Retinopathy of Prematurity (ROP) Can We Do Better?

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I dedicate this column to the late Dr. Andrew (Andy) Shennan, the founder of the perinatal program at Women's College Hospital (now at Sunnybrook Health Sciences Centre). To my teacher, my mentor and the man I owe my career as it is to, thank you. You have earned your place where there are no hospitals and no NICUs, where all the babies do is laugh and giggle and sleep.

Perhaps the most famous victim of ROP is Stevie Wonder. Born 6 weeks prematurely in 1950, he was one of many babies who had their incubators flooded with oxygen. (1) While Mr. Wonder may be one of the earliest and most recognisable cases of ROP, by the time he came along the use of supplemental oxygen in the management of infants had been a therapeutic intervention in the "first world" since the 1930s and 1940's. (2)

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Perhaps not surprisingly, the first case of what is now referred to as ROP was discovered in 1941. Between 1942 and 1945, a further 117 cases were discovered. The link between the new condition (then referred to as Retrolental Fibroplasia) and oxygen therapy was established in the early 1950s but by 1953 10,000 cases of blindness due to ROP had been diagnosed. (2)

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Without fully understanding the positive role of oxygen therapy, clinicians in the 1950s and 1960s restricted oxygen use during the first 2 to 6 days of life. This practice virtually eliminated ROP; however the incidence of spastic diplegia increased to about 25%. Furthermore, it was later estimated that for every case of blindness prevented by this practice, 16 babies died. Conversely, when oxygen was administered over 17 to 25 days or more, the rate of ROP increased to over 25% while spastic diplegia was seen in only 2-5% of infants. (2) This observation is similar to later studies on the use of higher or lower oxygen levels in infants.

Recent data suggests that we are not winning the war against ROP. A 2018 study found that 41.3% of premature infants developed ROP, and 12.5% of these infants are expected to develop severe ROP, almost exclusively in the sub-1251 gram cohort. (3) In the U.S. alone this represents over 2000 cases of blindness per year. (2) On the surface this is bad enough, considering the fact that blindness is associated with severely abnormal neurodevelopmental outcomes. Over half of those with unfavourable vision have a severe disability: 77% are unable to provide self-care; 50% have continence issues; 43% have motor disabilities, and 66% have altered personal-social skills. This represents a 3 to 10-fold increase compared to those with good vision. (2)

Technology in the NICU has exploded since the first cases of ROP were discovered. Nevertheless, this morbidity clearly remains one of the most significant sequelae of NICU patients, more than chronic lung disease, (4) one of the main foci of NICU quality improvement.

The advent of oxygen blenders and oxygen analyzers have allowed accurate FiO_2 delivery and measurement, and pulse oximetry (SpO_2) helps monitor blood oxygen levels in almost real-time. Still, while we know oxygen poses a substantial risk for the development of ROP, just how much oxygen to give (or not give as the case may be) remains a topic of hot debate.

Just as in the 1950s and 1960s, more recent studies have demonstrated the conundrum faced by NICU clinicians: give more oxygen and get more ROP or give less oxygen and face higher mortality; a perfect "catch 22". Or is it?

It is likely, not surprising to most clinicians that maintaining low serum oxygen levels (PaO_2) may have deleterious consequences and that maintaining high SpO_2 levels has different, although still dire consequences. Aside from higher rates of ROP, higher oxygen levels have been associated with CLD, periventricular leukomalacia (PVL), and may be a factor in white matter injury and carcinogenesis. In the STOPROP trial, there were more respiratory-related deaths in the higher SpO_2 group. (2)

While we are confident high SpO_2 is bad, the question is how low those levels can be and still be considered safe. While related studies consistently indicate that low SpO_2 is associated with higher mortality, this may not translate to higher mortality in clinical practice. Unlike in a study situation, bedside caregivers are not likely to allow their patients to have low SpO_2 for an extended length of time.

Consider the example of the unit in which I work. Concerned about possible increased mortality led to a shift in targeted SpO2 and related alarms upward from 88-92% with the "hard" alarm set at 80% and the high alarm at 96% to a target of 90-94% and an increase in the "hard" alarm to 85%. Some were surprised at the resulting significant increase in the incidence of ROP, an increase

significant enough to result in a resumption of previous parameters except for the low "hard" alarm being raised to 82%. Why did this happen?

Alarm fatigue is a continuing problem in intensive care units, NICU's included. The higher SpO_2 targets and related alarm parameters resulted in more alarms, which, in turn, led bedside caregivers to increase FiO_2 to achieve higher SpO_2 values since a high SpO_2 alarm is typically quieter and less annoying than a low alarm. While this happens with lower targeted SpO_2 as well, when targets were increased, the resulting SpO_2 increased further. The end result was nothing if not predictable.

"The visualisation of the vocal cords with the nasal CPAP apparatus in place is perhaps the most challenging aspect of MIST."

Speaking of alarm fatigue, in my opinion, the design of saturation monitors contributes to the practice of keeping babies' SpO_2 higher than ideal. A high SpO_2 alarm is generally a gentle "bing… bing… bing…" while a low SpO_2 sounds roughly like the sky is falling. While a delay function or longer averaging time is available, there seems to be a reluctance to use them. As well, the algorithms used may not allow enough time for a baby to self-recover. The monitors I am accustomed to using also send an alarm to the staff communication devices even if the alarm is silenced on the monitor immediately. Bedside caregivers are nothing if not human, and human nature leads to infants being maintained in enough oxygen to minimise annoying low SpO_2 alarms. A common lament is "you're not sitting here all day" when FiO_2 is weaned. While I am sympathetic, one's purpose at the bedside is not one's own appeasement.

All saturation monitors are not created equal. If the monitor dutifully displays a SpO_2 of 89% when lying in the bed its reliability must be called into question. The best monitors resist motion artifact and extraneous light interference fairly well; others, not so much. Servo-controlled combined blender/saturation monitor systems hold much promise; however, they are inevitably only as good as the signal received. Given a baby's movement, low perfusion, and use of bilirubin lights, any monitor used to servo-control a blender must be up to the task. Even without servo-control, I have often witnessed FiO_2 being increased for a "desaturation" when the signal display on the monitor is clearly showing artifact or a poor signal. There is evidence that the use of Masimo™ signal extraction technology may significantly reduce the incidence of ROP. (2)

I was told many years ago that oxygen desaturation in isolation and not associated with bradycardia was likely clinically insignificant. Although I am unaware of any evidence to support this statement, it may make sense from a physiological standpoint. I recall viewing a poster at a Pediatric Academic Societies conference several years ago that looked at hypoxia in rats. One group was exposed to 100% nitrogen for 10 minutes, another group was exposed to 100% nitrogen first for 5 minutes and then later for 10 minutes. While all in the former group died, surprisingly all those in the latter group survived. This raised two questions in my mind: 1) if desaturations are normal in the premature infant in utero and 2) if they serve to condition the brain for the relative hypoxemia of birth. After all, as humans, we experience the lowest SpO_2 levels at the hour of our birth and that of our death.

With judicious bedside monitoring, I believe it is safe to target SpO_2 of 88-92% in premature infants, with a "hard" low alarm of 80%. Babies should be given a minute or so to recover on their

own without increasing FiO_2, and the bedside caregiver should not allow SpO_2 to remain low for long. Adding a time-weighted factor to low alarms would make this even safer.

It can be easy to be discouraged to see the lack of improvement in ROP rates and evidence that does not support low SpO_2: "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_2 therapy, PaO_2 and SpO_2 levels". (2) Be that as it may, there are practices that respiratory clinicians and bedside caregivers should emulate, and those that should be avoided.

There is no debate about the deleterious effect of hyperoxia on the developing eye; rather, the debate is over what SpO_2 levels constitute hyperoxia in the premature infant. Knowing that oxygen also wreaks havoc on the developing lung, it behooves clinicians to use as little as possible to safely meet the needs of the patient.

It is all too common for a responder to a low SpO_2 alarm to increase FiO_2 and then leave the room to attend to another patient or task. Too often, the FiO_2 is left increased, and if the FiO_2 is normally 0.21, the high alarm is set at 100% and will give no warning of resulting hyperoxia. As a standard design feature, ventilators, including equipment providing non-invasive support (NIV), should incorporate a temporary FiO_2 increase function available in all modes. This would reduce inadvertent sustained increases in FiO_2.

It is also common practice in the NICU to pre-oxygenate babies when handling. This is sometimes done several minutes in advance, and the degree of increase is often not uniform, despite whatever policy may dictate. Pre-oxygenation should be done for as little time as possible, and certainly not minutes prior to handling. This increase should be limited as a matter of policy to 5-10% above baseline unless the need for more is demonstrated. As well, any infant whose SpO2 is >96% with a FiO_2 of 0.21 should not be pre-oxygenated at all, rather FiO_2 should be increased as required. SpO_2 level cannot be reliably estimated when PaO_2 is high, and a SpO_2 of 100% may represent a PaO_2 of 60 mmHg or 400 mmHg. (2)

When FiO_2 is increased, it should be to the lowest level to provide adequate SpO_2 and then returned to baseline judiciously as tolerated so as not to result in rebound desaturation. Rapid swings in PaO_2 lead to repeated vasoconstriction and dilation, which results in reperfusion injury.

The increasingly common use of NIV raises another important point. Avoidance of high SpO_2, as well as widely fluctuating SpO_2 from birth and during the first weeks, thereafter reduces the rate of severe ROP without increased mortality and results in lower rates of CLD. Given the frequency of bradycardia and desaturation episodes in very premature infants receiving NIV, we should be monitoring ROP rates in this group of patients very carefully. Some believe that proper, lung-protective ventilation with an endotracheal tube is preferable to NIV in the micro-premature infant. The truth will no doubt reveal itself, provided we are looking for it.

Permissive hypercapnia has become an accepted practice to reduce CLD, although CO2 should be controlled as carefully as possible in the first few days of life. While CO_2 has the opposite effect on cerebral and ocular vasculature, it makes sense that large, rapid swings in CO_2 levels would have the same deleterious effect as oxygen and may be a risk factor for ROP. A British study did not find an association with $PaCO_2$/$TcPCO_2$ fluctuations and ROP, although it does not indicate how rapidly these fluctuations occurred.5 Another article lists high $PaCO_2$ and low pH as possible risk factors,6 and within search results for "CO_2 and ROP" one will find a law firm linking CO_2 "Neonatal Breathing Mismanagement" and adverse outcomes including ROP. (7) Given the risk of litigation that raises it is likely a good idea to monitor CO_2 carefully and adjust ventilation accordingly.

As with all things medical, best practice is a moving target. Evidence drives practice, and evidence has been known to change. In the here and now, clinicians must work with the evidence we have. That evidence suggests that, yes, we can do better.

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