FINAL COMMENTS

Oxygen was entered into neonatal practice in the absence of any randomized studies. Furthermore, it has not been measured well and routinely, even today with SpO<sub>2</sub> monitors. However, it is one of the drugs most frequently used in NICU's, many times without any limits or control. If we jump now to recommending "lower oxygen saturations" without a reliable controlled trial, we may be condemning more children to death or severe disability than we ever save from blindness. However, to avoid or eradicate proven bad practices is not simply to use "lower oxygen saturations". Currently, ROP is an unfortunate growing global problem, a persistent sight-threatening complication of ELGA infants (GA < 28 wks) in the industrialized nations and also of larger preterm infants in the developing nations. The

visual outcome after severe ROP is unfavorable even if treated, and ROP is the most common cause of blindness.

The prevention of ROP may be possible by maintain a focus on research and also in clinical practice. Even though it is possible that in a not too distant future we may be able to use some preventive treatment, like drugs which modulate angiogenesis (VGEF or NPY receptor blockade, COX-2 inhibition, squalamine) or others like inositol, today we can change our culture and modify the relation between knowledge and the care the infants receive, changing clinical practice to eradicate 'bad practices'. We must not ignore the lessons of history, lest we are forced to repeat them, to the immense cost of these premature babies - the most vulnerable patients - and their families.

Our observations have shown us that in many cases, more important than what we see in routine practice may be what we do not see. This can be applied to what happens to many babies in delivery rooms or NICU's around the world in relation to oxygen dose, oxygenation and ROP.

"*The essential is invisible to the eye*", as Saint Exupery wrote in "The Little Prince".

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