Oxygen Therapy in the Neonatal Care Environment

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The use of oxygen in the treatment of neonates with respiratory distress has been reported for more than a century. Oxygen therapy is generally titrated to one or more measures of blood oxygenation and administered to reverse or prevent hypoxia. Individual responses to oxygen therapy vary greatly, depending on the particular cause of hypoxia and the degree of impairment. Despite this focused purpose, oxygen administration in this patient population has become complex. The longer we deliver this drug, the more we discover its beneficial and detrimental effects. New and innovative ways to deliver and monitor this therapy have improved outcomes. Despite this vast experience there still remain some unanswered questions regarding the use of oxygen in the neonatal environment. Nonetheless, oxygen is a major staple in our treatment arsenal for neonates. *Key words: oxygen; neonatal; infant, newborn; retinopathy of prematurity; oxygen inhalation therapy.* [Respir Care 2009;54(9):1193–1202. © 2009 Daedalus Enterprises]

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Introduction

The use of oxygen in the treatment of neonates with respiratory distress has been reported for more than a century. In 1907, Budin recommended oxygen "supplied through a funnel, the large opening of which is placed beside the infant's face," for the treatment of cyanotic episodes in newborns.[1] In the 1930s, Hess[2,3] developed an incubator (Fig. 1) capable of delivering approximately 40% oxygen for extended periods of time. By the 1940s, a

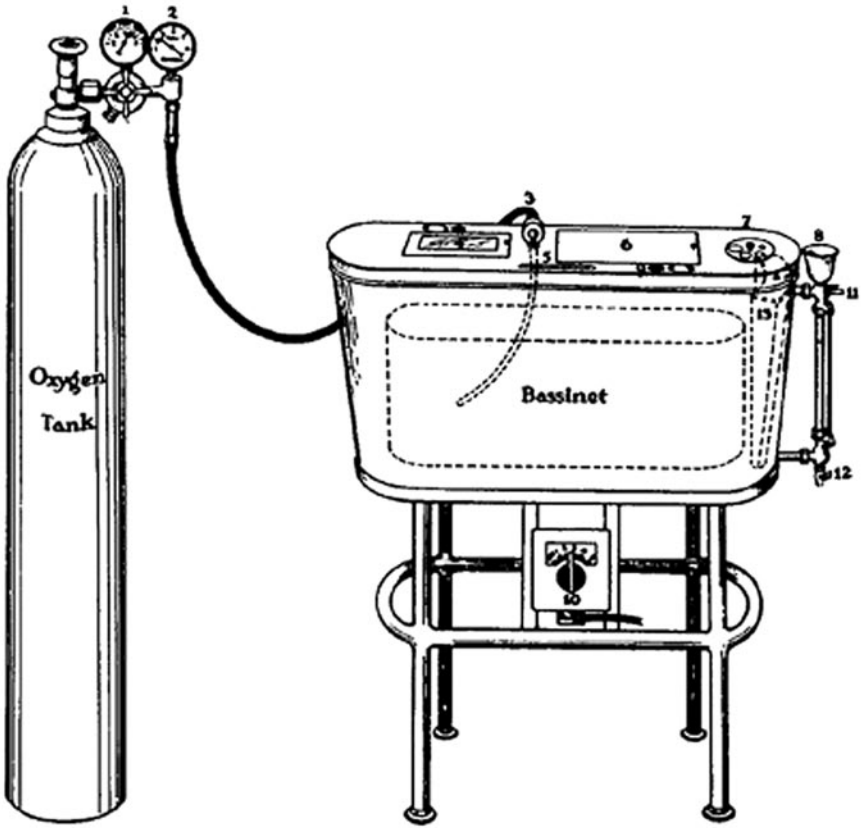

Fig. 1. Hess bed equipped with an oxygen therapy unit (A-side view). 1: Pressure gauge. 2: Oxygen flow regulator. 3: Flow meter. 4: Glass and metal hinged door for feeding purposes. 5: Thermometer window. 6: Metal hinged door for purposes of body care of the infant. 7: Ventilator with small and large exit openings. 8–12:Controls for maintaining temperature in water-jacket of the incubator. (From Reference 3, with permission.)

commercially available incubator capable of providing a high concentration of oxygen facilitated the liberal use of oxygen for the treatment of cyanosis, apnea, and periodic breathing in newborns.[1,4] Throughout this time, oxygen administration was guided by the clinical observations of skin color, as well as the rate, regularity, and work of breathing. It wasn't until the 1960s and 1970s that technology—micro-sampling of blood gases, transcutaneous oxygen monitoring, and, later, pulse oximetry—became available for more precise monitoring of physiologic effect.

The overall goal of oxygen therapy is to achieve adequate oxygenation using the lowest concentration of inspired oxygen. However, achieving this goal is complicated by a number of factors. Despite over 75 years of routine oxygen administration to newborn infants, the optimal level of oxygenation—one that avoids the detrimental effects of hypoxia on the one hand, and those caused by hyperoxia on the other—has not yet been clearly defined,[5-7] leading to wide variations in practice.[8] Even the term "adequate oxygenation" is not clear.[9] Other complicating factors in achieving the goals of neonatal oxygen therapy include patient size, tolerance of delivery devices, and variability in the use of delivery devices, which suggest that clinicians often lack adequate knowledge in the use of oxygen delivery equipment,[10] and the lack of training in the concepts of neonatal oxygenation and equipment used to monitor the effects of oxygen therapy.[11]

Physiologic Effects of Oxygen Therapy: Benefits and Adverse Effects

Despite its universal acceptance as a life-saving therapy for newborns, oxygen administration is associated with numerous physiologic effects, particularly when used to treat premature infants.

Treatment of Hypoxia

While oxygen therapy is generally titrated to some measure of arterial oxygenation in response to an abnormally

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low level of blood oxygen, or *hypoxemia*, oxygen is administered to the neonate to reverse or prevent hypoxia. Hypoxia is defined as a deficit of oxygen at the cellular level, and is commonly caused by one or more of the following: the reduced availability of oxygen at the alveolar level, due to pulmonary disease (hypoventilation, uneven matching of ventilation to perfusion, diffusion defects); intrapulmonary shunts or "right to left" cardiac shunts; reduced oxygen carrying capacity due to anemia or abnormal blood hemoglobin; or impaired oxygen delivery due to shock, heart failure, or localized decreases in perfusion.[12,13] Left untreated, hypoxia can lead to serious and permanent brain injury and death.[12]

Individual responses to oxygen therapy vary greatly, depending on the particular cause of hypoxia and the degree of impairment. Hypoxia caused by hypoventilation and ventilation-perfusion anomalies associated with pulmonary disease will be most responsive to oxygen therapy. Even large increases in F_{IO_2} will produce only small increases in available oxygen if hypoxia is caused by cardiac shunts, shock, and hemoglobin deficiency/dysfunction.[12,13] It should be stressed, however, that even small increases in oxygen availability may prevent life-threatening decompensation in the hypoxic neonate.

Oxidative Stress

The role of oxygen and oxidative stress in the development of a number of neonatal diseases has generated much interest. Oxidative stress has been defined as an imbalance between pro-oxidant and anti-oxidant forces in the body.[14] Pro-oxidants include oxygen radicals or reactive oxygen species, which can be cytotoxic because of their ability to alter cellular components and function. Reactive oxygen species are generated as a result of normal mitochondrial respiration, but also during the reperfusion phase of hypoxic tissue injury and in association with infection and inflammation.[15,16] Oxygen is "toxic" because of the production of reactive oxygen species; thus oxygen administration increases oxidative stress.

Antioxidant defenses include the enzymes superoxide dismutase, catalase, and glutathione. Nonenzymatic antioxidants start to cross the placenta in late gestation, and include vitamins A, C, E, and ubiquinone. Premature infants are at particular risk from oxidative stress because both endogenous and passively acquired exogenous antioxidant defense systems do not accelerate in maturation until late in the third trimester.[15,17,18] Investigators have attempted to reverse or prevent the damage associated with reactive oxygen species not only by appropriate oxygen administration but also by administering antioxidants; however, this therapy has not shown to be effective.[19] Saugstad has suggested the term *oxygen radical disease of neonatology* to encompass a variety of newborn diseases whose pathogenesis involves oxidative stress and injury, which include retinopathy of prematurity, bronchopulmonary dysplasia, necrotizing enterocholitis, and intraventricular hemorrhage.[20]

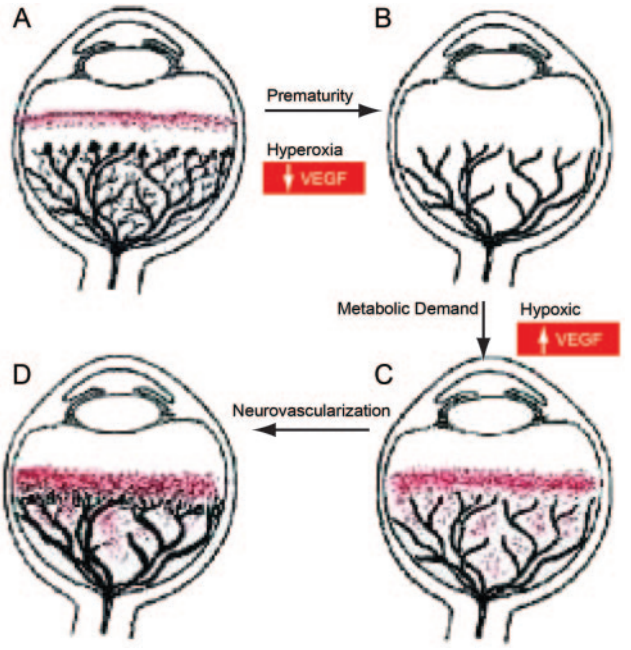

Fig. 2. The proposed role of vascular endothelial growth factor (VEGF). A: It is hypothesized that normal retinal vessel development is stimulated by production of VEGF (red) anterior to the developing vasculature. In addition, maintenance of some retinal vessels is dependent on VEGF. B: In the first phase of retinopathy of prematurity, exposure to relative hyperoxia after birth interrupts the gradient of physiologic hypoxia in the immature retina, leading to downregulation of VEGF production, with associated vasoobliteration and cessation of vessel growth. C: As the metabolic demand of the developing retina increases, the nonperfused portions of the retina become hypoxic and overproduce VEGF. D: Neovascularization occurs in response to overproduction of VEGF, producing retinopathy of prematurity. If VEGF production persists, then the retinopathy of prematurity will progress. (From Reference 26, with permission.)

Retinopathy of Prematurity

Though long recognized as a complication of oxygen therapy, retinopathy of prematurity remains a major cause of morbidity for premature infants.[21] Retinopathy of prematurity is a disease limited almost exclusively to premature infants and is characterized by abnormal vascularization of the retina, causing a range of vision impairment, including blindness. Much has been described in the literature regarding the role of supplemental oxygen in the development of retinopathy of prematurity.[22-24] The altered regulation of vascular endothelial growth factor has been suggested[25,26] as one of the factors in the pathogenesis of retinopathy of prematurity (Fig. 2). In premature

infants the retina is incompletely vascularized. In utero the arterial oxygen pressure of the fetus is 22–24 mm Hg. After premature birth, relative hyperoxia may downregulate vascular endothelial growth factor production. Administration of supplemental oxygen may lead to sustained hyperoxia, setting the stage for vaso-obliteration of existing vessels and arrest of the vascularization. Over time, as the metabolic demands of the developing eye increase, the immature non-perfused area of the retina becomes hypoxic and may overproduce vascular endothelial growth factor pathologically. High levels of vascular endothelial growth factor stimulate neovascularization of the retina, which in severe cases may result in retinal fibrosis and retinal detachment.

Observation studies in the 1950s demonstrated the clear link between the liberal use of oxygen and the development of retinopathy of prematurity, or retrolental fibroplasia, as it was then known.[27-30] One study by Kinsey et al, in 1956, that was not observation, demonstrated a 17% reduction in retinopathy of prematurity as well as a 9% reduction in blindness when curtailing oxygen therapy to room air within the first 48 hours.[30a] Of note, these studies provoked a drastic decrease in neonatal oxygen use that was associated not only with a reduction in retinopathy of prematurity, but also with an increase in newborn deaths and cerebral palsy.[31,32] With the improved survival of very-low-birth-weight infants during the past decade, retinopathy of prematurity continues to be a source of substantial morbidity. Wide intercenter variability exists in the incidence of severe (> stage 3) retinopathy of prematurity in different centers.[33,34] These differences could be attributed to the combination of many known and unknown factors; one explanation might be that differences in clinical practices affect the rates of retinopathy of prematurity. More recent studies have demonstrated an association between retinopathy of prematurity and high oxygen saturation,[8,35,36] and several studies suggest that fluctuations in oxygenation level may also have a role in its development.[35,37] It thus is possible that repeated cycles of hyperoxia and hypoxia favor the progression of retinopathy of prematurity.[38,39] While hyperoxia clearly plays a role, other risk factors include growth retardation, male sex, septicemia, and, most significantly, low gestational age and birth weight.[21] In addition, worsening retinopathy of prematurity has been linked to the overall severity of illness of the newborn and the extent of other complications.[40,41]

Chronic Lung Disease

Oxygen administration was identified as a risk factor in the development of neonatal chronic lung disease in early descriptions of bronchopulmonary dysplasia.[42,43] In animal studies, oxygen exposure has been shown to inhibit lung growth and deoxyribonucleic acid synthesis.[14] Markers of inflammation isolated from the tracheal lavage samples obtained from newborns in the first 3 days of life have been shown to correlate with oxygen exposure and the development of bronchopulmonary dysplasia.[44] As with retinopathy of prematurity, supplemental oxygen administration is only one factor in the pathogenesis of bronchopulmonary dysplasia, and the threshold for pulmonary toxicity remains unclear. Observational studies have associated the avoidance of hyperoxia with shorter duration of mechanical ventilation and oxygen dependence when lower oxygen saturation target ranges were maintained in premature infants from the time of birth.[8,36] Currently there are no controlled randomized trials that have evaluated whether a low versus high oxygen saturation strategy in the immediate postnatal period decreases the incidence of bronchopulmonary dysplasia.

The use of supplemental oxygen to maintain a targeted oxygen saturation measured via pulse oximetry (S_{pO_2}) > 93% for infants with established chronic lung disease has been advocated to decrease pulmonary vascular resistance and airways resistance, to decrease the risk of sudden infant death, and to promote growth.[45,46] However, 2 large randomized studies that compared different strategies for titrating supplemental oxygen for premature infants outside of the immediate newborn period failed to confirm these clinical benefits.[47,48] The Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity study, which compared a low-oxygen-saturation group targeting oxygen saturation of 89–94% versus a high-oxygen-saturation group targeting 96–99%, demonstrated no difference in mortality or development as secondary outcomes in the low-saturation group versus the higher-saturation group. Further, the study showed that the infants in the high-saturation arm had an increased incidence of pneumonia and chronic lung disease exacerbations, and that significantly more infants in the high-saturation group remained in hospital, on oxygen, and on diuretics at 50 weeks post-menstrual age.[47] The Benefits of Oxygen Saturation Targeting study demonstrated that extremely pre-term oxygen-dependent infants treated to maintain oxygen saturation between 91–94% had growth and development that was not significantly different from a group maintained with a target saturation range of 95–98%. In addition, the higher-saturation infants had a significantly higher rate of oxygen usage at 36 weeks post-menstrual age and home oxygen usage.[48]

Long-Term Outcomes

In a long-term outcomes study of term infants who had required extracorporeal membrane oxygenation for meconium aspiration syndrome/persistent pulmonary hypertension of the newborn, Boykin et al evaluated lung function at 10–15 years. That study found significant abnormalities

in lung function and that the most significant predictor of long-term pulmonary outcomes was the duration of oxygen use post-extracorporeal-membrane-oxygenation decannulation.[49]

Oxygen During Resuscitation

The use of 100% oxygen during neonatal resuscitation has also been challenged, on the premise that large and abrupt increases in blood oxygen level after birth can increase oxidative stress.[20] Several studies have compared the use of 21% to 100% oxygen during resuscitation. Three recent meta-analyses of these data concluded that the use of room air during the resuscitation of depressed newborns resulted in a significantly reduced risk of neonatal mortality.[50-52] The studies found no significant difference in the incidence of severe hypoxic encephalopathy between the 21% oxygen and 100% oxygen groups. Limitations to some of the studies in these analyses include a lack of blinding in some studies, and the exclusion of stillbirths.[9] In one small recent study, the resuscitation of premature newborns with 50% versus 100% oxygen did not reduce the incidence of bronchopulmonary dysplasia or improve other short-term outcomes.[53] The results of a recent study by Escrig et al[54] indicate that extremely premature newborns can be safely resuscitated with a low initial oxygen concentration. Related to the use of oxygen in the delivery room for resuscitation, limited evidence suggests that the exposure of newborns to oxygen for 3 min or longer immediately after birth increases the risk of childhood cancer.[55,56]

Oxygen Delivery Devices

Blow-By Oxygen

Blow-by oxygen delivery is the simplest and least cumbersome form of available devices to provide oxygen therapy to the neonate, but it is also the least reliable in delivering a specific F_{IO_2}. Blow-by oxygen can be achieved numerous ways, but is most commonly done by means of large-bore or oxygen tubing connected to a face tent or simple mask that is placed a relatively short distance from, and directed toward, the patient's face. This type of oxygen delivery is ideal for patients who cannot tolerate more cumbersome oxygen delivery devices and/or require a lesser amount of oxygen. There is limited evidence that suggests that blow-by therapy can deliver low concentrations of oxygen (0.3–0.4 at 10 L/min of flow) to an area large enough to provide some level of oxygen therapy to the neonate, assuming adequate positioning of the device.[57] Therefore, this type of therapy should be reserved for infants who do not a require high inspired oxygen concentration but may require short-term or intermittent oxygen therapy.

Oxygen Hood

An oxygen hood (cube) is a plastic enclosure that surrounds the head of the neonate, to which a continuous flow of humidified oxygen is supplied by means of an air-entrainment device or an air-oxygen blender. Fixed oxygen concentrations from 0.21 to 1.0 can be maintained with a minimum of 7 L/min oxygen flow into the hood. This minimum gas flow also ensures that exhaled carbon dioxide is flushed out and not rebreathed. Although an oxygen hood can theoretically deliver 1.0 F_{IO_2}, this device is best suited for patients who require less than 0.5 F_{IO_2}. Patients requiring higher F_{IO_2} can be managed in a hood, but it becomes increasingly difficult to maintain higher oxygen concentrations with the large neck opening and a less than optimal seal around the edges.[58-60] An oxygen hood is an ideal method of oxygen delivery for neonates who require higher fractional inspired oxygen concentrations but cannot tolerate more cumbersome oxygen delivery devices.

Low-Flow Nasal Cannula

Low-flow nasal cannula remains one of the most common and widely used neonatal oxygen delivery devices. This low-flow device delivers a fractional concentration of oxygen to the patient through 2 soft prongs that rest in the patient's anterior nares. The distal end of the cannula tubing is then attached to either a 100% oxygen source flow meter or to an air-oxygen blender. Finer et al found that oxygen concentrations delivered to the neonate via nasal cannula varied from 22% to 95% with a maximum flow rate of 2 L/min.[61] The precise F_{IO_2} actually delivered to the patient is contingent upon a number of factors, but most specifically on the set flow through the nasal cannula and its relation to the patient's inspiratory flow demand. An inspiratory flow demand greater than that supplied by the nasal cannula causes the exact F_{IO_2} delivered to the patient to be a blend of the nasally inhaled oxygen with entrained room air through the nares and mouth.[10,58,61] While actual oxygen concentrations delivered to the patient are variable, a nasal cannula remains a fairly trusted and effective method of offering oxygen therapy to the neonate.

High-Flow Nasal Cannula

Nasal cannula oxygen therapy is a staple and continues to be redefined to improve patient comfort, compliance, and outcomes. The concept of high flow and high humidity via a nasal cannula, however, is a fairly new concept and was first introduced by Vapotherm to the respiratory care community in the spring of 2002, after receiving Food and Drug Administration 510K clearance in the fall of 2001. Prior to high-flow nasal cannula, most clinicians

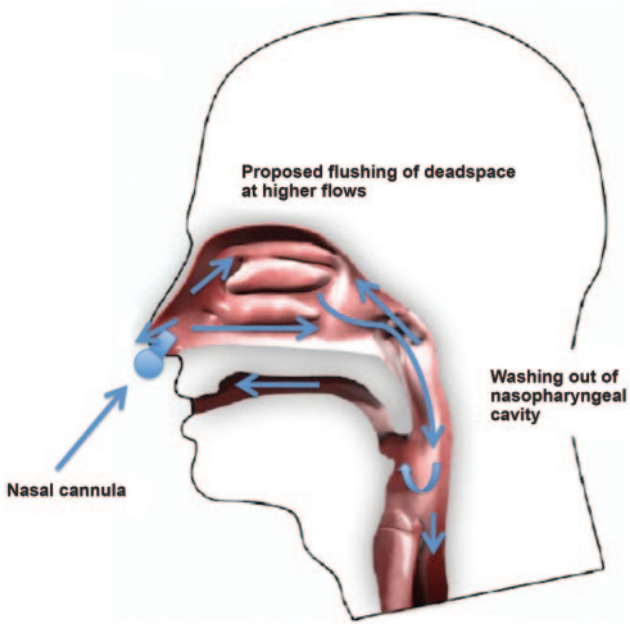

Fig. 3. Proposed reduction in nasopharyngeal dead space that leads to improving alveolar ventilation with high-flow nasal cannula.

considered it uncomfortable to use a flow of greater than 6 L/min via nasal cannula in adults; this was primarily due to the lack of adequate humidification available via nasal cannula delivery. Little consensus existed in the neonatal patient population on the parameters defining high-flow nasal cannula, but for our discussion high-flow nasal cannula is classified as a fixed-performance oxygen delivery system that is capable of delivering a specific oxygen concentration at flows that meet or exceed the inspiratory flow demand of the patient.[58] This type of oxygen delivery device is composed of traditional nasal cannula style prongs that rest in the patient's anterior nares and allow heated, humidified oxygen to be delivered at flow rates of 1–8 L/min, while an air-oxygen blender allows F_{IO_2} to be directly manipulated.[62] As higher flow rates are reached, set oxygen flows exceed demand, thus preventing the entrainment of room air, flushing dead space (Fig. 3), and affecting the delivery of higher, more precise fractional inspired oxygen concentrations. High-flow nasal cannula use has been adopted in many neonatal intensive care units for its ease of use and patient tolerance. It is also used because it is able to provide higher oxygen concentrations and inspiratory flows, thus providing a higher level of oxygenation support to the neonate than can be achieved by any of the other devices described above.

Improvements in oxygenation associated with high-flow nasal cannula may also be related to the creation of positive end-expiratory pressure. High-flow nasal cannula has been shown to significantly increase esophageal pressure[63,64] and pharyngeal pressure[65] in neonates. Locke et al demonstrated that in a group of premature infants, the amount of generated positive pressure varied not only with flow rate but with cannula size; the larger cannula size produced a mean pressure of 9.8 cm H_2O at a flow rate of 2 L/min.[64] Sreenan et al concluded that positive distending pressure could be predictably applied using high-flow nasal cannula at flow rates of 1–2.5 L/min and that high-flow nasal cannula is as effective as nasal continuous positive airway pressure (CPAP) when using frequency and duration of apnea, bradycardia, and oxygen desaturations as outcomes.[63] Using the Sreenan et al equation, Campell et al[66] compared the use of high-flow nasal cannula and nasal CPAP for preventing re-intubation in a group of premature infants. In this study the high-flow nasal cannula group had a significantly higher number of re-intubations, increased oxygen use, and more apnea and bradycardia episodes post-extubation. In their discussion, Campbell et al concluded that the equation for determining CPAP was not reproducible in this patient population.

Device-Related Complications

Device-related complications of nasally applied oxygen therapy include skin irritation from device materials,[67] nasal mucosal irritation, bleeding, and obstruction (particularly with gas flows rates $>$ 2 L/min),[68,69] inadvertent CPAP,[63,64] intrinsic contamination (Vapotherm specific),[70] subcutaneous scalp emphysema, pneumo-orbitis,[71] pneumocephalus (high-flow and low-flow cases),[72-74] and displacement leading to disruption of oxygen delivery. Of note, many of the mucosal irritation, bleeding, and obstruction events were experienced with devices that produced a low temperature and relative humidity. Potential complications of oxygen hoods include cold stress from unheated or inadequately heated gas,[75] bacterial contamination,[76,77] and high noise level, associated with hearing impairment.[78] More generally, the lack of adequately heated and humidified gas can lead to airways hyper-reactivity and mucociliary dysfunction[79-82]

Advances in Oxygen Therapy

Closed-Loop F_{IO_2} Regulation

Given the rapid onset and frequency of the episodes of hypoxemia and hyperoxemia that may routinely occur, maintaining S_{pO_2} within a desired range by manual F_{IO_2} adjustment on any device (nasal CPAP, nasal cannula, or mechanical ventilator) during each episode is a difficult and very time-consuming task. Health-care providers respond to high/low S_{pO_2} alarms, but because of their responsibilities under routine clinical conditions, their response time is not always consistent and optimal. In fact, historically, many choose to run S_{pO_2} on the upper end of normal because of their unfounded fear of brain injury

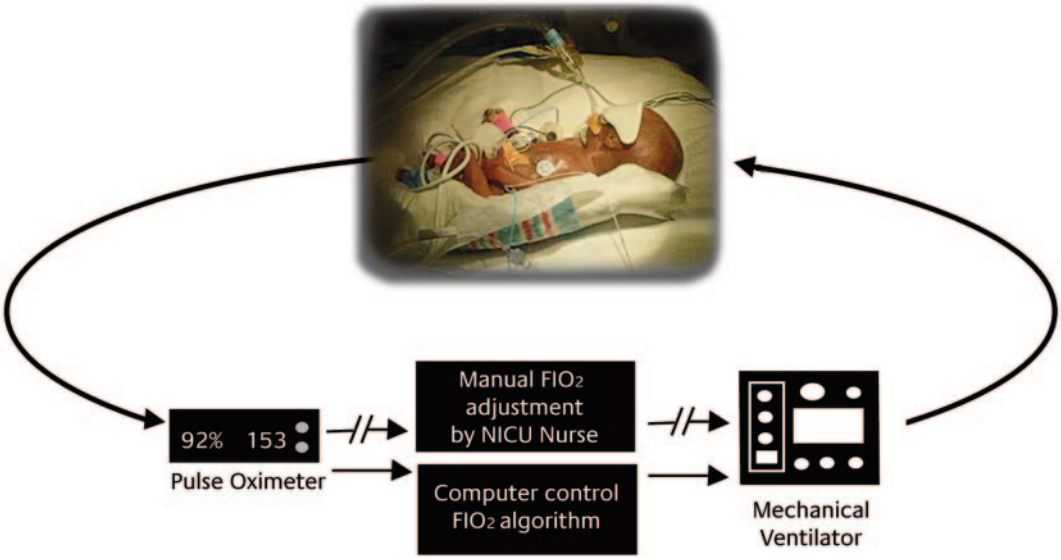

Fig. 4. Claure's and Bancalari's configuration of biofeedback to a computer algorithm, which then adjusted the fraction of inspired oxygen (F_{IO_2}), as compared to conventional manual adjustments by a dedicated nurse. S_{pO_2} = oxygen saturation measured via pulse oximetry. (Adapted from Reference 86).

over the fear of retinopathy of prematurity. This exposes these infants to periods of hypoxemia and hyperoxemia that may increase the risk of retinopathy of prematurity[38,39,83,84] and neonatal chronic lung disease, as mentioned above.[85] These limitations make the use of a system for automatic F_{IO_2} adjustment a desirable alternative. Bancalari and Claure found that an algorithm for closed-loop F_{IO_2} with a mechanical control (Fig. 4) to maintain S_{pO_2} within a target range was at least as effective as a fully dedicated nurse in maintaining S_{pO_2} within the target range, and it may be more effective than a nurse working under routine conditions.[86] While this may be helpful in keeping S_{pO_2} within range, a system not carefully alarmed could expose infants to a higher than acceptable concentration of oxygen in the face of atelectasis or hypoventilation. Unfortunately, at this time there is not an available Food and Drug Administration approved device to provide this type of closed-loop control.

New-Generation Pulse Oximetry

Continuous monitoring of oxygenation status by means of pulse oximetry in the neonatal intensive care unit is commonplace. Often, however, the reliability of the measurement is questioned when interference, such as patient motion, is detected. The number of pulse oximetry devices available to hospitals and clinicians is vast, with major medical companies constantly changing and improving technology. A new generation of motion-tolerant pulse oximeters has been designed to resist interference and improve clinical performance, most specifically by increasing accuracy, decreasing false alarms, and capturing true events. The introduction of new-generation oximeters, such as the Massimo SET, Nellcor N-395, Novametrics MARS, and Pillips Viridia 24C in the early 1990s has prompted a number of studies comparing the performances of the new-generation pulse oximeters to conventional oximeters, as well as comparing performances between the different brands of pulse oximeter.[87]

Recent studies in the neonatal population have proven that new-generation oximeters out-perform their older counterparts in their ability to more accurately detect true hypoxic and bradycardic events as well as reduce the number of false alarms in the setting of increased patient motion and low perfusion states. A study by Hay et al not only concluded that new-generation oximeters were superior in comparison with their older counterparts studied,[88] they found that even among the newer-generation systems there were differences. Additional studies have found similar data supporting the conclusions of Hay et al, starting a technology "war" over whose "signal processing algorithms" and sensors are the most promising of new-generation pulse oximeters available.[87,89-91]

The substantial advances that have been made in pulse oximetry technology allow more accurate detection of hypoxemic and bradycardic events in the neonatal population. The hope is that with these new technologies the number of clinician disregards for false alarms due to motion artifact will be reduced, therefore resulting in improved clinical performance and more judicious oxygen therapy as a result of a hypoxic or hyperoxic state. Most recently in pulse oximetry, Masimo has developed the capability of measuring amounts and types of hemoglobin,

which may lead to a more precise monitoring and control of oxygen delivery noninvasively.[92]

Discussion

Unresolved Questions

Many unresolved questions remain when discussing neonatal oxygen therapy, but one specific question that arises is which S_{pO_2} ranges are most appropriate for the newborn. This question is complex in that the most appropriate range may be different in different contexts. Many have conducted research with different S_{pO_2} ranges, showing equivocal if not better outcomes to higher S_{pO_2} ranges; however, there have not been consistent ranges among the studies. In a recent review of resuscitation and ongoing management of pre-term infants, Finer discusses his recommendation that an S_{pO_2} range of 85–93%, with alarms set ±1–2% above and below that range, was most appropriate.[17] However, this does not answer the question for near-term, term infants, or patients who have developed chronic lung disease and are susceptible to pulmonary hypertension. Further studies are needed to fully answer this question.

Two other unresolved questions are whether or not a high-flow nasal cannula can substitute for nasal CPAP and whether or not high-flow nasal cannula can replace the high F_{IO_2} oxygen hood. It is fairly clear that high-flow nasal cannula is a safe oxygen delivery device, as there have been hundreds of infants studied, with few adverse events.[62,63,66,68,70,93-96] It appears to have the same complications as traditional low-flow oxygen delivery devices, yet is able to provide a higher humidity content (mg/L), which is probably beneficial. It has been discovered that high-flow nasal cannula may provide positive pressure; however, it doesn't appear to be well controlled or replicable.[93] The real question lies in whether or not it needs to be well controlled or replicable? If you are using it as a primary CPAP device and attempting to develop treatment protocols for care, there needs to be additional randomized multicenter trials to better develop a flow algorithm for equivocal outcomes. That being said, if you decide to use high-flow nasal cannula as your primary CPAP delivery device, it must be monitored with alarms (disconnect, tube occlusion, F_{IO_2}). If you are using it as an alternative to CPAP due to skin breakdown, mother infant bonding, to improve developmental care, or as a high F_{IO_2} delivery device (for example oxygen hood), there appear to be multiple levels of support for its use. However, adoption has been slow for multiple reasons. Initially, it was the lack of evidence to support its use over current therapies, but more recently it has probably been cost. Currently, high-flow nasal cannula is reimbursed at the same level as a traditional nasal cannula, but with a substantially higher cost. Depending on which system you use, as well as on manufacturer agreements, a high-flow nasal cannula system can cost a department approximately $18–80. In addition, if a neonatal unit were to switch half of its CPAP patients over to high-flow nasal cannula, it could lose relative-value-unit justification for its respiratory therapy staffing model when the infants are at the same if not higher illness-severity level than some of their typical low-flow nasal cannula patients.

Future of Neonatal Oxygen Therapy

Oxygen is a drug that is essential in the treatment and prevention of neonatal hypoxia. However, the excessive use of oxygen can lead to serious and long-lasting adverse sequelae. Appropriate administration of oxygen will depend on controlled trials defining optimal ranges of oxygenation for the newborn targets that may change with different pathologies and at different stages of development. The types of oxygen delivery devices seem not as important as monitoring the effects of this therapy. Improvements in oxygen therapy monitoring technology help to improve a clinician's ability to most appropriately apply and deliver oxygen. If closed-loop F_{IO_2} management becomes available, it will be helpful; however, it needs to come with carefully thought-out limits. Additional improvements in humidification control and ease of use allow us to recommend optimal humidification with all oxygen therapy devices. High-flow nasal cannula proves to be an effective high-humidity, high-F_{IO_2} delivery device that is able to improve comfort and therapeutically hydrate the airway. High-flow nasal cannula should be considered as an alternative but not a primary replacement for CPAP until future studies can be conducted to prove otherwise.

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