A Theoretical and Practical Approach to Defining "Adequate Oxygenation" in the Preterm Newborn

Chad C. Andersen, MBBS,[a,b] Nicolette A. Hodyl, PhD,[a,b] Haresh M. Kirpalani, BM, MSc,[c] Michael J. Stark, PhD[a,b]

abstract

John Scott Haldane recognized that the administration of supplemental oxygen required titration in the individual. Although he made this observation in adults, it is equally applicable to the preterm newborn. But how, in practice, can the oxygen requirements in the preterm newborn be determined to avoid the consequences of too little and too much oxygen? Unfortunately, the current generation of oxygen saturation trials in preterm newborns guides saturation thresholds rather than individual oxygen requirements. For this reason, we propose an alternate model for the description of oxygen sufficiency. This model considers the adequacy of oxygen delivery relative to simultaneous consumption. We describe how measuring oxygen extraction or the venous oxygen reservoir could define a physiologically based definition of adequate oxygen. This definition would provide a clinically useful reference value while making irrelevant the absolute values of both oxygen delivery and consumption. Additional trials to test adjunctive, noninvasive measurements of oxygen status in high-risk preterm newborns are needed to minimize the effects of both insufficient and excessive oxygen exposure.

John Scott Haldane recognized almost 100 years ago that oxygen "want" and "excess" were both harmful.[1] He wrote, "... the probable risks of prolonged administration of pure oxygen must be borne in mind and balanced against the risks of allowing the oxygen want to continue. No fixed rule can be given". He concluded "... where prolonged administration of oxygen seems desirable the minimum quantity of oxygen which will remove the cyanosis should be carefully ascertained". Although Haldane made this observation in adults, the delicate balance between too much and too little oxygen also remains a challenge in neonatal medicine. This as yet unmet goal underscores how difficult it is to define "adequate oxygenation."

Adequacy implies being of sufficient quantity to satisfy a need. In the context of oxygen economy, adequacy can therefore be viewed as oxygen sufficiency in each living cell. However, it is not possible to establish adequacy with the current technology. Nonetheless, as a close approximation, "adequacy" can be best determined by an assessment of the amount of excess oxygen left over, after all the processes of cellular respiration are complete. This article will firstly describe the important components of oxygen physiology and will secondly develop a working definition of oxygen adequacy for use in the preterm newborn. Such a definition would enable clinicians to titrate oxygen exposure in a manner set out by Haldane.

[a]*Department of Neonatal Medicine, Women's and Children's Hospital, North Adelaide, South Australia, Australia;* [b]*Robinson Research Institute, School of Medicine, University of Adelaide, Adelaide, South Australia, Australia; and* [c]*Neonatal Division, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania*

Drs Andersen, Hodyl, Kirpalani, and Stark conceptualized, drafted, reviewed, and revised the manuscript, and approved the final manuscript as submitted.

DOI: 10.1542/peds.2016-1117

Accepted for publication Sep 15, 2016

Address correspondence to Chad C. Andersen, Department of Neonatal Medicine, Level 1, Queen Victoria Building, Women's and Children's Hospital, 72 King William Rd, North Adelaide, South Australia 5006, Australia. E-mail: chad.andersen@sa.gov.au

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to the article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

To cite: Andersen CC, Hodyl NA, Kirpalani HM, et al. A Theoretical and Practical Approach to Defining "Adequate Oxygenation" in the Preterm Newborn. *Pediatrics.* 2017;139(4):e20161117

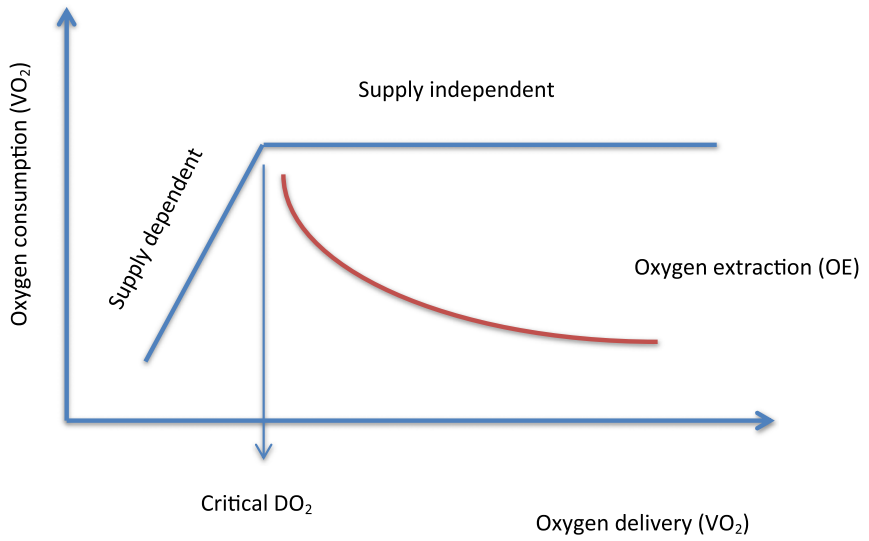

FIGURE 1
Schematic diagram of the relationship between systemic oxygen consumption, delivery, and extraction. The critical or anaerobic threshold can be identified from a change in the gradient of the curve or as a result of accumulation of lactate.

TABLE 1 Oxygen Kinetic Equations

OE (%)	VO_2 DO_2
CaO_2 (mL O_2/dL)	{[1.39 × [Hb] × $HbSaO_2$/100] + [0.003 × paO_2]}
CvO_2 (mL O_2/dL)	{[1.39 × [Hb] × $HbSvO_2$/100] + [0.003 × pvO_2]}
Systemic DO_2 (mL/min)	CO × CaO_2
VO_2 (mL/min)	(1) Indirect calorimetry; [(MV_i × FiO_2) − (MV_e × FeO_2)] (2) Reverse Fick; [CO × (C(a-v)O_2)]

Cao_2, arterial oxygen content; CvO_2, venous oxygen content; DO_2, oxygen delivery; FeO_2, expired oxygen concentration; Fio_2, fraction of inspired oxygen; $HbSaO_2$, arterial oxygen saturation; $HbSvO_2$, venous oxygen saturation; MV_e, minute ventilation (expired); MV_i, minute ventilation (inspired); OE, oxygen extraction; Pao_2, partial pressure of oxygen, arterial; Pvo_2, partial pressure of oxygen (venous); Vo_2, oxygen consumption.

OXYGEN PHYSIOLOGY

Overall System Architecture

Oxygen is fundamental to cellular energy production as oxygen moves down a concentration gradient from the alveolus to the mitochondrion. Although energy can be generated in anaerobic conditions, it is considerably more efficient in the presence of oxygen. Comparatively, 1 molecule of glucose generates 1270 kJ in aerobic conditions versus 67 kJ in anaerobic conditions.[2]

Oxygen kinetics describes the overall physiology of oxygen transport and use. This dynamic process, which differs within and between individuals, describes the transport of oxygen from the alveolus to the tissue for cellular metabolism, as well as the movement of waste products, principally CO_2, back to the lungs. Although oxygen delivery and consumption are distinct, they are in almost constant flux depending on both endogenous (temperature) and exogenous (exercise) factors.

The relationship between oxygen delivery and consumption is illustrated in Fig 1. At rest, oxygen delivery exceeds consumption, resulting in normoxic or aerobic conditions. As oxygen delivery falls, oxygen extraction will increase to maintain aerobic metabolism, but is limited by the finite oxygen store of the saturated hemoglobin (Hb) molecules. If tissue demands exceed this critical threshold, then anaerobic metabolism and lactic acidosis results. Hypoxic ischemia can therefore be identified from either the gradient of the delivery–consumption relationship, or from an accumulation of lactic acid as a consequence of anaerobic cellular energy production.

Oxygen kinetics varies in every newborn, with each having subtly different oxygen delivery and consumption. As such, neither delivery nor consumption alone characterizes the overall status of the oxygen physiologic relationship. By partitioning the constituent parts of oxygen physiology, it is more easily demonstrated that no single component can define overall oxygen adequacy in the preterm newborn.

Oxygen Extraction

Oxygen extraction is the proportion of oxygen unloaded from Hb into the tissue. Extraction is a dynamic process that is the end result of a changing oxygen gradient, tissue blood flow, and Hb-oxygen affinity. Thus, increases in oxygen extraction can buffer, or compensate for, decreased oxygen delivery and/or increased oxygen consumption. Mathematically, extraction is calculated as the ratio between oxygen consumption and delivery (Table 1). Because extraction is dependent on the establishment of an oxygen gradient from the alveolar–pulmonary capillary interface to the cell, its key determinants are factors that influence the oxygen gradient, including Hb affinity and capillary transit time. Accordingly, extraction is a summary measure of all the endogenous and exogenous influences on the oxygen physiology in an individual.

As a dynamic process, extraction can temporarily offset shortfalls of oxygen delivery or brief rises in consumption. This buffering function

has been demonstrated by Schulze et al[3] in very preterm newborns (n = 20, mean [SD]: birth weight, 1192 [396] g; gestational age, 28.7 [2.7] weeks) during the first 3 days of life. In these infants, inspired oxygen concentration was adjusted to achieve a cutaneous oximetry target of 91% to 94% or 95% to 98%. Throughout, both arterial and right atrial oxygen content as well as oxygen consumption (by indirect calorimetry) were measured. The lower oxygen saturation target resulted in a fall in the inspired oxygen concentration and decreased arterial oxygen content; however, no change in oxygen consumption was observed. Schulze et al[3] concluded that reducing the oxygen saturation target was only a minor challenge in these preterm newborns, because this resulted in a small increase in extraction while still leaving additional capacity in the venous compartment.

This finding allows us to frame 1 principle: if adequacy of oxygenation is judged either by calculated extraction or the amount of oxygen located in the venous compartment, then the absolute values of either oxygen delivery or consumption alone are not clinically informative. There are some practical limitations to this general principle that need to be considered, including the site of measurement. For instance, values of oxygen extraction measured in the periphery may not reflect systemic or global status, because each organ operates in different clinical conditions. For this reason, measuring oxygenation in high extraction organs, notably the brain or heart, may provide the best surrogate measure for assessment of oxygen delivery and consumption. To emphasize this, we will take each component of the oxygen cascade and examine its potential usefulness and limitations in clinical measurement.

Oxygen Delivery

Systemic oxygen delivery is primarily determined by flow and the carrying capacity of blood. Barcroft[4] first described the 3 key determinants of systemic oxygen delivery in 1920. He subsequently classified hypoxemia into: stagnant hypoxia (from low blood flow), anemic hypoxia (from low Hb), or hypoxic hypoxia (from low inspired oxygen tension). Of these, blood flow is the most critical for adequate oxygen delivery.[5–7]

Oxygen delivery is the product of cardiac output (CO) and blood oxygen carrying capacity (Table 1).

The oxygen carrying capacity of blood is largely determined by Hb concentration ([Hb]) and Hb-oxygen saturation, with only a small amount of oxygen dissolved in blood. In standard pressure and temperature conditions, the amount of dissolved oxygen is ∼1%[2] and considered clinically irrelevant. Additional factors that affect tissue oxygen delivery include the distance and pressure gradient between the oxygen-carrying red blood cell and the end organ cells.[2] Although these factors are important, particularly in the microvasculature where distance is reduced and the pressure gradient is the highest,[8] they do not greatly alter the overall system status. Thus, for the purposes of this review, we will focus on the key constituent parts.

Most nurseries practice in a clinical model that only considers the assessment and adjustment of oxygen delivery. Typically, this includes altering inspired oxygen to change oxygen saturation, transfusion of packed red blood cells in the setting of anemia, and pharmacological interventions (such as the use of inotropes) to improve blood flow to and from major organs, assessed by echocardiography.[9,10] Although these clinical interventions are important, they do not take into account oxygen consumption. They therefore provide incomplete information regarding oxygen delivery and consumption.

CO and Changes in Systemic Hemodynamics After Delivery

CO is the product of heart rate and stroke volume and is the most important determinant of oxygen delivery. Although flow is important to oxygen transport in normoxic conditions, it becomes particularly significant in hypoxic conditions, because extraction is critically dependent on blood flow. Several studies have examined the physiologic and pathophysiologic processes that occur during the transition to extrauterine life. In utero, umbilical venous blood flow increases from early gestation to term. However, umbilical venous blood flow is significantly lower in singletons with fetal growth restriction between 20 and 36 weeks compared with pregnancies where the fetus is appropriately grown for gestational age.[11–13] This finding renders the small for gestational age fetus particularly vulnerable to hypoxia given the importance of blood flow to oxygen delivery. The fetus may offset this risk both acutely with higher oxygen extraction and chronically with higher Hb concentration.

Systemic blood flow changes considerably after placental separation, with the newborn transitioning from a low to high systemic vascular resistance circuit,[14,15] and both right and left ventricular output increasing over the first 48 hours of life.[16] CO is dependent on preload and therefore venous return. Studies of superior vena cava flow during neonatal transition demonstrate low systemic blood flow in a subset of neonates in the immediate hours after preterm birth.[17,18] The risk factors for low superior vena cava flow defined from these trials include immaturity, a high mean airway pressure, and an open ductus arteriosis. Importantly,

there appears to be a clinical link between low(er) systemic blood flow and impaired brain function with those infants with right ventricular output values in the lowest quartile exhibiting lower median amplitude on simultaneous amplitude-integrated EEG.[19] In addition, Kluckow and others[18,20,21] demonstrated an association between a low systemic blood flow state, a surrogate for cerebral venous return, and a high risk of neonatal death or brain injury on ultrasound in the first 7 days. However, not all newborns with low systemic blood flow developed brain injury and not all newborns with a brain injury had preceding low systemic blood flow.[18] This finding illustrates the need for more detailed information about both oxygen delivery and consumption.

[Hb]

Despite many publications and randomized controlled trials, the optimal [Hb] in the preterm newborn is unclear. Anemia of prematurity is a multifactorial condition that results in relative anemia with a parallel poor bone marrow response.[22] Mostly, the anemia is defined by a combination of clinical symptoms and the [Hb] value. Although there are many strategies to minimize the depth of anemia, the majority of very preterm newborns still receive a packed red blood cell transfusion to increase oxygen carrying capacity.[23]

Typically, transfusion is determined from an algorithm designed on [Hb]/hematocrit thresholds and modified by chronologic age and the need for respiratory support. The current recommendations are based on a small number of randomized trials. The 2 largest trials (Premature Infants in Need of Transfusion,[24] Bell et al [25]) remain the basis of current transfusion practice. Both trials randomized high-risk preterm infants to either a liberal or restricted transfusion schedule. Whereas the Premature Infants in Need of Transfusion trial measured a composite of mortality and predischarge morbidities, the study by Bell and colleagues measured transfusion exposure. Meta-analyses concluded no clear benefit for either liberal or restrictive transfusion thresholds in very low birth weight newborns, although more long-term data were recommended.[24] Additional large trials using similar methodology are currently recruiting.[26,27]

Although the model of transfusion practice using predefined Hb or hematocrit thresholds is easy to understand, it is inconsistent with overall oxygen physiology. This is in part because inadequate tissue oxygenation from anemic hypoxia is difficult to define because each newborn has different oxygen delivery and consumption settings. As a result of the variation in both oxygen delivery and consumption in the individual newborn, there is no single threshold [Hb] value for transfusion that applies to all situations.[28] The clinical situations resulting in transfusion vary, yet fit comfortably in a model that considers oxygen kinetics. Early transfusion in the setting of relative anemic hypoxia could be used to favorably alter oxygenation through its effect on oxygen carrying capacity, particularly at a time when the risk of acquired brain injury is highest.[29] Later transfusion in the context of low [Hb] and poor bone marrow response in a convalescent newborn requires a different care pathway that may not relate as easily to contemporary oxygen kinetics because of the competing requirements for growth and other pathophysiologic demands.

Hb Affinity

The affinity of Hb for oxygen is best described by the dissociation curve of the relationship between Po_2 and Hb. The effect of altered relative affinity of Hb for oxygen is often overlooked in the newborn. Although it does not feature as a named variable in the oxygen delivery equation, altered affinity will affect both oxygen uptake at the pulmonary interface and oxygen unloading at the cellular level. It is therefore important to tissue oxygen delivery. Affinity is described by the $p50$ (ie, the arterial Po_2 when Hb is 50% saturated with oxygen). The $p50$ of fetal Hb is ~19.4 (1.8) mm Hg, whereas that of adult Hb is ~30.3 mm Hg.[30] A rightward shift in the oxygen dissociation curve occurs as a result of either lower pH, as would be seen with the accumulation of carbon dioxide as a byproduct of cellular metabolism as blood moves along the capillary, or increased temperature favoring tissue oxygen unloading.[2]

Empirically, the effect of altered affinity has been demonstrated in both preterm newborns[30–33] and lambs.[34] In a small prospective study, newborns with lower affinity red blood cells had higher extraction (showing improved tissue unloading) but at similar blood flow.[32] Van Ameringen and coworkers[34] performed a randomized trial of high- versus low-affinity Hb in preterm lambs with progressive anemia. Compared with lambs with native high-affinity red blood cells, those allocated to isovolaemic exchange with low-affinity maternal blood were more able to adequately oxygenate tissues during severe progressive anemia. These experiments demonstrate the effect of altered affinity on tissue oxygen delivery. Because affinity is not included in the oxygen delivery equation, its impact is not easily measured except by oxygen extraction.

Hb Oxygen Saturation

The outcomes of recent large randomized trials of oxygen saturation targets[35–37] in very preterm newborns have been inconclusive. Concerns remain about variations in methodology between

trials and Hb–oxygen algorithm differences, leading to uncertainty about collective outcomes.[38,39] In addition, there is a misconception that these trials determine an optimal oxygen requirement, although in reality, they define an optimal oxygen saturation target. This is an important distinction. It is very likely that a single saturation target would have different effects in infants with different oxygenation physiology, and therefore would not guarantee the prevention of hypoxic hypoxia in all neonates. To illustrate this, imagine 2 preterm neonates with the following hemodynamic characteristics: the first neonate has an [Hb] of 125 g/L, a CO of 120 mL/kg per min, and pulse oxygen saturation of 96% (systemic oxygen delivery = 20 mL/kg per min), whereas the second neonate has an [Hb] of 150 g/L, a CO of 200 mL/kg per min, and pulse oxygen saturation of 96% (systemic oxygen delivery = 40 mL/kg per min).[2] The first newborn has half the systemic oxygen delivery of the other, although both have similar oxygen saturation. It is easy to see that oxygen saturation is not a surrogate for the adequacy of oxygenation overall.

Oxygen Consumption

Oxygen consumption can be measured primarily by 2 techniques: (1) indirect calorimetry and (2) the reverse Fick method (Table 1), both of which are cumbersome in preterm newborns. Unsurprisingly, the oxygen consumption literature in preterm newborns is heterogeneous. Studies have included population subgroups (small versus appropriate size for gestational age, preterm versus term) in addition to different measurement techniques, thus making comparison difficult.

Indirect calorimetry measures total body oxygen consumption with either a bias flow circuit with hood, or via a sampling side port in a ventilator circuit. Indirect calorimetry has been used to demonstrate minimal oxygen consumption in low birth weight newborns, which changes minimally over the first 24 hours in different environmental (thermal) conditions.[40] However, the resting oxygen consumption rate changes with postnatal age[41] and is notably higher in newborns with bronchopulmonary dysplasia.[42]

More recently, the reverse Fick technique has been used to measure oxygen consumption. In this method, blood flow is multiplied by the arteriovenous substrate (oxygen) difference. This method thus excludes pulmonary oxygen consumption, resulting in a systematic bias compared with values that are determined by calorimetry. We have previously used this method to demonstrate an increase in oxygen consumption by 72 hours in preterm newborns born at <30 weeks' gestation.[43] This finding supports the concept of an increase in oxygen consumption with postnatal age, irrespective of assessment method employed.[41]

Available "normal" ranges for oxygen consumption are problematic because each is derived from slightly different populations by using dissimilar methods. Other factors known to influence consumption in the immediate newborn period include temperature,[40,41,44] pulmonary disease,[42] chorioamnionitis,[45] and maternal $MgSO_4$ therapy.[46] These factors do show, however, that oxygen consumption varies in response to both endogenous and exogenous factors, which differ between infants. As such, it is difficult to determine a reference or normal range that applies to each preterm newborn. However, the absolute rate of oxygen consumption would not be required if the clinician considers the adequacy of oxygenation to be determined by a measure of the equilibrium of the whole system.

INDIVIDUALIZATION OF OXYGEN EXPOSURE

Individualization of oxygen exposure requires continuous assessment of the overall status of oxygen kinetics in the newborn. However, there are a number of current barriers to the clinical application of this approach.

Central venous oxygen saturation provides a measure of the amount of oxygen left over after passage through the body. In essence, it is a measure of oxygen redundancy in the venous compartment. Although it has been used in adults and children post–cardiac surgery,[47] measurement requires an invasive central venous catheter, which has the attendant risks of thrombosis and infection. Its value in newborns is particularly dependent on the site of measurement.[48] This is because flow in the right atrium includes blood from a number of sources, which limits interpretation.[32,49] These include the lower body (mostly low extraction organs), the upper body (high extraction), and the left atrium (intraatrial shunt).

Noninvasive measurement of regional tissue saturation (rSO_2) is best facilitated with near infrared spectroscopy (NIRS). NIRS is based on continuous spectrometric measurement of oxygen dependent changes in the absorption properties of the chromophores, Hb and cytochrome aa3, in the near-infrared range. Changes in the concentration of oxygenated and deoxygenated Hb can be calculated from changes in light absorption between the emission and detection probes according to the modified Beer–Lambert law. NIRS is validated in preterm newborns[50] and measures oxygenated Hb in the tissue, whereas oximetry measures oxygenated Hb in the pulsatile blood vessel. Measurements derived by NIRS are dependent on a number of individual and interacting factors, all of which can influence tissue oxygenation. These factors include

the proportion of venous/arterial blood volume measured, arterial oxygen saturation, and oxygen consumption in the tissue of interest. Given that oxygen physiology is in constant flux, it is impossible to determine the contribution of each to NIRS measurements in isolation. For example, altered vascular tone will alter the proportion of arterial and venous blood volume under the measurement probe. This alteration will in turn change the proportion of oxygenated and deoxygenated Hb, and ultimately influence the derived measurement of rSO_2. Although this may be considered a limitation of NIRS, NIRS remains the best noninvasive clinical tool to assess end-organ perfusion, and the balance of oxygen delivery and consumption. Most NIRS devices assume a fixed venous to arterial compartment ratio, although this may change with alteration to posture (supine versus prone versus Trendelenburg).[51] Lastly, there is a subtle but meaningful difference between NIRS measured tissue oxygenation index and rSO_2.[51]

rSO_2 can be used either independently or as a surrogate for venous oxygen saturation in the calculation of oxygen extraction.[2] Reference ranges for cerebral rSO_2 in term and preterm newborns have been described. In the largest cohort (n = 999), Alderliesten and colleagues[52] described a reference range in preterm newborns (24–32 weeks' gestational age) in the first 3 days of life. In this population, cerebral rSO_2 increased with both maturity and chronologic age. In addition, small for gestational age newborns had comparatively higher rSO_2 values than appropriate for gestational age peers.[53] For example, the 10th, 50th, and 90th percentile for rSO_2 in the first 12 hours of life in preterm infants born at 24 to 25 weeks' gestation was 52%, 62%, and 72%, respectively, whereas in preterm infants born at 30 to 31 weeks' gestation, it was 58%, 68%, and 78%, respectively.

Recently, attention has focused on NIRS-derived cerebral rSO_2/tissue oxygenation index as a clinically relevant predictor of early acquired brain injury in the very preterm neonate.[43,54,55] Although reference ranges have been described, the threshold of injury in preterm neonates is unclear, and likely depends on the depth and duration of hypoxemia. This injury threshold has been described in piglets, where a cerebral rSO_2 threshold of ~50% predicted abnormalities of brain function (EEG) and energy production (brain lactate) in a model of mixed stagnant (carotid occlusion) and hypoxic hypoxia.[56]

The clinical feasibility of adjunctive measurement of cerebral rSO_2 in preterm newborns has been assessed in the SafeBOOSc study.[54] Newborns <28 weeks old were randomized to either nonvisible NIRS with standard care (control arm) or a combination of NIRS-measured cerebral rSO_2 and a treatment guideline within 3 hours of birth, continued until 72 hours of age. Staff used the treatment guideline, based solely on the constituents of systemic oxygen delivery, to keep a newborn within a cerebral rSO_2 target of 55% to 85%. Cumulative time and distance (depth) from the reference range (area under the curve) were used as primary outcomes. Although there was a significant reduction in duration and depth of hypoxia and hyperoxia in the intervention group compared with the control group (36.1 % hours [interquartile range, 9.2–79.5 % hours] vs 81.3 % hours [interquartile range, 38.5–181.3 % hours]), secondary clinical outcomes did not differ. This may be due to the focus on oxygen delivery alone, without consideration of concurrent oxygen consumption.

FUTURE DIRECTIONS

The body requires an excess of delivery over consumption, although the required margin of surplus oxygen is unclear. Although it is easier to define insufficient oxygenation or hypoxemia not least because of the accumulation of lactate, it is more difficult to establish what constitutes hyperoxia in the newborn. We propose that adequacy of oxygenation is best determined from either measurement of venous oxygen content or calculation of the oxygen extraction ratio. These 2 variables incorporate the amount of oxygen left after cellular respiration, thus providing a measure of oxygen redundancy.

The venous oxygen content can be measured by invasive (oxygen saturation in the pulmonary artery) or noninvasive methods (rSO_2). NIRS technology facilitates noninvasive measurement of tissue oxygen saturation, thereby enabling calculation of oxygen extraction in the preterm neonate. As already highlighted, NIRS methodology is not without limitations. Nonetheless, NIRS is, at present, the best technology to measure the status of the venous oxygen compartment.

If NIRS technology is to be used to determine tissue oxygen saturation, where is it likely to be the most informative? In the preterm newborn, the brain is likely to be the most appropriate site for assessment of overall oxygen status. It is both metabolically active and easily accessible with clear landmarks, thus making repeated measurements possible. Furthermore, as a high extraction organ at rest, it will likely act as a sentinel for system adequacy.

It is our view that a combination of regional (cerebral) oxygen extraction or cerebral rSO_2 and cutaneous oximetry could be easily used clinically to assess oxygen adequacy in the preterm newborn. In this

model, the preterm newborn would be assigned a target range for both extraction (or rSO_2) and oximetry, with inspired oxygen concentration adjusted to ensure the newborn remained within both target bands. This approach incorporates current clinical care pathways (ie, cutaneous oximetry) while adding adjunctive measures (cerebral oxygen extraction or rSO_2) to determine overall oxygen status. Clearly, this methodology requires additional study in a preterm population at risk for the consequence of both too much and too little oxygen.

CONCLUSIONS

Haldane recognized that oxygen physiology was dynamic, thus requiring titration in the individual. An alternate model for description of oxygen sufficiency is needed in preterm newborns, one that considers the relative adequacy of oxygen delivery in the context of contemporaneous consumption. In this paradigm, calculation of oxygen extraction with measurement of regional (cerebral) tissue saturation (NIRS) is likely to provide the reference value for the definition of adequacy, thereby making less relevant the absolute values of both oxygen delivery and consumption. This approach also allows the description of both hypoxemia and hyperoxemia. Additional trials with adjunctive noninvasive measurement of oxygen sufficiency are required in preterm populations at risk for the consequences of both insufficient and excessive oxygen exposure.

ABBREVIATIONS

CO: cardiac output
Hb: hemoglobin
[Hb]: hemoglobin concentration
NIRS: near infrared spectroscopy
rSO_2: regional tissue saturation

REFERENCES

1. Haldane JS. The therapeutic administration of oxygen. *BMJ*. 1917;1(2928):181–183
2. Nunn JF. *Applied Respiratory Physiology*. 3rd ed. London, United Kingdom: Butterworths; 1987
3. Schulze A, Whyte RK, Way RC, Sinclair JC. Effect of the arterial oxygenation level on cardiac output, oxygen extraction, and oxygen consumption in low birth weight infants receiving mechanical ventilation. *J Pediatr*. 1995;126(5 pt 1):777–784
4. Barcroft J. Physiological effects of insufficient oxygen supply. *Nature*. 1920;106(2656):125–129
5. Cain SM. Oxygen delivery and uptake in dogs during anemic and hypoxic hypoxia. *J Appl Physiol*. 1977;42(2):228–234
6. van der Hoeven MA, Maertzdorf WJ, Blanco CE. Mixed venous oxygen saturation and biochemical parameters of hypoxia during progressive hypoxemia in 10- to 14-day-old piglets. *Pediatr Res*. 1997;42(6):878–884
7. van der Hoeven MA, Maertzdorf WJ, Blanco CE. Relationship between mixed venous oxygen saturation and markers of tissue oxygenation in progressive hypoxic hypoxia and in isovolemic anemic hypoxia in 8- to 12-day-old piglets. *Crit Care Med*. 1999;27(9):1885–1892
8. Simmonds MJ, Detterich JA, Connes P. Nitric oxide, vasodilation and the red blood cell. *Biorheology*. 2014;51(2–3):121–134
9. Mertens L. Neonatologist performed echocardiography-hype, hope or nope. *Eur J Pediatr*. 2016;175(2):291–293
10. Kluckow M, Evans N. Point of care ultrasound in the NICU-training, accreditation and ownership. *Eur J Pediatr*. 2016;175(2):289–290
11. Boito S, Struijk PC, Ursem NT, Stijnen T, Wladimiroff JW. Umbilical venous volume flow in the normally developing and growth-restricted human fetus. *Ultrasound Obstet Gynecol*. 2002;19(4):344–349
12. Jouppila P, Kirkinen P. Umbilical vein blood flow as an indicator of fetal hypoxia. *Br J Obstet Gynaecol*. 1984;91(2):107–110
13. Laurin J, Lingman G, Marsál K, Persson PH. Fetal blood flow in pregnancies complicated by intrauterine growth retardation. *Obstet Gynecol*. 1987;69(6):895–902
14. Dawes GS. Pulmonary circulation in the foetus and new-born. *Br Med Bull*. 1966;22(1):61–65
15. Hooper SB, Te Pas AB, Lang J, et al. Cardiovascular transition at birth: a physiological sequence. *Pediatr Res*. 2015;77(5):608–614
16. Kluckow M, Evans N. Relationship between blood pressure and cardiac output in preterm infants requiring mechanical ventilation. *J Pediatr*. 1996;129(4):506–512
17. Kluckow M, Evans N. Superior vena cava flow in newborn infants: a novel marker of systemic blood flow. *Arch Dis Child Fetal Neonatal Ed*. 2000;82(3):F182–F187
18. Kluckow M, Evans N. Low superior vena cava flow and intraventricular haemorrhage in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2000;82(3):F188–F194
19. West CR, Groves AM, Williams CE, et al. Early low cardiac output is associated with compromised electroencephalographic activity in very preterm infants. *Pediatr Res*. 2006;59(4 pt 1):610–615
20. Miletin J, Dempsey EM. Low superior vena cava flow on day 1 and adverse outcome in the very low birthweight infant. *Arch Dis Child Fetal Neonatal Ed*. 2008;93(5):F368–F371
21. Holberton JR, Drew SM, Mori R, König K. The diagnostic value of a single measurement of superior vena cava flow in the first 24 h of life in very preterm infants. *Eur J Pediatr*. 2012;171(10):1489–1495
22. Strauss RG. Anaemia of prematurity: pathophysiology and treatment. *Blood Rev*. 2010;24(6):221–225
23. Keir AK, Yang J, Harrison A, Pelausa E, Shah PS; Canadian Neonatal Network. Temporal changes in blood product usage in preterm neonates born at less than 30 weeks' gestation in Canada. *Transfusion*. 2015;55(6):1340–1346

24. Whyte R, Kirpalani H. Low versus high haemoglobin concentration threshold for blood transfusion for preventing morbidity and mortality in very low birth weight infants. *Cochrane Database Syst Rev*. 2011;(11):CD000512

25. Bell EF, Strauss RG, Widness JA, et al. Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. *Pediatrics*. 2005;115(6):1685–1691

26. ETTNO Investigators. The 'Effects of Transfusion Thresholds on Neurocognitive Outcome of Extremely Low Birth-Weight Infants (ETTNO)' Study: background, aims, and study protocol. *Neonatology*. 2012;101(4):301–305

27. Transfusion of prematures trial (TOP). Available at: https://clinicaltrials.gov/ct2/show/NCT01702805. Accessed October 2012

28. Andersen CC, Keir AK, Kirpalani H, Stark MJ. Anaemia in the premature infant and red blood cell transfusion: new approaches to an age-old problem. *Curr Treat Options in Pediatr*. 2015;1(3):191–201

29. Andersen CC, Karayil SM, Hodyl NA, Stark MJ. Early red cell transfusion favourably alters cerebral oxygen extraction in very preterm newborns. *Arch Dis Child Fetal Neonatal Ed*. 2015;100(5):F433–F435

30. Delivoria-Papadopoulos M, Morrow G III, Oski FA. Exchange transfusion in the newborn infant with fresh and "old" blood: the role of storage on 2, 3-diphosphoglycerate, hemoglobin-oxygen affinity, and oxygen release. *J Pediatr*. 1971;79(6):898–903

31. Oski FA, Delivoria-Papadopoulos M. The shift to the left. *Pediatrics*. 1971;48(6):853–856

32. Hart J, Vemgal P, Cocks-Drew S, Harrison C, Andersen C. The relation between inferior vena cava oxygen saturation, superior vena cava flow, fractional oxygen extraction and haemoglobin affinity in sick newborns: a pilot study. *Acta Paediatr*. 2006;95(1):50–55

33. Gottuso MA, Williams ML, Oski FA. The role of exchange transfusions in the management of low-birth-weight infants with and without severe respiratory distress syndrome. II. Further observations and studies of mechanisms of action. *J Pediatr*. 1976;89(2):279–285

34. Van Ameringen MR, Fouron JC, Bard H, Le Guennec JC, Prosmanne J. Oxygenation in anemic newborn lambs with high or low oxygen affinity red cells. *Pediatr Res*. 1981;15(12):1500–1503

35. Carlo WA, Finer NN, Walsh MC, et al; SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med*. 2010;362(21):1959–1969

36. Schmidt B, Whyte RK, Asztalos EV, et al; Canadian Oxygen Trial (COT) Group. Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants: a randomized clinical trial. *JAMA*. 2013;309(20):2111–2120

37. Stenson BJ, Tarnow-Mordi WO, Darlow BA, et al; BOOST II United Kingdom Collaborative Group; BOOST II Australia Collaborative Group; BOOST II New Zealand Collaborative Group. Oxygen saturation and outcomes in preterm infants. *N Engl J Med*. 2013;368(22):2094–2104

38. Sola A, Golombek SG, Montes Bueno MT, et al. Safe oxygen saturation targeting and monitoring in preterm infants: can we avoid hypoxia and hyperoxia? *Acta Paediatr*. 2014;103(10):1009–1018

39. Lakshminrusimha S, Manja V, Mathew B, Suresh GK. Oxygen targeting in preterm infants: a physiological interpretation. *J Perinatol*. 2015;35(1):8–15

40. Sinclair JC. Thermal control in premature infants. *Annu Rev Med*. 1972;23:129–148

41. Sauer PJ, Dane HJ, Visser HK. Longitudinal studies on metabolic rate, heat loss, and energy cost of growth in low birth weight infants. *Pediatr Res*. 1984;18(3):254–259

42. Weinstein MR, Oh W. Oxygen consumption in infants with bronchopulmonary dysplasia. *J Pediatr*. 1981;99(6):958–961

43. Balegar KK, Stark MJ, Briggs N, Andersen CC. Early cerebral oxygen extraction and the risk of death or sonographic brain injury in very preterm infants. *J Pediatr*. 2014;164(3):475–480.e1

44. Adamson SK Jr, Gandy GM, James LS. The influence of thermal factors upon oxygen consumption of the newborn human infant. *J Pediatr*. 1965;66:495–508

45. Stark MJ, Hodyl NA, Belegar V KK, Andersen CC. Intrauterine inflammation, cerebral oxygen consumption and susceptibility to early brain injury in very preterm newborns. *Arch Dis Child Fetal Neonatal Ed*. 2016;101(2):F137–F142

46. Stark MJ, Hodyl NA, Andersen CC. Effects of antenatal magnesium sulfate treatment for neonatal neuroprotection on cerebral oxygen kinetics. *Pediatr Res*. 2015;78(3):310–314

47. Tweddell JS, Ghanayem NS, Mussatto KA, Mitchell ME, Lamers LJ, Musa NL, et al. Mixed venous oxygen saturation monitoring after stage 1 palliation for hypoplastic left heart syndrome. *Ann Thorac Surg*. 2007;84(4):1301–1310; discussion 1310–1311

48. Whyte RK. Mixed venous oxygen saturation in the newborn. Can we and should we measure it? *Scand J Clin Lab Invest Suppl*. 1990;203:203–211

49. van der Hoeven MA, Maertzdorf WJ, Blanco CE. Continuous central venous oxygen saturation (ScvO2) measurement using a fibre optic catheter in newborn infants. *Arch Dis Child Fetal Neonatal Ed*. 1996;74(3):F177–F181

50. Yoxall CW, Weindling AM. The measurement of peripheral venous oxyhemoglobin saturation in newborn infants by near infrared spectroscopy with venous occlusion. *Pediatr Res*. 1996;39(6):1103–1106

51. van Bel F, Lemmers P, Naulaers G. Monitoring neonatal regional cerebral oxygen saturation in clinical practice: value and pitfalls. *Neonatology*. 2008;94(4):237–244

52. Alderliesten T, Dix L, Baerts W, et al. Reference values of regional cerebral oxygen saturation during the first 3 days of life in preterm neonates. *Pediatr Res*. 2016;79(1–1):55–64

53. Cohen E, Baerts W, Alderliesten T, Derks J, Lemmers P, van Bel F. Growth restriction and gender influence cerebral oxygenation in preterm neonates. *Arch Dis Child Fetal Neonatal Ed*. 2016;101(2):F156–F161

54. Hyttel-Sorensen S, Pellicer A, Alderliesten T, et al. Cerebral near infrared spectroscopy oximetry in extremely preterm infants: phase II randomised clinical trial. *BMJ*. 2015;350:g7635

55. Alderliesten T, Lemmers PM, Smarius JJ, van de Vosse RE, Baerts W, van Bel F. Cerebral oxygenation, extraction, and autoregulation in very preterm infants who develop peri-intraventricular hemorrhage. *J Pediatr*. 2013;162(4):698–704.e2

56. Kurth CD, Levy WJ, McCann J. Near-infrared spectroscopy cerebral oxygen saturation thresholds for hypoxia-ischemia in piglets. *J Cereb Blood Flow Metab*. 2002;22(3):335–341

A Theoretical and Practical Approach to Defining ''Adequate Oxygenation'' in the Preterm Newborn

Chad C. Andersen, Nicolette A. Hodyl, Haresh M. Kirpalani and Michael J. Stark

Pediatrics 2017;139;
DOI: 10.1542/peds.2016-1117 originally published online March 21, 2017;

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

A Theoretical and Practical Approach to Defining ''Adequate Oxygenation'' in the Preterm Newborn

Chad C. Andersen, Nicolette A. Hodyl, Haresh M. Kirpalani and Michael J. Stark

Pediatrics 2017;139;
DOI: 10.1542/peds.2016-1117 originally published online March 21, 2017;